4164-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2017-N-6931]

Agency Information Collection Activities; Proposed Collection; Comment Request; Current Good Manufacturing Practices and Related Regulations for Blood and Blood Components; and Requirements for Donation Testing, Donor Notification, and "Lookback"

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA, Agency, or we) is announcing an opportunity for public comment on the proposed collection of certain information by the Agency. Under the Paperwork Reduction Act of 1995 (PRA), Federal agencies are required to publish notice in the *Federal Register* concerning each proposed collection of information, including each proposed extension of an existing collection of information, and to allow 60 days for public comment in response to the notice. This notice solicits comments on the collection of information requirements relating to FDA's regulation of current good manufacturing practice (CGMP) and related regulations for blood and blood components; and requirements for donation testing, donor notification, and "lookback".

DATES: Submit either electronic or written comments on the collection of information by [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*].

ADDRESSES: You may submit comments as follows. Please note that late, untimely filed comments will not be considered. Electronic comments must be submitted on or before [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. The https://www.regulations.gov electronic filing system will accept comments

until 11:59 p.m. Eastern Time at the end of [INSERT DATE 60 DAYS AFTER DATE OF PUBLICATION IN THE *FEDERAL REGISTER*]. Comments received by mail/hand delivery/courier (for written/paper submissions) will be considered timely if they are postmarked or the delivery service acceptance receipt is on or before that date.

Electronic Submissions

Submit electronic comments in the following way:

- Federal eRulemaking Portal: https://www.regulations.gov. Follow the instructions for submitting comments. Comments submitted electronically, including attachments, to https://www.regulations.gov will be posted to the docket unchanged. Because your comment will be made public, you are solely responsible for ensuring that your comment does not include any confidential information that you or a third party may not wish to be posted, such as medical information, your or anyone else's Social Security number, or confidential business information, such as a manufacturing process. Please note that if you include your name, contact information, or other information that identifies you in the body of your comments, that information will be posted on https://www.regulations.gov.
- If you want to submit a comment with confidential information that you do not wish to be made available to the public, submit the comment as a written/paper submission and in the manner detailed (see "Written/Paper Submissions" and "Instructions").

Written/Paper Submissions

Submit written/paper submissions as follows:

- Mail/Hand delivery/Courier (for written/paper submissions): Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852.

- For written/paper comments submitted to the Dockets Management Staff, FDA will post your comment, as well as any attachments, except for information submitted, marked and identified, as confidential, if submitted as detailed in "Instructions."

Instructions: All submissions received must include the Docket No. FDA-2017-N-6931 for "Current Good Manufacturing Practices and Related Regulations for Blood and Blood Components; and Requirements for Donation Testing, Donor Notification, and 'Lookback'." Received comments, those filed in a timely manner (see ADDRESSES), will be placed in the docket and, except for those submitted as "Confidential Submissions," publicly viewable at https://www.regulations.gov or at the Dockets Management Staff between 9 a.m. and 4 p.m., Monday through Friday, 240-402-7500.

- Confidential Submissions--To submit a comment with confidential information that you do not wish to be made publicly available, submit your comments only as a written/paper submission. You should submit two copies total. One copy will include the information you claim to be confidential with a heading or cover note that states "THIS DOCUMENT CONTAINS CONFIDENTIAL INFORMATION." The Agency will review this copy, including the claimed confidential information, in its consideration of comments. The second copy, which will have the claimed confidential information redacted/blacked out, will be available for public viewing and posted on https://www.regulations.gov. Submit both copies to the Dockets Management Staff. If you do not wish your name and contact information to be made publicly available, you can provide this information on the cover sheet and not in the body of your comments and you must identify this information as "confidential." Any information marked as "confidential" will not be disclosed except in accordance with 21 CFR 10.20 and other applicable disclosure law. For more information about FDA's posting of comments to public dockets, see 80 FR 56469, September 18, 2015, or access the information at: https://www.govinfo.gov/content/pkg/FR-2015-09-18/pdf/2015-23389.pdf.

