

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 16, 1270, and 1271

[Docket No. 1997N-484P]

Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is requiring human cell, tissue, and cellular and tissue-based product (HCT/P) establishments to follow current good tissue practice (CGTP), which governs the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps; recordkeeping; and the establishment of a quality program. The agency is also issuing new regulations pertaining to labeling, reporting, inspections, and enforcement that will apply to manufacturers of those HCT/Ps regulated solely under the authority of the Public Health Service Act (PHS Act), and not as drugs, devices, and/or biological products. The agency's actions are intended to improve protection of the public health while keeping regulatory burden to a minimum, which in turn would encourage significant innovation.

DATES: This rule is effective May 25, 2005.

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I. Introduction

This rule represents the culmination of FDA's efforts to establish a comprehensive new system for regulating HCT/Ps. The regulations now being issued require certain HCT/Ps to be manufactured in compliance with CGTP. The rule also contains provisions relating to establishment inspection and enforcement, as well as certain labeling and reporting requirements, which are applicable to those HCT/Ps regulated solely under the authority of section 361 of the PHS Act (42 U.S.C. 264) and the regulations in part 1271 (21 CFR part 1271), and not as drugs, devices, and/or biological products under the Federal Food, Drug, and Cosmetic Act (the act).

At this time we (FDA) are not responding to comments submitted on subparts D and E of the proposed rule relating to reproductive HCT/Ps. With two minor exceptions, the regulations in subparts D and E are not being finalized with respect to reproductive HCT/Ps described in § 1271.10 and regulated solely under section 361 of the PHS Act and the regulations in part 1271. The docket will remain open, and we ask that interested parties submit comments on communicable disease risks associated with reproductive HCT/ Ps and appropriate regulation to minimize those risks (other than that stipulated in part 1271 subparts A, B, C, and F, and §§ 1271.150(c) and 1271.155 in subpart D).

A. Background

In February 1997, FDA proposed a new, comprehensive approach to the regulation of human cellular and tissue-based products (now called human cells, tissues, and cellular and tissue-based products or HCT/Ps). The agency

announced its plans in two documents entitled “Reinventing the Regulation of Human Tissue” and “A Proposed Approach to the Regulation of Cellular and Tissue-based Products” (hereinafter “proposed approach document”). FDA requested written comments on its proposed approach and, on March 17, 1997, held a public meeting to solicit information and views from the interested public (62 FR 9721, March 4, 1997).

Since that time, the agency has published two final rules and one interim final rule to implement aspects of the proposed approach. On January 19, 2001, we issued regulations to create a new, unified system for registering HCT/P establishments and for listing their HCT/Ps (registration final rule, 66 FR 5447). Part of the definition of “human cells, tissues, or cellular or tissue-based products” became effective on January 21, 2004. On January 27, 2004 (69 FR 3823), we issued an interim final rule to except human dura mater and human heart valve allografts from the scope of that definition until all of the tissue rules became final. On May 25, 2004, we issued regulations requiring most cell and tissue donors to be tested and screened for relevant communicable diseases (donor-eligibility final rule, 69 FR 29786).

This rulemaking was initiated with a proposed rule on January 8, 2001 (Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement (66 FR 1508) (hereinafter “proposed rule’’)). In the proposed approach document, the agency stated that it would require that cells and tissues be handled according to procedures designed to prevent contamination and to preserve tissue function and integrity. The proposed rule would require establishments that manufacture HCT/Ps to comply with CGTP, which would include, among other things, proper handling, processing, labeling, and recordkeeping procedures. In

addition, the proposed regulations would require each establishment to maintain a “quality program” to ensure compliance with CGTP.

The proposed CGTP and other regulations would be contained in part 1271, along with provisions relating to establishment registration and donor eligibility that have previously been issued. We are now making those proposed regulations final for HCT/Ps collected on or after the effective date of this rule. We are also amending part 1270 (21 CFR part 1270), which now applies to certain HCT/Ps collected before the effective date of this rule, by modifying the definition of human tissue intended for transplantation (21 CFR 1270.3(j)) to limit its applicability to tissue collected before the effective date. We are not revoking part 1270 as previously proposed (66 FR 1508 at 1509). See section IV.B. of this document for further discussion.

Part 1271 contains six subparts. Subpart A of part 1271 sets forth scope and purpose as well as definitions. Subpart B of part 1271 contains registration procedures. Subpart C of part 1271 sets forth provisions for the screening and testing of donors to determine their eligibility. This rule puts in place three additional subparts. Subpart D of part 1271 contains the provisions on CGTP. Subpart E of part 1271 contains certain labeling and reporting requirements, and subpart F of part 1271 contains the inspection and enforcement provisions. The subparts apply as follows:

- Subparts A through D apply to all HCT/Ps, i.e., to those HCT/Ps described in § 1271.10 and regulated solely under section 361 of the PHS Act, and to those regulated as drugs, devices, and/or biological products; and
- Subparts E and F, which pertain to labeling, reporting, inspection, and enforcement, apply only to those HCT/Ps described in § 1271.10 and regulated solely under section 361 of the PHS Act.

However, as previously noted in section I of this document, with the exception of two provisions (§§ 1271.150(c) and 1271.155) subparts D and E are not being implemented for reproductive HCT/Ps described in § 1271.10 and regulated solely under section 361 of the PHS Act.

The publication of this final rule completes the set of regulations that implements FDA's proposed approach to regulating HCT/Ps. We recognize that over the course of this rulemaking, inadvertent errors or inconsistencies may have been introduced into the regulations. Accordingly, we anticipate that we may need to issue technical corrections in the future.

B. Legal Authority

FDA is issuing these new regulations under the authority of section 361 of the PHS Act. Under that section, by delegation from the Surgeon General and the Secretary of Health and Human Services, FDA may make and enforce regulations necessary to prevent the introduction, transmission, or spread of communicable diseases between the States or from foreign countries into the States. It is important to recognize that HCT/P manufacturing inevitably has interstate effects. HCT/Ps recovered in one State may be sent to another for processing, then shipped for use throughout the United States, or beyond. FDA has been involved in many recalls where HCT/Ps processed in a single establishment have been distributed in many States. In any event, intrastate transactions affecting interstate communicable disease transmission may also be regulated under section 361 of the PHS Act. (See *Louisiana v. Mathews*, 427 F. Supp. 174, 176 (E.D. La. 1977).)

Section 361 of the PHS Act authorizes FDA to issue regulations necessary to prevent the introduction, transmission, or spread of communicable diseases. Certain diseases, such as those caused by the human immunodeficiency virus

(HIV) and the hepatitis B and C viruses (HBV and HCV respectively), may be transmitted through the implantation, transplantation, infusion, or transfer of HCT/Ps derived from infected donors. The agency required, in another rule, that most cell and tissue donors be screened and tested for these and other relevant communicable diseases (donor-eligibility final rule, 69 FR 29786 at 29830). However, donor screening and testing, although crucial, are not sufficient to prevent the transmission of disease by HCT/Ps. Rather, each step in the manufacturing process needs to be appropriately controlled. Errors in labeling, mixups of testing records, failure to adequately clean work areas, and faulty packaging are examples of improper practices that could produce a product capable of transmitting disease to its recipient. Similarly, as noted in the proposed approach document, improper handling of an HCT/P can lead to bacterial or other pathogenic contamination of the HCT/P, or to cross-contamination between HCT/Ps, which in turn can endanger recipients. The agency has determined that the procedural provisions of this rule are necessary to ensure that the important protections created by these regulations are actually effected and are not simply empty promises. Only manufacturing conducted in accordance with established procedures can assure that HCT/Ps meet the standards in these rules. When processes are made up as the manufacturer goes along, mistakes inevitably are made. Moreover, review of procedures can be critical to determining the cause of a disease transmission. Without that analysis, it would be impossible to prevent a future occurrence, with possibly fatal consequences.

The record requirements of this rule are similarly necessary. A single donor may be the source of a large number of HCT/Ps. It may be discovered, long after the donation and transplantations have been completed, that, due

to an error in processing, the donor tissue was infected and capable of spreading communicable disease. Although it might be too late to prevent infections in the recipients, it would not be too late for the recipient to obtain treatment and take steps to avoid infecting others, such as close family members. Unless adequate records were maintained, and maintained for the period of time throughout which infections may be identified, it would be impossible to identify the recipients potentially infected by the donor's HCT/Ps. This would be a critical breakdown in the prevention of disease transmission.

Moreover, a single processing error, such as an improper practice that permitted bacterial contamination of all tissue processed at a location during a limited period of time, may also have wide ranging effects. Without reporting and study of adverse events involving the transmission of communicable disease, or involving the release of HCT/Ps presenting an increased risk of such transmission, common causes of seemingly isolated incidents would never come to light. Affected HCT/Ps would continue to place patients at risk of communicable disease. Accordingly, FDA has also determined that HCT/P tracking, maintenance and retention of records, and reporting of adverse reactions and HCT/P deviations are necessary to prevent the transmission of communicable disease through HCT/Ps.

The CGTP regulations govern the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps. CGTP requirements are a fundamental component of FDA's risk-based approach to regulating HCT/Ps. HCT/Ps regulated solely under section 361 of the PHS Act and the regulations in part 1271 are not regulated under the act or section 351 of the PHS Act (42 U.S.C. 262). By requiring that HCT/Ps meeting the criteria listed in

§ 1271.10 (361 HCT/Ps) be manufactured in compliance with CGTP, in combination with the other requirements in part 1271, the agency can ensure that 361 HCT/Ps are subject to sufficient regulatory controls to protect the public health.

HCT/Ps regulated as drugs, devices, and/or biological products, and not as 361 HCT/Ps, must be manufactured in accordance with CGTP, in addition to existing requirements. The CGTP regulations supplement the current good manufacturing practice (CGMP) and quality system (QS) regulations applicable to drugs, devices, and biological products in parts 210, 211, and 820 (21 CFR parts 210, 211, and 820). Thus, in keeping with the plan outlined in the proposed approach document, those HCT/Ps regulated as drugs, devices, and/or biological products are subject to CGMP regulations as well as to CGTP regulations. In the donor-eligibility final rule, the agency amended the existing CGMP regulations for drugs and the QS requirements for devices to reference the testing and screening provisions of part 1271, subpart C, as well as the CGTP procedures of part 1271, subpart D.

FDA is also relying on its authority under section 361 of the PHS Act for several reporting, labeling, inspection, and enforcement provisions. Because products regulated as drugs, devices, or biological products are already subject to similar requirements, these provisions in subparts E and F would apply only to 361 HCT/Ps. Subpart E of part 1271 contains regulations on reporting and labeling pertaining to 361 HCT/Ps and is discussed in section III.D. of this document. Subpart F of part 1271 contains inspection and enforcement provisions also applicable only to 361 HCT/Ps; the relevant discussion appears in section III.E of this document.

In addition, under section 368(a) of the PHS Act (42 U.S.C. 271), any person who violates a regulation prescribed under section 361 of the PHS Act may be punished by imprisonment for up to 1 year. Individuals may also be punished for violating such a regulation by a fine of up to \$100,000 if death has not resulted from the violation or up to \$250,000 if death has resulted. For organizational defendants, fines range up to \$200,000 and \$500,000. Individuals and organizations also face possible alternative fines based on the amount of gain or loss. (18 U.S.C. 3559 and 3571(b) to (d)). Federal District Courts also have jurisdiction to enjoin individuals and organizations from violating regulations implementing section 361 of the PHS Act. (See *Califano v. Yamasaki*, 442 U.S. 682, 704–05 (1979); *United States v. Beatrice Foods Co.*, 493 U.S. 961 (1975).)

II. Revisions to the Proposed Rule

A. Plain Language

On June 1, 1998, the Presidential Memorandum on Plain Language in Government Writing was issued in the **Federal Register** (63 FR 31885). The purpose of the plain language initiative is to create government documents that are easier to understand.

In response to this initiative, we have written the CGTP regulations in plain language. We have:

- Reorganized some regulatory sections for greater clarity, and
- Followed other plain-language conventions, such as using “must”

instead of “shall.”

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

B. HCT/P Definition

In the registration final rule, we discussed our decision to replace the term “human cellular and tissue-based products” with “human cells, tissues, and cellular and tissue-based products” (abbreviated “HCT/Ps”) (66 FR 5447 at 5455). For consistency, we have made the same change in this final rule.

Also in the registration final rule, we put into place a two-part definition of HCT/P to stagger the effective dates of the registration and listing regulations for different types of HCT/Ps. We stated in the registration final rule that, when all the regulations that make up part 1271 are issued, we would revoke § 1271.3(d)(1) and renumber paragraph (d)(2) as a conforming amendment. At that time the new regulatory framework contained in part 1271 would be instituted as a whole (66 FR 5447 at 5450). We recognized that unanticipated delays in completing the rulemaking for the remainder of part 1271 could occur, and we noted that, should the rulemaking proceedings be delayed past the anticipated 2-year timeframe, we would consider whether to maintain the 2-year effective date for the HCT/Ps described in § 1271.3(d)(2) or whether to extend that date (66 FR 5447 at 5449). Since the rulemaking proceedings were delayed past the original 2-year effective date of January 21, 2003, we delayed the effective date of § 1271.3(d)(2) until January 21, 2004 (68 FR 2690, January 21, 2003), on which date § 1271.3(d)(2) became effective.

On January 27, 2004, we issued an interim final rule excepting human dura mater and human heart valve allografts from the definition of HCT/P in § 1271.3(d) (69 FR 3823). We stated that, when the comprehensive framework is in place, FDA intends that human dura mater and human heart valves will be subject to it, and that FDA intends to revoke the interim rule at that time

(69 FR 3823 and 3824). With the effective date of this final rule, we are revoking the interim rule and revising the language in § 1271.3(d).

C. Function and Integrity

The proposed rule contained provisions addressing our concerns about the spread of communicable disease through the use of products whose function or integrity have been impaired (66 FR 1508 at 1510). As discussed in Comment 9, we have removed from the regulations all references to function or integrity.

D. Core CGTP Requirements

In drafting this rule, we have re-evaluated each requirement of the proposed rule to ensure that it either directly prevents the introduction, transmission, or spread of communicable diseases (e.g., the requirement to store HCT/Ps at an appropriate temperature), or that it supports such a requirement (e.g., the requirement to periodically review recorded temperatures to ensure that the temperatures have been within acceptable limits). We have removed requirements where the connection to the prevention of the introduction, transmission, or spread of communicable diseases may be more attenuated.

As a result of this analysis, these final regulations are organized differently from the proposed regulations and contain fewer requirements. “Core CGTP requirements” are listed in § 1271.150(b); these requirements are directly related to preventing the introduction, transmission, or spread of communicable diseases. Certain requirements in subparts D and E are now limited in their applicability to these core CGTP requirements (e.g., the required records management system in § 1271.270(b) relates solely to core CGTP requirements). We have also reorganized sections within these subparts

so that the core CGTP requirements appear first within a section, with supporting requirements following (e.g., § 1271.190 on facilities has been reorganized so that requirements for procedures and records, which are not core requirements, occur in paragraph (d)).

Due to the more limited nature of these final regulations, we have removed certain proposed requirements, despite their potential importance to an establishment's operations. We stress that their absence from these final regulations should not be seen as a determination that they are without value. Rather, at this time, we are issuing a more limited set of requirements than proposed. These requirements represent minimum expectations, but an establishment may decide to do more than this minimum.

E. Other Revisions

We are amending, rather than revoking, the regulations in part 1270. See section IV of this document for further discussion.

We have made changes from the proposal throughout the regulations to be more clear; to link the regulations more closely to preventing the transmission of communicable diseases, as discussed in section II.D of this document; and in response to comments discussed in section III of this document. These revisions include:

- Adding § 1271.145, which requires establishments to manufacture HCT/Ps in a way that prevents the introduction, transmission, or spread of communicable diseases;
- Revising the definitions for “adverse reaction,” “available for distribution,” “complaint,” “distribution,” “product deviation,” “processing,” “quality audit,” and “quality program”;

- Adding § 1271.215, which requires establishments to recover HCT/Ps in a way that does not cause contamination or cross-contamination during recovery, or otherwise increase the risk of the introduction, transmission, or spread of communicable disease through the use of the HCT/P;
 - Deleting proposed § 1271.220(b) *Processing material* and the definition of that term in proposed § 1271.3(hh);
 - Adding paragraph (b) to § 1271.265;
 - Adding language in § 1271.420 to facilitate rapid admissibility decisions for imported HCT/Ps that meet requirements, and to except cells and tissues from a sexually intimate partner, and peripheral blood stem/progenitor cells from the requirement for an admissibility decision; and
 - Adding pertinent references to “preventing the introduction, transmission, or spread of communicable diseases,” where it is useful to explain the purposes or scope of a requirement.

We have also made technical amendments to §§ 1271.10(a)(3) and 1271.22(b) and (c). Section 1271.10(a)(3) is revised by adding “water” and “crystalloids” to the exceptions because, as with sterilizing, preserving and storage agents, these substances generally do not raise safety concerns. Water or crystalloids (e.g., saline solution, Ringer’s lactate solution, or 5% dextrose in water) are typically added to lyophilized HCT/Ps by the user to reconstitute the HCT/P. We have also revised § 1271.10(a)(3) by replacing “the combination of the cell or tissue component with a drug or device” with “the combination of cells or tissues with an article.” We found that establishments were confused by the reference to drugs and devices in this context, and did not understand how to evaluate the drug or device function of the additive in the context of the product. By substituting the term “article,” we eliminate this ambiguity,

we focus more directly on the risks presented by such additives, and we therefore make this provision more consistent with the risk-based approach supporting the balance of the rule.

Section 1271.22 is revised by updating the mailcodes in paragraphs (b)(i) and (c)(i), by removing paragraph (b)(iv) since the Fax Information System is no longer in service, and by providing information for the electronic submission of Form FDA 3356.

Section 1271.45(a) is amended by adding that other CGTP requirements are set out in subpart D of part 1271. This statement clarifies that subparts C and D together constitute CGTP requirements.

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

We received 47 comments on the proposed rule. Several comments raised issues that were addressed in the registration final rule (e.g., determining the regulatory categorization of HCT/Ps). Responses to these comments may be found in the registration final rule at Comment 7 (66 FR 5447 at 5451), Comment 8 (66 FR 5447 at 5452), and Comment 30 (66 FR 5447 at 5459). Other comments on this rule raised issues relating to the donor-eligibility rule; we addressed these comments in the donor-eligibility final rule at Comment 25 (69 FR 29786 at 29796), Comment 32 (69 FR 29786 at 29799), Comment 48 (69 FR 29786 at 29806), Comment 59 (69 FR 29786 at 29809), and in section III.D.3 (69 FR 29786 at 29797).

A. General

1. General Comments

(Comment 1) Numerous comments supported the proposed rule. These comments called the rule well written and organized, easy to understand, comprehensive, and reasonable. One comment appreciated the philosophy we

adopted in defining objectives rather than specific methodologies. Another comment stated that the formulation of the proposed rule and the development of the entire regulatory framework were an enormous undertaking of great importance and timeliness.

(Response) We appreciate these supportive comments. We agree with those comments recognizing both the importance of this rule and the fact that it represents the culmination of our efforts to develop a comprehensive new system of regulation for HCT/Ps.

We also note that most of the comments we received on this rule were helpful and well organized. For example, many comments were arranged by section number of the proposed regulation and contained specific suggestions on how to revise each section, often including new language. We appreciate the care with which these comments were prepared.

(Comment 2) Some comments stated general opposition to the proposed rule. One comment stated that tissue banks are self-regulating and that the rules are unnecessary. This comment further asserted that smaller tissue banks have not been informed and have been ignored, while we worked only with large organizations.

(Response) We recognize that some comments oppose the proposed rule as a general matter and do not consider the new regulations necessary or beneficial. We disagree with those comments. We also disagree with the statement that, in developing these rules, we have consulted only large professional organizations and have ignored the concerns of small banks or failed to inform them of our rulemaking. Even before this rulemaking began, we took pains to make our intentions clear to all interested parties by issuing notices and rulemakings in the **Federal Register**, which is accessible to both

large and small organizations. We have held several public meetings on issues affecting the rulemaking that were open to all interested parties. We also prepared an analysis of the impact of the rulemaking on small entities in the proposed rule (66 FR 1508 at 1545). Moreover, this final rule incorporates many changes made in response to comments from a range of interested parties, including many small entities. We also will be issuing a small entity compliance guide, which will assist small entities in complying with part 1271.

(Comment 3) Several comments compared the proposed rule to industry standards. Three comments complimented us for the proposed rule's consistency with current good industry practice. In contrast, one comment argued that the proposed rule offered little additional benefit over industry standards currently in place. One comment asserted that the rule is reasonable to the extent it mirrors good manufacturing practice (GMP)/QS regulations for in vitro diagnostics and current bloodborne pathogen guidelines, but that many provisions are duplicative of the regulations and guidelines in place and create another layer of unnecessary recordkeeping. This comment stated that the rule goes beyond its original intent and places an undue regulatory burden, which would bring a halt to innovative activities.

(Response) The proposed requirements were based on current good industry practice and were intended to address what we consider to be important minimum criteria for the manufacture of HCT/Ps in a manner that effectively reduces the risk of communicable disease transmission. In developing the proposed CGTP regulations, we reviewed several sets of industry standards (66 FR 1508 at 1511). These comments indicate that we were successful in reflecting current good practices. We note that, to the extent

that industry standards are consistent with and at least as stringent as CGTP requirements and are appropriate for the operations conducted, an establishment may adopt industry's standard procedures as a way of complying with these regulations (§ 1271.180(d)). However, we decline to mandate compliance with the standards of a particular professional organization. Industry associations are welcome to submit their standards to the agency for potential adoption as guidance subject to public comment. (See 21 CFR 10.115.)

We disagree that these regulations require unnecessary recordkeeping or create an undue regulatory burden. In this final rule, we have made numerous changes to the regulatory provisions in response to comments; many of these changes will have the effect of reducing the regulatory burden from that originally proposed while still addressing communicable disease risks.

With respect to the comment on duplicative requirements applicable to HCT/Ps regulated as devices, drugs, and/or biological products, we note that § 1271.150(d) states that CGTP and CGMP regulations in parts 210 and 211 and the QS regulations in part 820 supplement each other unless the regulations explicitly provide otherwise. In the event of a conflict between applicable requirements, the regulations more specifically applicable to the product will supersede the more general requirements. FDA believes that, in the event of such a conflict, the more specifically applicable regulation would be found in part 1271. It is unnecessary to maintain two sets of records to indicate compliance with both CGTP and CGMP or QS requirements; a single set of records is adequate.

(Comment 4) Several comments requested that these regulations be phased in over time. Two comments requested a grace period of 1 to 2 years; one

comment requested a 2-year implementation period; and another comment requested an extension of the compliance deadline to 1 year after publication.

(Response) We understand the request for a long implementation period. However, recent reports of bacterial infections in patients who received HCT/Ps support the implementation of the CGTP requirements as soon as possible. (Ref. 1) The effective date of the CGTP final rule will coincide with the effective date of the previously issued donor eligibility requirements. We believe that this will provide an adequate amount of time to comply with the requirements in part 1271.

(Comment 5) Two comments opposed the retrospective application of any regulation or guidance to tissue recovered before its issuance, because tissue may have a shelf life of up to 5 years. The comments suggested that the final rule should apply to HCT/Ps recovered after the effective date, and that for tissues recovered before the effective date of the final rule, the regulations in part 1270 would continue to apply.

(Response) We agree that the final rule will apply to HCT/Ps recovered on or after the rule's effective date. Cells and tissue recovered before that date are subject to the regulations in effect at the time of recovery. The regulations in part 1270 are being amended in this rulemaking so that those regulations will continue to apply only to human tissue for transplantation recovered before the effective date of this rule. See section IV.B of this document for further discussion.

(Comment 6) One comment asserted that the regulations should cover the procurement and storage of human organs for transplant, reproductive cells (sperm and ova), and the storage of human milk.

(Response) Part 1271 does not apply to human organs or to human milk. Subparts D and E are not being implemented with respect to reproductive HCT/Ps, except for §§ 1271.150(c) and 1271.155.

(Comment 7) Several comments objected to the terms “manufacture” and “product” as inappropriate for use with respect to donated human tissue. One comment asserted that corneas are recovered and evaluated, not manufactured. Some comments suggested substitute terminology: e.g., “donor program” or “tissue service organization” instead of “manufacturer”; “handle” instead of “manufacture”; and “human cellular and tissue-based material” instead of “product.” One comment asserted that, because the terminology used in the rule does not correlate with eye bank practices, it was difficult to determine which sections apply to eye banking; this comment cited the additional terms “process,” “processing,” “processing material,” “validation,” and “verification.”

(Response) In the registration final rule, we changed the term “human cellular or tissue-based product” to “human cells, tissues, and cellular and tissue-based products,” or “HCT/Ps.” We made this change in response to comments that opposed calling donated tissue a “product.” In that final rule, we noted that we needed a term broad enough to cover both cells and tissues, and one that would include within its scope such diverse articles as unprocessed tissue, highly processed cells, and tissues that are combined with certain drugs or devices (66 FR 5447 at 5455). We believe the term “HCT/P” addresses the concerns expressed in the comments, and we will use that term in these regulations.

In the registration final rule, we also considered substituting a different term for “manufacture,” in response to similar comments, but were unable to

find a satisfactory replacement. Among other terms, we considered “handling,” but rejected it as too limited in scope. Thus, we have continued to use the word “manufacture” as an umbrella term to capture the many different actions that HCT/P establishments might take in preparing HCT/Ps for use (66 FR 5447 at 5455).

Many different types of establishments are involved in the recovery, screening, testing, processing, storage, labeling, packaging, and distribution related to HCT/Ps. Some of these may accurately be called tissue service organizations, donor programs, or tissue procurement organizations, and may certainly continue to call themselves by these names. However, these terms are too limited to cover those establishments that perform other manufacturing functions, and for that reason we decline to adopt any of these suggested terms in this regulation. We note that, although these rules at times refer to “manufacturers,” the more frequently used term is “establishment.”

With respect to the comment on the applicability of these regulations to eye banks, we discuss the applicability of specific sections throughout this final rule. We note that each establishment is required to comply only with those requirements that apply to the activities in which it engages. We are working, with input from industry and others, to develop guidances specific to different types of HCT/Ps; this effort is intended to help establishments comply with these CGTP requirements to control the risk of communicable disease transmission.

(Comment 8) Comments from eye banking organizations stated that eye and cornea banking differ from other tissue banking.

(Response) We acknowledge that, in some ways, eye banking differs from other tissue banking. However, since 1993, ocular tissue has been regulated

under the regulatory model for all human tissues for transplantation. Eye banks are similar to tissue banks in that they recover, process (although minimally), store, label, package, or distribute human tissue, screen and test the tissue donor, report adverse reactions, and track tissue. We have intentionally crafted broad CGTP regulations for flexibility with the expectation that each bank will specify its own operating procedures. In addition, we have stated that an establishment need only comply with those requirements that are applicable to the operations in which it engages.

2. Function and Integrity

The proposed CGTP requirements were intended, in part, to prevent the introduction, transmission, or spread of communicable disease by helping to ensure that the function and integrity of HCT/Ps are not impaired through improper manufacturing (proposed § 1271.150(a); see 66 FR 1508 at 1510). Many of the provisions of the proposed rule contained requirements intended to help ensure HCT/P function and integrity. For example, proposed § 1271.260 would require an establishment to control its storage areas to prevent conditions that may adversely affect function or integrity.

(Comment 9) Approximately nine comments objected to the proposed rule's provisions on function and integrity. Some of these comments criticized our justification for these provisions as weak or theoretical; these comments questioned whether the impairment of an HCT/P's function and integrity actually increases the risk of disease transmission. Other comments argued that section 361 of the PHS Act cannot be interpreted to cover an HCT/P's function and integrity. Several comments requested that the phrase be defined or deleted.

Several comments expressed concern that the provisions on function and integrity could be interpreted to mean that an establishment assess each HCT/P's function and integrity. These comments agreed generally with the concept of ensuring function and integrity, which they described as ensuring that an HCT/P is "fit for use," but asked the agency to clarify the relationship between the concept and a risk-based system.

Most comments on the general issue of function and integrity also objected to specific sections of the proposed rule where that term appears. These comments requested the deletion of, or a substitution for, the phrase "function and integrity," as well as related terms.

(Response) To increase clarity, and because of the confusion expressed by comments about the term "function and integrity," we have removed from the regulations all references to function or integrity. For the same reason, we have also removed references to the related terms, "deterioration" and "adverse effect."

To avoid repetition throughout this document, comment summaries do not contain references to function and integrity (or related terms), where we received comments on that issue. Moreover, references to function and integrity, deterioration, and adverse effect, have been removed from summaries of the provisions proposed in the proposed rule. References to function and integrity have been removed from discussions of the following proposed provisions: §§ 1271.3(bb) and (kk), 1271.160, 1271.200, 1271.210, 1271.220, 1271.260, 1271.265, 1271.350, and 1271.420.

B. Definitions (§ 1271.3)

We have grouped all definitions pertinent to part 1271 in a single definitions section (§ 1271.3), among the general provisions of subpart A. The

proposed rule contained proposed definitions from § 1271.3(ff) through (tt); these have been renumbered from § 1271.3(y) through (ll). We have also reordered the definitions to maintain some alphabetical order, and they are discussed according to their new order.

We have revised § 1271.3(d) by deleting paragraph (d)(1), as it is no longer applicable with the effective date of this rulemaking. We have added the terms “repair” and “reconstruction” to the definition of “homologous use” at § 1271.3(c) (the registration final rule, 66 FR 5447 at 5467), to provide a more complete and accurate description of the definition.

1. Adverse Reaction (§ 1271.3(y))

The proposed rule would define “adverse reaction” as a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the response may have been caused by the product (i.e., the relationship cannot be ruled out) (66 FR 1508 at 1520). Adverse reaction reporting requirements are set out in proposed § 1271.350(a).

(Comment 10) Several comments argued that the proposed definition of “adverse reaction” is too broad. One comment asserted that a transplant recipient could experience a reaction to a substance in a tissue even though the manufacturer followed CGTP requirements. One comment suggested changing “reasonable possibility” to “reasonable probability.”

(Response) The definition of “adverse reaction” is intended to capture those situations that may indicate a problem with an HCT/P and that a manufacturer should therefore investigate. A noxious and unintended response to a substance in an HCT/P would meet the definition of “adverse reaction,” and an establishment should evaluate the situation.

The receipt of adverse reaction reports enables us to evaluate potential relationships between reports. For example, if several separate establishments reported that a recipient of tissue that the establishments made available for distribution developed a wound infection with *Clostridium* sp., FDA might determine that a single establishment recovered or processed all of those tissues. An FDA investigation would be initiated.

It is important to note that not all adverse reactions are required to be investigated and reported. Section 1271.350(a) sets out those situations in which an establishment must make an adverse reaction report to us. An investigation is required when an adverse reaction involves a communicable disease. A report is required when such an adverse reaction is fatal or life-threatening; results in permanent impairment or damage; or necessitates medical or surgical intervention. The criteria set out in § 1271.350(a) limit the scope of the adverse reaction reporting requirement. As discussed in the preamble to the proposed rule (66 FR 1508 at 1520), this approach, and the definition of adverse reaction, are consistent with other rules we are developing and with international standards (See, e.g., “International Conference on Harmonisation; Guideline on Clinical Safety Data Management: Definitions and Standards for Expedited Reporting; Availability” (ICH guideline), 60 FR 11284, March 1, 1995).

We decline to replace the word “possibility” with the suggested term, “probability.” We interpret “reasonable possibility” to mean that there is a possible causal relationship between an adverse experience and an HCT/P; “there are facts (evidence) or arguments to suggest a causal relationship.” (ICH guidance, 60 FR 11284 at 11286).

(Comment 11) One comment questioned the phrase “the relationship cannot be ruled out.” This comment noted that there may be multiple possible causes of a patient’s problems, and that in some instances it may be unlikely that the HCT/P is responsible.

(Response) We have removed the phrase “the relationship cannot be ruled out” from the definition of “adverse reaction.” On further examination, we believe it is not helpful in explaining what is meant by “reasonable possibility.” We recognize that there may be situations in which there are multiple possible causes of a patient’s problem. Nevertheless, if one of the reasonable possibilities is that the HCT/P caused the problem, then this would meet the definition of “adverse reaction.” This would include situations in which the relationship between the response and the HCT/P is “unlikely” but nevertheless possible.

2. Available for Distribution (§ 1271.3(z))

The proposed regulations in § 1271.3(ff) would define “available for distribution” to mean that an HCT/P has been determined to meet all release specifications and to be suitable for distribution.

(Comment 12) One comment suggested this definition should be harmonized with the final rule on biologic product deviations (65 FR 66621 at 66634, November 7, 2000; 21 CFR 600.14) to clarify that reporting product deviations is only necessary after an HCT/P has left control of the establishment (i.e., has been distributed).

(Response) We agree that, under § 1271.350(b), you are required to report an HCT/P deviation only when the HCT/P has been distributed. However, we disagree that there is any need to modify the definition of “available for distribution” as requested by the comment. The phrase “available for

distribution” does not appear in § 1271.350(b). We have, however, removed the words “and to be suitable for distribution” from the definition of “available for distribution.” As defined in the final rule, an HCT/P is “available for distribution” if it has been determined to meet all release criteria.

We discuss the definition of “distribution” in Comment 16.

3. Complaint (§ 1271.3(aa))

Proposed § 1271.3(ii) would define “complaint” as any written, oral, or electronic communication that alleges that an HCT/P has transmitted or may have transmitted a communicable disease; or any other problem with an HCT/P that could result from the failure to comply with CGTP (66 FR 1508 at 1520).

(Comment 13) One comment stated that the definition is vague and would leave eye banks open to baseless accusations by recipients, family members, or physicians for graft failure that may have been due to other causes. According to this comment, eye banks should be given an opportunity to filter out unfounded complaints.

(Response) We have revised the definition to specify that information must relate to the potential for transmission of communicable disease, such as the failure to comply with current good tissue practice (which would include the donor eligibility regulations). However, we note that a complaint may come from any source and may be a written, oral, or electronic communication. Section 1271.320 requires each establishment to have procedures in place to evaluate complaints that relate to core CGTP requirements and to determine whether investigation is necessary.

(Comment 14) Several comments noted their belief that the proposed requirements on complaints would apply only to HCT/Ps that have been released to distribution.

(Response) We agree with these comments and revised the definition to apply to distributed HCT/Ps only.

(Comment 15) Two comments requested the deletion of proposed § 1271.3(ii)(3), which covered any other problem with an HCT/P that could result from the failure to comply with CGTP. Two other comments suggested that we revise proposed § 1271.3(ii)(3) to refer to deficiencies related to the identity, quality, durability, reliability, safety, or performance of a product after it is released for distribution. A third comment recommended that paragraph (ii)(3) be deleted or clarified to indicate its application to tissues released to distribution.

(Response) We decline to delete proposed § 1271.3(ii)(3), which has been renumbered as § 1271.3(aa)(2). As previously noted, we intend the requirements with respect to complaints to apply to HCT/Ps that have been distributed. It is necessary for all establishments to have in place a system to handle communications about problems with its distributed HCT/Ps. Some problems may be traced to a failure to comply with CGTP, which could lead to additional problems that increase the risk of communicable disease transmission if not corrected. Deleting proposed § 1271.3(ii)(3) would unduly narrow the scope of the definition, allowing establishments to ignore important communications about their products. (However, we note that, as discussed in Comment 13, we have specified that information under this paragraph must relate to the potential for transmission of communicable disease.)

4. Distribution (§ 1271.3(bb))

We proposed to define “distribution” in § 1271.3(jj) as any conveyance or shipment of HCT/Ps (including importation and exportation), whether or not such conveyance or shipment is entirely intrastate and whether or not

possession of the product is taken. We originally described our intended definition of “distribution” in the preamble to the registration proposed rule (63 FR 26744 at 26750), and we responded to several comments on “distribution” in the registration final rule (66 FR 5447 at 5456).

(Comment 16) One comment asserted that the definition of distribution in the proposed rule is inconsistent with the definition in the registration final rule. The comment pointed out that, in the preamble to the registration final rule, we agreed that an entity that does not take possession of HCT/Ps is not distributing them for the purposes of this rule.

(Response) The proposed rule, which contained the proposed codified definition of “distribution,” preceded the registration final rule, in which we indicated we would make changes to the proposed definition. We are now making the change to the definition that we discussed in the registration final rule; i.e., we have removed the phrase “whether or not possession is taken” from the definition and replaced it with “If an entity does not take physical possession of an HCT/P that entity is not considered a distributor.”

(Comment 17) One comment requested that we clarify that intracompany transfers of HCT/Ps are not included within the definition of “distribution,” consistent with FDA’s policy with respect to other medical products.

(Response) In response to this comment, we have modified the definition of “distribution” to mean any conveyance or shipment of an HCT/P “that has been determined to meet all release criteria.” This change is intended to make clear that the shipment of an HCT/P before it is ready for release would not be considered distribution (e.g., the movement of an HCT/P from a recovering establishment to a processing establishment). This sort of predistribution shipment might also take place between establishments that are part of the

same company. On the other hand, not all intracompany shipments are appropriately excepted from the definition of “distribution.” For example, releasing an HCT/P from a collection/processing facility to an operating room in the same facility would be considered distribution.

5. Establish and Maintain (§ 1271.3(cc))

Proposed § 1271.3(ll) would define “establish and maintain” as define, document (in writing or electronically), and implement, then follow, review, and, as needed, revise on an ongoing basis.

We received no comments on the proposed definition of “establish and maintain.”

6. HCT/P Deviation (§ 1271.3(dd))

Proposed § 1271.3(kk) would define “product deviation” as an event that represents a deviation from CGTP, applicable standards, or established specifications; or an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease agent or disease from an HCT/P to a recipient, or may lead to product contamination.

In response to comments on the term “product,” we have changed the defined term from “product deviation” to “HCT/P deviation” (see 66 FR 5447 at 5455). We have also narrowed the definition of HCT/P deviation by revising the phrase “a deviation from current good tissue practice, applicable standards, or established specifications” to read “a deviation from applicable regulations in this part or from applicable standards or established specifications that may relate to the prevention of communicable disease transmission or to the prevention of HCT/P contamination.”

Proposed § 1271.350(b) would require you to report those HCT/P deviations that could reasonably be expected to lead to a reportable adverse reaction.

(Comment 18) One comment suggested that we use the term “process deviation” instead of “product deviation,” because the definition refers to an event rather than to a deviation in the HCT/P.

(Response) We decline to make the suggested change because to do so could exclude problems that occur in areas of manufacture other than “processing,” such as recovery and storage, and would therefore be narrower than “HCT/P deviation.” Moreover, the term “process deviation” might introduce inconsistency with our reporting requirements in § 600.14 (21 CFR 600.14) for biological products other than blood and blood components. Establishments that manufacture HCT/Ps regulated under section 351 of the PHS Act will report under § 600.14. Establishments that manufacture HCT/Ps regulated as drugs or devices under the act will make any reports under drug and device reporting provisions.

(Comment 19) One comment noted that there are no established specifications for corneas, although there are proxy indicators (e.g., cell counts and cell morphology) that can be taken into account when evaluating tissue, and that outcomes may be dependent upon factors beyond an eye bank’s control.

(Response) We understand that an eye bank might not set specifications for corneas. However, we expect that an establishment will generally set out acceptable criteria for its HCT/Ps in its standard operating procedures. These criteria may relate to such factors as storage temperature, and although not considered specifications by the establishment, they serve much the same role.

Since storage temperature may relate to the prevention of communicable disease transmission or HCT/P contamination, a deviation from these criteria would be considered an HCT/P deviation. You must review the deviation to determine if it must be reported under § 1271.350(b).

7. Importer of Record (§ 1271.3(ee))

Proposed § 1271.3(tt) would define “importer of record” as “the person, establishment, or its representative responsible for making entry of imported goods in accordance with all laws affecting such importation.” (66 FR 1508 at 1552).

We received no comments on the proposed definition of “importer of record.”

8. Processing (§ 1271.3(ff))

Processing is one of the activities listed in the definition of “manufacture” in § 1271.3(e). The proposed rule would define “processing” in § 1271.3(mm) as any activity performed on an HCT/P other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution. Processing would include, but not be limited to, preparation, sterilization, steps to inactivate and remove adventitious agents, preservation for storage, and removal from storage. We have added to the definition “testing for microorganisms” because this activity may occur at this stage of manufacturing.

(Comment 20) One comment requested clarification of the terms “process” and “processing” as those terms are used in proposed §§ 1271.220 (process controls) and 1271.225 (process changes).

(Response) We believe that “process” is a generally understood term; one accepted definition of “process” is a “set of interrelated or interacting activities which transfers inputs into outputs” (International Standards Organization

(ISO) 9000:2000, 3.4.1). In the context of this final rule, the set of processing activities that an establishment performs on an HCT/P would be considered a “process.” We consider the proposed definition of “processing” to be sufficiently clear and have made no substantive changes to it.

(Comment 21) One comment from an eye bank requested clarification of “preparation,” “preservation for storage,” and “removal from storage.” The comment noted that corneas are stored in media to maintain viability but are not preserved for long-term storage.

(Response) We believe that these terms are generally understood; however, not all of them may be applicable to eye banks. We agree that corneas are usually not preserved for long-term storage, but nevertheless, they are preserved in a corneal storage media, even for short-term storage.

Examples of corneal processing may include gross and microscopic examination of the cornea, microbiological culture of the rim, preservation in a corneal storage media, and placement into and removal from the refrigerator.

9. Processing Material

The proposed rule would define “processing material” in § 1271.3(hh) as any material or substance that is used in, or to facilitate, processing, but which is not intended by the manufacturer to be included in the HCT/P when it is made available for distribution.

We have deleted the relevant provision on processing material, in proposed § 1271.220(b), and as a result are also deleting this definition.

10. Quality Audit (§ 1271.3(gg))

We proposed to define “quality audit” in § 1271.3(nn) as a documented, independent inspection and review of an establishment’s activities, including manufacturing and tracking, performed according to procedures, to verify, by

examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review.

We have revised the definition of quality audit to mean a documented, independent inspection and review of an establishment's activities related to core CGTP requirements. The definition further states that the purpose of a quality audit is to verify, by examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review.

(Comment 22) One comment recommended that we define "independent" or insert a reference to proposed § 1271.160(d)(2), which would require that a quality audit be performed by an individual who does not have direct responsibility for the processes being audited. Another comment asked us to clarify "independent inspection" and asked whether an employee could perform the independent inspection. A third comment asked whether an outside accreditation process could constitute an independent review.

(Response) We do not believe it is necessary to define "independent." We consider an inspection and review by an individual who does not have direct responsibility for the processes being audited to be "independent." This individual could be someone outside the firm, or could be an individual within the firm who does not have direct responsibility for the matters being audited. If an accreditation process is equivalent to an internal quality audit, it would be acceptable. We decline to add a reference to the quality audit provision of § 1271.160, which has been revised.

11. Quality Program (§ 1271.3(hh))

We proposed to define "quality program" in § 1271.3(oo) as an organization's comprehensive system for manufacturing and tracking HCT/Ps.

As defined, the program would include preventing, detecting, and correcting deficiencies that may lead to circumstances that increase the risk of introduction, transmission, or spread of communicable diseases.

We have revised the definition of “quality program” for clarity. The definition now states, in part, that a quality program is designed to prevent, detect, and correct deficiencies that may lead to circumstances that increase the risk of introduction, transmission, or spread of communicable diseases.

(Comment 23) One comment endorsed the concept of a quality program but noted that the preamble referred to an organization’s “method,” while the proposed definition used the term “system for manufacturing.” The comment suggested that we change the codified definition to reflect the preamble.

(Response) We decline to make the suggested change; rather, we note that it would have been clearer if we had referred in the preamble to a “system” rather than to a “method.” As stated in the preamble to the proposed rule (66 FR 1508 at 1513), we use the term “quality program” to refer to the set of activities, including management review, training, audits, and corrective and preventive actions, that represent a commitment on the part of an establishment’s management to the quality of its products. Whether this set of activities is regarded as a part of manufacture or as a separate system for overseeing manufacture, as preferred by the comment, is not material.

12. Recovery (§ 1271.3(ii))

Proposed § 1271.3(pp) would define “recovery” as the “process of obtaining from a donor cells or tissues that are intended for use in human implantation, transplantation, infusion, or transfer.” (66 FR 1508 at 1551 and 1552).

(Comment 24) One comment suggested rewording the definition of “recovery” to avoid referring to recovery as a process.

(Response) We agree with this comment. The word “process” in the definition of “recovery” could be confused with the definition of “processing” in proposed § 1271.3(mm), which does not include recovery. The definition now reads: Recovery means obtaining from a donor cells or tissues that are intended for use in human implantation, transplantation, infusion, or transfer.

13. Storage (§ 1271.3(jj))

Storage is one of the activities listed in the definition of manufacture in § 1271.3(e). We proposed to define “storage” in § 1271.3(qq) as holding HCT/Ps for future processing and/or distribution.

(Comment 25) One comment recommended that we clarify that the definition does not refer only to finished HCT/Ps ready for shipment and suggested that the definition refer also to “materials.”

(Response) Although we agree that the term “storage” does not apply only to finished HCT/Ps, but to HCT/Ps at any stage of processing, we do not consider a revision of the definition to be necessary. The term HCT/P encompasses HCT/Ps at any stage of manufacture, from recovery to distribution (66 FR 5447 at 5448). Moreover, the definition of “storage” refers to “future processing,” which indicates that the definition applies not only to finished products but also to cells or tissues that may be subject to future processing.

14. Validation (§ 1271.3(kk))

Proposed § 1271.3(rr) would define “validation” as confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. The definition went on to define validation of a process, or “process validation,” as establishing by objective evidence that

a process consistently produces a result or product meeting its predetermined specifications.

(Comment 26) One comment requested that we harmonize the proposed definition with that of the International Conference on Harmonisation (ICH). The comment suggested that the new definition read:

A documented program that provides a high degree of assurance that a specific process, method, or system will consistently produce a result meeting predetermined acceptance criteria.

(Response) We decline to make this change. Harmonization of the two definitions is unnecessary, because the proposed definition is consistent with the language suggested by the comment. The proposed definition is preferable, however, because it explains in more specific terms what is expected (e.g., “confirmation by examination”; “provision of objective evidence”). In addition, the proposed definition is consistent with the ISO 9000:2000 definition of validation (Quality management system—Fundamentals and vocabulary).

(Comment 27) Two comments questioned the use of the term “validation” throughout the proposed rule. These comments cited industry standards that require a level of review tailored to the type of processing used for a particular tissue (e.g., validation of certain shipping containers versus verification of other aspects of processing). The comments requested clarification that compliance with these standards would be deemed compliance with the rule’s validation requirements.

