

greater level of new effort will be required for quality assurance and quality management. The average annualized cost per small establishment not following current industry standards is estimated to be \$43,207 (\$2,160,341 total annualized costs / 50 small hematopoietic stem/progenitor cell establishments), and represents about 3 percent (\$43,207 / \$1.45 million) of average annual revenue.

Consultants estimate that two-thirds of all ART establishments could be classified as small entities, and have average annual revenues of approximately \$2.1 million. A typical ART establishment is expected to incur average annual and annualized costs of \$768. This figure represents approximately 0.04 percent (\$768 / \$2.1 million) of average annual revenues.

According to estimates by a semen banking industry expert, approximately 100,000 total daily intake (TDI) units are produced each year from collected and processed semen donations. An estimated 95 percent of that total production is handled by the largest 20 commercial establishments. Nineteen of these largest 20 establishments are estimated to have average annual revenues of approximately \$2.4 million, and only 1 establishment is estimated to have revenues greater than \$8.5 million per year. The remaining 5 percent of industry production, or 5,000 TDI units, are processed by very small semen banks that

typically function within a physician office practice (e.g., that of an obstetrician/gynecologist (Ob/Gyn)). Semen banking in these establishments is generally offered as an additional service to patients receiving fertility treatment, and is not a primary line of business.

The annual revenue for these individual physician practices is estimated to be \$692,000 per year, based on the average annual practice revenue per self-employed physician in the Ob/Gyn specialty category reported as \$627,000 in 1998 (Ref. 20), adjusted to year 2002 dollars based on inflation data reported by the Bureau of Labor Statistics (Ref. 27). Thus the majority of semen banks would be considered small entities.

The average annual and annualized costs associated with the inspection and enforcement provisions are estimated to be \$768 per affected ART establishment and semen bank. This figure represents approximately 0.03 percent ($\$768 / \2.4 million) of average annual revenues for the 19 small commercial semen banks, and about 0.11 percent ($\$768 / \$692,000$) for individual Ob/Gyn ART establishments and small physician practice-based semen banks.

Although these cost figures account for a much larger percentage of individual physician practice income, the semen banking provided by these establishments is considered to represent a small part of their overall business. For the

smallest banks, the estimated 5,000 TDI units supplied by the estimated 90 establishments in this category translate to an average volume of 55 units per establishment per year. With an estimated price of \$95 to \$145 per TDI unit (Ref. 30) and an estimated profit of 15 percent, these banks would realize, on average, a net income of \$12.40 to \$19.00 per unit, or a total net income of \$682 to \$1,045 for 55 units. This income would represent only 0.1 percent ($\$682 / \$692,000$) to 0.15 percent ($\$1,045 / \$692,000$) of the estimated annual practice revenue per self-employed physician in the Ob/Gyn specialty category.

In summary, the majority of establishments within each sector of the HCT/P industry are expected to qualify as small business entities. The actual cost impact on these entities is uncertain, because of the limited information available with which to describe current practices and the degree to which individual establishments follow voluntary industry standards within each HCT/P industry sector. Based on the limited available data and industry expert opinions, the agency estimates impacts that would result in an average annualized cost per small establishment subject to CGTPs in their entirety ranging from \$8,367 to \$12,087 for establishments that currently follow industry standards, and \$43,207 for establishments that do not currently follow industry quality standards. These annualized costs represent 0.6 percent to 0.83 percent of

estimated average annual revenues for firms currently following industry standards, and 3 percent of average annual revenues for firms not following industry standards.

The worst-case analysis assumes that an affected small entity will incur new costs for every provision of the CGTP final rule. While this represents a highly unlikely scenario for nearly all firms in the HCT/P industry sectors subject to CGTPs in their entirety, this analysis does provide a useful illustration of the maximum potential burden of the CGTP final rule. The agency estimates worst-case average annualized costs per small establishment ranging from \$21,602 to \$66,621 for establishments that currently follow industry standards, and \$83,483 for establishments that do not currently follow industry quality standards. These worst-case annualized costs for small entities, expressed as a percentage of estimated average annual revenue, range from 1.5 percent to 4.6 percent for firms currently following industry standards, and represent 5.8 percent of estimated average annual revenues for firms not following industry standards.

Establishments handling reproductive tissue are subject only to the inspection and enforcement provisions of the CGTP final rule as they apply to donor eligibility requirements under subpart C of part 1271. Small ART establishments and semen banks are expected to incur average annualized costs of \$768, which

represent between 0.03 and 0.11 percent of average annual revenues. The results of FDA's analysis of small entity impacts are summarized in table 14 of this document.

TABLE 14.--SUMMARY OF SMALL BUSINESS IMPACTS

No. of Small Establishments by Industry Sector	Average Annual Revenue per Small Establishment (in millions)	Average Annualized Cost per Small Establishment	Average Annualized Cost as a Percentage of Average Revenue	Worst-Case Costs for an affected Small Establishment	Worst-Case Costs as a Percentage of Average Revenue
Eye Banks (134 Establishments)	\$1.45	\$12,087	0.83%	\$39,750	2.7%
Conventional Tissue (129 Establishments)	\$1.45	\$11,678	0.8%	\$66,621	4.6%
Stem/Progenitor Cell Establishments Following Industry Standards (200 Establishments)	\$1.45	\$8,367	0.6%	\$21,602	1.5%
Stem/Progenitor Cell Establishments Not Following Industry Standards (50 Establishments)	\$1.45	\$43,207	3%	\$83,483	5.8%
ART Establishments (260 Establishments)	\$2.1	\$768	0.04%	\$768	0.04%
ob/gyn and small physician based practices	\$0.692	\$768	0.11	\$768	0.11
Semen Banks (19 Establishments)	\$2.4	\$768	0.03%	\$768	0.03%

The agency is uncertain about the accuracy of these estimates, however, because of the lack of revenue data for individual establishments. Because of the importance of this information in accurately assessing the impact on small entities, the agency requested detailed industry comment on individual firm revenues, the percentage of establishments that qualify as small entities, the percentage of ~~and extent to which~~ those establishments that comply with current industry

quality standards, and the extent of their compliance, and the specific areas where industry anticipates substantial differences between current manufacturing practices and the quality assurance elements specified under the CGTP final rule. For those areas of identified difference, the agency further requested estimates of the resources and costs required for establishment compliance. This analysis has incorporated information received during the comment period to the extent possible. Please see our responses to comments 172 through 197 at section III.F. of this document for details.

Although the CGTP final rule will impose some costs on small entities involved in the manufacture of HCT/Ps, the agency believes that this approach represents an effective means of protecting patient safety and public health. The less burdensome alternatives to the CGTP final rule involve fewer requirements for small entities (the vast majority of entities in this industry), but fail to provide fundamental assurances of product quality and safety. Reliance on industry professional organization voluntary standards or published FDA guidance for good tissue practice, rather than establishing a regulatory requirement, would not ensure uniform or consistent compliance and would preclude the agency's ability to effectively monitor HCT/Ps to ensure public health and safety. Given that each trade organization varies in their standards or guidelines,

regulatory requirements for good tissue practice would help to ensure consistency among manufacturers and across the various sectors of the HCT/P industry. Further, the adverse reaction reporting requirements of the CGTP final rule will provide valuable information that will allow the agency to identify and respond to emerging public health and safety risks associated with HCT/Ps. FDA finds that the CGTP final rule will enhance both public health and public confidence in the safety and quality of the nation's supply of HCT/Ps, while imposing only a minimum burden on the affected entities.

Another alternative would involve waiving some of the requirements for small establishments. However, as noted previously, nearly all establishments in this industry are small. Moreover, this alternative would increase HCT/P safety risks if small establishments that currently follow voluntary industry standards for good tissue practice choose to discontinue this practice due to an FDA-granted waiver. Furthermore, documentation and record retention provisions ensure that HCT/Ps can be tracked to their source in the event of infection or other adverse reactions that result from donor tissue characteristics.

In summary, the agency believes that abridged requirements for CGTP, based on voluntary standards or facility size criteria, would provide inadequate protection against the risk

of communicable disease transmission. Most notably, the current absence of regulation allows some establishments handling human tissues to ignore the standards established by industry professional associations and followed by a majority of entities in all sectors of the HCT/P industry.

FDA has made a number of revisions to this final rule, many in response to public comments on the proposed CGTP rule, that are expected to reduce the overall compliance burden on affected entities.

Provisions under § 1271.160(c) have been revised to require audits periodically rather than annually as stipulated under the CGTP proposed rule. However, the cost estimates presented in this analysis of economic impacts retain the assumption that audits will impose an annual burden so as to generate conservative estimates of overall compliance costs. The provisions proposed under § 1271.160(f), requiring complete validation of custom computer software used for making HCT/P-related decisions or determinations, have been changed to a requirement for validation or verification as appropriate. Verification is a less burdensome alternative that would apply to software not relied upon for making donor eligibility or HCT/P suitability decisions or determinations (e.g., inventory).

The proposed requirement under § 1271.180 for an annual review of all procedures has been removed, as has the

requirement for prior authorization of any deviation from an established procedure. Provisions proposed under § 1271.220(b) (process controls) requiring procedures for the use and removal of processing material have been deleted in response to comments. Proposed provisions under § 1271.230(e) requiring validation of all process changes and process deviations now require validation only of process changes. Requirements proposed under § 1271.265(e) for HCT/P packaging validation now allow for packaging validation or verification (a less burdensome alternative) as appropriate.

Provisions proposed under § 1271.290(d) and (e) requiring establishments to ensure each HCT/P is tracked from donor to recipient and from recipient to donor, now only require that establishments have a method of tracking in place. This will reduce the burden on affected entities because they no longer bear the responsibility of ensuring tracking with respect to their consignees. The proposed requirement for the reporting of all HCT/P deviations under § 1271.350(b) now only applies to distributed HCT/Ps and not to those still in inventory. Finally, language has been added to § 1271.420(b) to allow transportation to the consignee under quarantine of HCT/Ps offered for import to facilitate more rapid release of imported tissue products.

