Supporting Statement for
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

JUSTIFICATION

1. Need and Legal Basis

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 (Tab A) including Form FDA 3356 (Tab B). The information collection provisions are listed below:

21 CFR Section	Category	Description
1271.10(b)(1) and (b)(2)	Reporting	Requires domestic and foreign establishments that recover, process, store, label, package, or distribute any HCT/Ps, 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.
1271.21(a), and 1271.25(a) and (b)	Reporting	Requires the initial establishment registration and identification of 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 HCT/P establishments to submit an amendment if ownership or location of the establishment changes.
1271.55(a)	Reporting	Requires documentation of donor eligibility determination to accompany HCT/Ps.
1271.60(c) and (d)(2)	Reporting	Requires, when a product is shipped in quarantine before completion of screening and testing, the HCT/P establishment to provide the donor identification, a statement that the donor-eligibility determination is not completed and that the HCT/P is not to be used until the eligibility determination is completed. With the use of a product from an incompletely tested donor, the results of any completed donor screening and testing, and a list of any required screening and testing not yet completed must accompany the HCT/P.
1271.155(a)	Reporting	Permits establishments to submit a request for FDA approval of an exemption or alternative 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 relating 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)	Reporting	Requires establishments to investigate and to report to FDA any adverse reaction involving a communicable disease related to an HCT/P that was made available for distribution.
1271.350(b)(1) and (b)(2)	Reporting	Requires establishments to investigate and report all HCT/P deviation relating to the core CGTP requirements, if the deviation occurs in the establishment's facility or a facility under contract, agreement or other arrangement.
1271.370(b) and (c)	Reporting	Requires labeling of each HCT/P with the distinct identification code, the description of the type of HCT/P, expiration date, if any, and appropriate warnings. Each label or accompanying material must provide the name and address of the establishment that makes the HCT/P available for distribution, the storage temperature, other warnings, where appropriate, and instructions for use when related to the prevention of the introduction, transmission, or spread of communicable diseases.
1271.47(a), 1271.85(b)(2), 1271.160(b)(2), 1271.180(a), 1271.190(d)(1), 1271.200(b) and (c), 1271.230(a), 1271.250(a), 1271.265(e), and 1271.320(a)	Recordkeeping	Requires establishment to establish and maintain procedures for all steps that are performed in determining eligibility and other standard operating procedures under 21 CFR Part 1271.
1271.47(d)	Recordkeeping	Requires establishments to record and justify any departure from a procedure relevant to preventing risks of communicable disease transmission at the time of its occurrence and to make available for distribution any HCT/P from a donor whose eligibility is determined under such a departure unless a responsible person has determined that the departure does not increase the risks of communicable disease transmission through the use of the HCT/P.
1271.50(a)	Recordkeeping	Requires documentation of donor eligibility determination by a responsible person.
1271.55(d)(1)	Recordkeeping	Requires records used in determining the eligibility of a donor, i.e., results and interpretations of screening and testing, the donor eligibility determination, the name and address of the testing laboratory or laboratories, and the name of the responsible person who made the

		determination and the date, be maintained.
1271.55(d)(2)	Recordkeeping	Requires establishments to retain the original record and the statement of authenticity from the translator if any information on the donor is not in English.
1271.55(d)(4)	Recordkeeping	Requires establishments to retain 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 1271.65(b)(3)	Recordkeeping	Requires establishments, when using an HCT/P from an ineligible donor, to document that the recipient's physician received notification of the screening and testing results.
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.
1271.195(d)	Recordkeeping	Requires documentation of environmental control and monitoring activities.
1271.200(e)	Recordkeeping	Requires documentation of all 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 establishment of acceptable storage temperatures for HCT/Ps at each step of the manufacturing process to inhibit the growth of infectious agents and the maintenance and recording of storage temperatures of HCT/Ps.
1271.265(c)(1)	Recordkeeping	Requires documentation that all 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 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 the establishment.
1271.290(d) and (e)	Recordkeeping	Requires documentation of the establishment and maintenance 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 for the disposition of each HCT/P from the donor to the consignee or final disposition.
1271.320(b)	Recordkeeping	Requires documentation of each complaint that is received, including a review and evaluation.

Under section 361 of the Public Health Service Act (the PHS Act) (42 U.S.C. 264) (Tab C), 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 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). Form FDA 3356: Establishment Registration and Listing for Human Cells, Tissues, and Cellular and Tissue-Based Products is used to submit the required information (§§ 1271.10, 1271.21, 1271.25, and 1271.26).

