

also removed the second and third sentences of proposed paragraph (c), which related to direction for calibration; accuracy and precision limits; and corrective actions.

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

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

based on § 820.72, provides establishments with more flexibility than the proposed provision would have given.

(Comment 77) One comment asserted that the records requirement in proposed § 1271.200(e) should be limited to major equipment and should not include simple instruments that are regularly washed and disinfected or disposable equipment that has a validated procedure for cleaning and disinfecting.

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

9. Supplies and Reagents (§ 1271.210)

Proposed § 1271.210 would require the establishment to establish and maintain procedures for receiving supplies and reagents used in the manufacture of HCT/Ps. These items would be verified to meet specifications designed to prevent circumstances that increase the risk of introduction, transmission, or spread of communicable disease through HCT/P

contamination. Supplies and reagents are materials that might be used during manufacture, but do not include any material that might become a component of an HCT/P (66 FR 1508 at 1515).

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

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

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

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

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

and (b) are core CGTP requirements listed in § 1271.150(b); therefore, the requirement for establishing procedures under § 1271.180 applies to these two paragraphs.

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

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

(Comment 81) One comment asserted that the requirement is overly broad and requested that we allow establishments to write and maintain procedures for use of supplies and reagents that prevent circumstances that increase the risk of introduction, transmission, or spread of communicable disease.

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

(Comment 82) Proposed § 1271.210(c) contains records requirements, and paragraph (c)(3) would require records of the use of each supply or reagent, including the identification of each HCT/P manufactured with the supply or reagent. One comment

noted that, for many HCT/Ps, lots are small, and a requirement for separate records would present an enormous burden. Another comment questioned the utility of listing each product processed by each pipette or bottle of medium. A third comment asserted that, although the processing records for each hematopoietic stem/progenitor cell preparation should identify supplies and reagents used for processing, it would be prohibitively time-consuming to maintain separate records of each transplant prepared with each reagent.

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

10. Recovery (§ 1271.215)

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

11. Processing and Process Controls (§ 1271.220)

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

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

(Comment 83) One comment requested an exemption for eye banks from this section, because corneas are not processed in accordance with FDA's definition. Another comment asserted that the section is inapplicable to eye banks.

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

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

(Response) Requirements with respect to in-process control and testing are now contained in § 1271.220(c). We have also removed references to specifications from § 1271.220(a). That paragraph now requires that, if you are an establishment that processes HCT/Ps, you must process each HCT/P in a way that does

not cause contamination or cross-contamination during processing, and that prevents the introduction, transmission, or spread of communicable disease through the use of the HCT/P.

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

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

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

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

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

(Response) FDA is not requiring at this time that tissue be sterile, but we do expect aseptic techniques to be used during manufacturing to prevent contamination and cross-contamination. Indeed, it is the current industry practice to use aseptic techniques during recovery and processing. Whenever an activity is used in the processing of HCT/Ps, that activity must be controlled to limit the introduction of disease agents.

When technology progresses to the extent that viral clearance or sterilization is feasible, FDA may revise these CGTPs to require that HCT/Ps be sterile. FDA welcomes submissions as to when technology will have progressed to this point.

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

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

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

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

Pooling.

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

(Comment 89) Approximately six comments agreed with the proposed prohibition on pooling. Several comments pointed to an increased risk of infectious disease transmission associated with pooling, and asserted that pooling could increase the threat of previously unknown transmissible diseases. One comment asserted that there is a particularly high risk for Rh-negative women of childbearing age who receive tissue from Rh-positive donors. Two comments argued that pooling would impair the effectiveness of tissue recalls, because tracing to the source of a problem would be impossible. Comments also questioned the efficacy of processes used to manufacture pooled

HCT/Ps and noted that no process entirely eliminates the risk of infectious disease transmission. Two comments asserted that pooling would be distasteful to donors and their families.

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

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

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

- Careful screening of the donor for TSE and risk factors for TSE;

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

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

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

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

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

infected donor, is directly proportional to the prevalence of the agent in the donor population and the size of the pool.

(Comment 92) Several comments pointed out benefits of pooling. Two comments pointed to the need for pooling to obtain a sufficient dose of an HCT/P, especially in adults (e.g., from cord blood). One comment stated that pooling contributes to product consistency and uniformity.