As part of the development process for this final rule, FDA conducted an extensive outreach program in an effort to inform affected small entities and to request input regarding the potential economic impact. Representatives from CBER have given presentations on good tissue practice related issues at the annual conferences of many of the professional associations representing affected entities including ASRM, AATB, EBAA, and others. The agency has also engaged in outreach activities directed toward interested consumer groups such as RESOLVE and the American Infertility Association. At their request, FDA also held individual meetings with ASRM, EBAA, and AATB to discuss specific concerns regarding the impact of the CGTP rule. Some of these presentation materials and meeting minutes are available on the CBER Web page at <http://www.fda.gov/cber/tissue/min.htm>. Additional materials associated with the CGTP rule are available online at <http://www.fda.gov/cber/tissue/docs.htm>. Finally, in the proposed rule, FDA requested industry comment regarding the many assumptions upon which this analysis of economic impacts was based. In particular, we requested detailed industry comment regarding our estimates of: The number and type of entities affected, the extent of CGTP, compliance rates for firms in various sectors of the HCT/P industry, and the level of compliance costs. To the extent possible, we have incorporated

these comments and our responses into the preamble and analysis of economic impacts of this final rule.

The specific requirements for good tissue practice, the required recordkeeping, and the required types of professional skills are described in the economic analysis provided previously. This analysis includes an accounting of all major cost factors, with the exception of the reduced potential liability currently encountered by those marginal tissue establishments that fail to provide the level of protection from infectious disease that is considered a standard of good practice in other sectors of the tissue-based product industry. The relevant Federal rules that are related to this final rule are discussed in section II of this document. This economic analysis provides a summary of the private industry standards that overlap this final Federal standard, but as discussed, there is no current regulation of tissue that will duplicate this final rule. Consequently, FDA finds that this final rule will enhance both public health and public confidence in the safety and utility of HCT/Ps, while imposing only a minimum burden on the affected industry sectors.

VI. Environmental Impact

The agency has determined under 21 CFR 25.30(h) and (j) that this action is of a type that is categorically excluded from the preparation of an environmental assessment because these

actions, as a class, will not result in the production or distribution of any substance and therefore will not result in the production of any substance into the environment.

VII. Federalism Assessment

Executive Order 13132, dated August 4, 1999, establishes the procedure that Federal agencies must follow when formulating and implementing policies that have federalism implications. The Executive order described nine fundamental federalism principles, stressing the importance and sovereignty of State and local governments, and the contributions of individual states and communities to the development of enlightened public policy. Principles of federalism are inherent in the very structure of the Constitution and formalized in and protected by the tenth amendment. Regulations have federalism implications whenever they have a substantial direct effect on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Whenever a regulation has this result, the agency must prepare a federalism assessment.

The Executive order directs Federal agencies to:

- Encourage States to develop their own policies to achieve program objectives and to work with appropriate officials in other States;
- Where possible, defer to the States to establish standards;

- In determining whether to establish uniform national standards, consult with appropriate State and local officials as to the need for national standards and any alternatives that would limit the scope of national standards or otherwise preserve State prerogatives and authority; and

- Where national standards are required by Federal statutes, consult with appropriate State and local officials in developing those standards.

In the proposed rule (66 FR 1508 at 1551), we made the statement that we had analyzed the proposed rule in accordance with the principles set forth in Executive Order 13132, and that the proposed rule may raise federalism implications because it could preempt States' laws regarding donated human cells and tissues. We then invited comments from elected State and local government officials on:

- The need for the proposed CGTP to prevent communicable disease transmission through HCT/Ps;
- Alternatives that would limit the scope of such national requirements or otherwise preserve State prerogatives and authority;
- The proposed CGTP provisions; and
- Any other issues raised by the proposed rule that could affect State laws and authorities.

We received no comments from State officials on federalism issues.

This final rule represents the exercise of a core Federal function: "prevent[ing] the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession" (section 361(a) of the PHS Act; 42 U.S.C. 264). To prevent the transmission of communicable disease in the United States, including the interstate transmission of disease, uniform national standards for HCT/Ps are necessary. No State official commented otherwise. For these reasons, this rule is consistent with the federalism principles expressed in Executive Order 13132.

However, we received two comments requesting that we clearly state that this rulemaking's provisions preempt state tissue regulations.

We decline to make this statement. Section 361 was recently amended to provide,

Nothing in this section or section 363 [42 U.S.C. 266], or the regulations promulgated under such sections, may be construed as superseding any provision under State law (including regulations and including provisions established by political

subdivisions of States), except to the extent that such a provision conflicts with an exercise of Federal authority under this section or section 363.

(section 361(e); 42 U.S.C. 264(e)).

Accordingly, consistent with this provision, establishments must comply with applicable State law and regulations, unless the State provisions conflict with this exercise of Federal authority under section 361. In the event of such a conflict, these regulations would preempt the State provisions under ordinary principles of preemption. (Geier v. Honda, 529 U.S. 861 (2000).)

VIII. The Paperwork Reduction Act of 1995

This final rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501-3520). A description of these provisions is shown as follows with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing the instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

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

Description: Under the authority of section 361 of the PHS Act, FDA is requiring certain HCT/P establishments to follow CGTP, which includes information collection provisions such as the establishment and maintenance of SOPs, recordkeeping, reporting, and labeling of the HCT/Ps. The CGTP information collection provisions in this rulemaking provide: (1) Additional measures for preventing the introduction, transmission, or spread of communicable diseases; (2) step-by-step consistency in the manufacturing of the HCT/P; (3) necessary information to FDA for the purpose of protecting public health and safety; (4) accountability in the manufacturing of HCT/Ps; and (5) information facilitating the tracking of an HCT/P back to its original source or to a consignee.

Table 15 lists provisions that require reporting or disclosure of information to third parties, the Federal Government, or the public. Section 1271.155(a) permits the submission of a request for FDA approval of an exemption or an alternative from any requirement in subpart C or D of part 1271. Section 1271.290(c) requires the establishment to affix a distinct identification code to each HCT/P relating the HCT/P to the donor and all records pertaining to the HCT/P. Whenever an

establishment initially distributes an HCT/P to a consignee, § 1271.290(f) requires the establishment to inform the consignee, in writing, of the product tracking requirements and the methods the establishment uses to fulfill the requirements. Non-reproductive HCT/P establishments described in § 1271.10 are required under § 1271.350(a)(1) and (b)(1) to report to FDA adverse reactions (defined in § 1271.3(y)) and HCT/P deviations (defined in § 1271.3(dd)). Section 1271.370(b) and (c) requires establishments to include specific information either on the HCT/P label or in the package insert.

Table 16 lists recordkeeping provisions under this final rule. Nonreproductive HCT/P establishments are required to prepare and maintain written SOPs to meet the core CGTP requirements for all steps performed in the manufacturing of HCT/Ps. As calculated in table 16 of this document, the preparation of the SOPs would result in a one-time impact on establishments and, once composed and/or reviewed for compliance, SOPs would only be updated as necessary.

The requirement for reporting, SOPs, and recordkeeping in proposed §§ 1271.160(d)(3), 1271.160(f), 1271.170(d), 1271.195(a), 1271.210(a) and (b), 1271.220(b), 1271.225(b), 1271.230(b) and (d), 1271.270(c), 1271.290(f), and 1271.350(c) are not included in the final rule.

The SOP provisions under part 1271 include: (1) § 1271.160(b)(2) (receiving, investigation, evaluating, and documenting information relating to core CGTP requirements received from other sources and for sharing information with consignees and other establishments); (2) § 1271.180(a) (to meet core CGTP requirements for all steps performed in the manufacture of HCT/Ps); (3) § 1271.190(d)(1) (facility cleaning and sanitization); (4) § 1271.200(b) (cleaning, sanitizing, and maintenance of equipment); (5) § 1271.200(c) (calibration of equipment); (6) § 1271.230(a) (verification or validation of changes to a process); (7) § 1271.250(a) (controls for labeling HCT/Ps); (8) § 1271.265(e) (receipt, pre-distribution shipment, availability for distribution, and packaging and shipping of HCT/Ps); (9) § 1271.265(f) (suitable for return to inventory); (10) § 1271.270(b) (records management system); (11) § 1271.290(b)(1) (system of HCT/P tracking); and, (12) § 1271.320(a) (review, evaluation, and documentation of all complaints).

Part 1271 requires the following additional recordkeeping provisions listed under Table 16. Section 1271.155(f) requires an establishment operating under the terms of an exemption or alternative to maintain documentation of the terms and date of FDA approval. Section 1271.160(b)(3) requires documentation of corrective actions taken as a result of an audit of the quality

program. Section 1271.160(b)(6) requires documentation of HCT/P deviations. Section 1271.160(d) requires documentation of computer validation or verification activities and results when computers are used to comply with the core CGTP requirements for its intended use. Section 1271.190(d)(2) requires documentation of all significant facility cleaning and sanitation. Section 1271.195(d) requires documentation of environmental control and monitoring activities. Section 1271.200(e) requires documentation of all equipment maintenance, cleaning, sanitizing, calibration, and other activities. Section 1271.210(d) requires documentation of the receipt, verification, and use of each supply or reagent. Section 1271.230(a) requires documentation of validation activities when the results of a process cannot be fully verified by subsequent inspection and tests. Section 1271.230(c) requires documentation of the review and evaluation of a process and revalidation of the process, if necessary, when any changes to a validated process occur. Sections 1271.260(d) and (e) require documentation of the storage temperature of HCT/Ps and any corrective action taken when acceptable storage conditions are not met. Section 1271.265(c)(1) requires documentation that all release criteria are met before distribution of an HCT/P. Section 1271.265(c)(3) requires documentation of any departure from a procedure at the time of occurrence. Section 1271.265(e) requires documentation

of the receipt, pre-distribution shipment, distribution, and packaging and shipping of HCT/Ps. Section 1271.270(a) requires documentation of each step in manufacturing required in subparts C and D.