Docket: For access to the docket to read background documents or the electronic and written/paper comments received, go to https://www.regulations.gov and insert the docket number, found in brackets in the heading of this document, into the "Search" box and follow the prompts and/or go to the Dockets Management Staff, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852, 240-402-7500.

FOR FURTHER INFORMATION CONTACT: Amber Sanford, Office of Operations, Food and Drug Administration, Three White Flint North, 10A-12M, 11601 Landsdown St., North Bethesda, MD 20852, 301-796-8867, PRAStaff@fda.hhs.gov.

SUPPLEMENTARY INFORMATION: Under the PRA (44 U.S.C. 3501-3521), Federal Agencies must obtain approval from the Office of Management and Budget (OMB) for each collection of information they conduct or sponsor. "Collection of information" is defined in 44 U.S.C. 3502(3) and 5 CFR 1320.3(c) and includes Agency requests or requirements that members of the public submit reports, keep records, or provide information to a third party. Section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)) requires Federal Agencies to provide a 60-day notice in the *Federal Register* concerning each proposed collection of information, including each proposed extension of an existing collection of information, before submitting the collection to OMB for approval. To comply with this requirement, FDA is publishing notice of the proposed collection of information set forth in this document.

With respect to the following collection of information, FDA invites comments on these topics: (1) whether the proposed collection of information is necessary for the proper performance of FDA's functions, including whether the information will have practical utility; (2) the accuracy of FDA's estimate of the burden of the proposed collection of information, including the validity of the methodology and assumptions used; (3) ways to enhance the quality, utility, and clarity of the information to be collected; and (4) ways to minimize the burden of the collection of information on respondents, including through the use of automated collection techniques, when appropriate, and other forms of information technology.

Current Good Manufacturing Practices and Related Regulations for Blood and Blood Components; and Requirements for Donation Testing, Donor Notification, and "Lookback"

OMB Control Number 0910-0116-Extension

This information collection supports Agency regulations. All blood and blood components introduced or delivered for introduction into interstate commerce are subject to section 351(a) of the Public Health Service Act (PHS Act) (42 U.S.C. 262(a)). Section 351(a) requires that manufacturers of biological products, which include blood and blood components intended for further manufacturing into products, have a license, issued upon a demonstration that the product is safe, pure, and potent and that the manufacturing establishment meets all applicable standards, including those prescribed in the FDA regulations designed to ensure the continued safety, purity, and potency of the product. In addition, under section 361 of the PHS Act (42 U.S.C. 264), by delegation from the Secretary of Health and Human Services, FDA may make and enforce regulations necessary to prevent the introduction, transmission, or spread of communicable diseases from foreign countries into the States or possessions, or from one State or possession into any other State or possession.

Section 351(j) of the PHS Act states that the Federal Food, Drug, and Cosmetic Act (FD&C Act) also applies to biological products. Blood and blood components for transfusion or for further manufacturing into products are drugs, as that term is defined in section 201(g)(1) of the FD&C Act (21 U.S.C. 321(g)(1)). Because blood and blood components are drugs under the FD&C Act, blood and plasma establishments must comply with the provisions and related regulatory scheme of the FD&C Act. For example, under section 501 of the FD&C Act (21 U.S.C. 351(a)), drugs are deemed "adulterated" if the methods used in their manufacturing, processing, packing, or holding do not conform to CGMP and related regulations.

The CGMP regulations (part 606) (21 CFR part 606) and related regulations implement FDA's statutory authority to ensure the safety, purity, and potency of blood and blood components. The public health objective in testing human blood donations for evidence of

relevant transfusion-transmitted infections and in notifying donors is to prevent the transmission of relevant transfusion-transmitted infections. For example, the "lookback" requirements are intended to help ensure the continued safety of the blood supply by providing necessary information to consignees of blood and blood components and appropriate notification of recipients of blood components that are at increased risk for transmitting human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection.

