correct ''Amendment No. 61–107, 63–30, 65–41, 108–18, 121–280 and 135–78'' to read ''Amendment Nos. 61–107, 63–30, 65–41, 108–18, 121–280 and 135–79''.

Issued in Washington, DC on June 6, 2001.

Donald Byrne,

Assistant Chief Counsel, Regulations Division.

[FR Doc. 01–14656 Filed 6–8–01; 8:45 am]

BILLING CODE 4910–13–M

DEPARTMENT OF TRANSPORTATION

Federal Aviation Administration

14 CFR Part 121 and 135

[Docket No. FAA–2000–7119; Amendment No. 121–281 and 135–80]

RIN 2120–AG89

Emergency Medical Equipment; Correction

AGENCY: Federal Aviation Administration (FAA), DOT.

ACTION: Final rule; correction.

SUMMARY: This document contains a correction to the final rule, published in the **Federal Register** on April 12, 2001 (66 FR 19028). That final rule responds to the Aviation Medical Assistance Act of 1998 by requiring that air carrier operators carry automated external defibrillators on large, passenger-carrying aircraft and augment currently required emergency medical kits.

FOR FURTHER INFORMATION CONTACT: Judi citrenbaum, (202) 267–9689.

Correction of Publication

In the final rule FR Doc. 01–8923, beginning on page 19028 in the **Federal Register** issue of April 12, 2001, make the following corrections:

1. On page 19028, in column 1, in the heading section, beginning on line 5, correct ''Amendment No. 121–280 and 135–78'' to read ''Amendment Nos. 121–281 and 135–80''.

Issued in Washington, DC, on June 6, 2001.

Donald Byrne,

Assistant Chief Counsel, Regulations Division.

[FR Doc. 01–14657 Filed 6–8–01; 8:45 am]

BILLING CODE 4910–13–M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 606, 607, 610, 640, 660, and 809

[Docket No. 98N–0581]

Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is revising the general biological product standards applicable to human blood and blood components by updating the hepatitis B virus (HBV) and human immunodeficiency virus (HIV) testing requirements, by adding testing requirements for hepatitis C virus (HCV), human T-lymphotropic virus (HTLV), and by adding requirements for supplemental (i.e., additional, more specific) testing approved for such use by FDA when a donation is found to be reactive for any of the required screening tests for evidence of infection due to communicable disease agents. The agency also is requiring manufacturers of certain test kits to use reference panels, when available, to verify the acceptable sensitivity and specificity of each lot. This final rule is intended to help protect the safety and ensure the quality of the Nation's blood supply, to enhance the safety of medical devices containing blood or blood components, to provide FDA with clear enforcement authority, and to promote consistency in the industry. Elsewhere in this issue of the **Federal Register**, FDA is publishing a rule requiring blood and plasma establishments to notify donors, including autologous donors, whenever the donor is deferred or determined not to be suitable for current or future donations of blood and blood components.

DATES: This rule is effective December 10, 2001.

FOR FURTHER INFORMATION CONTACT: Paula S. McKeever, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, 301–827–6210.

SUPPLEMENTARY INFORMATION:

I. Background

Requirements for testing blood donors for hepatitis B surface antigen (HBsAg) and antibody to human immunodeficiency virus (anti-HIV) are currently codified in part 610 (21 CFR part 610), and requirements for performing a serological test for syphilis are codified in part 640 (21 CFR part 640). The agency has issued various guidance documents to registered blood and plasma establishments providing recommendations for testing for antibody to hepatitis B core antigen (anti-HBc), antibody to human T-lymphotropic virus types I and II (anti-HTLV I/II), antibody to hepatitis C virus (anti-HCV), and HIV–1 p 24 antigen. The purposes of the guidance documents are to assist blood and plasma establishments in protecting the safety of the blood supply and to establish policies with the intent of promoting consistency in the industry. These guidance documents represent the agency's current thinking on the appropriate testing of human blood donors for evidence of infection due to various communicable disease agents. Through inspection, we (FDA) determined that blood and plasma establishments generally have been following these recommendations. However, there have been instances where there have been variations in testing and in the determination of suitability of the blood based on the testing results. Accordingly, we proposed a regulation requiring testing consistent with our current recommendations and industry practice.