Section 1271.270(e) requires documentation of the name and address, and a list of responsibilities of any establishment that performs a manufacturing step for you. Sections 1271.290(d) and (e) require documentation of the disposition of each non-reproductive HCT/P as part of its tracking method. Section 1271.320(b) requires an establishment to maintain a record of each complaint that it receives, including a review and evaluation.

Section 1271.270(d) requires the retention of all records for a period of 10 years after their creation. Records pertaining to a particular nonreproductive HCT/P are required to be retained at least 10 years after the date of administration. If the date of administration is not known, then records are required to be retained at least 10 years after the date of the HCT/P's distribution, disposition, or expiration, whichever is latest. This retention time is necessary because certain nonreproductive HCT/Ps have long storage periods. In addition, advances in medical technology have created opportunities for diagnosis and therapy for up to 10 years after recipient

exposure to an HCT/P from a donor later determined to be at risk for communicable disease agents or diseases.

Description of Respondents: For-profit and not-for-profit institutions.

As required by section 3506(c)(2)(B) of the PRA, we provided an opportunity for public comment on the information collection requirements of the proposed rule (66 FR 1508 at 1548). ~~Under the PRA, OMB filed a comment stating that "FDA shall review any comments related to the information collection requirements in the proposed GTP rule and shall address these comments in the preamble of the final rule."~~ No comments on the information collection burden estimate were submitted to the docket. However, we respond to comments on the utility of the information collection in section III. of this document, e.g., response to comment 68 addresses the utility and burden of retaining facility cleaning and sanitation records for 10 years.

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

TABLE 15.--ESTIMATED ANNUAL REPORTING BURDEN¹

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
1271.155(a)	1,302	1	1,302	3	3,906
1271.290(c)	93	52.2	4,855	0.08	388
1271.290(f)	227	1	227	1	227
1271.350(a)(1)	792	6	4,752	1	4,752
1271.350(b)(1)	792	2	1,584	1	1,584
1271.370(b) and (c)	93	52.2	4,855	0.25	1,214
Total					12,071

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

TABLE 16.--ESTIMATED ANNUAL RECORDKEEPING BURDEN¹

21 CFR Section	No. Of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Record	Total Hours
One-time Burden (Creation of SOPs)	93	12	1,116	16	17,856
	134	3	402	16	6,432
One-time Burden (Review of existing SOPs for compliance)	699	12	8,388	8	67,104
	134	9	1,206	8	9,648
SOP Maintenance (See previous list of 12 SOPs)	792	12	9,504	2	19,008
1271.155(f)	792	1	792	0.25	198
1271.160(b)(3)	93	12	1,116	1	1,116
1271.160(b)(6)	227	12	2,724	1	2,724
1271.160(d)	227	12	2,724	1	2,724
1271.190(d)(2)	93	12	1,116	1	1,116
1271.195(d)	227	12	2,724	1	2,724
1271.200(e)	93	12	1,116	1	1,116
1271.210(d)	93	12	1,116	1	1,116
1271.230(a)	227	12	2,724	1	2,724
1271.230(c)	360	1	360	1	360
1271.260(d)	227	12	2,724	0.25	681
1271.260(e)	93	365	33,945	0.08	2,716
1271.265(c)(1)	227	1,079.8	245,105	0.08	19,608
1271.265(c)(3)	592	1	592	1	592
1271.265(e)	93	1,622.6	150,905	0.08	12,072
1271.270(a)	227	1,079.8	245,105	0.25	61,276
1271.270(e)	227	2	454	0.5	227
1271.290(d) and (e)	93	1,622.6	150,905	0.25	37,726
1271.320(b)	93	5	465	1	465
Total					271,329

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

Under this final rule, 12 SOPs are required as previously described. FDA is assuming that approximately 93 nonreproductive HCT/P establishments would create all 12 SOPs, and 134 nonreproductive HCT/P establishments would create 3 SOPs, for a total of 1,518 records; and we estimate that it

would take 16 hours per new SOP for a total of 24,288 hours as a one-time burden. We estimate that up to 12 SOPs would already exist for each nonreproductive HCT/P establishment as a result of complying with current applicable regulations or following industry organizational standards. We estimate that approximately 699 nonreproductive HCT/P establishments would review all 12 SOPs, and 134 nonreproductive HCT/P establishments would revise 9 SOPs. Each review would take approximately 8 hours per SOP for a total one-time burden of 76,752 hours.

Once the SOPs are created, annual SOP maintenance of existing SOPs is estimated to involve 2 hours annually per SOP. An additional hour for clerical time is added to the 1 hour per SOP stated in the proposed rule. Annual total hours for maintaining the SOPs is estimated at 19,008 hours.

In some cases, the estimated burden may appear to be lower or higher than the burden experienced by individual establishments. The estimated burden in these charts is an estimated average burden, taking into account the range of impact each regulation may have. In estimating the burden, FDA compared the regulations with the current voluntary standards of a number of industry organizations, such as, AATB, EBAA, AABB, FACT, NMDP, and CAP. In those cases where a voluntary industry standard appears to be equivalent to a regulation, FDA has assumed that any reporting or recordkeeping burden is a

customary and usual business practice of establishments who are members of those organizations and no additional burden is calculated here. In some cases establishments affected by this rule may already be required to comply with regulations for manufacturers of human drugs or biological products, e.g., 21 CFR parts 210, 211, 312, 314, 600, and 606. FDA attributes the decrease in total burden hours in the final rule (283,400 hours) from the total burden hours in the proposed rule (621,573 hours) to:

- Not including certain proposed information collection burden in the final rule;
- Not applying the information collection burden to reproductive HCT/P establishments; and
- Industry strengthening their current standards.

FDA has estimated the reporting (table 15 of this document) and recordkeeping (table 16 of this document) burdens based upon our institutional experience with comparable recordkeeping and reporting provisions applicable to the human drug and biological product industries, recent information from trade organizations related to the manufacturing of non-reproductive HCT/Ps utilizing cells and tissues, and data provided by the Eastern Research Group (ERG), a consulting firm hired by FDA to prepare an economic analysis of the potential economic impact on semen banks and ART facilities.

We have estimated that there are approximately 792 nonreproductive HCT/P manufacturers (approximately 166 conventional tissue establishments, 134 eye tissue establishments, 425 peripheral and cord blood stem/progenitor cells, and 67 manufacturers of licensed biological products or devices). For the number of respondents for requesting a variance under § 1271.155(a) in table 15 of this document, we added 510 reproductive HCT/P establishments. FDA obtained these estimates of manufacturers (including percentage of members and nonmembers) from the various trade organizations and our registration systems for HCT/P, biological product, and device manufacturers. The total number of respondents and recordkeepers, 1,302, in the tables is decreased for each provision by the estimated number of establishments that follow, as usual and customary practice, the applicable established trade organizational standards comparable to the GTP requirements, i.e., AATB, EBAA, FACT, AABB, NMDP, or CAP. FDA based the estimated numbers for "Number of Respondents" and "Number of Recordkeepers" on information provided by the trade organizations and FDA registration databases.

FDA based the estimated numbers for "Annual Frequency per Response," "Total Annual Responses", Annual Frequency per Recordkeeping", and "Total Annual Records" on information received from the trade organizations, institutional experience

with similar requirements (Good Manufacturing Practice), general information provided to FDA during inspections of manufacturers of human tissue intended for transplantation, and information gathered by ERG.

The estimates for "Hours per Response" or "Hours per Record" were calculated using comparable burdens under drug GMP regulations (21 CFR part 211) and GMP for blood and blood components (21 Part 606) or by using the information provided by ERG, e.g., time spent on §§ 1271.190(c)(4) (documentation of cleaning and sanitation) and 1271.195(c) (documentation of environmental control and monitoring activities) was an estimate provided by ERG.

The information collection requirements of this final rule have been submitted to OMB for review. Before the effective date of this final rule, we will publish a notice in the FEDERAL REGISTER announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

IX. References

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

Friday. (FDA has verified the Web site addresses, but we are not responsible for subsequent changes to the Web site after this document publishes in the FEDERAL REGISTER.)

1. U.S. Department of Health and Human Services, Center for Disease Control and Prevention, "Update: Allograft-Associated Bacterial Infections--United States," Morbidity and Mortality Weekly Report, vol. 51, no. 10, pp. 207-210, March 15, 2002.

2. Diringer, H. and H.R. Braig, "Infectivity of Unconventional Viruses in Dura Mater," Lancet, pp. 439-440, 1989.

3. U.S. Department of Health and Human Services, Food and Drug Administration, Center for Devices and Radiological Health, "Class II Special Controls Guidance Document: Human Dura Mater; Draft Guidance for Industry and FDA," October 2002.

4. U.S. Department of Health and Human Services, Food and Drug Administration, Transmissible Spongiform Encephalopathies Advisory Committee Meeting Transcript, pp. 1-100, June 26, 2002.

5. Wilhelmus, K. R., R. D. Stulting, J. Sugar, and M. M. Khan, "Primary Corneal Graft Failure," Archives of Ophthalmology, vol. 113, pp. 1497-1502, December 1995.

6. Remeijer, L., P. Doornenbal, A. J. M. Geerards, W. A. Rijneveld, and W. H. Beekhuis, "Newly Acquired Herpes Simplex Virus Keratitis After Penetrating Keratoplasty," Ophthalmology, vol. 104, No. 4, pp. 648-652, April 1997.

7. Health Care Utilization Project (HCUP), Nationwide Inpatient Sample (NIS) for 2000, Outcomes for Principle Procedure 13, Corneal transplant, Available online at <http://ahrq.gov/data/hcup/hcupnis.htm>~~http://www.hcup-us.ahrq.gov/nisoverview.jsp~~.

8. Health Care Financing Review, 2000 Statistical Supplement, Submitted Charges per Person Served, Calendar Year 1998, U.S. Department of Health and Human Services, Center for Medicare and Medicaid Services, Table 59, pp. 226-227.

9. Lord, C. F., M. C. Gebhardt, W. W. Tomford, and H. J. Mankin, "Infection in Bone Allograft: Incidence, Nature and Treatment," The Journal of Bone and Joint Surgery, vol. 70-A, No. 3, pp. 369-376, March 1988.