(Response) We are retaining the prohibition on pooling during manufacturing in § 1271.220(b). We continue to believe that, in general, the risks of pooling HCT/Ps (increased risk of communicable disease transmission) outweigh the benefits of pooling. For some biological products, e.g., plasma derivatives, the benefits of pooling outweigh the risks. In the case of plasma derivatives, pooling contributes to product consistency. In fact, 21 CFR 640.102(d) requires that material from not less than 1,000 donors be pooled to make immune globulin. For plasma derivatives, it is necessary to pool plasma from many donors to obtain an adequate amount of product to treat one recipient (i.e., a sufficient dose). In addition, pooling plasma may dilute the viral burden or provide neutralizing antibodies that may inactivate any virus present in the pool. However, these benefits of pooling do not apply, in general, to the pooling of HCT/Ps from many donors. For instance, tendons from different donors would not need to be

pooled to provide consistency or to obtain a sufficient dose. Neither would bones pooled from different donors provide neutralizing antibodies to inactivate any virus present in the pool, since neutralizing antibodies are present in plasma. In the case of cord blood, most of the plasma is removed during processing, so that pooling of cord blood from different donors would not provide sufficient neutralizing antibodies to neutralize any virus present in the pool. Furthermore, when cord blood units from more than one donor are administered to an adult recipient to obtain a sufficient dose, the units are generally given sequentially and are not pooled.

In order for us to determine whether any benefits to pooling HCT/Ps from different donors outweigh the risks in a particular case, we would need additional data. Such data may be submitted and evaluated under a request for an alternative or exemption in § 1271.155.

(Comment 93) Several comments asserted that the risks of pooling could be mitigated through validated procedures for clearing pathogens or sterilizing the pooled HCT/Ps. One of these comments suggested additional regulatory language that would permit pooling where it is necessary and does not create an unreasonable risk of communicable disease transmission. Another comment proposed that the final rule should allow the

pooling of stem cell products from two or more donors, as long as the resulting pooled product is transplanted into only one recipient.

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

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

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

In-process control and testing.

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

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

We note that paragraph (c) includes the prevention of bacterial and other contamination. Compliance with this paragraph requires checking the results of testing at various steps in processing (for example, by sampling in-process HCT/Ps). The sample selected for testing (e.g., culture) must

be representative of the entire HCT/P. This may not be the case if a small snip of the HCT/P or companion tissue (i.e., tissue adjacent to the HCT/P that is processed along with the HCT/P) is cultured. The MMWR cited in section III.C.1 of this document recommended that performing both destructive (i.e., performed on tissue that had been ground up) and swab cultures (of the tissue surface) should be considered (Ref. 1).

Dura mater.

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

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

(Response) We disagree that FDA is endorsing the concept of an acceptable level of TSE risk. The donor-eligibility rule

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

We disagree that the requirement to use a validated

treatment reduces infectivity, this process can also decrease the clinical utility of the dura mater. Therefore,

§ 1271.220(d) requires use of a published validated process when one becomes available.

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

We recognize that, due to a variety of circumstances, you may not be aware when there is a published, validated process that reduces the risk of TSE. We intend to follow the good guidance practices set out in 21 CFR 10.115 to advise you when we have identified the existence of a published, validated process that reduces the risk of TSE and we would ordinarily solicit public comment before issuing a final guidance.

12. Process Changes (§ 1271.225)

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

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

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

Under § 1271.150(b), an establishment need only comply with those requirements applicable to the operations in which it engages (§ 1271.150(b)). Thus, if you are an establishment that does not engage in the processing of HCT/Ps, you do not need to comply with § 1271.225. We have discussed the meaning of

"processing" at Comment 20. We disagree that it is necessary to narrow the provision, which is intended to apply to the full range of HCT/P establishments engaged in processing.

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

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

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

(Response) We have removed the requirement for documenting all changes to an established process and the rationale for such

a change. We have maintained the proposed requirement for communicating approved changes to appropriate personnel in a timely manner; however, it no longer appears in paragraph (b), which has been deleted.

13. Process Validation (§ 1271.230)

Where the results of a process cannot be fully verified by subsequent inspection and tests, proposed § 1271.230 would require the process to be validated and approved according to established procedures. The validation activities, results, and the date and signature of the individual approving the validation would be documented. Re-validation would be required where appropriate in the case of changes to a validated procedure.

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

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

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

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

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

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

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

increase the risk of communicable disease transmission to the recipient, a written justification for not revalidating should be sufficient.

(Response) We disagree with the comments' suggestion to delete "fully." The term "fully verified" has been used with respect to process validation in ISO standards for years. Moreover, the term is used in the QS regulation on process validation applicable to medical devices (§ 820.75(a)).

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

In accordance with § 1271.150(e) ("where appropriate"), we agree that an assessment with written justification for not revalidating a change to a validated process would be sufficient

under § 1271.230(c) if the establishment can show that the change does not increase the risk of communicable disease transmission to the recipient.

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

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

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

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

14. Labeling Controls (§ 1271.250)

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

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

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

(Comment 104) One comment criticized as burdensome the proposed requirement for procedures to ensure that each product

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

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

important that the administering physician have in hand specific and accurate information about the HCT/P; availability of the documentation in another part of a facility is insufficient.