2. <u>Information Users</u>

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: a distinct identification code; a statement, based on the screening and testing results, that the donor is determined to be eligible or ineligible; and a summary of the records used to determine eligibility. The summary of records must contain 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; a listing and interpretation of the results of all communicable disease tests performed; the name and address of the establishment determining the eligibility of the donor; and, 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. Improved Information Technology

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. 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. Duplication 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. Small Businesses

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, Training, and Manufacturers Assistance provides assistance to small businesses subject to FDA's regulatory requirements.

6. Less Frequent Collection

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

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. *Federal Register* Notice/Outside Consultation

In accordance with 5 CFR 1320.8(d), FDA published a 60-day notice requesting public comment on the information collection provisions in the *Federal Register* on January 26, 2007 (72 FR 3858). *No comments were received from the public.*

9. Payment/Gift to Respondent

No payment or gift was provided to respondents.

10. Confidentiality

The confidentiality of information received by FDA is consistent with the Freedom of Information Act and FDA's regulations under 21 CFR Part 20. HCT/P establishments are not required to reveal any proprietary or trade secret information to be in compliance with the requirements under 21 CFR Part 1271.

11. Sensitive Questions

Questions of a sensitive nature, such as high-risk behavior related to the transmission of human immunodeficiency virus (HIV) and hepatitis, 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, e.g., whether the donor was exposed to a communicable disease by participating in certain activities that are known to transmit communicable diseases. Donors not meeting 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. Such information would remain confidential by assigning a distinct identification code to the donor instead of using a name. FDA may review such information during an inspection.

12. Burden Estimate (Total Hours and Wages)

The total annual estimated burden imposed by this collection of information is 3,086,113.65 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)[1]	2,017	1	2,017	0.5	1,008.5
1271.10(b)(1) and (b)(2), 1271.21(a), and 1271.25(a) and (b)[1]	241	1	241	0.75	180.75
1271.10(b)(2), 1271.21(c)(ii) and 1271.25(c)[1]	3,289	1	3,289	0.5	1,644.50
1271.26[1]	500	1	500	0.25	125
1271.55(a)	1,536	1,091.87	1,677,105	0.5	838,552.50
1271.60(c) and (d)(2)	1,200	208.33	250,000	0.5	125,000
1271.155(a)	8	1	8	3	24
1271.290(c)	1,449	1,071.16	1,552,105	0.08	124,168.4
1271.290(f)	1,449	1	1,449	1	1,449
1271.350(a)(1)	42	1.60	67	1	67
1271.350(b)(1) and (b)(2)	81	1.78	144	1	144
1271.370(b) and (c)	1,449	1,071.16	1,552,105	0.25	388,026.25
Total					1,480,389.80

[1] Using Form FDA 3356.

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]	241	1	241	48	11,568
SOP Update[1]	2,017	1	2,017	24	48,408
1271.47(d)	1,009	1	1,009	1	1,009
1271.50(a)	2,017	38.64	77,944	5	389,720
1271.55(d)(1)	2,017	38.64	77,944	1	77,944
1271.55(d)(2)	2,017	1	2,017	1	2,017
1271.55(d)(4)	2,017	1	2,017	120	242,040
1271.60(d)(3) and 1271.65(b)(3)	605	1	605	2	1,210
1271.155(f)	8	1	8	0.25	2
1271.160(b)(3) and (b)(6)	1,449	12	17,388	1	17,388
1271.160(d)	1,449	12	17,388	1	17,388
1271.190(d)(2)	1,449	12	17,388	1	17,388
1271.195(d)	1,449	12	17,388	1	17,388
1271.200(e)	1,449	12	17,388	1	17,388
1271.210(d)	1,449	12	17,388	1	17,388
1271.230(a)	1,449	12	17,388	1	17,388
1271.230(c)	1,449	1	1,449	1	1,449
1271.260(d)	1,449	12	17,388	0.25	4,347

1271.260(e)	1,449	365	528,885	0.08	42,310.8
1271.265(c)(1)	1,449	1,071.16	1,552,105	0.08	124,168.4
1271.265(c)(3)	725	1	725	1	725
1271.265(e)	1,449	1,071.16	1,552,105	0.08	124,168.4
1271.270(a)	1,449	1,071.16	1,552,105	0.25	388,026.25
1271.270(e)	1,614	2	3,228	0.5	1,614
1271.290(d) and (e)	1,449	50.34	72,944	0.25	18,236
1271.320(b)	1,009	5	5,045	1	5,045
Total					1,605,723.85