10. Hardin, C. K., "Banked Bone," Otolaryngologic Clinics of North America, vol. 27, No. 5, pp. 911-925, October 1994.

11. Detailed Diagnoses and Procedures Data, National Hospital Discharge Survey 2000, Series 13, No. 153, Table 46, p. 153, November 2002.

12. Abecassis, M. M., "Transmission of Cytomegalovirus by Skin Allograft," Tissue and Cell Report, vol. 2, No. 1, pp. 14-17, 1995.

13. Gala, J., A. Vandenbroucke, B. Vandercam, J. Pirnay, N. Delferriere, and G. Burronboy, "Human Immunodeficiency Virus in Fresh or Cryopreserved Postmortem Skin: Potential Implications

for Skin Handling and Allografting," Journal of Clinical Pathology, vol. 50, pp. 481-484, 1997.

14. Kuehnert, M. J., E. Clark, S. R. Lockhart, D. R. Soll, J. Chia, and W. R. Jarvis, "Candida Albicans Endocarditis Associated with a Contaminated Aortic Valve Allograft: Implications for Regulation of Allograft Processing," Clinical Infectious Diseases, vol. 27, pp. 688-91, October 1998.

15. Webb, I. J., F. S. Coral, J. W. Andersen, A. D. Elias, R. W. Finberg, L. M. Nadler, J. Ritz, and K. C. Anderson, "Sources and Sequelae of Bacterial Contamination of Hematopoietic Stem Cell Components: Implications for the Safety of Hematotherapy and Graft Engineering," Transfusion, vol. 36, pp. 782-788, 1996.

16. Price, K. J., P. F. Thall, S. K. Kish, V. R. Shannon, and B. S. Andersson, "Prognostic Indicators for Blood and Marrow Transplant Patients Admitted to an Intensive Care Unit," American Journal of Respiratory Critical Care Medicine, vol. 158, pp. 876-884, 1998.

17. Espinosa, M. T. F., R. Fox, R. J. Creger, and H. M. Lazarus, "Microbiologic Contamination of Peripheral Blood Progenitor Cells Collected for Hematopoietic Cell Transplantation," Transfusion, vol. 36, pp. 789-793, 1996.

18. Kogler, G., J. Callejas, P. Hakenberg, J. Enczmann, O. Adams, W. Daubener, C. Krempe, U. Gobel, T. Somville, and P.

Wernet, "Hematopoietic Transplant Potential of Unrelated Cord Blood: Critical Issues," Journal of Hematotherapy, vol. 5, pp. 105-116, 1996.

19. Prottas, Jeffrey, "A Study of the Tissue Procurement and Distribution System of the United States," Brandeis University, FDA/HRSA Contract No. 240-090-0048, October 1995.

20. American Medical Association, Center for Health Policy Research, Physician Socioeconomic Statistics, 2002 Edition, Table 41, p. 83, 2002.

21. North American Industry Classification System (NAICS), available online at <http://www.naics.com>.

22. U.S. Small Business Administration, Office of Size Standards, Table of Size Standards, Sector 62, Health Care and Social Assistance, 2002.

23. HCUP, NIS for 2000, Outcomes for Principle Procedure 157, Amputation of Lower Extremity, available online at <http://ahrq.gov/data/hcup/hcupnis.htm><http://www.hcup-us.ahrq.gov/nisoverview.jsp>.

24. AHRQ, HCUP, NIS for 2000, Outcomes for Principle Procedure 43, Heart Valve Procedures, available online at <http://ahrq.gov/hcup/hcupnis.htm> <http://www.hcup-us.ahrq.gov/nisoverview.jsp>.

25. "Blood Collection and Transfusion in the United States in 1997," Transfusion, vol. 42, pp. 1253-1300, 2002.

26. AHRQ, HCUP, NIS for 2000, Outcomes for Principle Procedure 3, Bacterial Infection, Unspecified Site, available online at ~~<http://ahrq.gov/hcup/hcupnis.htm>~~ <http://www.hcup-us.ahrq.gov/nisoverview.jsp>.

27. U.S. Department of Labor, Bureau of Labor Statistics, Available online at <http://www.bls.gov/cpi>.

28. AHRQ, HCUP, NIS for 2001, Outcomes for Principle Procedure 142, Partial Excision of Bone, available online at ~~<http://ahrq.gov/hcup/hcupnis.htm>~~ <http://www.hcup-us.ahrq.gov/nisoverview.jsp>.

29. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, American Society for Reproductive Medicine and RESOLVE, 1999 Assisted Reproductive Technology Success Rates: National Summary and Fertility Clinic Reports, 2000.

30. Fee Schedule 1/98, Donor Semen 0.5cc and Donor Semen 0.8cc-1.0cc, The Sperm Bank of California, at <http://www.thespermbankofca.org/fees.html>
~~<http://frwebgate.access.gpo.gov/cgi-bin/leaving.cgi?from=leavingFR.html&log=linklog&to=http://www.thespermbankofca.org/fees96.htm>~~

31. Hogan, R. N., P. Brown, and E. Heck, "Risk of Prion Disease Transmission From Ocular Donor Tissue Transplantation," Cornea, vol. 18, No. 1, 1999, pp. 2-11.

32. U.S. Department of Labor, Bureau of Labor Statistics,
"Employer Costs for Employee Compensation per hour worked for
Civilian Workers in Private Industry and State and local
Governments, March 2003, available online at <http://www.bls.gov>.

List of Subjects

21 CFR part 16

Administrative practice and procedure.

21 CFR part 1270

Communicable diseases, HIV/AIDS, Reporting and recordkeeping requirements.

21 CFR part 1271

Communicable diseases, HIV/AIDS, Human cells, tissues, and cellular and tissue-based products, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, Chapter I of title 21 of the Code of Federal Regulations is amended as follows:

1. The authority citation for 21 CFR part 16 continues to read as follows:

AUTHORITY: 15 U.S.C. 1451-1461; 21 U.S.C. 141-149, 321-394, 467f, 679, 821, 1034; 28 U.S.C. 2112; 42 U.S.C. 201-262, 263b, 364.

2. Section 16.1 is amended in paragraph (b)(2) by numerically adding an entry for § 1271.440(e) to read as follows:

§ 16.1 Scope.

* * * * *

(b) * * *

(2) * * *

§ 1271.440(e) relating to the retention, recall, and destruction of human cells, tissues, and cellular and tissue-based products (HCT/Ps), and/or the cessation of manufacturing HCT/Ps.

PART 1270--HUMAN TISSUE INTENDED FOR TRANSPLANTATION

3. The authority citation for 21 CFR part 1270 continues to read as follows:

AUTHORITY: 42 U.S.C. 216, 243, 264, 271.

4. Section 1270.3 is amended by revising paragraph (j) introductory text to read as follows:

§ 1270.3 Definitions

* * * * *

(j) Human tissue, for the purpose of this part means any tissue derived from a human body and recovered before ~~insert~~ ~~date 180 days after date of publication in the FEDERAL REGISTER~~ May 25, 2005, which:

* * * * *

PART 1271--HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS

5. The authority citation for 21 CFR part 1271 continues to read as follows:

AUTHORITY: 42 U.S.C. 216, 243, 263a, 264, 271.

6. Section 1271.3 is amended by revising paragraphs (c) and (d) and by adding paragraphs (y) through (ll) to read as follows:

§ 1271.3 How does FDA define important terms in this part?

* * * * *

(c) Homologous use means the repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function or functions in the recipient as in the donor.

(d) Human cells, tissues, or cellular or tissue-based products (HCT/Ps) means articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient. Examples of HCT/Ps include, but are not limited to, bone, ligament, skin, dura mater, heart valve, cornea, hematopoietic stem/progenitor cells derived from peripheral and cord blood, manipulated autologous chondrocytes, epithelial cells on a synthetic matrix, and semen or other reproductive tissue. The following articles are not considered HCT/Ps:

- (1) Vascularized human organs for transplantation;
- (2) Whole blood or blood components or blood derivative products subject to listing under parts 607 and 207 of this chapter, respectively;

(3) Secreted or extracted human products, such as milk, collagen, and cell factors; except that semen is considered an HCT/P;

(4) Minimally manipulated bone marrow for homologous use and not combined with a drug or a device (except for a sterilizing, preserving, or storage agent, if the addition of the agent does not raise new clinical safety concerns with respect to the bone marrow);

(5) Ancillary products used in the manufacture of HCT/P;

(6) Cells, tissues, and organs derived from animals other than humans; and

(7) In vitro diagnostic products as defined in § 809.3(a) of this chapter.

* * * * *

(y) Adverse reaction means a noxious and unintended response to any HCT/P for which there is a reasonable possibility that the HCT/P caused the response.

(z) Available for distribution means that the HCT/P has been determined to meet all release criteria.

(aa) Complaint means any written, oral, or electronic communication about a distributed HCT/P that alleges:

(1) That an HCT/P has transmitted or may have transmitted a communicable disease to the recipient of the HCT/P; or

(2) Any other problem with an HCT/P relating to the potential for transmission of communicable disease, such as the failure to comply with current good tissue practice.

(bb) Distribution means any conveyance or shipment (including importation and exportation) of an HCT/P that has been determined to meet all release criteria, whether or not such conveyance or shipment is entirely intrastate. If an entity does not take physical possession of an HCT/P, the entity is not considered a distributor.

(cc) Establish and maintain means define, document (in writing or electronically), and implement; then follow, review, and, as needed, revise on an ongoing basis.

(dd) HCT/P deviation means an event:

(1) That represents a deviation from applicable regulations in this part or from applicable standards or established specifications that relate to the prevention of communicable disease transmission or HCT/P contamination; or

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

(ee) Importer of record means the person, establishment, or its representative responsible for making entry of imported goods in accordance with all laws affecting such importation.

(ff) Processing means any activity performed on an HCT/P, other than recovery, donor screening, donor testing, storage, labeling, packaging, or distribution, such as testing for microorganisms, preparation, sterilization, steps to inactivate or remove adventitious agents, preservation for storage, and removal from storage.

