HUMAN CELLS, TISSUES, AND CELLULAR AND TISSUE-BASED PRODUCTS (HCT/Ps): ESTABLISHMENT REGISTRATION AND LISTING; FORM FDA 3356; ELIGIBILITY DETERMINATION FOR DONORS; AND CURRENT GOOD TISSUE PRACTICE

0910-0543

SUPPORTING STATEMENT

Justification

1. Circumstances Making the Collection of Information Necessary

The Food and Drug Administration (FDA) is requesting an extension of Office of Management and Budget (OMB) Control No. 0910-0543 and OMB approval of the information collection provisions in 21 CFR Part 1271 including Form FDA 3356. The information collection provisions are listed below:

21 CFR Section	Category	Description
1271.10(b)(1) and (b)(2) and 1271.21(b)	Reporting	Requires domestic and foreign establishments that recover, process, store, label, package, or distribute an HCT/P described in § 1271.10(a), or that perform screening or testing of the cell or tissue donor to register with FDA and submit a list of each HCT/P manufactured; and requires establishments to update registration annually.
1271.21(a), and 1271.25(a) and (b)	Reporting	Requires establishments to follow certain procedures for initial registration and listing of HCT/Ps; and identifies the required initial registration and HCT/P listing information.
1271.10(b)(2), 1271.21(c) (ii) and 1271.25(c)	Reporting	Requires establishments to submit HCT/P listing updates when an HCT/P is changed, and identifies the required HCT/P listing update information.
1271.26	Reporting	Requires establishments to submit an amendment if ownership or location of the establishment changes.
1271.55(a)	Reporting	Requires certain records to accompany an HCT/P once the donor eligibility determination has been made
1271.60(c) and (d)(2)	Reporting	Requires, when a product is shipped in quarantine before completion of screening and testing, the HCT/P must be accompanied by records identifying the donor, stating that the donor-eligibility determination has not been completed; and stating that the product must not be used until the eligibility determination has been completed. When an HCT/P is used in cases of documented urgent medical need, the results of any completed donor screening and testing, and a list of any required screening and testing not yet completed also must accompany the HCT/P.

1271.155(a)	Reporting	Permits the submission of a request for FDA approval of an exemption from or alternative to from any requirement in 21 CFR Part 1271 subpart C or D.
1271.290(c)	Reporting	Requires establishments to affix a distinct identification code to each HCT/P that it manufactures that relates the HCT/P to the donor and all records pertaining to the HCT/P.
1271.290(f)	Reporting	Requires establishments to inform the consignee, in writing, of the product tracking requirements and the methods the establishment uses to fulfill the requirements.
1271.350(a)(1) and (a)(3)	Reporting	Requires non-reproductive HCT/P establishments to investigate and report to FDA any adverse reactions using Form FDA 3500A.
1271.370(b) and (c)	Reporting	Requires establishments to include specific information either on the HCT/P label or with the HCT/P.
1271.47(a), 1271.85(b)(2), 1271.160(b)(2) and (d)(1), 1271.180(a), 1271.190(d)(1), 1271.200(b) and (c), 1271.230(a), 1271.250(a), and 1271.265(e), 1271.265(f), 1271.270(b), 1271.290(b)(1), 1271.320(a)	Recordkeeping	Requires establishment to establish and maintain procedures: (1) for all steps that are performed in determining eligibility; (2) appropriate to meet core Current Good Tissue Practice (CGTP) requirements that are performed in the manufacture of HCT/Ps; and (3) for other standard operating procedures under 21 CFR Part 1271.
1271.47(d)	Recordkeeping	Requires HCT/P establishments to record and justify any departure from a procedure relevant to preventing risks of communicable disease transmission at the time of its occurrence.
1271.50(a)	Recordkeeping	Requires documentation of donor eligibility determination by a responsible person.
1271.55(d)(1)/ 1271.270(d)	Recordkeeping	Requires records used in determining the eligibility of a donor, i.e., results and interpretations of testing for relevant communicable disease agents, the donor eligibility determination, the name and address of the testing laboratory or laboratories, and the name of the responsible person (defined in §1271.3(t) who made the donor eligibility determination and the date of the determination, must be maintained.
1271.55(d)(2)	Recordkeeping	Requires establishments, if any information on the donor is not in English, to retain the original record, and its translation to English and accompanied by a statement of authenticity from the translator.
1271.55(d)(4)	Recordkeeping	Requires HCT/P establishments to retain the records