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

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

15. Storage (§ 1271.260)

Proposed § 1271.260 would require each establishment to control its storage areas and stock rooms to prevent mixups, commingling, deterioration, contamination, and cross-contamination of HCT/Ps and supplies, and to prevent improper

release for distribution. The establishment would also be required to store the HCT/Ps at an appropriate temperature, assign an expiration date for the HCT/P where appropriate, and take and document corrective action when indicated.

One comment supported this section as proposed.

(Comment 106) We received several comments on the storage temperature and period requirements in proposed § 1271.260(b). Some comments asked whether establishments must validate storage temperatures and periods, and noted that many of these have been established by the tissue industry based on experience. Another comment cited specific industry standards for eye banks. One comment asserted that the proposed parameters for setting storage temperature may not be optimal at the same temperature.

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

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

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

(Response) The requirement for establishing an expiration date is qualified by the term, "where appropriate." Section 1271.150(e) explains that a requirement is "appropriate" unless an establishment can justify otherwise, and maintains documentation of that justification. We consider it appropriate to assign expiration dates for "fresh" (i.e., noncryopreserved) HCT/Ps, and for those HCT/Ps that are thawed after cryopreservation and storage. If such applicable expiration dates have been established by industry or medical practice and meet the requirements of this section, you may use those dates for your HCT/Ps, whether "fresh" or cryopreserved. If scientific data do not exist for establishing expiration dates, then no expiration date is required at this time. We encourage the industry to perform studies to establish expiration dates for those HCT/Ps that currently do not have expiration dates.

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

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

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

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

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

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

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

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

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

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

(Response) You should tailor your acceptance procedures to the specific HCT/P and circumstances. As the comments point out, in some instances opening a sealed shipping container could potentially damage an HCT/P. In designing your acceptance procedures, you should take into account this possibility, as well as alternate ways of inspecting the HCT/P (e.g., inspection of container, ensuring proper temperature has been maintained during transit). If, after receiving the HCT/P, you hold it in storage, your storage conditions must comply with § 1271.260.

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

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

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

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

(Response) The requirements in § 1271.265(c) are intended to apply to the establishment that first makes an HCT/P available for distribution (defined in § 1271.3(z)). This establishment, which may or may not be the actual distributor, needs to have procedures in place under § 1271.265(e) for determining that an HCT/P may be made available for distribution, including release criteria designed to prevent communicable disease transmission. The regulation specifies that you must not make available for distribution any HCT/P that is in quarantine, is contaminated, is recovered from a donor who has been determined to be ineligible or for whom a donor-eligibility determination has not been completed (except as provided under §§ 1271.60, 1271.65, and 1271.90), or that otherwise does not meet release criteria designed to prevent

communicable disease transmission. Release criteria include criteria for releasing a product under § 1271.60, § 1271.65, or § 1271.90 that ensure, among other things, that the conditions for such release are met and that the HCT/P is labeled with the warnings required by the regulations.

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

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

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

(Comment 113) Proposed § 1271.265(e) would require that appropriate shipping conditions be defined for each type of product to be maintained during transit. One comment questioned whether shipping conditions must be defined for each type of

graft (e.g., femur ring, bone powder) or for each type of tissue (freeze-dried bone).

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

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

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

17. Records (§ 1271.270)

Proposed § 1271.270 would require establishments to maintain records concurrently with the performance of each significant step required in subparts C and D. A records management system would be established and maintained. Records would be maintained: Electronically, as original paper records,

or as true copies; 10 years after their creation; and for contracts, agreements, and other arrangements with another establishment to perform a step in manufacturing. One comment from a professional organization supported the goal of this provision, which it identified as chain of custody.

(Comment 115) One comment on § 1271.270(b) asserted that maintaining records organized by product type is not practical and that it is more useful to organize records by donor. Another comment asserted that detailing how to organize records is an unnecessary intrusion and that the example given was unduly complicated.

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

that the requirement for a records management system applies only to core CGTP requirements.

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

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

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

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

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

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

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

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

(Comment 119) Proposed paragraph (e) would require an establishment to make provisions for all records to be maintained for the required period in the event that the establishment ceases operation. One comment asserted that it is not practical for an establishment to retain records if it has gone out of business.

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

18. Tracking (§ 1271.290)

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

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

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

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

(Comment 120) We received several comments in support of the proposed requirements. One comment responded to our request for comments from establishments that have already developed and implemented tracking systems about the success or failure of those systems (66 FR 1508 at 1519). This comment described its successful tracking system and noted that tracking fulfills its ongoing responsibility to the patients who have received its tissues. The establishment provides hospitals with peeloff labels that identify each unique product and the bank that provided it, and also with tracking logs for the hospitals to use to control inventory. Information on the use of the HCT/P is returned to the tissue bank by the hospital in a self-addressed envelope and then entered into the establishment's database. The establishment sends regular reminders to

hospitals notifying them of tissue for which it has not received transplant records. The comment noted that hospitals willingly participate, and it cited a high (85 to 100 percent) return of transplant records.