(gg) Quality audit means a documented, independent inspection and review of an establishment's activities related to core CGTP requirements. The purpose of a quality audit is to verify, by examination and evaluation of objective evidence, the degree of compliance with those aspects of the quality program under review.

(hh) Quality program means an organization's comprehensive system for manufacturing and tracking HCT/Ps in accordance with this part. A quality program is designed to prevent, detect, and correct deficiencies that may lead to circumstances that increase the risk of introduction, transmission, or spread of communicable diseases.

(ii) Recovery means obtaining from a human donor cells or tissues that are intended for use in human implantation, transplantation, infusion, or transfer.

(jj) Storage means holding HCT/Ps for future processing and/or distribution.

(kk) Validation means confirmation by examination and provision of objective evidence that particular requirements can consistently be fulfilled. Validation of a process, or process validation, means establishing by objective evidence that a process consistently produces a result or HCT/P meeting its predetermined specifications.

(ll) Verification means confirmation by examination and provision of objective evidence that specified requirements have been fulfilled.

7. Section 1271.10 is amended by revising paragraph (a)(3) to read as follows:

§ 1271.10 Are my HCT/Ps regulated solely under section 361 of the PHS Act and the regulations in this part, and if so what must I do?

(a) * * *

(3) The manufacture of the HCT/P does not involve the combination of the cells or tissues with another article, except for water, crystalloids, or a sterilizing, preserving, or storage agent, provided that the addition of water, crystalloids, or the sterilizing, preserving, or storage agent does not raise new clinical safety concerns with respect to the HCT/P; and

* * * * *

8. Section 1271.22 is revised to read as follows:

§ 1271.22 How and where do I register and submit an HCT/P list?

(a) You must use Form FDA 3356 for:

- (1) Establishment registration,
- (2) HCT/P listings, and
- (3) Updates of registration and HCT/P listing.

(b) You may obtain Form FDA 3356:

(1) By writing to the Center for Biologics Evaluation and Research (HFM-775), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, Attention: Tissue Establishment Registration Coordinator;

(2) By contacting any Food and Drug Administration district office;

(3) By calling the CBER Voice Information System at 1-800-835-4709 or 301-827-1800; or

(4) By connecting to

<http://forms.psc.gov/forms/FDA/fda.html>

<http://www.fda.gov/opacom/morechoices/fdaforms/cber.html> on the Internet.

(c) (1) You may submit Form FDA 3356 to the Center for Biologics Evaluation and Research (HFM-775), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, Attention: Tissue Establishment Registration Coordinator; or

(2) You may submit Form FDA 3356 electronically through a secure web server at <http://www.fda.gov/cber/tissue/tisreg.htm>.

9. Section 1271.45 is amended in paragraph (a), after the second sentence, by adding a sentence to read as follows:

§ 1271.45 What requirements does this subpart contain?

(a) * * * Other CGTP requirements are set out in subpart D of this part.

* * * * *

10. Part 1271 is amended by adding subpart D, consisting of §§ 1271.145 through 1271.320, to read as follows:

Subpart D--Current Good Tissue Practice
Sec.

1271.145 Prevention of the introduction, transmission, or spread of communicable diseases.

1271.150 Current good tissue practice requirements.

1271.155 Exemptions and alternatives.

1271.160 Establishment and maintenance of a quality program.

1271.170 Personnel.

1271.180 Procedures.

1271.190 Facilities.

1271.195 Environmental control and monitoring.

1271.200 Equipment.

1271.210 Supplies and reagents.

1271.215 Recovery.

1271.220 Processing and process controls.

1271.225 Process changes.

1271.230 Process validation.

1271.250 Labeling controls.

1271.260 Storage.

1271.265 Receipt, predistribution shipment, and distribution of
an HCT/P.

1271.270 Records.

1271.290 Tracking.

1271.320 Complaint file.

Subpart D--Current Good Tissue Practice

§ 1271.145 Prevention of the introduction, transmission, or
spread of communicable diseases.

You must recover, process, store, label, package, and
distribute HCT/Ps, and screen and test cell and tissue donors,
in a way that prevents the introduction, transmission, or spread
of communicable diseases.

§ 1271.150 Current good tissue practice requirements.

(a) General. This subpart D and subpart C of this part set
forth current good tissue practice (CGTP) requirements. You must
follow CGTP requirements to prevent the introduction,
transmission, or spread of communicable diseases by HCT/Ps
(e.g., by ensuring that the HCT/Ps do not contain communicable
disease agents, that they are not contaminated, and that they do
not become contaminated during manufacturing). Communicable
diseases include, but are not limited to, those transmitted by

viruses, bacteria, fungi, parasites, and transmissible spongiform encephalopathy agents. CGTP requirements govern the methods used in, and the facilities and controls used for, the manufacture of HCT/Ps, including but not limited to all steps in recovery, donor screening, donor testing, processing, storage, labeling, packaging, and distribution. The CGTP provisions specifically governing determinations of donor eligibility, including donor screening and testing, are set out separately in subpart C of this part.

(b) Core CGTP requirements. The following are core CGTP requirements:

(1) Requirements relating to facilities in § 1271.190(a) and (b);

(2) Requirements relating to environmental control in § 1271.195(a);

(3) Requirements relating to equipment in § 1271.200(a);

(4) Requirements relating to supplies and reagents in § 1271.210(a) and (b);

(5) Requirements relating to recovery in § 1271.215;

(6) Requirements relating to processing and process controls in § 1271.220;

(7) Requirements relating to labeling controls in § 1271.250(a) and (b);

(8) Requirements relating to storage in § 1271.260 (a) through (d);

(9) Requirements relating to receipt, predistribution shipment, and distribution of an HCT/P in § 1271.265(a) through (d); and

(10) Requirements relating to donor eligibility determinations, donor screening, and donor testing in §§ 1271.50, 1271.75, 1271.80, and 1271.85.

(c) Compliance with applicable requirements--(1)

Manufacturing arrangements (i) If you are an establishment that engages in only some operations subject to the regulations in this subpart and subpart C of this part, and not others, then you need only comply with those requirements applicable to the operations that you perform.

(ii) If you engage another establishment (e.g., a laboratory to perform communicable disease testing, or an irradiation facility to perform terminal sterilization), under a contract, agreement, or other arrangement, to perform any step in manufacture for you, that establishment is responsible for complying with requirements applicable to that manufacturing step.

(iii) Before entering into a contract, agreement, or other arrangement with another establishment to perform any step in manufacture for you, you must ensure that the establishment

complies with applicable CGTP requirements. If, during the course of this contract, agreement, or other arrangement, you become aware of information suggesting that the establishment may no longer be in compliance with such requirements, you must take reasonable steps to ensure the establishment complies with those requirements. If you determine that the establishment is not in compliance with those requirements, you must terminate your contract, agreement, or other arrangement with the establishment.

(2) If you are the establishment that determines that an HCT/P meets all release criteria and makes the HCT/P available for distribution, whether or not you are the actual distributor, you are responsible for reviewing manufacturing and tracking records to determine that the HCT/P has been manufactured and tracked in compliance with the requirements of this subpart and subpart C of this part and any other applicable requirements.

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

(d) Compliance with parts 210, 211, and 820 of this chapter. With respect to HCT/Ps that are drugs (subject to

review under an application submitted under section 505 of the Federal Food, Drug, and Cosmetic Act or under a biological product license application under section 351 of the Public Health Service Act) or that are devices (subject to premarket review or notification under the device provisions of the act or under a biological product license application under section 351 of the Public Health Service Act), the procedures contained in this subpart and in subpart C of this part and the current good manufacturing practice regulations in parts 210 and 211 of this chapter and the quality system regulations in part 820 of this chapter supplement, and do not supersede, each other unless the regulations explicitly provide otherwise. In the event that a regulation in part 1271 of this chapter is in conflict with a requirement in parts 210, 211, or 820 of this chapter, the regulations more specifically applicable to the product in question will supersede the more general.

(e) Where appropriate. When a requirement is qualified by "where appropriate," it is deemed to be "appropriate" unless you can document justification otherwise. A requirement is "appropriate" if nonimplementation of the requirement could reasonably be expected to result in the HCT/P not meeting its specified requirements related to prevention of introduction, transmission, or spread of communicable diseases, or in your inability to carry out any necessary corrective action.

§ 1271.155 Exemptions and alternatives.

(a) General. You may request an exemption from or alternative to any requirement in subpart C or D of this part.

(b) Request for exemption or alternative. Submit your request under this section to the Director of the appropriate Center (the Director), e.g., the Center for Biologics Evaluation and Research or the Center for Devices and Radiological Health. The request must be accompanied by supporting documentation, including all relevant valid scientific data, and must contain either:

(1) Information justifying the requested exemption from the requirement, or

(2) A description of a proposed alternative method of meeting the requirement.

(c) Criteria for granting an exemption or alternative. The Director may grant an exemption or alternative if he or she finds that such action is consistent with the goals of protecting the public health and/or preventing the introduction, transmission, or spread of communicable diseases and that:

(1) The information submitted justifies an exemption; or

(2) The proposed alternative satisfies the purpose of the requirement.

(d) Form of request. You must ordinarily make your request for an exemption or alternative in writing (hard copy or

electronically). However, if circumstances make it difficult (e.g., there is inadequate time) to submit your request in writing, you may make the request orally, and the Director may orally grant an exemption or alternative. You must follow your oral request with an immediate written request, to which the Director will respond in writing.

(e) Operation under exemption or alternative. You must not begin operating under the terms of a requested exemption or alternative until the exemption or alternative has been granted. You may apply for an extension of an exemption or alternative beyond its expiration date, if any.

(f) Documentation. If you operate under the terms of an exemption or alternative, you must maintain documentation of:

- (1) FDA's grant of the exemption or alternative, and
- (2) The date on which you began operating under the terms of the exemption or alternative.