The information collection requirements in the CGMP, donation testing, donor notification, and "lookback" regulations provide FDA with the necessary information to perform its duty to ensure the safety, purity, and potency of blood and blood components. These requirements establish accountability and traceability in the processing and handling of blood and blood components and enable FDA to perform meaningful inspections.

The recordkeeping requirements serve preventive and remedial purposes. The third-party disclosure requirements identify various blood and blood components and important properties of the product, demonstrate that the CGMP requirements have been met, and facilitate the tracing of a product back to its original source. The reporting requirements inform FDA's Center for Biologics Evaluation and Research (CBER) of certain information that may require immediate corrective action.

Respondents to this collection of information are licensed and unlicensed blood establishments that collect blood and blood components, including Source Plasma and Source Leukocytes, inspected by FDA, and transfusion services inspected by Centers for Medicare and Medicaid Services (CMS). Based on information received from CBER's database systems, there are approximately 864 licensed Source Plasma establishments and approximately 1,789 licensed blood collection establishments, for an estimated total of 2,653 (864 +1,789) licensed blood collection establishments. Also, there are an estimated total of 817 unlicensed, registered blood collection establishments for an approximate total of 3,470 collection establishments (864 + 1,789 + 817 = 3,470 establishments). Of these establishments, approximately 856 perform

plateletpheresis (777) and leukapheresis (79). These establishments annually collect approximately 73.7 million units of Whole Blood and blood components, including Source Plasma and Source Leukocytes, and are required to follow FDA "lookback" procedures. In addition, there are another estimated 4,961 establishments that fall under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) (formerly referred to as facilities approved for Medicare reimbursement) that transfuse blood and blood components.

The following reporting and recordkeeping estimates are based on information provided by industry, CMS, and FDA experience. Based on information from industry, we estimate that there are approximately 53.5 million donations of Source Plasma from approximately 2.5 million donors and approximately 12.3 million donations of Whole Blood and apheresis Red Blood Cells including approximately 10,000 (approximately 0.081 percent of 12.3 million) autologous donations, from approximately 9 million donors. Assuming each autologous donor makes an average of 1.1 donations, FDA estimates that there are approximately 9,090 autologous donors (10,000 autologous/1.1 average donations).

FDA estimates that approximately 0.53 percent (56,000 ÷ 10,654,000) of the 77,000 donations that are donated specifically for the use of an identified recipient would be tested under the dedicated donors' testing provisions in § 610.40(c)(1)(ii).

Under §§ 610.40(g)(2) and (h)(2)(ii)(A), Source Leukocytes, a licensed product that is used in the manufacture of interferon, which requires rapid preparation from blood, is currently shipped prior to completion of testing for evidence of relevant transfusion-transmitted infections. Shipments of Source Leukocytes are approved under a biologics license application and each shipment does not have to be reported to the Agency. Based on information from CBER's database system, FDA receives less than one application per year from manufacturers of Source Leukocytes. However, for calculation purposes, we are estimating one application annually.

According to CBER's database system, there are approximately 15 licensed manufacturers that ship known reactive human blood or blood components under

§§ 610.40(h)(2)(ii)(C) and (D). FDA estimates that each manufacturer would ship an estimated 1 unit of human blood or blood components per month (12 per year) that would require two labels; one as reactive for the appropriate screening test under § 610.40(h)(2)(ii)(C), and the other stating the exempted use specifically approved by FDA under § 610.40(h)(2)(ii)(D).

Based on information received from industry, we estimate that approximately 7,500 donations that test reactive by a screening test for syphilis and are determined to be biological false positives by additional testing annually. These units would be labeled according to § 610.40(h)(2)(vi).