In the **Federal Register** of August 19, 1999 (64 FR 45340), we published a proposed rule to revise the testing requirements codified in part 610. The proposed rule would require:

- Each donation of human blood or blood component, including autologous donations, to be tested for evidence of infection due to HIV, types 1 and 2; HBV; HCV; and HTLV, types I and II;
- Each donation that tests reactive for any of the required screening tests for evidence of infection due to communicable disease agents, to be further tested using a supplemental (additional, more specific) test that has been approved for such use by FDA;
- The required testing to be performed by a laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) or meeting equivalent requirements as described by Health Care Financing Administration (HCFA), and registered with FDA in accordance with part 607 (21 CFR part 607);
- Deferral from future donations of donors who test reactive;
- Criteria for release or shipment of human blood or blood components prior to completion of testing under limited circumstances;

• Restrictions on shipment or use of human blood or blood components that test reactive when screened for evidence of infection; and

• Manufacturers of approved test kits used for testing donations of human blood and blood components for evidence of infection due to communicable disease agents, or for use in the diagnosis, or monitoring of HIV, to verify an acceptable sensitivity and specificity of each lot of test kit using a reference panel obtained from FDA, or an FDA designated source, when available.

We provided 90 days for comments on the proposed rule.

In the same **Federal Register** issue (64 FR 45355), we proposed new § 630.6 to require blood and plasma establishments to notify donors of deferral based on evidence of infection due to communicable disease agents or failure to satisfy donor suitability criteria. We intended to finalize the donor notification rule and issue it simultaneously with this document.

On November 9, 1999, we announced a public workshop held on November 22, 1999, and extended to December 22, 1999, the comment period on both proposed rules, entitled ''Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents,'' and ''General Requirements for Blood, Blood Components, and Blood Derivatives; Notification of Deferred Donors.'' The purpose of the public meeting was to provide a public forum for gathering information and views regarding the proposed rules.

II. Highlights and Summary of the Final Rule

A. Plain Language

We have written the final rule using plain language consistent with the presidential memorandum on plain language in government writing, dated June 1, 1998. We have adopted the plain language approach to make the rule more accessible and understandable to the public. As a result, we have used pronouns in describing who must comply, e.g., ''you'' refers, in the appropriate context, to an establishment that collects blood or blood components or to an establishment that is a consignee of a collecting establishment. We also have used ''must'' instead of ''shall,'' and are using charts to clarify provisions.

B. Test Requirements (§ 610.40)

In § 610.40(a) of the final rule, we require the use of screening tests for evidence of infection due to communicable disease agents, i.e., HIV, types 1 and 2; HBV; HCV; and HTLV, types I and II, for each donation of human blood and blood component. In § 610.40(b), we are requiring testing using one or more tests to reduce adequately and appropriately the risk of disease transmission. We are allowing for future advancements in testing methodologies by not specifying the test marker(s) for each disease agent. Further testing is required of all donations, including autologous (some exceptions apply) that are reactive when screened for evidence of infection due to any of the communicable disease agents, using supplemental (additional, more specific) tests approved for such use by FDA in § 610.40(e). (See section IV of this document.) We have eliminated the use of the term ''repeatedly reactive'' and replaced it with ''reactive.'' The terminology was revised to allow for future technology in testing, where the process of repeating an initial reactive result in duplicate would no longer be appropriate. However, for the test technologies recommended in current guidance, ''reactive'' means ''repeatedly reactive,'' because the manufacturers' instructions for current tests require duplicate retesting after an initial reactive result.

Specified exceptions to the testing requirements in § 610.40(c) are described as they apply to a dedicated donor (a donor whose collections are used by an identified recipient, see section V.B of this document), a donor of Source Plasma, a donor of blood or blood components intended as a component of, or used to prepare, a medical device (see section II.D of this document), and samples used or distributed for clinical laboratory testing or research purposes and not intended for administration to humans or in the manufacture of a product.

In § 610.40(d) of the final rule, we have created a separate paragraph for autologous donations. Testing of autologous donations is not required under this section unless an autologous donation of blood or blood components potentially could be used for allogeneic transfusion or shipped to another establishment. If shipped to an establishment that does not permit the use of autologous donations for allogeneic use, only the first donation in each 30 day period must be tested as discussed in section V of this document.

