



**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**[Docket No. FDA-2013-N-0731]**

**Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Human Cells, Tissues, and Cellular and Tissue-Based Products: Establishment Registration and Listing; Eligibility Determination for Donors; and Current Good Tissue Practice**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Notice.

**SUMMARY:** The Food and Drug Administration (FDA) is announcing that a proposed collection of information has been submitted to the Office of Management and Budget (OMB) for review and clearance under the Paperwork Reduction Act of 1995.

**DATES:** Submit written comments (including recommendations) on the collection of information by **[INSERT DATE 30 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]**.

**ADDRESSES:** To ensure that comments on the information collection are received, OMB recommends that written comments be submitted to <https://www.reginfo.gov/public/do/PRAMain>. Find this particular information collection by selecting “Currently under Review - Open for Public Comments” or by using the search function. The OMB control number for this information collection is 0910-0543. Also include the FDA docket number found in brackets in the heading of this document.

**FOR FURTHER INFORMATION CONTACT:** Domini Bean, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-5733, PRAStaff@fda.hhs.gov.

**SUPPLEMENTARY INFORMATION:** In compliance with 44 U.S.C. 3507, FDA has submitted the following proposed collection of information to OMB for review and clearance.

Human Cells, Tissues, and Cellular and Tissue-Based Products: Establishment Registration and Listing; Eligibility Determination for Donors; and Current Good Tissue Practice

OMB Control Number 0910-0543--Extension

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 electronic establishment registration and listing using an electronic system, eligibility determination for donors, and current good tissue practice (CGTP).

#### I. Electronic Establishment Registration and Listing

The regulations in part 1271 (21 CFR part 1271) require domestic and foreign establishments that recover, process, store, label, package, or distribute an HCT/P regulated solely under section 361 of the PHS Act and described in § 1271.10(a) (21 CFR 1271.10(a)), or that perform screening or testing of the cell or tissue donor, to register electronically with FDA (§§ 1271.1(a) (21 CFR 1271.1(a)) and 1271.10(b)(1)) and submit a list electronically of each HCT/P manufactured (§§ 1271.1(a) and 1271.10(b)(2)). Section 1271.21(a) (21 CFR

1271.21(a)) requires an establishment to follow certain procedures for initial registration and listing of HCT/Ps, and § 1271.25(a) and (b) (21 CFR 1271.25(a) and (b)) identify the required initial registration and HCT/P listing information. Section 1271.21(b), in brief, requires an annual update of the establishment registration. Section 1271.21(c)(ii) requires establishments to submit HCT/P listing updates if a change as described in § 1271.25(c) has occurred. Section 1271.25(c) identifies the required HCT/P listing update information. Section 1271.26 (21 CFR 1271.26) requires establishments to submit an amendment if ownership or location of the establishment changes, or if there is a change in the U.S. agent's name, address, telephone number, or email address. FDA requires the use of an electronic registration and listing system entitled "eHCTERS" (Electronic Human Cell and Tissue Establishment Registration System) to submit the required information (§§ 1271.10, 1271.21, 1271.25, and 1271.26)). Under § 1271.23 (21 CFR 1271.23), manufacturers may request a waiver from the requirements in 21 CFR 1271.22 that information must be provided to FDA in electronic format.

## II. Eligibility Determination for Donors

In brief, FDA requires certain HCT/P establishments described in § 1271.1(b) to determine donor eligibility based on donor screening and testing for relevant communicable disease agents and diseases except as provided under 21 CFR 1271.90. The documented determination of a donor's eligibility is made by a responsible person as defined in § 1271.3(t) (21 CFR 1271.3(t)) and is based on the results of required donor screening, which includes a donor medical history interview (defined in § 1271.3(n)), and testing (§ 1271.50(a) (21 CFR 1271.50(a))). Certain records must accompany an HCT/P once the donor-eligibility determination has been made (§ 1271.55(a) (21 CFR 1271.55(a))). This requirement applies both to an HCT/P from a donor who is determined to be eligible as well as to an HCT/P from a

