4164-01-P

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 or we) 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: Fax written comments 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 faxed to the Office of Information and Regulatory Affairs, OMB, Attn: FDA Desk Officer, FAX: 202-395-7285, or emailed to oira_submission@omb.eop.gov. All comments should be identified with the OMB control number 0910-0543. Also include the FDA docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT: For specific questions for FDA related to this document, contact JonnaLynn Capezzuto, Office of Operations, Food and Drug Administration,

Three White Flint North, 10A63, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-3794.

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 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).

Establishment Registration and Listing; Form FDA 3356

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 described in § 1271.10(a), or that perform screening or testing of the cell or tissue donor to register with FDA (§ 1271.10(b)(1)) and submit a list of each HCT/P manufactured (§ 1271.10(b)(2)). Section 1271.21(a) requires an establishment to follow certain procedures for initial registration and listing of HCT/Ps, and § 1271.25(a) and (b) identifies 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 requires establishments to submit an amendment if ownership or location of the establishment changes. FDA requires the use of a registration and listing form, Form FDA 3356: Establishment Registration and Listing for Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), to submit the required information (§§ 1271.10, 1271.21, 1271.25, and 1271.26)). To further facilitate the ease and speed of submissions, electronic submission is accepted at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/EstablishmentRegistration/TissueEstablishmentRegistration/default.htm.

Form FDA 3356 is being revised as follows: (1) Adding import contact information including an e-mail address and phone number; (2) deleting columns related to HCT/Ps subject to registration and listing under 21 CFR part 207 or 807; and (3) revising the instructions accordingly. The estimated burden is not affected by these changes.

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 § 1271.90. The documented determination of a donor's eligibility is made by a responsible person as defined in § 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)). Certain records must accompany an HCT/P once the donor-eligibility determination has been made (§ 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). 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 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 a 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 (d)(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)), including the use of a product from a donor of viable, leukocyte-rich cells or tissue testing reactive for cytomegalovirus (§ 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)).

Current Good Tissue Practice

FDA requires HCT/P establishments to follow CGTP (§ 1271.1(b)). Section 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) 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 (a)(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) requires establishments to include specific information either on the HCT/P label or with the HCT/P.

The standard operating procedures (SOP) provisions under part 1271 include the following: (1) Section 1271.160(b)(2) (receiving, investigation, evaluating, and documenting information relating to core CGTP requirements, including complaints, 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) and (c) (validation of a process and review and evaluation of changes to a validated process); (7) § 1271.250(a) (controls for labeling HCT/Ps); (8) § 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) (records management system); (11) § 1271.290(b)(1) (system of HCT/P tracking); and (12) § 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) 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 § 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) 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 this 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) requires importers of HCT/Ps to notify 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, or perform donor screening or testing. The estimates provided 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 2,218 HCT/P establishments (conventional tissue, eye tissue, peripheral blood stem cell, stem cell products from cord blood, reproductive tissue, and sperm banks), including 667 manufacturers of HCT/P products 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 182 new establishments have registered with FDA (§§ 1271.10(b)(1) and (b)(2) and 1271.25(a) and (b)). There are an estimated 1,221 listing updates (§§ 1271.10(b)(2), 1271.21(c)(ii), and 1271.25(c)) and 588 location/ownership amendments (§ 1271.26).

Under § 1271.55(a), an estimated total of 2,206,890 HCT/Ps (which include conventional tissues, eye tissues, hematopoetic stem cells/progenitor cells, and reproductive cells and tissues), and an estimated total of 2,066,890 non-reproductive cells and tissues (total HCT/Ps minus reproductive cells and tissues) are distributed per year by an estimated 1,551 establishments (2,218 − 667 = 1,551) with approved applications).

Under § 1271.60(c) and (d)(2), FDA estimates that 1,375 establishments shipped an estimated 572,000 HCT/P under quarantine, and that an estimated 25 establishments requested 78 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 1,561 non-reproductive HCT/P establishments label each of their 2,066,890 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 34 HCT/P establishments submitted 166 adverse reaction reports with 136 involving a communicable disease (§ 1271.350(a)(1)).

FDA estimates that 182 new establishments will create SOPs, and that 2,218 establishments will review and revise existing SOPs annually.