(Response) Where the appropriate action depends on the type of tissue or processing, the rule provides establishments with the flexibility to determine whether verification or validation is appropriate (e.g., §§ 1271.210(c)

and 1271.225). Verification activities may be sufficient for certain processes if the results can be adequately determined through inspection and testing methods. When full and complete verification cannot be achieved, the process must be validated. The manufacturer should have the requisite knowledge of the processes and operations conducted at its facility to determine which actions are needed.

FDA cannot make a determination that compliance with professional standards ensures compliance with the validation requirements of this rule. Each establishment will need to assess its operations to make sure the applicable requirements of the CGTP regulation are met. We encourage professional organizations and others to submit drafts of proposed guidance in this area for FDA to consider for possible adoption.

15. Verification (§ 1271.3(nn))

Proposed § 1271.3(ss) would define “verification” as “confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.” (66 FR 1508 at 1552).

We received no comments on the proposed definition of “verification,” and it is unchanged.

C. Part 1271, Subpart D—Current Good Tissue Practice

Part 1271, subpart D, sets forth CGTP requirements. We have added, in § 1271.145, an explicit statement of the basic requirement that underpins all of the provisions of this subpart. Section 1271.145 states that you must recover, process, store, label, package, and distribute HCT/Ps, and screen and test cell and tissue donors, in a way that prevents the introduction, transmission, or spread of communicable diseases.

1. Current Good Tissue Practice Requirements (§ 1271.150)

General (§ 1271.150(a))

Proposed § 1271.150(a) states in part that the CGTP requirements are intended to prevent the introduction, transmission, or spread of communicable disease through the use of HCT/Ps by helping to ensure that they do not contain communicable disease agents and that they do not become contaminated during manufacturing. We have revised this sentence for clarity, have added the phrase “that they are not contaminated,” and have included the statement that “you must follow CGTP requirements.”

We have also added to § 1271.150(a) the statement that communicable diseases include, but are not limited to, those transmitted by viruses, bacteria, fungi, parasites, and transmissible spongiform encephalopathy (TSE) agents. Although the proposed CGTP requirements were intended to prevent contamination of HCT/Ps with these agents (e.g., see 66 FR 1508 at 1509, 1510, 1514, and 1515), we believe that these examples of communicable disease make this provision more clear.

A 2002 *Morbidity and Mortality Weekly Report* (MMWR) discusses 26 cases of bacterial infection associated with musculoskeletal allografts and reinforces the importance of following CGTP to prevent the contamination of HCT/Ps with such communicable disease agents. In the MMWR, the Centers for Disease Control and Prevention (CDC) make several significant recommendations on preventing bacterial contamination. Among other things, the CDC states that “[s]terilization of tissue that does not adversely affect the functioning of tissue when transplanted into patients is the best way to reduce the risk for allograft-associated infections.” Throughout this final rule, we discuss the CDC’s recommendations and note the applicability of specific

provisions of the final rule to the prevention of bacterial contamination (Ref. 1).

Core CGTP Requirements (§ 1271.150(b))

Paragraph (b) lists the core CGTP requirements, discussed in section II.D of this document. We have identified the following as core CGTP requirements: § 1271.190(a) and (b) (relating to facilities); § 1271.195(a) (environmental controls); § 1271.200(a) (equipment); § 1271.210(a) and (b) (supplies and reagents); § 1271.215 (recovery); § 1271.220 (processing and process controls); § 1271.250(a) and (b) (labeling controls); § 1271.260(a) through (d) (storage); § 1271.265(a) through (d) (receipt, predistribution shipment, and distribution); and §§ 1271.50, 1271.75, 1271.80, and 1271.85 (donor eligibility determinations, donor screening, and donor testing).

Compliance With Applicable Requirements (§ 1271.150(c)(1))

Proposed § 1271.150(b)(1) states that an establishment that engages in only some operations subject to the regulations in this subpart and subpart C of this part need only comply with those requirements applicable to the operations in which it engages. It further states that when an establishment engages a second establishment to perform any step in manufacturing, the second establishment would be required to comply with the requirements applicable to that manufacturing step. In addition, the first establishment would be responsible for ensuring that the work at the other establishment is performed in compliance with subparts C and D. Proposed paragraph (b) of § 1271.150 has been redesignated as paragraph (c).

The following table summarizes the responsibilities that are assigned in the final rule to each manufacturer when multiple establishments are involved in manufacturing an HCT/P:

TABLE 1a

If you:	You must:
Perform any step in the manufacture of an HCT/P	Follow CGTP (subparts C and D) (§ 1271.150(a)) as it relates to that step.
Perform only some and not all operations of manufacturing, and do not make the HCT/P available for distribution	<ol style="list-style-type: none"> 1. Follow only those requirements applicable to the operations you perform (§ 1271.150(c)(1)). 2. When you receive the HCT/P, determine whether the HCT/P meets all pre-established criteria, designed to prevent communicable disease transmission, for acceptance or rejection, and place the HCT/P in quarantine as appropriate (§ 1271.265(a)). 3. When you prepare to ship an HCT/P, ship the HCT/P only in quarantine and after determining criteria designed to prevent communicable disease are met (§ 1271.265(b)). 4. Investigate all HCT/P deviations related to a distributed HCT/P for which you performed a manufacturing step and report any deviation related to core CGTP requirements that occurred in your facility or in a facility that performs a manufacturing step for you under contract, agreement, or other arrangement (§ 1271.350(b)(1) and (b)(2)).
Engage another establishment to perform any step in manufacturing for you under contract, agreement, or other arrangement	<ol style="list-style-type: none"> 1. Enter into and maintain such an arrangement only with a reliable establishment that complies with applicable CGTP requirements. (§ 1271.150(c)(1)). 2. Investigate all HCT/P deviations related to a distributed HCT/P for which you performed a manufacturing step and report any deviation related to core CGTP requirements that occurred in your facility or in a facility that performs a manufacturing step for you under contract, agreement, or other arrangement (§ 1271.350(b)(1) and (b)(2)).
Make the HCT/P available for distribution	<ol style="list-style-type: none"> 1. Review manufacturing and tracking records to determine that the HCT/P meets all the release criteria (§§ 1271.150(c)(2) and 1271.265(c)) and maintain records relevant to the release determination (§ 1271.270(a)). 2. Ensure that manufacturing and tracking records demonstrate that the HCT/P has been manufactured and tracked from recovery to the consignee following CGTP (§§ 1271.150(c)(2) and 1271.290). 3. Investigate and report any adverse reaction involving a communicable disease (§ 1271.350(a)). 4. Investigate all HCT/P deviations related to any step in the manufacture of a distributed HCT/P that you performed, and report any HCT/P deviation relating to core CGTP requirements if the deviation occurred in your facility or in a facility that performed a manufacturing step for you under contract, agreement, or other arrangement (§ 1271.350(b)(1) and (b)(2)).

(Comment 28) Several comments objected to the statement in proposed § 1271.150(b)(1) that an establishment that engages another establishment under a contract, agreement, or other arrangement, to perform any step in the manufacturing process, is responsible for ensuring that the work is performed in compliance with the CGTP and donor-eligibility requirements. One comment asserted that the language is too broad and open to interpretation, and could make eye banks responsible for ensuring that entities such as couriers, medical examiner's offices, and laboratories meet regulatory requirements applicable to the subcontracted function. Another comment asked whether an establishment must inspect Federal Express, UPS, or the Postal Service to ensure that they comply with the regulations when shipping corneas.

(Response) We have revised the language of the proposed rule. Under § 1271.150(c)(1), if an establishment (e.g., an eye bank) engages another establishment to perform a manufacturing step, under a contract, agreement,

or other arrangement, it must enter into and maintain such an arrangement only with a reliable establishment that complies with applicable CGTP requirements. Under this provision, an establishment should choose its partners with care. This requirement extends to relationships with establishments such as medical examiner offices and laboratories, but it does not apply with respect to carriers, such as Federal Express, UPS, or the Postal Service, who are exempt from the regulations in this part as noted in § 1271.15(c).

(Comment 29) One comment stated that it is unrealistic to require validation of a subcontractor's work on each tissue, and that it is expensive and nearly impossible to find staff with specific expertise to review each type of subcontractor. Another comment stated that eye banks are not qualified to be responsible for ensuring compliance by subcontractors and recommended that compliance by subcontractors be deemed met by a letter of intent from the subcontractor. This comment also asserted that eye banks do not have the expertise to inspect or validate a blood testing laboratory or Bausch & Lomb.

One comment suggested that an initial audit of the contractor should be sufficient. Another comment suggested that each establishment have a system in place designed to ensure that the contractor's work is performed in compliance with the regulatory requirements.

(Response) Section 1271.150(c)(1) is intended to clarify the relationship between you and another establishment that performs one or more steps in manufacture for you (e.g., a procurer engages an outside testing laboratory to perform communicable disease tests for it; a processor engages an outside firm to perform terminal sterilization, such as irradiation, on the final HCT/P). (We have added these examples to the regulation.) You do not have to validate the

processes of these outside firms (who are themselves subject to the regulations in part 1271), and we appreciate the fact that you may lack the expertise to do so. However, you are required to enter into and maintain such arrangements only with establishments that comply with applicable CGTP requirements.

We note that there are many ways of performing the due diligence necessary when entering into a manufacturing arrangement with another establishment. The example of an initial audit provided by the comment is one method. Other ways of learning about another establishment before you enter into an arrangement with it might include reviewing test kit package inserts and a testing laboratory's standard operating procedures (SOPs); and reviewing an establishment's compliance history. If you intend to enter into an arrangement with an establishment that does not have a compliance history, review of that establishment's SOPs might assist in ascertaining that entity's compliance status.

Although we recognize the usefulness of an initial audit before entering into an arrangement with another establishment, we note that an initial audit would not satisfy this requirement throughout the term of a continuing relationship. Under § 1271.150(c)(1), you may not ignore information that indicates that a company that performs work for you is not in compliance with applicable CGTP requirements. For example, if you have reason to suspect that an establishment performing work for you is not in compliance with those requirements, you would need to take appropriate action and determine whether the establishment is still in compliance with CGTP. Other regulations in part 1271 may also apply with regard to products manufactured, in part, by an establishment that does not comply with applicable requirements. For example, § 1271.145 provides, "You must * * * store * * * and distribute

HCT/Ps * * * in a way that prevents the introduction, transmission, or spread of communicable diseases.” You may also have obligations under §§ 1271.160, 1271.265, 1271.320, and 1271.350. If you determine that the establishment is not in compliance with applicable CGTP requirements, you must terminate your contract, agreement, or other arrangement with that establishment. If you determine that an exemption or alternative from this requirement would be consistent with the goals of protecting the public health and/or preventing the introduction, transmission, or spread of communicable diseases, and you either have information that would justify an exemption, or have a proposed alternative that would satisfy the purpose of this requirement, you may seek an exemption or alternative under § 1271.155.

We intend to issue guidance, which will further elaborate on your responsibilities for ensuring that another establishment that performs one or more steps in manufacture for you is in compliance with part 1271. Our economic impact analysis also indicates that the methods described in this response are not overly costly or burdensome.

(Comment 30) One comment suggested limiting an establishment’s responsibility toward contractors to ensuring that the contractor is a registered tissue bank establishment.

(Response) We agree that establishments under contract must register with FDA. However, we note that some individuals who recover cells or tissue under contract, agreement, or other arrangement are excepted from registration under § 1271.15(f); this is one reason that it would not be sufficient to limit an establishment’s responsibility to ensuring that a contractor is registered. Moreover, although registration is an important component of the regulation of HCT/P establishments, such a requirement would not go far enough toward

safeguarding the public against the communicable disease risks associated with HCT/Ps. Therefore, if you engage another establishment under a contract, agreement, or other arrangement to perform any step in manufacture for you, you must first determine that the establishment complies with applicable CGTP requirements, and you must investigate further if you receive information suggesting that the establishment may no longer be in compliance with those requirements.

Compliance With Applicable Requirements (§ 1271.150(c)(2))

Proposed § 1271.150(b)(2) explained how we would assign ultimate responsibility for an HCT/P. That paragraph states that the establishment that determines that an HCT/P meets release criteria and makes it available for distribution, whether or not it is the actual distributor, is responsible for ensuring that the HCT/P has been manufactured in compliance with the requirement of subparts C and D and any other applicable requirements. In § 1271.150(c)(2), we have added the responsibility for tracking (consistent with § 1271.290).

(Comment 31) Under proposed § 1271.150(b)(2), the establishment that determines that an HCT/P meets release criteria and makes it available for distribution would be responsible for ensuring that the HCT/P has been manufactured in compliance with the requirements in subparts C and D and any other applicable requirements. Several comments agreed with this allocation of responsibility or with the “cascading” set of responsibilities discussed in the preamble to the proposed rule, under which

* * * an establishment would be responsible for ensuring that its own operations comply with applicable requirements, and also would bear the burden of proof that

operations performed by other establishments prior to its receipt of the cells or tissue were performed in compliance with applicable requirements (66 FR 1508 at 1512).

One comment asserted that, although the proposed allocation of responsibility was the most reasonable of those considered, it was unclear what sort of documentation would be sufficient to ensure that establishments that handled the HCT/P before receipt were in compliance (in particular, international donor centers), and another comment asserted that proposed § 1271.150(b) would require every company to collect and store documents for all other companies participating in the manufacturing process.

One comment stated that the more prudent approach would be to hold each establishment specifically responsible for the activities that went before. Another proposed that, since more than one establishment may actually make an HCT/P available for distribution, the last establishment that releases the product should be responsible. Another comment recommended that overall responsibility for compliance be assigned only to establishments within the United States.

(Response) We have revised proposed § 1271.150(b)(2) (and renumbered it § 1271.150(c)(2)) to state that if you are the establishment that determines that an HCT/P meets all release criteria and makes the HCT/P available for distribution, whether or not you are the actual distributor, you are responsible for reviewing manufacturing and tracking records to determine that the HCT/P has been manufactured and tracked in compliance with the requirements of this subpart and subpart C of this part and any other applicable requirements. This record review would include, for example, reviewing documentation of donor test results for relevant communicable disease agents to determine that results are negative or nonreactive and that appropriate

testing was performed (§§ 1271.80 and 1271.85); matching the distinct identification code on the HCT/P container with the code in the summary of records (§ 1271.290)c); reviewing records pertaining to donor screening for risk factors for and clinical evidence of relevant communicable disease agents (§ 1271.75); reviewing records pertaining to storage temperature (§ 1271.260), processing (§ 1271.220), and other manufacturing steps. The requirement applies to any establishment that makes an HCT/P available for distribution, whether it is foreign or domestic, and whether or not another establishment may later make it again available for distribution. An establishment that makes the HCT/P available for distribution must maintain the records in question.

Section 1271.150(c)(2) ties in closely with § 1271.265, which covers receipt, predistribution shipment, and distribution of an HCT/P. Section 1271.265(c) sets out requirements for making an HCT/P available for distribution, including reviewing records pertaining to the HCT/P, and, on the basis of that record review, verifying and documenting that the release criteria have been met.

(Comment 32) One comment discussed the following scenario. If the first establishment releases the HCT/P to a consignee under its own label, releases it to another distributor, or releases it back to the contracting firm (which may in turn serve as a distributor), then the first establishment is responsible for ensuring that the HCT/P has been manufactured in compliance with CGTP. This comment stated that, if its interpretation of the proposal was correct, then it endorsed the proposal.

(Response) The examples provided by the comment illustrate three different ways in which an establishment might make an HCT/P available for distribution. Under § 1271.150(c)(2), the establishment has the same

responsibility in each case: To review manufacturing and tracking records to determine that the HCT/P has been manufactured and tracked in compliance with regulatory requirements.

(Comment 33) One comment asked for further clarification, stating that it is not clear whether the responsibility pertains to the manufacturing facility or just the distributor. If the distributor were an institutional laboratory that receives an HCT/P that was processed at a commercial laboratory, then the requirement would be unduly burdensome, according to the comment.

(Response) In the situation described, the institutional laboratory is not the establishment that makes the HCT/P available for distribution, and would not be ultimately responsible. In fact, an institutional laboratory (e.g., hospital bone bank) that does no further manufacturing of the HCT/P, but only receives the finished HCT/P from a commercial tissue processor, and “distributes” the HCT/P in the same facility, is excepted from these regulations (§ 1271.15(d)). However, if the institutional laboratory performs additional manufacturing steps on the HCT/P, this laboratory is then considered a “processor” and is subject to the CGTP requirements.

(Comment 34) One comment asserted that responsibility should be apportioned appropriately among the entities involved. This comment recommended avoiding a situation where screening by various entities would lead to numerous re-contacts of donor families.

(Response) It is not our intention to have various establishments re-contact the donor’s family to reconfirm the medical history, for example. The initial establishment that performed the donor medical history interview would document the findings. The establishment that made the HCT/P available for distribution would review the records of the findings to make sure that all

release criteria (including donor eligibility) were met, and would retain the documented findings.

(Comment 35) When there are multiple establishments involved in the manufacture of an HCT/P, one comment suggested that we limit the penalties only to the noncompliant establishment.

(Response) Generally, we will not take enforcement action against all parties involved in the manufacturing of HCT/Ps. We will evaluate all available information related to the violative activities and the circumstances concerning the event. If circumstances indicate that multiple parties have not complied with the applicable regulations, we may take enforcement action as appropriate.

Compliance With Applicable Requirements (§ 1271.150(c)(3))

Paragraph (c)(3) of § 1271.150 states that with the exception of §§ 1271.150(c) and 1271.155 of this subpart, the regulations in this subpart are not being implemented for reproductive HCT/Ps described in § 1271.10 and regulated solely under section 361 of the PHS Act and the regulations in this part, or for the establishments that manufacture them.

Compliance With Parts 210, 211, and 820 of this Chapter (§ 1271.150(d))

Proposed 1271.150(c) explains, in part, that for HCT/Ps regulated as biological drugs or devices, the procedures contained in this subpart and in subpart C, and the procedures contained in parts 210, 211, and 820, supplement rather than supersede each other.

(Comment 36) We received one comment on proposed § 1271.150(c). This comment asserted that the last sentence in that paragraph provides no useful guidance and should be deleted. The last sentence in proposed § 1271.150(c) stated

In the event that it is impossible to comply with all applicable regulations in these parts, the regulations specifically applicable to the biological drug or device in question shall supersede any other requirements. (66 FR 1508 at 1552.)

(Response) In the preamble of the proposed rule, we explained why an HCT/P regulated as a biological drug or device must comply with part 1271 (CGTP) as well as parts 210 and 211 (CGMP) or 820 (QS). CGMP and QS do not contain requirements written explicitly to prevent the spread of communicable disease. CGTP is focused on preventing circumstances that increase the risk of the introduction, transmission, or spread of communicable disease, which makes CGTP regulations less extensive than CGMP and QS regulations. Therefore, CGTP and CGMP or QS are intended to supplement each other. In the event that a regulation in part 1271 is in conflict with a requirement in parts 210, 211, or 820 of this chapter, the regulations more specifically applicable to the product in question will supersede the more general. FDA believes that, in the event of such a conflict, the more specifically applicable regulation would be found in part 1271.

Where Appropriate (§ 1271.150(e))

“Where appropriate” in proposed § 1271.150(d) would mean that a practice is required unless the establishment can document justification otherwise. A requirement would be considered “appropriate” if nonimplementation could reasonably be expected to result in the product’s not meeting its specified requirements related to prevention of introduction, transmission, or spread of communicable disease agents and diseases, or in the establishment’s inability to carry out any necessary corrective action.

We received no comments on this section.

2. Exemptions and Alternatives (§ 1271.155)

Proposed § 1271.155 sets out the procedures that an establishment must follow to request an exemption from, or an alternative to, a CGTP requirement, as well as the criteria that the Center Director will follow in considering such a request. In the final rule, we have modified § 1271.155(b) to allow requests for exemptions or alternatives to be submitted to the appropriate Center Director (e.g., the Center for Biologics Evaluation and Research (CBER) or the Center for Devices and Radiological Health), rather than only the CBER Director. We have revised § 1271.155(d) for clarity; instead of referring to “limited circumstances,” the final regulation states that, if circumstances make it difficult (e.g., there is inadequate time) to submit your request in writing, you may make the request orally.

We have also added § 1271.155(g), which in a public health emergency permits the Director to issue an exemption or alternative to any requirement in part 1271 of title 21 of the Code of Federal Regulations. An exemption or alternative under this section may be necessary to help ensure that certain HCT/Ps will be available in a specified location to respond to an unanticipated immediate need for such HCT/Ps.

(Comment 37) One comment recommended that § 1271.155 should be implemented first, and that the remaining provisions of the rule should be implemented 2 years later.

(Response) We do not agree with this comment. It is not clear why implementation of the exemption provisions should precede implementation of the rest of the final rule. If the requirements are not in effect, then an exemption request is not necessary.

(Comment 38) One comment noted that international establishments that produce peripheral blood stem cells and umbilical cord blood units are subject to their own national and regional regulatory requirements. The comment stated its assumption that these establishments would submit their foreign government's regulations to FDA under § 1271.155.

(Response) The comment's assumption is incorrect. A foreign establishment that distributes HCT/Ps in this country must comply with FDA regulations. It is a foreign establishment's responsibility to determine whether complying with the foreign government's requirements would also satisfy FDA requirements. If a foreign establishment identifies a discrepancy (e.g., an area where FDA regulations are more stringent or in conflict), the establishment may request an exemption or alternative under § 1271.155, and FDA will consider whether the request is justified by the evidence submitted.

(Comment 39) One comment recommended that the rule establish a maximum time period of 30 working days for an agency decision on a request for an exemption or alternative.

(Response) Although we agree that timely decisions are important, we disagree that this regulation should contain a specific timeframe. Depending on the nature of the request, more or less time may be needed to give the request adequate consideration. We note that other FDA regulations dealing with exemptions do not specify a deadline for a reply (see, e.g., § 640.120 (21 CFR 640.120) and 21 CFR 803.19). The time for our review of requests under § 640.120 for variances related to the blood regulations has varied from two weeks to four months, depending on the complexity and urgency of the request. We intend to respond to variance requests under § 1271.155 within

similar timeframes, with our time to respond tied to the complexity and urgency of the request.

(Comment 40) One comment asserted that the criteria in proposed § 1271.155(c) for granting an exemption or alternative are too narrow, in that they do not afford an establishment an exemption or alternative to a particular requirement not relevant to the tissue in question. The comment suggested adding the phrase: “and that such goals are not impaired by an exemption or alternative.”

(Response) We disagree with this comment. The suggested language is unnecessary and would narrow the criteria for granting an exemption or alternative. We note that if a requirement is not relevant to a particular establishment’s operations, it is not necessary to request an exemption (§ 1271.150(c)(1)).

We have, however, modified the criteria for granting an exemption or alternative in § 1271.155(c) to permit the Center Director greater flexibility in responding to critical medical needs. That paragraph now reads, in part

The Director may grant an exemption or alternative if he or she finds that such action is consistent with the goals of protecting the public health and/or preventing the introduction, transmission, or spread of communicable disease.

(Comment 41) One comment noted that proposed § 1271.155(d) and (e) are internally inconsistent, because paragraph (d) would allow for an oral request and reply, but paragraph (e) states that an establishment must not begin operating under the terms of a requested exemption or alternative until it had been granted in writing. The comment asked us to clarify that orally granted exemptions and alternatives would have immediate effect, and that an

establishment would not be required to wait for a written statement from the agency.

(Response) We agree with this comment and have deleted the words “in writing” from § 1271.155(e).

(Comment 42) Another comment stated that FDA should evaluate how a small entity may qualify for reasonable exemptions and alternatives.

(Response) We have written § 1271.155(b) to apply to both large and small entities. Supporting documentation that either justifies a requested exemption, or describes a proposed alternative, must accompany a request. To assist all establishments, large and small, in pursuing appropriate exemptions and alternatives, we intend to make available to the public on the CBER Web site information concerning exemptions and alternatives that have been granted, while following statutory requirements prohibiting public disclosure of confidential information.

3. Quality Program (§ 1271.160)

Proposed § 1271.160 would require an establishment that performs any step in the manufacture of an HCT/P to establish and maintain a quality program that is appropriate for the specific HCT/Ps manufactured and the manufacturing steps performed, and that meets the requirements of subpart D of part 1271.

Section 1271.160 of this final regulation requires instead that the quality program address all core CGTP requirements. We have also removed two items from the list in § 1271.160(b) of a quality program’s functions: Proposed paragraph (b)(5) (on monitoring systems) and proposed paragraph (b)(6) (on record maintenance systems).

(Comment 43) One comment strongly supported the requirement for a quality program. Another comment appreciated the differentiation between the quality program and the quality system requirement for devices and blood products. This comment stated that giving tissue banks flexibility in how defined functions are accomplished, and not requiring the employment of staff free of other responsibilities, recognizes the undue burden that it would create. In contrast, two other comments asserted that eye banks would have to hire separate quality control employees, which would be time consuming and expensive.

(Response) We appreciate the comments supporting the requirement. We note that the regulation does not require an establishment to hire a separate quality control employee; moreover, we have removed the requirement for the designation of an individual with authority over the program (proposed § 1271.160(c)).

(Comment 44) Two comments supported the idea that a quality program should be commensurate with the manufacturing steps performed and the types of tissues involved. These comments requested that FDA distinguish between “quality programs” and other quality requirements, to ensure that establishments are not held to unsuitable quality requirements.

(Response) The quality program required under § 1271.160 is a system that each establishment sets up to ensure its compliance with core CGTP requirements. These regulations do not contain generalized quality requirements.

(Comment 45) We received three comments on proposed § 1271.160(b)(2), which would require procedures for sharing with other establishments that are known to have recovered cells or tissue from the same donor any information

pertaining to the possible contamination of the HCT/P or the potential transmission of communicable disease by the HCT/P. One comment asserted that it would not be appropriate to share information about an autologous donor's baseline viral status with another establishment. This comment also expressed concern that the required procedure would be inconsistent with the requirement in proposed § 1271.270 pertaining to donor confidentiality. The other two comments suggested narrowing the provision so that establishments would not be required to disclose proprietary information to competitors.

(Response) We decline to modify the requirement as requested. The purpose of this requirement is to ensure that, if an establishment learns that a donor is ineligible or that an HCT/P is contaminated, the establishment has a procedure in place for informing consignees and other establishments that are known to have recovered cells or tissues from the same donor. Recognizing that other establishments may have received HCT/Ps from the same donor, even if they did not recover them, we have added to this list, "other establishments that are known to have performed manufacturing steps with respect to the same HCT/P."

There is no requirement that an establishment disclose customer lists, manufacturing processes, or other proprietary information to competitors. Moreover, these procedures can be designed so that patient confidentiality is not compromised.

With respect to the comment on sharing information about an autologous donor, we are unable to envision a situation where this requirement would necessitate such a disclosure. Since HCT/Ps for other recipients would not be recovered from the autologous donor, there would be no need to share information regarding the donor's baseline viral status.

(Comment 46) Proposed § 1271.160(b)(7) would require establishments to investigate and document all product deviations in manufacturing. (These are now referred to as “HCT/P deviations.”) One comment asserted that product deviation review and analyses should be treated in the same manner as internal audits (i.e., not available for review on inspection). Two comments asserted that the periodic audit of product deviations and collation of complaint files are tools of quality management and that FDA should guarantee the confidentiality of these quality management activities.

(Response) We have renumbered proposed paragraph (b)(7) as (b)(6) and removed the requirement for a periodic review and analysis of HCT/P deviations. Under the final regulation, you are required to investigate and document HCT/P deviations and trends of HCT/P deviations relating to core CGTP requirements and to make reports if required to do so under § 1271.350(b) or other applicable regulations.

(Comment 47) One comment requested that we limit the requirement for reporting product deviations to those identified post-release.

(Response) The reporting requirement in § 1271.350(b)(1) applies only to distributed HCT/Ps, regardless of the time at which the deviation is identified.

(Comment 48) Two comments asked us to clarify that § 1271.160(b)(7) includes only product deviations in manufacturing that would increase the risk of disease transmission.

(Response) The term “HCT/P deviation” is defined in § 1271.3(dd) of this final rule to include events that may increase the risk of communicable disease transmission, because they: (1) Represent a deviation from applicable regulations in this part or from applicable standards or established specifications relating to the prevention of communicable disease transmission

or HCT/P contamination, or (2) constitute an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease or may lead to HCT/P contamination.

(Comment 49) Under proposed § 1271.160(c), one or more designated persons would have authority over the quality program, and these persons would report to management at least once a year on the performance of the quality program, unless more frequent reports are necessary. If these persons also perform other tasks in the establishment, they must not have final oversight over their own work.

Two comments on this provision asserted that the requirement for independent oversight is too stringent. One comment stated that, in small laboratories with only a single technician, it may not be possible for an independent person to have oversight. The other comment recommended that the oversight requirement be dropped as costly and impracticable.

(Response) We have removed this requirement from the final rule.

Audits

(Comment 50) One comment requested more flexible language to replace the requirement for a comprehensive quality audit no less than once in 12 months. Another comment asserted that the requirement for an annual comprehensive audit is more stringent than the requirements applicable to blood component processing.

(Response) In response to these comments, we have revised proposed § 1271.160(d). Section 1271.160(c) now requires only that a quality audit of core CGTP activities be performed periodically for management review. The new language provides establishments with a greater degree of flexibility in determining how and when to audit their quality programs. We also may issue

future guidance making recommendations on what we would consider to be a periodic audit.

(Comment 51) Two comments asserted that internal audit findings should not be available to FDA representatives.

(Response) With respect to quality audits, while some firms choose to provide quality audits to FDA, FDA's current practice is generally not to review or copy the actual quality audit reports during routine inspections and investigations except in certain limited circumstances (FDA Compliance Policy Guide 130.300). However, the firm should have a mechanism to demonstrate to the FDA representative that quality audits are being performed and that corrective actions are being implemented when problems are identified.

Computers

Proposed § 1271.160(e) would require establishments to validate computer software used as part of manufacturing or tracking or for maintaining data relating to those activities.

(Comment 52) One comment asserted that it is reasonable to require that computer systems used in manufacturing and data maintenance be tested to confirm that they perform as intended, and that the testing and results be documented. This comment asked us to confirm that we are distinguishing between this limited requirement and the term "validation" as it has been applied to computer systems identified as medical devices.

(Response) We agree with this comment. Therefore, we revised the requirement in § 1271.160(d) to permit verification or validation of the computer software for its intended use.

(Comment 53) Several comments opposed the proposed requirement on computer software validation. One comment asserted that software validation

can be a financial burden and stated that the requirement should be implemented to the extent validation will minimize the risk of disease transmission during the manufacturing process. The comment further noted that there was no exemption in this provision for general-purpose software (e.g., spreadsheet, database, and word processing software) intended for broad general use, which are currently exempt from most of the general controls under the act. Two comments suggested limiting the scope of the requirement to the most necessary areas, to encourage the use of software programs in lieu of manual recordkeeping. Another comment asked that we amend the provision to reflect that software must be validated only if it is relied upon as the sole data source for the decisionmaking processes of the quality system.

(Response) We do not intend that the requirements for computer validation be unduly burdensome. As a result of these comments, we are modifying the requirements in § 1271.160(d). This section now applies only to software that you rely upon to comply with core CGTP requirements. You must validate the performance of software for its intended use only if the software is custom software or commercially available software that has been customized or programmed (including software programmed to perform a user-defined calculation or table) to perform a function related to core CGTP requirements. If you rely on commercially distributed, noncustom, software to perform a function related to core CGTP requirements, then you are only required to verify the performance of that software for its intended use. With these changes, we have limited the scope of this provision so that it applies to computer software that directly affects communicable disease transmission risks. If such software is inappropriately designed, implemented, or used, the software may increase the risk of communicable disease transmission, perhaps

by authorizing the release of HCT/Ps from an infectious donor, or by recording screening test results inaccurately. However, we recognize that commercially distributed general use software has undergone more rigorous testing before it is distributed. When such general use software is used without modification to comply with core GTP requirements, it is adequate for the establishment only to verify the performance of the software for its intended use, rather than undertaking more onerous validation.

For example, an eye bank that uses commercially distributed software (e.g., spreadsheet, database, word processing) to comply with a core CGTP requirement such as control of storage areas (§ 1271.260(a)), but not for making decisions or determinations, must verify that this general purpose software can be used reliably in such a way, but would not have to validate the software. Verification in a situation such as this is not intended to be onerous. However, if the eye bank decided to modify and use commercially available computer software for determining donor eligibility, the modifications would increase the risk of problems and the eye bank would then be required to validate the software for this intended use.

(Comment 54) One comment noted that eye banks do not use computers as decisionmaking instruments, but only for information storage and retrieval, word processing, and form printing. This comment asserted that appropriate validation in this instance should entail: (1) Routine backup of computer system, (2) physical check of computer printout against paper chart, and (3) signoff by final supervisor before tissue release.

(Response) The examples provided are not core CGTP requirements and so the requirements of § 1271.160(d) would not apply.

4. Organization and Personnel (§ 1271.170)

Proposed § 1271.170 would require establishments to maintain an adequate organizational structure and sufficient personnel with the necessary education, experience, training and retraining to ensure competent performance of their assigned functions. Personnel records documenting these requirements would be required.

(Comment 55) Two comments supported § 1271.170 as proposed. One comment agreed that tissue bank personnel should be educated concerning the possible consequences of improperly performing their duties, and noted that unacceptable tissue practices could have monumental implications in disease transmission. This comment further asserted that recordkeeping on personnel training is appropriate.

(Response) We appreciate the supportive comments. However, we have removed both of these proposed requirements from § 1271.170. Section 1271.170 also does not require an establishment to maintain an adequate organization structure.

(Comment 56) One comment asserted that FDA should set guidelines for the credentials of tissue bank directors.

(Response) We have not included in the regulations requirements for specific credentials. Instead, we require that personnel have the necessary education, experience, and training to ensure competent performance of their assigned functions. Professional organizations, accrediting bodies, and States may decide to develop guidelines for certain personnel credentials.

(Comment 57) One comment from a professional organization suggested replacing the phrase “education and experience” in proposed § 1271.170(b) with “training and documentation of competency.”

(Response) We agree with the comment that “training” should be added to the requirements in § 1271.170(b), and we have made this change; however, we disagree with the proposal to remove “education and experience.” As revised, § 1271.170(b) requires you to have personnel with the necessary education, experience, and training to ensure competent performance of their assigned functions.

(Comment 58) One comment on proposed § 1271.170(c) asserted that it is unclear what criteria a company should use to determine the qualifications of laboratory personnel.

(Response) There are a variety of ways to comply with the requirement in § 1271.170(c) that an establishment train all personnel to perform their assigned responsibilities adequately. Each establishment should establish its own criteria. Some examples of criteria an establishment might use to determine the qualifications of laboratory personnel include: Achievement of a minimum score on a written test, direct observation and evaluation by a supervisor, successful completion of continuing education courses (e.g., passing an examination), accreditation or proficiency testing by an outside organization.

5. Procedures (§ 1271.180)

Proposed § 1271.180 would require establishments to establish and maintain procedures for all significant steps that it performs in the manufacture of HCT/Ps.

We have reorganized § 1271.180 by dividing it into paragraphs for greater clarity and ease of reading. In addition, § 1271.180 now requires you to establish and maintain procedures appropriate to meet core CGTP requirements for all steps that you perform in the manufacture of HCT/Ps and

further requires that these procedures be designed to prevent circumstances that increase the risk of the introduction, transmission, or spread of communicable diseases through the use of HCT/Ps.

We note that, depending on the activities that you perform, your procedures may need to cover such issues as the length of time a cadaver may be stored, or the conditions of storage (e.g., temperature). Moreover, to prevent the recovery of contaminated cells or tissues, you need to establish and maintain procedures to prevent the recovery of cells or tissue from a septic donor or from an area of the body where there is a localized infection. The MMWR report cited in section III.C.1 of this document (Ref. 1) discussed a case in which tissue probably became hematogenously seeded by bowel flora before harvesting. The report noted that factors that may contribute to such contamination include the time interval between death and tissue retrieval, delays in refrigeration, and mode of death (e.g., trauma). The procedures of an establishment that recovers cells and tissue should appropriately address these possible causes of HCT/P contamination to comply with § 1271.180(a).

(Comment 59) One comment supported the section as proposed. Another comment asked for examples of what does or does not constitute a “significant step” and asked how it differs from “any step” in the quality program requirements.

(Response) A “significant step” is a step in manufacturing listed in the definition of “manufacture” in current § 1271.3(e), i.e., all steps in the recovery, processing, storage, labeling, packaging, or distribution, and the screening and testing of the donor, and is not considered different from “any step in the manufacture of human cellular and tissue-based products.” Therefore, we have removed the term “significant” from § 1271.180(a).

(Comment 60) Proposed § 1271.180 would require establishments to review and, if necessary, revise all procedures at least once in a 12-month period. One comment objected to the specificity of this requirement, citing the more flexible requirements in the CGMP and QS regulations.

(Response) We agree with this comment and note that the comparable requirements in the CGMP and QS regulations (§§ 211.100 and 820.40) do not require an annual review of procedures. For this reason, we are deleting the proposed requirement in § 1271.180 that all procedures be reviewed on an annual basis. However, we note that the periodic quality audit required under § 1271.160(c) should include a review of an establishment's SOPs.

(Comment 61) Several comments objected to the proposed requirement that deviations from procedures be authorized in advance, because deviations are not foreseeable and cannot be authorized before they occur. One comment suggested requiring a justification for the deviation to be recorded at the time of the occurrence, and requiring approval of the deviation by a responsible person before release of the tissue.

(Response) We agree with these comments and have modified the requirement in accordance with the suggestion; the requirement, which is now located in § 1271.265, requires an establishment to record and justify any departure from a procedure at the time of its occurrence, rather than before. (We replaced the word "deviation" with the word "departure" to avoid confusion with the defined term "HCT/P deviation.") The provision further states that you must not make available for distribution any HCT/P manufactured under a departure from a procedure designed to protect against risks of communicable disease transmission, unless a responsible person has determined that the departure does not increase the risk of communicable

disease transmission through the use of the HCT/P. For example, if the technician at the recovery site uses a different brand of sterile gauze because the brand stated in the standard operating procedures is not available, the establishment may make the HCT/P available for distribution provided that the departure was recorded and justified at the time, and the responsible person determines that the substitution did not increase the risks of communicable disease transmission.

(Comment 62) Proposed § 1271.180 would require obsolete procedures to be archived for at least 10 years. One comment suggested that a longer retention period of 10 years after transplantation would be more appropriate and consistent with record retention requirements in § 1271.270.

(Response) We have removed this requirement from the final regulation. However, although we do not require you to retain obsolete procedures, under § 1271.270(d) you are required to retain records for 10 years unless otherwise stated.

6. Facilities (§ 1271.190)

Proposed § 1271.190 would require that any facility used in the manufacture of products be of suitable size, construction, and location to facilitate cleaning, relevant maintenance, and proper operations; be maintained in a good state of repair; and have adequate lighting, ventilation, plumbing, drainage, and washing and toilet facilities. Proposed § 1271.190 also contained requirements relating to the division of a facility into operational areas, and relating to facility cleaning and sanitation.

Section 1271.190 has been reorganized.

(Comment 63) Three comments objected that proposed § 1271.190 is too broad and asserted that it should be limited to requirements for preventing the transmission of disease. Two comments suggested new language.

(Response) In response to these comments, we have revised the language of § 1271.190, reflecting the suggested language. The first sentence of § 1271.190(a) now states that any facility used in the manufacture of HCT/Ps “must be of suitable size, construction, and location to prevent contamination of HCT/Ps with communicable disease agents and to ensure orderly handling of HCT/Ps without mixups.”

(Comment 64) One comment on proposed § 1271.190(a) questioned the interpretation of “suitable size, construction, and location.” Another comment asked us to clarify the meaning of “location.”

(Response) As discussed in the previous comment, we have changed the wording of § 1271.190(a) to make it clear that the suitability of a facility’s size, construction, and location relates to preventing the contamination of HCT/Ps with communicable disease agents and ensuring orderly handling of HCT/Ps. We do not believe any other change is necessary. We decline to dictate specific requirements for an HCT/P establishment’s size, construction, and location; it is more appropriate for establishments to make these determinations for themselves, based on the objectives set out in this regulation.

By location, the regulation refers to the facility’s site. Some examples of unsuitable locations for an HCT/P establishment, because of the risk of transmission of communicable disease, might include a site on a loading dock or in the same building as a slaughterhouse.

(Comment 65) One comment asserted that, if an establishment is a tenant in a building, then bringing a problem to the attention of the building

management, with the understanding that a response would occur in a reasonable time period, should be an acceptable way of complying with this section.

(Response) An establishment that is a tenant should ensure that, under its rental agreement, the landlord will undertake the activities required in this section on a routine basis and within a reasonable amount of time. In this situation, a responsible establishment would communicate regularly with the landlord to bring problems to the landlord's attention in a timely manner. However, if a facility's conditions are such that the establishment is unable to manufacture HCT/Ps in an acceptable manner, then manufacturing activities should stop immediately; in this situation, where immediate repairs are required, simply notifying the landlord is not sufficient.

(Comment 66) One comment requested a modification to proposed § 1271.190(a) to delete the requirement for toilet facilities.

(Response) We decline to delete the requirement for toilet facilities. However, we have modified the requirement so that it now refers to "access to sinks and toilets." As modified, the regulation requires toilets to be accessible, but not necessarily within the establishment. We have further revised the last sentence of paragraph (a) to state that you must provide lighting, ventilation, plumbing, drainage, and access to sinks and toilets to prevent the introduction, transmission, or spread of communicable disease.

(Comment 67) One comment on proposed § 1271.190(c) asserted that developing and maintaining procedures for routine cleaning and maintenance, such as trash removal, cleaning toilets, and sweeping floors, would be a waste of time and resources.

(Response) We disagree. Maintaining a clean facility is fundamental to an establishment's ability to prevent the contamination of HCT/Ps. Without procedures in place, this important responsibility may be left to chance. An establishment's procedures might state, for example, how often a particular floor is to be mopped and which disinfectant must be used. Such procedures are basic elements of communicable disease prevention and are not trivial matters.

We recognize, however, that not all cleaning and sanitation that you may perform will relate to these requirements (e.g., vacuuming the lobby); thus, we have modified paragraph (d)(1) to limit its scope to procedures for facility cleaning and sanitation for the purpose of preventing transmission of communicable disease. We have made a similar change to paragraph (b)(1), which now requires you to maintain facilities in a clean, sanitary, and orderly manner, to prevent the transmission of communicable disease.

The requirements for facility cleaning in proposed paragraphs (c)(1) and (c)(2) are now in paragraph (b); the requirement for procedures in proposed § 1271.190(c)(3) is contained in § 1271.190(d)(1); and the requirement for record retention in proposed § 1271.190(c)(4) is contained in § 1271.190(d)(2).

(Comment 68) Another comment asked for clarification of the phrase "significant cleaning and sanitation activities" in proposed § 1271.190(c)(4). This comment opposed a requirement to keep mopping records for 10 years, but supported keeping records of changing the air handling filters.

(Response) For clarity, we have removed the word "significant" from § 1271.190(c)(4), now renumbered as paragraph (d)(2). This paragraph now requires you to document and maintain records of "all cleaning and sanitation activities performed to prevent contamination of HCT/Ps." Generally, cleaning

and sanitation activities performed in the manufacturing area would be performed to prevent contamination of HCT/Ps, while these activities performed elsewhere in the establishment (e.g., business offices, lobby) would not be performed for that purpose. Thus, all sanitation activities in certain areas would need to be documented. Although it is not necessary to maintain actual mopping records, you do need to document that cleaning in accordance with procedures took place (e.g., by having the person performing this task initial a log).

We also agree with the comment regarding record retention and we have revised the requirement for retaining records of facility cleaning and sanitation activities from 10 years to 3 years, which allows the records to be available for an inspection cycle.

7. Environmental Control and Monitoring (§ 1271.195)

Proposed § 1271.195 would require establishments to establish and maintain procedures to adequately control and monitor environmental conditions and to provide proper conditions for operations. It would also require inspections and recordkeeping.

We have reorganized § 1271.195. The requirement for environmental monitoring in proposed paragraph (a) is now contained in paragraph (c). Moreover, paragraph (a) no longer requires the establishment and maintenance of procedures for the control and monitoring of environmental conditions. That paragraph now states, in part, that “you must adequately control environmental conditions.”

(Comment 69) Three comments discussed the applicability of this section to eye banking. One comment asserted that because corneas remain in closed, sealed vials once final placement in media occurs, the requirement for control

and monitoring of ventilation and air filtration systems would not apply. Two other comments cited the use of laminar flow hoods in work on eye tissue and argued that the installation of a major environmental control system would be cost prohibitive and unnecessary.

(Response) Rather than require environmental control and monitoring by all establishments in all situations, we have adopted a flexible approach that allows each establishment to assess its particular needs. Thus, § 1271.195(a) requires environmental control and monitoring “where environmental conditions could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment, or accidental exposure of HCT/Ps to communicable disease agents.” In those situations, you must adequately control environmental conditions and provide proper conditions for operations. The regulation lists control activities or systems that must be employed, where appropriate. (“Where appropriate” is explained in § 1271.150(e).) It may not be necessary to institute a facility-wide control system in situations where work on HCT/Ps is performed in a controlled environment (e.g., use of a laminar hood that is subject to control).

(Comment 70) Proposed § 1271.195(a)(3) would require cleaning and disinfecting of rooms and equipment to ensure aseptic processing operations, where appropriate. Two comments asserted that, where other control systems to prevent contamination are in place, cleaning and disinfection of rooms and equipment are not necessary.

(Response) The regulation allows establishments to develop environmental control systems that are appropriate to their activities. If control systems are in place to prevent contamination, then an establishment should institute measures to ensure that these controls are performing as intended. It appears

unlikely, however, that cleaning and disinfection would not be a necessary component of controls.

(Comment 71) Proposed § 1271.195(a)(5) would require environmental monitoring for organisms, where appropriate. One comment asserted that there is no expert consensus on which organisms to monitor and that the regulation should be more specific.

(Response) We agree that there is no expert consensus on a single list of organisms for which all facilities should monitor; however, we disagree that it is necessary for us to provide a list in this regulation. Conditions may differ from facility to facility (and even from room to room within a facility), with common microorganisms found in one area but not another. Each establishment should determine the microorganisms that may exist in its facilities and design its monitoring program accordingly.

FDA has issued a draft guidance document entitled “Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing, Current Good Manufacturing Practice,” dated August 2003, (<http://www.fda.gov/cber/gdlns/steraseptic.htm>) that may provide useful information to an HCT/P establishment that is developing procedures on environmental control and monitoring. Information on environmental monitoring may also be found in the U.S. Pharmacopoeia.

The requirement for monitoring for microorganisms in proposed § 1271.195(a)(5) has been moved to § 1271.195(c).

8. Equipment (§ 1271.200)

Proposed § 1271.200 would require that equipment used in the manufacture of HCT/Ps be appropriately designed for its use, and be suitably located and installed to facilitate operations, including cleaning and

maintenance. It also contained requirements for procedures and schedules, calibration of equipment, inspections, and records.