(g) Issuance of an exemption or alternative by the Director. In a public health emergency, the Director may issue an exemption from, or alternative to, any requirement in part 1271. The Director may issue an exemption or alternative under this section if the exemption or alternative is necessary to assure that certain HCT/Ps will be available in a specified location to respond to an unanticipated immediate need for those HCT/Ps.

§ 1271.160 Establishment and maintenance of a quality program.

(a) General. If you are an establishment that performs any step in the manufacture of HCT/Ps, you must establish and maintain a quality program intended to prevent the introduction, transmission, or spread of communicable diseases through the manufacture and use of HCT/Ps. The quality program must be appropriate for the specific HCT/Ps manufactured and the manufacturing steps performed. The quality program must address all core CGTP requirements listed in § 1271.150(b).

(b) Functions. Functions of the quality program must include:

(1) Establishing and maintaining appropriate procedures relating to core CGTP requirements, and ensuring compliance with the requirements of § 1271.180 with respect to such procedures, including review, approval, and revision;

(2) Ensuring that procedures exist for receiving, investigating, evaluating, and documenting information relating to core CGTP requirements, including complaints, and for sharing any information pertaining to the possible contamination of the HCT/P or the potential for transmission of a communicable disease by the HCT/P with the following:

(i) Other establishments that are known to have recovered HCT/Ps from the same donor;

(iv) The date(s) of the corrective action.

(4) Ensuring the proper training and education of personnel involved in activities related to core CGTP requirements;

(5) Establishing and maintaining appropriate monitoring systems as necessary to comply with the requirements of this subpart (e.g., environmental monitoring);

(6) Investigating and documenting HCT/P deviations and trends of HCT/P deviations relating to core CGTP requirements and making reports if required under § 1271.350(b) or other applicable regulations. Each investigation must include a review and evaluation of the HCT/P deviation, the efforts made to determine the cause, and the implementation of corrective action(s) to address the HCT/P deviation and prevent recurrence.

(c) Audits. You must periodically perform for management review a quality audit, as defined in § 1271.3(gg), of activities related to core CGTP requirements.

(d) Computers. You must validate the performance of computer software for the intended use, and the performance of any changes to that software for the intended use, if you rely upon the software to comply with core CGTP requirements and if the software either is custom software or is commercially available software that has been customized or programmed (including software programmed to perform a user defined calculation or table) to perform a function related to core CGTP

requirements. You must verify the performance of all other software for the intended use if you rely upon it to comply with core CGTP requirements. You must approve and document these activities and results before implementation.

§ 1271.170 Personnel.

(a) General. You must have personnel sufficient to ensure compliance with the requirements of this part.

(b) Competent performance of functions. You must have personnel with the necessary education, experience, and training to ensure competent performance of their assigned functions. Personnel must perform only those activities for which they are qualified and authorized.

(c) Training. You must train all personnel, and retrain as necessary, to perform their assigned responsibilities adequately.

§ 1271.180 Procedures.

(a) General. You must establish and maintain procedures appropriate to meet core CGTP requirements for all steps that you perform in the manufacture of HCT/Ps. You must design these procedures to prevent circumstances that increase the risk of the introduction, transmission, or spread of communicable diseases through the use of HCT/Ps.

(b) Review and approval. Before implementation, a responsible person must review and approve these procedures.

(c) Availability. These procedures must be readily available to the personnel in the area where the operations to which they relate are performed, or in a nearby area if such availability is impractical.

(d) Standard procedures. If you adopt current standard procedures from another organization, you must verify that the procedures meet the requirements of this part and are appropriate for your operations.

§ 1271.190 Facilities.

(a) General. Any facility used in the manufacture of HCT/Ps must be of suitable size, construction, and location to prevent contamination of HCT/Ps with communicable disease agents and to ensure orderly handling of HCT/Ps without mix-ups. You must maintain the facility in a good state of repair. You must provide lighting, ventilation, plumbing, drainage, and access to sinks and toilets that are adequate to prevent the introduction, transmission, or spread of communicable disease.

(b) Facility cleaning and sanitation. (1) You must maintain any facility used in the manufacture of HCT/Ps in a clean, sanitary, and orderly manner, to prevent the introduction, transmission, or spread of communicable disease.

(2) You must dispose of sewage, trash, and other refuse in a timely, safe, and sanitary manner.

(c) Operations. You must divide a facility used in the manufacture of HCT/Ps into separate or defined areas of adequate size for each operation that takes place in the facility, or you must establish and maintain other control systems to prevent improper labeling, mix-ups, contamination, cross-contamination, and accidental exposure of HCT/Ps to communicable disease agents.

(d) Procedures and records. (1) You must establish and maintain procedures for facility cleaning and sanitation for the purpose of preventing the introduction, transmission, or spread of communicable disease. These procedures must assign responsibility for sanitation and must describe in sufficient detail the cleaning methods to be used and the schedule for cleaning the facility.

(2) You must document, and maintain records of, all cleaning and sanitation activities performed to prevent contamination of HCT/Ps. You must retain such records 3 years after their creation.

§ 1271.195 Environmental control and monitoring.

(a) Environmental control. Where environmental conditions could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment, or accidental exposure of HCT/Ps to communicable disease agents, you must adequately control environmental conditions and provide proper conditions

for operations. Where appropriate, you must provide for the following control activities or systems:

- (1) Temperature and humidity controls;
- (2) Ventilation and air filtration;
- (3) Cleaning and disinfecting of rooms and equipment to ensure aseptic processing operations; and
- (4) Maintenance of equipment used to control conditions necessary for aseptic processing operations.

(b) Inspections. You must inspect each environmental control system periodically to verify that the system, including necessary equipment, is adequate and functioning properly. You must take appropriate corrective action as necessary.

(c) Environmental monitoring. You must monitor environmental conditions where environmental conditions could reasonably be expected to cause contamination or cross-contamination of HCT/Ps or equipment, or accidental exposure of HCT/Ps to communicable disease agents. Where appropriate, you must provide environmental monitoring for microorganisms.

(d) Records. You must document, and maintain records of, environmental control and monitoring activities.

§ 1271.200 Equipment.

(a) General. To prevent the introduction, transmission, or spread of communicable diseases, equipment used in the manufacture of HCT/Ps must be of appropriate design for its use

and must be suitably located and installed to facilitate operations, including cleaning and maintenance. Any automated, mechanical, electronic, or other equipment used for inspection, measuring, or testing in accordance with this part must be capable of producing valid results. You must clean, sanitize, and maintain equipment according to established schedules.

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

(c) Calibration of equipment. Where appropriate, you must routinely calibrate according to established procedures and schedules all automated, mechanical, electronic, or other equipment used for inspection, measuring, and testing in accordance with this part.

(d) Inspections. You must routinely inspect equipment for cleanliness, sanitation, and calibration, and to ensure adherence to applicable equipment maintenance schedules.

(e) Records. You must document and maintain records of all equipment maintenance, cleaning, sanitizing, calibration, and other activities performed in accordance with this section. You

must display records of recent maintenance, cleaning, sanitizing, calibration, and other activities on or near each piece of equipment, or make the records readily available to the individuals responsible for performing these activities and to the personnel using the equipment. You must maintain records of the use of each piece of equipment, including the identification of each HCT/P manufactured with that equipment.

§ 1271.210 Supplies and reagents.

(a) Verification. You must not use supplies and reagents until they have been verified to meet specifications designed to prevent circumstances that increase the risk of the introduction, transmission, or spread of communicable diseases. Verification may be accomplished by the establishment that uses the supply or reagent, or by the vendor of the supply or reagent.

(b) Reagents. Reagents used in processing and preservation of HCT/Ps must be sterile, where appropriate.

(c) In-house reagents. You must validate and/or verify the processes used for production of in-house reagents.

(d) Records. You must maintain the following records pertaining to supplies and reagents:

(1) Records of the receipt of each supply or reagent, including the type, quantity, manufacturer, lot number, date of receipt, and expiration date;

(2) Records of the verification of each supply or reagent, including test results or, in the case of vendor verification, a certificate of analysis from the vendor; and

(3) Records of the lot of supply or reagent used in the manufacture of each HCT/P.

§ 1271.215 Recovery.

If you are an establishment that recovers HCT/Ps, you must recover each HCT/P in a way that does not cause contamination or cross-contamination during recovery, or otherwise increase the risk of the introduction, transmission, or spread of communicable disease through the use of the HCT/P.

§ 1271.220 Processing and Process controls.

(a) General. If you are an establishment that processes HCT/Ps, you must process each HCT/P in a way that does not cause contamination or cross-contamination during processing, and that prevents the introduction, transmission, or spread of communicable disease through the use of the HCT/P.

(b) Pooling. Human cells or tissue from two or more donors must not be pooled (placed in physical contact or mixed in a single receptacle) during manufacturing.

(c) In-process control and testing. You must ensure that specified requirements, consistent with paragraph (a) of this section, for in-process controls are met, and that each in-process HCT/P is controlled until the required inspection and

tests or other verification activities have been completed, or necessary approvals are received and documented. Sampling of in-process HCT/Ps must be representative of the material to be evaluated.

(d) Dura mater. (1) When there is a published validated process that reduces the risk of transmissible spongiform encephalopathy, you must use this process for dura mater (or an equivalent process that you have validated), unless following this process adversely affects the clinical utility of the dura mater.

(2) When you use a published validated process, you must verify such a process in your establishment.

§ 1271.225 Process changes.

Any change to a process must be verified or validated in accordance with § 1271.230, to ensure that the change does not create an adverse impact elsewhere in the operation, and must be approved before implementation by a responsible person with appropriate knowledge and background. You must communicate approved changes to the appropriate personnel in a timely manner.

§ 1271.230 Process validation.

(a) General. Where the results of processing described in § 1271.220 cannot be fully verified by subsequent inspection and tests, you must validate and approve the process according to

established procedures. The validation activities and results must be documented, including the date and signature of the individual(s) approving the validation.

(b) Written representation. Any written representation that your processing methods reduce the risk of transmission of communicable disease by an HCT/P, including but not limited to, a representation of sterility or pathogen inactivation of an HCT/P, must be based on a fully verified or validated process.