In § 610.40(f), testing required under § 610.40(a), (b), and (e) must be performed by a laboratory registered under part 607 and either certified to perform testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) under 42 CFR part 493 or has met equivalent requirements as determined by HCFA under those provisions. Therefore, § 607.65(g) is removed, formerly exempting from registration clinical laboratories that are approved for Medicare reimbursement and are engaged in the testing of blood products in support of other registered blood establishments.

Release or shipment prior to completion of testing in § 610.40(g) may occur in appropriately documented emergency medical situations, or when approved in writing by FDA, provided that the shipping establishment notifies the consignee that test results are not yet available, that the tests for communicable disease agents are completed as soon as possible, and that the results are provided promptly to the consignee.

Under § 610.40(h), an establishment must not ship or use blood or blood components that have a reactive screening test for a communicable disease agent(s) or reactive serological test for syphilis, or that were collected from a donor with a previous record of a reactive screening test for a communicable disease agent(s) or reactive serological test for syphilis. Exceptions to this requirement are:

• For blood and blood components from autologous donors when labeled as required in § 610.40(d);

• When approval in writing is obtained from FDA and the blood or blood component is labeled as required under § 610.40(h)(2)(ii);

• Samples for use or distribution, if intended for clinical laboratory testing or research and not intended for administration in humans or for further manufacturing use;

• When a collection from a donor with a record of a reactive screening test result tests negative and the donor is shown, or previously was shown, to be suitable by an acceptable requalification method; and

• When a collection from a donor, who tests reactive for anti-HBc and otherwise is determined to be suitable, may be used for further manufacturing into plasma derivatives without prior FDA approval or the ''BIOHAZARD'' legend.

C. Donor Deferral (§ 610.41)

Under § 610.41(a), any donor of blood and blood components, including an autologous donor, who tests reactive for a communicable disease agent(s) described under § 610.40(a) or reactive with a serological test for syphilis must be deferred from future donations. Exceptions apply as follows:

• A donor who tests reactive for anti-HTLV I/II or anti-HBc only once is permitted to donate again without being deferred from further donation unless there is further testing using an approved supplemental (additional, more specific) test;

• A deferred donor who tests reactive for HIV, types 1 and 2, HBV, HCV, HTLV types I and II, or syphilis may donate blood or blood components to be shipped or used under the provisions described in § 610.40(h)(2)(ii);

• A deferred donor who showed evidence of infection due to HBsAg when previously tested may donate blood or blood components to be used in the preparation of Hepatitis B Immune Globulin (Human) provided the donor's current donation tests nonreactive for HBsAg and the donor otherwise is determined to be suitable;

• A deferred donor who tests reactive for anti-HBc or for evidence of infection due to HTLV, types I and II, may serve as a donor of Source Plasma collected for further manufacturing use;

• A deferred donor who tests reactive by a screening test for syphilis may serve as a donor of human blood and blood components, if the donation is further tested by an adequate and appropriate test demonstrating that the reactive screening test is a biological false positive; and

• A deferred donor who tests reactive for a communicable disease agent(s) described under § 610.40(a) or reactive with a serological test for syphilis may serve as an autologous donor.

Under new § 630.6 in the donor notification rule found elsewhere in this issue of the **Federal Register**, all deferred donors, including those deferred donors who may serve as donors under specified conditions described in § 610.41, must be notified of their deferral.

Under § 610.41(b) the regulations permit the reentry of a deferred donor into the donor pool when the donor is requalified by a process or method (algorithm) approved by FDA for such purpose.

D. Medical Devices (§§ 610.42 and 610.44)

In the proposed rule, we discussed the need for labeling of medical devices manufactured from reactive blood or blood components. In the final rule, we have changed the text of § 610.42 to require labeling for all medical devices that contain blood or a blood component as a medical device component, and not just in vitro diagnostic products. Under § 610.42(a), when a medical device contains human blood or a human blood component as a component of the final device and the human blood or blood component was found to be reactive by a screening test for a communicable disease agent(s) or reactive by a serological test for syphilis then the device labeling 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). Other labeling requirements in subchapter H (Medical Devices) of chapter I would also apply. We also are allowing for an exemption approved by FDA to the statement of warning in circumstances where the reactivity of the human blood or blood component in the device presents no significant health risk through the use of the device.

