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NOTE TO FDA Dockets Management Branch  
DOCKET NO.: 1997N-484P  
SUBJECT: OMB Changes  
PUB DATE: 11/24/04

The September 30, 1993, Executive Order 12866--Regulatory Planning and Review sets forth the Administration's principles and requirements for the Federal regulatory process. Under section 6(a)(3)(E) of the Executive Order, for "significant regulatory actions," Federal agencies must make certain information available to the public after publication of the regulatory action in the Federal Register.

Pursuant to the Executive Order, FDA has attached Tab A, for significant regulatory actions, in this docket the following information:

- 1) A copy of the draft regulatory action as submitted to the Office of Management and Budget's (OMB) Office of Information and Regulatory Affairs (OIRA) for review including any materials or assessments, required by the Executive Order, that accompanied the draft;
- 2) The substantive changes between the draft submitted to OIRA for review and the action subsequently announced, indicated by the redline changes to the draft; and
- 3) Those changes in the regulatory action that were made at the suggestion or recommendation of OIRA, indicated by the redline changes to the draft

  
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(HF-26)

Attachment(s)

1997N-0484P

REF 1

OCT 29 2004 OMB Changes.

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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SUPPLEMENTARY INFORMATION:

TABLE OF CONTENTS

- I. Introduction
  - A. Background
  - B. Legal Authority
- II. Revisions to the Proposed Rule
  - A. Plain Language
  - B. HCT/P Definition
  - C. Function and Integrity
  - D. Core CGTP Requirements
  - E. Other Revisions
- III. Comments on the Proposed Rule and FDA's Responses
  - A. General
  - B. Definitions (§ 1271.3)
  - C. Part 1271, Subpart D--Current Good Tissue Practice
  - D. Part 1271, Subpart E--Additional Requirements for  
Establishments Described in § 1271.10
  - E. Part 1271, Subpart F--Inspection and Enforcement of  
Establishments Described in § 1271.10

- F. Economic Impacts
- IV. Effective Date of 21 CFR Part 1271 and Applicability of 21 CFR Part 1270
  - A. Effective Date for Part 1271
  - B. Applicability of Part 1270
- V. Analysis of Economic Impacts
- VI. Environmental Impact
- VII. Federalism Assessment
- VIII. The Paperwork Reduction Act of 1995
- IX. References

#### 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 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 (68~~9~~ 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(11) 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"> <li>1. Follow only those requirements applicable to the operations you perform (§ 1271.150(c)(1)).</li> <li>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)).</li> <li>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)).</li> <li>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)).</li> </ol>
Engage another establishment to perform any step in manufacturing for you under contract, agreement, or other arrangement	<ol style="list-style-type: none"> <li>1. Enter into and maintain such an arrangement only with a reliable establishment that complies with applicable CGTP requirements. (§ 1271.150(c)(1)).</li> <li>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)).</li> </ol>
Make the HCT/P available for distribution	<ol style="list-style-type: none"> <li>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)).</li> <li>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).</li> <li>3. Investigate and report any adverse reaction involving a communicable</li> </ol>

TABLE 1a

If you ...	You must ...
	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~~facilities~~." As modified, the regulation requires ~~toilets~~facilities 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, ~~washing facilities,~~ and access to sinks and toilets~~facilities~~ ~~that are adequate~~ 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 paragraph (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