(Comment 72) One comment asserted that the proposed requirement is overly broad and that the regulation should allow establishments to write and maintain procedures for use of equipment, cleaning, and calibration that prevent circumstances that increase the risk of introduction, transmission, or spread of communicable disease. Another comment asked whether the requirements in § 1271.200 should be limited to concerns of communicable disease transmission.

(Response) We agree with the comments that § 1271.200 should be limited to concerns of communicable disease transmission. Therefore, the first sentence of § 1271.200(a) now reads

To prevent the introduction, transmission, or spread of communicable diseases, equipment used in the manufacture of HCT/Ps must be of appropriate design for its use and must be suitably located and installed to facilitate operations, including cleaning and maintenance.

Under § 1271.200(b), an establishment must establish and maintain procedures for cleaning, sanitizing, and maintaining equipment to prevent malfunctions, contamination or cross-contamination, accidental exposure of HCT/Ps to communicable disease agents, and other events that could reasonably be expected to result in the introduction, transmission, or spread of communicable diseases.

(Comment 73) Several comments asked that vendor validation and maintenance records be acceptable for compliance with § 1271.200.

(Response) You may use vendor validation and maintenance records to demonstrate compliance with § 1271.200; however, you are still responsible

for having a system in place designed to ensure that the services provided by the contractor are adequate and in compliance with applicable requirements. Section 1271.150 addresses the question of work performed by other establishments or contractors.

(Comment 74) Proposed § 1271.200(a) would require, in part, that any automated, mechanical, electronic, computer, or other equipment used for inspection, measuring, and testing be capable of producing valid results. One comment asked us to clarify the meaning of “valid results” in proposed § 1271.200(a). The comment stated that valid results may be obtained through appropriate validation and/or calibration of equipment.

(Response) We agree that “capable of producing valid results” does not mean validation of equipment. The requirement is for the equipment to work properly, thereby providing “valid results.” This may be accomplished by calibrating, inspecting, and maintaining equipment. (See e.g., “Medical Devices; Current Good Manufacturing Practice (CGMP) Final Rule; Quality System Regulation,” 61 FR 52602, October 7, 1996.)

(Comment 75) Proposed § 1271.200(c) would require calibration of all automated, mechanical, electronic, computer, or other equipment used for inspection, measuring, and testing. One comment objected to the requirement for calibration of computers because computers do not make measurements, and asserted that validation should be sufficient. Another comment stated that the calibration of slit lamps is not practical.

(Response) We have revised paragraph (c) in response to these comments. First, we have removed computers from the listed types of equipment in this paragraph and in paragraph (a). Second, we have added “where appropriate” to the first sentence of the paragraph. We have made these changes because

we recognize that there are certain pieces of equipment that cannot be calibrated (e.g., computers, slit lamps). We have also removed the second and third sentences of proposed paragraph (c), which related to direction for calibration; accuracy and precision limits; and corrective actions.

(Comment 76) Approximately eight comments objected to the requirement in proposed § 1271.200(e) that records of recent maintenance, cleaning, sanitizing, calibration, and other activities be kept “at each piece of equipment.” One comment recommended that facilities be allowed the flexibility to maintain the records in a location that is easily accessible to the equipment but not directly at the equipment site. Another comment agreed that these records must be maintained but noted that it is important to keep the amount of paper to a minimum in a clean room environment and suggested that the documents need only be readily retrievable. One comment noted that records cannot physically be kept on small instruments such as pipettes and suggested the use of a central repository.

(Response) We agree with these comments and have revised the regulation. Section 1271.200(e) now states, in part, that you must display records of recent maintenance, cleaning, sanitizing, calibration, and other activities on or near each piece of equipment, or make the records readily available to the individuals responsible for performing these activities and to the personnel using the equipment. This new language, which is based on § 820.72, provides establishments with more flexibility than the proposed provision would have given.

(Comment 77) One comment asserted that the records requirement in proposed § 1271.200(e) should be limited to major equipment and should not include simple instruments that are regularly washed and disinfected or

disposable equipment that has a validated procedure for cleaning and disinfecting.

(Response) We disagree with the suggestion to exempt simple instruments from the requirements of this rule. Records for cleaning and maintenance of instruments, tools, and other equipment used or reused in the manufacturing of HCT/Ps must be kept to document that the items were adequately cleaned and maintained to prevent their contamination or cross-contamination by communicable disease agents. Single-use instruments, tools, or other equipment would not be subject to the requirement if they are used only one time and are disposed of after use.

9. Supplies and Reagents (§ 1271.210)

Proposed § 1271.210 would require the establishment to establish and maintain procedures for receiving supplies and reagents used in the manufacture of HCT/Ps. These items would be verified to meet specifications designed to prevent circumstances that increase the risk of introduction, transmission, or spread of communicable disease through HCT/P contamination. Supplies and reagents are materials that might be used during manufacture, but do not include any material that might become a component of an HCT/P (66 FR 1508 at 1515).

We have reorganized § 1271.210. The requirement for validation or verification of the production of in-house reagents is now in paragraph (c) and refers to processes instead of procedures; records requirements are now in paragraph (d).

(Comment 78) One comment supported the regulation as proposed, noting however that compliance would be costly.

(Response) We address concerns about compliance costs separately, in section V of this document.

(Comment 79) One comment on proposed § 1271.210(a) questioned whether the receipt requirements pertained to supplies used solely in the recovery of human tissues.

(Response) Section 1271.210 applies to all steps in the manufacture of HCT/Ps, including recovery. Use of a contaminated or otherwise defective supply or reagent in the manufacture of an HCT/P could lead to such problems as the introduction of a disease agent or the failure to properly preserve the HCT/P. It is important for establishments to establish and maintain procedures for receiving supplies and reagents, including verification, at each step of manufacture, beginning with recovery. We note that § 1271.210(a) no longer contains a requirement for procedures. However, § 1271.210(a) and (b) are core CGTP requirements listed in § 1271.150(b); therefore, the requirement for establishing procedures under § 1271.180 applies to these two paragraphs.

(Comment 80) One comment asked whether vendor verification is required for all supplies or only for those that come in contact with the donor or the recovered tissue.

(Response) Verification by you or the supply vendor is required for all supplies and reagents that may be used in the course of manufacture, not simply those that may come in contact with a donor or an HCT/P. For example, a reagent used in donor testing must be verified, even if it does not come into contact with the donor or the donated tissue.

(Comment 81) One comment asserted that the requirement is overly broad and requested that we allow establishments to write and maintain procedures

for use of supplies and reagents that prevent circumstances that increase the risk of introduction, transmission, or spread of communicable disease.

(Response) We have narrowed § 1271.210 to apply more specifically to preventing the introduction, transmission, or spread of communicable diseases.

(Comment 82) Proposed § 1271.210(c) contains records requirements, and paragraph (c)(3) would require records of the use of each supply or reagent, including the identification of each HCT/P manufactured with the supply or reagent. One comment noted that, for many HCT/Ps, lots are small, and a requirement for separate records would present an enormous burden. Another comment questioned the utility of listing each product processed by each pipette or bottle of medium. A third comment asserted that, although the processing records for each hematopoietic stem/progenitor cell preparation should identify supplies and reagents used for processing, it would be prohibitively time-consuming to maintain separate records of each transplant prepared with each reagent.

(Response) You should establish a system under which particular lots of supplies and reagents can be linked to individual HCT/Ps. This does not require an individual record for each HCT/P prepared with each reagent, as the comment suggested. Therefore, we have added “lot” to renumbered paragraph (d)(3) to make clear the lesser burden. We have also added “quantity” so that the establishment may find all supplies and reagents received in the event of a recall by the manufacturer. Maintaining the records required in paragraph (d)(3) will enable you to do a cross-check to determine which lots of supplies and reagents were used at a particular time and which HCT/Ps were processed during that same time period (e.g., if there is a recall of a particular lot of reagent or supplies).

10. Recovery (§ 1271.215)

This final rule includes a new section specific to the recovery of cells and tissues, § 1271.215. This section states that, if you are an establishment that recovers HCT/Ps, you must recover each HCT/P in a way that does not cause contamination or cross-contamination during recovery, or otherwise increase the risk of the introduction, transmission, or spread of communicable disease through the use of the HCT/P. This requirement was implicit in the proposed rule (e.g., § 1271.180); however, in reorganizing the rule we have determined that it is necessary to make this requirement explicit. Section 1271.215 is listed as a core CGTP requirement in § 1271.150(b). As discussed in section III.C.5 of this document, you must establish and maintain procedures for cell and tissue recovery.

11. Processing and Process Controls (§ 1271.220)

Proposed § 1271.220 would require an establishment engaged in processing to develop, conduct, control, and monitor its manufacturing processes to ensure that each HCT/P conforms to specifications, is not contaminated, and is manufactured so as to prevent transmission of communicable disease by the HCT/P. Proposed § 1271.220 also contains requirements with respect to processing materials, pooling, and in-process monitoring.

We have moved the provision on dura mater from proposed § 1271.230(c) to § 1271.220(d); we address comments on the proposed provision with other comments on proposed § 1271.230.

(Comment 83) One comment requested an exemption for eye banks from this section, because corneas are not processed in accordance with FDA's

definition. Another comment asserted that the section is inapplicable to eye banks.

(Response) We disagree. Eye banks that perform even minimal processing must control their processes. At Comment 21, we explain the applicability of the term “processing” to eye banking.

(Comment 84) Proposed § 1271.220(a) would require, in part, that each establishment develop, conduct, control, and monitor its manufacturing processes to ensure that each HCT/P conforms to specifications. One comment required that we define “specifications.” Another comment noted that there are no specifications set for corneas, but that criteria are determined by local medical directors in conjunction with professional standards.

(Response) Requirements with respect to in-process control and testing are now contained in § 1271.220(c). We have also removed references to specifications from § 1271.220(a). That paragraph now requires that, if you are an establishment that processes HCT/Ps, you must process each HCT/P in a way that does not cause contamination or cross-contamination during processing, and that prevents the introduction, transmission, or spread of communicable disease through the use of the HCT/P.

We recognize, however, that the term “specifications” appears elsewhere in this regulation (e.g., § 1271.3(dd), definition of “HCT/P deviation”). We noted in the preamble to the proposed rule that, by “specifications,” we meant those criteria established by a manufacturer for an HCT/P that must be met at defined stages in the manufacturing process and before the product is made available for distribution (66 FR 1508 at 1516). Ordinarily, an establishment will set specifications for various operations within its facility, not just

processing. Because we believe the term is generally well understood, we do not consider it necessary to define the term in this rule.

As noted in our response to Comment 19, we understand that an eye bank might not set specifications for corneas. However, we expect that an establishment will generally set out acceptability criteria for its HCT/Ps in its standard operating procedures.

(Comment 85) One comment requested clarification of the requirement for monitoring and control of validated processes. This comment asked if the quality review is sufficient to ensure that specific processes continue to be met.

(Response) We have removed from § 1271.220(a) the specific requirement for monitoring and control of processes. However, we believe that, to ensure that you are processing HCT/Ps in a way that does not cause contamination or cross-contamination during processing, and that prevents the introduction, transmission, or spread of communicable disease through the use of the HCT/P, a firm should establish appropriate, objective mechanisms to control and monitor each validated process. This may include a variety of activities, e.g., statistical process-control methods, review of product acceptance criteria and results, as well as a meaningful quality audit.

(Comment 86) One comment asserted that we seem to be requiring that tissue be sterile and that decontamination processes be validated to produce tissue that is not contaminated or is sterile. The comment asserted that viable tissue cannot be made sterile and that reducing bioburden is not the same as eradicating contamination.

(Response) FDA is not requiring at this time that tissue be sterile, but we do expect aseptic techniques to be used during manufacturing to prevent contamination and cross-contamination. Indeed, it is the current industry

practice to use aseptic techniques during recovery and processing. Whenever an activity is used in the processing of HCT/Ps, that activity must be controlled to limit the introduction of disease agents. When technology progresses to the extent that viral clearance or sterilization is feasible, FDA may revise these CGTPs to require that HCT/Ps be sterile. FDA welcomes submissions as to when technology will have progressed to this point.

(Comment 87) One comment on proposed § 1271.220(a) requested clarification of the term “manufacturing process.”

(Response) We have re-examined our use of the phrase “manufacturing process” in § 1271.220(a) and have concluded that it is confusing. Processing is one of the steps in manufacture, as defined in § 1271.3(e). Because §§ 1271.220, 1271.225, and 1271.230 pertain only to processing, rather than to the other steps in manufacture, we have replaced “manufacturing process” with “process.”

(Comment 88) We received five comments on proposed § 1271.220(b), which addressed processing materials. Two comments noted that it is not always possible to document that a processing material has been removed from an HCT/P, and that validated procedures should be sufficient. One comment proposed the use of published data and industry practice to determine whether a processing material or its residues may elicit an adverse reaction. This comment also recognized that product labeling may be used to warn potential users with respect to the possible presence of residues.

(Response) We have removed proposed paragraph (b) in its entirety from § 1271.220 and renumbered the paragraphs accordingly.

Pooling.

Proposed § 1271.220(c) states that human cells or tissues from two or more donors shall not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing. We noted that commingling of cells or tissues from a single infected donor with cells or tissues from other donors could contaminate the entire pooled quantity, greatly increasing the risk of exposure to infectious agents to recipients of the pooled materials (66 FR 1508 at 1516). Proposed paragraph (c) has been renumbered as (b).

(Comment 89) Approximately six comments agreed with the proposed prohibition on pooling. Several comments pointed to an increased risk of infectious disease transmission associated with pooling, and asserted that pooling could increase the threat of previously unknown transmissible diseases. One comment asserted that there is a particularly high risk for Rh-negative women of childbearing age who receive tissue from Rh-positive donors. Two comments argued that pooling would impair the effectiveness of tissue recalls, because tracing to the source of a problem would be impossible. Comments also questioned the efficacy of processes used to manufacture pooled HCT/Ps and noted that no process entirely eliminates the risk of infectious disease transmission. Two comments asserted that pooling would be distasteful to donors and their families.

(Response) These comments raise valid concerns. We agree in particular with the concerns expressed about the increased risk of communicable disease transmission and the difficulty of tracking pooled HCT/Ps.

(Comment 90) Approximately 10 comments opposed our proposal to prohibit the pooling of cells or tissues. Several comments argued that the proposed regulation is too restrictive and could stifle new technologies.

(Response) Although we are aware of promising new technologies that involve the pooling of cells from two or more donors, we remain concerned about the infectious disease risks inherent in pooling. On June 26, 2002, FDA consulted the Transmissible Spongiform Encephalopathies Advisory Committee (TSEAC) about the validation of procedures to prevent contamination and cross-contamination of HCT/Ps by TSE agents. At this meeting, speakers presented information on the three approaches that could be taken to reduce the risk of TSE transmission:

- Careful screening of the donor for TSE and risk factors for TSE;
- Control of the recovery and processing of cells and tissues to prevent contamination and cross-contamination; and
- Use of steps during processing to remove or inactivate any TSE agents that may be present.

One of the processing controls discussed was the use of single donor aseptic recovery and processing, rather than a process that would involve pooling of cells or tissues from two or more donors. When asked about specific measures and controls appropriate to prevent TSE agent transmission (e.g., single donor aseptic processing), the committee voted unanimously that single donor processing should be considered the gold standard, but that a pooled process may be appropriate under certain circumstances with adequate controls. The committee members did not discuss which circumstances and what controls would be adequate.

Under § 1271.155, an establishment may submit a request for an alternative or exemption from the prohibition from pooling provided that it has data showing that the processing method adequately addresses the risks associated with pooling.

(Comment 91) Two comments opposed our assertion that commingling cells or tissues from different donors, who have been screened and tested, would increase the risk to recipients of exposure to infectious agents.

(Response) We disagree with these comments. Screening and testing of donors, although crucial, does not completely eliminate infectious disease risk, for several reasons. The donor may be in the “window period” during which he or she may be infectious (i.e., have viral marker levels that are below detection by current tests). Chronic carriers of a disease may be immuno-silent; i.e., they do not mount an antibody response. In addition, laboratory errors may be made, or an HCT/P may be released improperly. Moreover, current tests may not detect all genetic variants of a particular virus, or a donor may be infected with an “emerging infectious disease,” for which screening measures or tests have not been developed. Finally, there may be questions about the accuracy of current tests that are not approved by FDA for use with cadaveric specimens and about the reliability of donor histories obtained from another person (not the donor). Each of these risks is small, and presents a small chance of leading to communicable disease transmission to a single HCT/P recipient. However, the risk is magnified when HCT/Ps from different donors are pooled during manufacture. Information provided at the TSEAC meeting described previously showed that the risk of exposing a recipient to an infectious disease agent contained in a pool, where one or more units in the pool were recovered from an infected donor, is directly proportional to the prevalence of the agent in the donor population and the size of the pool.

(Comment 92) Several comments pointed out benefits of pooling. Two comments pointed to the need for pooling to obtain a sufficient dose of an

HCT/P, especially in adults (e.g., from cord blood). One comment stated that pooling contributes to product consistency and uniformity.

(Response) We are retaining the prohibition on pooling during manufacturing in § 1271.220(b). We continue to believe that, in general, the risks of pooling HCT/Ps (increased risk of communicable disease transmission) outweigh the benefits of pooling. For some biological products, e.g., plasma derivatives, the benefits of pooling outweigh the risks. In the case of plasma derivatives, pooling contributes to product consistency. In fact, 21 CFR 640.102(d) requires that material from not less than 1,000 donors be pooled to make immune globulin. For plasma derivatives, it is necessary to pool plasma from many donors to obtain an adequate amount of product to treat one recipient (i.e., a sufficient dose). In addition, pooling plasma may dilute the viral burden or provide neutralizing antibodies that may inactivate any virus present in the pool. However, these benefits of pooling do not apply, in general, to the pooling of HCT/Ps from many donors. For instance, tendons from different donors would not need to be pooled to provide consistency or to obtain a sufficient dose. Neither would bones pooled from different donors provide neutralizing antibodies to inactivate any virus present in the pool, since neutralizing antibodies are present in plasma. In the case of cord blood, most of the plasma is removed during processing, so that pooling of cord blood from different donors would not provide sufficient neutralizing antibodies to neutralize any virus present in the pool. Furthermore, when cord blood units from more than one donor are administered to an adult recipient to obtain a sufficient dose, the units are generally given sequentially and are not pooled.

In order for us to determine whether any benefits to pooling HCT/Ps from different donors outweigh the risks in a particular case, we would need

additional data. Such data may be submitted and evaluated under a request for an alternative or exemption in § 1271.155.

(Comment 93) Several comments asserted that the risks of pooling could be mitigated through validated procedures for clearing pathogens or sterilizing the pooled HCT/Ps. One of these comments suggested additional regulatory language that would permit pooling where it is necessary and does not create an unreasonable risk of communicable disease transmission. Another comment proposed that the final rule should allow the pooling of stem cell products from two or more donors, as long as the resulting pooled product is transplanted into only one recipient.

(Response) We agree that, in some instances, it may be appropriate to assess the risks and benefits of pooling. Such assessment could be submitted under § 1271.155 in a request for an exemption or alternative to the prohibition on pooling in § 1271.220(b). However, we decline to modify the proposed regulation as suggested and, for the reasons explained in Comments 89 through 92, we have retained the general prohibition on pooling.

(Comment 94) One comment that supported proposed § 1271.220(c) asserted that no waivers or exceptions should be allowed that would permit pooling.

(Response) We disagree with this comment. Although we remain very concerned about the communicable disease risks associated with pooling, we do not rule out the possibility that pooling may be appropriate in some specific situations. We will consider requests for exemptions from or alternatives to § 1271.220(b) under the provisions of § 1271.155. At the June 2002 TSEAC meeting described previously, the committee members supported the possibility that exemptions from the proposed pooling prohibition might be

appropriate, but did not discuss criteria upon which to grant such an exemption.

In-process control and testing.

Proposed § 1271.220(d) would require procedures to ensure that specified requirements for in-process HCT/Ps are met. These procedures must ensure that an in-process HCT/P is controlled until the required inspection and tests or other verification activities have been completed or necessary approvals are received and documented. In addition, sampling of in-process HCT/Ps must be representative of the material to be evaluated.

There were no comments on this provision, which has been renumbered paragraph (c). We have revised this paragraph to cover in-process control and testing. Paragraph (c) requires you to ensure that specified requirements, consistent with paragraph (a) of this section, for in-process controls are met, and that each in-process HCT/P is controlled until the required inspection and tests or other verification activities have been completed, or necessary approvals are received and documented. Sampling of in-process HCT/Ps must be representative of the material to be evaluated.

We note that paragraph (c) includes the prevention of bacterial and other contamination. Compliance with this paragraph requires checking the results of testing at various steps in processing (for example, by sampling in-process HCT/Ps). The sample selected for testing (e.g., culture) must be representative of the entire HCT/P. This may not be the case if a small snip of the HCT/P or companion tissue (i.e., tissue adjacent to the HCT/P that is processed along with the HCT/P) is cultured. The MMWR cited in section III.C.1 of this document recommended that performing both destructive (i.e., performed on

tissue that had been ground up) and swab cultures (of the tissue surface) should be considered (Ref. 1).

Dura mater.

Proposed § 1271.230(c) would require dura mater to be processed using a validated procedure that reduces TSE while preserving the clinical utility of the product. We have moved proposed § 1271.230(c) to § 1271.220(d) because it relates more closely to processing and process controls than to process validation.

(Comment 95) Three comments objected to proposed § 1271.230(c). One comment urged us to eliminate the provision, because FDA should not endorse the concept of an acceptable level of TSE risk, and another comment asserted that there is no acceptable level of TSE contamination. Another comment opined that the proposed rule is arbitrary because FDA has not validated methods for decontaminating tissue contaminated with prions.

(Response) We disagree that FDA is endorsing the concept of an acceptable level of TSE risk. The donor-eligibility rule requires screening of all HCT/P donors for TSE risk factors and testing of dura mater donors (see §§ 1271.75(a) and 1271.85(e)). In this rule, we are requiring additional processing safeguards to reduce the level of the TSE agent that may be present in dura mater, even after a donor has been determined to be eligible based on screening and testing. Taken together, these requirements are intended to help prevent the transmission of TSE by dura mater and should by no means be considered to endorse an acceptable level of risk. Eliminating proposed § 1271.230(c) would decrease the safeguards in place and elevate the risk; we decline to take this step.

We disagree that the requirement to use a validated procedure is arbitrary or that it is necessary for FDA to validate procedures for the removal of the TSE agent in human tissue. TSEAC has recommended treating human dura mater with sodium hydroxide (June 26, 2002), and in the preamble to the proposed rule we cited a sodium hydroxide (NaOH) protocol as an example of a validated procedure (66 FR 1508 at 1517). The TSEAC recommendation was based on a study in an animal model, in which 1.0N NaOH treatment reduced Creutzfeldt Jakob Disease (CJD) infectivity (Refs. 2, 3, and 4). However, we realize that this method is not being used for reducing TSE infectivity in human dura mater distributed at this time, and that there are no other validated methods currently available. Although 1.0N NaOH treatment reduces infectivity, this process can also decrease the clinical utility of the dura mater. Therefore, § 1271.220(d) requires use of a published validated process when one becomes available.

As new validated processes become available, they will be published in the literature. You do not have to validate the published procedure; rather you must verify that the previously validated process has been fully and properly implemented in your establishment. We recognize that processing methods may be developed that reduce the risk of TSE but that render the HCT/P no longer useful for its purpose. Accordingly, you are not required to implement a process if it adversely affects the clinical utility of the dura mater. Alternatively, you may validate an equivalent procedure for use in your establishment that is at least as effective as the published procedure, without adversely affecting the clinical utility of the dura mater.

We recognize that, due to a variety of circumstances, you may not be aware when there is a published, validated process that reduces the risk of TSE. We

intend to follow the good guidance practices set out in 21 CFR 10.115 to advise you when we have identified the existence of a published, validated process that reduces the risk of TSE, and we would ordinarily solicit public comment before issuing a final guidance.

12. Process Changes (§ 1271.225)

Proposed § 1271.225 would require the establishment to establish and maintain procedures for making changes to a process. Such changes would be verified or validated, and approved by a responsible person before implementation. We have removed from § 1271.225 the requirement that establishments have procedures for making process changes.

(Comment 96) One comment asserted that this section does not apply to eye banks and that they should not be required to comply. Another comment from an eye bank stated that the section is too broad and should be narrowed.

(Response) Section 1271.225 applies to establishments engaged in the processing of HCT/Ps, including eye banks that perform processing activities. For example, a switch from one brand of storage solution to another would be a process change. In this situation, the eye bank must verify that the new process performs as intended in a manner that does not introduce, transmit, or spread communicable disease agents.

Under § 1271.150(b), an establishment need only comply with those requirements applicable to the operations in which it engages (§ 1271.150(b)). Thus, if you are an establishment that does not engage in the processing of HCT/Ps, you do not need to comply with § 1271.225. We have discussed the meaning of “processing” at Comment 20. We disagree that it is necessary to narrow the provision, which is intended to apply to the full range of HCT/P establishments engaged in processing.

(Comment 97) One comment on proposed § 1271.225(a) asserted that most, but not all, changes will need to be verified or validated. As examples of simple changes that should not require verification or validation, the comment cited requirements for additional training or changes in location or storage of records. The comment suggested that we add the phrase “if appropriate as determined by a risk assessment.”

(Response) Under § 1271.225, if you are an establishment engaged in the processing of HCT/Ps, you are required to verify or validate any change to a process, to ensure that the change does not create an adverse impact elsewhere in the operation. The examples cited by the comment are not examples of process changes.

(Comment 98) Proposed § 1271.225(b) contained requirements for maintaining change records. One comment agreed that records of the rationale for each change should be maintained, calling this requirement a real time saver. Another comment asserted that § 1271.225(b) is more stringent than the comparable requirement for blood.

(Response) We have removed the requirement for documenting all changes to an established process and the rationale for such a change. We have maintained the proposed requirement for communicating approved changes to appropriate personnel in a timely manner; however, it no longer appears in paragraph (b), which has been deleted.

13. Process Validation (§ 1271.230)

Where the results of a process cannot be fully verified by subsequent inspection and tests, proposed § 1271.230 would require the process to be validated and approved according to established procedures. The validation activities, results, and the date and signature of the individual approving the

validation would be documented. Re-validation would be required where appropriate in the case of changes to a validated procedure.

We have revised § 1271.230. Paragraph (a) now refers to processing described in § 1271.220. Paragraph (b) now refers to written representations, rather than claims, and is more limited than proposed. Paragraph (c) on dura mater is now § 1271.220(d). Paragraph (d) requiring procedures for the monitoring and control of validated processes has been deleted. For clarity, we have deleted the word “deviations” from proposed § 1271.230(e), now § 1271.230(c); that paragraph now refers only to changes to a validated process.

(Comment 99) Several comments asserted that the requirement for process validation in proposed § 1271.230 does not apply to eye banking. One comment cited the use of annually validated mechanical devices used in processing eye tissue and the evaluation of tissue by trained personnel.

Another comment asserted that the rule is vague as to which processes a company should validate and approve and how the validation and approval should be conducted. This comment further asserted that the rule fails to take into account the unique biological characteristics of the various human cell and tissue types (e.g., musculoskeletal tissue).

(Response) We have carefully worded § 1271.230 to take into account the uniqueness of various HCT/Ps. Thus, § 1271.230(a) requires validation of a process where the results of processing described in § 1271.220 cannot be fully verified by subsequent inspection and tests. Rather than being vague, this language recognizes that an establishment has specific knowledge of the HCT/Ps it manufactures, including when verification activities will suffice and when process validation is required because results cannot be fully verified. We agree that the control and results of the processes performed at eye banks

may be able to be achieved through verification activities; in this case, validation would not be required.

(Comment 100) One comment asserted that the documentation of eye and tissue banking successes in medical literature should constitute sufficient objective evidence for procedures that have been in use for years and that documentation of meeting predetermined specifications should only be required for new procedures that are not consistent with pre-existing standards and practices.

(Response) We disagree. Medical literature alone is insufficient to verify or validate the processes performed at a specific establishment. Each establishment that performs steps in the processing of HCT/Ps must demonstrate that it has validated or verified a given process at that particular establishment and that it is capable of controlling that process. These steps must be taken for all processes conducted by an establishment, regardless of when the process was initiated or how long the process has been in place.

(Comment 101) Proposed § 1271.230(a) states, in part, that where the results of a process cannot be fully verified by subsequent inspection and tests, the process shall be validated and approved according to established procedures. Two comments recommended deleting the word “fully” from this provision, arguing that it is too broad and could be subject to inconsistent application. These comments asserted that, once a process has been validated, if changes are required that do not increase the risk of communicable disease transmission to the recipient, a written justification for not revalidating should be sufficient.

(Response) We disagree with the comments’ suggestion to delete “fully.” The term “fully verified” has been used with respect to process validation in

ISO standards for years. Moreover, the term is used in the QS regulation on process validation applicable to medical devices (§ 820.75(a)).

The MMWR discussed at III.C.1 of this document cited CDC concerns with bacteriostasis (i.e., the arrestment or inhibition of bacterial growth and reproduction) (Ref. 1). The report surmised that because tissues later implicated in patient deaths were cultured only after suspension in an antibiotic/antifungal solution, residual antibiotics on the tissues might have caused a false-negative culture result because of bacteriostasis. Undetected organisms in stasis can later multiply (e.g., once an HCT/P has been transplanted into a patient and the residual antibiotic is metabolized so that it no longer inhibits growth of the bacteria). Therefore, we recommend that a validated microbiological culturing process include bacteriostatic and fungistatic testing.

In accordance with § 1271.150(e) (“where appropriate”), we agree that an assessment with written justification for not revalidating a change to a validated process would be sufficient under § 1271.230(c) if the establishment can show that the change does not increase the risk of communicable disease transmission to the recipient.

(Comment 102) Proposed § 1271.230(b) states, in part, that any process-related claim in labeling or promotional materials, e.g., a claim for sterility or viral inactivation, must be based on a validated process. One comment asked why, if verification is performed on each and every finished product, this could not be claimed in labeling. Three comments asked us to allow sterility claims based on verification rather than validation when technology limitations exist and when established manufacturing approaches have not led to clinical problems.

(Response) We agree with these comments and have modified § 1271.230(b) to include verification as well as validation. That paragraph now requires that any written representation that your processing methods reduce the risk of transmission of communicable disease by an HCT/P, including but not limited to a representation of sterility or pathogen inactivation of an HCT/P, be based “on a fully verified or validated process.”

(Comment 103) One comment suggested deleting claims for sterility or viral inactivation from proposed § 1271.230(b) and creating a new paragraph that specifically addresses the validation of processes intended to achieve sterility or viral clearance.

(Response) We decline to make this change. Providing specific methods for validation or verification of processes is not within the scope of this rulemaking. However, we have narrowed paragraph (b) so that it no longer covers “any process-related claim,” but now is limited to any written representation that your processing methods reduce the risk of transmission of communicable disease by an HCT/P, including but not limited to, a representation of sterility or pathogen inactivation of an HCT/P.

14. Labeling Controls (§ 1271.250)

Proposed § 1271.250 would require procedures to control the labeling of HCT/Ps, designed to ensure proper product identification and prevent mixups. These procedures would include verification of label accuracy, legibility, and integrity; they would further ensure that each HCT/P be labeled in accordance with all applicable requirements.

We have reorganized this section into three paragraphs for clarity and have corrected the cross-references to labeling requirements in part 1271.

Two comments supported this section as consistent with industry standards applicable to eye banking.

(Comment 104) One comment criticized as burdensome the proposed requirement for procedures to ensure that each product made available for distribution is accompanied by documentation of the donor eligibility determination as required under § 1271.55. This comment asserted that, if the product is going from the laboratory to the clinical unit of the same program, detailed documentation of donor testing does not need to accompany the HCT/P, as it can be found in the laboratory. According to the comment, such documentation of testing only makes sense if distribution means distribution outside of the institution.

(Response) We disagree with this comment. As discussed at Comment 17, distribution includes the intracompany shipment of a finished HCT/P; e.g., the release of an HCT/P from a collection/processing facility to an operating room in the same facility. Similarly, the release of an HCT/P from a laboratory to the clinical unit of the same program is distribution, and the HCT/P must be accompanied by the documentation required by § 1271.55. We have modified § 1271.55 in the donor-eligibility final rule (69 FR 29786 at 29831) to remove the requirement that an HCT/P be accompanied either by the relevant medical records or a summary of those records; that section now requires HCT/Ps to be accompanied by a distinct identification code, a statement of whether or not the donor has been determined eligible, and a summary of the records used to determine donor eligibility. This requirement is not burdensome. Moreover, it is very important that the administering physician have in hand specific and accurate information about the HCT/P; availability of the documentation in another part of a facility is insufficient.

(Comment 105) One comment asserted that the type of information called for is exorbitant for the identification of individual transplant products. This comment requested that the rules be streamlined along the lines of industry standards that provide for coded identification of donor, identification of intended recipient, and critical information regarding donor eligibility and type of processing used.

(Response) We disagree that the labeling information required by these rules is excessive. A review of the industry standards cited by the comment indicates that they specify the same information as required by these regulations, as well as additional information not required under these regulations; e.g., the identification of intended recipient, the type of processing used (Foundation for the Accreditation of Cellular Therapy (FACT) 2002; American Association of Blood Banks (AABB) 2002).

15. Storage (§ 1271.260)

Proposed § 1271.260 would require each establishment to control its storage areas and stock rooms to prevent mixups, commingling, deterioration, contamination, and cross-contamination of HCT/Ps and supplies, and to prevent improper release for distribution. The establishment would also be required to store the HCT/Ps at an appropriate temperature, assign an expiration date for the HCT/P where appropriate, and take and document corrective action when indicated.

One comment supported this section as proposed.

(Comment 106) We received several comments on the storage temperature and period requirements in proposed § 1271.260(b). Some comments asked whether establishments must validate storage temperatures and periods, and noted that many of these have been established by the tissue industry based

on experience. Another comment cited specific industry standards for eye banks. One comment asserted that the proposed parameters for setting storage temperature may not be optimal at the same temperature.

(Response) Voluntary standards issued by professional organizations exist for many aspects of these regulations, and we agree that establishments may follow these established industry standards where the standards meet the requirements set forth in this section. However, these standards may only apply to specific HCT/P types (e.g., corneas) and, moreover, are not always sufficiently comprehensive to include all of the requirements in this rule. Alternatively, establishments may establish and validate their own criteria for storage temperature and storage period, as determined for specific HCT/Ps stored in their facilities.

The regulation (§ 1271.260(b)) now requires storage at an appropriate temperature. Section 1271.260(e) requires you to establish acceptable temperature limits to inhibit the growth of infectious agents.

(Comment 107) Proposed § 1271.260(c) would require establishments to assign expiration dates to their HCT/Ps, where appropriate. Two comments stated that the safe duration of cryopreservation for hematopoietic stem/progenitor cells is unknown and will take years to validate.

(Response) The requirement for establishing an expiration date is qualified by the term, “where appropriate.” Section 1271.150(e) explains that a requirement is “appropriate” unless an establishment can justify otherwise, and maintains documentation of that justification. We consider it appropriate to assign expiration dates for “fresh” (i.e., noncryopreserved) HCT/Ps, and for those HCT/Ps that are thawed after cryopreservation and storage. If such applicable expiration dates have been established by industry or medical

practice and meet the requirements of this section, you may use those dates for your HCT/Ps, whether “fresh” or cryopreserved. If scientific data do not exist for establishing expiration dates, then no expiration date is required at this time. We encourage the industry to perform studies to establish expiration dates for those HCT/Ps that currently do not have expiration dates.

We have modified § 1271.260(c)(2) to refer to “processing,” rather than “processing procedures,” to avoid redundancy.

16. Receipt, Predistribution Shipment, and Distribution of an HCT/P (§ 1271.265)

Proposed § 1271.265 would require establishments to establish and maintain procedures for receipt, acceptance or rejection, distribution, and destruction or other disposition of HCT/Ps; and document these activities.

Several comments supported proposed § 1271.265. One comment indicated that the provisions are worthwhile, and another comment supported documenting the identity of the consignee.

We have reorganized § 1271.265. Paragraphs (a) through (d) now contain substantive requirements with respect to receipt, predistribution shipment, distribution, packaging and shipping. Each of these is a core CGTP requirement. Paragraph (e) requires you to establish and maintain procedures for activities under paragraphs (a) through (d) and to document these activities. (This documentation must include, for example, the identification of the HCT/P; in this rule we have specified that you must also document the establishment that supplied the HCT/P (e.g., by maintaining receipt records).) Paragraph (f) relates to returns to inventory, as proposed.

(Comment 108) One comment asked for clarification to ensure that all donated materials are subject to § 1271.265, regardless of their processing status.

(Response) We agree that all donated materials are subject to this section. The definition of HCT/P covers cells and tissues at all stages of manufacture, from recovery through distribution (66 FR 5447 at 5448).

Although we do not believe it is necessary to modify § 1271.265 as suggested by the comment, we have made a related change, by adding a new provision on “pre-distribution shipment” (§ 1271.265(b)). This change is necessitated by our revision of the definition of “distribution,” discussed at Comment 17, to refer to the conveyance or shipment of an HCT/P that has been determined to meet all release criteria. Predistribution shipment includes, for example, shipment of an HCT/P within your establishment or to another establishment, or shipment from an establishment that recovers cells or tissue to an establishment that packages them.

Section 1271.265(b) states that if you ship an HCT/P within your establishment or between establishments (e.g., procurer to processor) and the HCT/P is not available for distribution as described in paragraph (c) of this section, you must ship the HCT/P in quarantine.

(Comment 109) Proposed § 1271.265(b) would require each incoming HCT/P to be inspected according to established procedures. Two comments on proposed § 1271.265(b) asked if it is sufficient to inspect a shipping container for physical damage, or if the containers must be opened.

(Response) You should tailor your acceptance procedures to the specific HCT/P and circumstances. As the comments point out, in some instances opening a sealed shipping container could potentially damage an HCT/P. In

designing your acceptance procedures, you should take into account this possibility, as well as alternate ways of inspecting the HCT/P (e.g., inspection of container, ensuring proper temperature has been maintained during transit). If, after receiving the HCT/P, you hold it in storage, your storage conditions must comply with § 1271.260.

The MMWR cited at section III.C.1 of this document recommended that, to minimize the potential of bacterial contamination, tissue should be cultured before suspension in antimicrobial solutions, and if bacteria are isolated, all tissue from the same donor should be discarded if it cannot be sterilized (Ref.1). Where appropriate, your acceptance procedures should include tests and should spell out criteria for rejecting incoming HCT/Ps. Preprocessing cultures may be appropriate in some situations.

(Comment 110) One comment on proposed § 1271.265(c) (availability for distribution) asserted that “deterioration” is vague and open to interpretation.

(Response) By “deterioration,” we mean decay or decomposition. However, in response to Comment 9 we have removed references to “deterioration” from the CGTPs, including § 1271.265.

(Comment 111) One comment on proposed § 1271.265(c) asserted that the requirements for making an HCT/P available for distribution should not apply to distributors themselves.

(Response) The requirements in § 1271.265(c) are intended to apply to the establishment that first makes an HCT/P available for distribution (defined in § 1271.3(z)). This establishment, which may or may not be the actual distributor, needs to have procedures in place under § 1271.265(e) for determining that an HCT/P may be made available for distribution, including release criteria designed to prevent communicable disease transmission. The

regulation specifies that you must not make available for distribution any HCT/P that is in quarantine, is contaminated, is recovered from a donor who has been determined to be ineligible or for whom a donor-eligibility determination has not been completed (except as provided under §§ 1271.60, 1271.65, and 1271.90), or that otherwise does not meet release criteria designed to prevent communicable disease transmission. Release criteria include criteria for releasing a product under § 1271.60, § 1271.65, or § 1271.90 that ensure, among other things, that the conditions for such release are met and that the HCT/P is labeled with the warnings required by the regulations.

(Comment 112) Proposed § 1271.265(d) would require packaging and shipping containers to be designed, validated, and constructed to protect the HCT/P from contamination during customary conditions of processing, storage, handling, and distribution. The final rule requires that packaging and shipping containers protect HCT/Ps from contamination.

Three comments on proposed § 1271.265(d) suggested that verification of packaging containers is more appropriate than validation.

(Response) We agree that either validation or verification may be appropriate ways of ensuring the adequacy of packaging and shipping containers. Please note, however, that the final rule has been revised so that it does not require either verification or validation of packaging and shipping containers.

(Comment 113) Proposed § 1271.265(e) would require that appropriate shipping conditions be defined for each type of product to be maintained during transit. One comment questioned whether shipping conditions must be defined for each type of graft (e.g., femur ring, bone powder) or for each type of tissue (freeze-dried bone).

(Response) The final rule renumbers this provision as § 1271.265(d), combines it with the provision on packaging, and provides each establishment with the flexibility to determine whether to establish shipping conditions for each type of graft or for each type of tissue. Either approach may be appropriate.

(Comment 114) One comment on proposed § 1271.265(f) stated that the requirement to establish procedures for returning HCT/Ps to inventory is not applicable to all HCT/Ps.

(Response) We agree that some establishments may not engage in all activities covered by the CGTPs. Under § 1271.150(c), establishments need only comply with the requirements that are applicable to the operations in which they engage. Thus, an establishment that does not return HCT/Ps to inventory is not required to establish procedures for that activity.

17. Records (§ 1271.270)

Proposed § 1271.270 would require establishments to maintain records concurrently with the performance of each significant step required in subparts C and D. A records management system would be established and maintained. Records would be maintained: Electronically, as original paper records, or as true copies; 10 years after their creation; and for contracts, agreements, and other arrangements with another establishment to perform a step in manufacturing. One comment from a professional organization supported the goal of this provision, which it identified as chain of custody.

(Comment 115) One comment on § 1271.270(b) asserted that maintaining records organized by product type is not practical and that it is more useful to organize records by donor. Another comment asserted that detailing how

to organize records is an unnecessary intrusion and that the example given was unduly complicated.

(Response) In response to the first comment, we have deleted the words “of each type” from the third sentence of § 1271.270(b), so that it now reads: “Records pertinent to the manufacture of HCT/Ps * * * must also be maintained and organized under the records management system.” In response to the second comment, we note that, although paragraph (b) requires you to establish and maintain a records management system, it does not specify the details of such a system. It is the responsibility of the establishment to organize its records in a useful manner. The example given in the preamble to the proposed rule was intended simply to explain, to those unfamiliar with the term, what is meant by a “records management system” (66 FR 1508 at 1518). We have revised paragraph (b) so that the requirement for a records management system applies only to core CGTP requirements.

(Comment 116) We received two comments on the requirement in proposed § 1271.270(c) that information on the identity and relevant medical records of a donor must be in English or, if in another language, must be translated to English and accompanied by a statement of authenticity by the translator that specifically identifies the translated document.

(Response) Proposed paragraph (c) of § 1271.270 would relate to the donor-eligibility requirements in subpart C of part 1271. In the donor-eligibility final rule (69 FR 29786 at 29831), we incorporated the contents of proposed § 1271.270(c) into the records requirements in § 1271.55 and responded to these comments. We are now removing proposed paragraph (c) from § 1271.270.

(Comment 117) Proposed § 1271.270(e) would require records to be kept for 10 years. We specifically requested comments on whether there are specific types of record for which retention period shorter than 10 years would be appropriate (66 FR 1508 at 1518).

Two comments responded that a 10-year record retention is appropriate, and one of these comments cited an industry standard requiring records to be maintained 10 years.

(Response) We have maintained the 10-year record retention requirement for all records. Proposed § 1271.270(e) has been renumbered § 1271.270(d).

(Comment 118) Three comments pointed out that the record retention requirement in proposed § 1271.270(e) is confusing, and each of these comments suggested new language. One suggestion would require that the establishment retain records for 10 years after transplantation, or after expiration if transplant date is unknown. Two comments suggested that we require the retention of records for a minimum of 10 years after creation, 10 years after the expiration of a HCT/P, or 10 years after the appropriate disposition of dura mater.

(Response) We have revised proposed paragraph (e) by replacing the words “implantation, transplantation, infusion, or transfer” with “administration.” The second sentence of § 1271.270(d) now reads

However, you must retain the records pertaining to a particular HCT/P at least 10 years after the date of its administration, or if the date of administration is not known, then at least 10 years after the date of the HCT/P’s distribution, disposition, or expiration, whichever is latest.

(Comment 119) Proposed paragraph (e) would require an establishment to make provisions for all records to be maintained for the required period in

the event that the establishment ceases operation. One comment asserted that it is not practical for an establishment to retain records if it has gone out of business.

(Response) We encourage you to make provisions for keeping records in the event that your establishment goes out of business, because some communicable disease have very long incubation periods before symptoms appear (e.g., CJD). However, because of difficulties in enforcing the proposed requirement, we have removed it from the final regulation.

18. Tracking (§ 1271.290)

Proposed § 1271.290 would require each establishment that performs any step in manufacturing to set up a system for tracking each HCT/P so that the HCT/P may be tracked from donor to recipient and recipient to donor.

We have clarified that tracking requirements apply to those facilities that handle the HCT/P. If you do not handle the HCT/P (e.g., you are the testing laboratory that receives a blood specimen, but you do not actually handle the HCT/P), you do not have to participate in the tracking requirements.

We have also added language to clarify that the purpose of a tracking system is to facilitate the investigation of actual or suspected transmission of communicable disease and any appropriate and timely corrective action.

Finally, we have revised the tracking provisions to require a system that enables tracking to and from the consignee, rather than to and from the recipient, and have added that labeling includes information designed to facilitate effective tracking, using the distinct identification code, from the donor to the recipient and from the recipient to the donor.

(Comment 120) We received several comments in support of the proposed requirements. One comment responded to our request for comments from

establishments that have already developed and implemented tracking systems about the success or failure of those systems (66 FR 1508 at 1519). This comment described its successful tracking system and noted that tracking fulfills its ongoing responsibility to the patients who have received its tissues. The establishment provides hospitals with peeloff labels that identify each unique product and the bank that provided it, and also with tracking logs for the hospitals to use to control inventory. Information on the use of the HCT/P is returned to the tissue bank by the hospital in a self-addressed envelope and then entered into the establishment's database. The establishment sends regular reminders to hospitals notifying them of tissue for which it has not received transplant records. The comment noted that hospitals willingly participate, and it cited a high (85 to 100 percent) return of transplant records.

(Response) We appreciate this detailed information and believe it demonstrates both the feasibility and the importance of developing a functioning tracking system.

(Comment 121) Two comments argued that the proposed requirements could not be justified based on risk and were inconsistent with industry standards. The comments also asserted that the proposed tracking requirement would require collection of confidential patient information in conflict with privacy regulations issued under the Health Insurance Portability and Accountability Act (45 CFR parts 160 and 164). Those regulations were finalized on December 28, 2000 (65 FR 82462), and amended on August 14, 2002 (67 FR 53182).

