4160-01-P

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. FDA-2011-N-0511]

Agency Information Collection Activities; Submission for Office of Management and Budget Review; Comment Request; Current Good Manufacturing Practices and Related Regulations for Blood and Blood Components; and Requirements for Donor Testing, Donor Notification, and "Lookback"

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: 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 0910-0116. Also include the FDA docket number found in brackets in the heading of this document.

FOR FURTHER INFORMATION CONTACT:

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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.

Current Good Manufacturing Practices and Related Regulations for Blood and Blood Components; and Requirements for Donor Testing, Donor Notification, and "Lookback"--(OMB Control Number 0910-0116)--Extension

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). Section 351(a) of the PHS Act requires that manufacturers of biological products, which include blood and blood components intended for further manufacture into injectable 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 also applies to biological products. Blood and blood components for transfusion or for further manufacture into injectable products are drugs, as that term is defined in section 201(g)(1) of the Federal, Food, Drug, and Cosmetics Act (21 U.S.C. 321(g)(1)). Because blood and blood components are drugs under the Federal, Food, Drug, and Cosmetics Act, blood and plasma establishments must comply with the substantive provisions and related regulatory scheme of the act. For example, under section 501 of the Federal, Food, Drug, and Cosmetic 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 current good manufacturing practice (CGMP) and related regulations.

The CGMP regulations in 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 donors for evidence of infection due to communicable disease agents and in notifying donors is to prevent the transmission of communicable disease. For example, the "lookback" requirements are intended to help ensure the continued safety of the blood supply by providing necessary information to users of blood and blood components and appropriate notification of recipients of transfusion who are at increased risk for transmitting human immunodeficiency virus (HIV) or hepatitis C virus (HCV) infection.

The information collection requirements in the CGMP, donor 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 disclosure requirements identify the 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 of certain information that may require immediate corrective action.

Under the reporting requirements, § 606.170(b), in brief, requires that facilities notify FDA's Center for Biologics Evaluation and Research (CBER), as soon as possible after confirming a complication of blood collection or transfusion to be fatal. The collecting facility is to report donor fatalities, and the compatibility testing facility is to report recipient fatalities. The regulation also requires the reporting facility to submit a written report of the investigation within 7 days after the fatality. In fiscal year 2010, FDA received 76 of these reports.

Section 610.40(c)(1)(ii) in part 610 (21 CFR part 610), in brief, requires that each donation dedicated to a single identified recipient be labeled as required under § 606.121 and with a label containing the name and identifying information of the recipient.

Section 610.40(g)(2) requires an establishment to obtain written approval from FDA to ship human blood or blood components for further manufacturing use prior to completion of testing for evidence of infection due to certain communicable disease agents.

Section 610.40(h)(2)(ii)(A), in brief, requires an establishment to obtain written approval from FDA to use or ship human blood or blood components found to be reactive by a screening test for evidence of certain communicable disease agent(s) or collected from a donor with a record of a reactive screening test. Furthermore, §§ 610.40(h)(2)(ii)(C) and (h)(2)(ii)(D), in

brief, require an establishment to label certain reactive human blood and blood components with the appropriate screening test results, and, if they are intended for further manufacturing use into injectable products, to include a statement on the label indicating the exempted use specifically approved by FDA. Finally, § 610.40(h)(2)(vi) requires each donation of human blood or blood components, excluding Source Plasma, that tests reactive by a screening test for syphilis and is determined to be a biological false positive to be labeled with both test results.

Section 610.42(a) requires a warning statement "indicating that the product was manufactured from a donation found to be reactive by a screening test for evidence of infection due to the identified communicable disease agent(s)" in the labeling for medical devices containing human blood or a blood component found to be reactive by a screening test for evidence of infection due to a communicable disease agent(s) or syphilis.

In brief, §§ 610.46 and 610.47 require blood collecting establishments to establish, maintain, and follow an appropriate system for performing HIV and HCV prospective "lookback" when: (1) A donor tests reactive for evidence of HIV or HCV infection; or (2) the collecting establishment becomes aware of other reliable test results or information indicating evidence of HIV or HCV infection ("prospective lookback") (see §§ 610.46(a)(1) and 610.47(a)(1)). The requirement for "an appropriate system" requires the collecting establishment to design standard operating procedures (SOPs) to identify and quarantine all blood and blood components previously collected from a donor who later tests reactive for evidence of HIV or HCV infection, or when the collecting establishment is made aware of other reliable test results or information indicating evidence of HIV or HCV infection. Within 3 calendar days of the donor testing reactive by an HIV or HCV screening test or the collecting establishment becoming aware of other reliable test results or information, the collecting establishment must, among other

things, notify consignees to quarantine all identified previously collected in-date blood and blood components (§§ 610.46(a)(1)(ii)(B) and 610.47(a)(1)(ii)(B)) and, within 45 days, notify the consignees of supplemental test results, or the results of a reactive screening test if there is no available supplemental test that is approved for such use by FDA (§§ 610.46(a)(3) and 610.47(a)(3)).