(c) Changes. When changes to a validated process subject to § 1271.230(a) occur, you must review and evaluate the process and perform revalidation where appropriate. You must document these activities.

§ 1271.250 Labeling controls.

(a) General. You must establish and maintain procedures to control the labeling of HCT/Ps. You must design these procedures to ensure proper HCT/P identification and to prevent mix-ups.

(b) Verification. Procedures must include verification of label accuracy, legibility, and integrity.

(c) Labeling requirements. Procedures must ensure that each HCT/P is labeled in accordance with all applicable labeling requirements, including those in §§ 1271.55, 1271.60, 1271.65, 1271.90, 1271.290, and 1271.370, and that each HCT/P made

available for distribution is accompanied by documentation of the donor eligibility determination as required under § 1271.55. § 1271.260 Storage.

(a) Control of storage areas. You must control your storage areas and stock rooms to prevent:

(1) Mix-ups, contamination, and cross-contamination of HCT/Ps, supplies, and reagents, and

(2) An HCT/P from being improperly made available for distribution.

(b) Temperature. You must store HCT/Ps at an appropriate temperature.

(c) Expiration date. Where appropriate, you must assign an expiration date to each HCT/P based on the following factors:

(1) HCT/P type;

(2) Processing, including the method of preservation;

(3) Storage conditions; and

(4) Packaging.

(d) Corrective action. You must take and document corrective action whenever proper storage conditions are not met.

(e) Acceptable temperature limits. You must establish acceptable temperature limits for storage of HCT/Ps at each step of the manufacturing process to inhibit the growth of infectious agents. You must maintain and record storage temperatures for

HCT/Ps. You must periodically review recorded temperatures to ensure that temperatures have been within acceptable limits.

§ 1271.265 Receipt, predistribution shipment, and distribution of an HCT/P.

(a) Receipt. You must evaluate each incoming HCT/P for the presence and significance of microorganisms and inspect for damage and contamination. You must determine whether to accept, reject, or place in quarantine each incoming HCT/P, based upon pre-established criteria designed to prevent communicable disease transmission.

(b) Predistribution shipment. If you ship an HCT/P within your establishment or between establishments (e.g., procurer to processor) and the HCT/P is not available for distribution as described in paragraph (c) of this section, you must first determine and document whether pre-established criteria designed to prevent communicable disease transmission have been met, and you must ship the HCT/P in quarantine.

(c) Availability for distribution. (1) Before making an HCT/P available for distribution, you must review manufacturing and tracking records pertaining to the HCT/P, and, on the basis of that record review, you must verify and document that the release criteria have been met. A responsible person must document and date the determination that an HCT/P is available for distribution.

(2) You must not make available for distribution an HCT/P that is in quarantine, is contaminated, is recovered from a donor who has been determined to be ineligible or for whom a donor-eligibility determination has not been completed (except as provided under §§ 1271.60, 1271.65, and 1271.90), or that otherwise does not meet release criteria designed to prevent communicable disease transmission.

(3) You must not make available for distribution any HCT/P manufactured under a departure from a procedure relevant to preventing risks of communicable disease transmission, unless a responsible person has determined that the departure does not increase the risk of communicable disease through the use of the HCT/P. You must record and justify any departure from a procedure at the time of its occurrence.

(d) Packaging and shipping. Packaging and shipping containers must be designed and constructed to protect the HCT/P from contamination. For each type of HCT/P, you must establish appropriate shipping conditions to be maintained during transit.

(e) Procedures. You must establish and maintain procedures, including release criteria, for the activities in paragraphs (a) through (d) of this section. You must document these activities. Documentation must include:

(1) Identification of the HCT/P and the establishment that supplied the HCT/P;

- (2) Activities performed and the results of each activity;
- (3) Date(s) of activity;
- (4) Quantity of HCT/P subject to the activity; and
- (5) Disposition of the HCT/P (e.g., identity of consignee).

(f) Return to inventory. You must establish and maintain procedures to determine if an HCT/P that is returned to your establishment is suitable to be returned to inventory.

§ 1271.270 Records.

(a) General. You must maintain records concurrently with the performance of each step required in this subpart and subpart C of this part. Any requirement in this part that an action be documented involves the creation of a record, which is subject to the requirements of this section. All records must be accurate, indelible, and legible. The records must identify the person performing the work and the dates of the various entries, and must be as detailed as necessary to provide a complete history of the work performed and to relate the records to the particular HCT/P involved.

(b) Records management system. You must establish and maintain a records management system relating to core CGTP requirements. Under this system, records pertaining to a particular HCT/P must be maintained in such a way as to facilitate review of the HCT/Ps history before making it

available for distribution and, if necessary, subsequent to the HCT/Ps release as part of a followup evaluation or investigation. Records pertinent to the manufacture of HCT/Ps (e.g., labeling and packaging procedures, and equipment logs) must also be maintained and organized under the records management system. If records are maintained in more than one location, then the records management system must be designed to ensure prompt identification, location, and retrieval of all records.

(c) Methods of retention. You may maintain records required under this subpart electronically, as original paper records, or as true copies such as photocopies, microfiche, or microfilm. Equipment that is necessary to make the records available and legible, such as computer and reader equipment, must be readily available. Records stored in electronic systems must be backed up.

(d) Length of retention. You must retain all records for 10 years after their creation, unless stated otherwise in this part. However, you must retain the records pertaining to a particular HCT/P at least 10 years after the date of its administration, or if the date of administration is not known, then at least 10 years after the date of the HCT/Ps distribution, disposition, or expiration, whichever is latest.

You must retain records for archived specimens of dura mater for 10 years after the appropriate disposition of the specimens.

(e) Contracts and agreements. You must maintain the name and address and a list of the responsibilities of any establishment that performs a manufacturing step for you. This information must be available during an inspection conducted under § 1271.400.

§ 1271.290 Tracking.

(a) General. If you perform any step in the manufacture of an HCT/P in which you handle the HCT/P, you must track each such HCT/P in accordance with this section, to facilitate the investigation of actual or suspected transmission of communicable disease and take appropriate and timely corrective action.

(b) System of HCT/P tracking. (1) You must establish and maintain a system of HCT/P tracking that enables the tracking of all HCT/Ps from:

(i) The donor to the consignee or final disposition; and

(ii) The consignee or final disposition to the donor.

(2) Alternatively, if you are an establishment that performs some but not all of the steps in the manufacture of an HCT/P in which you handle the HCT/P, you may participate in a system of HCT/P tracking established and maintained by another establishment responsible for other steps in the manufacture of

the same HCT/P, provided that the tracking system complies with all the requirements of this section.

(c) Distinct identification code. As part of your tracking system, you must ensure: That each HCT/P that you manufacture is assigned and labeled with a distinct identification code, e.g., alphanumeric, that relates the HCT/P to the donor and to all records pertaining to the HCT/P; and that labeling includes information designed to facilitate effective tracking, using the distinct identification code, from the donor to the recipient and from the recipient to the donor. Except in the case of autologous or directed donations, you must create such a code specifically for tracking, and it may not include an individual's name, social security number, or medical record number. You may adopt a distinct identification code assigned by another establishment engaged in the manufacturing process, or you may assign a new code. If you assign a new code to an HCT/P, you must establish and maintain procedures for relating the new code to the old code.

(d) Tracking from consignee to donor. As part of your tracking system, you must establish and maintain a method for recording the distinct identification code and type of each HCT/P distributed to a consignee to enable tracking from the consignee to the donor.

(e) Tracking from donor to consignee or final disposition.

As part of your tracking system, you must establish and maintain a method for documenting the disposition of each of your HCT/Ps, to enable tracking from the donor to the consignee or final disposition. The information you maintain must permit the prompt identification of the consignee of the HCT/P, if any.

(f) Consignees. At or before the time of distribution of an HCT/P to a consignee, you must inform the consignee in writing of the requirements in this section and of the tracking system that you have established and are maintaining to comply with these requirements.

(g) Requirements specific to dura mater donors. You must archive appropriate specimens from each donor of dura mater, under appropriate storage conditions, and for the appropriate duration, to enable testing of the archived material for evidence of transmissible spongiform encephalopathy, and to enable appropriate disposition of any affected nonadministered dura mater tissue, if necessary.

§ 1271.320 Complaint file.

(a) Procedures. You must establish and maintain procedures for the review, evaluation, and documentation of complaints as defined in 1271.3(aa), relating to core current good tissue practice (CGTP) requirements, and the investigation of complaints as appropriate.

(b) Complaint file. You must maintain a record of complaints that you receive in a file designated for complaints. The complaint file must contain sufficient information about each complaint for proper review and evaluation of the complaint (including the distinct identification code of the HCT/P that is the subject of the complaint) and for determining whether the complaint is an isolated event or represents a trend. You must make the complaint file available for review and copying upon request from FDA.

(c) Review and evaluation of complaints. You must review and evaluate each complaint relating to core CGTP requirements to determine if the complaint is related to an HCT/P deviation or to an adverse reaction, and to determine if a report under § 1271.350 or another applicable regulation is required. As soon as practical, you must review, evaluate, and investigate each complaint that represents an event required to be reported to FDA, as described in § 1271.350. You must review and evaluate a complaint relating to core CGTP requirements that does not represent an event required to be reported to determine whether an investigation is necessary; an investigation may include referring a copy of the complaint to another establishment that performed manufacturing steps pertinent to the complaint. When no investigation is made, you must maintain a record that includes the reason no investigation was made, and

the name of the individual(s) responsible for the decision not to investigate.

11. Part 1271 is amended by adding subpart E, consisting of §§ 1271.330 through 1271.370, to read as follows:

Subpart E--Additional Requirements for Establishments Described
in § 1271.10

Sec.

1271.330 Applicability.

1271.350 Reporting.

1271.370 Labeling.

Subpart E--Additional Requi

(a) Adverse reaction reports. (1) You must investigate any adverse reaction involving a communicable disease related to an HCT/P that you made available for distribution. You must report to FDA an adverse reaction involving a communicable disease if it:

- (i) Is fatal;
- (ii) Is life-threatening;
- (iii) Results in permanent impairment of a body function or permanent damage to body structure; or
- (iv) Necessitates medical or surgical intervention, including hospitalization.