In proposed § 610.44, manufacturers of test kits would be required to use, when available, a reference panel obtained from FDA or from a FDA designated source to verify the sensitivity and specificity of kits approved for use in testing donations of blood and blood components for communicable disease agents listed in § 610.40(a) and for an HIV test approved for use in the diagnosis and monitoring of HIV.

In the final rule, we are amending the requirements to clarify that when available and appropriate, a manufacturer must use panels that have been provided or identified by FDA to verify acceptable sensitivity and specificity of kits used to test donations of human blood and blood components, including licensed supplemental (additional, more specific) tests. The agency is making this change after reviewing 21 CFR 660.46. That regulation recognizes that official lot release may not be required after a manufacturer consistently produces a product that meets specifications. Consistent with this policy, the agency has recognized that less strict reference standard testing requirements may be appropriate in some situations. Accordingly, FDA has revised 1§ 610.44 to require use of reference panels only when such use is appropriate and panels are available. Moreover, FDA may determine that reference panel testing of each lot is not appropriate, based on a manufacturer's consistent prior production of products of acceptable sensitivity and specificity. In that situation, intermittent testing of lots may be appropriate.

FDA also is clarifying that § 610.44(a)(2) requires manufacturers of an HIV test kit approved for use in diagnosis, prognosis, or monitoring to use an FDA provided or designated reference panel, when available and appropriate to assure acceptable sensitivity and specificity of each lot of test kit. When available and appropriate, FDA expects the manufacturer to perform testing using the panel to assure that each lot meets acceptable sensitivity and specificity.

The agency also is making a conforming amendment to § 809.20(b) (21 CFR 809.20(b)), to make clear that § 610.44 applies to all HIV test kits that are biological products, and are approved for diagnosis, prognosis, or monitoring, including any such kits reviewed under the medical device authorities.

In the proposed rule, we stated that as technology and scientific knowledge advance, and the demands placed on the blood industry change, there will continue to be instances when a regulation will become outdated or where unanticipated circumstances may warrant a departure from a regulation. To allow for flexibility in such cases, we discussed the availability of approval for exemption upon written request from a manufacturer to FDA. We also noted that, under § 640.120, applicants may submit requests for exceptions or alternatives to regulations regarding blood, blood components, or blood products. Consistent with this policy, we created a similar provision in the final rule that is applicable to the labeling of medical devices in § 610.42, and distribution of lots found not to be acceptable for sensitivity and specificity in § 610.44. We would approve an exception or alternative under these sections only if we concluded that the safety, purity, potency, and effectiveness of the final product were adequately assured. Manufacturers may submit, in writing to FDA, a request for an exception or alternative to §§ 610.42(a) and 610.44(b). In limited circumstances, a request and approval may be made orally followed by a written request and written approval.

E. Technical Amendments

We also made technical changes to existing regulations, consistent with this rulemaking. We removed §§ 606.121(g), 607.65(g), 610.45, 640.2(d), and 660.42. We revised §§ 640.5(f) and 640.67 for consistency with § 610.40, and in §§ 606.121(h)(2) and (h)(3), 640.14, 640.23(a), 640.33(a), and 640.53(a) we deleted ''§ 610.45.'' We have amended §§ 606.121(e)(5)(ii) and 640.70(a)(2) to conform with the labeling requirement in § 610.40(h)(2)(ii)(E), and amended § 809.20(b) to conform with § 610.44.

III. Testing for Syphilis

In the proposed rule, we solicited comments, with supporting data, from the public in regard to the value of such a test as a marker of high risk behavior, as a surrogate test for other communicable diseases, and as a screen for syphilis in blood and blood components to prevent transfusion-related transmission. We recognized that many scientists, including some members of the blood banking community, continue to advocate the elimination of the serological test for syphilis as a testing requirement. Comments were received and are discussed in comment 28 of this document. We have concluded that there are insufficient data to justify eliminating the requirement for a serological test for syphilis. Therefore, §§ 640.5(a) and 640.65(b) remain in effect at this time. The agency remains interested in receiving scientific data to clarify the value of performing serologic tests for syphilis on donations of blood and plasma.