		pertaining to HCT/Ps at least 10 years after the date of administration, distribution, disposition, or expiration, whichever is latest.
1271.60(d)(3) and (d)(4) and 1271.65(b)(3)(iii)	Recordkeeping	Requires, when an HCT/P is used in cases of documented urgent need or from a donor who has been determined to be ineligible (as permitted under § 1271.65), documentation by the HCT/P establishment showing that the recipient's physician received notification that the testing and screening were not complete (in cases of urgent medical need), and upon the completion of the donor-eligibility determination, of the results of the determination.
1271.155(f)	Recordkeeping	Requires an establishment operating under the terms of an exemption or alternative to maintain documentation of the terms and date of FDA approval.
1271.160(b)(3) and (b)(6)	Recordkeeping	Requires documentation of corrective actions taken as a result of an audit of the quality program and of HCT/P deviations relating to core CGTP.
1271.160(d)	Recordkeeping	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.
1271.190(d)(2)	Recordkeeping	Requires documentation of all significant facility cleaning and sanitation performed to prevent contamination of HCT/Ps.
1271.195(d)	Recordkeeping	Requires documentation of environmental control and monitoring activities.
1271.200(e)	Recordkeeping	Requires documentation of equipment maintenance, cleaning, sanitizing, calibration, and other activities.
1271.210(d)	Recordkeeping	Requires documentation of the receipt, verification, and use of each supply or reagent.
1271.230(a)	Recordkeeping	Requires documentation of validation activities when the results of a process cannot be fully verified by subsequent inspection and tests.
1271.230(c)	Recordkeeping	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.
1271.260(d)	Recordkeeping	Requires documentation of any corrective action taken whenever proper storage conditions are not met.
1271.260(e)	Recordkeeping	Requires documentation of storage temperatures for HCT/Ps.
1271.265(c)(1)	Recordkeeping	Requires documentation that release criteria are met before distribution of an HCT/P.
1271.265(c)(3)	Recordkeeping	Requires documentation of any departure from a procedure at the time of its occurrence.
1271.265(e)	Recordkeeping	Requires documentation of the receipt, pre-distribution shipment, distribution, and packaging and shipping of

		HCT/Ps.
1271.270(a)	Recordkeeping	Requires documentation of each step in manufacturing required in Part 1271, subparts C and D.
1271.270(e)	Recordkeeping	Requires documentation of the name and address, and a list of responsibilities of any establishment that performs a manufacturing step for an establishment.
1271.290(d) and (e)	Recordkeeping	Requires documentation of 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 and to enable tracking from the donor to the consignee or final disposition.
1271.320(b)	Recordkeeping	Requires an establishment to maintain a record of each complaint that it receives, and that the record contains relevant information for proper review and evaluation.

Under section 361 of the Public Health Service Act (the PHS Act) (42 U.S.C. 264), FDA may issue and enforce regulations necessary to prevent the introduction, transmission, or spread of communicable diseases between the States or possessions or from foreign countries into the States. As derivatives of the human body, all human cells, tissues, and cellular and tissue-based products (HCT/Ps) pose some risk of carrying pathogens that could potentially infect recipients or handlers. FDA has issued regulations related to HCT/Ps involving establishment registration and listing using Form FDA 3356; eligibility determination for donors; and current good tissue practice (CGTP). FDA requires the use of Form FDA 3356: Establishment Registration and Listing for Human Cells, Tissues, and Cellular and Tissue-Based Products to submit the required information (§§ 1271.10, 1271.21, 1271.25, and 1271.26).