(2) You must submit each report on a Form FDA-3500A to the address in paragraph (a) (5) of this section within 15 calendar days of initial receipt of the information.

(3) You must, as soon as practical, investigate all adverse reactions that are the subject of these 15-day reports and must submit followup reports within 15 calendar days of the receipt of new information or as requested by FDA. If additional information is not obtainable, a followup report may be required that describes briefly the steps taken to seek additional information and the reasons why it could not be obtained.

(4) You may obtain copies of the reporting form (FDA-3500A) from the Center for Biologics Evaluation and Research (see address in paragraph (a) (5) of this section). Electronic Form

FDA-3500A may be obtained at <http://www.fda.gov/medwatch> or at <http://forms.psc.govwww.hhs.gov/forms/FDA/fda.html>. You may obtain additional supplies of the form from the Consolidated Forms and Publications Distribution Center, 3222 Hubbard Rd., Landover, MD 20785.

(5) You must submit two copies of each report described in this paragraph to the Center for Biologics Evaluation and Research (HFM-210), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448. FDA may waive the requirement for the second copy in appropriate circumstances.

(b) Reports of HCT/P deviations. (1) You must investigate all HCT/P deviations related to a distributed HCT/P for which you performed a manufacturing step.

(2) You must report any such HCT/P deviation relating to the core CGTP requirements, if the HCT/P deviation occurred in your facility or in a facility that performed a manufacturing step for you under contract, agreement, or other arrangement. Each report must contain a description of the HCT/P deviation, information relevant to the event and the manufacture of the HCT/P involved, and information on all follow-up actions that have been or will be taken in response to the HCT/P deviation (e.g., recalls).

(3) You must report each such HCT/P deviation that relates to a core CGTP requirement on Form FDA-3486 available at

<http://www.fda.gov/cber/biodev/bpdrform.pdf>, within 45 days of the discovery of the event either electronically at <http://www.fda.gov/cber/biodev/biodevsub.htm> or by mail to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research (HFM-600), 1401 Rockville Pike, suite 200N, Rockville, MD 20852-1448.

§ 1271.370 Labeling.

The following requirements apply in addition to § 1271.55, 1271.60, 1271.65, and 1271.90:

(a) You must label each HCT/P made available for distribution clearly and accurately.

(b) The following information must appear on the HCT/P label:

(1) Distinct identification code affixed to the HCT/P container, and assigned in accordance with § 1271.290(c);

(2) Description of the type of HCT/P;

(3) Expiration date, if any; and

(4) Warnings required under § 1271.60(d)(2), 1271.65(b)(2), or 1271.90(b), if applicable.

(c) The following information must either appear on the HCT/P label or accompany the HCT/P:

(1) Name and address of the establishment that determines that the HCT/P meets release criteria and makes the HCT/P available for distribution;

- (2) Storage temperature;
- (3) Other warnings, where appropriate; and
- (4) Instructions for use when related to the prevention of the introduction, transmission, or spread of communicable diseases.

12. Part 1271 is amended by adding subpart F, consisting of §§ 1271.390 through 1271.440, to read as follows:

Subpart F--Inspection and Enforcement of Establishments

Described in § 1271.10

Sec.

1271.390 Applicability.

1271.400 Inspections.

1271.420 HCT/Ps offered for import.

1271.440 Orders of retention, recall, destruction, and
cessation of manufacturing.

Subpart F--Inspection and Enforcement of Establishments

Described in § 1271.10

§ 1271.390 Applicability.

The provisions set forth in this subpart are applicable only to HCT/Ps described in § 1271.10 and regulated solely under section 361 of the Public Health Service Act and the regulations in this part, and to the establishments that manufacture those HCT/Ps. HCT/Ps that are drugs or devices regulated under the act, or are biological products regulated under section 351 of

the Public Health Service Act, are not subject to the regulations set forth in this subpart.

§ 1271.400 Inspections.

(a) If you are an establishment that manufactures HCT/Ps described in § 1271.10, whether or not under contract, you must permit the Food and Drug Administration (FDA) to inspect any manufacturing location at any reasonable time and in a reasonable manner to determine compliance with applicable provisions of this part. The inspection will be conducted as necessary in the judgment of the FDA and may include, your establishment, facilities, equipment, finished and unfinished materials, containers, processes, HCT/Ps, procedures, labeling, records, files, papers, and controls required to be maintained under the part. The inspection may be made with or without prior notification and will ordinarily be made during regular business hours.

(b) The frequency of inspection will be at the agency's discretion.

(c) FDA will call upon the most responsible person available at the time of the inspection of the establishment and may question the personnel of the establishment as necessary to determine compliance with the provisions of this part.

(d) FDA's representatives may take samples, may review and copy any records required to be kept under this part, and may

use other appropriate means to record evidence of observations during inspections conducted under this subpart.

(e) The public disclosure of records containing the name or other positive identification of donors or recipients of HCT/Ps will be handled in accordance with FDA's procedures on disclosure of information as set forth in parts 20 and 21 of this chapter.

§ 1271.420 HCT/Ps offered for import.

(a) Except as provided in paragraphs (c) and (d) of this section, when an HCT/P is offered for import, the importer of record must notify, either before or at the time of importation, the director of the district of the Food and Drug Administration (FDA) having jurisdiction over the port of entry through which the HCT/P is imported or offered for import, or such officer of the district as the director may designate to act in his or her behalf in administering and enforcing this part, and must provide sufficient information for FDA to make an admissibility decision.

(b) Except as provided in paragraphs (c) and (d) of this section, an HCT/P offered for import must be held intact by the importer or consignee, under conditions necessary to prevent transmission of communicable disease, until an admissibility decision is made by FDA. The HCT/P may be transported under quarantine to the consignee, while the FDA district reviews the

documentation accompanying the HCT/P. When FDA makes a decision regarding the admissibility of the HCT/P, FDA will notify the importer of record.

(c) This section does not apply to reproductive HCT/Ps regulated solely under section 361 of the Public Health Service Act and the regulations in this part, and donated by a sexually intimate partner of the recipient for reproductive use.

(d) This section does not apply to peripheral blood stem/progenitor cells regulated solely under section 361 of the Public Health Service Act and the regulations in this part, except that paragraphs (a) and (b) of this section apply when circumstances occur under which such imported peripheral blood stem/progenitor cells may present an unreasonable risk of communicable disease transmission which indicates the need to review the information referenced in paragraph (a) of this section.

§ 1271.440 Orders of retention, recall, destruction, and cessation of manufacturing.

(a) Upon an agency finding that there are reasonable grounds to believe that an HCT/P is a violative HCT/P because it was manufactured in violation of the regulations in this part and, therefore, the conditions of manufacture of the HCT/P do not provide adequate protections against risks of communicable disease transmission; or the HCT/P is infected or contaminated

so as to be a source of dangerous infection to humans; or an establishment is in violation of the regulations in this part and, therefore, does not provide adequate protections against the risks of communicable disease transmission, the Food and Drug Administration (FDA) may take one or more of the following actions:

(1) Serve upon the person who distributed the HCT/P a written order that the HCT/P be recalled and/or destroyed, as appropriate, and upon persons in possession of the HCT/P that the HCT/P must be retained until it is recalled by the distributor, destroyed, or disposed of as agreed by FDA, or the safety of the HCT/P is confirmed;

(2) Take possession of and/or destroy the violative HCT/P;
or

(3) Serve upon the establishment an order to cease manufacturing until compliance with the regulations of this part has been achieved. When FDA determines there are reasonable grounds to believe there is a danger to health, such order will be effective immediately. In other situations, such order will be effective after one of the following events, whichever is later:

(i) Passage of 5 working days from the establishment's receipt of the order; or

(ii) If the establishment requests a hearing in accordance with paragraph (e) and part 16 of this chapter, a decision in, and in accordance with, those proceedings.

(b) A written order issued under paragraph (a) of this section will state with particularity the facts that justify the order.

(c) (1) A written order issued under paragraph (a) (1) of this section will ordinarily provide that the HCT/P be recalled and/or destroyed within 5 working days from the date of receipt of the order. After receipt of an order issued under paragraph (a) (1) of this section, the establishment in possession of the HCT/P must not distribute or dispose of the HCT/P in any manner except to recall and/or destroy the HCT/P consistent with the provisions of the order, under the supervision of FDA.

(2) In lieu of paragraph (c) (1) of this section, other arrangements for assuring the proper disposition of the HCT/P may be agreed upon by the person receiving the written order and FDA. Such arrangements may include, among others, providing FDA with records or other written information that adequately ensure that the HCT/P has been recovered, processed, stored, and distributed in conformance with this part, and that, except as provided under §§ 1271.60, 1271.65, and 1271.90, the donor of the cells or tissue for the HCT/P has been determined to be eligible.

(d) A written order issued under paragraph (a) (3) of this section will specify the regulations with which you must achieve compliance and will ordinarily specify the particular operations covered by the order. After receipt of an order that is in effect and issued under paragraph (a) (3) of this section, you must not resume operations without prior written authorization of FDA.

(e) The recipient of an order issued under this section may request a hearing in accordance with part 16 of this chapter. To request a hearing, the recipient of the written order or prior possessor of such HCT/P must make the request within 5 working days of receipt of a written order for retention, recall, destruction, and/or cessation (or within 5 working days of the agency's possession of an HCT/P under paragraph (a) (2) of this section), in accordance with part 16 of this chapter. An order of destruction will be held in abeyance pending resolution of the hearing request. Upon request under part 16 of this chapter, FDA will provide an opportunity for an expedited hearing for an order of cessation that is not stayed by the Commissioner of Food and Drugs.

(f) FDA will not issue an order for the destruction of reproductive tissue under paragraph (a) (1) of this section, nor will it carry out such destruction itself under paragraph (a) (2) of this section.

Dated: _____

Dated: _____

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