donor who is determined to be ineligible or where the donor-eligibility determination is not complete if there is a documented urgent medical need, as defined in § 1271.3(u) (§§ 1271.60 and 1271.65 (21 CFR 1271.60 and 1271.65)). Once the donor-eligibility determination has been made, the HCT/P must be accompanied by a summary of records used to make the donor-eligibility determination (§ 1271.55(b)), and a statement whether, based on the results of the screening and testing of the donor, the donor is determined to be eligible or ineligible (§ 1271.55(a)(2)). 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)(1)). If any information on the donor is not in English, the original record must be maintained and translated to English and accompanied by a statement of authenticity by the translator (§ 1271.55(d)(2)). HCT/P establishments must retain the records pertaining to a particular HCT/P at least 10 years after the date of its administration, or, if the date of administration is not known, then at least 10 years after the date of the HCT/P's distribution, disposition, or expiration, whichever is latest (§ 1271.55(d)(4)).

When a product is shipped in quarantine, as defined in § 1271.3(q), before completion of screening and testing, the HCT/P must be accompanied by records identifying the donor (e.g., by a distinct identification code affixed to the HCT/P container) stating that the donor-eligibility determination has not been completed and stating that the product must not be implanted, transplanted, infused, or transferred until completion of the donor-eligibility determination, except in cases of urgent medical need, as defined in § 1271.3(u) (§ 1271.60(c)). 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 that has not yet been completed also must accompany the HCT/P (§ 1271.60(d)(2)). When a HCT/P is used in cases of urgent medical need or from a donor who has been determined to be ineligible (as permitted under § 1271.65), documentation by the HCT/P establishment is required, 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 (§§ 1271.60(d)(3) and (4), and 1271.65(b)(3)).

An HCT/P establishment is also required to establish and maintain procedures for all steps that are performed in determining eligibility (§ 1271.47(a) (21 CFR 1271.47(a)), including the use of a product from a donor of viable, leukocyte-rich cells or tissue testing reactive for cytomegalovirus (§ 1271.85(b)(2) (21 CFR 1271.85(b)(2))). The HCT/P establishment must record and justify any departure from a procedure relevant to preventing risks of communicable disease transmission at the time of its occurrence (§ 1271.47(d)).

### III. Current Good Tissue Practice

FDA requires HCT/P establishments that manufacture HCT/Ps that are regulated solely under section 361 of the PHS Act to follow CGTP (§ 1271.1(b)). Section 1271.155(a) (21 CFR 1271.155(a)) permits the submission of a request for FDA approval of an exemption from or an alternative to any requirement in subpart C or D of part 1271. Section 1271.290(c) (21 CFR 1271.290(c)) requires establishments to affix a distinct identification code to each HCT/P that they manufacture that relates the HCT/P to the donor and to all records pertaining to the HCT/P. Whenever an establishment 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 these requirements. Non-reproductive HCT/P establishments described in § 1271.10 are required under § 1271.350(a)(1) and (3) (21 CFR 1271.350(a)(1) and (3)) to investigate and report to FDA adverse reactions (defined in § 1271.3(y)) using Form FDA-3500A (§ 1271.350(a)(2)). Form FDA-3500A is approved under OMB control number 0910-0291. Section 1271.370(b) and (c) (21 CFR 1271.370(b) and (c)) requires establishments to include specific information either on the HCT/P label or with the HCT/P.