Human blood or a blood component with a reactive screening test, as a component of a medical device, is an integral part of the medical device, e.g. a positive control for an in vitro diagnostic testing kit. It is usual and customary business practice for manufacturers to include on the container label a warning statement indicating that the product was manufactured from a donation found to be reactive for the identified relevant transfusion-transmitted infection(s). In addition, on the rare occasion when a human blood or blood component with a reactive screening test is the only component available for a medical device that does not require a reactive component, then a warning statement must be affixed to the medical device. To account for this rare occasion under § 610.42(a), we estimate that the warning statement would be necessary no more than once a year.

FDA estimates that approximately 3,100 repeat donors will test reactive on a screening test for HIV. We also estimate that an average of three components was made from each donation. Under §§ 610.46(a)(1)(ii)(B) and (a)(3), this estimate results in 9,300 (3,100 × 3) notifications of the HIV screening test results to consignees by collecting establishments for the purpose of quarantining affected blood and blood components, and another 9,300 (3,100 × 3) notifications to consignees of subsequent test results.

We estimate that approximately 4,961 consignees will be required under § 610.46(b)(3) to notify transfusion recipients, their legal representatives, or physicians of record an average of

0.35 times per year resulting in a total number of 1,755 (585 confirmed positive repeat donors × 3) notifications. Also, under § 610.46(b)(3), we estimate and include the time to gather test results and records for each recipient and to accommodate multiple attempts to contact the recipient.

Furthermore, we estimate that approximately 6,800 repeat donors per year would test reactive for antibody to HCV. Under §§ 610.47(a)(1)(ii)(B) and 610.47(a)(3), collecting establishments would notify the consignee 2 times for each of the 20,400 (6,800 × 3 components) components prepared from these donations, once for quarantine purposes and again with additional HCV test results for a total of 40,800 (2 × 20,400) notifications as an annual ongoing burden. Under § 610.47(b)(3), we estimate that approximately 4,961 consignees would notify approximately 2,050 recipients or their physicians of record annually.

Based on industry estimates, approximately 18.15 percent of approximately 14,018,000 million potential donors (2,544,000 donors) who come to donate annually are determined not to be eligible for donation prior to collection because of failure to satisfy eligibility criteria. It is the usual and customary business practice of approximately 2,606 (1,789 + 817) blood collecting establishments to notify onsite and to explain why the donor is determined not to be suitable for donating. Based on such available information, we estimate that two-thirds (1,737) of the 2,606 blood collecting establishments provided onsite additional information and counseling to a donor determined not to be eligible for donation as usual and customary business practice. Consequently, we estimate that only approximately one-third, or 869 of the 2,606 blood collecting establishments would need to provide, under § 630.40(a), additional information and onsite counseling to the estimated 848,000 (one-third of approximately 2,544,000) ineligible donors.

It is estimated that another 0.6 percent of 14,018,000 potential donors (84,108 donors) are deferred annually based on test results. We estimate that approximately 95 percent of the establishments that collect 99 percent of the blood and blood components notify donors who

have reactive test results for HIV, Hepatitis B Virus, HCV, Human T-Lymphotropic Virus, and syphilis as usual and customary business practice. Consequently, 5 percent of the 2,653 licensed establishments (133) collecting 1 percent (841) of the deferred donors (84,108) would notify donors under § 630.40(a).

As part of usual and customary business practice, collecting establishments notify an autologous donor's referring physician of reactive test results obtained during the donation process required under § 630.40(d)(1). However, we estimate that approximately 5 percent of the 1,789 blood collection establishments (89) may not notify the referring physicians of the estimated 2 percent of 10,000 autologous donors with the initial reactive test results (200) as their usual and customary business practice.

The recordkeeping chart reflects the estimate that approximately 95 percent of the recordkeepers, which collect 99 percent of the blood supply, have developed standard operating procedures (SOPs) as part of their customary and usual business practice. Establishments may minimize burdens associated with CGMP and related regulations by using model standards developed by industries' accreditation organizations. These accreditation organizations represent almost all registered blood establishments.