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

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

(Response) We disagree. Not only are these requirements justified by the communicable disease risks posed by HCT/Ps, but they are consistent with industry standards. AATB standards require traceability and dispensing records by the tissue dispensing service (medical, dental, hospital facility, physician's office) (See the American Association of Tissue Banks (AATB) Standards 2002, L4.000). The Eye Bank Association of America (EBAA) medical standards require that recipient

identification readily traceable to each unique graft number be retained in the eye banks' records (See EBAA Medical Standards 2002, M1.400).

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

In the unusual event that an establishment met the definition of covered entity, the establishment's disclosure of individually identifiable health information would be subject to the privacy rule. However, the privacy rule allows covered entities to share de-identified health information for any purpose and includes requirements for determining whether information is de-identified. (45 CFR 164.502(d), 164.514(a)-(c)). Further, a covered entity may assign a code to otherwise de-identified data, if the code is not derived from or related

to information about the individual and is not otherwise capable of being translated so as to identify the individual, and if the covered entity does not use or disclose the code or other means of record identification for any other purpose, and does not disclose the mechanism for reidentification (45 CFR 164.514(c)). Thus, an establishment that is a covered entity is not in violation of the privacy rule if it discloses information de-identified in accordance with 45 CFR 164.514(a)-(c), including a distinct identification code that meets the requirements of 45 CFR 164.514(c).

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

We note that a consignee may on occasion wish to disclose protected health information to an establishment. For example, a consignee may wish to report to the establishment that a recipient of an HCT/P developed an infection at the site of the transplant. Under the public health activities provisions of the privacy rule, the rule permits, but does not require, entities that meet the definition of a covered entity to disclose protected health information to persons subject to the

jurisdiction of FDA with respect to an FDA-regulated product or activity for which that person has responsibility, for the purpose of activities related to the quality, safety or effectiveness of such FDA-regulated product or activity (45 CFR 164.512(b)(1)(iii)). The rule specifically identifies tracking FDA-regulated products as a purpose permitting such disclosures, along with collecting and reporting adverse events and enabling product recalls, repairs, replacement, or lookback (45 CFR 164.512(b)(1)(iii)(A), (b)(1)(iii)(B), and (b)(1)(iii)(C)). Finally, in the event that one of the previously mentioned provisions is not applicable, covered entities may disclose protected health information pursuant to an authorization from the individual or the individual's personal representative (45 CFR 164.502(g)(1) and 164.508). We further discuss the applicability of the privacy rules in the context of donor eligibility in Comment 4 to the donor eligibility rule (69 FR 29786 at 29790).

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

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

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

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

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

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

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

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

(Response) Section 1271.290(b) provides establishments with the flexibility to participate in the tracking system set up by another establishment, provided that the system complies with all requirements in this section. However, the responsibility lies with each establishment involved in the manufacture of an HCT/P. For example, if only the establishment that made the HCT/P available for distribution were responsible for tracking, establishments "upstream" would not necessarily

participate. This would not enable tracking from donor to consignee because the distributor would not have the information for linking the consignee to the donor, since the establishment performing recovery would be the only entity that would know the identity of the donor.

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

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

We have added to paragraph (c) the requirement that labeling include information designed to facilitate effective tracking, using the distinct identification code, from the donor to the recipient and from the recipient to the donor. Although § 1271.290 does not require establishments to establish a tracking system from the recipient to the donor and from the donor to the recipient, this labeling requirement will enable such tracking to be performed. An example of a labeling

statement that would comply with this requirement is:

"IMPORTANT NOTICE TO END-USER: Please record this distinct identification code in your records and in the patient's file."

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

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

(Comment 128) Proposed § 1271.290(d) would require an establishment to ensure that the identifier and type of HCT/P that is implanted into a recipient be recorded in the recipient's medical records, or in other pertinent records, to enable tracking from the recipient to the donor.

One comment asserted that the manufacturer has no authority over the content of the medical record and suggested that the manufacturer provide paper documentation appropriate for the medical record and notice of the Federal regulations requiring that the information be placed in the medical record. Another comment asserted that, because of tissue establishment's inability to mandate hospital compliance, FDA should revise

proposed § 1271.290(d) to allow tracking to the production lot, or eliminate the provision altogether.