(Response) We disagree. Not only are these requirements justified by the communicable disease risks posed by HCT/Ps, but they are consistent with industry standards. AATB standards require traceability and dispensing

records by the tissue dispensing service (medical, dental, hospital facility, physician's office) (See the American Association of Tissue Banks (AATB) Standards 2002, L4.000). The Eye Bank Association of America (EBAA) medical standards require that recipient identification readily traceable to each unique graft number be retained in the eye banks' records (See EBAA Medical Standards 2002, M1.400).

The proposed tracking requirements are not inconsistent with the HIPAA privacy regulation, which sets up protections for individually identifiable health information. The privacy rule applies only to "covered entities": e.g., health plans, health care clearinghouses, and health care providers conducting certain transactions in electronic form (45 CFR 164.104). HCT/P establishments subject to the tracking requirements are unlikely to meet the definition of a covered entity. Thus, the privacy regulation would not apply to their activities, and the use in product tracking of a distinct identification code by an entity that is not covered by that rule would not be subject to the privacy rule.

In the unusual event that an establishment met the definition of covered entity, the establishment's disclosure of individually identifiable health information would be subject to the privacy rule. However, the privacy rule allows covered entities to share de-identified health information for any purpose and includes requirements for determining whether information is de-identified. (45 CFR 164.502(d), 164.514(a)-(c)). Further, a covered entity may assign a code to otherwise de-identified data, if the code is not derived from or related to information about the individual and is not otherwise capable of being translated so as to identify the individual, and if the covered entity does not use or disclose the code or other means of record identification for any other purpose, and does not disclose the mechanism for reidentification

(45 CFR 164.514(c)). Thus, an establishment that is a covered entity is not in violation of the privacy rule if it discloses information de-identified in accordance with 45 CFR 164.514(a)-(c), including a distinct identification code that meets the requirements of 45 CFR 164.514(c).

Consignees are likely to meet the definition of a covered entity, and would therefore be covered by the privacy rule. However, the tracking provision does not require consignees to provide individually identifiable health information; it requires only that establishments be able to track HCT/Ps to consignees.

We note that a consignee may on occasion wish to disclose protected health information to an establishment. For example, a consignee may wish to report to the establishment that a recipient of an HCT/P developed an infection at the site of the transplant. Under the public health activities provisions of the privacy rule, the rule permits, but does not require, entities that meet the definition of a covered entity to disclose protected health information to persons subject to the jurisdiction of FDA with respect to an FDA-regulated product or activity for which that person has responsibility, for the purpose of activities related to the quality, safety or effectiveness of such FDA-regulated product or activity (45 CFR 164.512(b)(1)(iii)). The rule specifically identifies tracking FDA-regulated products as a purpose permitting such disclosures, along with collecting and reporting adverse events and enabling product recalls, repairs, replacement, or lookback (45 CFR 164.512(b)(1)(iii)(A), (b)(1)(iii)(B), and (b)(1)(iii)(C)). Finally, in the event that one of the previously mentioned provisions is not applicable, covered entities may disclose protected health information pursuant to an authorization from the individual or the individual's personal representative (45 CFR 164.502(g)(1) and 164.508). We further discuss the applicability of the privacy rules in the

context of donor eligibility in Comment 4 to the donor eligibility rule (69 FR 29786 at 29790).

(Comment 122) One comment suggested that the regulations should refer to “tracing” instead of “tracking,” to avoid confusion with device tracking.

(Response) We disagree. The term “tracking” adequately defines the operations being performed with respect to the HCT/P and is a term that is recognizable by industry.

(Comment 123) Several comments from eye banks asked for an exception for corneas that are distributed internationally, noting the difficulty of obtaining information on recipients. One of these comments asked that the consignee’s signature and intended disposition be acceptable.

(Response) We decline to grant an exception for corneas that are distributed internationally. However, we note that the tracking requirements in § 1271.290 do not require tracking to the recipient level, but rather to the consignee. In the case of international distribution, obtaining the consignee’s signature and intended disposition is acceptable.

(Comment 124) Two comments asserted that it would be impossible to comply with proposed § 1271.290 unless all establishments adopt a uniform tracking method, and further opined that many vendors may elect not to participate in tracking due to the potential disclosure of proprietary information.

(Response) We disagree with these comments. We prefer to provide establishments with flexibility in complying with § 1271.290, and for that reason we decline to mandate a uniform tracking method. It is unclear why it would be impossible to comply with the requirement in the absence of uniformity. It is also unclear what proprietary information would be disclosed

via a tracking system. However, we note that each establishment has the choice of maintaining its own tracking method or participating in the system developed by another establishment; a vendor who shares the concerns expressed by these comments may choose not to participate in another establishment's tracking system. We have revised § 1271.290 to clarify that a "system" involves the tracking of an HCT/P from the donor to the consignee or from the consignee to the donor; and that a "method" is an action that enables tracking.

(Comment 125) One comment on proposed § 1271.290(b) asserted that a single designated establishment should collect tracking information and maintain the entire history of collection, processing, and release. Another comment argued that tracking responsibilities should be placed on the entity that makes the product available for distribution, and that subsequent entities (i.e., distributors) should be allowed to follow that entity's existing tracking procedures.

(Response) Section 1271.290(b) provides establishments with the flexibility to participate in the tracking system set up by another establishment, provided that the system complies with all requirements in this section. However, the responsibility lies with each establishment involved in the manufacture of an HCT/P. For example, if only the establishment that made the HCT/P available for distribution were responsible for tracking, establishments "upstream" would not necessarily participate. This would not enable tracking from donor to consignee because the distributor would not have the information for linking the consignee to the donor, since the establishment performing recovery would be the only entity that would know the identity of the donor.

(Comment 126) Proposed § 1271.290(c) would require establishments to ensure that each HCT/P that it manufactures is assigned and labeled with a distinct identification code that relates the HCT/P to the donor and to all records pertaining to the HCT/P. One comment on this provision asked us to clarify that a single identification code may be used for an entire lot of morselized structural tissue of the same type from the same donor, even if the lot is distributed in more than one immediate container.

(Response) We agree with this comment's interpretation of the regulation.

We have added to paragraph (c) the requirement that labeling include information designed to facilitate effective tracking, using the distinct identification code, from the donor to the recipient and from the recipient to the donor. Although § 1271.290 does not require establishments to establish a tracking system from the recipient to the donor and from the donor to the recipient, this labeling requirement will enable such tracking to be performed. An example of a labeling statement that would comply with this requirement is: "IMPORTANT NOTICE TO END-USER: Please record this distinct identification code in your records and in the patient's file."

(Comment 127) One comment asked us to permit tracking from production lot rather than from donor. This method would apply to lot-processed or batch-processed products manufactured using a validated sterilization method.

(Response) We decline to modify the regulation to make the requested change. However, we would consider a request for an alternative submitted under § 1271.155. The requestor should show that the proposed alternative tracking method satisfies the purposes of the requirement in § 1271.290(e).

(Comment 128) Proposed § 1271.290(d) would require an establishment to ensure that the identifier and type of HCT/P that is implanted into a recipient

be recorded in the recipient's medical records, or in other pertinent records, to enable tracking from the recipient to the donor.

One comment asserted that the manufacturer has no authority over the content of the medical record and suggested that the manufacturer provide paper documentation appropriate for the medical record and notice of the Federal regulations requiring that the information be placed in the medical record. Another comment asserted that, because of tissue establishment's inability to mandate hospital compliance, FDA should revise proposed § 1271.290(d) to allow tracking to the production lot, or eliminate the provision altogether.

(Response) We have revised paragraph (d) to remove the requirement for ensuring that information on an HCT/P is recorded in a recipient's medical records or other pertinent records. That paragraph now requires an establishment to establish and maintain a method for recording the distinct identification code and type of each HCT/P distributed to a consignee to enable tracking from the consignee to the donor.

In response to Comment 126, we discuss the new requirement in paragraph (c) for label information designed to facilitate tracking between recipient and donor.

(Comment 129) Proposed § 1271.290(e) would require establishments to document, and maintain records of, the disposition of each HCT/P, to enable tracking from the donor to the recipient or final disposition. This information must permit the prompt identification of the recipient of the HCT/P, if any.

One comment asked us to specify an acceptable timeframe for the identification of the recipient. Another comment asked whether, with regard to "prompt" identification, the name and hospital or social security number

are sufficient information to allow identification. A third comment suggested requiring tracking, not to the recipient, but to the distributor, transplant facility, or transplanting surgeon, as appropriate. This comment asserted that neither tissue banks nor the agency has the authority to mandate hospital or physician compliance with the tissue banks request for recipient information.

(Response) FDA agrees that it cannot mandate hospital or physician compliance, and we have revised paragraph (e) to require tracking to the consignee, rather than to the recipient. However, as described in Comment 119, we note that successful tracking systems have been implemented, in which hospitals readily participate. In addition, hospitals accredited by the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) are required to keep records that permit tracking of any tissue from the donor or source facility to all recipients or other final disposition. (Joint Committee, 2000–2001, “Comprehensive Accreditation Manual for Pathology and Clinical Laboratory Services,” pp. QC 36–37.)

We decline to specify a timeframe for the identification of the consignee, because the timeframe may vary with the circumstances.

(Comment 130) One comment asked for a clarification of the term “consignee.” This comment asked whether a hospital that receives an HCT/P is considered the consignee, or if the surgeon who uses the HCT/P is the consignee.

(Response) Either or both parties may be the consignee, depending on the particular situation. Generally, the person and/or entity to which an HCT/P is distributed would be considered the consignee.

(Comment 131) Proposed § 1271.290(f) would require establishments, at or before the time of distribution of an HCT/P, to inform the consignee in

writing of the regulatory requirements and of the tracking method that the establishment has put into place. The establishment would also be required to document that the consignee agreed to participate in its tracking method and to take all necessary steps to ensure compliance with the requirements of § 1271.290.

Several comments questioned how proposed § 1271.290(f) would work. One comment asked whether a signed agreement would have to be obtained before sending the tissue, and noted that this would be difficult. This comment also asked who should be authorized to sign the agreement. Another comment noted that it sends a “tissue usage form” with its tissues, but that many facilities do not return the form; this comment further noted that a contract does not always exist between a tissue bank and the end user. Several comments asserted that tissue banks lack the authority or means to ensure compliance with the regulation and should not be held responsible for gathering tracking information, and one comment asked how far an eye bank must go to demonstrate that it has attempted to obtain an agreement from the consignee. One comment stated that a tissue facility cannot and should not withhold tissue for a prior failure of a facility to provide required documentation, and that if it did so, another source of tissues would be sought.

One comment expressed concern that: (1) Establishments may develop agreements that are least burdensome rather than most effective; (2) an establishment would not be able to provide an HCT/P to a consignee in an emergency until the consignee developed a tracking system; (3) the tracking requirements conflict with the new privacy rules, because a tissue establishment must review recipient records to ascertain whether a consignee maintained an adequate system; (4) patients change practitioners or localities

without providing their new addresses; and (5) it would be unwieldy and unrealistic for an establishment with thousands of consignees to take all necessary steps to ensure their compliance.

(Response) We have removed the requirement in proposed paragraph (f) to obtain agreement from a consignee to participate in an establishment's tracking system.

19. Complaint Files (§ 1271.320)

Proposed § 1271.320 would require each establishment to establish and maintain procedures for the prompt review, evaluation, and documentation of all complaints, and the investigation of complaints as appropriate. We defined "complaint" in proposed § 1271.3(ii) and have made several changes to that definition, now renumbered § 1271.3(aa), which are discussed at Comment 13.

We have revised § 1271.320 so that its requirements relate to the core CGTP requirements.

(Comment 132) One comment asked us to clarify the meaning of "promptly."

(Response) We expect complaints to be investigated quickly enough to meet the reporting requirements, in case the complaint necessitates reporting. However, because the interpretation of the term "promptly" is somewhat vague, we have replaced "promptly" in paragraph (c) with "as soon as practical."

(Comment 133) Two comments raised concerns about the requirement in proposed § 1271.320(b) that confidential complaint files be made available for review and copying upon request from an authorized FDA employee.

(Response) We recognize the comments' concerns about maintaining donor and patient confidentiality. When copying complaint files, the agency will take

steps to protect the identity of the donor or patient in conformance with 21 CFR parts 20 and 21.

*D. Part 1271, Subpart E—Additional Requirements for Establishments
Described in § 1271.10*

1. Applicability (§ 1271.330)

Proposed § 1271.330 explained that the regulations in subpart E would be applicable only to HCT/Ps described in § 1271.10, i.e., regulated solely under section 361 of the PHS Act and the regulations in part 1271.

We received no comments on this section. We have, however, modified § 1271.330 to state that the provisions in subpart E (on reporting and labeling) are currently being implemented only for nonreproductive HCT/Ps described in § 1271.10 and regulated solely under 361 of the PHS Act and the regulations in this part, and the establishments that manufacture them.

2. Reporting Requirements (§ 1271.350)

Proposed § 1271.350(a) sets out requirements for reporting adverse reactions, and § 1271.350(b) deals with reports of product deviations (now called “HCT/P deviations”).

(Comment 134) One comment on proposed § 1271.350 stated that the section is unnecessarily burdensome because a professional organization already requires reporting, and requested “deemed status” for that organization.

(Response) We disagree that these reporting requirements are duplicative. Reporting to professional organizations is not required under these regulations. More importantly, we do not receive reports of adverse reactions and HCT/P deviations from professional organizations.

Adverse Reaction Reporting (§ 1271.350(a))

(Comment 135) Several comments asserted that our authority to require adverse reaction reports is limited to those that involve the transmission of communicable disease or product contamination. Three comments requested that reportable adverse reactions be defined, for corneas, as any communicable or other disease transmitted by and attributable to transplantation of donor eye tissue, including infection and biologic dysfunction, and any systemic infectious disease that develops in a recipient. One comment requested that the rule be revised to take into account that transplants can be rejected or cause reactions such as graft-versus-host disease.

(Response) You are now required to investigate any adverse reaction involving a communicable disease. You must make a report if the adverse reaction meets one of the criteria set out in § 1271.350(a)(1). We decline to set out specific requirements for corneas but note that the situations described in the comments would meet the requirements in § 1271.350(a) for reporting adverse reactions. Problems not connected with communicable disease transmission are not required to be reported e.g., primary graft failure.

(Comment 136) One comment suggested limiting reporting requirements to adverse reactions “directly related to the product” to reflect that an HCT/P establishment is not responsible for reporting communicable disease transmission from other sources (e.g., blood products administered during surgery).

(Response) We decline to make the suggested change. It may take longer than 15 days for an establishment to determine whether or not an adverse reaction is directly related to an HCT/P. For the protection of the public health, it is more important for information about the transmission of a communicable

disease or HCT/P contamination to be reported to us within 15 days, even if further followup indicates that communicable disease transmission came from a source other than the HCT/P.

However, we note that in cases where there is no reasonable possibility of a relationship between an unintended and noxious response and the HCT/P, then the event would not be considered an adverse reaction under § 1271.3(y), and reporting would not be required under § 1271.350(a).

(Comment 137) One comment asked whether, if the investigation of a complaint points to a cause other than a failure of an eye bank's good tissue practice, the eye bank is required to report these results.

(Response) If immediate investigation indicates that there is not a reasonable possibility of a relationship between an unintended and noxious response and the HCT/P, then the event is not considered an adverse reaction and you are not required to report it. If, however, there exists a reasonable possibility that the HCT/P caused the event, then the event is an adverse reaction and it may be reportable under § 1271.350(a). If, after you have made a required report, you discover additional information, you must report this information to the agency under § 1271.350(a)(3) within 15 calendar days of receipt of the new information. If your investigation determines that the HCT/P did not cause the unintended and noxious response, then you must submit this information to FDA.

(Comment 138) Proposed § 1271.350(a) would require you to make reports of adverse reactions to us within 15 calendar days of the initial receipt of the information. Several comments suggested extending this timeframe to 30 days to allow for more thorough follow-up; one comment suggested 30 to 60 days;

and another comment suggested 30 days, in the absence of death or disease transmission.

(Response) We disagree with these comments. The timeframe set out in § CFR 1271.350(a) is consistent with adverse reaction reporting requirements for other regulated products (see 21 CFR 314.80 and 600.80; Medical Device Reporting is required within 10 days (21 CFR 803.10)). The adverse reactions that must be reported to the agency under § 1271.350(a) warrant action in less than 1 or 2 months. It is reasonable for us to require reporting without delay of an adverse reaction that is fatal or life-threatening, results in permanent impairment of a body function or permanent damage to body structure, or necessitates medical or surgical intervention, including hospitalization. We recognize that followup may be appropriate, and § 1271.350(a)(3) sets out procedures for submitting new information to the agency or responding to an agency request for additional information.

(Comment 139) Several comments objected to the breadth of the proposed requirement for reporting cases where medical or surgical intervention is required. Two comments suggested adding the phrase “to preclude permanent impairment of a body function or permanent damage to a body structure” for consistency with medical device reporting regulations (see § 803.3(bb)).

(Response) We decline to make the suggested change because the communicable disease risks with HCT/Ps are different from the types of risks associated with most medical devices. It is important for FDA to know of infections that may have been caused by HCT/Ps even if permanent impairment of a body function or permanent damage to a body structure is not likely, because such infections may alert us to broader issues (e.g., a positive donor who was the source of additional HCT/Ps; CGTP failures in the

establishment). For this reason, we would generally consider that an infection at the site of a transplant would be reportable under § 1271.350(a).

(Comment 140) One comment stated that it is unclear which establishment must report adverse reactions to FDA.

(Response) Any establishment that receives information (e.g., through a complaint) about an adverse reaction related to an HCT/P that it made available for distribution must comply with § 1271.350(a). We have inserted this language into § 1271.350(a) for clarity.

(Comment 141) One comment noted that it may be important to specify the need to facilitate, encourage, and even solicit adverse reaction information by establishments themselves. The comment further noted that the probability of receiving this information may be determined in part by the presence or absence of a well-defined active followup program implemented by the establishment.

(Response) We agree with this comment and encourage establishments to develop programs to help them comply with the reporting requirements in § 1271.350.

HCT/P Deviation Reporting (§ 1271.350(b))

(Comment 142) One comment on proposed § 1271.350(b) asserted that the regulation should not require reporting of minor or unimportant deviations. Two comments criticized the proposed reporting requirement as burdensome and questioned the agency's capacity to review submitted reports. These comments suggested limiting reports to instances involving issues of disease transmission.

(Response) We have modified the proposed definition of HCT/P deviation. An HCT/P deviation as defined in § 1271.3(dd) is limited to an event that

represents a deviation from applicable regulations or established specifications that may relate to the prevention of communicable disease transmission or HCT/P contamination; or that is an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease or may lead to HCT/P contamination.

(Comment 143) Two comments asked for clarification of whether deviations must be reported if the HCT/P is not distributed.

(Response) As in the proposed rule, reporting of HCT/P deviations is required only when the involved HCT/P has been distributed.

We have also clarified that the establishment must investigate all HCT/P deviations related to a distributed HCT/P for which the establishment performed a manufacturing step.

(Comment 144) One comment suggested changing the requirement to report “as soon as possible” to a maximum reporting period of 45 days.

(Response) We agree with this comment and have made the suggested change. In this regard, we wish to emphasize that HCT/P establishments should not wait to report deviations until after completing their corrective actions. Rather, HCT/P establishments should submit deviation reports as soon as possible but no later than 45 days after the date that the establishment first discovers information reasonably suggesting a reportable event has occurred. The reports should include information on the intended followup to be taken if followup is not completed prior to submission of the report.

(Comment 145) One comment pointed out discrepancies between proposed § 1271.350(b) and the biologic product deviations final rule, and suggested that reporting requirements be harmonized.

(Response) We have largely harmonized § 1271.350(b) with § 600.14(b), as suggested by the comment. In addition, we have clarified in § 1271.350(b)(2) your obligation to report an HCT/P deviation relating to the core CGTP requirements, if the HCT/P deviation occurs in your facility or in a facility that performs a manufacturing step for you under contract, agreement, or other arrangement. The establishment responsible for reporting HCT/P deviations relating to the core CGTP requirements would receive the necessary information from a contract establishment in accordance with § 1271.160(b)(2).

3. Labeling (§ 1271.370)

Proposed § 1271.370 would have required clear and accurate labels for each HCT/P.

Proposed § 1271.370 would apply only to 361 HCT/Ps; HCT/Ps regulated as drugs, devices, and/or biological products are subject to labeling requirements currently in place. The regulations under 21 CFR parts 201 and 610 will apply to HCT/Ps regulated as drugs and/or biological products, as will relevant statutory provisions and any conditions of product licensure or approval. HCT/Ps regulated as devices are subject to the labeling requirements in 21 CFR part 801, in addition to the provisions of the act and any applicable conditions of approval or clearance. In the proposed rule, we proposed to interpret several current regulations as encompassing the information set out in proposed § 1271.370(a), and stated that we would expect the information listed in that section to appear on the label or package insert of those products regulated as biological drugs or devices (66 FR 1508 at 1522). We received no comments on this proposal.

To coordinate with the requirement in § 1271.290(c) that you label each HCT/P with a distinct identification code, we have added to § 1271.370 the requirement that this code be affixed to the HCT/P container.

(Comment 146) One comment stated that the required label information would not fit on vials and requested that this information be permitted on labeling. Another comment asserted that putting the name and address of the establishment that determined donor eligibility on the label would breach donor/recipient confidentiality and suggested that this information appear instead in the package insert.

(Response) The establishment name and address information is important to enable traceability if needed. However, we recognize the difficulty in fitting this information on the HCT/P label, and we have changed the regulation in § 1271.370(c) to require that this information must either appear on the HCT/P label or accompany the HCT/P. We also note that when we use the term “label” in this subpart, we mean either: (1) Affix to the HCT/P container, or (2) attach a tie-tag with the appropriate information to the container.

(Comment 147) Proposed § 1271.370(a)(3)(ii) would require warnings on the label or package insert, where appropriate. One comment stated that guidance is needed on “warnings.”

(Response) In §§ 1271.60, 1271.65, and 1271.90 of the donor-eligibility final rule, we now require warning statements related to informing the recipient about certain unusual circumstances, e.g., “WARNING: Advise patient of communicable disease risk” when an HCT/P is distributed before completion of the donor eligibility determination. These warning statements must appear on the HCT/P label. In addition, the establishment should determine what other information the user needs to know before using an HCT/

P; this information would be considered “other warnings” (we have revised § 1271.370(c)(3)). Other warnings would include information about risks resulting from procedures to reduce communicable disease risks during the manufacture of an HCT/P. An example would be a warning that the product was processed aseptically and is not sterile (e.g., may harbor microorganisms).

Because certain warnings are required to appear on the label itself, we have added § 1271.370(b)(4), which lists, as information that must appear on the label, warnings required under § 1271.60, § 1271.65, or § 1271.90, if applicable.

(Comment 148) One comment stated that some of the labeling provisions exceed the statutory authority because the relationship to communicable disease transmission is too attenuated.

(Response) We have revised § 1271.370 to strengthen the connection between the labeling requirements and the prevention of communicable disease. For example, § 1271.370(c)(4) now requires instructions for use when related to the prevention of the introduction, transmission, or spread of communicable diseases. Other information we have required to be included in the labeling is intended to facilitate proper use and tracking of the HCT/P; both are essential to prevent the spread of communicable disease. We have removed proposed paragraph (b); § 1271.370 no longer covers claims.

(Comment 149) One comment on proposed § 1271.370(b) asserted that HCT/Ps with claims for reconstruction or repair should be regulated under section 351 of the PHS Act because it cannot be assumed, in the absence of substantial clinical evidence, that these products perform as intended. The comment provided as an example autologous expanded cartilage.

(Response) As previously noted, we have removed the proposed provision on claims from § 1271.370. However, the comment's scope extends beyond the proposed language, and for that reason we note our disagreement. HCT/Ps with claims for "reconstruction or repair" can be appropriately regulated solely under section 361 of the PHS Act if such HCT/Ps meet all of the criteria in § 1271.10, including minimal manipulation and homologous use. To further clarify this point, we have added the terms "repair" and "reconstruction" to the definition of "homologous use" under § 1271.3(c).

The example provided by the comment is not appropriate. Autologous expanded cartilage cells are not regulated solely under section 361 because they are more than minimally manipulated when they are cultured and, thus, do not meet the criteria in § 1271.10.

(Comment 150) Two comments asserted that proposed § 1271.370(b)(2) is unnecessary and could create confusion regarding the definition of homologous use. These comments suggested removing the paragraph in question and allowing the existing definition of "homologous use" to stand as the sole definition.

(Response) We agree with this comment and have removed the proposed paragraph on claims from § 1271.370. "Homologous use" is defined in § 1271.3(c)(the registration final rule) as "the replacement or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor." As previously noted, we have added reconstruction and repair to the definition of "homologous use" under § 1271.3(c).

(Comment 151) One comment asserted that we should clarify this rule to identify examples of homologous use claims.

(Response) This rule no longer contains language relating to homologous use claims. However, we take this opportunity to note that the examples of homologous and nonhomologous claims given in the registration final rule are still valid, with one exception (see 66 FR 5447 at 5458). After reviewing additional data from one manufacturer, we now consider the use of that manufacturer's minimally manipulated amniotic membrane alone for ocular repair as homologous. However, when amniotic membrane is combined with limbal stem cells, such an HCT/P is regulated under section 351 of the PHS Act.

E. Part 1271, Subpart F—Inspection and Enforcement of Establishments Described in § 1271.10

1. Applicability (§ 1271.390)

Proposed subpart F of part 1271 contains provisions on inspections; HCT/Ps offered for import; and orders of retention, recall, destruction, and cessation of manufacturing. Subpart F would apply only to those establishments described in § 1271.10 (i.e., those establishments that manufacture HCT/Ps regulated solely under the authority of section 361 of the PHS Act and the regulations in part 1271, and not as drugs, devices, and/or biological products). We received no comments on this section.

2. Inspections (§ 1271.400)

Proposed § 1271.400 would require an establishment to permit an authorized representative of FDA at any reasonable time and in a reasonable manner to inspect the establishment.

(Comment 152) In the proposed rule, we invited comments on possible alternative inspection and enforcement provisions that would leverage our

resources, be cost-effective, and achieve the public health goals of the proposed rule (66 FR 1508 at 1523). We received four comments in response to this request. These comments suggested third-party inspections, training of FDA representatives by professional organizations, and special recognition for accreditation.

(Response) We appreciate these helpful comments. Instituting a third-party inspectional process would require additional resources (for startup) and would also require that establishments have an inspectional history. Because many HCT/P establishments do not have an inspectional history, and because of resource limitations, we decline to adopt this approach at present. However, we intend to reconsider the idea in the future.

The suggestion that the agency and industry organizations partner to train FDA representatives is also a good idea, and would represent the continuation of existing FDA practice. To date, both EBAA and AATB have participated in regional training courses for FDA representatives, and we hope to continue this useful practice.

The suggestion that special recognition be given to establishments that are accredited by a professional association has already been implemented, in that we give establishments that are not accredited a higher priority for inspection.

(Comment 153) One comment suggested amending § 1271.400 to require that FDA representatives be appropriately trained to examine establishments that manufacture HCT/Ps according to the type of tissue manufactured by the facility.

(Response) We decline to modify § 1271.400 as suggested. FDA representatives receive significant training on an ongoing basis, and they will continue to do so.

(Comment 154) One comment expressed concern that inspections would disrupt the practice of reproductive medicine.

(Response) FDA inspections involve document review; interviewing employees; and physical inspection of equipment, products, labeling, facilities, and operations. We conduct these activities in a manner that is as unobtrusive as possible, and our expectation is that an establishment will be able to conduct business as usual during the course of an inspection. FDA has extensive experience conducting inspections in a variety of clinical settings (e.g., hospital bloodbanks performing time-critical activities and confidential donor screening).

We recognize and understand that responsible personnel at times may be involved in procedures that make them temporarily unavailable to the FDA representative. In this situation, the FDA representative will perform some other aspect of the inspection that does not require the responsible person's presence until that person is again available to be interviewed.

Inspections will focus on assessing compliance with applicable requirements; to make this clear, we have added the word "applicable" to the first sentence of § 1271.400(a). For example, the inspection of an establishment that engages solely in processing would address processing-related requirements, rather than donor testing and screening. With respect to establishments that manufacture reproductive HCT/Ps regulated solely under section 361 of the PHS Act and these regulations, an inspection would be limited to issues of compliance with the donor-eligibility requirements contained in subpart C of this part, but would not consider compliance with the requirements in subparts D and E.

(Comment 155) One comment stated that it is not appropriate for the interpretation of SOPs and the validation of tissue banks to be subject to the individual regulatory representative's judgment and that a more standard approach is needed.

(Response) We agree with the concerns expressed by this comment, and note that for several years FDA has used a standard approach for tissue establishment inspections. Compliance Program 7341.002 (Inspection of Tissue Establishments) provides standard inspectional, regulatory, and administrative guidance to all FDA representatives involved in conducting inspections of human tissue establishments and to management personnel who evaluate the results of those inspections. FDA representatives evaluate the adequacy of a firm's SOPs and process validation or verification on site. All observations they may record on a Form FDA-483 are subject to further review by FDA management, to ensure consistency with FDA regulations, before any regulatory action is taken. The firm can respond to items recorded on the Form FDA-483 during the discussion with the FDA representative at the conclusion of the inspection or subsequently in writing, if the firm wishes to do so.

(Comment 156) Two comments on proposed § 1271.400(a) requested that we provide from 1 to 5 days notice before an inspection.

(Response) FDA has tried a variety of announced and unannounced inspection procedures in the past. Our current practice is generally not to preannounce inspections because such a commitment affects the overall productivity of field staff. An establishment must be in compliance at all times, which should make it unnecessary to preannounce an inspection for the establishment to "prepare" for an inspection. For clarity, we have modified

the language of the final regulation to state that an inspection may be made with or without “prior notification.”

(Comment 157) Proposed § 1271.400(c) states that FDA’s representative will call upon the most responsible person available at the time of an inspection. Three comments requested that this representative be the executive director or a person functioning in that position at the time of the inspection. One comment pointed out that eye banks are usually small and that key staff may be out of the bank performing other duties.

(Response) We decline to modify the regulation as requested. Firms should have a plan in place to instruct their staff exactly who would accompany an FDA representative in the absence of the most responsible person. The FDA representative will determine whether or not a meaningful inspection can be conducted, given the available personnel.

(Comment 158) Proposed § 1271.400(c) also states that the FDA representative conducting an inspection may question the personnel of the establishment, as the representative deems necessary. One comment objected to the exercise of our discretion, if unfettered, to question any employee and stated that, historically, FDA has allowed companies to designate spokespeople. Another comment asserted that FDA should question a senior official who is well acquainted with the SOPs of the facility (not just the most responsible person available).

(Response) It is agency practice for the FDA representative conducting an inspection to observe and interview employees to determine if they are performing their various functions in accordance with the firm’s current SOPs, to determine if activities are being documented concurrently with the performance of each significant step, and to evaluate if employees are properly

trained and supervised. We agree that it is a good idea to make a spokesperson available to accompany the FDA representative and provide historical, statistical, and administrative information about the company. All employees at an establishment should be well acquainted with the SOPs related to their work in that establishment.

(Comment 159) Under proposed § 1271.400(d), FDA's representative may review and copy any records required to be kept under part 1271 and may take photographs or make videotapes. One comment questioned FDA's intentions with respect to records of quality assurance activities. Another comment asked that this section be revised to exempt from FDA review records of management review, quality audits, supplier evaluations, and other types of information (e.g., financial). One comment suggested new language limiting reproduction to data that would relate to possible communicable disease transmission and/or biologic dysfunction of tissue.

(Response) The FDA representative may review and copy any records required to be kept under part 1271. Financial records and personnel records are not required records under part 1271. Given the scope of the requirements in part 1271 and their focus on preventing the introduction, transmission, or spread of communicable disease, it is unnecessary to limit § 1271.400 as suggested. With respect to quality audits, while some firms choose to provide quality audits to FDA, FDA's current practice is generally not to request or copy the actual quality audit reports except in certain limited circumstances (FDA Compliance Policy Guide 130.300). However, the firm should have a mechanism to demonstrate to the FDA representative that quality audits are being performed and that corrective actions are being implemented when problems have been identified.

(Comment 160) Several comments questioned the provisions of proposed § 1271.400(d) on photography and videos. Two comments questioned the agency's authority to do so.

(Response) FDA's practice is to record images (e.g., by way of photographs or videotapes) to accurately record the conditions in an establishment. These tools may be employed as long as the inspection is lawful. See *United States v. Gel Spice Co.*, 601 F. Supp. 1214, 1220 (E.D.N.Y. 1985); *United States v. Acri Wholesale Grocery Co.*, 409 F. Supp. 529, 532–533 (S.D. Iowa 1976). Inspections conducted under regulations issued under section 361 of the PHS Act are lawful. However, we have modified the wording of § 1271.400(d) to delete the specific references to photographs and videotapes, and to state instead that FDA's representatives may use other appropriate means to record evidence of observations during inspections conducted under this subpart.

FDA also has the authority to take samples to support observational findings. To clarify this previously implied capability, we have added to § 1271.400(d) that FDA also may take samples.

4. Imports (§ 1271.420)

When an HCT/P is offered for entry, proposed § 1271.420 would require the importer of record to notify the director of the district of the FDA having jurisdiction over the port of entry. The HCT/P would be held intact until it is released by FDA.

We have made several revisions to § 1271.420(a) and (b) for clarity and for consistency with agency import policy. We have replaced the phrase “offered for entry” with the more accurate phrase, “imported or offered for import.” Consistent with other agency regulations, HCT/Ps “imported or offered for import” include, not only those HCT/Ps imported or offered for

import into the United States for use, storage, or distribution in the United States, but also those imported or offered for import for transshipment through the United States to another country, for future export, or for use in a United States Foreign Trade Zone. (See, e.g., “Prior Notice of Imported Food Under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002,” interim final rule, 68 FR 58974 at 58990 and 58991, October 10, 2003.)

We have specified in paragraph (a) that notification of the director of the FDA district having jurisdiction over the port of entry may occur either before or at the time of importation. The term “port of entry” is defined in 19 CFR 101.1 as any place designated by Executive order of the President, by order of the Secretary of the Treasury, or by act of Congress, at which a Customs officer is authorized to accept entries of merchandise, to collect duties, and to enforce the various provisions of the Customs and navigation laws. To make certain that importers understand our expectations (e.g., accompanying records required under § 1271.55, and entry information required by United States Bureau of Customs and Border Protection), we have added the requirement that the importer of record must provide sufficient information for FDA to make an admissibility decision.

Finally, we have replaced the phrase in proposed paragraph (b), “until it is released by FDA,” with “until an admissibility decision is made,” which more accurately reflects FDA’s actions.

(Comment 161) One comment suggested the addition of language to clarify that the regulation only applies to HCT/Ps “intended for clinical use.”

(Response) We agree that § 1271.420 applies only to HCT/Ps intended for clinical use, but we do not consider it necessary to modify the regulation as

suggested. The regulations in part 1271 do not apply to establishments that use HCT/Ps solely for nonclinical scientific or educational purposes (§ 1271.15(a)); moreover, § 1271.3(d) defines an HCT/P as intended for implantation, transplantation, infusion, or transfer into another human (i.e., clinical use).

(Comment 162) One comment requested an exemption for reproductive HCT/Ps imported under the authority of the owner of the reproductive materials.

(Response) We have modified § 1271.420 to except from its provisions reproductive HCT/Ps regulated solely under section 361 of the PHS Act and the regulations in this part, and donated by a sexually intimate partner of the recipient for reproductive use. (See § 1271.420(c).)

(Comment 163) One comment asked about the relationship between the proposed FDA inspection and inspections of hematopoietic stem/progenitor cells currently performed by other agencies, such as the Department of Transportation (DOT).

(Response) The inspection that FDA will conduct with respect to imported HCT/Ps is distinct from inspections conducted by other agencies. For example, DOT inspects for compliance with its labeling and packaging regulations, whereas FDA inspects for compliance with the regulations that require accompanying documentation and labeling information about donor screening and testing.

(Comment 164) Proposed § 1271.420(b) would require that an HCT/P offered for import must be held intact until it is released by FDA. Four comments on this provision raised strong objections to this provision because of its potential adverse effect on imported hematopoietic stem/progenitor cells.

These comments asserted that any delay is life-threatening and that these HCT/Ps should be immediately cleared through customs.

(Response) Prior to infusion, recipients of peripheral blood stem/progenitor cells undergo a myeloablative treatment regimen (i.e., high dose chemotherapy and total body irradiation), which may have begun before importation takes place. We agree with the comments' concerns about the risk of delay in this situation and have accordingly revised § 1271.420. Section 1271.420(d) states that this section does not apply to peripheral blood stem/progenitor cells regulated solely under section 361 of the PHS Act and the regulations in this part, except that paragraphs (a) and (b) apply when circumstances occur under which such imported peripheral blood stem/progenitor cells may present an unreasonable risk of communicable disease transmission, which indicates the need to review the information referenced in paragraph (a). We believe this provision affords access to peripheral blood stem/progenitor cells and appropriate public health protection. We also believe that situations in which information would be needed for review under paragraph (a) will be rare or unlikely to occur. Because the regulations in subpart F apply only to those HCT/Ps regulated solely under section 361 of the PHS Act and the regulations in part 1271, the exception in paragraph (d) affects only the subset of peripheral blood stem/progenitor cells that are regulated in this way (e.g., those for autologous use, or allogeneic use in a first-degree or second-degree blood relative). In the event that issues arise with respect to imports of peripheral blood stem/progenitor cells that are regulated as biological drugs, and so are subject to the import provisions in section 801 of the act (21 U.S.C 381), we would consider those issues and take appropriate actions.

Consideration of these comments has led us to make a clarification to § 1271.420(b) that will apply to HCT/Ps that are not excepted from these import provisions. Paragraph (b) states that an HCT/P offered for import must be held intact by the importer or the consignee, under conditions necessary to prevent transmission of communicable disease, until an admissibility decision is made by FDA. Under paragraph (b), the HCT/P may be transported under quarantine to the consignee, while FDA reviews the documentation accompanying the HCT/P. While the HCT/P is being held intact pending an admissibility determination, under conditions that prevent the transmission of communicable disease, the HCT/P cannot be manipulated in any way or administered. If the FDA district office determines that the entry is in compliance with the appropriate FDA regulations, the district office will notify the importer of record. Under paragraph (a), the importer can facilitate the entry process by notifying the FDA district office before the actual import occurs.

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

Proposed § 1271.440 describes the procedures FDA would use to issue orders for the retention, recall, and destruction of HCT/Ps and for the cessation of manufacturing operations. Under the proposed rule, we would issue such orders upon an agency finding that an HCT/P or establishment is in violation of the regulations in subparts C and D.

(Comment 165) Several comments asserted that these enforcement actions are too dramatic and far-reaching. One comment argued that the standard for taking these actions should be higher than mere CGTP deficiencies and should involve imminent danger to public health. One comment asserted that the

regulation should define procedures to be followed to protect the rights of the manufacturer to due process.

(Response) We disagree with the view that the proposed enforcement procedures for noncompliance with CGTP regulations are too dramatic and far-reaching. However, to address the concerns raised in these comments, FDA has revised the proposed procedures for serving upon an establishment an order to cease manufacturing. We have clarified that an order to cease manufacturing will be effective immediately only when the agency finds that there are reasonable grounds to believe that there is a danger to health. In other circumstances, the order will be effective after one of the following events, whichever is later:

- Passage of 5 working days from the establishment's receipt of the order;

or

- If the establishment requests a hearing in accordance with paragraph (e) and part 16 (21 CFR part 16), a decision in, and in accordance with, those proceedings.

FDA reiterates that, as stated in § 1271.440(e), part 16 provides an opportunity to request a hearing concerning any matter related to orders of retention, recall, destruction, and cessation of manufacturing of HCT/Ps (§ 16.1(b)(2)). Part 16 permits FDA to

* * * take such action pending a hearing * * * as the Commissioner concludes is necessary to protect the public health, except where expressly prohibited by statute or regulation. A hearing to consider action already taken, and not stayed by the Commissioner, will be conducted on an expedited basis. (Emphasis added).

(§ 16.24(d))

If FDA issues an order to cease one or more steps in the manufacture of an HCT/P, or issues an immediately effective order to retain, recall, and/or

destroy the HCT/P, and the Commissioner of Food and Drugs (the Commissioner) does not stay the order upon receiving a hearing request, FDA will provide an opportunity for an expedited hearing. (See § 1271.440(e).) As a technical amendment, we are revising § 16.1(b)(2) by adding § 1271.440(e).

(Comment 166) One comment stated that these enforcement actions should relate to a violation that may result in communicable disease transmission.

(Response) We agree. This final rule, issued under the authority of section 361 of the PHS Act, is intended to help prevent the introduction, transmission, or spread of communicable disease. In response to this comment, we have revised paragraph (a) to state that a violative HCT/P includes an HCT/P that is infected or contaminated so as to be a source of dangerous infection to humans. We have also revised that paragraph in two other ways. Rather than simply referring to an HCT/P or an establishment “in violation of the regulations of this part,” the regulation now refers to

* * * reasonable grounds to believe that an HCT/P is a violative HCT/P because it was manufactured in violation of the regulations in this part and, therefore, the conditions of manufacture of the HCT/P do not provide adequate protections against risks of communicable disease transmission * * * or an establishment is in violation of the regulations in this part and, therefore, does not provide adequate protections against the risks of communicable disease transmission.

(Comment 167) One comment asked for clarification of the term “recall” and suggested that “notification” might be a more appropriate term in cases where the tissue has already been transplanted.

(Response) Recall is an effective method of removing or correcting consumer products that are in violation of laws administered by FDA (§ 7.40(a)) (21 CFR 7.40(a)). Public notification is an important part of a recall strategy (see 21 CFR 7.50), especially where physical recall may be impossible

or impractical. Guidelines on voluntary recalls, including public notification, are set out in §§ 7.40 through 7.59 (21 CFR 7.40 through 7.59). To the extent applicable, FDA follows the same policy regarding notifications for mandatory recalls. The term “recall” encompasses all elements of a recall strategy, including notification, and no change to the rule is necessary.

(Comment 168) One comment noted that issuance of a recall or destruction order creates a potential for raising public alarm, and suggested the addition of a new paragraph requiring FDA to conduct a followup investigation to determine the reasonableness and necessity of its initial findings.

(Response) Concerns about raising public alarm upon issuance of an order of recall or destruction are no greater than those associated with ordered recalls of other regulated products. FDA does not intend to pursue minor violations of part 1271, but would take regulatory action in urgent situations to protect public health.

(Comment 169) One comment requested that FDA acknowledge the limitations on corrective actions arising from the ownership status of reproductive HCT/Ps.

(Response) We acknowledge the difficulty of the issues raised by the comment, and we note that the provisions of § 1271.440 provide the agency with a range of enforcement options. For example, in some instances a firm working with FDA could develop a recall strategy that involved notification of affected parties. We have added paragraph (f) to § 1271.440, which states that FDA will neither issue an order for the destruction of reproductive tissue, nor will it carry out such destruction itself.

(Comment 170) One comment asserted that the order to cease manufacturing under proposed § 1271.440 violates the Due Process Clause of

the Fifth Amendment of the United States Constitution. Citing *Bell v. Burson*, 402 U.S. 535, 542 (1971), the comment stated that, under the Due Process Clause, before a State seeks to terminate an entitlement (e.g., pursuit of a profession), it must provide notice and opportunity for hearing appropriate to the nature of the case before the termination becomes effective, “except in emergency situations.” The comment noted that although proposed § 1271.440 permits a facility to request a hearing, it does not provide a date on which a hearing must be held or that a hearing must be held at all. This provision also does not specify when a decision regarding the validity of the order is to be made. The comment also observed that an order under proposed § 1271.440 could be of potentially infinite duration, lasting as long as the agency believes that regulatory compliance has not been achieved. Another comment also asserted that, under *American Bus Ass’n v. Slater*, 231 F.3d 1 (D.C. Cir. 2000), this provision exceeds FDA’s statutory authority under section 361 of the PHS Act and is invalid.

(Response) We disagree that § 1271.440 is either unconstitutional or outside the agency’s statutory authority. Under section 361 of the PHS Act, FDA is expressly authorized to enforce the regulations it issues to prevent the introduction, transmission, or spread of communicable disease through such means as inspection, disinfection, sanitation, destruction, and “other measures as in [FDA’s] judgment may be necessary.” Orders to retain, recall, destroy, or cease manufacturing are such other measures that we have concluded are necessary to prevent communicable disease transmission. An order to cease manufacturing does not terminate any interest or right related to the pursuit of a profession. Such an order is intended for use in situations when needed to prevent the spread of communicable disease and is lawful so long as we

provide an opportunity for a hearing “at a meaningful time and in a meaningful manner”; the hearing does not need to be provided before the order issues.

Armstrong v. Manzo, 380 U.S. 545, 552 (1965). To clarify this intent we have added language to § 1271.440(a)(3) stating that an order to cease manufacturing until compliance with the regulations in part 1271 has been achieved will have immediate effect only when FDA determines that there are reasonable grounds to believe that there is a danger to health if the establishment continues to manufacture (see Comment 165 of this document).

Under § 1271.440 of this final rule, any person who receives an order to cease manufacture will have the opportunity to request an expedited hearing in accordance with part 16. We have also included a statement in § 1271.440(e) that FDA will provide an opportunity for an expedited hearing on an order of cessation that is not stayed by the Commissioner, when a request for a hearing is made in accordance with part 16. We decline to provide a specific timeframe within which a hearing must be held or within which a final decision must be rendered. Each request for a hearing should be reviewed within the timeframe appropriate for its specific circumstances. Some cases may need resolution within a few days, while other, more complicated cases may need more time to prepare for a hearing or to resolve the issues.

The comment’s reliance on *American Bus Ass’n v. Slater* is misplaced. In *American Bus*, the United States Court of Appeals for the District of Columbia invalidated a Federal regulation that imposed money penalties (a fine), which was not expressly authorized under the Americans with Disabilities Act (ADA). The ADA explicitly provided for injunctive or similar preventive relief and permitted civil proceedings for money damages, but was silent about the imposition of money penalties. The Court held that “Congress

unambiguously intended to preclude [the Department of Transportation] from authorizing money damages.” (231 F.3d at 4.) By contrast, section 361 of the PHS Act expressly authorizes FDA to enforce regulations using such means as

* * * inspection, fumigation, disinfection, sanitation, pest extermination, destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous infection to human beings, and other measures, as in [FDA’s] judgment may be necessary.

Like an order of fumigation, disinfection, and sanitation, an order to cease manufacturing is a remedial action taken to put important protections in place to prevent communicable disease transmission. Unlike the fine in *American Bus*, it is not a punitive action.