2. Purpose and Use of the Information Collection

The information FDA receives from establishments complying with registration and listing requirements is necessary to regulate the industries involved with the recovery, screening, testing, processing, storage, and distribution of HCT/Ps. The information allows FDA to efficiently and effectively handle emerging public health concerns related to HCT/Ps. The information also aids FDA to monitor the industry, to distribute educational materials, and to inform the industry about FDA requirements, guidances, and policies, and to identify entities that may be subject to FDA regulation.

Documentation of donor eligibility determination provides to the user that all of the donor's medical history and social behavior were reviewed for high risk for or clinical evidence of communicable diseases, and that all of the required testing was completed. Each distributed HCT/P must have the following accompanying documentation: (1) a distinct identification code; (2) a statement, based on the screening and testing results, that the donor is determined to be eligible or ineligible; and (3) a summary of the records used to determine eligibility. The summary of records must contain: (1) a statement that the testing was performed by a CLIA certified laboratory or by a laboratory that has met equivalent requirements as determined by the Centers for Medicare and Medicaid Services; (2) a listing and interpretation of the results of all communicable disease tests performed; (3) the name and address of the establishment determining the eligibility of the donor; and (4) in the case of an HCT/P from a donor determined to be ineligible based on screening and released for use under § 1271.65(b), a statement noting the reason for the ineligible determination.

Other reporting and recordkeeping requirements in 21 CFR Part 1271 are designed to fully disclose the screening and testing results to the user when using products from donors who are determined to be ineligible or whose eligibility has not yet been determined in an urgent medical need. The distributing establishment is also to document that the HCT/P establishment notified the physician that the screening and testing are not completed. HCT/P establishments are required to maintain records for a minimum of 10 years. Certain HCT/Ps have long storage periods and advances in medical diagnosis and therapy also have created opportunities for disease prevention or treatment many years after a recipient's exposure to a donor later determined to be at risk for communicable disease agents or diseases.

The CGTP information collection provisions provide: (1) additional measures for preventing the introduction, transmission, or spread of communicable disease; (2) step-by step consistency in the manufacturing of the product; (3) necessary information to FDA for the purpose of protecting public health and safety; (4) accountability in the manufacturing of cellular and tissue-based products; and (5) information facilitating the tracking of a product back to its original source or to a consignee or final disposition.

3. Use of Improved Information Technology and Burden Reduction

To facilitate establishment registration and listing, FDA has developed Form FDA 3356 that may be submitted electronically through a secure web server or in paper form by mail or FAX. Establishments may maintain records electronically or as original paper records, or as true copies such as photocopies, microfiche, or microfilm. Electronic recordkeeping is specifically referred to in the regulations under § 1271.270(c). Advanced methods of recordkeeping, e.g., by an electronic method, have improved the ability of HCT/P establishments to more easily maintain and retrieve records of donor eligibility determinations, and CGTP. FDA is not aware of any other improved technology to reduce the burden.

4. Efforts to identify Duplication and Use of Similar Information

Manufacturers of drug or device products that incorporate human cells or tissues register only using Form FDA 3356. To avoid duplication, FDA issued technical amendments to 21 CFR Parts 210, 211, and 820. These amendments state that in the event of a conflict between applicable regulations in Parts 210, 211, and 820 and the regulations in part 1271, the regulation specifically applicable to the product in question must supersede the more general. No other component of FDA or other government agencies requires similar information or data to be submitted. This information is not available from any other source.

5. Impact on Small Businesses or Other Small Entities

Although FDA must apply the statutory and regulatory requirements equally to all enterprises, FDA does provide special help to small businesses. The Center for Biologics Evaluation and Research (CBER), Office of Communications, Outreach, and Development, Division of Manufacturer's Assistance and Training provides assistance to small businesses.