FDA estimates that 1,109 HCT/P establishments (2,218 ×50 percent = 1,109) and 781 non-reproductive HCT/P establishments (1,561 ×50 percent = 781) 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 665 HCT/P establishments (2,218 × 30 percent = 665) 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 1,774 HCT/P establishments (2,218 × 80 percent = 1,774) have to maintain records for an average of 2 contract establishments to perform their manufacturing process (§ 1271.270(e) and 1,249 HCT/P establishments (1,561 × 80 percent = 1,249)) 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 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 on respondents.

In the Federal Register of September 7, 2016 (81 FR 61685), we published a 60-day notice requesting public comment on the proposed extension of this collection of information. One comment was received beyond the scope of the four information collection topics solicited and therefore we have not discussed it in this document.

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

Table 1--Estimated Annual Reporting Burden[1]

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours[3]
1271.10(b)(1) and 1271.21(b)[2]	2,218	1	2,218	.5 (30 minutes)	1,109

1271.10(b)(1) and (b)(2), 1271.21(a), and 1271.25(a) and (b)[2]	182	1	182	.75 (45 minutes)	137
1271.10(b)(2), 1271.21(c)(2)(ii) and 1271.25(c)[2]	1,221	1	1,221	.5 (30 minutes)	611
1271.26[2]	588	1	588	.25 (15 minutes)	147
1271.155(a)	25	3.12	78	3	234
1271.350(a)(1) and (a)(3)	34	4.88	166	1	166
1271.420(a)	200	2.8	560	.25 (15 minutes)	140
Total					2,544

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] Using Form FDA 3356.
[3] Rounded to the nearest whole number.

Table 2--Estimated Annual Recordkeeping Burden[1]

21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours[3]
New SOPs[2]	182	1	182	48	8,736
SOP Update[2]	2,218	1	2,218	24	53,232
1271.47(d)	1,109	1	1,109	1	1,109
1271.50(a)	2,218	49.15	109,019	5	545,095
1271.55(d)(1)	2,218	49.15	109,019	1	109,019
1271.55(d)(2)	2,218	1	2,218	1	2,218
1271.55(d)(4)	2,218	1	2,218	120	266,160
1271.60(d)(3) and (d)(4) 1271.65(b)(3)(iii)	665	1	665	2	1,330
1271.155(f)	25	3.12	78	.25 (15 minutes)	20
1271.160(b)(3) and (b)(6)	1,561	12	18,732	1	18,732
1271.160(d)	1,561	12	18,732	1	18,732
1271.190(d)(2)	1,561	12	18,732	1	18,732
1271.195(d)	1,561	12	18,732	1	18,732
1271.200(e)	1,561	12	18,732	1	18,732
1271.210(d)	1,561	12	18,732	1	18,732
1271.230(a)	1,561	12	18,732	1	18,732
1271.230(c)	1,561	1	1,561	1	1,561
1271.260(d)	1,561	12	18,732	.25 (15 minutes)	4,683
1271.260(e)	1,561	365	569,765	.083 (5 minutes)	47,291
1271.265(c)(1)	1,561	1,324.08	2,066,890	.083 (5 minutes)	171,552
1271.265(c)(3)	781	1	781	1	781
1271.265(e)	1,561	1,324.08	2,066,890	.083 (5 minutes)	171,552
1271.270(a)	1,561	1,324.08	2,066,890	.25	516,723

21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours[3]
				(15 minutes)	
1271.270(e)	1,774	2	3,548	.5 (30 minutes)	1,774
1271.290(d) and (e)	1,561	66.25	103,419	.25 (15 minutes)	25,855
1271.320(b)	1,249	5	6,245	1	6,245
Total					2,066,060

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] 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), 1271.265(e), 1271.265(f), 1271.270(b) and (d), 1271.290(b)(1), and 1271.320(a).
[3] Rounded to the nearest whole number.

Table 3--Estimated Annual Third-Party Disclosure Burden[1]

21 CFR Section	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
1271.55(a)	1,551	1,422.88	2,206,890	.5 (30 minutes)	1,103,445
1271.60(c) and (d)(2)	1,375	416	572,000	.5 (30 minutes)	286,000
1271.290(c)	1,561	1,324.08	2,066,890	.083 (5 minutes)	171,552
1271.290(f)	1,561	1	1,561	1	1,561
1271.370(b) and (c)	1,561	1,324.08	2,066,890	.25 (15 minutes)	516,723
Total					2,079,281

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

Dated: March 28, 2017.

Anna K. Abram,

Deputy Commissioner for Policy, Planning, Legislation, and Analysis.
[FR Doc. 2017-06398 Filed: 3/30/2017 8:45 am; Publication Date: 3/31/2017]