As explained in the proposed rule and earlier in this response, it is FDA’s judgment that an order to cease manufacture of an HCT/P may be necessary to prevent the introduction, transmission, or spread of communicable diseases. Such an order would be issued where violations created an urgent situation involving a communicable disease, because an establishment is in violation of the regulations in this part and, therefore, does not provide adequate protections against the risks of communicable disease transmission (e.g., an establishment fails to test donors in compliance with subpart C of part 1271). By contrast, we would not issue an order to cease manufacture to punish an establishment for past violations or violations that do not result in an urgent situation.

(Comment 171) One comment asserted that the 5-day timeframe for recall or destruction in proposed § 1271.440(c) is inadequate.

(Response) FDA disagrees that 5 days is an insufficient timeframe.

However, we recognize that circumstances may exist or occur that would require a time period other than the prescribed 5 working days for the implementation of corrective action or recall and/or destruction of HCT/Ps. Accordingly, we note that § 1271.440(c)(1), which states that “[a] written order issued under paragraph (a)(1) of this section will ordinarily provide that the HCT/P be recalled and/or destroyed within 5 working days from the date of receipt of the order” (emphasis added), provides for circumstances where we determine that an alternate timeframe is appropriate. The response to comment 167 describes the recall guidelines. In the event that FDA issues an order of destruction for HCT/Ps, such destruction would occur in accordance with applicable local, State, and Federal laws (i.e., Environmental Protection Agency) and under FDA supervision.

F. Economic Impacts

(Comment 172) Three comments suggested that the CGTP rule would impose significant cost burdens on affected entities and that FDA has significantly underestimated the compliance costs.

(Response) We disagree. Our analysis of economic impacts suggests that the cost burden of the CGTP final rule will not be significant. Further, these comments did not provide any data that refute FDA’s cost estimates or suggest alternative estimates of compliance costs.

(Comment 173) Three comments provided alternative estimates of the financial impact/compliance costs of the CGTP rule for eye banks ranging from \$41,533 to \$180,000 per year. One of these comments suggested that the financial impact of the CGTP rule could force many eye banks out of business.

(Response) FDA is unable to assess these comments as no information or data were provided to support the estimates of financial impact/compliance costs. The agency does not anticipate a significant economic impact on the eye bank industry because nearly all eye banks are believed to be following the current EBAA standards, which meet or exceed most requirements of the CGTP rule. We therefore disagree that the impact of the rule could force many eye banks out of business.

(Comment 174) One comment stated that most of the requirements of the CGTP rule are not difficult to meet but will require additional steps and documentation. The comment also suggested that all eye banks will have to increase quality control efforts and hire a separate quality control employee to track each provision of the program which will be time consuming and expensive.

(Response) FDA realizes that the CGTP rule will impose some additional financial burden on affected entities. However, eye bank personnel who oversee the quality assurance program currently required under EBAA standards perform duties similar to those required under the CGTP final rule. Therefore, the agency does not believe that a separate quality control employee will be required. Further, FDA's analysis of economic impacts suggests that these requirements will not be overly time consuming or expensive.

(Comment 175) One comment indicated that all eye banks would have to add or revise a procedure to handle complaints and that FDA's estimate of two complaints per year is too low, especially for large volume eye banks.

(Response) The agency recognizes that some eye banks may experience a greater number of complaints. However, this estimate is designed to be representative of the number of complaints handled annually by a typical

entity. The comment did not provide an alternative estimate of the number of complaints reported annually.

(Comment 176) One comment suggested that FDA (implicitly) assumed that all primary graft failures will be prevented under the rule, and provided no evidence to support any reduction in re-transplants required. Two comments suggested that FDA misinterpreted the results of a study of eye banks by Wilhelmus, et al. (1995), and failed to acknowledge the author's conclusion that no clearly defined factor accounted for most cases of primary graft failure. Two comments suggested that FDA has overstated both the risk of primary corneal graft failure and the benefits of the rule, and that it is unlikely that CGTPs will have a significant impact.

(Response) The analysis of economic impacts has been revised to eliminate the implicit assumption that all cases of primary corneal graft failure will be prevented by the CGTP rule. The evidence on the risk, incidence and causes of primary graft failure is limited, and mostly mixed and inconclusive. While no clearly defined factor accounts for most cases of primary corneal graft failure, storage conditions (i.e. preservation media and duration) are identified in a number of studies as a possible explanatory factor, and are regulated under the CGTP final rule. The possibility that implementation of CGTPs may reduce the risk of primary corneal graft failure and generate public health benefits cannot be ruled out.

(Comment 177) One comment noted that a study reported in the journal *Cornea* (1994), found that eye bank-related factors were not important in explaining primary corneal graft failure despite the author's initial suspicions and hypothesis. Thus, FDA's cost savings estimate is greatly exaggerated.

(Response) FDA has revised its estimate of the benefits of implementing the CGTP final rule for eye banks in response to comments received, and based on additional and more recent information. However, the study cited in the comment also reports, “interpretation of the results of this study is limited by the small sample size, which may preclude the detection of some associations,” and, “(m)issing data for relevant variables, most notably eye bank factors, make interpretation of related results difficult.” (emphasis added). The comment does not provide any alternative estimates of benefits.

(Comment 178) One comment indicated that, in 1999, primary corneal graft failure occurred in only 42 cases and intraocular infection in only 14 cases out of approximately 40,000 transplants. Another comment noted that the 1994 Agency for Health Care Policy Research data referenced by FDA suggests 7,443 corneal transplants were performed that year, while the actual number reported to EBAA was 35,022.

(Response) FDA has revised the analysis of impacts of the CGTP final rule to address these comments and to incorporate the most current information available.

(Comment 179) One comment objected to the use of 1996 labor statistics to derive tissue bank employee wages.

(Response) The agency has updated the wage estimates used in the analysis of impacts of the CGTP final rule to reflect current labor costs.

(Comment 180) One comment objected to FDA’s identification of the laboratory director and medical director as the same individual.

(Response) According to industry consultants, the medical director often serves as the laboratory director, particularly in small tissue facilities. Since all 134 eye banks, and a majority of facilities in the other HCT/P industry

sectors, are believed to meet the criteria characterizing small entities in the relevant industry sector, FDA viewed this as an appropriate simplifying assumption.

(Comment 181) One comment noted that FDA did not add clerical expense for the revision of minor policies and procedures.

(Response) We agree that clerical expense may be incurred in the revision or preparation of a minor procedure. Therefore, FDA has added clerical expense for both the revision and preparation of a minor procedure to the cost impact estimates for the CGTP final rule.

(Comment 182) One comment objected to FDA's bundling of the cost of preparing or revising procedures with training costs.

(Response) As procedural changes generally necessitate the training or retraining of employees, the agency views such bundling as both logical and reasonable.

(Comment 183) One comment suggested that several sections of the rule lack cost estimates because no basis for predicting such costs exists.

(Response) Some requirements reviewed in the analysis of economic impacts show no costs because they are expected to impose no new financial burden on affected entities, not because there is no basis for predicting these costs. More specifically, no cost estimate is provided for a section or provision of the CGTP rule if analysis showed the requirement: (1) Does not apply, (2) has no new cost impact, or (3) is met by another subsection of the rule.

(Comment 184) One comment argued that FDA has underestimated the compliance costs for stem cell facilities, and presents alternative compliance cost figures based on FDA's analysis of economic impacts.

(Response) The compliance cost figures provided in the comment are not comparable to FDA's cost estimates for a number of reasons. First, the cost

estimates provided in the comment fail to recognize and reflect an important difference between one-time costs and annual or recurring costs. Second, FDA's cost estimates are weighted based on the proportion of entities in each sector of the HCT/P industry estimated to be noncompliant with individual provisions of the CGTP rule. These noncompliance rates (weights) are based on information obtained from industry professional associations and communication with industry consultants. The cost estimates in the comment are not adjusted to reflect the estimated rates of industry noncompliance.

(Comment 185) One comment noted that the Foundation for the Accreditation of Cellular Therapy (FACT) is already inspecting to standards that are very close to the proposed regulations.

(Response) FDA does not dispute this, but following the FACT standards is voluntary, and evidence does not show that 100 percent of entities in the stem cell sector are currently following these standards. FDA believes that mandatory requirements are necessary to adequately protect public health and safety.

(Comment 186) One comment suggested that the requirement for oversight and audits would impose costs that might significantly reduce the number of participants in the National Marrow Donor Program.

(Response) We disagree. With respect to provisions governing oversight and audits, the agency notes the following. Section 1271.160(c) is expected to impose no new financial burden on affected entities. Section 1271.160(d) is expected to impose an additional burden of \$228 on entities currently following FACT standards, and \$1,140 in additional costs on firms not following these standards. Thus, the maximum burden on any one firm of these provisions is \$1,140 per year. The agency does not view this as a significant

cost burden, nor do we believe that these provisions will significantly reduce the number of donor centers participating in the National Marrow Donor Program.

(Comment 187) One comment expressed serious concerns and reservations regarding the accuracy of FDA's estimates of the risks associated with hematopoietic stem/progenitor cell transplants, and the costs and benefits of the proposed rule. Two comments argued that the costs for a bone marrow transplant are much different in 2001 than they were in 1994, and that much of the cost is for supportive care and not due to contamination of the graft. Therefore, the benefits of the rule are overstated.

(Response) FDA has revised the analysis of impacts for stem cell facilities to reflect the most recent available risk and cost information. The agency points out that the cost for a bone marrow transplant was presented in the analysis of impacts of the proposed rule for illustrative purposes only, and was not used directly in generating an estimate of the benefits of the CGTP rule for stem cell facilities.

(Comment 188) One comment suggested that the impact of the software validation requirements on small tissue facilities would be beyond the means of many and could force them out of business. The comment suggested that § 1271.160(e) be amended to require software validation only if it is relied upon as the sole source of data for quality-related decisionmaking.

(Response) With respect to computer software validation FDA assumed: (1) None of the affected entities currently validate custom software, (2) 10 percent of all facilities in each sector have developed custom software requiring validation, and (3) validation of custom software will require 60 hours of laboratory supervisor time (\$36 per hour, total cost = \$2,160 per

affected entity). We have modified § 1271.160(e) to indicate that either validation or verification can be performed, whichever is appropriate. Verification is less burdensome.

(Comment 189) One comment suggested that annual human heart valve allograft distribution is likely ten-fold lower (5,000–6,000) than the 61,000 annually referenced in the preamble and, further, that fewer than 10 infections per year are caused by contaminated valves since direct reports by implanting surgeons suggests less than 1 per year.

(Response) FDA has revised the analysis of impacts of the CGTP final rule to reflect both information provided in the comment and information on the risks associated with human heart valve allograft reported in the clinical literature.

(Comment 190) One comment expressed concern that the CGTP rule will be particularly onerous on small business, and would like FDA to ensure that they are not creating artificial market barriers by implementing the rule.

(Response) Nearly all facilities in the HCT/P industry are recognized as small entities and most would be similarly affected by the rule. Further, the requirements of the CGTP final rule are largely met, and in some cases exceeded, by the voluntary standards firms are required to meet to gain accreditation by professional associations in their respective HCT/P industry sectors. Finally, the agency's analysis suggests that the cost burden of the CGTP rule will not be significant (expressed as a percentage of average annual firm revenues) and, therefore, should not constitute a market barrier to small business.

(Comment 191) One comment noted that FDA chose not to certify that the rule would not have a significant economic impact on a substantial number

of small entities. The comment suggested that FDA should increase its outreach to small entities in an effort to obtain the information necessary to fully assess the rule's impacts before finalization.

(Response) FDA's analysis of economic impacts is based on: Information obtained under the registration final rule; administrative data on the number of facilities within each industry sector; and the number of entities accredited by various industry associations. FDA also obtained information from individual experts identified through contact with the various industry professional associations. We explicitly recognized the uncertainty of our estimates with respect to the number of facilities in each sector, degree of compliance with current industry standards and impact of the rule on affected entities. In the proposed rule, FDA requested detailed industry comment regarding our analysis of impacts, and data sources and underlying assumptions. Finally, the agency made presentations at the annual conferences of several industry professional associations, and held individual meetings with many of these groups at their request. We believe this represents a significant level of outreach and information gathering effort.

(Comment 192) One comment suggested that, upon publication of the final rule, FDA should address all comments received regarding small business impacts and provide an assessment of small business revenues that are likely to be affected.

(Response) FDA has provided responses to all comments received in the preamble to the final rule. A comprehensive assessment of the rule's effects on small business entities is provided in the analysis of economic impacts as required under the Regulatory Flexibility Act.

(Comment 193) One comment noted that if FDA significantly underestimated firm revenues, the rule's resultant costs to firms could be far greater than those estimated.

(Response) FDA believes that if average firm revenues were significantly underestimated, then the rule's resultant costs would appear greater (as a percentage of revenues) than they really are, thereby overstating the impact of the rule. We believe the comment intended to address the effect of FDA having overestimated firm revenues. In this case, compliance costs (expressed as a percentage of revenues) would appear smaller than they really are, thereby understating the impact of the rule.

Nevertheless, FDA's estimates of average annual revenues were obtained from a variety of sources including a published study of the tissue banking industry, information obtained from industry consultants and other published data sources. In the CGTP proposed rule, FDA requested detailed industry comment on the distribution of firm revenues in the HCT/P industry, and also on our estimates of average revenue per firm. We received no detailed information in response to our request, and no comments provided alternative estimates of annual firm revenues.

(Comment 194) One comment suggested that § 1271.155 of the rule seems to allow all businesses affected by the regulation to seek an exemption or alternative from the requirements of the rule.

(Response) While an exemption from or an alternative to a particular provision of the rule may be requested by any business, the granting of such a request is by no means assured. The entity requesting an exemption or alternative must demonstrate that the exemption is justified based on scientific data and other evidence, and that the alternative satisfies the purpose of the

requirement. Section 1271.155 does not provide a mechanism by which all businesses may become generally exempt from compliance with the CGTP rule.

(Comment 195) One comment assumes that § 1271.155 is FDA's attempt to comply with section 603(c) of the Regulatory Flexibility Act, which requires agencies to identify any significant alternatives available to small entities in their initial regulatory flexibility analysis.

(Response) This assumption is incorrect. The agency has written the CGTP rule broadly so as to allow comprehensive regulatory oversight of the diverse HCT/P industry. Section 1271.155 is designed to provide some flexibility, recognizing that an exemption from, or alternative to, a specific provision may be appropriate given the unique properties of a particular HCT/P.

(Comment 196) One comment noted that the FDA estimates between 75 percent and 100 percent of affected entities are already compliant with the provisions of the CGTP rule, and questions whether the rule will create another layer of unnecessary recordkeeping and training requirements for the affected firms.

(Response) Because compliance with current voluntary industry standards is less than 100%, FDA believes the CGTP rule is the best way to establish a consistent standard of safety for marginal firms not currently following voluntary industry standards and guidelines, and to protect public health and safety. We believe that the recordkeeping and training requirements are necessary to achieve the desired public health and safety goals.

(Comment 197) One comment expressed concern that the ultimate responsibility is placed in the hands of the firm distributing the HCT/P, while other firms will also be involved in manufacturing. Noting that the distributor is responsible for maintaining documentation from all other companies

involved in manufacturing the HCT/P, the comment expressed concern that this will place an unacceptable burden on small entities, and suggests that, to minimize this burden, FDA should adopt an alternative approach, discussed in the proposed rule, using a cascading set of responsibilities.

(Response) Before Comment 28, we set out a table to assist establishments in understanding their responsibilities when multiple establishment are involved in manufacturing an HCT/P. At Comments 28 through 35 we discuss the allocation of responsibilities in § 1271.150(c) and 1271.265. FDA believes that this approach is largely consistent with the cascading set of responsibilities described in the comment and discussed at Comment 31. Both approaches place responsibility on each establishment that performs manufacturing functions, with the establishment that makes the product available for distribution ultimately responsible for ensuring that the manufacturing and tracking records for an HCT/P demonstrate that it has been manufactured and tracked in compliance with the requirements of this subpart and subpart D.

IV. Effective Date of 21 CFR Part 1271 and Applicability of 21 CFR Part 1270

A. Effective Date for Part 1271

This final rule is effective May 25, 2005. All HCT/Ps recovered on or after the effective date must be in compliance with applicable requirements in part 1271.

As of the effective date, establishments that manufacture HCT/Ps defined in § 1271.3(d) that are regulated solely under the authority of section 361 of the PHS Act (as described in § 1271.10) must comply with all applicable requirements in part 1271, whether or not the HCT/P enters into interstate commerce.

The regulations under 21 CFR 207.20(f) and 807.20(d) require establishments that manufacture HCT/Ps that are regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the act to register and list their HCT/Ps following the procedures in subpart B of part 1271. Section 1271.21 requires HCT/P establishments to register and list every HCT/P that the establishment manufactures within 5 days after beginning operations, or within 30 days of the effective date of the registration regulation, whichever is later. HCT/P establishments that manufacture HCT/Ps subject to investigational new drug (IND) or investigational device exemption (IDE) provisions are not required to register and list their HCT/Ps until the investigational HCT/P is approved through a Biologics License Application (BLA), a New Drug Application (NDA), or a Premarket Approval Application (PMA); or cleared through a Premarket Notification Submission (510(k)).

As required by §§ 210.1(c), 211.1(b), and 820.1(a), establishments that manufacture HCT/Ps that are regulated as drugs, devices, and/or biological products under section 351 of the PHS Act also must comply with the requirements in subparts C and D of part 1271 in addition to all other applicable regulations.

B. Applicability of Part 1270

The retrospective application of part 1271 to human tissue, defined in § 1270.3(j), recovered before the effective date of the final rule would be overly burdensome and impractical. Therefore, we are not concurrently revoking part 1270 with the effective date of part 1271 as stated in the proposed rule (66 FR 1508 at 1524). However, we intend to revoke part 1270 in the future when we are confident that there is no human tissue regulated under 1270 available for use.

Part 1270 applies now only to human tissue defined in § 1270.3(j) and recovered before May 25, 2005. We have amended § 1270.3(j) to implement this provision. Products that meet the definition of HCT/P in § 1271.3(d) that are recovered before May 25, 2005, and that have been regulated as drugs, devices, and/or biological products under section 351 of the PHS Act and/or the act will continue to be subject to the applicable requirements for drugs, devices, and/or biological products.

V. Analysis of Economic Impacts

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

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. The majority of establishments within the HCT/P industry that will be affected by this final rule can be classified as small business entities, and a number of these establishments will incur new costs. Because of the limited information with which to characterize the current good tissue practice at many of these establishments, and thus the increased effort required to meet

the standards of the final rule, the cost impact on small business entities is uncertain. Therefore, the following analysis, along with other relevant sections of this preamble, represents FDA's final regulatory flexibility analysis.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing

* * any rule that includes any Federal mandate that may result in the expenditure by State, local and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.

The current threshold after adjustment for inflation is \$ 110 million. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

Based on the following economic analysis, FDA estimates that the total one-time costs to comply with this final rule will be approximately \$6.91 million, and that the total annual or recurring costs will be about \$7.13 million. These figures imply a total annualized cost estimate for the CGTP final rule of approximately \$7.94 million to \$8.11 million. The average annualized cost of CGTPs per affected small entity, expressed as a percentage of average annual revenue, ranges from 0.6 percent to 3 percent. This range of small entity impacts reflects uncertainty with respect to the current practices of affected entities and differences in the impact of the CGTP final rule across the various sectors of the HCT/P industry.

A. Risks Associated with HCT/Ps

FDA has conducted an extensive search for information with which to quantitatively assess and characterize the risks associated with HCT/Ps, but has found very little information available. The primary reason for this lack

of information is the absence of mandatory reporting requirements for adverse events, including the incidence of communicable disease transmission and graft failure, associated with HCT/Ps. The CGTP final rule will help to improve upon this situation by requiring entities that make HCT/Ps available for distribution to report to the agency any adverse reaction that meets the requirements of § 1271.350(a), as well as reports of HCT/P deviations required in § 1271.350(b). This information will be highly valuable to the agency in identifying and addressing areas of existing and emerging public health and safety risks associated with HCT/Ps. The available information regarding the risks associated with HCT/Ps known to the agency is summarized in the discussion that follows. Specific examples of risks associated with individual HCT/Ps are discussed in detail in section C of this analysis of economic impacts.

The HCT/P industry is currently growing and evolving rapidly. Since the CGTP proposed rule was published in January 2001, there have been significant increases in both the number of tissue donors and manufacturing establishments, as well as the number of HCT/Ps processed, distributed, and transplanted. Estimates of the current number of establishments in each sector of the HCT/P industry are presented in table 1b, along with recent information reflecting the approximate numbers of tissue donors and tissue products produced annually.

TABLE 1b.—NUMBERS OF HCT/P ESTABLISHMENTS, TISSUE DONORS AND PRODUCTS PRODUCED BY MAJOR INDUSTRY SECTOR

Type of HCT/P	Number of Establishments ¹	Number of Donors	Number of Products Produced Annually
Eye Tissue ²	134	47,796	94,186
Conventional Tissue ³	166	20,000	750,000
Hematopoietic Stem/Progenitor Cells ⁴	425	5,700	6,031
Reproductive Tissue ⁵	510	4,640	122,200

¹ Information obtained under the registration and listing final rule or provided by HCT/P industry professional associations. See section B.1 and table 3 of this analysis of economic impacts for additional details.

² EBAA, 1999.

³ AATB, 1999.

⁴ AABB/FACT, 1999.

⁵ The American Society of Reproductive Medicine (ASRM), 1999.

One source of potential communicable disease transmission risk associated with HCT/Ps is a lack of standard quality assurance procedures and recordkeeping requirements intended to ensure compliance with such procedures. Currently, in every major sector of the HCT/P industry, professional organizations have in place standards specifying appropriate operating procedures that establishments should follow to ensure that the products produced are safe for use and of high quality. Individual establishments in the various sectors of the HCT/P industry may also apply for accreditation through these professional organizations, which periodically inspect member establishments to ensure that they are following the appropriate standards. However, as discussed in detail in V.B and C of this economic analysis, following industry standards and seeking accreditation through the professional organizations is voluntary, and the rates of compliance and accreditation within the various sectors of the HCT/P industry vary significantly. Furthermore, there are currently no comprehensive monitoring or enforcement mechanisms governing establishments that choose not to follow voluntary industry standards or seek accreditation, and that may produce and distribute for use HCT/Ps that may present a serious threat to public health and safety.

The agency is aware of numerous reports of adverse health events and several patient deaths that have been linked to HCT/Ps. Transplantation of tissue has resulted in transmission of viral, bacterial, fungal, and other diseases, although such instances are rare. Some of these adverse events have been associated with HCT/Ps produced by large entities that do not follow voluntary industry standards and are not accredited by their respective professional associations. In March of 2002, the CDC published the results of

their investigation of 26 reported cases of tissue allograft-associated infection, one of which resulted in the death of the patient (Ref.1). The CDC concluded that of the 26 reported cases, “14 (were) associated with a single tissue processor,” and further suggested that their

* * * findings * * * have important implications for patient safety and indicate that current federal regulations and industry standards on processing and quality control methods need to be enhanced and implemented to prevent * * * allograft-associated infections.

Problems due to inadequate product processing and quality controls, contributing to post-operative infection and/or graft failure, are one category of the many potential causes of the reported adverse health events associated with HCT/Ps. Implementation of the CGTP final rule, by establishing an enforceable set of product quality assurance procedures and standards, is expected to reduce the risk of communicable disease transmission as well as the incidence of other types of adverse health events associated with HCT/Ps.

Recent information on the number of infections following surgery, incidence of communicable disease transmission, graft failures, and additional surgeries required as a result for various types of HCT/Ps is summarized in table 2 of this document. Although these numbers suggest that the risks associated with the various types of HCT/Ps are relatively low, it is important to consider the limitations of these data.

It is highly unlikely that the available data provide an accurate accounting of the true risks associated with HCT/Ps because there is currently no mandatory reporting requirement for adverse health events, including communicable disease transmission and graft failure, associated with tissues.

Thus, the case reports that are known to the agency are almost certainly not representative of the risks associated with HCT/Ps, because a significant number of these events may go unreported. In the eye banking industry, the EBAA requests that adverse event information be voluntarily reported, but acknowledges that not all members provide this information. The AATB does not request information on the number of adverse events reported to accredited conventional tissue banks. Further, the New York Department of Health indicated that they know of no entity that collects information on graft failures or repeat surgeries due to complications associated with musculoskeletal tissues. Thus, despite a significant effort on the part of the agency, very little information with which to identify and quantify the risks associated with various types of HCT/Ps was found. In summary, the limited information presented in this analysis of impacts is not likely representative of the true risks associated with HCT/Ps, because no mandatory adverse event reporting requirements exist, the information that is available is reported voluntarily and, in some sectors of the tissue industry, the necessary information is not available because it is not collected by any source.

TABLE 2.—SUMMARY OF AVAILABLE HCT/P RISK INFORMATION¹

Type of HCT/P	Number of Transplants	Number of Infections	Number of Graft Failures	Additional Surgeries Required
Ocular (Eye) ²	33,035	9	37	37
Musculoskeletal ⁴	NDF ³	52	NDF	4
Heart Valve Allografts ⁵	4,000	26	41	41
Hematopoietic Stem/Progenitor Cells; Peripheral Blood ⁶	18,123 (in 1997)	NDF	NDF	NDF
Hematopoietic Stem/Progenitor Cells; Cord Blood ⁷	2000 (from 1988 to 2002, inclusive)	NDF	NDF	NDF

¹ Annual data except as noted otherwise.

² EBAA, 2001 Statistical Report.

³ NDF: Denotes No Data Found or Available.

⁴ AATB, 2001.

⁵ FDA, CDRH, Office of Surveillance and Biometrics, 2001.

⁶ *Transfusion*, vol. 42, 2002.

⁷ *Current Opinion in Oncology*, vol. 14, No. 2, March 2002.

The agency obtained additional information on the risks associated with HCT/Ps by reviewing establishment inspection reports (EIRs) filed by agency

inspectors. The following information summarizes some of the inspector's observations made in the course of their inspections of establishments processing human tissues. This information was obtained from a manual search of approximately 150 EIR reports filed in 2000 and 2001, and reflects observations from 15 of the 150 EIRs that were not citable under 21 CFR part 1271, but would be citable under 21 CFR part 1271. As such, this discussion is not a comprehensive assessment of the results of FDA inspections of HCT/P processing establishments. Instead, it is intended to provide an illustration of the type of processing and quality assurance problems that currently exist in the tissue industry, and that would be addressed through implementation of the CGTP final rule.

Failure to validate procedures for various stages of HCT/P processing was identified in 8 of the 15 reports. More specifically, observations included failure to validate procedures for the prevention of infectious disease contamination and cross-contamination during processing, and failure to prepare written procedures for designating and identifying quarantined tissue. Failure to document the destruction or disposition of human tissue, failure to designate and identify the person responsible for making the determination that an HCT/P was suitable for transplantation, and/or failure to accompany quarantined tissue with records indicating the tissue was not determined to be suitable for transplantation were identified in 5 of the 15 reports. Failure to maintain adequate records of each significant step in the processing of human tissues and/or performance of infectious disease screening, as well as failure to maintain accurate records thereof, were cited in 6 of the 15 inspection reports. Finally, failure to prepare and follow written procedures for all significant steps for obtaining, reviewing, and assessing the relevant

medical records of tissue donors, or failure to provide along with dispensed tissue a summary of the records of the donor eligibility determination, were cited in 7 of the 15 inspection reports. Although this summary of examples of FDA inspector's observations related to provisions under part 1270 is not comprehensive, it does indicate the type of procedures and quality control problems observed in HCT/P processing establishments in 2000 and 2001. Each example could have an adverse impact on the HCT/P, and all are further addressed by various provisions of the CGTP final rule.

To gain additional insights into the risks associated with HCT/Ps, FDA also reviewed reports of adverse events associated with human tissue products submitted through the MedWatch system. Between 2000 and 2001, FDA received 21 voluntary MedWatch reports of problems associated with HCT/Ps. Because there is no mandatory requirement for reporting adverse reactions involving tissue products, the extent to which these reported events are representative of the risks associated with HCT/Ps during this period is unclear. It is likely, however, that a significant number of adverse events associated with HCT/Ps are unreported under the current voluntary MedWatch system. The 21 reported adverse events included: 4 patient deaths (3 of which were probably due to underlying disease and not directly attributable to HCT/Ps); 5 life-threatening situations; 5 surgical or other medical interventions; 2 cases of permanent disability; 9 additional hospitalizations; and 7 cases of mold contamination of HCT/P packaging material. Many of the potential underlying causes of these voluntarily reported adverse events are addressed by various provisions of the CGTP final rule, implementation of which is expected to reduce communicable disease transmission risks and the number of adverse events associated with the various types of HCT/Ps.

B. Estimated Cost Impact

With the CGTP final rule, FDA is furthering completion of the set of proposals that represent a comprehensive new system for regulating the rapidly evolving HCT/P industry. Manufacturers of HCT/Ps may need to make certain changes to their operations to comply with this rule, such as creating new procedures revising existing procedures, and providing additional documentation. This final rule, in its entirety, affects several types of entities involved in the manufacture of HCT/Ps including eye banks, conventional tissue banks and establishments processing hematopoietic stem/progenitor cells. As explained elsewhere in this preamble, Assisted Reproductive Technology (ART) establishments and semen banks are subject only to the inspection and enforcement provisions of the CGTP final rule as they apply to donor eligibility requirements under subpart C. As such, reproductive tissue establishments will be only minimally affected by this final rule.

Information obtained under the registration final rule forms the basis for FDA's estimates of the number of affected eye banks and conventional tissue banks. The agency's estimates of the number of affected eye banks, hematopoietic stem/progenitor cell establishments, ART establishments, and semen banks rely heavily on information obtained from various professional organizations associated with the HCT/P industry. Where good statistical data are not available, FDA's cost impact estimates have incorporated the quantitative judgments of individual experts identified through contacts with HCT/P industry professional associations. Because of the lack of comprehensive data with which to characterize patterns of current practice within each affected industry sector, and the importance of this data for development of an accurate assessment of cost impact, FDA requested detailed

industry comment on the number of establishments involved in the manufacture of HCT/Ps, and the net change in quality assurance efforts needed for those establishments to comply with the CGTP proposed rule. To the extent possible, this information has been incorporated into FDA's analysis of the economic impact of this final rule.

1. The Number and Type of Entities Affected

The analysis of the economic impact of this final rule is organized around four major subgroups: Eye banks, conventional tissue banks, hematopoietic stem/progenitor cell establishments, and reproductive tissue establishments. The number of establishments and the percentage of establishments that follow current industry standards are summarized in table 3 of this document. In estimating net new costs for eye banks, conventional tissue banks and hematopoietic stem/progenitor cell establishments, it is critical to account for establishment compliance with existing industry standards. In a number of these HCT/P sectors, current industry standards for many manufacturing operations meet or exceed the specifications in this final rule. Establishments following those standards will experience very little impact in complying with the new FDA standards.

As presented in table 3 of this document, FDA has a record of 134 registered establishments listing eye tissue including 96 eye banks, approximately 93 of which are currently accredited by the EBAA. According to industry experts, virtually all operating eye banks currently comply with EBAA medical and procedural standards for quality control. For affected eye banks, the incremental costs associated with this final rule result from additional quality assurance steps and process documentation as specified under the CGTP final rule.

FDA has a record of 166 registered tissue banks involved in the manufacture of other conventional HCT/Ps, e.g., skin allografts, bone allografts, fascia, tendons and ligaments (hereafter referred to as “conventional tissue banks”). The AATB lists approximately 75 accredited tissue banks and projects another 40 to 60 members unaccredited. Industry sources report that approximately 75 to 80 percent of these establishments currently follow the voluntary standards established by the AATB. For these establishments, there will be some additional cost associated with review of this final rule and with alignment of their current SOPs with FDA’s new requirements. There may also be some additional recurring cost, where documentation and quality control required under the CGTP final rule extend beyond current practice. For the remaining 20 to 25 percent of establishments not following the AATB standards, the cost of compliance will be somewhat higher. These establishments may need to establish more formal procedures and quality control measures, and may need to devote additional staff hours to performing these procedures and processing controls.

Establishments that produce hematopoietic stem/progenitor cells from peripheral blood or from umbilical cord blood will also be affected by this final rule. FDA finds that available data with which to estimate the number of peripheral blood stem/progenitor cell (PBSC) establishments and evaluate current practices are quite limited, and the actual number of PBSC establishments may range from 200 to 400. As of April 2002, CBER has a record of 178 voluntarily registered establishments listing “stem cell” as a type of product or establishment. The National Marrow Donor Program (NMDP), which includes establishments that recover PBSCs, lists approximately 92 donor centers and 113 collection centers. Approximately 150 establishments

involved with PBSCs are currently accredited by the AABB and an estimated 107 are accredited by the Foundation for the Accreditation of Cellular Therapy (FACT). Industry sources estimate that 80 of these establishments are seeking dual AABB/FACT accreditation, suggesting an unduplicated count of approximately 200 PBSC establishments assumed to be accredited by AABB and/or FACT. However, the number and manufacturing practices of nonaccredited establishments are unknown. The International Bone Marrow Transplant Registry/Autologous Blood and Marrow Transplant Registry (IBMTR/ABMTR) estimates that the total number of peripheral blood or bone marrow establishments may be as high as 400 (e.g., 200 more than the number estimated to be accredited by AABB and/or FACT), but the number of IBMTR/ABMTR-estimated establishments that actually process peripheral blood (as opposed to bone marrow) is uncertain. For the purposes of this analysis, FDA has assumed that 400 PBSC establishments will be affected by this final rule.

Although there is no single national organization that keeps track of the number of establishments for umbilical cord blood banking, FDA estimates that there are approximately 25 cord blood banks currently operating in the United States. These establishments would also seek accreditation through FACT or AABB. Based on this information, the agency estimates that a total of 425 establishments involved in manufacturing hematopoietic stem/progenitor cells would be affected by this final rule.

In addition, 67 establishments produce licensed biological products or approved medical devices that are currently regulated under the act and/or section 351 of the PHS Act, but would be subject to the provisions of this final rule. The impact of CGTPs on these firms is expected to be minimal because they are already subject to existing CGMP regulations for drugs or QS

regulations for medical devices. Those requirements are largely consistent with the requirements of this final rule.

Finally, the inspection and enforcement provisions of this final rule, as they apply to donor eligibility requirements under subpart C, will affect establishments involved with reproductive tissue, primarily ART establishments and semen banks. For purposes of this discussion, references to ART establishments include infertility clinics, as well as andrology and embryology laboratories. The ASRM has a membership of approximately 400 fertility centers, 370 of which have provided reports for the 1999 Society for Assisted Reproductive Technology registry (Ref. 29). The ASRM also has a 1996 list of approximately 110 semen banks operating in the United States. Based on conversations with consultants, most ART and commercial semen banking establishments currently adhere to industry standards similar to those in the CGTP final rule. There are currently 11 semen banks accredited by the AATB and, according to industry consultants, the remaining commercial semen banks are licensed by State health agencies, including the California Department of Health and the New York Department of Health.

Semen banks and andrology laboratories at ART establishments are also regulated under the Clinical Laboratory Improvement Amendment (CLIA) of 1988.

The Committee on Laboratory Accreditation and JCAHO also inspect embryo laboratories for accreditation. The requirements for accreditation by the College of American Pathologists (CAP), which accredits ART establishments, closely resemble those in the CGTP final rule, with a few exceptions. Consultants estimate that as many as 80 percent of ART establishments may currently comply with the CAP requirements.

TABLE 3.—ESTIMATED PERCENTAGE OF ESTABLISHMENTS THAT FOLLOW VOLUNTARY INDUSTRY STANDARDS

Affected Industry	Relevant Voluntary Industry Standards	Percentage of Firms Following Voluntary Industry Standards
Eye Tissue: 134 FDA Registered Establishments	EBAA	100 %
Conventional Tissue: (e.g., pericardium, dura mater, heart valves, skin allograft, bone allograft, fascia, tendons, ligaments, other viable) 166 FDA Registered Establishments	AATB	75 to 80%
Stem/Progenitor Cells: Peripheral Blood (PB): 400 establishments Cord Blood (CB): 25 establishments	AABB or FACT AABB or FACT	85 % of accredited PB establishments 100 % of all CB establishments
Reproductive Tissue: Semen Banks: 110 establishments	AATB; CAP accreditation; State Licensed (e.g., NY, CA); and/or CLIA-certified	20 largest establishments (accounting for 95% of total production)
Reproductive Tissue: ART Establishments: 400 establishments	CAP accreditation; State Licensed (e.g., NY, CA); ASRM guidelines	80 %

2. Estimated Impact on Eye Banks, Conventional Tissue Banks and Hematopoietic Stem/Progenitor Cell Establishments

In the sections that follow, the agency considers each of the provisions of this final rule and estimates the impact on establishments in those sectors of the HCT/P industry subject to CGTPs in their entirety. The impact analysis distinguishes expected cost impacts based on both facility size and estimated rates of current adherence to voluntary industry standards. Based on size standards established by the U.S. Small Business Administration (SBA), a small establishment in this industry sector (the North American Industry Classification Scheme (NAICS) code 621991, Blood and Organ Banks) has annual receipts of less than \$8.5 million (Refs. 21 and 22).

TABLE 4.—ESTIMATED COST PER ESTABLISHMENT AND ESTIMATED PERCENTAGE OF ESTABLISHMENTS AFFECTED BY THE CGTP FINAL RULE¹

21 CFR Section	Title	Eye Tissue Establishments	Conventional Tissue Sm./Lrg.	Stem/Progenitor Cell Establishments
1271.150	Current Good Tissue Practice Requirements	—	—	—
1271.155	Exemptions and Alternatives	—	—	—
1271.160	Establishment and Maintenance of a Quality Program: General			
	-Establishment with Minor Deficiencies	\$511 (95%)	\$511/\$1,278 (23%)	\$511 (80%)
	-Establishment with Major Deficiencies	\$2,498 (5%)	\$2,498/\$4,832 (5%)	\$2,498 (5%)
	-Cost for Additional Quality Control Work	\$1,344 (95%)	\$1,344 (23%)	\$1,344 (80%)
(b)(2)	Procedures for Sharing Information	\$380 (95%)	\$760/\$2,172 (23%)	\$760 (80%)
(b)(3)	Corrective Actions	\$456 (95%)	\$912 (23%)	\$912 (80%)
(b)(6)	Investigations	\$2,214 (95%)	\$2,214 (23%)	\$2,214 (80%)
(c)	Audits	\$456 (95%)	\$912/\$1,824 (23%)	\$912 (80%)
(d)	Validate Custom Computer Software	\$2,160 (10%)	\$2,160 (10%)	\$2,160 (10%)
1271.170	Organization and Personnel:			
(b)	Competent Personnel	—	\$15,560 (23%)	\$15,560 (95%)

TABLE 4.—ESTIMATED COST PER ESTABLISHMENT AND ESTIMATED PERCENTAGE OF ESTABLISHMENTS AFFECTED BY THE CGTP FINAL RULE¹—Continued

21 CFR Section	Title	Eye Tissue Establishments	Conventional Tissue Sm./Lrg.	Stem/Progenitor Cell Establishments
(c)	Training	—	\$2,476/\$3,104 (23%)	\$2,476 (95%)
1271.180	Procedures—General Requirements	\$9,120 (5%)	\$9,120 (23%)	\$9,120 (95%)
1271.190	Establishments:			
(d)(1)	Cleaning and Sanitation Procedures	\$348 (5%)	\$348/\$532 (23%)	\$348 (95%)
(d)(2)	Cleaning and Sanitation Records	—	—	—
1271.195	Environmental Control and Monitoring:			
(a)	Environmental Control	—	\$348/\$532 (23%)	\$348 (95%)
(b)(c)	Inspections and Monitoring	\$1,000 (5%)	—	\$1,000 (95%)
(d)	Records	\$174 (95%)	\$174/\$348 (23%)	\$174 (95%)
1271.200	Equipment:			
(b)	Procedures/Schedules—Cleaning, Sanitizing and Maintenance	—	\$1,460/\$2,979 (23%)	\$1,460 (95%)
(c)	Calibration	—	\$1,460/\$2,979 (23%)	\$1,460 (95%)
(d)	Inspections	\$216 (95%)	\$432/\$684 (23%)	\$216 (95%)
(e)	Records			
	-of Cleaning, Sanitizing and Calibration Activities	\$174 (95%)	\$348/\$696 (23%)	\$174 (95%)
	-of the Use of Each Piece of Equipment	\$696 (95%)	\$1,392/\$2,784 (23%)	\$1,392 (95%)
1271.210	Supplies and Reagents:			
(a)	Verification	\$131 (95%)	\$348/\$532 (23%)	\$348 (95%)
(c)	In-house Reagents	—	\$348/\$532 (23%)	\$348 (95%)
(d)(1)	Records of Receipt, Verification, and Lot	\$174 (95%)	\$174/\$348 (23%)	\$174 (95%)
1271.220	Process Controls:			
	In-Process Monitoring Procedures	\$380 (95%)	\$380/\$1,086 (23%)	\$760 (95%)
1271.225	Process Changes:			
	Validation of Process Changes	\$760 (95%)	\$760/\$2,172 (23%)	\$760 (95%)
	Records/Documentation	\$456 (95%)	\$456/\$912 (95%)	\$456 (95%)
1271.230	Process Validation:			
(a)	General	\$1,700 (95%)	\$1,700 (95%)	\$1,700 (95%)
	Procedures	\$1,520 (95%)	\$760/\$2,172 (95%)	\$1,520 (95%)
(c)	Validation/Revalidation of Process Changes	\$850 (95%)	\$1,700 (95%)	\$1,140 (95%)
1271.250	Labeling Controls:			
(a)(b)	Procedures	\$380 (5%)	\$380/\$1,086 (5%)	\$380 (95%)
1271.260	Storage	—	—	—
1271.265	Receipt, Pre-Distribution Shipment and Distribution:			
	Recordkeeping and Documentation	\$864 (5%)	\$1,728/\$3,456 (5%)	\$3,456 (5%)
(a)	Procedures—Receiving Activities	—	\$380/\$1,086 (23%)	\$760 (95%)
(c)	Procedures—Availability for Distribution	—	\$380/\$1,086 (23%)	\$760 (95%)
(d)	Packaging and Shipping	\$1,392 (95%)	\$1,392 (95%)	\$576 (95%)
(f)	Procedures—Return to Inventory	—	\$348/\$532 (23%)	\$348 (95%)
1271.270	Records:			
(a)	General	\$728 (95%)	\$728/\$1,618 (95%)	\$728 (95%)
(b)	Records Management System	\$3,040 (95%)	\$3,040/\$6,080 (23%)	\$3,040 (95%)
(d)	Length of Retention	\$18 (5%)	\$18 (23%)	\$18 (95%)
1271.290	Tracking:			
(b)(c)	System of Product Tracking: General Requirements	\$760 (5%)	\$380/\$1,086 (23%)	\$380 (95%)
(d)(e)	System of Product Tracking: Specific Requirements	\$1,728 (5%)	\$3,456/\$6,912 (23%)	\$3,456 (95%)
(f)	Consignees	\$1,520 (5%)	\$1,520 (23%)	\$1,520 (95%)
1271.320	Complaint File:			
(a)	Procedures	\$131 (95%)	\$348/\$532 (23%)	\$348 (95%)
(b)	Complaint File	—	—	—
(c)	Review and Evaluation of Complaints	\$608 (95%)	\$608/\$1,216 (23%)	\$608 (95%)
1271.350	Reporting	\$592 (100%)	\$592 (100%)	\$592 (100%)
1271.370	Labeling	—	—	—
1271.400	Inspections			
(a)	General	\$768 (100%)	\$768 (100%)	\$768 (100%)
1271.420	HCT/Ps Offered for Import	—	—	—
1271.440	Orders of Retention, Recall, Destruction and Cessation of Manufacturing	—	—	—

¹ Only subsections expected to impose new compliance costs for a particular industry sector are shown. No cost is estimated for a subsection if analysis revealed that the requirements: (1) do not apply, (2) have no new cost impact, or (3) are met by another subsection of the CGTP final rule. Estimated noncompliance rates are in parentheses.

As indicated by the information in table 4 of this document, the impact of the CGTP final rule varies significantly, depending upon the sector of the HCT/P industry, size of the affected entity and the particular provision. For many of the CGTP provisions, the establishment level impact will entail development of new procedures, or revision of existing procedures. The scope and degree of complexity of these changes will vary. FDA expects that the staff typically involved in the development, revision, and finalization of establishment procedures will include technicians, clerical staff, lab supervisors, and the lab director. Although FDA did not specify personnel requirements for individual provisions of the CGTP final rule, for purposes of industry-wide estimation, the agency's cost analysis relies on standardized estimates of the type of personnel, level of effort, and hourly labor cost for revising or establishing each type of procedure. Table 5 of this document summarizes the agency's assumptions, which are based on published wage and benefits data and input from HCT/P industry consultants.¹

TABLE 5.—ESTIMATED LEVEL OF EFFORT AND COST PER PROCEDURE REVISED OR PREPARED TO COMPLY WITH THE CGTP FINAL RULE

Category:	Minor Procedures		Major Procedures	
	Revise Existing	Prepare New	Revise Existing	Prepare New
Small Establishment				
Total level of staff effort	3 hrs.	7 hrs.	8 hrs.	16 hrs.
Cost (rounded)	\$131	\$348	\$380	\$760
Large Establishment				
Total level of staff effort	5 hrs.	13 hrs.	27 hrs.	54 hrs.
Cost (rounded)	\$192	\$532	\$1,086	\$2,172

¹ A detailed presentation of level of effort and cost assumptions for nonreproductive tissue establishments is provided in FDA's *Cost Impacts of the Proposed Current Good Tissue Practice Rule on Eye Banks, Conventional Tissue Banks, and Stem Cell Facilities: Background Paper*, April 1999, and for reproductive tissue facilities in *Cost Impacts of the Proposed Current Good Tissue Practice Rule on Semen Banks and ART Facilities*, February 1999, prepared by Eastern Research Group (ERG), Inc. These documents are available in docket 97N-484P.