IV. Relevant Guidance

Over time, we have issued guidance representing the agency's current thinking on the adequate and appropriate testing of blood and blood component donations for evidence of infection due to various communicable disease agents. Because we are not specifying the test or tests to be used in this regulation, we are listing in the following table the test or tests we currently believe reduce adequately and appropriately the risk for transmission of communicable disease agents.

TABLE 1.—SCREENING TESTS

Tests	Whole Blood and Blood Components Including Recovered Plasma	Components of, or Used to Prepare, Medical Devices Containing Viable Leukocytes	Components of, or Used to Prepare, Medical Devices Not Containing Viable Leukocytes	Source Plasma
Serological Test for Syphilis (STS)	X	X	X	X
Antibodies to HIV, types 1 and 2 (anti-HIV)	X	X	X	X
HIV–1 Antigen (HIV–1 Ag)	X	X	X	X
Hepatitis B Surface Antigen (HBsAg)	X	X	X	X
Antibody to Hepatitis B Core Antigen (anti-HBc)	X	X[1]	X[1]	
Antibody to Hepatitis C Virus Encoded Antigen (anti-HCV)	X	X	X	X
Antibodies to HTLV, types I and II (anti-HTLV I/II)	X	X		

[1] Anti-HBc testing not recommended for donations intended solely for further manufacturing into in vitro medical devices.

TABLE 2.—ADDITIONAL MORE SPECIFIC TESTS

Tests	STS	anti-HIV	HIV–1Ag	HBsAg	anti-HBc	anti-HCV	anti-HTLV I/II
Approved Supplemental Tests	X	X	X[1]	X[1]		X	

[1] A neutralization assay is performed as part of the screening test procedure for a reactive sample.

As technology advances, we intend to regularly issue guidance describing those tests that we believe would adequately and appropriately reduce the risk of transmission of communicable disease agents. Unless we determine that prior public participation is not feasible or appropriate, we intend to issue such guidance in draft, giving the opportunity for public comment and for manufacturers to prepare to use any appropriate new testing technologies. When prior public participation is not feasible or appropriate, for example, when immediate action is necessary to protect the public health, we may immediately implement the guidance.

We have prepared a list of guidance documents that currently are applicable to these regulations. They are listed in order by date of issuance.

- Recommendations for the Management of Donors and Units that are Initially Reactive for Hepatitis B Surface Antigen (HBsAg); December 2, 1987
- HTLV–I Antibody Testing; November 29, 1988
- FDA Recommendations Concerning Testing for Antibody to Hepatitis B Core Antigen (Anti-HBc); September 10, 1991
- Clarification of FDA Recommendations for Donor Deferral and Product Distribution Based on the Results of Syphilis Testing; December 12, 1991
- Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Encoded Antigen (Anti-HCV); April 23, 1992
- Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products; April 23, 1992
- Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV) [Supplements previous guidance April 23, 1992]; August 5, 1993
- Donor Suitability Related to Laboratory Testing for Viral Hepatitis and a History of Viral Hepatitis; December 22, 1993
- Recommendations for Donor Screening with a Licensed Test for HIV–1 Antigen; August 8, 1995
- Additional Recommendations for Donor Screening with a Licensed Test Kit for HIV–1 Antigen [Supplements previous guidance August 8, 1995]; March 14, 1996
- Additional Recommendations for Testing Whole Blood, Blood Components, Source Plasma, and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV) [Supplements previous HCV guidance—April 23, 1992 and August 5, 1993]; May 16, 1996
- Guidance for Industry: Donor Screening for Antibodies to HTLV–II; August 15, 1997
- Guidance for Industry: Errors and Accidents Regarding Saline Dilution of

Samples Used for Viral Marker Testing; June 11, 1998

The guidance documents referenced in this document or otherwise applicable to the testing of donors of blood and blood components may be obtained from the Office of Communication, Training, and Manufacturers Assistance (HFM–40), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448. Send one self-addressed adhesive label to assist that office in processing your requests. The guidance documents may also be obtained by mail by calling the CBER Voice Information System at 1–800–835–4709 or 301–827–1800, or by FAX by calling the FAX Information System at 1–888–CBER–FAX or 301–827–3844. Persons with access to the Internet may connect to CBER at http://www.fda.gov/cber/publications.htm.