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

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

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

One comment asked us to specify an acceptable timeframe for the identification of the recipient. Another comment asked whether, with regard to "prompt" identification, the name and hospital or social security number are sufficient information to allow identification. A third comment suggested requiring tracking, not to the recipient, but to the distributor,

transplant facility, or transplanting surgeon, as appropriate. This comment asserted that neither tissue banks nor the agency has the authority to mandate hospital or physician compliance with the tissue banks request for recipient information.

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

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

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

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

(Comment 131) Proposed § 1271.290(f) would require establishments, at or before the time of distribution of an HCT/P, to inform the consignee in writing of the regulatory requirements and of the tracking method that the establishment has put into place. The establishment would also be required to document that the consignee agreed to participate in its tracking method and to take all necessary steps to ensure compliance with the requirements of § 1271.290.

Several comments questioned how proposed § 1271.290(f) would work. One comment asked whether a signed agreement would have to be obtained before sending the tissue, and noted that this would be difficult. This comment also asked who should be authorized to sign the agreement. Another comment noted that it sends a "tissue usage form" with its tissues, but that many facilities do not return the form; this comment further noted that a contract does not always exist between a tissue bank and the end user. Several comments asserted that tissue banks lack the authority or means to ensure compliance with the regulation and should not be held responsible for gathering tracking information, and one comment asked how far an eye bank must go

to demonstrate that it has attempted to obtain an agreement from the consignee. One comment stated that a tissue facility cannot and should not withhold tissue for a prior failure of a facility to provide required documentation, and that if it did so, another source of tissues would be sought.

One comment expressed concern that: (1) Establishments may develop agreements that are least burdensome rather than most effective; (2) an establishment would not be able to provide an HCT/P to a consignee in an emergency until the consignee developed a tracking system; (3) the tracking requirements conflict with the new privacy rules, because a tissue establishment must review recipient records to ascertain whether a consignee maintained an adequate system; (4) patients change practitioners or localities without providing their new addresses; and (5) it would be unwieldy and unrealistic for an establishment with thousands of consignees to take all necessary steps to ensure their compliance.

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

19. Complaint Files (§ 1271.320)

Proposed § 1271.320 would require each establishment to establish and maintain procedures for the prompt review,

evaluation, and documentation of all complaints, and the investigation of complaints as appropriate. We defined "complaint" in proposed § 1271.3(ii) and have made several changes to that definition, now renumbered § 1271.3(aa), which are discussed at Comment 13.

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

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

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

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

(Response) We recognize the comments' concerns about maintaining donor and patient confidentiality. When copying complaint files, the agency will take steps to protect the identity of the donor or patient in conformance with 21 CFR parts 20 and 21.

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

1. Applicability (§ 1271.330)

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

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

2. Reporting Requirements (§ 1271.350)

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

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

(Response) We disagree that these reporting requirements are duplicative. Reporting to professional organizations is not required under these regulations. More importantly, we do not

receive reports of adverse reactions and HCT/P deviations from professional organizations.

Adverse Reaction Reporting (§ 1271.350(a))

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

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

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

(Response) We decline to make the suggested change. It may take longer than 15 days for an establishment to determine whether or not an adverse reaction is directly related to an HCT/P. For the protection of the public health, it is more important for information about the transmission of a communicable disease or HCT/P contamination to be reported to us within 15 days, even if further followup indicates that communicable disease transmission came from a source other than the HCT/P.

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

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

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

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

(Response) We disagree with these comments. The timeframe set out in § CFR 1271.350(a) is consistent with adverse reaction reporting requirements for other regulated products (see 21 CFR 314.80 and 600.80; Medical Device Reporting is required within

10 days (21 CFR 803.10)). The adverse reactions that must be reported to the agency under § 1271.350(a) warrant action in less than 1 or 2 months. It is reasonable for us to require reporting without delay of an adverse reaction that is fatal or life-threatening, results in permanent impairment of a body function or permanent damage to body structure, or necessitates medical or surgical intervention, including hospitalization. We recognize that followup may be appropriate, and § 1271.350(a)(3) sets out procedures for submitting new information to the agency or responding to an agency request for additional information.

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

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

donor who was the source of additional HCT/Ps; CGTP failures in the establishment). For this reason, we would generally consider that an infection at the site of a transplant would be reportable under § 1271.350(a).

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

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

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

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

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

(Comment 142) One comment on proposed § 1271.350(b) asserted that the regulation should not require reporting of

minor or unimportant deviations. Two comments criticized the proposed reporting requirement as burdensome and questioned the agency's capacity to review submitted reports. These comments suggested limiting reports to instances involving issues of disease transmission.

(Response) We have modified the proposed definition of HCT/P deviation. An HCT/P deviation as defined in § 1271.3(dd) is limited to an event that represents a deviation from applicable regulations or established specifications that may relate to the prevention of communicable disease transmission or HCT/P contamination; or that is an unexpected or unforeseeable event that may relate to the transmission or potential transmission of a communicable disease or may lead to HCT/P contamination.