The analysis of cost impacts for HCT/P industry sectors subject to CGTPs in their entirety is summarized in the following discussion of the rule's individual provisions, and the expected type and extent of industry impact. The pertinent section of the final rule is noted to facilitate reference to the related cost estimates presented in table 4 of this document.

a. Section 1271.150—current good tissue practice: general. The final rule requires manufacturers of HCT/Ps to follow CGTPs. Section 1271.150(a) provides an overview of CGTPs but does not present specific compliance requirements. The specific requirements are addressed in subsequent sections. Section 1271.150(b) lists the core CGTP requirements, and § 1271.150(c) addresses compliance with applicable requirements for those entities subject to CGTPs. Section 1271.150(d) explains the relationship between the CGTP rule and regulations specifically applicable to biological drugs or devices, and paragraph (e) defines the term “where appropriate” in relation to the rule. Section 1271.150(b) through (e) will not generate any compliance costs for the HCT/P industry because no specific requirements are specified.

b. Section 1271.155—exemptions and alternatives. The CGTP final rule allows establishments to request an exemption or alternative from FDA for certain provisions of the rule. There is currently no basis for predicting the number of industry requests for exemptions or alternatives, or for predicting the effect of these actions on compliance costs. Because of a high degree of similarity between CGTPs and current voluntary industry standards, FDA anticipates that very few establishments will consider it appropriate to be exempted from the provisions of this final rule.

c. Section 1271.160—establishment and maintenance of a quality program. The final rule requires that establishments establish and maintain

a quality program. The quality program must include: Procedures relating to core CGTP requirements, procedures for exchanging information with other establishments known to have recovered cells or tissue from the same donor, appropriate corrective actions related to core CGTP requirements, proper training and education of personnel involved in activities related to core CGTP requirements, appropriate monitoring systems, investigation and documentation of HCT/P deviations related to core CGTP requirements, audits, computer software validation or verification, and other procedures specific to the quality program. Several of these functions are further specified in subsequent provisions of the rule, and the impact is estimated in the context of those provisions.

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

Although the sharing of information is an industry-wide practice, some small establishments, particularly those not following current industry standards, may not have written procedures and forms for this task. FDA estimates that 95 percent of eye banks, 23 percent of conventional tissue banks not following the current AATB standards, and 80 percent of the hematopoietic

stem/progenitor cell establishments not following the FACT or AABB standards, will need to prepare a major procedure to address this requirement.

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

FDA estimates that 95 percent of eye banks, 23 percent of conventional tissue banks, and 80 percent of hematopoietic stem/progenitor cell establishments not following industry standards will need to invest additional time to meet these new requirements. The incremental time burden to administer corrective actions and document these activities is estimated to be an additional 1/2-hour per month of laboratory director time at establishments that already perform this activity to a lesser extent, and an additional hour per month at all other establishments that will be newly affected by this provision. As discussed in the background papers prepared by FDA and Eastern Research Group (ERG), and shown in table 4 of this document, for newly required investigations in tissue establishments, FDA estimates an additional cost per year of \$2,214 for an additional 2 hours per month for the laboratory director to investigate and document deficiencies, and an additional 1/2 hour each for the laboratory supervisor and lab technician to participate in the investigations.

A number of establishments will also need to institute other requirements of the quality program, including periodic audits, computer software validation or verification, and procedures specific to the quality program. Audits are part of the industry standards published by the AATB, EBAA, FACT, and AABB. However, some establishments following these standards may need to do some additional recordkeeping, and establishments not following standards will

need to begin to conduct audits. Referring to table 4 of this document, FDA assumes that up to 95 percent of eye banks will increase their audit efforts, including additional lab director time to prepare for and perform the periodic audit. An estimated 23 percent of conventional tissue banks will allocate additional resources for audits, with a higher allocation of hours at larger establishments, to prepare for, and to conduct, the audit. For hemapoietic stem/progenitor cell establishments, FDA estimates that there will be no additional auditing required at establishments following FACT or AABB standards, but an estimated 80 percent of establishments not following industry standards will need to spend additional time to prepare for and to conduct periodic audits.

Section 1271.160 of the CGTP final rule further stipulates that establishments must validate or verify, as appropriate, the computer software used in their operations when it is used in the performance of core (good tissue practice (GTP) functions. Validation would be required for custom software used in core GTP functions. However, for off the shelf commercial software packages (e.g., for data storage and retrieval, recordkeeping, etc.) used as intended by the software manufacturer, it would be adequate for the establishment, when using such products in the performance of core GTP functions, to verify the product's performance. Such products are already validated or verified by the software vendor.

FDA assumes that none of the affected establishments currently validate or verify their custom software and that approximately 10 percent of eye banks, conventional tissue banks and hematopoietic stem/progenitor cell establishments have developed custom software that will require full validation or verification under this final rule. Because we received no specific

comments regarding these assumptions in response to the proposed rule, we have retained them here. Although the scope of such work can vary, FDA estimates that the custom software in use has a limited scope of application, and that an average of 60 hours of work by the laboratory supervisor will be required to validate or verify custom computer software at an establishment. Detailed presentations of these assumptions are provided in section 2.4.3 of the background papers (see footnote 1 of this document) 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 indicated that establishments have quality systems in place, but that most establishments are not aware of some minor elements of CGTPs that should be included in their 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 banks, and up to 80 percent of hematopoietic stem/progenitor cell establishments will have minor deficiencies that will require them to revise one minor and one major procedure. In addition, FDA estimates that 5 percent of all eye banks, and conventional tissue banks and hematopoietic stem/progenitor cell establishments not following voluntary industry standards may identify major deficiencies, and will need to prepare five minor procedures and one major procedure to address those problems.

The agency further assumes that establishments may generally need to perform some additional quality control work to comply with the quality program requirements in the CGTP final rule. Although some tasks will not require any additional time to perform, FDA estimates that approximately 1 hour per month each for the laboratory director and supervisor may be needed.

The agency estimates that 95 percent of all eye banks, 23 percent of conventional tissue banks, and approximately 80 percent of hematopoietic stem/progenitor cell establishments will need to allocate additional staff time for this purpose.

d. Section 1271.170—personnel. This final rule requires establishments to employ sufficient personnel with the necessary education, experience, and training to ensure competent performance of their assigned functions. The EBAA, AATB, FACT, 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 eye banks, conventional tissue banks and hematopoietic stem/progenitor cell establishments will already be compliant with these provisions of the CGTP rule. Those establishments in the conventional tissue and hematopoietic stem/progenitor cell manufacturing sectors that do not follow industry standards will incur new costs. The cost of this staffing effort is estimated to be approximately \$15,560 per affected establishment.

FDA anticipates that the 23 percent of conventional tissue banks and 95 percent of hematopoietic stem/progenitor cell establishments not following industry standards will incur new training costs to comply with the personnel provisions of the CGTP final rule. For a small tissue establishment, these costs are estimated to average \$2,476. The CGTP final rule also requires that records of personnel qualifications and training be maintained, but because existing industry standards address personnel recordkeeping, FDA assumes that the cost to comply with this requirement will be negligible. Details of these assumptions are provided in section 2.4.4 of the background papers (see footnote 1 of this document) by FDA and ERG.

e. Section 1271.180—procedures: general requirements. The CGTP final rule requires establishments to establish and maintain written procedures appropriate to meet core CGTP requirements for all steps performed in the manufacture of HCT/Ps. FDA anticipates a negligible incremental cost for most establishments following industry standards, and an additional 120 hours of laboratory director time for establishments not following the current industry standards. FDA estimates that 5 percent of eye banks will need to expand their current efforts, and that 23 percent of conventional tissue banks and 95 percent of hematopoietic stem/progenitor cell establishments will incur new costs.

f. Section 1271.190—facilities. This final rule stipulates a number of requirements regarding facilities covering operations, size, construction, location, lighting, ventilation, plumbing, drainage and access to sinks and toilets. A facility used in the manufacture of HCT/Ps must be of suitable size, construction, and location to prevent contamination of HCT/Ps with communicable disease agents and to ensure orderly handling of HCT/Ps without mix-ups. Cleaning and sanitation requirements are also outlined, including requirements for written procedures, schedules, and documentation of these activities.

Based on discussions with industry experts, FDA estimates that nearly all establishments that follow industry standards will not incur any new costs under these provisions of the CGTP final rule. However, some establishments that generally adhere to cleaning standards do not have written procedures. Thus, FDA estimates that 5 percent of all eye banks, in addition to 23 percent of the conventional tissue banks and 95 percent of all hematopoietic stem/progenitor cell establishments, will incur the cost of writing a minor procedure for cleaning. The facilities provision of the CGTP final rule also requires that

records of cleaning be maintained. This requirement is met by establishments following industry standards, and is expected to have a negligible impact on establishments not following the current voluntary standards.

g. Section 1271.195—environmental control and monitoring. Where environmental conditions could reasonably be expected to cause contamination or cross-contamination, or accidental exposure of HCT/Ps to communicable disease agents, environmental conditions must be adequately controlled. The final rule also requires that environmental control systems be monitored and periodically inspected, and that environmental control and monitoring activities be documented. The impact of this provision of the CGTP rule varies by industry sector. For affected eye banks, the EBAA standards already contain similar provisions, however, some additional costs may be incurred for periodic inspection of 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 of equipment. FDA anticipates that conventional tissue banks following AATB standards will experience no new costs, but that the remaining 23 percent of establishments will need to prepare a minor procedure for control and monitoring of ventilation and air filtration.

The current FACT and AABB standards do not require written procedures for environmental control and monitoring. FDA therefore estimates that 95 percent of all hematopoietic stem/progenitor cell establishments will need to develop a minor procedure for control and monitoring of ventilation and air filtration systems to comply with the CGTP rule. However, because the industry standards do provide for appropriate environmental controls, FDA assumes that some establishments are performing the necessary control and

monitoring activities. The agency estimates that as many as half of the establishments currently following industry standards may already be conducting routine inspections of their environmental control equipment. It is assumed that the remaining 50 percent of those establishments, and 95 percent of hematopoietic stem/progenitor cell establishments assumed not to be following industry standards, will incur additional costs to periodically inspect equipment and perform recordkeeping related to environmental control. Table 4 of this document provides estimates of cost per establishment associated with these efforts.

h. Section 1271.200—equipment. This final rule requires that appropriate equipment be used in processing HCT/Ps to prevent the introduction, transmission, or spread of communicable disease. Cleaning, sanitizing, maintenance, and calibration of equipment must be performed according to established schedules and procedures; equipment must be regularly inspected for adherence to applicable procedures and schedules; and all such activities must be documented. In addition, establishments must keep records of each use of each piece of equipment, including the identification of each HCT/P manufactured with that piece of equipment.

The standards related to equipment, as specified by AATB, EBAA, FACT, and AABB, generally address maintenance procedures, and recordkeeping related to maintenance. However, this final rule extends beyond industry standards of EBAA, FACT, and AABB in the areas of equipment inspection and recordkeeping. Based on information provided by industry sources, FDA believes that some of the larger HCT/P establishments may already be performing the required equipment inspection and recordkeeping.

FDA therefore estimates that 95 percent of all eye banks will allocate an additional 1/2-hour per month for the laboratory supervisor to inspect equipment, an additional 1/2-hour per month of technician time to document equipment cleaning and calibration, and 2 additional hours per month for a technician to record each use of the equipment.

The estimated 23 percent of conventional tissue banks that currently do not follow AATB standards will also incur new costs related to the equipment provisions. FDA estimates that small establishments will prepare one minor procedure for calibration, and for cleaning and other maintenance for each of six pieces of equipment. In addition, small establishments 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 of technician time to record each use of the equipment. FDA estimates that large establishments will need to write minor procedures for each of eight pieces of equipment, will 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 establishments simultaneously preparing multiple procedures related to equipment will 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 required to prepare six to eight minor equipment maintenance procedures.

It is expected that hematopoietic stem/progenitor cell establishments will also be required to perform additional work to align current practice with the

CGTP requirements. Current FACT procedures provide for routine maintenance and calibration of equipment. In addition, the AABB standards recommend that SOPs be established for proper equipment maintenance and monitoring. To further develop procedures to address routine maintenance and recordkeeping under the CGTP rule, FDA estimates that 95 percent of all hematopoietic stem/progenitor cell establishments will prepare a minor procedure for calibration of each of six pieces of equipment. In addition to the preparation of procedures, lab personnel will be involved in carrying out the necessary maintenance work, estimated to require an additional 1/2 hour of lab supervisor time per month for routine inspection of equipment, an additional 1/2 hour per month for lab technicians to document cleaning and calibration work, and an additional 4 hours per month of lab technician time to record each use of equipment. In addition, most cell establishments that do not currently follow FACT or AABB standards will incur the cost of preparing a minor procedure for cleaning and sanitizing, and for routine maintenance of each of six pieces of equipment. Section 2.4.8 of the FDA and ERG background papers (see footnote 1 of this document) provide detailed presentations of these assumptions.

i. Section 1271.210—supplies and reagents. The CGTP rule requires manufacturers to verify that supplies and reagents used in the manufacture of HCT/Ps meet specifications designed to prevent circumstances that increase the risk of introduction, transmission, or spread of communicable disease. Verification of quality may be accomplished by the establishment that uses the supply or reagent, or the vendor of the supply or reagent. This final rule also requires documentation of the receipt and verification of supplies or

reagents used in HCT/P processing, and of the lot of supply or reagent used in the manufacture of each HCT/P.

The existing industry standards address some or all of these activities, and the estimated impact per establishment varies accordingly. EBAA standards specify that sterilized supplies and reagents must contain sterilization dates and method, or appropriate expiration dates. However, the agency estimates that up to 95 percent of eye banks will need to devote additional resources to receipt and verification activities, and will devote additional staff time to recording the receipt of supplies and reagents. Similarly, FACT 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 hematopoietic stem/progenitor cell establishments will expand on their current supply and reagent related recordkeeping to comply with these CGTP provisions.

The current AATB standards address most of the requirements for supplies and reagents included in the final rule. FDA assumes that the estimated 23 percent of conventional tissue establishments that do not follow these standards will require additional resources for in-house reagent receipt and verification, and will devote additional staff time to keeping records of the receipt and verification of supplies and reagents. The estimated costs per establishment for these provisions are presented in table 4 of this document.

j. Section 1271.215—recovery. The CGTP final rule requires that each HCT/P be recovered in a way that does not cause contamination or cross contamination during recovery, or otherwise increase the risk of the introduction, transmission, or spread of communicable disease through the use

of the HCT/P. Because this section does not impose any specific requirements it is not expected to impose any identifiable compliance costs.

k. Section 1271.220—processing and process controls. The CGTP final rule requires establishments to process HCT/Ps in a way that does not cause contamination or cross-contamination during processing, and that prevents the introduction, transmission, or spread of communicable disease. An establishment processing HCT/Ps is responsible for ensuring that each in-process HCT/P is controlled until the results of any required inspections, testing, verification activities or approvals are received and documented. The standards for tissue banking specified by the AATB include activities to address these process controls, but the EBAA, FACT, and AABB standards do not include specific requirements for in-process monitoring. FDA estimates that 95 percent of eye banks, 23 percent of conventional tissue banks, and 95 percent of hematopoietic stem/progenitor cell establishments will need to prepare a minor procedure related to process monitoring.

l. Section 1271.225—process changes. This final rule requires establishments to verify or validate any changes to established procedures to ensure that the change does not create an adverse impact elsewhere in the operation. Process changes must be approved before implementation by a responsible person and approved changes must be communicated to appropriate personnel in a timely manner. The current standards for AATB, FACT, and the AABB provide for SOPs for process changes, although recordkeeping procedures are not specified. Current EBAA standards do not provide for SOPs for process changes. FDA therefore estimates that nearly all eye banks will need to prepare a major procedure for process changes, and

will allocate an additional 1/2 hour of lab director time to document process changes.

FDA anticipates that the 23 percent of conventional tissue banks not following the AATB standards will need to prepare a major procedure related to process changes, and that nearly all tissue banks will increase related recordkeeping. The agency estimates that small conventional tissue banks will spend an additional 1/2 hour per month of lab director time to document process changes, and that large establishments would allocate an additional hour of lab director time per month for this activity. FDA anticipates that almost all hematopoietic stem/progenitor cell establishments that do not follow FACT or AABB standards will need to prepare a major procedure to address process changes. In addition, FDA estimates that 95 percent of all hematopoietic stem/progenitor cell establishments will also allocate an additional half hour of lab director time per month to document process changes. The associated costs per establishment are presented in table 4 of this document.

m. Section 1271.230—process validation. This final rule requires establishments to validate processes that cannot be verified through subsequent inspection and testing, and that the validation activities and results be documented. Current EBAA standards do not require process validation. Based on information provided by industry sources, FDA believes that some of the larger eye banks may already be performing the required process validation. Although current AATB, FACT, and AABB standards include provisions for process validation and related recordkeeping, industry experts indicate that additional validation work will be required at nearly all establishments under the CGTP final rule. FDA therefore estimates that 95 percent of all eye banks,

conventional tissue banks, and all hematopoietic stem/progenitor cell establishments not following AABB or FACT voluntary standards, will prepare two major procedures related to process validation, and 95 percent of conventional tissue banks and hematopoietic stem/progenitor cell establishments will revise two major procedures. Further, FDA estimates that 95 percent of all establishments in each sector of the HCT/P industry will devote additional staff time to perform process validation. Details of these assumptions are provided in section 2.4.12 of the background papers (see footnote 1 of this document) by ERG and FDA.

In addition to the initial validation work, the CGTP final rule requires revalidation when changes to a validated process occur. The agency estimates that approximately 95 percent of eye banks, conventional tissue banks, and hematopoietic stem/progenitor cell establishments will need to allocate an additional 20 to 40 hours of laboratory staff time annually for procedure revalidation. Costs for these provisions of the CGTP rule are presented in table 4.

n. Section 1271.250—labeling controls. The CGTP rule requires establishments to establish and maintain written procedures for controlling the labeling of products. These procedures must ensure proper identification of products and include various checks and verifications. Each product must also be accompanied by a summary of donor eligibility information, if applicable.

According to consultants and industry contacts, labeling controls are usual and customary practice in all sectors of the HCT/P industry. FDA anticipates that only about 5 percent of eye banks, conventional tissue banks and hematopoietic stem/progenitor cell processing establishments will need to perform additional work to comply with the CGTP labeling controls. FDA

estimates that such establishments will need to revise a major procedure for proper identification of products.

o. Section 1271.260—storage. The CGTP final rule requires that storage areas be controlled to prevent mixups, contamination, cross-contamination, and to prevent an HCT/P from being improperly made available for distribution. Temperature must be monitored and limits established, including expiration dating where appropriate. Each of the relevant HCT/P industry standards contains provisions regarding storage practices. Based on agency review of current industry standards, and conversations with experts about current practices at HCT/P establishments, FDA anticipates that virtually all establishments already comply with these provisions of the CGTP rule. These provisions are therefore expected to produce no new cost impact for eye banks, conventional tissue banks and hematopoietic stem/progenitor cell processing establishments.

p. Section 1271.265—receipt, predistribution shipment, and distribution. The CGTP final rule requires that procedures be established and maintained for receipt (e.g., determination of whether to accept, reject, or place the HCT/P in quarantine), predistribution shipment, and distribution of HCT/Ps. Documentation of each of the aforementioned activities, when performed, is also required. Packaging and shipping containers must be designed and constructed to protect the HCT/P from contamination, and appropriate shipping conditions must be established and maintained during transit. Procedures must 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 most provisions related to this area of quality control are included in each of the relevant industry standards.

The primary impact of the CGTP provisions for product receipt, predistribution shipment, and distribution, thus, involves procedures development for establishments that do not currently follow industry standards. FDA estimates that 5 percent of eye banks, conventional tissue banks, and hematopoietic stem/progenitor cell establishments will increase lab supervisor time to document the receipt of products.

The agency estimates that conventional tissue banks not following AATB standards will 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 hematopoietic stem/progenitor cell establishments will write one major procedure addressing receiving activities. Establishments following FACT or AABB standards will also need to revise a major procedure for product distribution, while all other establishments will need to prepare a new major procedure for product distribution, as well as a minor procedure for the handling of products returned to inventory. Details of these assumptions are presented in section 2.4.15 of the background papers (see footnote 1 of this document) by ERG and FDA and the estimated costs per establishment for these activities are presented in table 4 of this document.

q. Section 1271.270—records. The CGTP rule requires that records be maintained for all steps required in this subpart and subpart C of this part. A records management system relating only to core CGTP requirements must be established and maintained. Records pertaining to a particular HCT/P must be maintained for at least 10 years after the date of administration, if known, or at least 10 years after the date of the HCT/P's distribution, disposition or expiration, whichever is latest. This final rule also requires that records be kept

of any contracts or agreements. Although many components of the required recordkeeping system are addressed under individual provisions of the CGTP rule, there may be a few minor gaps in the records system of an establishment that would be addressed under this general provision. The agency therefore estimates that approximately 95 percent of all eye banks, conventional tissue banks, and hematopoietic stem/progenitor cell establishments that do not follow FACT or AABB standards, will write at least one minor procedure, and revise one major procedure related to recordkeeping.

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

Various industry standards specify record retention, although the time periods vary somewhat. Of those establishments following industry standards, approximately 95 percent of eye banks and 75 percent to 80 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 establishments, and the hematopoietic stem/progenitor cell establishments that do not currently follow industry standards, FDA estimates increased record retention costs based on the cost of storing an additional five boxes (2.4 cubic feet each) of records per year for 5 years. The estimated record retention costs should be viewed as maximum potential burdens since affected entities have the option to retain the required records in more cost-effective (e.g., electronic) formats and because some establishments already retain records for 10 years.

The retention standards of FACT and AABB for records related to products are different from those concerned with facility and equipment maintenance, and personnel education and training. All records related to hematopoietic stem/progenitor cell products must be retained indefinitely whereas records related to facility and equipment maintenance and personnel training must be retained for only 5 years.

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

r. Section 1271.290—tracking. This final rule stipulates the steps needed to properly track a product from donor to consignee or final disposition and vice versa. The CGTP rule requires that establishments maintain a method for product tracking and that each product is assigned and labeled with a distinct identification code (identifier). If a new identifier is assigned during the manufacturing process, procedures must be in place for relating the new identifier to the old identifier. The establishment that manufactured the product must also keep track of the disposition of each product, so that the consignee can be easily identified. Establishments must also inform consignees

in writing of the requirements of this section and of the established tracking method. In addition, labeling must include information designed to facilitate effective tracking from the donor to the recipient and from the recipient to the donor.

Product “traceability” is a familiar concept and common practice in the eye banking, conventional tissue and hematopoietic stem/progenitor cell processing industries. 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 banks will need to enhance current tracking systems, prepare one major procedure related to product tracking, spend additional staff time each month to identify and document consignee information, and allocate additional laboratory director time to inform the consignees who receive products and ensure the tracking requirements are met.

Conventional tissue banks following AATB standards are able to trace all products from donation source to product recipient. Conventional tissue establishments not following AATB requirements will need to revise a major procedure to address product tracking, and to allocate additional staff time each month to obtain and record information about product consignees. The FACT and AABB standards for product tracking in hematopoietic stem/progenitor cell establishments recommend that the establishment 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 hematopoietic stem/progenitor cell establishments will, on a one-time basis, allocate an additional 20 hours of laboratory supervisor time to inform consignees who will receive

products of tracking systems and requirements. In addition, FDA estimates that 95 percent of hematopoietic stem/progenitor cell establishments that are not following FACT or AABB standards will need to revise a major procedure related to product tracking, and will need to allocate additional staff hours each month for consignee documentation. The estimated costs per establishment to perform these activities are presented in table 4 of this document.

s. Section 1271.320—complaint file. The CGTP final rule requires establishments to maintain procedures for the review, evaluation, and documentation of complaints relating to core CGTP requirements, and the investigation of complaints as appropriate. Establishments are required to review and evaluate complaints as soon as practical and to determine whether each complaint represents an event that must be reported to FDA. Documentation of the review and evaluation is required, even if no reporting is made. FDA finds that the AATB, FACT, and AABB standards explicitly address procedures for, or recordkeeping related to, complaints. Based on discussions with industry experts, the agency anticipates that nearly all establishments currently track, albeit informally, the complaints received from consignees and recipients. Establishments that must prepare new written procedures for review and handling of complaints would incur additional costs under these CGTP provisions. The agency estimates that the additional costs for establishments to maintain a complaint file would be negligible.

To fully comply with these provisions of the CGTP rule, FDA estimates that 95 percent of all eye banks will revise a minor procedure to include the required handling of complaints, and allocate some additional staff time each year to review complaints. FDA assumes that conventional tissue banks

following AATB standards will already be performing the necessary activities, but the estimated 23 percent of establishments not following AATB standards will need to prepare a minor procedure for complaint handling, and allocate additional laboratory director time each year to review any complaints received.

Although the industry standards for hematopoietic stem/progenitor cell processing require that records be maintained of both donor and recipient complaints, the CGTP rule requires that establishments also have written procedures for complaint review. FDA therefore estimates that 95 percent of hematopoietic stem/progenitor cell establishments will write a minor procedure to handle complaints, and that 95 percent of all establishments that do not follow industry standards will also allocate additional time for yearly review and handling of complaints. Details of these assumptions are presented in section 2.4.18 of the background papers (see footnote 1 of this document) by FDA and ERG.

t. Section 1271.350—reporting. This final rule requires establishments to investigate adverse reaction reports and report to FDA any adverse reactions, involving a communicable disease, that are fatal, life-threatening, result in permanent impairment of the body, or necessitate medical or surgical intervention, including hospitalization. In addition, the final rule requires establishments to investigate all HCT/P deviations and report to FDA any deviation related to core CGTP requirements if the deviation occurs in the establishment's facility or in a facility that performs a manufacturing step under contract, agreement, or other arrangement with the establishment. In our economic analysis of the proposed CGTP rule, we assumed that these provisions would result in negligible new costs for affected entities. However,

because these are new FDA reporting requirements, the agency believes that additional costs will be incurred by all eye banks, conventional tissue banks, and hematopoietic stem/progenitor cell establishments. The agency further estimates that a typical affected establishment will submit an average of six Form FDA 3500A (adverse reaction) reports and two Form FDA 3486 (HCT/P deviation) reports per year, requiring an additional 8 hours of laboratory director time. The associated costs are presented in table 4 of this document.

u. Section 1271.370—labeling. The CGTP rule requires that products be labeled clearly and accurately, with information including a description of the HCT/P along with its distinct identification code, the name and address of the manufacturer, a description of the product and the product expiration date. The storage temperature, appropriate warnings, and adequate instructions for use when related to the prevention of the introduction, transmission, or spread of communicable disease must also be provided on the label or on a package insert.

Industry consultants inform FDA that the required elements are typically present on the labels of products manufactured by eye banks, conventional tissue banks, and hematopoietic stem/progenitor cell establishments. Proper labeling is considered very important to these industries, to prevent the misuse of their products. FDA assumes, therefore, that establishments in the various sectors of the HCT/P industry are already compliant with these provisions of the CGTP final rule, and that the cost impact will be negligible.

v. Section 1271.400—inspections. FDA could conduct inspections of any facility subject to the CGTP final rule. FDA will typically 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 this final rule. The agency estimates that all industry establishments, both domestic and foreign, will be subject to this provision of the CGTP final rule, and inspections will occur periodically. FDA estimates that up to 16 hours of laboratory technician time will 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 will be needed for activities related to the inspection. This is expected to impose a cost of approximately \$768 per establishment per inspection.

w. Section 1271.420—HCT/Ps offered for import. The CGTP final rule requires importers of HCT/Ps to notify the FDA district director having jurisdiction over the port of entry through which the HCT/P is imported or offered for import. The HCT/P must be held intact or transported under quarantine until it is inspected and released by FDA. There is currently very limited use of imported HCT/Ps that would trigger activities for compliance with this provision of the CGTP final rule. FDA therefore estimates the current cost for industry compliance with this requirement to be negligible.

x. Section 1271.440—orders of retention, recall, and cessation of manufacturing. Firms in the HCT/P industry may incur costs to comply with orders issued under this provision. There is little available data on which to base estimates of the future frequency and scope of HCT/P industry conditions and practices that would necessitate such actions on the part of FDA. The agency anticipates that orders issued under this provision of the CGTP final rule will be rare. FDA estimates that the yearly costs to the HCT/P industry resulting from such orders will therefore be negligible.

3. Estimated Impact on Reproductive Tissue Establishments

As explained elsewhere in this preamble, establishments involved with reproductive tissue (e.g., ART establishments and semen banks) are subject only to the CGTP inspection and enforcement provisions of § 1271.400 as they apply to donor eligibility requirements under subpart C. The impact of these provisions is described in the following section and the estimated cost impact is presented in table 6 of this document.

TABLE 6.—ESTIMATED COST PER ESTABLISHMENT AND ESTIMATED PERCENTAGE OF REPRODUCTIVE TISSUE ESTABLISHMENTS AFFECTED BY THE CGTP FINAL RULE

21 CFR Section	Title	ART Establishments	Semen Banks
1271.400	Inspections	\$768 (100%)	\$768 (100%)

a. Section 1271.400—inspections. FDA could conduct inspections of any facility subject to subpart F. This provision affects reproductive tissue establishments only insofar as it applies to the donor eligibility requirements under subpart C, and not to CGTPs generally. FDA will typically interact primarily with one responsible person for each establishment, but other personnel may also be involved in the inspection. FDA could inspect the donor eligibility related procedures and records of reproductive tissue establishments, and could review and copy any records required to be kept under this final rule.

The agency estimates that all ART and semen bank establishments, whether domestic or foreign, will be subject to this provision of the CGTP final rule, and inspections will occur periodically. FDA estimates that up to 16 hours of laboratory technician time will be necessary, to accompany the FDA inspector through the establishment and to support the inspector's information needs, and that up to 4 hours of laboratory director time will be needed for activities related to the inspection. This is expected to impose a cost of approximately \$768 per establishment per inspection. This is the only

provision of the CGTP final rule that applies to establishments involved with reproductive tissues.

4. Summary of Estimated One-Time, Annual, and Annualized Cost Impacts

The costs for each section of the CGTP final rule are computed as the product of the estimated number of affected establishments (table 3 of this document), the estimated compliance cost per establishment, and the estimated percentage of establishments not currently following CGTPs (table 4 of this document), and are presented by HCT/P industry sector in tables 7 through 11 of this document. The total one-time and annual compliance costs, summed over all provisions of the CGTP rule, are also presented by HCT/P industry sector in these tables. The aggregate one-time and annual compliance costs for all sectors of the HCT/P industry are summarized in table 12 of this document. The total annualized cost estimates presented in tables 7 through 12 of this document include both the estimated annual and one-time costs, such as are incurred to prepare new procedures, and are annualized over 10 years using both 7 percent and 3 percent discount rates.

TABLE 7.—AGGREGATE COMPLIANCE COSTS FOR EYE BANKS

21 CFR Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs ¹	Total Annualized Costs ²
1271.150	CGTP Requirements	\$0	\$0	\$0	\$0
1271.155	Exemptions & Alternatives	\$0	\$0	\$0	\$0
1271.160	Quality Program	\$159,038	\$569,031	\$591,674	\$587,675
1271.170	Personnel	\$0	\$0	\$0	\$0
1271.180	Procedures	\$0	\$61,104	\$61,104	\$61,104
1271.190	Facilities	2,328	\$0	\$331	\$273
1271.195	Environmental Control & Monitoring	\$0	\$28,550	\$28,850	\$28,850
1271.200	Equipment	\$0	\$138,248	\$138,248	\$138,248
1271.210	Supplies & Reagents	\$16,613	\$22,150	\$24,515	\$24,098
1271.215	Recovery	\$0	\$0	\$0	\$0
1271.220	Processing and Process Controls	\$48,374	\$0	\$6,887	\$5,671
1271.225	Process Changes	\$96,748	\$58,049	\$71,824	\$69,391
1271.230	Process Validation	\$409,906	\$108,205	\$166,566	\$156,258

TABLE 7.—AGGREGATE COMPLIANCE COSTS FOR EYE BANKS—Continued

21 CFR Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs ¹	Total Annualized Costs ²
1271.250	Labeling Controls	\$2,456	\$0	\$362	\$298
1271.260	Storage	\$0	\$0	\$0	\$0
1271.265	Receipt, Predistribution Shipment & Distribution	\$0	\$182,990	\$182,990	\$182,990
1271.270	Records	\$479,603	\$121	\$68,405	\$56,345
1271.290	Tracking	\$15,276	\$11,578	\$13,753	\$13,368
1271.320	Complaint File	\$16,613	\$77,398	\$79,764	\$79,364
1271.350	Reporting	\$0	\$81,472	\$81,472	\$81,472
1271.370	Labeling	\$0	\$0	\$0	\$0
1271.400	Inspections	\$0	\$102,912	\$102,912	\$102,912
1271.420	HCT/Ps Offered for Import	\$0	\$0	\$0	\$0
1271.440	Orders of Retention, Recall, Destruction and Cessation of Manufacturing	\$0	\$0	\$0	\$0
Total	All Sections	\$1,247,044	\$1,442,108	\$1,619,659	\$1,588,300

¹ Over 10 years at 7 percent interest.

² Over 10 years at 3 percent interest.

TABLE 8.—AGGREGATE COMPLIANCE COSTS FOR CONVENTIONAL TISSUE ESTABLISHMENTS

21 CFR Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs ¹	Total Annualized Costs ²
1271.150	CGTP Requirements	\$0	\$0	\$0	\$0
1271.155	Exemptions & Alternatives	\$0	\$0	\$0	\$0
1271.160	Quality Program	\$127,960	\$213,246	\$231,464	\$228,247
1271.170	Personnel	\$594,081	\$101,444	\$186,028	\$171,088
1271.180	Procedures	\$0	\$348,202	\$348,202	\$348,202
1271.190	Facilities	\$14,838	\$0	\$2,113	\$1,739
1271.195	Environmental Control & Monitoring	\$14,838	\$8,124	\$10,237	\$9,863
1271.200	Equipment	\$137,313	\$101,411	\$120,961	\$117,508
1271.210	Supplies & Reagents	\$29,676	\$8,124	\$12,349	\$11,603
1271.215	Recovery	\$0	\$0	\$0	\$0
1271.220	Processing and Process Controls	\$20,516	\$0	\$2,921	\$2,405
1271.225	Process Changes	\$41,033	\$87,940	\$93,782	\$92,750
1271.230	Process Validation	\$437,574	\$268,090	\$330,391	\$319,387
1271.250	Labeling Controls	\$4,460	\$0	\$635	\$523
1271.260	Storage	\$0	\$0	\$0	\$0
1271.265	Receipt, Predistribution Shipment & Distribution	\$55,871	\$237,058	\$245,012	\$243,607
1271.270	Records	\$287,965	\$687	\$41,687	\$34,446
1271.290	Tracking	\$78,550	\$161,361	\$172,544	\$170,569
1271.320	Complaint File	\$14,837	\$28,388	\$30,500	\$30,127
1271.350	Reporting	\$0	\$100,928	\$100,928	\$100,928
1271.370	Labeling	\$0	\$0	\$0	\$0
1271.400	Inspections	\$0	\$127,488	\$127,488	\$127,488
1271.420	HCT/Ps Offered for Import	\$0	\$0	\$0	\$0

TABLE 8.—AGGREGATE COMPLIANCE COSTS FOR CONVENTIONAL TISSUE ESTABLISHMENTS—Continued

21 CFR Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs ¹	Total Annualized Costs ²
1271.440	Orders of Retention, Recall, Destruction and Cessation of Manufacturing	\$0	\$0	\$0	\$0
Total	All Sections	\$1,859,510	\$1,792,489	\$2,057,241	\$2,010,480

^a Over 10 years at 7 percent interest^b Over 10 years at 3 percent interest

TABLE 9.—AGGREGATE COMPLIANCE COSTS FOR HEMATOPOIETIC STEM/PROGENITOR CELL ESTABLISHMENTS

Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs ^a	Total Annualized Costs ^b
1271.150	CGTP Requirements	\$0	\$0	\$0	\$0
1271.155	Exemptions & Alternatives	\$0	\$0	\$0	\$0
1271.160	Quality Program	\$208,354	\$457,200	\$486,865	\$481,625
1271.170	Personnel	\$739,100	\$117,610	\$222,841	\$204,255
1271.180	Procedures	\$0	\$433,200	\$433,200	\$433,200
1271.190	Facilities	\$90,784	\$665,000	\$677,926	\$675,643
1271.195	Environmental Control & Monitoring	\$90,784	\$205,458	\$218,383	\$216,100
1271.200	Equipment	\$450,621	\$465,548	\$529,706	\$518,374
1271.210	Supplies & Reagents	\$135,185	\$8,265	\$27,512	\$24,113
1271.215	Recovery	\$0	\$0	\$0	\$0
1271.220	Processing and Process Controls	\$198,550	\$0	\$28,269	\$23,276
1271.225	Process Changes	\$36,100	\$119,130	\$124,270	\$123,362
1271.230	Process Validation	\$678,775	\$297,825	\$394,467	\$372,398
1271.250	Labeling Controls	\$5,225	\$0	\$744	\$613
1271.260	Storage	\$0	\$0	\$0	\$0
1271.265	Receipt, Predistribution Shipment & Distribution	\$482,861	\$28,080	\$96,829	\$84,686
1271.270	Records	\$178,956	\$2,880	\$28,359	\$23,859
1271.290	Tracking	\$415,150	\$164,160	\$223,268	\$212,828
1271.320	Complaint File	\$90,784	\$158,840	\$171,766	\$169,483
1271.350	Reporting	\$0	\$167,200	\$167,200	\$167,200
1271.370	Labeling	\$0	\$0	\$0	\$0
1271.400	Inspections	\$0	\$211,200	\$211,200	\$211,200
1271.420	HCT/Ps Offered for Import	\$0	\$0	\$0	\$0
1271.440	Orders of Retention, Recall, Destruction and Cessation of Manufacturing	\$0	\$0	\$0	\$0
Total	All Sections	\$3,801,230	\$3,501,595	\$4,042,805	\$3,947,215

¹ Over 10 years at 7 percent interest.² Over 10 years at 3 percent interest.

TABLE 10.—AGGREGATE COMPLIANCE COSTS FOR ART ESTABLISHMENTS

21 CFR Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs ¹	Total Annualized Costs ²
1271.400	Inspections	\$0	\$307,200	\$307,200	\$307,200
Total	All Sections	\$0	\$307,200	\$307,200	\$307,200

¹ Over 10 years at 7 percent interest.² Over 10 years at 3 percent interest.

TABLE 11.—AGGREGATE COMPLIANCE COSTS FOR SEMEN BANKS

21 CFR Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs ¹	Total Annualized Costs ²
1271.400	Inspections	\$0	\$84,480	\$84,480	\$84,480
Total	All Sections	\$0	\$84,480	\$84,480	\$84,480

¹ Over 10 years at 7 percent interest.

² Over 10 years at 3 percent interest.

TABLE 12.—AGGREGATE COMPLIANCE COSTS FOR ALL HCT/P INDUSTRY SECTORS

21 CFR Section	Title	One-Time Costs	Annual Costs	Total Annualized Costs ¹	Total Annualized Costs ²
1271.150	CGTP Requirements	\$0	\$0	\$0	\$0
1271.155	Exemptions & Alternatives	\$0	\$0	\$0	\$0
1271.160	Quality Program	\$495,351	\$1,239,477	\$1,310,003	\$1,297,547
1271.170	Personnel	\$1,333,181	\$219,054	\$408,869	\$375,343
1271.180	Procedures	\$0	\$842,506	\$842,506	\$842,506
1271.190	Facilities	\$107,950	\$665,000	\$680,370	\$677,655
1271.195	Environmental Control & Monitoring	\$105,622	\$242,432	\$257,470	\$254,814
1271.200	Equipment	\$587,933	\$705,206	\$788,914	\$774,130
1271.210	Supplies & Reagents	\$181,473	\$38,539	\$64,377	\$59,813
1271.215	Recovery	\$0	\$0	\$0	\$0
1271.220	Processing and Process Controls	\$267,440	\$0	\$38,077	\$31,352
1271.225	Process Changes	\$173,881	\$265,118	\$289,875	\$285,503
1271.230	Process Validation	\$1,526,255	\$674,120	\$891,424	\$853,044
1271.250	Labeling Controls	\$12,231	\$0	\$1,741	\$1,434
1271.260	Storage	\$0	\$0	\$0	\$0
1271.265	Receipt, Predistribution Shipment & Distribution	\$538,732	\$448,128	\$524,831	\$511,284
1271.270	Records	\$946,524	\$3,688	\$138,452	\$114,649
1271.290	Tracking	\$508,976	\$337,098	\$409,565	\$396,766
1271.320	Complaint File	\$122,235	\$264,626	\$282,029	\$278,956
1271.350	Reporting	\$0	\$349,600	\$349,600	\$349,600
1271.370	Labeling	\$0	\$0	\$0	\$0
1271.400	Inspections	\$0	\$833,280	\$833,280	\$833,280
1271.420	HCT/Ps Offered for Import	\$0	\$0	\$0	\$0
1271.440	Orders of Retention, Recall, Destruction and Cessation of Manufacturing	\$0	\$0	\$0	\$0
Total	All Sections	\$6,907,784	\$7,127,872	\$8,111,384	\$7,937,674

¹ Over 10 years at 7 percent interest.

² Over 10 years at 3 percent interest.

As shown in table 7 of this document, the total one-time costs for the eye banking industry are estimated to be \$1.25 million, and annual costs are estimated at \$1.44 million. These figures generate a total annualized cost estimate of \$1.59 million to \$1.62 million. For the conventional tissue industry

(table 8 of this document), aggregate one-time costs and annual costs are estimated at \$1.86 million and \$1.79 million, respectively. These figures correspond to an estimated annualized cost of \$2.01 million to \$2.06 million. The hematopoietic stem/progenitor cell industry (table 9 of this document) is estimated to incur a one-time cost of \$3.8 million and annual costs of \$3.5 million, yielding an annualized cost estimate of \$3.95 million to \$4.04 million. ART establishments and semen banks are expected to incur no one-time costs under the CGTP final rule because they are subject only to the inspection and enforcement provisions as they relate to donor eligibility requirements under subpart C. The total annual and annualized costs for ART establishments and semen banks are estimated to be \$0.31 million and \$0.08 million, respectively. These cost estimates are presented in tables 10 and 11 of this document.

Table 12 of this document summarizes the total estimated cost impacts for all HCT/P industry sectors. FDA estimates the aggregate one-time compliance costs of the CGTP final rule to be \$6.9 million. Annual costs, aggregated across all sectors of the HCT/P industry, are estimated to be \$7.13 million. These estimates correspond to a total annualized cost estimate of \$7.94 million to \$8.1 million for the CGTP final rule applied to all major sectors of the HCT/P industry.

C. Estimated Benefits of the CGTP Final Rule

The purpose of the CGTP final rule is to prevent the introduction, transmission, or spread of communicable disease through the use of HCT/Ps. Although voluntary industry standards exist for most of the affected products, FDA finds that public safety cannot be assured or effectively protected through reliance on these informal mechanisms. The existing industry standards also vary to some extent in their comprehensiveness, and there are variations in

the extent to which firms in the affected industry sectors follow these voluntary standards.

For example, most industry consultants providing input for this analysis agreed that quality standards, such as those in the CGTP final rule, and similar standards recommended by industry, could substantially reduce the risk of HCT/P product contamination by communicable disease agents. However, most of these experts also agreed 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 establishments are not currently following adequate quality control procedures. A regulatory requirement for quality systems and recordkeeping would provide the incentives needed to bring marginal establishments to a more uniform and appropriately high standard of quality in HCT/P processing.

The primary beneficiaries of the CGTP final rule are the patients who receive HCT/Ps. Benefits to patients result from improved outcomes due to reduced risks of communicable disease transmission. Society as a whole will benefit from implementation of CGTPs due to improved safety of the supply of HCT/Ps, and reductions in health care and other costs associated with treating the complications arising from the use of contaminated tissue products. The discussion that follows considers some of the potential benefits of CGTPs based on a survey of the clinical literature.

Recent clinical literature indicates that each type of HCT/P affected by the CGTP final rule has documented communicable disease transmission risk that may be the result of contamination or other problems resulting from processing, or other steps in manufacturing. Although the limited number of adverse events reported in the clinical literature suggests a relatively low risk

of communicable disease transmission associated with HCT/Ps, it is important to note that this evidence is generally based on analysis of a limited number of voluntarily reported incidents. The reported HCT/P problems provide a basis for assessing the magnitude of the potential benefit from further reducing the incidence of events that contribute to or increase the risk of communicable disease transmission. In some cases involving eye tissue, conventional tissue, or hematopoietic stem/progenitor cell products, HCT/P problems have required medical intervention to treat infection, or to replace an implanted HCT/P. In some clinical applications, HCT/P related problems have increased the risk of patient morbidity or mortality. In general, FDA anticipates that the risk of communicable disease transmission will decline, and patient outcomes will improve, as a result of industry compliance with the provisions of the CGTP final rule.

The sections that follow describe specific product-related problems associated with communicable disease transmission that are at least partly attributable to a lack of uniform and enforceable standards in HCT/P manufacturing. The costs of correcting these problems are considered, to gauge the potential magnitude of the benefits associated with improvements in manufacturing processes brought about through implementation of CGTPs. The discussion is organized by type of HCT/P.

1. Eye Tissue

Primary corneal graft failure is a key adverse outcome of concern following corneal tissue transplant. Such failures result in additional graft attempts, and each attempt increases the risk of communicable disease transmission by exposing the recipient to another HCT/P, and 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. 5), donor infectivity (e.g., with Herpes Simplex Virus and CJD) (Refs. 8 and 31), length of product storage, type of storage medium, and shipping distance from the eye bank to the recipient site. In an analysis of factors contributing to primary corneal graft failure, Wilhelmus et al. (Ref. 5) found that “the 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, even with modern eye bank screening and preservation procedures, a donor corneal storage time greater than 1 week increases the risk of primary corneal graft failure by more than two-fold.

Wilhelmus et al. include in their analysis a summary of selected findings of studies published between 1971 and 1994 that report the incidence of primary graft failure for corneal transplants using 4 degrees Celsius preservation, and a variety of preservation methods. The rates of primary graft failure reported ranged from 0.9 percent 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 verification of quality and documentation of the receipt of supplies and reagents used in HCT/P processing. The authors found that 86 cases (approximately 59 percent of all cases studied) of primary corneal graft failure shared preservation media from the same lots. These findings underline the importance of the CGTP requirement for verification of quality and

documentation of receipt for each particular lot of processing media used in the manufacture of uniquely labeled and traceable products.

Primary corneal graft failure typically requires repeat surgery to replace the failed graft. The Agency for Healthcare Research and Quality (AHRQ), reports 598 total discharges for Principal Procedure 13, Corneal transplant, with a mean hospital length of stay (LOS) of 3.5 days and a mean hospital charge of \$14,233 in 2000 (Ref.7). The estimated rate of primary graft failure, which may result from one or more aspects of cornea collection, processing, or distribution, ranges from 0.1 percent (based on the number of cases voluntarily reported to EBAA for the period 1991–1993, and again in 2001) 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 45,897 corneal transplants reported by the EBAA in 1999, the estimated number of cases of primary graft failure may range from 46 cases $[0.001 \times 45,897]$ to 413 cases $[0.009 \times 45,897]$ per year. The lowest estimate of the incidence of primary corneal graft failure reported by Wilhelmus et al. (0.9 percent) was used in this calculation to produce a conservative estimate of the number of cases, and in response to public comments on the proposed CGTP rule. The total cost of replacement of a failed corneal graft is estimated to include \$654 of physician services (Ref.8), including an office visit to diagnose the graft failure before hospitalization, and initial and followup physician visits during patient hospitalization for the repeated corneal transplant. It also includes one followup physician office visit to assess the outcome of the second transplant. The patient is estimated to further incur at least 1 week of time lost from work for doctor visits, hospitalization, and recovery of visual function after surgery. The cost of this

patient time loss is estimated at \$957.20, based on a 40-hour work week and U.S. average employer costs for employee compensation of \$23.93 (Ref. 32). Thus, the current annual cost impact of primary corneal graft failure may range from \$728,833 (46 x (\$14,233 + \$654 + \$957.20)) to \$6,543,655 (413 x (\$14,233 + \$654 + \$957.20)).