The standard operating procedures (SOPs) provisions under part 1271 include the following: (1) section 1271.160(b)(2) (21 CFR 1271.160(b)(2)) (receiving, investigating, evaluating, and documenting information relating to core CGTP requirements, including complaints, and for sharing information with consignees and other establishments); (2) § 1271.180(a) (21 CFR 1271.180(a)) (to meet core CGTP requirements for all steps performed in the manufacture of HCT/Ps); (3) § 1271.190(d)(1) (21 CFR 1271.190(d)(1)) (facility cleaning and sanitization); (4) § 1271.200(b) (21 CFR 1271.200(b)) (cleaning, sanitizing, and maintenance of equipment); (5) § 1271.200(c) (calibration of equipment); (6) § 1271.230(a) and (c) (21 CFR 1271.230(a) and (c)) (validation of a process and review and evaluation of changes to a validated process); (7) § 1271.250(a) (21 CFR 1271.250(a)) (controls for labeling HCT/Ps); (8) § 1271.265(e) (21 CFR 1271.265(e)) (receipt, predistribution shipment, availability for distribution, and packaging and shipping of HCT/Ps); (9) § 1271.265(f) (suitable for return to inventory); (10) § 1271.270(b) (21 CFR 1271.270(b)) (records management system); (11) § 1271.290(b)(1) (21 CFR 1271.290(b)(1)) (system of HCT/P tracking); and (12) § 1271.320(a) (21 CFR 1271.320(a)) (review, evaluation, and documentation of complaints as defined in § 1271.3(aa)).

Section 1271.155(f) requires an establishment operating under the terms of an exemption or alternative to maintain documentation of FDA's grant of the exemption or approval and the date on which it began operating under the terms of the exemption or alternative. Section 1271.160(b)(3) requires the quality program of an establishment that performs any step in the manufacture of HCT/Ps to document corrective actions relating to core CGTP requirements. Section 1271.160(b)(6) requires documentation of HCT/P deviations. Section 1271.160(d) requires, in brief, documentation of validation of computer software if the establishment relies upon it to comply with core CGTP requirements. Section 1271.190(d)(2) requires documentation of all cleaning and sanitation activities performed to prevent contamination of HCT/Ps. 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) (21 CFR 1271.210(d)) requires, in brief, documentation of the receipt, verification, and use of each supply or reagent. Section 1271.230(a) requires documentation of validation activities and results when the results of processing described in 21 CFR 1271.220 cannot be fully verified by subsequent inspection and tests. Section 1271.230(c) requires that when changes to a validated process subject to § 1271.230(a) occur, documentation of the review and evaluation of the process and revalidation, if necessary, must occur. Section 1271.260(d) and (e) (21 CFR 1271.260(d) and (e)) requires documentation of any corrective action taken when proper storage conditions are not met and documentation of the storage temperature for HCT/Ps. Section 1271.265(c)(1) requires documentation that all release criteria have been met before distribution of an HCT/P. Section 1271.265(c)(3) requires documentation of any departure from a procedure relevant to preventing risks of communicable disease transmission at the time of occurrence. Section 1271.265(e)

requires documentation of the activities in paragraphs (a) through (d) of that section, which must include identification of the HCT/P and the establishment that supplied the HCT/P, activities performed and the results of each activity, date(s) of activity, quantity of HCT/P subject to the activity, and disposition of the HCT/P. Section 1271.270(a) requires documentation of each step in manufacturing required in part 1271, 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 the establishment. Section 1271.290(d) and (e) require 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. Section 1271.320(b) requires an establishment to maintain a record of each complaint that it receives. The complaint file must contain sufficient information about each complaint for proper review and evaluation of the complaint and for determining whether the complaint is an isolated event or represents a trend.

Section 1271.420(a) (21 CFR 1271.420(a)) requires importers of HCT/Ps to notify the FDA District Director having jurisdiction over the port of entry through which the HCT/Ps are offered for import. The HCT/Ps must be held intact or transported under quarantine until they are inspected and released by FDA.