6. Consequences of Collecting the Information Less Frequency

Less frequent collection of information would not provide FDA the information needed to prevent the transmission of communicable disease by HCT/Ps through monitoring, and communication with the cell and tissue industry. The documentation of donor eligibility, the summary of records, and the information provided to physicians on the donor's eligibility when a product is used in an urgent medical need is the minimum necessary to keep the industry informed of the eligibility of each and every donor of HCT/Ps. The reporting and recordkeeping requirements of CGTP are designed to impose minimum burden on industry while preventing the introduction, transmission, or spread of communicable disease through the use of HCT/Ps.

There are no technical or legal obstacles to reducing the burden.

7. Special Circumstances Relating to the Guidelines of 5 CFR 1320.5

The reporting burden under 21 CFR Part 1271, subparts C and D require respondents to provide information more often than quarterly, i.e., for each individual HCT/P. This information includes an identification code number, which protects patient/donor confidential information.

8. Comments in Response to the Federal Register Notice and Efforts to Consult Outside the Agency

In accordance with 5 CFR 1320.8(d), FDA published a 60-day notice for public comment in the **Federal Register** of March 11, 2010 (75 FR 11545). No comments were received from the public.

9. Explanation of Any Payment or Gift to Respondents

No payment or gift has been or will be provided to respondents.

10. Assurance of Confidentiality provided to respondents

The confidentiality of information received by FDA is consistent with the Freedom of Information Act (FOIA) and FDA's published regulations of "Public Information" under 21 CFR Part 20. Inspectors may copy records as part of the inspection of a tissue establishment. Such information may be copied to document distribution of potentially infectious tissue. This information is for internal use and may be subject to, in whole or in part, the FOIA and applicable FDA regulations.

11. Justification for Sensitive Questions

Questions of a sensitive nature, such as sexual behavior and other matters that are commonly considered private must be asked by the HCT/P establishments as part of the donor medical history evaluation. The answers to these questions help determine the eligibility of a donor. Donors that do not meet certain criteria would be determined ineligible to donate. This information is necessary to prevent the transmission of relevant communicable diseases and to protect the public health. FDA may review such information during an inspection.

12. Estimates of Annualized Burden Hours and Costs

The total annual estimated burden imposed by this collection of information is 3,873,944 hours annually.

Table 1.--Estimated Annual Reporting Burden					
21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
1271.10(b)(1) and (b)(2), and 1271.21(b)[1]	2,281	1	2,281	0.5	1,141
1271.10(b)(1) and (b)(2), 1271.21(a), and 1271.25(a) and (b)[1]	251	1	251	0.75	188
1271.10(b)(2), 1271.21(c)(2)(ii) and 1271.25(c)[1]	2,230	1	2,230	0.5	1,115
1271.26[1]	565	1	565	0.25	141
1271.55(a)	1,589	1,364	2,167,396	0.5	1,083,698
1271.60(c) and (d)(2)	1,375	208	286,000	0.5	143,000
1271.155(a)	18	1	18	3	54
1271.290(c)	1,694	1,196	2,026,024	0.083	168,835
1271.290(f)	1,694	1	1,694	1	1,694
1271.350(a)(1) and (a)(3)[2]	38	2	76	1	76
1271.370(b) and (c)	1,694	1,196	2,026,024	0.25	506,506
Total					1,906,448

[1] Using Form FDA 3356.