V. Comments on the Proposed Rule

We received 24 letters of comment on the proposed rule, most of which raised multiple issues. The comments were submitted by blood centers, hospitals, transfusion services, trade associations, and professional associations. A number of comments expressly supported our revision of communicable disease testing requirements to incorporate the agency's guidance and industry practice into one comprehensive regulatory framework to help ensure the safety of the blood supply. A summary of the comments and the agency's responses follow.

A. Testing of Autologous Donations

In the proposed rule, each donation of autologous blood and blood component would be tested for evidence of infection due to the following communicable disease agents: HIV, types 1 and 2; HBV; HCV; and HTLV, types I and II. The testing would be performed using screening tests approved for such use by FDA. One or more such tests would be performed as necessary to reduce adequately and appropriately the risk of transmission of communicable disease. Restrictions on shipment or use would not apply to autologous blood and blood components provided the autologous blood and blood components are labeled appropriately. We requested comments on alternatives (including the rationale) to testing each autologous donation, such as procedural or labeling improvements. A majority of comments submitted to us responded to this issue.

(Comment 1) Six comments support testing autologous donations in the same manner as allogeneic donations. The comments argue that a significant error rate in the use of autologous blood for allogeneic use or use in preparing a product, makes the current risks to recipients of blood and blood components unacceptable. They further argue that testing will reduce these risks, as well as the risk to healthcare workers from inadvertent exposure. Several of these comments recommend that autologous donations testing reactive for a communicable disease agent(s) should not be exempt from the restrictions on shipment and use in the proposed rule. They argue that positive donations of autologous blood should be discarded to protect the health of healthcare workers and to prevent inadvertent use of such autologous blood for allogeneic transfusions.

Eleven comments oppose testing of autologous donations for evidence of infection due to communicable disease agents. These comments argue that testing would not significantly reduce the risk of inadvertent allogeneic transfusions with autologous blood and blood components because testing alone does not address the process errors that cause inadvertent allogeneic transfusions. Errors in labeling and handling autologous blood will occur regardless of whether donations are tested. Several comments argue that we presented no data to suggest testing will reduce inadvertent allogeneic transfusion. One comment points out that inadvertent allogeneic transfusion errors occur despite the fact that an estimated 60 to 70 percent of autologous donations currently are tested. The comments that argue against testing instead support regulation that focuses on improving quality assurance systems. These comments recommend optimizing labeling, separating processing paths and segregating storage for autologous donations, as well as requiring multiple identifications of recipients to address directly all (autologous and allogeneic) transfusion errors. Finally, comments opposed to testing autologous donations argue that the significant costs of testing are unwarranted given the lack of clinical utility. They argue that in many cases, particularly in small, rural hospitals where patients will have few alternatives, the costs of testing will be prohibitive and will result in reduced availability of autologous services. Several comments also suggest that reduced availability of autologous donations will result in an increase in allogeneic use with its attenuated risks outweighing any minor increase in safety from testing autologous donations.

A number of comments recommend an intermediate position between testing all autologous donations and testing none. Three comments support testing only one in a series of autologous donations, noting that many autologous donors donate multiple donations in a short timeframe, therefore, testing each donation would result in significant costs without any appreciable increase in safety to the blood supply. One comment calls for testing autologous donations once in 30 days if the autologous donation is to be shipped from the collection establishment before transfusion. If the donation is collected and transfused in the same facility, the comment recommends no testing be required. The same comment supports labeling all autologous donations with a unique label stating ''FOR AUTOLOGOUS USE ONLY'' and all reactive or untested donations with a ''BIOHAZARD'' legend. Further, the comment calls for prohibiting establishments from using autologous donations as allogeneic donations. The comment argues that requiring testing every 30 days for shipped autologous donations, labeling changes, and preventing the use of autologous blood and blood components for allogeneic transfusion are better, more cost-efficient methods of protecting patients and health care personnel.