Under § 606.160(b)(1)(ix), we estimate the total annual records based on the approximately 2,544,000 donors determined not to be eligible to donate and each of the estimated 2,628,108 (2,544,000 + 84,108) donors deferred based on reactive test results for evidence of infection because of relevant transfusion-transmitted infections. Under § 606.160(b)(1)(xi), only the 1,789 registered blood establishments collect autologous donations and, therefore, are required to notify referring physicians. We estimate that 4.5 percent of the 9,090 autologous donors (409) will be deferred under § 610.41, which in turn will lead to the notification of their referring physicians.

Under § 610.41(b), FDA estimates that there would be 25 submissions for requalification of donors each requiring 7 hours per submission. In addition, FDA estimates that there would be

only 3 notifications for requalification of donors under § 630.35(b) which would also require 7 hours for each submission.

FDA permits the shipment of untested or incompletely tested human blood or blood components in rare medical emergencies and when appropriately documented (§ 610.40(g)(1)). We estimate the recordkeeping under § 610.40(g)(1) to be minimal with one or fewer occurrences per year. The reporting of test results to the consignee in § 610.40(g) is part of the usual and customary business practice of blood establishments.

The average burden per response (hours) and average burden per recordkeeping (hours) are based on estimates received from industry or FDA experience with similar reporting or recordkeeping requirements.

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

Table 1.--Estimated Annual Reporting Burden[1]

21 CFR Section; Activity	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
606.170(b)[2]; Donor or recipient fatality reporting	81	1	81	20	1,620
610.40(g)(2); Application for approval to ship	1	1	1	1	1
610.41(b); Request for requalification of donor	2,653	0.0094	25	7	175
610.40(h)(2)(ii)(A); Application for approval for shipment or use	1	1	1	1	1
630.35(b); Request for requalification of donor	2,653	0.00113	3	7	21
Total					1,818

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] The reporting requirement in § 640.73, which addresses the reporting of fatal donor reactions, is included in the estimate for § 606.170(b).

Table 2. -Estimated Annual Recordkeeping Burden[1]

21 CFR Section; Activity	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
606.100(b)[2]; Maintenance of SOPs	422[5]	1	422	24	10,128
606.100(c); Records of investigations	422[5]	10	4,220	1	4,220
606.110(a)[3]; Documentation donor's health permits plateletpheresis or leukapheresis	43[6]	1	43	0.5 (30 minutes)	22
606.151(e); Records of emergency transfusions	422[5]	12	5,064	0.08 (5 minutes)	405
606.160[4]; Records of collection, processing,	422[5]	907.583	383,000	0.75 (45 minutes)	287,250

compatibility testing, storage, and distribution of each unit of blood and blood components					
606.160(b)(1)(viii); HIV consignee notification	1,789 4,961	10.4533 3.6537	18,701 18,126	0.17 (10 minutes) 0.17 (10 minutes)	3,179 3,081
606.160(b)(1)(viii); HCV consignee notification	1,789 4,961	22.8060 8.2241	40,800 40,800	0.17 (10 minutes) 0.17 (10 minutes)	6,936 6,936
HIV recipient notification	4,961	0.3538	1,755	0.17 (10 minutes)	298
HCV recipient notification	4,961	0.4132	2,050	0.17 (10 minutes)	349
606.160(b)(1)(ix); Donor notification records	3,470	757.380	2,628,109	0.05 (3 minutes)	131,405
606.160(b)(1)(xi); Physician notification records	1,789	0.2286	409	0.05 (3 minutes)	20.5
606.165; Distribution and receipt records	422[5]	907.583	383,000	0.08 (5 minutes)	30,640
606.170(a); Adverse reaction records	422[5]	12	5,064	1	5,064
610.40(g)(1); Documentation of medical emergency	3,470	1	3,470	0.5 (30 minutes)	1,735
630.15(a)(1)(ii)(B); Documentation required for dedicated donation	1,789	1	1,789	1	1,789
630.20(c); Documentation of exceptional medical need	1,789	1	1,789	1	1,789
Total					495,247