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

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

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

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

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

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

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

deviations relating to the core CGTP requirements would receive the necessary information from a contract establishment in accordance with § 1271.160(b)(2).

3. Labeling (§ 1271.370)

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

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

To coordinate with the requirement in § 1271.290(c) that you label each HCT/P with a distinct identification code, we

have added to § 1271.370 the requirement that this code be affixed to the HCT/P container.

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

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

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

(Response) In §§ 1271.60, 1271.65, and 1271.90 of the donor-eligibility final rule, we now require warning statements related to informing the recipient about certain unusual

circumstances, e.g., "WARNING: Advise patient of communicable disease risk" when an HCT/P is distributed before completion of the donor eligibility determination. These warning statements must appear on the HCT/P label. In addition, the establishment should determine what other information the user needs to know before using an HCT/P; this information would be considered "other warnings" (we have revised § 1271.370(c)(3)). Other warnings would include information about risks resulting from procedures to reduce communicable disease risks during the manufacture of an HCT/P. An example would be a warning that the product was processed aseptically and is not sterile (e.g., may harbor microorganisms).

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

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

(Response) We have revised § 1271.370 to strengthen the connection between the labeling requirements and the prevention of communicable disease. For example, § 1271.370(c)(4) now

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

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

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

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

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

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

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

(Response) This rule no longer contains language relating to homologous use claims. However, we take this opportunity to note that the examples of homologous and nonhomologous claims

given in the registration final rule are still valid, with one exception (see 66 FR 5447 at 5458). After reviewing additional data from one manufacturer, we now consider the use of that manufacturer's minimally manipulated amniotic membrane alone for ocular repair as homologous. However, when amniotic membrane is combined with limbal stem cells, such an HCT/P is regulated under section 351 of the PHS Act.

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

1. Applicability (§ 1271.390)

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

2. Inspections (§ 1271.400)

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

(Comment 152) In the proposed rule, we invited comments on possible alternative inspection and enforcement provisions that would leverage our resources, be cost-effective, and achieve the public health goals of the proposed rule (66 FR 1508 at 1523). We received four comments in response to this request. These comments suggested third-party inspections, training of FDA representatives by professional organizations, and special recognition for accreditation.

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

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

courses for FDA representatives, and we hope to continue this useful practice.

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

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

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

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

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

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

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

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

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

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

(Response) FDA has tried a variety of announced and unannounced inspection procedures in the past. Our current practice is generally not to preannounce inspections because such a commitment affects the overall productivity of field staff. An establishment must be in compliance at all times,

which should make it unnecessary to preannounce an inspection for the establishment to "prepare" for an inspection. For clarity, we have modified the language of the final regulation to state that an inspection may be made with or without "prior notification."

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

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

(Comment 158) Proposed § 1271.400(c) also states that the FDA representative conducting an inspection may question the personnel of the establishment, as the representative deems necessary. One comment objected to the exercise of our discretion, if unfettered, to question any employee and stated

that, historically, FDA has allowed companies to designate spokespeople. Another comment asserted that FDA should question a senior official who is well acquainted with the SOPs of the facility (not just the most responsible person available).

(Response) It is agency practice for the FDA representative conducting an inspection to observe and interview employees to determine if they are performing their various functions in accordance with the firm's current SOPs, to determine if activities are being documented concurrently with the performance of each significant step, and to evaluate if employees are properly trained and supervised. We agree that it is a good idea to make a spokesperson available to accompany the FDA representative and provide historical, statistical, and administrative information about the company. All employees at an establishment should be well acquainted with the SOPs related to their work in that establishment.

(Comment 159) Under proposed § 1271.400(d), FDA's representative may review and copy any records required to be kept under part 1271 and may take photographs or make videotapes. One comment questioned FDA's intentions with respect to records of quality assurance activities. Another comment asked that this section be revised to exempt from FDA review records of management review, quality audits, supplier evaluations, and other types of information (e.g., financial).

One comment suggested new language limiting reproduction to data that would relate to possible communicable disease transmission and/or biologic dysfunction of tissue.

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

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

(Response) FDA's practice is to record images (e.g., by way of photographs or videotapes) to accurately record the conditions in an establishment. These tools may be employed as long as the inspection is lawful. See United States v. Gel

Spice Co., 601 F. Supp. 1214, 1220 (E.D.N.Y. 1985); United States v. Acri Wholesale Grocery Co., 409 F. Supp. 529, 532-533 (S.D. Iowa 1976). Inspections conducted under regulations issued under section 361 of the PHS Act are lawful. However, we have modified the wording of § 1271.400(d) to delete the specific references to photographs and videotapes, and to state instead that FDA's representatives may use other appropriate means to record evidence of observations during inspections conducted under this subpart.