Based on the comments submitted and our own evaluation, the agency has concluded that its proposal to test all autologous donations in the same manner as allogeneic donations should be amended. While communicable disease testing plays a major role in improving the safety of the allogeneic blood supply, we are not convinced that the testing of all autologous donations is necessary to improve the safety of the general blood supply. It is the inadvertent improper use of autologous donations, rather than the product itself, which poses risk to the public health. Many of the incidents involving autologous donations that compromise transfusion safety are caused by process or clerical error. As one comment points out, these errors occur regardless of whether the autologous donation is tested and its communicable disease status is known. We are persuaded that such errors involving autologous donations can be better addressed by changes in labeling and processing of autologous donations. We believe that clearly marking autologous donations as ''DONOR UNTESTED,'' as well as with the autologous label (§ 606.121(i) (21 CFR 606.121(i))), will alert healthcare workers that they could be handling potentially infectious products and

should take appropriate precautions. We believe that not requiring testing of autologous donations will help assure continued autologous services at certain small, rural blood establishments, which do not use autologous donations for allogeneic use. We believe that these labeling changes will sufficiently increase the safety of autologous transfusions without compromising the availability of these services.

However, we have concluded that under certain circumstances there is a potential risk to blood safety from autologous donations, and under those circumstances labeling changes alone are insufficient to protect the public health. First, blood establishments that permit autologous donations to be used for allogeneic transfusions run a potentially greater risk of erroneous transfusion of an autologous donation to an unintended recipient. We are requiring that establishments that maintain a program permitting allogeneic use of autologous donations test each autologous donation collected regardless of whether the particular blood or blood component is ''crossed-over'' for allogeneic use. Positive and reactive donations must be labeled with a ''BIOHAZARD'' legend as well as with the label ''FOR AUTOLOGOUS USE ONLY'' as required under § 606.121(i). Autologous donations that test negative for evidence of infection due to communicable disease agents must be labeled ''FOR AUTOLOGOUS USE ONLY'' as further specified under § 606.121(i). The agency believes that blood establishments that use autologous donations for allogeneic uses should be subject to these additional safety measures to prevent erroneous allogeneic uses. The agency believes that for such establishments the additional margin of safety achieved by testing all donations in the establishment's inventory and labeling reactive donations with a ''BIOHAZARD'' legend is necessary to protect the public health.

The second area in autologous transfusion services that presents additional safety concerns is the shipment of autologous products from the collection facility to another establishment. Errors, including clerical errors in inventory management and breakage of autologous donations, may occur when the product is handled by a variety of individuals and facilities throughout collection, transport, storage, and transfusion. We are requiring that blood establishments that ship autologous products to other establishments that do not use autologous donations for allogeneic use must test the first autologous donation collected at the beginning of each 30-day period for evidence of infection due to communicable disease agents. We believe a minimum requirement of testing the autologous donor's blood at least once in 30 days is sufficient because autologous donations are usually given in a series over a short timeframe. Because these donations are not intended to be transfused into any other recipient than the donor, testing once in 30 days for evidence of infection due to communicable disease agents will give an added measure of safety to those handling the blood without the costs of testing each autologous donation. Thus, if an autologous donor donated three times over a 30-day period and the establishment ships the autologous donations to another establishment that does not allow use of autologous donations for allogeneic transfusion, the rule requires, at a minimum, that the establishment test the first collection only. If the donor donated a fourth time on the 31st day or later, the establishment must test the fourth collection.

(Comment 2) One comment raises several additional arguments against testing autologous donations including: Testing may give a false sense of increased protection resulting in decreased attention and more errors; testing may result in denial of services to patients or loss of autologous donor programs; and testing of autologous donations constitutes the practice of medicine since autologous donors are patients under a doctor's care.

We do not believe that testing of autologous donations will result in decreased attention and more errors. Communicable disease testing of allogeneic blood and blood components has been an important and effective tool to ensure the safety of the blood supply. Testing of autologous donations, which are shipped to or collected in an establishment that maintains a program that uses autologous blood and blood components for allogeneic transfusion will provide an additional margin of safety against a potentially greater risk of error. We do not believe that communicable disease testing of autologous donations will result in a denial of such services to patients or in the loss of such programs. We are not requiring testing of autologous blood and blood components except when an establishment has a program allowing the use of autologous donations for allogeneic transfusion, or ships the autologous donations from the collecting facility. We believe this approach allows services and programs for autologous collections to continue while protecting potential allogeneic recipients and healthcare workers who may be exposed to biohazardous blood or blood components.

The comment views the testing of autologous donations as practice of medicine. However, we do not consider testing of autologous donations to be practice of medicine, but to be a safeguard in protecting the public health when autologous donations are made available for allogeneic use or when others may be exposed to potentially hazardous donations during shipment of autologous donations by the collecting establishment. This policy responds to a recommendation in the February 1997 report issued by the General Accounting Office entitled ''Blood Supply: FDA Oversight and Remaining Issues of Safety.''