The risk, incidence, and cost of treating primary corneal graft failure will be reduced through the implementation of CGTPs, due to provisions requiring the validation of processing methods and process quality controls, the verification of supplies and reagents, and improved documentation. The total annualized cost to eye banks of implementing the CGTP final rule is estimated to be \$1.61 million to \$1.65 million, and the total cost of repeat surgery, hospitalization, physician's services and work loss associated with primary corneal graft failure is estimated to be \$15,844.20 per occurrence (\$14,233 + \$654 + \$957.20). Based on these estimates, if implementation of the CGTP final rule were to result in approximately 104 fewer cases (\$1.65 million / \$15,844 per case) of primary corneal graft failure per year, the benefits realized (in the form of avoided health care costs and income loss due to time away from work) would exceed the total annualized cost to eye banks, thereby making the rule cost effective for this sector of the HCT/P industry.

A reduction of 104 cases represents a 25 percent reduction (104 fewer cases / 413 total cases) in the risk of corneal graft failure (from 0.9 percent to 0.675 percent) based on the lowest rate reported by Wilhelmus et al. Due to uncertainty with respect to the actual risk of primary corneal graft failure, and the degree to which CGTPs would reduce this already uncertain risk, FDA is not able to determine whether or not implementation of this final rule would generate this level of risk reduction. No attempt was made to estimate the

benefits of any potential reduction in the risk of intraocular infection (another HCT/P-related problem associated with eye tissue) resulting from implementation of CGTPs due to a lack of data.

2. Conventional Tissue

Conventional tissue refers to a wide range of HCT/Ps including pericardium, dura mater, heart valves, skin allograft, bone allograft, fascia, tendons, and ligaments. FDA's survey of the clinical literature indicates that bone, skin and heart valve allografts each present a different potential for communicable disease transmission risk and graft failure, and thus different levels of potential benefits from improved processing procedures and quality assurance steps in HCT/P manufacture. The discussion that follows considers these three distinct conventional tissue products and thus areas of potential benefit.

a. *Bone allograft.* An analysis of the incidence, nature, and treatment of infection associated with bone allograft by Lord et al. (Ref.9), 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 patients) of the infected allografts 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 infected grafts), highlighting the critical need for HCT/Ps that are free from contamination by communicable disease agents. Other factors cited include duration of the

operation, loss of blood, injury to soft tissue, and skin sloughing during the operation.

The importance of process validation is also implied by Hardin (Ref.10) in a review of banked bone allograft processes. In describing methods for sterilization, Hardin identifies ethylene oxide as one of the chemicals used, but indicates that its effectiveness may nonetheless be questionable, because of reports of graft failures in which residues of ethylene oxide have been implicated, 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 x an estimated 0.82 failure rate for infected bone allograft), and the conservative assumption that all graft failures would be treatable through repeat surgery to replace the bone allograft, the associated healthcare costs could be on the order of \$60 million per year ($\$59,679,928 = 0.057 \times 44,000 \times (\$22,497 + \$1,133)$). This figure is based on a national level estimate of 44,000 bone allografts per year (Ref.11), and a mean hospital charge of \$22,497 for Principle Procedure 142, Partial excision of bone (Ref. 28). Physician costs per hospitalization are estimated to be \$1,133, based on submitted charges per person served in the Orthopedic Surgery Physician Specialty category (Ref. 8).

The reported average length of hospital stay for bone surgery is approximately 6.3 days (Ref. 28). The estimated cost of patient time lost assumes that repeat surgery would require at least 1 week of time away from work, at an estimated value of \$957.20, based on a 40-hour work week and average hourly compensation of \$23.93 (Ref.32). This yields an estimated total patient time cost of \$2,400,658 ($0.057 \times 44,000 \times \9357.20). Thus, the total

annual cost of bone allograft failure due to contamination is estimated to be approximately \$62 million ($\$62,080,586 = \$59,679,928 + \$2,400,658$).

If bone allograft failures result in amputation, the direct and indirect costs would be significantly higher. For example, the direct cost per hospitalization for lower extremity amputation is estimated to be \$30,820 based on AHRQ Healthcare Cost and Utilization Project (HCUP) data (Ref. 23). Moreover, permanent disability following amputation imposes extremely high costs on the patient, the patient's family, and on society as a whole. The AHRQ HCUP data also report 5,200 in-hospital deaths and a 4.5 percent death rate associated with these amputation procedures.

FDA is uncertain about the extent to which the estimated cost impact will be reduced through implementation of the CGTP final rule for two reasons. First, many graft failures result from transplantation procedures and other factors not related to bone allograft manufacture, or from a combination of factors. Second, some establishments may have already developed new bone processing methods that may greatly reduce infection risk. If as much as 90 percent of the estimated risk is actually attributable to other factors, or has already been addressed through better manufacturing processes, the benefit from CGTPs applied to the remainder of bone tissue processes and establishments would be on the order of \$6.2 million ($\$62,080,586 \times 0.10$) per year. The total annualized cost of the CGTP final rule for all conventional tissue banks is estimated to be \$2.03 million to 2.07 million, and the estimated total cost of treatment for infected bone allograft, including hospitalization, physician's office visits and work loss is \$24,587.20 per occurrence. If implementation of the CGTP final rule resulted approximately 84 fewer cases of infected bone allograft requiring repeat surgery ($\$2,073,547 / \$24,587.2 =$

84.3), the benefits of CGTPs would exceed the estimated total annualized costs for all conventional tissue banks. This reduction in the number of cases of bone allograft infection corresponds to a 3.3 percent reduction (84.3 fewer cases / 2,525.6 potential cases) in risk based on the information used as the basis for this analysis.

b. *Skin allograft.* Skin allografts represent another type of HCT/P that is critically dependent on processing and quality controls to prevent the manufacture, distribution and/or use of contaminated products. The clinical literature reports cases of cytomegalovirus (CMV) transmission due to skin donor infection (Ref.12), and HIV contamination from infected donor skin tissue and subsequent tissue processing (Ref.13). 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 injuries and are therefore susceptible to potentially life-threatening CMV infections. These include pneumonitis, retinitis, gastroenteritis, hepatitis, and neurological complications (Ref. 12). Contamination of skin allograft can also significantly affect burn patient survival. Because the clinical literature does not provide summary estimates of the risk of contamination associated with skin allograft, the agency is unable to quantify the level of associated risk. Although implementation of the CGTP final rule is expected to reduce the risk of contaminated skin allograft, and thereby improve burn patient outcomes, FDA could not quantify this source of expected patient benefits due to a lack of necessary information.

c. *Heart Valve Allografts.* Heart valve allografts, another of the many types of conventional tissue products, provides another compelling case for HCT/

P production process validation and quality control. Human heart valve contaminants not effectively removed in tissue processing have resulted in serious infections that, at a minimum, require valve replacement and may also result in patient death. Sources of contamination of a heart valve allograft include the donor, the environment during harvesting and processing, and the operating room during implantation. Microbial contamination of human heart valves 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.14) common contaminants found before disinfection consist of gastrointestinal and skin flora (including coliforms), viridans group streptococci, *Staphylococcus aureus*, *S. epidermidis*, and *Bacillus* species. In general, bacterial contamination can be effectively removed through standard disinfection procedures used in most accredited conventional 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 of heart valve allograft 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 tissue disinfection regimens is not effective in eradicating fungal contamination.

Fungal endocarditis is a rare but potentially fatal complication of allograft heart 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 0.85 percent). In one reported case, the infected patient needed subsequent surgery to replace the valve and required treatment with 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 patients who had acquired fungal endocarditis after heart valve allograft implantation died within 2 weeks of diagnosis.

In their study, Kuehnert et al. describe the process controls used by AATB-affiliated establishments including the establishment, validation and documentation of decontamination protocols. Because these regimens have not been found effective against fungal contamination, AATB-affiliated establishments routinely discard tissue with documented fungal contamination. However, according to Kuehnert et al., the supplier of over 85 percent of all heart valve allografts (approximately 41,000 since 1984) 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 results in tissue being distributed for use in patients.

The CGTP final rule requires that all establishments use validated procedures and that HCT/Ps meet all release criteria before they are made available for distribution. Based on the rates of infection and mortality risk reported by Kuehnert et al., and an estimated 5,000 to 6,000 human heart valve allografts per year (these figures were reported to the agency by the largest supplier of this type of HCT/P in their comment on the proposed rule), there may be an estimated 43 ($0.0085 \times 5,000$) to 51 ($0.0085 \times 6,000$) cases of fungal endocarditis each year. These cases of fungal endocarditis may further cause an estimated 17 ($0.0085 \times 0.40 \times 5000$) to 20 patient deaths per year (0.0085

x 0.40 x 6,000). Fungal endocarditis may result from a variety of peri- or post-operative factors including infection of the valve allograft itself. While highly uncertain, one comment suggested that as many as one-third of all cases of fungal endocarditis may be caused by contaminated valve allografts. Based on this information, FDA expects that there may be as many as 14 to 17 cases of heart valve contamination causing fungal endocarditis along with 5 to 7 patient deaths each year. Changes in processing procedures based on the CGTP requirements will help to avoid cases of fungal endocarditis and, perhaps, some of the resulting deaths. Substantial health care cost savings will also be achieved through improved processing controls and avoided adverse events due to implementation of the CGTP final rule.

AHRQ reports 82,874 total hospital discharges for Principle Procedure 43, Heart Valve Procedures in 2000 with a mean LOS of 11.1 days and mean hospital charges of \$78,494 (Ref. 24). The AHRQ also reports 4,986 in-hospital deaths (and a 6.0 percent death rate) associated with these procedures. If patients undergoing this procedure were to lose 2 weeks of time away from work, the value of this work loss, based on a 40-hour work week and an average hourly compensation of \$ 23.93 (Ref. 32), would be \$1,914 per case. Based on reported average charges of \$78,494 per hospitalization for implantation of a heart valve allograft (Ref. 24), estimated physician charges of \$6,796 per case, including repeat surgery and patient care during the average 11.1-day hospital stay, and 2 weeks of patient work loss, the total cost of treating cases of heart valve contamination causing fungal endocarditis would be between \$1,220,862 (14 x (\$78,494 + \$6,796 + \$1,914.4)) and \$1,482,475 (17 x (\$78,494 + \$6,796 + \$1,914.4)). These estimates should be viewed as conservative because they reflect only the costs associated with contaminated

heart valve allografts causing fungal endocarditis, and do not consider the costs associated with the more common bacteria-induced early onset allograft valve endocarditis. No estimate of the potential benefit of CGTPs in reducing the cost of treating early onset allograft valve endocarditis was generated due to a lack of necessary information.

The total annualized costs of the CGTP final rule for conventional tissue banks are estimated to be \$2.03 million to \$2.07 million. The total costs associated with infected bone allografts and contaminated heart valve allografts causing fungal endocarditis are estimated to be between \$61.3 million (\$60.1 million + \$1.2 million) and \$61.6 million (\$60.1 million + \$1.5 million). If implementation of the CGTP final rule were to reduce these estimated costs by 3.3 percent, the estimated annual cost savings, or benefit, would exceed the estimated compliance costs. Thus, a 3.3 percent reduction in the cost associated with only two HCT/P-related problems would make the CGTP final rule cost effective for the conventional tissue industry.

3. Hematopoietic Stem/Progenitor Cells

Promising outcomes from use of peripheral blood stem/progenitor cells (PBSC) and cord blood-derived stem/progenitor cells (CBSC) in lieu of bone marrow have resulted in increased collection and use of these products in hematopoietic stem/progenitor cell transplants. For example, recent studies have reported the use of PBSC (rather than bone marrow) in 54 percent (Ref. 15) and 62 percent of cases, respectively (Ref. 16). However, studies of hematopoietic stem/progenitor cell products indicate that products manufactured by this industry may become contaminated during collection and processing. Moreover, the therapy-induced immunosuppression of the oncology patients who receive these products places them at particularly high

risk for serious infection and subsequent mortality. Manufacturing methods conforming to CGTP are necessary to prevent this threat to the safety and effectiveness of hematopoietic stem/progenitor cell therapies. For example, investigations of PBSC have reported that the large quantity of blood that must be processed to obtain adequate numbers of hematopoietic stem/progenitor 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. 20).

Another quality concern with PBSC involves the maintenance of the sterile integrity of the apheresis catheter and component throughout the period of leukapheresis, cryopreservation, thawing, and transfusion (Espinosa et al., 1996) (Ref. 17). Webb et al. (Ref. 18) 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 bacteremia-induced fever and other clinical sequelae are generally considered reversible, infections present more serious risks for hematopoietic stem/progenitor cell recipients than for the overall population. Survival rates for hematopoietic stem/progenitor cell transplantation are significantly reduced for patients who become critically ill. In a study of survival rates among hematopoietic stem/progenitor cell recipients admitted to an intensive care unit, Price et al. (Ref. 16) 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., controlling for other risk factors such as patient intubation, type of transplant, source of hematopoietic stem/progenitor cells, human leukocyte

antigen compatibility, type of malignancy and patient age, also found infection to be a significant predictor of mortality.

Based on reported blood collection and transfusion statistics (Ref. 25), a total of 32,291 units of PBSCs were collected, and 18,123 units transfused, in the United States in 1997 (the use of PBSCs has been increasing steadily since that time). Thus, an estimated 60 patients per year ($18,123 \text{ PBSC transfusions} \times 0.024 \times 0.137$) 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 (Ref. 15), and 18,123 hematopoietic stem/progenitor cell transplants performed in 1997. Costs of treating patients who become infected after receiving contaminated hematopoietic stem/progenitor cell products are estimated based on 8,985 AHRQ-reported total discharges for Principle Procedure 3, Bacterial Infection, Unspecified Site, with average hospital charges of \$21,221 per 6.9-day patient stay (Ref. 26). Estimated total health care costs also include physician costs of \$918 assuming one initial in-hospital visit, and daily followup visits during the patient stay (Ref. 8). Patient income loss is valued at \$1,914 based on estimated hourly compensation of \$23.93 (Ref. 32) and an estimated 2 weeks away from work. Thus, the total annual cost impact of infection following transplant of contaminated PBSC products is estimated to be \$1,443,180 ($60 \times (\$21,221 + \$918 + \$1,914)$).

In addition to health care and time away from work costs, reducing the risk of contaminated PBSC products could result in avoiding 26 excess hematopoietic stem/progenitor cell patient deaths per year, due to infection. This number reflects the excess mortality risk reported for hematopoietic stem/progenitor cell recipients with infection versus those without infection. It is

based on the following: (18,123 transplant procedures per year) x (2.41 percent PBSC patients receiving contaminated product) x (13.7 percent patients receiving contaminated product develop infection) x (44 percent excess mortality risk for hematopoietic stem/progenitor cell recipients with a probable infection). This estimate suggests a risk of death due to infection resulting from a contaminated hematopoietic stem/progenitor cell transplant of approximately 0.14 percent (26 deaths / 18,123 hematopoietic stem/progenitor cell transplants). FDA currently has no basis for predicting how many of these deaths might be avoided through implementation of the CGTP final rule.

As bacterial contamination has also been documented in studies of cord blood processing, the CGTP requirements for staff training and process validation will likely support risk and cost reduction efforts across the 25 CBSC establishments. For example, a study by Kogler et al. (Ref. 18) found that, during the initial 6 months of a 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. Due to a lack of data regarding the incidence and risks associated with CBSC procedures, FDA currently has no basis for predicting the magnitude of benefits that might be realized from implementation of the CGTP final rule in this HCT/P industry sector.

D. Summary of cGTP Benefits

This analysis of the potential benefits of the CGTP final rule has considered its impact on major sectors of the HCT/P industry by focusing on problems associated with HCT/Ps cited in the literature, and the costs of correcting those problems. This review suggests that current industry voluntary standards are not followed uniformly, and that implementation of the CGTP

final rule has the potential to generate economic benefits by reducing communicable disease transmission risks, improving product safety, and by reducing the costs associated with correcting HCT/P related problems.

Table 13 of this document provides a summary of the particular products, problems identified and their associated costs based on the agency's survey of the literature. FDA estimated the associated health care costs based on reported risks, national level database estimates of the numbers of patients undergoing related procedures, and estimates of the direct medical costs associated with those procedures. These estimates also reflect the cost of work loss experienced by patients undergoing treatment to correct HCT/P related problems.

Rather than attempting to generate point estimates of the benefits of the CGTP rule, the agency has chosen to present the results of this analysis of potential benefits in cost-effectiveness or break-even terms. There are several reasons for this. First, the current or baseline risks associated with the various types of HCT/Ps are unknown because the data required to establish these risks is either not readily available or is not currently collected by any entity. The lack of comprehensive risk data for the HCT/P industry is due primarily to a lack of mandatory reporting requirements for adverse health events associated with human tissues, a situation that is addressed by the reporting requirements of the CGTP final rule. Second, given that the current baseline risks associated with various types of HCT/Ps are uncertain, FDA has no basis for determining defensible estimates of the degree to which implementation of the CGTP final rule might be expected to reduce these already uncertain risks. Finally, while limited data with which to characterize a few of the risks associated with a select few of the many and diverse HCT/Ps, it is not possible

to fully characterize all of the potential problems associated with all of the HCT/Ps that would be affected by this rule. Thus, it is not possible to develop comprehensive estimates of the aggregate benefits of the CGTP final rule.

TABLE 13.—SUMMARY OF CGTP BENEFITS

HCT/P Industry Sector	HCT/P-Related Problem	Avoided Treatment Outcome	Estimated Cost of Treatment	Cost-Effective Percent Reduction in Cost/Risk
Eye Tissue	Primary Corneal Graft Failure	Repeat Surgery	\$.729 to \$6.5 million \$15,844 per case	25%
Conventional Tissue	Bone Allograft Infection/Graft Failure	Repeat Surgery/Amputation	\$62 million \$24,587 per case	3.2%
Conventional Tissue	Heart Valve Fungal Endocarditis	Repeat Surgery (Death)	\$1.2 to \$1.5 million \$87,204 per case	3.3%
Hematopoietic Stem/Progenitor Cells	PBSC Transplant Infection	Hospitalization (Death)	\$1.4 million \$24,053 per case 26 deaths	Unable to Determine

Additional uncertainties associated with estimating the benefits of the CGTP final rule include: The actual extent of current compliance in each of the affected industry sectors, the direct impact of HCT/P related problems on patient outcomes, and the precise size of the affected patient populations. Because of the limits of available data, the forgoing analysis has focused on a limited set of HCT/Ps. It is not certain how well these data represent the most critical areas, or actual levels of risk, associated with the many and varied products produced by the HCT/P industry. For some products, such as demineralized bone, the industry has achieved important advances in processing that have improved the safety and effectiveness of products. Thus, the analysis of benefits based on problem reports from several years ago, may overstate the potential for improvements in the current industry practice. In other cases, the publication of the recent reports suggests that deficiencies still exist within current practices. These areas present important opportunities to avoid product failures due to HCT/P-related problems, which lead to unnecessary communicable disease transmission risks and greater health care costs.

E. Small Entity Impacts

The Regulatory Flexibility Act requires agencies to assess whether a rule may have a significant economic impact on a substantial number of small entities. Based on size standards established by the SBA, a small establishment in this industry sector (NAICS code 621991, Blood and Organ Banks) has annual receipts of less than \$8.5 million (Refs. 21 and 22). In every sector of the HCT/P industry, the majority of establishments are estimated to be classified as small entities. However, because of the large number of entities currently following industry voluntary standards, the increase in costs is expected to be limited primarily to establishments that do not follow those existing standards. To assess the impact of the CGTP rule on small businesses, FDA first calculated the ratio of average compliance costs to average annual revenues, assuming that all establishments will incur similar costs. The small entity impacts estimated below also focus on establishments that will be newly compliant under the CGTP final rule, and thus will experience the greatest potential new cost burden. Although current quality management practices at nonaccredited establishments may vary, and not every facility will incur every new cost estimated in table 4 of this document, the analysis that follows also considers a worst-case scenario in which every estimated cost is incurred by an establishment, to provide additional insight as to the maximum potential impact on small entities. While some firms may have lower than estimated average revenues, making them potentially more sensitive to cost increases, FDA does not know the distribution of firms by revenues because this information is not readily available. Therefore, the agency requested detailed industry comment regarding our average annual revenue assumptions in the CGTP proposed rule. To the extent possible, information obtained during the

comment period has been incorporated into this analysis of the small entity impacts of the CGTP final rule. The results of this analysis are summarized in table 14 of this document.

A 1995 study of conventional tissue banks (Ref. 19) reports average annual revenues of \$1.23 million per establishment, which translates into \$1.45 million per establishment (in the year 2002 dollars) based on inflation data reported by the Bureau of Labor Statistics (Ref. 27). Most eye banks, conventional tissue banks and hematopoietic stem/progenitor cell establishments were assumed to have a comparable level of average revenues in the proposed rule, and that assumption is retained here.

Within the eye banking industry, experts estimate that virtually all of the 134 establishments would be classified as small, and all are believed to follow the current industry (EBAA) standards. The average annual revenue per eye bank is estimated at \$1.45 million. If an eye bank were to incur every new cost estimated for establishments in that industry sector, the total cost impact, including total one-time and annual costs, would be \$39,750, which represents 2.7 percent ($\$39,750 / \1.45 million) of estimated annual revenues. Average annualized compliance costs are estimated to be \$12,087 ($\$1,619,659 \text{ total annualized costs} / 134 \text{ small eye banks}$), and represents 0.83 percent ($\$12,087 / \1.45 million) of average annual revenues per firm.

In the conventional tissue banking industry, an estimated 75 to 80 percent of the total of 166 establishments may be classified as small entities. Industry experts also estimate that 75 to 80 percent of those establishments currently follow AATB standards, which generally meet or exceed the requirements of the CGTP final rule. Based on the assumed levels of increased effort and costs shown in table 4 of this document, the remaining 20 to 25 percent of small

establishments that do not follow current AATB standards could incur up to \$66,621 in total incremental costs, including both one-time and annual costs, assuming that every potential area of new quality management effort will be needed under the worst-case scenario. The average annual revenue per small conventional tissue bank is estimated at \$1.45 million. Thus, the estimated maximum potential new costs would represent approximately 4.6 percent ($\$66,621 / \1.45 million) of this average annual revenue figure. The average total annualized cost for a small conventional tissue bank is estimated to be \$11,678 ($\$1,506,433 \text{ total annualized costs} / 129 \text{ small conventional tissue banks}$), and represents 0.8 percent ($\$11,678 / \1.45 million) of average annual revenues.

The agency estimates that approximately 250 hematopoietic stem/progenitor cell establishments may be classified as small entities, and that these establishments have average annual revenues of \$1.45 million. An estimated 200 (or 80 percent) of these small establishments follow the current FACT or AABB standards but will incur some additional costs. If one of these establishments were to incur new costs for each of the relevant provisions identified in table 4 of this document, the total incremental cost per establishment, including total one-time and annual costs, would be approximately \$21,602. This figure represents approximately 1.5 percent ($\$21,602 / \1.45 million) of estimated annual revenues. The estimated 50 (or 20 percent of) small hematopoietic stem/progenitor cell establishments that do not currently comply with AABB or FACT standards will incur greater costs, as shown in table 4 of this document. If one of these establishments were assumed to incur every new cost identified in the cost analysis, the total one-time and annual costs would be approximately \$83,483. This represents

approximately 5.8 percent ($\$83,483 / \1.45 million) of average annual revenues.

The average annualized costs incurred by small hematopoietic stem/progenitor cell establishments would also vary depending on current practices and the degree to which establishments follow AABB or FACT standards. If a small hematopoietic stem/progenitor cell establishment is currently following industry standards, the average annualized cost associated with the CGTP final rule is estimated to be $\$8,367$ ($\$1,673,301$ total annualized costs / 200 small hematopoietic stem/progenitor cell establishments), and represents approximately 0.58 percent ($\$8,367 / \1.45 million) of the average annual revenue of these firms. However, if a small establishment is not following the current industry standards, a greater level of new effort will be required for quality assurance and quality management. The average annualized cost per small establishment not following current industry standards is estimated to be $\$43,207$ ($\$2,160,341$ total annualized costs / 50 small hematopoietic stem/progenitor cell establishments), and represents about 3 percent ($\$43,207 / \1.45 million) of average annual revenue.

Consultants estimate that two-thirds of all ART establishments could be classified as small entities, and have average annual revenues of approximately $\$2.1$ million. A typical ART establishment is expected to incur average annual and annualized costs of $\$768$. This figure represents approximately 0.04 percent ($\$768 / \2.1 million) of average annual revenues.

According to estimates by a semen banking industry expert, approximately 100,000 total daily intake (TDI) units are produced each year from collected and processed semen donations. An estimated 95 percent of that total production is handled by the largest 20 commercial establishments. Nineteen

of these largest 20 establishments are estimated to have average annual revenues of approximately \$2.4 million, and only 1 establishment is estimated to have revenues greater than \$8.5 million per year. The remaining 5 percent of industry production, or 5,000 TDI units, are processed by very small semen banks that typically function within a physician office practice (e.g., that of an obstetrician/gynecologist (Ob/Gyn)). Semen banking in these establishments is generally offered as an additional service to patients receiving fertility treatment, and is not a primary line of business.

The annual revenue for these individual physician practices is estimated to be \$692,000 per year, based on the average annual practice revenue per self-employed physician in the Ob/Gyn specialty category reported as \$627,000 in 1998 (Ref. 20), adjusted to year 2002 dollars based on inflation data reported by the Bureau of Labor Statistics (Ref. 27). Thus the majority of semen banks would be considered small entities.

The average annual and annualized costs associated with the inspection and enforcement provisions are estimated to be \$768 per affected ART establishment and semen bank. This figure represents approximately 0.03 percent ($\$768 / \2.4 million) of average annual revenues for the 19 small commercial semen banks, and about 0.11 percent ($\$768 / \$692,000$) for individual Ob/Gyn ART establishments and small physician practice-based semen banks.

Although these cost figures account for a much larger percentage of individual physician practice income, the semen banking provided by these establishments is considered to represent a small part of their overall business. For the smallest banks, the estimated 5,000 TDI units supplied by the estimated 90 establishments in this category translate to an average volume of 55 units

per establishment per year. With an estimated price of \$95 to \$145 per TDI unit (Ref. 30) and an estimated profit of 15 percent, these banks would realize, on average, a net income of \$12.40 to \$19.00 per unit, or a total net income of \$682 to \$1,045 for 55 units. This income would represent only 0.1 percent ($\$682 / \$692,000$) to 0.15 percent ($\$1,045 / \$692,000$) of the estimated annual practice revenue per self-employed physician in the Ob/Gyn specialty category.

In summary, the majority of establishments within each sector of the HCT/P industry are expected to qualify as small business entities. The actual cost impact on these entities is uncertain, because of the limited information available with which to describe current practices and the degree to which individual establishments follow voluntary industry standards within each HCT/P industry sector. Based on the limited available data and industry expert opinions, the agency estimates impacts that would result in an average annualized cost per small establishment subject to CGTPs in their entirety ranging from \$8,367 to \$12,087 for establishments that currently follow industry standards, and \$43,207 for establishments that do not currently follow industry quality standards. These annualized costs represent 0.6 percent to 0.83 percent of estimated average annual revenues for firms currently following industry standards, and 3 percent of average annual revenues for firms not following industry standards.

The worst-case analysis assumes that an affected small entity will incur new costs for every provision of the CGTP final rule. While this represents a highly unlikely scenario for nearly all firms in the HCT/P industry sectors subject to CGTPs in their entirety, this analysis does provide a useful illustration of the maximum potential burden of the CGTP final rule. The agency estimates worst-case average annualized costs per small establishment

ranging from \$21,602 to \$66,621 for establishments that currently follow industry standards, and \$83,483 for establishments that do not currently follow industry quality standards. These worst-case annualized costs for small entities, expressed as a percentage of estimated average annual revenue, range from 1.5 percent to 4.6 percent for firms currently following industry standards, and represent 5.8 percent of estimated average annual revenues for firms not following industry standards.

Establishments handling reproductive tissue are subject only to the inspection and enforcement provisions of the CGTP final rule as they apply to donor eligibility requirements under subpart C of part 1271. Small ART establishments and semen banks are expected to incur average annualized costs of \$768, which represent between 0.03 and 0.11 percent of average annual revenues. The results of FDA's analysis of small entity impacts are summarized in table 14 of this document.

TABLE 14.—SUMMARY OF SMALL BUSINESS IMPACTS

No. of Small Establishments by Industry Sector	Average Annual Revenue per Small Establishment (in millions)	Average Annualized Cost per Small Establishment	Average Annualized Cost as a Percentage of Average Revenue	Worst-Case Costs for an affected Small Establishment	Worst-Case Costs as a Percentage of Average Revenue
Eye Banks (134 Establishments)	\$1.45	\$12,087	0.83%	\$39,750	2.7%
Conventional Tissue (129 Establishments)	\$1.45	\$11,678	0.8%	\$66,621	4.6%
Stem/Progenitor Cell Establishments Following Industry Standards (200 Establishments)	\$1.45	\$8,367	0.6%	\$21,602	1.5%
Stem/Progenitor Cell Establishments Not Following Industry Standards (50 Establishments)	\$1.45	\$43,207	3%	\$83,483	5.8%
ART Establishments (260 Establishments)	\$2.1	\$768	0.04%	\$768	0.04%
Ob/Gyn and small physician based practices	\$0.692	\$768	0.11	\$768	0.11
Semen Banks (19 Establishments)	\$2.4	\$768	0.03%	\$768	0.03%

The agency is uncertain about the accuracy of these estimates, however, because of the lack of revenue data for individual establishments. Because of the importance of this information in accurately assessing the impact on small entities, the agency requested detailed industry comment on individual firm revenues, the percentage of establishments that qualify as small entities, the

percentage of those establishments that comply with current industry quality standards and the extent of their compliance, and the specific areas where industry anticipates substantial differences between current manufacturing practices and the quality assurance elements specified under the CGTP final rule. For those areas of identified difference, the agency further requested estimates of the resources and costs required for establishment compliance. This analysis has incorporated information received during the comment period to the extent possible. Please see our responses to comments 172 through 197 at section III.F. of this document for details.

Although the CGTP final rule will impose some costs on small entities involved in the manufacture of HCT/Ps, the agency believes that this approach represents an effective means of protecting patient safety and public health. The less burdensome alternatives to the CGTP final rule involve fewer requirements for small entities (the vast majority of entities in this industry), but fail to provide fundamental assurances of product quality and safety. Reliance on industry professional organization voluntary standards or published FDA guidance 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 HCT/Ps to ensure public health and safety. Given that each trade organization varies in their standards or guidelines, regulatory requirements for good tissue practice would help to ensure consistency among manufacturers and across the various sectors of the HCT/P industry. Further, the adverse reaction reporting requirements of the CGTP final rule will provide valuable information that will allow the agency to identify and respond to emerging public health and safety risks associated with HCT/Ps. FDA finds that the CGTP final rule will enhance

both public health and public confidence in the safety and quality of the nation's supply of HCT/Ps, while imposing only a minimum burden on the affected entities.

Another alternative would involve waiving some of the requirements for small establishments. However, as noted previously, nearly all establishments in this industry are small. Moreover, this alternative would increase HCT/P safety risks if small establishments that currently follow voluntary industry standards for good tissue practice choose to discontinue this practice due to an FDA-granted waiver. Furthermore, documentation and record retention provisions ensure that HCT/Ps can be tracked to their source in the event of infection or other adverse reactions that result from donor tissue characteristics.

In summary, the agency believes that abridged requirements for CGTP, based on voluntary standards or facility size criteria, would provide inadequate protection against the risk of communicable disease transmission. Most notably, the current absence of regulation allows some establishments handling human tissues to ignore the standards established by industry professional associations and followed by a majority of entities in all sectors of the HCT/P industry.

FDA has made a number of revisions to this final rule, many in response to public comments on the proposed CGTP rule, that are expected to reduce the overall compliance burden on affected entities.

Provisions under § 1271.160(c) have been revised to require audits periodically rather than annually as stipulated under the CGTP proposed rule. However, the cost estimates presented in this analysis of economic impacts retain the assumption that audits will impose an annual burden so as to

generate conservative estimates of overall compliance costs. The provisions proposed under § 1271.160(f), requiring complete validation of custom computer software used for making HCT/P-related decisions or determinations, have been changed to a requirement for validation or verification as appropriate. Verification is a less burdensome alternative that would apply to software not relied upon for making donor eligibility or HCT/P suitability decisions or determinations (e.g., inventory).

The proposed requirement under § 1271.180 for an annual review of all procedures has been removed, as has the requirement for prior authorization of any deviation from an established procedure. Provisions proposed under § 1271.220(b) (process controls) requiring procedures for the use and removal of processing material have been deleted in response to comments. Proposed provisions under § 1271.230(e) requiring validation of all process changes and process deviations now require validation only of process changes. Requirements proposed under § 1271.265(e) for HCT/P packaging validation now allow for packaging validation or verification (a less burdensome alternative) as appropriate.

Provisions proposed under § 1271.290(d) and (e) requiring establishments to ensure each HCT/P is tracked from donor to recipient and from recipient to donor, now only require that establishments have a method of tracking in place. This will reduce the burden on affected entities because they no longer bear the responsibility of ensuring tracking with respect to their consignees. The proposed requirement for the reporting of all HCT/P deviations under § 1271.350(b) now only applies to distributed HCT/Ps and not to those still in inventory. Finally, language has been added to § 1271.420(b) to allow

transportation to the consignee under quarantine of HCT/Ps offered for import to facilitate more rapid release of imported tissue products.

As part of the development process for this final rule, FDA conducted an extensive outreach program in an effort to inform affected small entities and to request input regarding the potential economic impact. Representatives from CBER have given presentations on good tissue practice related issues at the annual conferences of many of the professional associations representing affected entities including ASRM, AATB, EBAA, and others. The agency has also engaged in outreach activities directed toward interested consumer groups such as RESOLVE and the American Infertility Association. At their request, FDA also held individual meetings with ASRM, EBAA, and AATB to discuss specific concerns regarding the impact of the CGTP rule. Some of these presentation materials and meeting minutes are available on the CBER Web page at <http://www.fda.gov/cber/tissue/min.htm>. Additional materials associated with the CGTP rule are available online at <http://www.fda.gov/cber/tissue/docs.htm>. Finally, in the proposed rule, FDA requested industry comment regarding the many assumptions upon which this analysis of economic impacts was based. In particular, we requested detailed industry comment regarding our estimates of: The number and type of entities affected, the extent of CGTP, compliance rates for firms in various sectors of the HCT/P industry, and the level of compliance costs. To the extent possible, we have incorporated these comments and our responses into the preamble and analysis of economic impacts of this final rule.

The specific requirements for good tissue practice, the required recordkeeping, and the required types of professional skills are described in the economic analysis provided previously. This analysis includes an

accounting of all major cost factors, with the exception of the reduced potential liability currently encountered by those marginal tissue establishments that fail to provide the level of protection from infectious disease that is considered a standard of good practice in other sectors of the tissue-based product industry. The relevant Federal rules that are related to this final rule are discussed in section II of this document. This economic analysis provides a summary of the private industry standards that overlap this final Federal standard, but as discussed, there is no current regulation of tissue that will duplicate this final rule. Consequently, FDA finds that this final rule will enhance both public health and public confidence in the safety and utility of HCT/Ps, while imposing only a minimum burden on the affected industry sectors.

VI. Environmental Impact

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

VII. Federalism Assessment

Executive Order 13132, dated August 4, 1999, establishes the procedure that Federal agencies must follow when formulating and implementing policies that have federalism implications. The Executive order described nine fundamental federalism principles, stressing the importance and sovereignty of State and local governments, and the contributions of individual states and communities to the development of enlightened public policy. Principles of federalism are inherent in the very structure of the Constitution and formalized in and protected by the tenth amendment. Regulations have federalism

implications whenever they have a substantial direct effect on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Whenever a regulation has this result, the agency must prepare a federalism assessment.

The Executive order directs Federal agencies to:

- Encourage States to develop their own policies to achieve program objectives and to work with appropriate officials in other States;
- Where possible, defer to the States to establish standards;
- In determining whether to establish uniform national standards, consult with appropriate State and local officials as to the need for national standards and any alternatives that would limit the scope of national standards or otherwise preserve State prerogatives and authority; and
- Where national standards are required by Federal statutes, consult with appropriate State and local officials in developing those standards.

In the proposed rule (66 FR 1508 at 1551), we made the statement that we had analyzed the proposed rule in accordance with the principles set forth in Executive Order 13132, and that the proposed rule may raise federalism implications because it could preempt States' laws regarding donated human cells and tissues. We then invited comments from elected State and local government officials on:

- The need for the proposed CGTP to prevent communicable disease transmission through HCT/Ps;
- Alternatives that would limit the scope of such national requirements or otherwise preserve State prerogatives and authority;
- The proposed CGTP provisions; and

- Any other issues raised by the proposed rule that could affect State laws and authorities.

We received no comments from State officials on federalism issues.

This final rule represents the exercise of a core Federal function: “prevent[ing] the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession” (section 361(a) of the PHS Act; 42 U.S.C. 264). To prevent the transmission of communicable disease in the United States, including the interstate transmission of disease, uniform national standards for HCT/Ps are necessary. No State official commented otherwise. For these reasons, this rule is consistent with the federalism principles expressed in Executive Order 13132.

However, we received two comments requesting that we clearly state that this rulemaking’s provisions preempt state tissue regulations.

We decline to make this statement. Section 361 was recently amended to provide,

Nothing in this section or section 363 [42 U.S.C. 266], or the regulations promulgated under such sections, may be construed as superseding any provision under State law (including regulations and including provisions established by political subdivisions of States), except to the extent that such a provision conflicts with an exercise of Federal authority under this section or section 363.

(section 361(e); 42 U.S.C. 264(e)).

Accordingly, consistent with this provision, establishments must comply with applicable State law and regulations, unless the State provisions conflict with this exercise of Federal authority under section 361. In the event of such

a conflict, these regulations would preempt the State provisions under ordinary principles of preemption. (*Geier v. Honda*, 529 U.S. 861 (2000).)

VIII. The Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). A description of these provisions is shown as follows 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.

Title: Current Good Tissue Practice for Human Cell, Tissue, and Cellular and Tissue-Based Product Establishments; Inspection and Enforcement.

Description: Under the authority of section 361 of the PHS Act, FDA is requiring certain HCT/P establishments to follow CGTP, which includes information collection provisions such as the establishment and maintenance of SOPs, recordkeeping, reporting, and labeling of the HCT/Ps. The CGTP information collection provisions in this rulemaking provide: (1) Additional measures for preventing the introduction, transmission, or spread of communicable diseases; (2) step-by-step consistency in the manufacturing of the HCT/P; (3) necessary information to FDA for the purpose of protecting public health and safety; (4) accountability in the manufacturing of HCT/Ps; and (5) information facilitating the tracking of an HCT/P back to its original source or to a consignee.

Table 15 lists provisions that require reporting or disclosure of information to third parties, the Federal Government, or the public. Section 1271.155(a) permits 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. Section 1271.290(c) requires the establishment to affix a distinct identification code to each HCT/P relating the HCT/P to the donor and all records pertaining to the HCT/P. Whenever an establishment initially distributes an HCT/P to a consignee, § 1271.290(f) requires the establishment to inform the consignee, in writing, of the product tracking requirements and the methods the establishment uses to fulfill the requirements. Non-reproductive HCT/P establishments described in § 1271.10 are required under § 1271.350(a)(1) and (b)(1) to report to FDA adverse reactions (defined in § 1271.3(y)) and HCT/P deviations (defined in § 1271.3(dd)). Section 1271.370(b) and (c) requires establishments to include specific information either on the HCT/P label or in the package insert.

Table 16 lists recordkeeping provisions under this final rule.

Nonreproductive HCT/P establishments are required to prepare and maintain written SOPs to meet the core CGTP requirements for all steps performed in the manufacturing of HCT/Ps. As calculated in table 16 of this document, the preparation of the SOPs would result in a one-time impact on establishments and, once composed and/or reviewed for compliance, SOPs would only be updated as necessary.

The requirement for reporting, SOPs, and recordkeeping in proposed §§ 1271.160(d)(3), 1271.160(f), 1271.170(d), 1271.195(a), 1271.210(a) and (b), 1271.220(b), 1271.225(b), 1271.230(b) and (d), 1271.270(c), 1271.290(f), and 1271.350(c) are not included in the final rule.

The SOP provisions under part 1271 include: (1) § 1271.160(b)(2) (receiving, investigation, evaluating, and documenting information relating to core CGTP requirements received from other sources and for sharing

information with consignees and other establishments); (2) § 1271.180(a) (to meet core CGTP requirements for all steps performed in the manufacture of HCT/Ps); (3) § 1271.190(d)(1) (facility cleaning and sanitization); (4) § 1271.200(b) (cleaning, sanitizing, and maintenance of equipment); (5) § 1271.200(c) (calibration of equipment); (6) § 1271.230(a) (verification or validation of changes to a process); (7) § 1271.250(a) (controls for labeling HCT/Ps); (8) § 1271.265(e) (receipt, pre-distribution shipment, availability for distribution, and packaging and shipping of HCT/Ps); (9) § 1271.265(f) (suitable for return to inventory); (10) § 1271.270(b) (records management system); (11) § 1271.290(b)(1) (system of HCT/P tracking); and, (12) § 1271.320(a) (review, evaluation, and documentation of all complaints).

Part 1271 requires the following additional recordkeeping provisions listed under Table 16. Section 1271.155(f) requires 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) requires documentation of corrective actions taken as a result of an audit of the quality program. Section 1271.160(b)(6) requires documentation of HCT/P deviations. Section 1271.160(d) requires documentation of computer validation or verification activities and results when computers are used to comply with the core CGTP requirements for its intended use. Section 1271.190(d)(2) requires documentation of all significant facility cleaning and sanitation. Section 1271.195(d) requires documentation of environmental control and monitoring activities. Section 1271.200(e) requires documentation of all equipment maintenance, cleaning, sanitizing, calibration, and other activities. Section 1271.210(d) requires documentation of the receipt, verification, and use of each supply or reagent. Section 1271.230(a) requires documentation of validation

activities when the results of a process cannot be fully verified by subsequent inspection and tests. Section 1271.230(c) requires documentation of the review and evaluation of a process and revalidation of the process, if necessary, when any changes to a validated process occur. Sections 1271.260(d) and (e) require documentation of the storage temperature of HCT/Ps and any corrective action taken when acceptable storage conditions are not met. Section 1271.265(c)(1) requires documentation that all release criteria are met before distribution of an HCT/P. Section 1271.265(c)(3) requires documentation of any departure from a procedure at the time of occurrence. Section 1271.265(e) requires documentation of the receipt, pre-distribution shipment, distribution, and packaging and shipping of HCT/Ps. Section 1271.270(a) requires documentation of each step in manufacturing required in subparts C and D.

Section 1271.270(e) requires documentation of the name and address, and a list of responsibilities of any establishment that performs a manufacturing step for you. Sections 1271.290(d) and (e) require documentation of the disposition of each non-reproductive HCT/P as part of its tracking method. Section 1271.320(b) requires an establishment to maintain a record of each complaint that it receives, including a review and evaluation.

Section 1271.270(d) requires the retention of all records for a period of 10 years after their creation. Records pertaining to a particular nonreproductive HCT/P are required to be retained at least 10 years after the date of administration. If the date of administration is not known, then records are required to be retained at least 10 years after the date of the HCT/P's distribution, disposition, or expiration, whichever is latest. This retention time is necessary because certain nonreproductive HCT/Ps 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 an HCT/P from a donor later determined to be at risk for communicable disease agents or diseases.

Description of Respondents: For-profit and not-for-profit institutions.

As required by section 3506(c)(2)(B) of the PRA, we provided an opportunity for public comment on the information collection requirements of the proposed rule (66 FR 1508 at 1548). No comments on the information collection burden estimate were submitted to the docket. However, we respond to comments on the utility of the information collection in section III of this document, e.g., response to comment 68 addresses the utility and burden of retaining facility cleaning and sanitation records for 10 years.

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

TABLE 15.—ESTIMATED ANNUAL REPORTING BURDEN¹

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
1271.155(a)	1,302	1	1,302	3	3,906
1271.290(c)	93	52.2	4,855	0.08	388
1271.290(f)	227	1	227	1	227
1271.350(a)(1)	792	6	4,752	1	4,752
1271.350(b)(1)	792	2	1,584	1	1,584
1271.370(b) and (c)	93	52.2	4,855	0.25	1,214
Total					12,071

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

TABLE 16.—ESTIMATED ANNUAL RECORDKEEPING BURDEN¹

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Record	Total Hours
One-time Burden (Creation of SOPs)	93	12	1,116	16	17,856
	134	3	402	16	6,432
One-time Burden (Review of existing SOPs for compliance)	699	12	8,388	8	67,104
	134	9	1,206	8	9,648
SOP Maintenance (See previous list of 12 SOPs)	792	12	9,504	2	19,008
1271.155(f)	792	1	792	0.25	198
1271.160(b)(3)	93	12	1,116	1	1,116
1271.160(b)(6)	227	12	2,724	1	2,724
1271.160(d)	227	12	2,724	1	2,724

TABLE 16.—ESTIMATED ANNUAL RECORDKEEPING BURDEN¹—Continued

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Record	Total Hours
1271.190(d)(2)	93	12	1,116	1	1,116
1271.195(d)	227	12	2,724	1	2,724
1271.200(e)	93	12	1,116	1	1,116
1271.210(d)	93	12	1,116	1	1,116
1271.230(a)	227	12	2,724	1	2,724
1271.230(c)	360	1	360	1	360
1271.260(d)	227	12	2,724	0.25	681
1271.260(e)	93	365	33,945	0.08	2,716
1271.265(c)(1)	227	1,079.8	245,105	0.08	19,608
1271.265(c)(3)	592	1	592	1	592
1271.265(e)	93	1,622.6	150,905	0.08	12,072
1271.270(a)	227	1,079.8	245,105	0.25	61,276
1271.270(e)	227	2	454	0.5	227
1271.290(d) and (e)	93	1,622.6	150,905	0.25	37,726
1271.320(b)	93	5	465	1	465
Total					271,329

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

Under this final rule, 12 SOPs are required as previously described. FDA is assuming that approximately 93 nonreproductive HCT/P establishments would create all 12 SOPs, and 134 nonreproductive HCT/P establishments would create 3 SOPs, for a total of 1,518 records; and we estimate that it would take 16 hours per new SOP for a total of 24,288 hours as a one-time burden. We estimate that up to 12 SOPs would already exist for each nonreproductive HCT/P establishment as a result of complying with current applicable regulations or following industry organizational standards. We estimate that approximately 699 nonreproductive HCT/P establishments would review all 12 SOPs, and 134 nonreproductive HCT/P establishments would revise 9 SOPs. Each review would take approximately 8 hours per SOP for a total one-time burden of 76,752 hours.