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

4. Imports (§ 1271.420)

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

We have made several revisions to § 1271.420(a) and (b) for clarity and for consistency with agency import policy. We have replaced the phrase "offered for entry" with the more accurate phrase, "imported or offered for import." Consistent with other agency regulations, HCT/Ps "imported or offered for import"

include, not only those HCT/Ps imported or offered for import into the United States for use, storage, or distribution in the United States, but also those imported or offered for import for transshipment through the United States to another country, for future export, or for use in a United States Foreign Trade Zone. (See, e.g., "Prior Notice of Imported Food Under the Public Health Security and Bioterrorism Preparedness and Response Act of 2002," interim final rule, 68 FR 58974 at 58990 and 58991, October 10, 2003.)

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

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

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

(Response) We agree that § 1271.420 applies only to HCT/Ps intended for clinical use, but we do not consider it necessary to modify the regulation as suggested. The regulations in part 1271 do not apply to establishments that use HCT/Ps solely for nonclinical scientific or educational purposes (§ 1271.15(a)); moreover, § 1271.3(d) defines an HCT/P as intended for implantation, transplantation, infusion, or transfer into another human (i.e., clinical use).

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

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

(Comment 163) One comment asked about the relationship between the proposed FDA inspection and inspections of

hematopoietic stem/progenitor cells currently performed by other agencies, such as the Department of Transportation (DOT).

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

(Comment 164) Proposed § 1271.420(b) would require that an HCT/P offered for import must be held intact until it is released by FDA. Four comments on this provision raised strong objections to this provision because of its potential adverse effect on imported hematopoietic stem/progenitor cells. These comments asserted that any delay is life-threatening and that these HCT/Ps should be immediately cleared through customs.

(Response) Prior to infusion, recipients of peripheral blood stem/progenitor cells undergo a myeloablative treatment regimen (i.e., high dose chemotherapy and total body irradiation), which may have begun before importation takes place. We agree with the comments' concerns about the risk of delay in this situation and have accordingly revised § 1271.420. Section 1271.420(d) states that this section does not apply to peripheral blood stem/progenitor cells regulated solely under

section 361 of the PHS Act and the regulations in this part, except that paragraphs (a) and (b) apply when circumstances occur under which such imported peripheral blood stem/progenitor cells may present an unreasonable risk of communicable disease transmission, which indicates the need to review the information referenced in paragraph (a). We believe this provision affords access to peripheral blood stem/progenitor cells and appropriate public health protection. We also believe that situations in which information would be needed for review under paragraph (a) will be rare or unlikely to occur. Because the regulations in subpart F apply only to those HCT/Ps regulated solely under section 361 of the PHS Act and the regulations in part 1271, the exception in paragraph (d) affects only the subset of peripheral blood stem/progenitor cells that are regulated in this way (e.g., those for autologous use, or allogeneic use in a first-degree or second-degree blood relative). In the event that issues arise with respect to imports of peripheral blood stem/progenitor cells that are regulated as biological drugs, and so are subject to the import provisions in section 801 of the act (21 U.S.C 381), we would consider those issues and take appropriate actions.

Consideration of these comments has led us to make a clarification to § 1271.420(b) that will apply to HCT/Ps that are not excepted from these import provisions. Paragraph (b)

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

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

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

(Comment 165) Several comments asserted that these enforcement actions are too dramatic and far-reaching. One comment argued that the standard for taking these actions should be higher than mere CGTP deficiencies and should involve imminent danger to public health. One comment asserted that the regulation should define procedures to be followed to protect the rights of the manufacturer to due process.

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

- Passage of 5 working days from the establishment's receipt of the order; or
- If the establishment requests a hearing in accordance with paragraph (e) and part 16 (21 CFR part 16), a decision in, and in accordance with, those proceedings.

FDA reiterates that, as stated in § 1271.440(e), part 16 provides an opportunity to request a hearing concerning any

matter related to orders of retention, recall, destruction, and cessation of manufacturing of HCT/Ps (§ 16.1(b)(2)). Part 16 permits FDA to

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

(§ 16.24(d))

If FDA issues an order to cease one or more steps in the manufacture of an HCT/P, or issues an immediately effective order to retain, recall, and/or destroy the HCT/P, and the Commissioner of Food and Drugs (the Commissioner) does not stay the order upon receiving a hearing request, FDA will provide an opportunity for an expedited hearing. (See § 1271.440(e).) As a technical amendment, we are revising § 16.1(b)(2) by adding § 1271.440(e).

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

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

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

(Comment 167) One comment asked for clarification of the term "recall" and suggested that "notification" might be a more

appropriate term in cases where the tissue has already been transplanted.