2 Using Form FDA 3500A (approved under OMB Control No. 0910-0291).

Table 2.--Estimated Annual Recordkeeping Burden					
21 CFR Section	No. of Record-keepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Record	Total Hours
New SOPs[1]	251	1	251	48	12,048
SOP Update[1]	2,281	1	2,281	24	54,744
1271.47(d)	1,141	1	1,141	1	1,141
1271.50(a)	2,281	40	91,240	5	456,200
1271.55(d)(1)	2,281	40	91,240	1	91,240
1271.55(d)(2)	2,281	1	2,281	1	2,281
1271.55(d)(4)/1271.270(d)	2,281	1	2,281	120	273,720
1271.60(d)(3) and (d)(4), 1271.65(b)(3)(iii)	684	1	684	2	1,368
1271.155(f)	18	1	18	0.25	5
1271.160(b)(3) and (b)(6)	1,694	12	20,328	1	20,328
1271.160(d)	1,694	12	20,328	1	20,328
1271.190(d)(2)	1,694	12	20,328	1	20,328
1271.195(d)	1,694	12	20,328	1	20,328
1271.200(e)	1,694	12	20,328	1	20,328

1271.210(d)	1,694	12	20,328	1	20,328
1271.230(a)	1,694	12	20,328	1	20,328
1271.230(c)	1,694	1	1,694	1	1,694
1271.260(d)	1,694	12	20,328	0.25	5,082
1271.260(e)	1,694	365	618,310	0.083	51,526
1271.265(c)(1)	1,694	1,196	2,026,024	0.083	168,835
1271.265(c)(3)	847	1	847	1	847
1271.265(e)	1,694	1,196	2,026,024	0.083	168,835
1271.270(a)	1,694	1,196	2,026,024	0.25	506,506
1271.270(e)	1,824	2	3,648	0.5	1,824
1271.290(d) and (e)	1,694	51	86,394	0.25	21,599
1271.320(b)	1,141	5	5,705	1	5,705
Total					1,967,496

[1] §§1271.47(a), 1271.85(b)(2), 1271.160(b)(2) and (d)(1), 1271.180(a), 1271.190(d)(1), 1271.200(b), 1271.200(c), 1271.230(a), 1271.250(a), and 1271.265(e), 1271.265(f), 1271.270(b), 1271.290(b)(1), 1271.320(a).

Respondents to this information collection are establishments that recover, process, store, label, package or distribute any HCT/P, or perform donor screening or testing. The estimates provided below are based on the most recent available information from FDA's database system and trade organizations. The hours per response and hours per record are based on data provided by the Eastern Research Group, or FDA experience with similar recordkeeping or reporting requirements.

There are an estimated 2,281 HCT/P (conventional tissue, eye tissue, peripheral blood stem cell, stem cell products from cord blood, reproductive tissue, and sperm banks) establishments, including 692 manufacturers of HCT/P products regulated under the Federal Food, Drug, and Cosmetics Act and section 351 of the PHS Act, that have registered and listed with FDA. In addition, we estimate that 251 new establishments have registered with FDA (§§1271.10(b)(1) and (b)(2) and 1271.25(a) and (b)). There are an estimated 2,230 listing updates (1271.10(b)(2), 1271.21(c)(2)(ii) and 1271.25(c)) and 565 location/ownership amendments (§1271.26).

Under § 1271.55(a), an estimated 2,167,396 HCT/Ps (which include conventional tissues, eye tissues, hematopoetic stem cells/progenitor cells, and reproductive cells and tissues), and an estimated 2,026,024 non-reproductive cells and tissues (total HCT/Ps minus reproductive cells and tissues) are distributed per year by an estimated 1,589 establishments (2,281 - 692 = 1,589 establishments with approved applications).

Under §1271.60(c) and (d)(2), FDA estimates that 1,375 establishments shipped an estimated 286,000 HCT/P under quarantine, and that an estimated 18 establishments requested an exemption from or alternative to any requirement under 1271 subpart C or D, specifically under § 1271.155(a).

Under §§ 1271.290(c) and 1271.370(b) and (c), an estimated 1,694 non-reproductive HCT/P establishments label each of their 2,026,024 HCT/Ps with certain information. These establishments are also required to inform their consignees in writing of the requirements for tracking and of their established tracking system under § 1271.290(f).

FDA estimates 38 HCT/P establishments submitted 76 adverse reaction reports (AERs) involving a communicable disease (§ 1271.350(a)(1)).