Consignees also must establish, maintain, and follow an appropriate system for performing HIV and HCV "lookback" when notified by the collecting establishment that they have received blood and blood components previously collected from donors who later tested reactive for evidence of HIV or HCV infection, or when the collecting establishment is made aware of other reliable test results or information indicating evidence of HIV or HCV infection in a donor (§§ 610.46(b) and 610.47(b)). This provision for a system requires the consignee to establish SOPs (standard operating procedures) for, among other things, notifying transfusion recipients of blood and blood components, or the recipient's physician of record or legal representative, when such action is indicated by the results of the supplemental (additional, more specific) tests or a reactive screening test if there is no available supplemental test that is approved for such use by FDA, or if under an investigational new drug application (IND) or an investigational device exemption (IDE), is exempted for such use by FDA. The consignee must make reasonable attempts to perform the notification within 12 weeks of receipt of the supplemental test result or receipt of a reactive screening test result when there is no available supplemental test that is approved for such use by FDA, or if under an IND or IDE, is exempted for such use by FDA (§§ 610.46(b)(3) and 610.47(b)(3)).

Section 630.6(a) (21 CFR 630.6(a)) requires an establishment to make reasonable attempts to notify any donor who has been deferred as required by § 610.41, or who has been

determined not to be eligible as a donor. Section 630.6(d)(1) requires an establishment to provide certain information to the referring physician of an autologous donor who is deferred based on the results of tests as described in § 610.41.

Under the recordkeeping requirements, § 606.100(b), in brief, requires that written SOPs be maintained for all steps to be followed in the collection, processing, compatibility testing, storage, and distribution of blood and blood components used for transfusion and further manufacturing purposes. Section 606.100(c) requires the review of all records pertinent to the lot or unit of blood prior to release or distribution. Any unexplained discrepancy or the failure of a lot or unit of final product to meet any of its specifications must be thoroughly investigated, and the investigation, including conclusions and followup, must be recorded.

In brief, § 606.110(a) provides that the use of plateletpheresis and leukaphesis procedures to obtain a product for a specific recipient may be at variance with the additional standards for that specific product if, among other things, the physician certifies in writing that the donor's health permits plateletpheresis or leukapheresis. Section 606.110(b) requires establishments to request prior approval from CBER for plasmapheresis of donors who do not meet donor requirements. The information collection requirements for § 606.110(b) are approved under OMB control number 0910-0338 and, therefore, are not reflected in tables 1 and 2 of this document.

Section 606.151(e) requires that SOPs for compatibility testing include procedures to expedite transfusion in life-threatening emergencies; records of all such incidents must be maintained, including complete documentation justifying the emergency action, which must be signed by a physician.

So that each significant step in the collection, processing, compatibility testing, storage, and distribution of each unit of blood and blood components can be clearly traced, § 606.160 requires that legible and indelible contemporaneous records of each such step be made and maintained for no less than 10 years. Section 606.160(b)(1)(viii) requires records of the quarantine, notification, testing and disposition performed under the HIV and HCV "lookback" provisions. Furthermore, § 606.160(b)(1)(ix) requires a blood collection establishment to maintain records of notification of donors deferred or determined not to be eligible for donation, including appropriate followup. Section 606.160(b)(1)(xi) requires an establishment to maintain records of notification of the referring physician of a deferred autologous donor, including appropriate followup.

Section 606.165 (21 CFR 606.165), in brief, requires that distribution and receipt records be maintained to facilitate recalls, if necessary.

Section 606.170(a) requires records to be maintained of any reports of complaints of adverse reactions arising as a result of blood collection or transfusion. Each such report must be thoroughly investigated, and a written report, including conclusions and followup, must be prepared and maintained. When an investigation concludes that the product caused the transfusion reaction, copies of all such written reports must be forwarded to and maintained by the manufacturer or collecting facility.

Section 610.40(g)(1) requires an establishment to appropriately document a medical emergency for the release of human blood or blood components prior to completion of required testing.