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] The recordkeeping requirements in §§ 606.171, 630.5(d), 630.10(c)(1) and (2), and 640.66, which address the maintenance of SOPs, are included in the estimate for § 606.100(b).
[3] The recordkeeping requirements in § 640.27(b), which address the maintenance of donor health records for the plateletpheresis, are included in the estimate for § 606.110(a).
[4] The recordkeeping requirements in §§ 606.110(a)(2), 630.5(b)(1)(i), 630.10(f)(2) and (4), 630.10(g)(2)(i), 630.15(a)(1)(ii)(A) and (B), 630.15(b)(2), (b)(7)(i) and (iii), 630.20(a) and (b), 640.21(e)(4), 640.25(b)(4) and (c)(1), 640.31(b), 640.33(b), 640.51(b), 640.53(b) and (c), 640.56(b) and (d), 630.15(b)(2), 640.65(b)(2)(i), 640.65(b)(2)(i), 640.71(b)(1), 640.72, 640.73, and 640.76(a) and (b), which address the maintenance of various records are included in the estimate for § 606.160.
[5] Five percent of establishments that fall under CLIA that transfuse blood and components and FDA-registered blood establishments (0.05 × 4,961 + 3,470 = 422).
[6] Five percent of plateletpheresis and leukapheresis establishments (0.05 × 856 = 43).

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

21 CFR Section; Activity	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
606.145(c); Notification of bacterial contamination of platelets	4,961	0.2822	1,400	0.02 (90 seconds)	28
606.170(a); Reports of transfusion reaction	422[2]	12	5,064	0.5 (30 minutes)	2,532
610.40(c)(1)(ii); Labeling of donation dedicated to single recipient	3,470	0.0395	137	0.08 (5 minutes)	11
610.40(h)(2)(ii)(C) and (D); Labeling of reactive	15	12	180	0.2 (12 minutes)	36

blood and blood components					
610.40(h)(2)(vi); Labeling of reactive blood and blood components	3,470	2.1614	7,500	0.08 (5 minutes)	600
610.42(a); Warning statement for medical devices	1	1	1	1	1
610.46(a)(1)(ii)(B); Notification to consignees to quarantine (HIV "lookback")	1,789	5.1984	9,300	0.17 (10 minutes)	1,581
610.46(a)(3); Notification to consignees of further testing	1,789	5.1984	9,300	0.17 (10 minutes)	1,581
610.46(b)(3); Notification to recipients	4,961	0.3528	1,750	1	1,750
610.47(a)(1)(ii)(B); Notification to consignees to quarantine (HCV "lookback")	1,789	11.4030	20,400	0.17 (10 minutes)	3,468
610.47(a)(3); Notification to consignees of further testing	1,789	11.4030	20,400	0.17 (10 minutes)	3,468
610.47(b)(3); Notification to recipients	4,961	0.4132	2,050	1	2,050
630.40(a); Notification of donors determined not to be eligible for donation	869	975.834	848,000	0.08 (5 minutes)	67,840
630.40(a); Notification of donors deferred based on reactive test results	133	6.323	841	1.5	1,262
630.40(d)(1); Notification to physician of autologous donor	89	2.247	200	1	200
Total					86,408

[1] There are no capital costs or operating and maintenance costs associated with this collection of information.
[2] Five percent of establishments that fall under CLIA that transfuse blood and components and FDA-registered blood establishments (0.05 × 4,961 + 3,470 = 422).

The burden for this information collection has changed since the last OMB approval. FDA estimates that the total burden for this collection will be 583,473 hours (1,818 reporting + 495,247 recordkeeping + 86,408 third-party disclosure). Our estimated burden for the information collection reflects an overall increase of 79,024 hours. We attribute this adjustment to an increase in the number of blood establishments during the last 3 years.

Dated: February 10, 2021.

Lauren K. Roth,

Acting Principal Associate Commissioner for Policy.

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