[1] §§1271.47(a), 1271.85(b)(2), 1271.160(b)(2), 1271.180(a), 1271.190(d)(1), 1271.200(b), 1271.200(c), 1271.230(a), 1271.250(a), and 1271.265(e), and 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 information from FDA's database system and trade organizations for 2006. 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 2,017 HCT/P (conventional tissue, eye tissue, peripheral blood stem cell, stem cell products from cord blood, reproductive tissue, and sperm banks) establishments, including 481 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 241 new establishments have registered with FDA (§§1271.10(b)(1) and (b)(2) and 1271.25(a) and (b)). There are an estimated 3,289 listing updates (1271.10(b)(2), 1271.21(c)(2)(ii) and 1271.25(c)) and 500 location/ownership amendments (§1271.26).

Under § 1271.55(a), an estimated 1,677,105 HCT/Ps (approximately 1,500,000 conventional tissues, 44,186 eye tissues, 7,919 hematopoetic stem cells/progenitor cells (total of 1,552,105 non-reproductive cells and tissues), and 125,000 reproductive cells and tissues) are distributed per year by an estimated 1,536 establishments (2,017-481 establishments with approved applications).

Under §1271.60(c), FDA estimates that 1,200 establishments shipped an estimated 250,000 HCT/P under quarantine, and that an estimated 8 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), the estimated 1,449 non-reproductive HCT/P establishments label each of their 1,552,105 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 42 HCT/P establishments submitted 67 adverse reaction reports (AERs) involving communicable disease (§ 1271.350(a)(1)), and 81 establishments submitted 144 deviation reports relating to the core CGTP requirements (§ 1271.350(b)(1)).

FDA estimates that 241 new establishments will create SOPs, and that 2,017 establishments will review and revise existing SOPs annually.

FDA estimates that 1,009 HCT/P establishments (2,017x50%=1,009) and 725 non-reproductive

HCT/P establishments (1,449x50%=725) 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 77,944 donors (approximately 23,295 conventional tissue donors, 42,649 eye tissue donors, 7,000 peripheral and cord blood stem cell donors (72,944 non-reproductive cells and tissue donors), and 5,000 reproductive cell and tissue donors).

FDA estimates that 605 HCT/P establishments (2,017x30%=605) document an urgent medical need of the product to notify the physician using the HCT/P (§ 1271.60(d)(3) and 1271.65(b)(3)).

FDA also estimates that 1614 HCT/P establishments (2,017x80%=4031614) have to maintain records for an average of 2 contract establishments to perform their manufacturing process (§ 1271.270(e) and 1,009 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	1,480,389.80	$46	$68,097,930.80
Recordkeeping	1,605,723.85	$35	$56,200,334.75
Total			$124,298,265.55

The reporting cost estimate is based on an average pay rate of $46 an hour. The average is based on the salaries of a medical director ($69/hour), a mid-level supervisor ($42/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 ($28/hour). The recordkeeping cost estimate is based on an average pay rate of $35/hour of the 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. Capital Costs (Maintenance of Capital Costs)

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

14. Cost to Federal Government

The estimated annualized cost to FDA is $3,378,621.68.

Activity	Number of Responses	Hours per Response	Cost per Hour	Total Cost
Registration and Listing	6,047	2.78	$38.5	$647,210.41
Exemption or Alternative Request	8	3	$61	$1,464.00
Establishment (non-reproductive) Inspection	725	69	$52	$2,601,300.00
Establishment (reproductive) Inspection	142	17	$52	$125,528.00
AER triage/review	67	0.5	$38.5	$1,289.75
Deviation report data entry/review	144	0.33	$38.5	$1,829.52
Total				$3,378,621.68

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. There are approximately 1449 establishments that would be inspected on a biennial basis (725) by GS-13/5. The estimated time include inspection, reviewing records and writing up a report. There are approximately 568 (2,017-1,449) reproductive HCT/P establishments that would be inspected for compliance with the donor eligibility requirements every 4 years (142). This cost is also based on the combined costs for triage and review of AERs, review and data entry of HCT/P deviation reports, and review and assessment of requests for exemptions or alternatives. The salary estimates include benefits but no overhead costs.

15. Program or Burden Changes

The 2004 burden estimate for 0910-0543 was 866,240. The increase in burden to 3,086,113.65 is attributed to the consolidation of OMB packages: 0910-0469 and 0910-0559 and an increase in the number of establishments as well as total annual responses and records based on updated information since the issuance of the Eligibility Determination for Donors of HCT/Ps and CGTP final rules.

16. Publication and Tabulation Dates

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

17. Display of OMB Approval Date

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"

Not applicable.