In addition to the CGMP regulations in part 606, there are regulations in part 640 (21 CFR part 640) that require additional standards for certain blood and blood components as follows: Sections 640.3(a)(1), (a)(2), and (f); 640.4(a)(1) and (a)(2); 640.25(b)(4) and (c)(1); 640.27(b); 640.31(b); 640.33(b); 640.51(b); 640.53(b) and (c); 640.56(b) and (d); 640.61; 640.63(b)(3), (e)(1), and (e)(3); 640.65(b)(2); 640.66; 640.71(b)(1); 640.72; 640.73; and 640.76(a) and (b). The information collection requirements and estimated burdens for these regulations are included in the part 606 burden estimates, as described in tables 1 and 2 of this document.

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 other transfusion services inspected by Centers for Medicare and Medicaid Services (CMS). Based on information received from CBER's database systems, there are approximately 31 licensed Source Plasma establishments with multiple locations and approximately 1,675 registered blood collection establishments, for an estimated total of 1,706 establishments. Of these establishments, approximately 1,032 perform plateletpheresis and leukopheresis. These establishments annually collect approximately 38.3 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 4,059 establishments that fall under the Clinical Laboratory Improvement Amendments of 1988 (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 received from industry, we

estimate that there are approximately 21 million donations of Source Plasma from approximately 2 million donors and approximately 17.3 million donations of Whole Blood, including approximately 261,000 (approximately 1.5 percent of 17.3 million) autologous donations, from approximately 10.9 million donors. Assuming each autologous donor makes an average of 2 donations, FDA estimates that there are approximately 130,500 autologous donors.

FDA estimates that approximately 5 percent (3,600 of the 72,000 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 certain communicable disease agents. Shipments of Source Leukocytes are pre-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.

Under §§ 610.40(h)(2)(ii)(C) and (h)(2)(ii)(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). According to CBER's database system, there are approximately 40 licensed manufacturers that ship known reactive human blood or blood components.

Based on information we received from industry, we estimate that approximately 18,000 donations: (1) Annually test reactive by a screening test for syphilis; (2) are determined to be

biological false positives by additional testing; and (3) are labeled accordingly (§ 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 that identifies the communicable disease agent. 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 3,500 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 10,500 (3,500 x 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 10,500 (3,500 x 3) notifications to consignees of subsequent test results. We estimate an average of 10 minutes per notification of consignees.

We estimate that § 610.46(b)(3) will require 4,059 consignees 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 x 3) notifications. Under § 610.46(b)(3), we also estimate 1 hour to accommodate 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 7,800 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 23,400 (7,800 x 3 components) components prepared from these donations, once for quarantine purposes and again with additional HCV test results for a total of 46,800 notifications as an annual ongoing burden. Under § 610.47(b)(3), we estimate that approximately 4,059 consignees would notify approximately 2,050 recipients or their physicians of record annually. Finally, we estimate 1 hour to complete notification.

Based on industry estimates, approximately 13 percent of approximately 10 million potential donors (1.3 million 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 1,675 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 (1,117) of the 1,675 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 one-third, or 558, approximately, blood collecting establishments would need to provide, under § 630.6(a), additional information and onsite counseling to the estimated 433,000 (one-third of approximately 1.3 million) ineligible donors.

It is estimated that another 4.5 percent of 10 million potential donors (450,000 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 (HBV), HCV, Human T-Lymphotropic Virus (HTLV), and syphilis as usual and customary business practice. Consequently, 5 percent

of the 1,706 establishments (85) collecting 1 percent (4,500) of the deferred donors (450,000) would notify donors under § 630.6(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 § 630.6(d)(1). However, we estimate that approximately 5 percent of the 1,675 blood collection establishments (84) may not notify the referring physicians of the estimated 2 percent of 130,500 autologous donors with the initial reactive test results (2,610) 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 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 1.3 million donors determined not to be eligible to donate and each of the estimated 1.75 million (1.3 million + 450,000) donors deferred based on reactive test results for evidence of infection because of communicable disease agents. Under § 606.160(b)(1)(xi), only the 1,675 registered blood establishments collect autologous donations and, therefore, are required to notify referring physicians. We estimate that 4.5 percent of the 130,500 autologous donors (5,872) will be deferred under § 610.41, which in turn will lead to the notification of their referring physicians.

FDA has concluded that the use of untested or incompletely tested but appropriately documented human blood or blood components in rare medical emergencies should not be prohibited. 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) does not create a new burden for respondents because it is the usual and customary business practice or procedure to finish the testing and provide the results to the manufacturer responsible for labeling the blood products.