Respondents to this information collection are establishments that recover, process, store, label, package, or distribute any HCT/P that is regulated solely under section 361 of the PHS Act or perform donor screening or testing. The estimates provided below are based on 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 2,736 HCT/P establishments (conventional tissue, eye tissue, peripheral blood stem cell, stem cell products from cord blood, reproductive tissue, and sperm banks), including 1,004 manufacturers of HCT/Ps regulated under the Federal Food, Drug, and Cosmetic Act and section 351 of the PHS Act (42 U.S.C 262), that have registered and listed with FDA. In addition, we estimate that 193 new establishments have registered with FDA (§§ 1271.10(b)(1) and (2) and 1271.25(a) and (b)). There are an estimated 1,062 listing updates (§§ 1271.10(b)(2), 1271.21(c)(ii), and 1271.25(c)) and 358 location/ownership amendments (§ 1271.26).

Under § 1271.23, FDA estimates an average of one waiver request annually.

Under § 1271.55(a), an estimated total of 2,594,415 HCT/Ps (which include conventional tissues, eye tissues, hematopoietic stem cells/progenitor cells, and reproductive cells and tissues), and an estimated total of 2,454,415 non-reproductive cells and tissues (total HCT/Ps minus reproductive cells and tissues) are distributed per year by an estimated 1,632 establishments ( $2,736 - 1,104 = 1,632$ ).

Under § 1271.60(c) and (d)(2), FDA estimates that 1,611 establishments shipped an estimated 572,000 HCT/P under quarantine, and that an estimated 15 establishments requested 64 exemptions from or alternative to any requirement under part 1271, subpart C or D, specifically under § 1271.155(a).

Under §§ 1271.290(c) and 1271.370(b) and (c), the estimated 2,109 non-reproductive HCT/P establishments label each of their 2,441,644 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 13 HCT/P establishments submitted 188 adverse reaction reports with 162 involving a communicable disease (§ 1271.350(a)(1)).

FDA estimates that 193 new establishments will create SOPs, and that 2,736 establishments will review and revise existing SOPs annually.

FDA estimates that 1,368 HCT/P establishments ( $2,736 \times 50 \text{ percent} = 1,368$ ) and 1,055 non-reproductive HCT/P establishments ( $2,109 \times 50 \text{ percent} = 1,055$ ) 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 109,019 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 103,419 non-reproductive cells and tissue donors (total donors minus reproductive cell and tissue donors).

FDA estimates that 821 HCT/P establishments ( $2,736 \times 30 \text{ percent} = 821$ ) 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 2,189 HCT/P establishments ( $2,736 \times 80 \text{ percent} = 2,189$ ) have to maintain records for an average of 2 contract establishments to perform their manufacturing process (§ 1271.270(e) and 1,687 HCT/P establishments ( $2,109 \times 80 \text{ percent} = 1,687$ ) maintain an average of 5 complaint records annually (§ 1271.320(b)).

FDA estimates that under § 1271.420(a), 200 establishments will submit 560 reports of HCT/Ps offered for imports.

In the *Federal Register* of December 5, 2019 (84 FR 66673), we published a 60-day notice requesting public comment on the proposed collection of information. No comments were received.

We estimate the burden of the information collection as follows:

Table 1.--Estimated Annual Reporting Burden<sup>1</sup>

21 CFR Part 1271; Human Cells, Tissues, and Cellular and Tissue-Based Products	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours <sup>3</sup>
1271.10(b)(1) and 1271.21(b) <sup>2</sup>	2,736	1	2,736	0.5 (30 minutes)	1,368
1271.10(b)(1) and (2), 1271.21(a), and 1271.25(a) and (b) <sup>2</sup>	193	1	193	0.75 (45 minutes)	145
1271.10(b)(2), 1271.21(c)(2)(ii), and 1271.25(c) <sup>2</sup>	1,062	1	1,062	0.5 (30 minutes)	531
1271.23	1	1	1	1	1
1271.26 <sup>2</sup>	358	1	358	0.25 (15 minutes)	90
1271.155(a)	15	4.27	64	3	192
1271.350(a)(1) and (3)	13	14.46	188	1	188
1271.420(a)	200	2.8	560	0.25 (15 minutes)	140
Total					2,655

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

<sup>2</sup> Using eHCTERS.