FDA estimates that 251 new establishments will create SOPs, and that 2,281 establishments will review and revise existing SOPs annually.

FDA estimates that 1,141 HCT/P establishments (2,281 x 50% = 1,141) and 847 non-reproductive HCT/P establishments (1,694 x 50% = 847) record and justify a departure from the procedures (§ 1271.47(d) and § 1271.265(c)(3)).

Under §1271.50(a), HCT/P establishments are required to have a documented medical history interview about the donor's medical history and relevant social behavior as part of the donor's relevant medical records for each of the estimated total of 91,240 donors (which include conventional tissue donors, eye tissue donors, peripheral and cord blood stem cell donors, and reproductive cell and tissue donors), and the estimated total of 86,394 non-reproductive cells and tissue donors (total donors minus reproductive cell and tissue donors).

FDA estimates that 684 HCT/P establishments (2,281 x 30% = 684) document an urgent medical need for an HCT/P and notify the physician using the HCT/P (§ 1271.60(d)(3) and (d)(4) and 1271.65(b)(3)(iii)).

FDA also estimates that 1,824 HCT/P establishments (2,281 x 80% = 1,824) have to maintain records for an average of 2 contract establishments that perform a manufacturing process step for them (§ 1271.270(e), and 1,141 HCT/P establishments maintain an average of 5 complaint records annually (§ 1271.320(b)).

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.

Cost to Respondents

The estimated annual cost to respondents is $124,298,265.55.

Activity	No. of Hours	Cost per Hour	Total Cost
Reporting	1,906,448	$53	$101,041,744.00
Recordkeeping	1,967,496	$40	$ 78,699,840.00
Total			$179,741,584.00

The reporting cost estimate is based on an average pay rate of $53 an hour. The average is based on the salaries of a medical director ($79/hour), a mid-level supervisor ($48/hour, responsible for completing and submitting the registration and/or listing information; creating, reviewing, or updating SOPs; or on other reporting responsibilities), and a medical technician ($32/hour). The recordkeeping cost estimate is based on an average pay rate of $40/hour of a mid-level professional and a medical technician who are involved with the documentation and maintenance of records. The estimated average hourly pay rate includes benefits but no overhead costs.

13. Estimates of Other Total Annual Cost Burden to Respondents and Record Keepers

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

14. Annualized Cost to the Federal Government

The estimated annualized cost to FDA is $4,150,110.00.

Activity	Number of Responses	Hours per Response	Cost per Hour	Total Cost
Registration and Listing	5,327	3	$42	$671,202
Exemption or Alternative Request	18	3	$67	$3,618
Establishment (non-reproductive) Inspection	847	69	$57	$3,331,251
Establishment (reproductive) Inspection	147	17	$57	$142,443
AER triage/review	76	1/2	$42	$1,596
Total				$4,150,110

The estimated cost is based on 2 FTEs (GS-7/5 and GS-13/5) who process and review the registration form, input the data, and maintain the database; and who triage and review AERs. There are approximately 1,694 non-reproductive HCT/P establishments that would be inspected on a biennial basis (847) by a FDA Inspector at an average grade of GS-13/5. The estimated time include inspection, reviewing records and writing up a report. There are approximately 587 (2,281 - 1,694 = 587) reproductive HCT/P establishments that would be inspected for compliance with the donor eligibility requirements every 4 years (147 per year). This cost is also based on FDA regulatory review staff who process and review the requests for exemptions or alternatives. The salary estimates include benefits but no overhead costs.

15. Explanation for Program Changes or Adjustments

. The increase in burden is attributed to the increase in the number of establishments reporting and this increased the total number of annual responses.

16. Plans for Tabulation and Publication and Project Time Schedule

There are no tabulated results to publish for this information collection.

17. Reason(s) Display of OMB Expiration Date is Inappropriate

FDA is not seeking approval to exempt the display of the expiration date of the OMB approval.

18. Exceptions to Certification for Paperwork Reduction Act Submissions

N/A.