(Response) Recall is an effective method of removing or correcting consumer products that are in violation of laws administered by FDA (§ 7.40(a)) (21 CFR 7.40(a)). Public notification is an important part of a recall strategy (see 21 CFR 7.50), especially where physical recall may be impossible or impractical. Guidelines on voluntary recalls, including public notification, are set out in §§ 7.40 through 7.59 (21 CFR 7.40 through 7.59). To the extent applicable, FDA follows the same policy regarding notifications for mandatory recalls. The term "recall" encompasses all elements of a recall strategy, including notification, and no change to the rule is necessary.

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

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

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

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

(Comment 170) One comment asserted that the order to cease manufacturing under proposed § 1271.440 violates the Due Process Clause of the Fifth Amendment of the United States Constitution. Citing Bell v. Burson, 402 U.S. 535, 542 (1971), the comment stated that, under the Due Process Clause, before a State seeks to terminate an entitlement (e.g., pursuit of a profession), it must provide notice and opportunity for hearing appropriate to the nature of the case before the termination becomes effective, "except in emergency situations." The comment noted that although proposed § 1271.440 permits a facility to request a hearing, it does not provide a date on which a hearing must be held or that a hearing must be held at all. This provision also

does not specify when a decision regarding the validity of the order is to be made. The comment also observed that an order under proposed § 1271.440 could be of potentially infinite duration, lasting as long as the agency believes that regulatory compliance has not been achieved. Another comment also asserted that, under American Bus Ass'n v. Slater, 231 F.3d 1 (D.C. Cir. 2000), this provision exceeds FDA's statutory authority under section 361 of the PHS Act and is invalid.

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

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

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

The comment's reliance on American Bus Ass'n v. Slater is misplaced. In American Bus, the United States Court of Appeals for the District of Columbia invalidated a Federal regulation that imposed money penalties (a fine), which was not expressly authorized under the Americans with Disabilities Act (ADA). The ADA explicitly provided for injunctive or similar preventive relief and permitted civil proceedings for money damages, but was silent about the imposition of money penalties. The Court held that "Congress unambiguously intended to preclude [the Department of Transportation] from authorizing money damages." (231 F.3d at 4.) By contrast, section 361 of the PHS Act expressly authorizes FDA to enforce regulations using such means as

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

Like an order of fumigation, disinfection, and sanitation, an order to cease manufacturing is a remedial action taken to put important protections in place to prevent communicable disease

transmission. Unlike the fine in American Bus, it is not a punitive action.

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

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

(Response) FDA disagrees that 5 days is an insufficient timeframe. However, we recognize that circumstances may exist or occur that would require a time period other than the prescribed 5 working days for the implementation of corrective action or recall and/or destruction of HCT/Ps. Accordingly, we note that § 1271.440(c)(1), which states that "[a] written order issued

under paragraph (a)(1) of this section will ordinarily provide that the HCT/P be recalled and/or destroyed within 5 working days from the date of receipt of the order" (emphasis added), provides for circumstances where we determine that an alternate timeframe is appropriate. The response to comment 167 describes the recall guidelines. In the event that FDA issues an order of destruction for HCT/Ps, such destruction would occur in accordance with applicable local, state, and Federal laws (i.e., Environmental Protection Agency) and under FDA supervision.

F. Economic Impacts

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

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

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

these comments suggested that the financial impact of the CGTP rule could force many eye banks out of business.

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

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

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

suggests that these requirements will not be overly time consuming or expensive.

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

(Response) The agency recognizes that some eye banks may experience a greater number of complaints. However, this estimate is designed to be representative of the number of complaints handled annually by a typical entity. The comment did not provide an alternative estimate of the number of complaints reported annually.

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

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

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

(Response) FDA has revised its estimate of the benefits of implementing the CGTP final rule for eye banks in response to comments received, and based on additional and more recent information. However, the study cited in the comment also reports, "interpretation of the results of this study is limited by the small sample size, which may preclude the detection of some associations," and, "(m)issing data for relevant variables,

most notably eye bank factors, make interpretation of related results difficult." (emphasis added). The comment does not provide any alternative estimates of benefits.

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

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

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

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

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

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

majority of facilities in the other HCT/P industry sectors, are believed to meet the criteria characterizing small entities in the relevant industry sector, FDA viewed this as an appropriate simplifying assumption.

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

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

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

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

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

(Response) Some requirements reviewed in the analysis of economic impacts show no costs because they are expected to impose no new financial burden on affected entities, not because there is no basis for predicting these costs. More

specifically, no cost estimate is provided for a section or provision of the CGTP rule if analysis showed the requirement: (1) Does not apply, (2) has no new cost impact, or (3) is met by another subsection of the rule.

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

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

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