<sup>3</sup> Rounded to the nearest whole number.

Table 2.--Estimated Annual Recordkeeping Burden<sup>1</sup>

21 CFR Part 1271; Human Cells, Tissues, and Cellular and Tissue-Based Products	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours <sup>3</sup>
New SOPs <sup>2</sup>	193	1	193	48	9,264
SOP Update <sup>2</sup>	2,736	1	2,736	24	65,664
1271.47(d)	1,368	1	1,368	1	1,368
1271.50(a)	2,736	39.846	109,019	5	545,095
1271.55(d)(1)	2,736	39.846	109,019	1	109,019
1271.55(d)(2)	2,736	1	2,736	1	2,736
1271.55(d)(4)	2,736	1	2,736	120	328,320
1271.60(d)(3) and (4); 1271.65(b)(3)(iii)	821	1	821	2	1,642
1271.155(f)	15	4.27	64	0.25 (15 minutes)	16
1271.160(b)(3) and (6)	2,109	12	25,308	1	25,308
1271.160(d)	2,109	12	25,308	1	25,308
1271.190(d)(2)	2,109	12	25,308	1	25,308

1271.195(d)	2,109	12	25,308	1	25,308
1271.200(e)	2,109	12	25,308	1	25,308
1271.210(d)	2,109	12	25,308	1	25,308
1271.230(a)	2,109	12	25,308	1	25,308
1271.230(c)	2,109	1	2,109	1	2,109
1271.260(d)	2,109	12	25,308	0.25 (15 minutes)	6,327
1271.260(e)	2,109	365	769,785	0.083 (5 minutes)	63,892
1271.265(c)(1)	2,109	1,163.781	2,454,415	0.083 (5 minutes)	203,716
1271.265(c)(3)	1,055	1	1,055	1	1,055
1271.265(e)	2,109	1,163.781	2,454,415	0.083 (5 minutes)	203,716
1271.270(a)	2,109	1,163.781	2,454,415	0.25 (15 minutes)	613,604
1271.270(e)	2,189	2	4,378	0.5 (30 minutes)	2,189
1271.290(d) and (e)	2,109	49.037	103,419	0.25 (15 minutes)	25,855
1271.320(b)	1,687	5	8,435	1	8,435
Total					2,371,178

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

<sup>2</sup> Sections 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).

<sup>3</sup> Rounded to the nearest whole number.

Table 3.--Estimated Annual Third-Party Disclosure Burden<sup>1</sup>

21 CFR Part 1271; Human Cells, Tissues, and Cellular and Tissue-Based Products	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
1271.55(a)	1,632	1,589.715	2,594,415	0.5 (30 minutes)	1,297,208
1271.60(c) and (d)(2)	1,611	355.06	572,000	0.5 (30 minutes)	286,000
1271.290(c)	2,109	1,163.781	2,454,415	0.083 (5 minutes)	203,716
1271.290(f)	2,109	1	2,109	1	2,109
1271.370(b) and (c)	2,109	1,163.781	2,454,415	0.25 (15 minutes)	613,604
Total					2,402,637

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

<sup>2</sup> Rounded to the nearest whole number.

Our estimated burden for the information collection reflects an overall increase of 628,585 hours (111 reporting burden hours; 305,118 recordkeeping hours; and 323,356 disclosure burden hours) and a corresponding increase of annual responses, annual records, and

annual disclosures. We attribute this adjustment to an increase in the number of HCT/P establishments and an increase in the number of HCT/Ps distributed over the past few years.

Dated: March 26, 2020.

**Lowell J. Schiller,**

*Principal Associate Commissioner for Policy.*

[FR Doc. 2020-06981 Filed: 4/2/2020 8:45 am; Publication Date: 4/3/2020]