Once the SOPs are created, annual SOP maintenance of existing SOPs is estimated to involve 2 hours annually per SOP. An additional hour for clerical

time is added to the 1 hour per SOP stated in the proposed rule. Annual total hours for maintaining the SOPs is estimated at 19,008 hours.

In some cases, the estimated burden may appear to be lower or higher than the burden experienced by individual establishments. The estimated burden in these charts is an estimated average burden, taking into account the range of impact each regulation may have. In estimating the burden, FDA compared the regulations with the current voluntary standards of a number of industry organizations, such as, AATB, EBAA, AABB, FACT, NMDP, and CAP. In those cases where a voluntary industry standard appears to be equivalent to a regulation, FDA has assumed that any reporting or recordkeeping burden is a customary and usual business practice of establishments who are members of those organizations and no additional burden is calculated here. In some cases establishments affected by this rule may already be required to comply with regulations for manufacturers of human drugs or biological products, e.g., 21 CFR parts 210, 211, 312, 314, 600, and 606. FDA attributes the decrease in total burden hours in the final rule (283,400 hours) from the total burden hours in the proposed rule (621,573 hours) to:

- Not including certain proposed information collection burden in the final rule;
- Not applying the information collection burden to reproductive HCT/P establishments; and
- Industry strengthening their current standards.

FDA has estimated the reporting (table 15 of this document) and recordkeeping (table 16 of this document) burdens based upon our institutional experience with comparable recordkeeping and reporting provisions applicable

to the human drug and biological product industries, recent information from trade organizations related to the manufacturing of non-reproductive HCT/Ps utilizing cells and tissues, and data provided by the Eastern Research Group (ERG), a consulting firm hired by FDA to prepare an economic analysis of the potential economic impact on semen banks and ART facilities.

We have estimated that there are approximately 792 nonreproductive HCT/P manufacturers (approximately 166 conventional tissue establishments, 134 eye tissue establishments, 425 peripheral and cord blood stem/progenitor cells, and 67 manufacturers of licensed biological products or devices). For the number of respondents for requesting a variance under § 1271.155(a) in table 15 of this document, we added 510 reproductive HCT/P establishments. FDA obtained these estimates of manufacturers (including percentage of members and nonmembers) from the various trade organizations and our registration systems for HCT/P, biological product, and device manufacturers. The total number of respondents and recordkeepers, 1,302, in the tables is decreased for each provision by the estimated number of establishments that follow, as usual and customary practice, the applicable established trade organizational standards comparable to the GTP requirements, i.e., AATB, EBAA, FACT, AABB, NMDP, or CAP. FDA based the estimated numbers for “Number of Respondents” and “Number of Recordkeepers” on information provided by the trade organizations and FDA registration databases.

FDA based the estimated numbers for “Annual Frequency per Response,” “Total Annual Responses,” “Annual Frequency per Recordkeeping,” and “Total Annual Records” on information received from the trade organizations, institutional experience with similar requirements (Good Manufacturing Practice), general information provided to FDA during inspections of

manufacturers of human tissue intended for transplantation, and information gathered by ERG.

The estimates for “Hours per Response” or “Hours per Record” were calculated using comparable burdens under drug GMP regulations (21 CFR part 211) and GMP for blood and blood components (21 Part 606) or by using the information provided by ERG, e.g., time spent on §§ 1271.190(c)(4) (documentation of cleaning and sanitation) and 1271.195(c) (documentation of environmental control and monitoring activities) was an estimate provided by ERG.

The information collection requirements of this final rule have been approved by OMB. The OMB control number is 0910–0559; it expires 11/30/07. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

IX. References

The following references have been placed on display in the Dockets Management Branch (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but we are not responsible for subsequent changes to the Web site after this document publishes in the **Federal Register**.)

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List of Subjects*21 CFR part 16*

Administrative practice and procedure.

21 CFR part 1270

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

21 CFR part 1271

Communicable diseases, HIV/AIDS, Human cells, tissues, and cellular and tissue-based products, Reporting and recordkeeping requirements.

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

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

Authority: 15 U.S.C. 1451–1461; 21 U.S.C. 141–149, 321–394, 467f, 679, 821, 1034; 28 U.S.C. 2112; 42 U.S.C. 201–262, 263b, 364.

■ 2. Section 16.1 is amended in paragraph (b)(2) by numerically adding an entry for § 1271.440(e) to read as follows:

§ 16.1 Scope.

* * * * *

(b) * * *

(2) * * *

§ 1271.440(e) relating to the retention, recall, and destruction of human cells, tissues, and cellular and tissue-based products (HCT/Ps), and/or the cessation of manufacturing HCT/Ps.

PART 1270—HUMAN TISSUE INTENDED FOR TRANSPLANTATION

- 3. The authority citation for 21 CFR part 1270 continues to read as follows:

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

- 4. Section 1270.3 is amended by revising paragraph (j) introductory text to read as follows:

§ 1270.3 Definitions

* * * * *

(j) *Human tissue, for the purpose of this part* means any tissue derived from a human body and recovered before May 25, 2005, which:

* * * * *

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

- 5. The authority citation for 21 CFR part 1271 continues to read as follows:

Authority: 42 U.S.C. 216, 243, 263a, 264, 271.

- 6. Section 1271.3 is amended by revising paragraphs (c) and (d) and by adding paragraphs (y) through (ll) to read as follows:

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

* * * * *

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

(d) *Human cells, tissues, or cellular or tissue-based products (HCT/Ps)* means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament,

skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue. The following articles are not considered HCT/Ps:

(1) Vascularized human organs for transplantation;

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

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

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

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

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

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

* * * * *

(y) *Adverse reaction* means a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response.

(z) *Available for distribution* means that the HCT/P has been determined to meet all release criteria.

(aa) *Complaint* means any written, oral, or electronic communication about a distributed HCT/P that alleges:

(1) That an HCT/P has transmitted or may have transmitted a communicable disease to the recipient of the HCT/P; or

(2) Any other problem with an HCT/P relating to the potential for transmission of communicable disease, such as the failure to comply with current good tissue practice.

(bb) *Distribution* means any conveyance or shipment (including importation and exportation) of an HCT/P that has been determined to meet all release criteria, whether or not such conveyance or shipment is entirely intrastate. If an entity does not take physical possession of an HCT/P, the entity is not considered a distributor.

(cc) *Establish and maintain* means define, document (in writing or electronically), and implement; then follow, review, and, as needed, revise on an ongoing basis.

(dd) *HCT/P deviation* means an event:

(1) That represents a deviation from applicable regulations in this part or from applicable standards or established specifications that relate to the prevention of communicable disease transmission or HCT/P contamination; or

(2) That is an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease or may lead to HCT/P contamination.

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

(ff) *Processing* means any activity performed on an HCT/P, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage.

(gg) *Quality audit* means a documented, independent inspection and review of an establishment's activities related to core CGTP requirements. The purpose of a quality audit is to verify, by examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review.

(hh) *Quality program* means an organization's comprehensive system for manufacturing and tracking HCT/Ps in accordance with this part. A quality program is designed to prevent, detect, and correct deficiencies that may lead to circumstances that increase the risk of introduction, transmission, or spread of communicable diseases.

(ii) *Recovery* means obtaining from a human donor cells or tissues that are intended for use in human implantation, transplantation, infusion, or transfer.

(jj) *Storage* means holding HCT/Ps for future processing and/or distribution.

(kk) *Validation* means confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. Validation of a process, or *process validation*, means establishing by objective evidence that a process consistently produces a result or HCT/P meeting its predetermined specifications.

(ll) *Verification* means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

■ 7. Section 1271.10 is amended by revising paragraph (a)(3) to read as follows:

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

(a) * * *

(3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

* * * * *

■ 8. Section 1271.22 is revised to read as follows:

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

(a) You must use Form FDA 3356 for:

- (1) Establishment registration,
- (2) HCT/P listings, and
- (3) Updates of registration and HCT/P listing.

(b) You may obtain Form FDA 3356:

(1) By writing to the Center for Biologics Evaluation and Research (HFM-775), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, Attention: Tissue Establishment Registration Coordinator;

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

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

(4) By connecting to *<http://www.fda.gov/opacom/morechoices/fdaforms/cber.html>* on the Internet.

(c)(1) You may submit Form FDA 3356 to the Center for Biologics Evaluation and Research (HFM-775), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, Attention: Tissue Establishment Registration Coordinator; or

(2) You may submit Form FDA 3356 electronically through a secure web server at *<http://www.fda.gov/cber/tissue/tisreg.htm>*.

■ 9. Section 1271.45 is amended in paragraph (a), after the second sentence, by adding a sentence to read as follows:

§ 1271.45 What requirements does this subpart contain?

(a) * * * Other CGTP requirements are set out in subpart D of this part.

* * * * *

■ 10. Part 1271 is amended by adding subpart D, consisting of §§ 1271.145 through 1271.320, to read as follows:

Subpart D—Current Good Tissue Practice

Sec.

1271.145 Prevention of the introduction, transmission, or spread of communicable diseases.

1271.150 Current good tissue practice requirements.

1271.155 Exemptions and alternatives.

1271.160 Establishment and maintenance of a quality program.

1271.170 Personnel.

1271.180 Procedures.

1271.190 Facilities.

1271.195 Environmental control and monitoring.

1271.200 Equipment.

1271.210 Supplies and reagents.

1271.215 Recovery.

1271.220 Processing and process controls.

1271.225 Process changes.

1271.230 Process validation.

1271.250 Labeling controls.

1271.260 Storage.

1271.265 Receipt, predistribution shipment, and distribution of an HCT/P.

1271.270 Records.

1271.290 Tracking.

1271.320 Complaint file.

Subpart D—Current Good Tissue Practice

§ 1271.145 Prevention of the introduction, transmission, or spread of communicable diseases.

You must recover, process, store, label, package, and distribute HCT/Ps, and screen and test cell and tissue donors, in a way that prevents the introduction, transmission, or spread of communicable diseases.

§ 1271.150 Current good tissue practice requirements.

(a) *General.* This subpart D and subpart C of this part set forth current good tissue practice (CGTP) requirements. You must follow CGTP requirements to prevent the introduction, transmission, or spread of communicable diseases by HCT/Ps (e.g., by ensuring that the HCT/Ps do not contain communicable disease agents, that they are not contaminated, and that they do not become contaminated during manufacturing). Communicable diseases include, but are not limited to, those transmitted by viruses, bacteria, fungi, parasites, and transmissible spongiform encephalopathy agents. CGTP requirements govern the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps, including but not limited to all steps in recovery, donor screening, donor testing, processing, storage, labeling, packaging, and distribution. The CGTP provisions specifically governing determinations of donor eligibility, including donor screening and testing, are set out separately in subpart C of this part.

(b) *Core CGTP requirements.* The following are core CGTP requirements:

- (1) Requirements relating to facilities in § 1271.190(a) and (b);
- (2) Requirements relating to environmental control in § 1271.195(a);
- (3) Requirements relating to equipment in § 1271.200(a);
- (4) Requirements relating to supplies and reagents in § 1271.210(a) and (b);
- (5) Requirements relating to recovery in § 1271.215;
- (6) Requirements relating to processing and process controls in § 1271.220;
- (7) Requirements relating to labeling controls in § 1271.250(a) and (b);
- (8) Requirements relating to storage in § 1271.260 (a) through (d);
- (9) Requirements relating to receipt, predistribution shipment, and distribution of an HCT/P in § 1271.265(a) through (d); and
- (10) Requirements relating to donor eligibility determinations, donor screening, and donor testing in §§ 1271.50, 1271.75, 1271.80, and 1271.85.

(c) *Compliance with applicable requirements*—(1) *Manufacturing arrangements* (i) If you are an establishment that engages in only some operations subject to the regulations in this subpart and subpart C of this part, and not others, then you need only comply with those requirements applicable to the operations that you perform.

(ii) If you engage another establishment (e.g., a laboratory to perform communicable disease testing, or an irradiation facility to perform terminal sterilization), under a contract, agreement, or other arrangement, to perform any step in manufacture for you, that establishment is responsible for complying with requirements applicable to that manufacturing step.

(iii) Before entering into a contract, agreement, or other arrangement with another establishment to perform any step in manufacture for you, you must ensure that the establishment complies with applicable CGTP requirements. If, during the course of this contract, agreement, or other arrangement, you become aware of information suggesting that the establishment may no longer

be in compliance with such requirements, you must take reasonable steps to ensure the establishment complies with those requirements. If you determine that the establishment is not in compliance with those requirements, you must terminate your contract, agreement, or other arrangement with the establishment.

(2) If you are the establishment that determines that an HCT/P meets all release criteria and makes the HCT/P available for distribution, whether or not you are the actual distributor, you are responsible for reviewing manufacturing and tracking records to determine that the HCT/P has been manufactured and tracked in compliance with the requirements of this subpart and subpart C of this part and any other applicable requirements.

(3) With the exception of §§ 1271.150(c) and 1271.155 of this subpart, the regulations in this subpart are not being implemented for reproductive HCT/Ps described in § 1271.10 and regulated solely under section 361 of the Public Health Service Act and the regulations in this part, or for the establishments that manufacture them.

(d) *Compliance with parts 210, 211, and 820 of this chapter.* With respect to HCT/Ps that are drugs (subject to review under an application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act or under a biological product license application under section 351 of the Public Health Service Act) or that are devices (subject to premarket review or notification under the device provisions of the act or under a biological product license application under section 351 of the Public Health Service Act), the procedures contained in this subpart and in subpart C of this part and the current good manufacturing practice regulations in parts 210 and 211 of this chapter and the quality system regulations in part 820 of this chapter supplement, and do

not supersede, each other unless the regulations explicitly provide otherwise. In the event that a regulation in part 1271 of this chapter is in conflict with a requirement in parts 210, 211, or 820 of this chapter, the regulations more specifically applicable to the product in question will supersede the more general.

(e) *Where appropriate.* When a requirement is qualified by “where appropriate,” it is deemed to be “appropriate” unless you can document justification otherwise. A requirement is “appropriate” if nonimplementation of the requirement could reasonably be expected to result in the HCT/P not meeting its specified requirements related to prevention of introduction, transmission, or spread of communicable diseases, or in your inability to carry out any necessary corrective action.

§ 1271.155 Exemptions and alternatives.

(a) *General.* You may request an exemption from or alternative to any requirement in subpart C or D of this part.

(b) *Request for exemption or alternative.* Submit your request under this section to the Director of the appropriate Center (the Director), e.g., the Center for Biologics Evaluation and Research or the Center for Devices and Radiological Health. The request must be accompanied by supporting documentation, including all relevant valid scientific data, and must contain either:

(1) Information justifying the requested exemption from the requirement,
or

(2) A description of a proposed alternative method of meeting the requirement.

(c) *Criteria for granting an exemption or alternative.* The Director may grant an exemption or alternative if he or she finds that such action is

consistent with the goals of protecting the public health and/or preventing the introduction, transmission, or spread of communicable diseases and that:

- (1) The information submitted justifies an exemption; or
- (2) The proposed alternative satisfies the purpose of the requirement.

(d) *Form of request.* You must ordinarily make your request for an exemption or alternative in writing (hard copy or electronically). However, if circumstances make it difficult (e.g., there is inadequate time) to submit your request in writing, you may make the request orally, and the Director may orally grant an exemption or alternative. You must follow your oral request with an immediate written request, to which the Director will respond in writing.

(e) *Operation under exemption or alternative.* You must not begin operating under the terms of a requested exemption or alternative until the exemption or alternative has been granted. You may apply for an extension of an exemption or alternative beyond its expiration date, if any.

(f) *Documentation.* If you operate under the terms of an exemption or alternative, you must maintain documentation of:

- (1) FDA's grant of the exemption or alternative, and
- (2) The date on which you began operating under the terms of the exemption or alternative.

(g) *Issuance of an exemption or alternative by the Director.* In a public health emergency, the Director may issue an exemption from, or alternative to, any requirement in part 1271. The Director may issue an exemption or alternative under this section if the exemption or alternative is necessary to assure that certain HCT/Ps will be available in a specified location to respond to an unanticipated immediate need for those HCT/Ps.

§ 1271.160 Establishment and maintenance of a quality program.

(a) *General.* If you are an establishment that performs any step in the manufacture of HCT/Ps, you must establish and maintain a quality program intended to prevent the introduction, transmission, or spread of communicable diseases through the manufacture and use of HCT/Ps. The quality program must be appropriate for the specific HCT/Ps manufactured and the manufacturing steps performed. The quality program must address all core CGTP requirements listed in § 1271.150(b).

(b) *Functions.* Functions of the quality program must include:

(1) Establishing and maintaining appropriate procedures relating to core CGTP requirements, and ensuring compliance with the requirements of § 1271.180 with respect to such procedures, including review, approval, and revision;

(2) Ensuring that procedures exist for receiving, investigating, evaluating, and documenting information relating to core CGTP requirements, including complaints, and for sharing any information pertaining to the possible contamination of the HCT/P or the potential for transmission of a communicable disease by the HCT/P with the following:

(i) Other establishments that are known to have recovered HCT/Ps from the same donor;

(ii) Other establishments that are known to have performed manufacturing steps with respect to the same HCT/P; and

(iii) Relating to consignees, in the case of such information received after the HCT/P is made available for distribution, shipped to the consignee, or administered to the recipient, procedures must include provisions for assessing risk and appropriate followup, and evaluating the effect this information has on the HCT/P and for the notification of all entities to whom the affected HCT/

P was distributed, the quarantine and recall of the HCT/P, and/or reporting to FDA, as necessary.

(3) Ensuring that appropriate corrective actions relating to core CGTP requirements, including reaudits of deficiencies, are taken and documented, as necessary. You must verify corrective actions to ensure that such actions are effective and are in compliance with CGTP. Where appropriate, corrective actions must include both short-term action to address the immediate problem and long-term action to prevent the problem's recurrence. Documentation of corrective actions must include, where appropriate:

- (i) Identification of the HCT/P affected and a description of its disposition;
- (ii) The nature of the problem requiring corrective action;
- (iii) A description of the corrective action taken; and
- (iv) The date(s) of the corrective action.

(4) Ensuring the proper training and education of personnel involved in activities related to core CGTP requirements;

(5) Establishing and maintaining appropriate monitoring systems as necessary to comply with the requirements of this subpart (e.g., environmental monitoring);

(6) Investigating and documenting HCT/P deviations and trends of HCT/P deviations relating to core CGTP requirements and making reports if required under § 1271.350(b) or other applicable regulations. Each investigation must include a review and evaluation of the HCT/P deviation, the efforts made to determine the cause, and the implementation of corrective action(s) to address the HCT/P deviation and prevent recurrence.

(c) *Audits.* You must periodically perform for management review a quality audit, as defined in § 1271.3(gg), of activities related to core CGTP requirements.

(d) *Computers*. You must validate the performance of computer software for the intended use, and the performance of any changes to that software for the intended use, if you rely upon the software to comply with core CGTP requirements and if the software either is custom software or is commercially available software that has been customized or programmed (including software programmed to perform a user defined calculation or table) to perform a function related to core CGTP requirements. You must verify the performance of all other software for the intended use if you rely upon it to comply with core CGTP requirements. You must approve and document these activities and results before implementation.

§ 1271.170 Personnel.

(a) *General*. You must have personnel sufficient to ensure compliance with the requirements of this part.

(b) *Competent performance of functions*. You must have personnel with the necessary education, experience, and training to ensure competent performance of their assigned functions. Personnel must perform only those activities for which they are qualified and authorized.

(c) *Training*. You must train all personnel, and retrain as necessary, to perform their assigned responsibilities adequately.

§ 1271.180 Procedures.

(a) *General*. You must establish and maintain procedures appropriate to meet core CGTP requirements for all steps that you perform in the manufacture of HCT/Ps. You must design these procedures to prevent circumstances that increase the risk of the introduction, transmission, or spread of communicable diseases through the use of HCT/Ps.

(b) *Review and approval*. Before implementation, a responsible person must review and approve these procedures.

(c) *Availability*. These procedures must be readily available to the personnel in the area where the operations to which they relate are performed, or in a nearby area if such availability is impractical.

(d) *Standard procedures*. If you adopt current standard procedures from another organization, you must verify that the procedures meet the requirements of this part and are appropriate for your operations.

§ 1271.190 Facilities.

(a) *General*. Any facility used in the manufacture of HCT/Ps must be of suitable size, construction, and location to prevent contamination of HCT/Ps with communicable disease agents and to ensure orderly handling of HCT/Ps without mix-ups. You must maintain the facility in a good state of repair. You must provide lighting, ventilation, plumbing, drainage, and access to sinks and toilets that are adequate to prevent the introduction, transmission, or spread of communicable disease.

(b) *Facility cleaning and sanitation*. (1) You must maintain any facility used in the manufacture of HCT/Ps in a clean, sanitary, and orderly manner, to prevent the introduction, transmission, or spread of communicable disease.

(2) You must dispose of sewage, trash, and other refuse in a timely, safe, and sanitary manner.

(c) *Operations*. You must divide a facility used in the manufacture of HCT/Ps into separate or defined areas of adequate size for each operation that takes place in the facility, or you must establish and maintain other control systems to prevent improper labeling, mix-ups, contamination, cross-contamination, and accidental exposure of HCT/Ps to communicable disease agents.

(d) *Procedures and records*. (1) You must establish and maintain procedures for facility cleaning and sanitation for the purpose of preventing the introduction, transmission, or spread of communicable disease. These

procedures must assign responsibility for sanitation and must describe in sufficient detail the cleaning methods to be used and the schedule for cleaning the facility.

(2) You must document, and maintain records of, all cleaning and sanitation activities performed to prevent contamination of HCT/Ps. You must retain such records 3 years after their creation.

§ 1271.195 Environmental control and monitoring.

(a) *Environmental control.* Where environmental conditions could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment, or accidental exposure of HCT/Ps to communicable disease agents, you must adequately control environmental conditions and provide proper conditions for operations. Where appropriate, you must provide for the following control activities or systems:

(1) Temperature and humidity controls;

(2) Ventilation and air filtration;

(3) Cleaning and disinfecting of rooms and equipment to ensure aseptic processing operations; and

(4) Maintenance of equipment used to control conditions necessary for aseptic processing operations.

(b) *Inspections.* You must inspect each environmental control system periodically to verify that the system, including necessary equipment, is adequate and functioning properly. You must take appropriate corrective action as necessary.

(c) *Environmental monitoring.* You must monitor environmental conditions where environmental conditions could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment, or

accidental exposure of HCT/Ps to communicable disease agents. Where appropriate, you must provide environmental monitoring for microorganisms.

(d) *Records.* You must document, and maintain records of, environmental control and monitoring activities.

§ 1271.200 Equipment.

(a) *General.* To prevent the introduction, transmission, or spread of communicable diseases, equipment used in the manufacture of HCT/Ps must be of appropriate design for its use and must be suitably located and installed to facilitate operations, including cleaning and maintenance. Any automated, mechanical, electronic, or other equipment used for inspection, measuring, or testing in accordance with this part must be capable of producing valid results. You must clean, sanitize, and maintain equipment according to established schedules.

(b) *Procedures and schedules.* You must establish and maintain procedures for cleaning, sanitizing, and maintaining equipment to prevent malfunctions, contamination or cross-contamination, accidental exposure of HCT/Ps to communicable disease agents, and other events that could reasonably be expected to result in the introduction, transmission, or spread of communicable diseases.

(c) *Calibration of equipment.* Where appropriate, you must routinely calibrate according to established procedures and schedules all automated, mechanical, electronic, or other equipment used for inspection, measuring, and testing in accordance with this part.

(d) *Inspections.* You must routinely inspect equipment for cleanliness, sanitation, and calibration, and to ensure adherence to applicable equipment maintenance schedules.

(e) *Records*. You must document and maintain records of all equipment maintenance, cleaning, sanitizing, calibration, and other activities performed in accordance with this section. You must display records of recent maintenance, cleaning, sanitizing, calibration, and other activities on or near each piece of equipment, or make the records readily available to the individuals responsible for performing these activities and to the personnel using the equipment. You must maintain records of the use of each piece of equipment, including the identification of each HCT/P manufactured with that equipment.

§ 1271.210 Supplies and reagents.

(a) *Verification*. You must not use supplies and reagents until they have been verified to meet specifications designed to prevent circumstances that increase the risk of the introduction, transmission, or spread of communicable diseases. Verification may be accomplished by the establishment that uses the supply or reagent, or by the vendor of the supply or reagent.

(b) *Reagents*. Reagents used in processing and preservation of HCT/Ps must be sterile, where appropriate.

(c) *In-house reagents*. You must validate and/or verify the processes used for production of in-house reagents.

(d) *Records*. You must maintain the following records pertaining to supplies and reagents:

(1) Records of the receipt of each supply or reagent, including the type, quantity, manufacturer, lot number, date of receipt, and expiration date;

(2) Records of the verification of each supply or reagent, including test results or, in the case of vendor verification, a certificate of analysis from the vendor; and

(3) Records of the lot of supply or reagent used in the manufacture of each HCT/P.

§ 1271.215 Recovery.

If you are an establishment that recovers HCT/Ps, you must recover each HCT/P in a way that does not cause contamination or cross-contamination during recovery, or otherwise increase the risk of the introduction, transmission, or spread of communicable disease through the use of the HCT/P.

§ 1271.220 Processing and Process controls.

(a) *General.* If you are an establishment that processes HCT/Ps, you must process each HCT/P in a way that does not cause contamination or cross-contamination during processing, and that prevents the introduction, transmission, or spread of communicable disease through the use of the HCT/P.

(b) *Pooling.* Human cells or tissue from two or more donors must not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing.

(c) *In-process control and testing.* You must ensure that specified requirements, consistent with paragraph (a) of this section, for in-process controls are met, and that each in-process HCT/P is controlled until the required inspection and tests or other verification activities have been completed, or necessary approvals are received and documented. Sampling of in-process HCT/Ps must be representative of the material to be evaluated.

(d) *Dura mater.* (1) When there is a published validated process that reduces the risk of transmissible spongiform encephalopathy, you must use this process for dura mater (or an equivalent process that you have validated),

unless following this process adversely affects the clinical utility of the dura mater.

(2) When you use a published validated process, you must verify such a process in your establishment.

§ 1271.225 Process changes.

Any change to a process must be verified or validated in accordance with § 1271.230, to ensure that the change does not create an adverse impact elsewhere in the operation, and must be approved before implementation by a responsible person with appropriate knowledge and background. You must communicate approved changes to the appropriate personnel in a timely manner.

§ 1271.230 Process validation.

(a) *General.* Where the results of processing described in § 1271.220 cannot be fully verified by subsequent inspection and tests, you must validate and approve the process according to established procedures. The validation activities and results must be documented, including the date and signature of the individual(s) approving the validation.

(b) *Written representation.* Any written representation that your processing methods reduce the risk of transmission of communicable disease by an HCT/P, including but not limited to, a representation of sterility or pathogen inactivation of an HCT/P, must be based on a fully verified or validated process.

(c) *Changes.* When changes to a validated process subject to paragraph(a) of this section occur, you must review and evaluate the process and perform revalidation where appropriate. You must document these activities.

§ 1271.250 Labeling controls.

(a) *General.* You must establish and maintain procedures to control the labeling of HCT/Ps. You must design these procedures to ensure proper HCT/P identification and to prevent mix-ups.

(b) *Verification.* Procedures must include verification of label accuracy, legibility, and integrity.

(c) *Labeling requirements.* Procedures must ensure that each HCT/P is labeled in accordance with all applicable labeling requirements, including those in §§ 1271.55, 1271.60, 1271.65, 1271.90, 1271.290, and 1271.370, and that each HCT/P made available for distribution is accompanied by documentation of the donor eligibility determination as required under § 1271.55.

§ 1271.260 Storage.

(a) *Control of storage areas.* You must control your storage areas and stock rooms to prevent:

(1) Mix-ups, contamination, and cross-contamination of HCT/Ps, supplies, and reagents, and

(2) An HCT/P from being improperly made available for distribution.

(b) *Temperature.* You must store HCT/Ps at an appropriate temperature.

(c) *Expiration date.* Where appropriate, you must assign an expiration date to each HCT/P based on the following factors:

(1) HCT/P type;

(2) Processing, including the method of preservation;

(3) Storage conditions; and

(4) Packaging.

(d) *Corrective action.* You must take and document corrective action whenever proper storage conditions are not met.

(e) *Acceptable temperature limits.* You must establish acceptable temperature limits for storage of HCT/Ps at each step of the manufacturing process to inhibit the growth of infectious agents. You must maintain and record storage temperatures for HCT/Ps. You must periodically review recorded temperatures to ensure that temperatures have been within acceptable limits.

§ 1271.265 Receipt, predistribution shipment, and distribution of an HCT/P.

(a) *Receipt.* You must evaluate each incoming HCT/P for the presence and significance of microorganisms and inspect for damage and contamination. You must determine whether to accept, reject, or place in quarantine each incoming HCT/P, based upon pre-established criteria designed to prevent communicable disease transmission.

(b) *Predistribution shipment.* If you ship an HCT/P within your establishment or between establishments (e.g., procurer to processor) and the HCT/P is not available for distribution as described in paragraph (c) of this section, you must first determine and document whether pre-established criteria designed to prevent communicable disease transmission have been met, and you must ship the HCT/P in quarantine.

(c) *Availability for distribution.* (1) Before making an HCT/P available for distribution, you must review manufacturing and tracking records pertaining to the HCT/P, and, on the basis of that record review, you must verify and document that the release criteria have been met. A responsible person must document and date the determination that an HCT/P is available for distribution.

(2) You must not make available for distribution an HCT/P that is in quarantine, is contaminated, is recovered from a donor who has been

determined to be ineligible or for whom a donor-eligibility determination has not been completed (except as provided under §§ 1271.60, 1271.65, and 1271.90), or that otherwise does not meet release criteria designed to prevent communicable disease transmission.

(3) You must not make available for distribution any HCT/P manufactured under a departure from a procedure relevant to preventing risks of communicable disease transmission, unless a responsible person has determined that the departure does not increase the risk of communicable disease through the use of the HCT/P. You must record and justify any departure from a procedure at the time of its occurrence.

(d) *Packaging and shipping.* Packaging and shipping containers must be designed and constructed to protect the HCT/P from contamination. For each type of HCT/P, you must establish appropriate shipping conditions to be maintained during transit.

(e) *Procedures.* You must establish and maintain procedures, including release criteria, for the activities in paragraphs (a) through (d) of this section. You must document these activities. Documentation must include:

(1) Identification of the HCT/P and the establishment that supplied the HCT/P;

(2) Activities performed and the results of each activity;

(3) Date(s) of activity;

(4) Quantity of HCT/P subject to the activity; and

(5) Disposition of the HCT/P (e.g., identity of consignee).

(f) *Return to inventory.* You must establish and maintain procedures to determine if an HCT/P that is returned to your establishment is suitable to be returned to inventory.

§ 1271.270 Records.

(a) *General.* You must maintain records concurrently with the performance of each step required in this subpart and subpart C of this part. Any requirement in this part that an action be documented involves the creation of a record, which is subject to the requirements of this section. All records must be accurate, indelible, and legible. The records must identify the person performing the work and the dates of the various entries, and must be as detailed as necessary to provide a complete history of the work performed and to relate the records to the particular HCT/P involved.

(b) *Records management system.* You must establish and maintain a records management system relating to core CGTP requirements. Under this system, records pertaining to a particular HCT/P must be maintained in such a way as to facilitate review of the HCT/Ps history before making it available for distribution and, if necessary, subsequent to the HCT/Ps release as part of a followup evaluation or investigation. Records pertinent to the manufacture of HCT/Ps (e.g., labeling and packaging procedures, and equipment logs) must also be maintained and organized under the records management system. If records are maintained in more than one location, then the records management system must be designed to ensure prompt identification, location, and retrieval of all records.

(c) *Methods of retention.* You may maintain records required under this subpart electronically, as original paper records, or as true copies such as photocopies, microfiche, or microfilm. Equipment that is necessary to make the records available and legible, such as computer and reader equipment, must be readily available. Records stored in electronic systems must be backed up.

(d) *Length of retention.* You must retain all records for 10 years after their creation, unless stated otherwise in this part. However, you must retain the records pertaining to a particular HCT/P at least 10 years after the date of its administration, or if the date of administration is not known, then at least 10 years after the date of the HCT/Ps distribution, disposition, or expiration, whichever is latest. You must retain records for archived specimens of dura mater for 10 years after the appropriate disposition of the specimens.

(e) *Contracts and agreements.* You must maintain the name and address and a list of the responsibilities of any establishment that performs a manufacturing step for you. This information must be available during an inspection conducted under § 1271.400.

§ 1271.290 Tracking.

(a) *General.* If you perform any step in the manufacture of an HCT/P in which you handle the HCT/P, you must track each such HCT/P in accordance with this section, to facilitate the investigation of actual or suspected transmission of communicable disease and take appropriate and timely corrective action.

(b) *System of HCT/P tracking.* (1) You must establish and maintain a system of HCT/P tracking that enables the tracking of all HCT/Ps from:

- (i) The donor to the consignee or final disposition; and
- (ii) The consignee or final disposition to the donor.

(2) Alternatively, if you are an establishment that performs some but not all of the steps in the manufacture of an HCT/P in which you handle the HCT/P, you may participate in a system of HCT/P tracking established and maintained by another establishment responsible for other steps in the manufacture of the same HCT/P, provided that the tracking system complies with all the requirements of this section.

(c) *Distinct identification code.* As part of your tracking system, you must ensure: That each HCT/P that you manufacture is assigned and labeled with a distinct identification code, e.g., alphanumeric, that relates the HCT/P to the donor and to all records pertaining to the HCT/P; and that labeling includes information designed to facilitate effective tracking, using the distinct identification code, from the donor to the recipient and from the recipient to the donor. Except in the case of autologous or directed donations, you must create such a code specifically for tracking, and it may not include an individual's name, social security number, or medical record number. You may adopt a distinct identification code assigned by another establishment engaged in the manufacturing process, or you may assign a new code. If you assign a new code to an HCT/P, you must establish and maintain procedures for relating the new code to the old code.

(d) *Tracking from consignee to donor.* As part of your tracking system, you must establish and maintain a method for recording the distinct identification code and type of each HCT/P distributed to a consignee to enable tracking from the consignee to the donor.

(e) *Tracking from donor to consignee or final disposition.* As part of your tracking system, you must establish and maintain a method for documenting the disposition of each of your HCT/Ps, to enable tracking from the donor to the consignee or final disposition. The information you maintain must permit the prompt identification of the consignee of the HCT/P, if any.

(f) *Consignees.* At or before the time of distribution of an HCT/P to a consignee, you must inform the consignee in writing of the requirements in this section and of the tracking system that you have established and are maintaining to comply with these requirements.

(g) *Requirements specific to dura mater donors.* You must archive appropriate specimens from each donor of dura mater, under appropriate storage conditions, and for the appropriate duration, to enable testing of the archived material for evidence of transmissible spongiform encephalopathy, and to enable appropriate disposition of any affected nonadministered dura mater tissue, if necessary.

§ 1271.320 Complaint file.

(a) *Procedures.* You must establish and maintain procedures for the review, evaluation, and documentation of complaints as defined in § 1271.3(aa), relating to core current good tissue practice (CGTP) requirements, and the investigation of complaints as appropriate.

(b) *Complaint file.* You must maintain a record of complaints that you receive in a file designated for complaints. The complaint file must contain sufficient information about each complaint for proper review and evaluation of the complaint (including the distinct identification code of the HCT/P that is the subject of the complaint) and for determining whether the complaint is an isolated event or represents a trend. You must make the complaint file available for review and copying upon request from FDA.

(c) *Review and evaluation of complaints.* You must review and evaluate each complaint relating to core CGTP requirements to determine if the complaint is related to an HCT/P deviation or to an adverse reaction, and to determine if a report under § 1271.350 or another applicable regulation is required. As soon as practical, you must review, evaluate, and investigate each complaint that represents an event required to be reported to FDA, as described in § 1271.350. You must review and evaluate a complaint relating to core CGTP requirements that does not represent an event required to be reported to

determine whether an investigation is necessary; an investigation may include referring a copy of the complaint to another establishment that performed manufacturing steps pertinent to the complaint. When no investigation is made, you must maintain a record that includes the reason no investigation was made, and the name of the individual(s) responsible for the decision not to investigate.

■ 11. Part 1271 is amended by adding subpart E, consisting of §§ 1271.330 through 1271.370, to read as follows:

Subpart E—Additional Requirements for Establishments Described in § 1271.10

Sec.

1271.330 Applicability.

1271.350 Reporting.

1271.370 Labeling.

Subpart E—Additional Requirements for Establishments Described in § 1271.10

§ 1271.330 Applicability.

The provisions set forth in this subpart are being implemented for nonreproductive HCT/Ps described in § 1271.10 and regulated solely under section 361 of the Public Health Service Act and the regulations in this part, and for the establishments that manufacture those HCT/Ps. HCT/Ps that are drugs or devices regulated under the act, or are biological products regulated under section 351 of the Public Health Service Act, are not subject to the regulations set forth in this subpart.

§ 1271.350 Reporting.

(a) *Adverse reaction reports.* (1) You must investigate any adverse reaction involving a communicable disease related to an HCT/P that you made available

for distribution. You must report to FDA an adverse reaction involving a communicable disease if it:

(i) Is fatal;

(ii) Is life-threatening;

(iii) Results in permanent impairment of a body function or permanent damage to body structure; or

(iv) Necessitates medical or surgical intervention, including hospitalization.

(2) You must submit each report on a Form FDA-3500A to the address in paragraph (a)(5) of this section within 15 calendar days of initial receipt of the information.

(3) You must, as soon as practical, investigate all adverse reactions that are the subject of these 15-day reports and must submit followup reports within 15 calendar days of the receipt of new information or as requested by FDA. If additional information is not obtainable, a followup report may be required that describes briefly the steps taken to seek additional information and the reasons why it could not be obtained.

(4) You may obtain copies of the reporting form (FDA-3500A) from the Center for Biologics Evaluation and Research (see address in paragraph (a)(5) of this section). Electronic Form FDA-3500A may be obtained at <http://www.fda.gov/medwatch> or at <http://www.hhs.gov/forms>.

(5) You must submit two copies of each report described in this paragraph to the Center for Biologics Evaluation and Research (HFM-210), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448. FDA may waive the requirement for the second copy in appropriate circumstances.

(b) *Reports of HCT/P deviations.* (1) You must investigate all HCT/P deviations related to a distributed HCT/P for which you performed a manufacturing step.

(2) You must report any such HCT/P deviation relating to the core CGTP requirements, if the HCT/P deviation occurred in your facility or in a facility that performed a manufacturing step for you under contract, agreement, or other arrangement. Each report must contain a description of the HCT/P deviation, information relevant to the event and the manufacture of the HCT/P involved, and information on all follow-up actions that have been or will be taken in response to the HCT/P deviation (e.g., recalls).

(3) You must report each such HCT/P deviation that relates to a core CGTP requirement on Form FDA-3486 available at <http://www.fda.gov/cber/biodev/bpdrform.pdf>, within 45 days of the discovery of the event either electronically at <http://www.fda.gov/cber/biodev/biodevsub.htm> or by mail to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research (HFM-600), 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448.

§ 1271.370 Labeling.

The following requirements apply in addition to §§ 1271.55, 1271.60, 1271.65, and 1271.90:

(a) You must label each HCT/P made available for distribution clearly and accurately.

(b) The following information must appear on the HCT/P label:

(1) Distinct identification code affixed to the HCT/P container, and assigned in accordance with § 1271.290(c);

(2) Description of the type of HCT/P;

(3) Expiration date, if any; and

(4) Warnings required under §§ 1271.60(d)(2), 1271.65(b)(2), or 1271.90(b), if applicable.

(c) The following information must either appear on the HCT/P label or accompany the HCT/P:

- (1) Name and address of the establishment that determines that the HCT/P meets release criteria and makes the HCT/P available for distribution;
- (2) Storage temperature;
- (3) Other warnings, where appropriate; and
- (4) Instructions for use when related to the prevention of the introduction, transmission, or spread of communicable diseases.

■ 12. Part 1271 is amended by adding subpart F, consisting of §§ 1271.390 through 1271.440, to read as follows:

Subpart F—Inspection and Enforcement of Establishments Described in § 1271.10

Sec.

1271.390 Applicability.

1271.400 Inspections.

1271.420 HCT/Ps offered for import.

1271.440 Orders of retention, recall, destruction, and cessation of manufacturing.

Subpart F—Inspection and Enforcement of Establishments Described in § 1271.10

§ 1271.390 Applicability.

The provisions set forth in this subpart are applicable only to HCT/Ps described in § 1271.10 and regulated solely under section 361 of the Public Health Service Act and the regulations in this part, and to the establishments that manufacture those HCT/Ps. HCT/Ps that are drugs or devices regulated under the act, or are biological products regulated under section 351 of the

Public Health Service Act, are not subject to the regulations set forth in this subpart.

§ 1271.400 Inspections.

(a) If you are an establishment that manufactures HCT/Ps described in § 1271.10, whether or not under contract, you must permit the Food and Drug Administration (FDA) to inspect any manufacturing location at any reasonable time and in a reasonable manner to determine compliance with applicable provisions of this part. The inspection will be conducted as necessary in the judgment of the FDA and may include your establishment, facilities, equipment, finished and unfinished materials, containers, processes, HCT/Ps, procedures, labeling, records, files, papers, and controls required to be maintained under the part. The inspection may be made with or without prior notification and will ordinarily be made during regular business hours.

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

(c) FDA will call upon the most responsible person available at the time of the inspection of the establishment and may question the personnel of the establishment as necessary to determine compliance with the provisions of this part.

(d) FDA's representatives may take samples, may review and copy any records required to be kept under this part, and may use other appropriate means to record evidence of observations during inspections conducted under this subpart.

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

§ 1271.420 HCT/Ps offered for import.

(a) Except as provided in paragraphs (c) and (d) of this section, when an HCT/P is offered for import, the importer of record must notify, either before or at the time of importation, the director of the district of the Food and Drug Administration (FDA) having jurisdiction over the port of entry through which the HCT/P is imported or offered for import, or such officer of the district as the director may designate to act in his or her behalf in administering and enforcing this part, and must provide sufficient information for FDA to make an admissibility decision.

(b) Except as provided in paragraphs (c) and (d) of this section, an HCT/P offered for import must be held intact by the importer or consignee, under conditions necessary to prevent transmission of communicable disease, until an admissibility decision is made by FDA. The HCT/P may be transported under quarantine to the consignee, while the FDA district reviews the documentation accompanying the HCT/P. When FDA makes a decision regarding the admissibility of the HCT/P, FDA will notify the importer of record.

(c) This section does not apply to reproductive HCT/Ps regulated solely under section 361 of the Public Health Service Act and the regulations in this part, and donated by a sexually intimate partner of the recipient for reproductive use.

(d) This section does not apply to peripheral blood stem/progenitor cells regulated solely under section 361 of the Public Health Service Act and the regulations in this part, except that paragraphs (a) and (b) of this section apply when circumstances occur under which such imported peripheral blood stem/progenitor cells may present an unreasonable risk of communicable disease

transmission which indicates the need to review the information referenced in paragraph (a) of this section.

§ 1271.440 Orders of retention, recall, destruction, and cessation of manufacturing.

(a) Upon an agency finding that there are reasonable grounds to believe that an HCT/P is a violative HCT/P because it was manufactured in violation of the regulations in this part and, therefore, the conditions of manufacture of the HCT/P do not provide adequate protections against risks of communicable disease transmission; or the HCT/P is infected or contaminated so as to be a source of dangerous infection to humans; or an establishment is in violation of the regulations in this part and, therefore, does not provide adequate protections against the risks of communicable disease transmission, the Food and Drug Administration (FDA) may take one or more of the following actions:

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

(2) Take possession of and/or destroy the violative HCT/P; or

(3) Serve upon the establishment an order to cease manufacturing until compliance with the regulations of this part has been achieved. When FDA determines there are reasonable grounds to believe there is a danger to health, such order will be effective immediately. In other situations, such order will be effective after one of the following events, whichever is later:

(i) Passage of 5 working days from the establishment's receipt of the order;

or

(ii) If the establishment requests a hearing in accordance with paragraph (e) of this section and part 16 of this chapter, a decision in, and in accordance with, those proceedings.

(b) A written order issued under paragraph (a) of this section will state with particularity the facts that justify the order.

(c)(1) A written order issued under paragraph (a)(1) of this section will ordinarily provide that the HCT/P be recalled and/or destroyed within 5 working days from the date of receipt of the order. After receipt of an order issued under paragraph (a)(1) of this section, the establishment in possession of the HCT/P must not distribute or dispose of the HCT/P in any manner except to recall and/or destroy the HCT/P consistent with the provisions of the order, under the supervision of FDA.

(2) In lieu of paragraph (c)(1) of this section, other arrangements for assuring the proper disposition of the HCT/P may be agreed upon by the person receiving the written order and FDA. Such arrangements may include, among others, providing FDA with records or other written information that adequately ensure that the HCT/P has been recovered, processed, stored, and distributed in conformance with this part, and that, except as provided under §§ 1271.60, 1271.65, and 1271.90, the donor of the cells or tissue for the HCT/P has been determined to be eligible.

(d) A written order issued under paragraph (a)(3) of this section will specify the regulations with which you must achieve compliance and will ordinarily specify the particular operations covered by the order. After receipt of an order that is in effect and issued under paragraph (a)(3) of this section, you must not resume operations without prior written authorization of FDA.

(e) The recipient of an order issued under this section may request a hearing in accordance with part 16 of this chapter. To request a hearing, the recipient of the written order or prior possessor of such HCT/P must make the request within 5 working days of receipt of a written order for retention, recall, destruction, and/or cessation (or within 5 working days of the agency's possession of an HCT/P under paragraph (a)(2) of this section), in accordance with part 16 of this chapter. An order of destruction will be held in abeyance pending resolution of the hearing request. Upon request under part 16 of this chapter, FDA will provide an opportunity for an expedited hearing for an order of cessation that is not stayed by the Commissioner of Food and Drugs.

(f) FDA will not issue an order for the destruction of reproductive tissue under paragraph (a)(1) of this section, nor will it carry out such destruction itself under paragraph (a)(2) of this section.

Dated: June 17, 2004.

Lester Crawford,

Acting Commissioner of Food and Drugs.

Dated: September 16, 2004.

Tommy G. Thompson,

Secretary of Health and Human Services.

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