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

In the Federal Register of July 28, 2011 (76 FR 45262), FDA published a 60-day notice requesting public comment on the proposed collection of information. No comments were received.

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

Table 1.--Estimated Annual Reporting Burden

21 CFR Section	No. of Respondents	No. of Responses per Respondent	Total Annual Responses	Average Burden per Response	Total Hours
606.170(b)[1]	76	1	76	20	1,520
610.40(g)(2)	1	1	1	1	1
610.40(h)(2)(ii)(A)	1	1	1	1	1
Total					1,522

[1] 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

21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
606.100(b)[1]	288[4]	1.20	346	24	6,912
606.100(c)	288[4]	10	2,880	1	2,880
606.110(a)[2]	52[5]	1	52	0.50 (30 min.)	26
606.151(e)	288[4]	12	3,456	0.08 (5 min.)	276
606.160[3]	288[4]	1,329.86	383,000	0.75 (45 min.)	287,250
606.160(b)(1)(viii)					
HIV consignee notification	1,675 4,059	12.54 5.17	21,000 21,000	.17 (10 min.) 3,570 .17 (10 min.)	3,570 3,570
HCV consignee notification	1,675 4,059	27.94 11.53	46,800 46,800	.17 (10 min.) .17 (10 min.)	7,956 7,956
HIV recipient notification	4,059	0.43	1,755	.17 (10 min.)	298
HCV recipient notification	4,059	0.51	2,050	.17 (10 min.)	349
606.160(b)(1)(ix)	1,706	1,025.79	1,750,000	0.05 (3 min.)	87,500
606.160(b)(1)(xi)	1,675	3.51	5,872	0.05 (3 min.)	294
606.165	288[5]	1,329.86	383,000	0.08 (5 min.)	30,640
606.170(a)	288[5]	12	3,456	1	3,456
610.40(g)(1)	1,706	1	1,706	0.50 (30 min.)	853
Total					443,786

[1] The recordkeeping requirements in §§ 640.3(a)(1), 640.4(a)(1), and 640.66, which address the maintenance of SOPs, are included in the estimate for § 606.100(b).

[2] 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).

[3] The recordkeeping requirements in §§ 640.3(a)(2) and (f); 640.4(a)(2); 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); 640.61; 640.63(b)(3), (e)(1), and (e)(3); 640.65(b)(2); 640.71(b)(1); 640.72; and 640.76(a) and (b), which address the maintenance of various records are included in the estimate for § 606.160.

[4] Five percent of establishments that fall under the Clinical Laboratory Improvement Amendments of 1988 that transfuse blood and components and FDA-registered blood establishments (0.05 x 4,059 + 1,706).

[5] Five percent of plateletpheresis and leukopheresis establishments (0.05 x 1,032).

Table 3.--Estimated Annual Third-Party Disclosure Burden

21 CFR Section	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure	Total Hours
606.170(a)	288[1]	1.20	346	0.50 (30 min.)	173
610.40(c)(1)(ii)	1,706	2.11	3,600	0.08 (5 min.)	288
610.40(h)(2)(ii)(C) and (h)(2)(ii)(D)	40	12	480	0.20 (12 min.)	96
610.40(h)(2)(vi)	1,706	10.55	18,000	0.08 (5 min.)	1,440
610.42(a)	1	1	1	1	1
610.46(a)(1)(ii)(B)	1,675	6.27	10,500	0.17 (10 min.)	1,785
610.46(a)(3)	1,675	6.27	10,500	0.17 (10 min.)	1,785
610.46(b)(3)	4,059	0.43	1,755	1	1,755
610.47(a)(1)(ii)(B)	1,675	13.97	23,400	0.17 (10 min.)	3,978
610.47(a)(3)	1,675	13.97	23,400	0.17 (10 min.)	3,978
610.47(b)(3)	4,059	0.51	2,050	1	2,050
630.6(a)[2]	558	755.98	433,000	0.08 (5 min.)	34,640
630.6(a)[3]	85	52.94	4,500	1.50 (90 min.)	6,750
630.6(d)(1)	84	31.07	2,610	1	2,610
Total					61,329

[1]Five percent of establishments that fall under the Clinical Laboratory Improvement Amendments of 1988 that transfuse blood and components and FDA- registered blood establishments (0.05 x 4,059 + 1,706).
[2] Notification of donors determined not to be eligible for donation based on failure to satisfy eligibility criteria.
[3] Notification of donors deferred based on reactive test results for evidence of infection due to communicable disease agents.

Dated: December 16, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

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