(Comment 3) Two comments argue that testing and labeling autologous blood and blood components can seriously jeopardize the confidentiality of the donor's communicable disease status.

We do not believe the required testing and labeling of autologous donations will seriously compromise the donor's confidentiality. The final rule does not require most autologous donors to be tested, and labeling on untested autologous donations will not raise confidentiality issues. In addition, the label will not identify in any manner the donor's particular communicable disease status. The ''BIOHAZARD'' legend on donations from autologous donors who test positive or reactive will serve as a necessary alert for blood healthcare workers and help prevent transfusion errors. We recommend that autologous donors be informed beforehand if their donations will be tested for evidence of infection due to communicable disease agents. Thus, autologous donors may choose not to donate in a setting where testing is required.

(Comment 4) Seven comments raise the issue of what to do with autologous blood or blood components that test reactive by one or more of the communicable disease agents identified in § 610.40(a). Several of these comments point out that blood establishments are under ethical and legal constraints that would prevent them from discarding test positive autologous donations. Several comments suggest that under a recent Supreme Court decision it may be a violation of the American with Disabilities Act (''ADA'') to deny HIV-infected patients the right to use their own blood. Two comments strongly support discarding autologous donations testing reactive. These comments argue that the risks from

keeping these positive donations in blood inventories are too great. The comments argue these donations should be treated similarly to blood from a positive allogeneic donor and discarded.

We are not prohibiting blood establishments from transfusing positive donors with their own blood. These donations, however, if made available for autologous use must be labeled ''FOR AUTOLOGOUS USE ONLY'' and also with a ''BIOHAZARD'' legend.

(Comment 5) Several comments call for prohibiting the use of autologous donations for allogeneic transfusion for all blood collection establishments. The comments argue that the benefit of testing would be negated if test positive autologous donations remain in the system subject to the processing errors that can occur when use of autologous donations for allogeneic transfusions is permitted.

The agency has determined that this final rulemaking is not the appropriate venue to institute a requirement prohibiting use of autologous donations for allogeneic use. However, we believe that this issue should be considered further in the more general context of medical errors. In the interim, we believe that requiring blood establishments that continue the practice of using autologous donations for allogeneic transfusions to test and appropriately label all their autologous donations will help control errors involving autologous donations testing reactive for a communicable disease agent(s).

(Comment 6) Four comments point out that the proposed rule does not address perioperative autologous blood collections. Two comments suggest that requiring testing of perioperative collections would effectively eliminate them because testing would not be completed in time for donations to be used. One comment suggests the final rule should contain an exception for intraoperatively salvaged blood.

We are not proposing testing of perioperative blood collections. These blood or blood components are collected and used within the same facility where the operation is being performed, and are not intended for allogeneic use. They also do not become part of the transfusion center's or blood collection establishment's inventories. Therefore, we do not consider perioperative blood or blood component donations subject to testing for evidence of infections under the purview of the final rule.

(Comment 7) Four comments suggest that we deal with the issue of the inappropriate use of recovered plasma for further manufacture from untested or communicable disease marker reactive autologous blood by banning the use of untested or reactive recovered plasma or by requiring testing of autologous blood to be used for salvage.

Under 21 CFR 606.100(b)(18), blood establishments are required to establish and maintain standard operating procedures (SOP's) for recovered plasma. If a blood establishment intends to use recovered plasma from an untested donation for further manufacturing use, the donation would then be considered an allogeneic donation subject to the testing requirements for allogeneic donations under the final rule. The use of untested or reactive autologous blood for further manufacturing is prohibited unless exempted under § 610.40(h)(2).

B. Exception for Dedicated Apheresis Donations

We requested comments on whether to exempt from testing for evidence of infection due to communicable disease agents each donation from a dedicated apheresis donor (defined in section I.B of this document) and instead test such donors only once in each 30-day period.

(Comment 8) Eight comments responded to this request. One comment opposes a once in each 30-day period testing exception for dedicated apheresis donors, arguing that recipients of these donations are entitled to the same protection as other recipients of blood components. The remaining seven comments support allowing testing of dedicated apheresis donors only once every 30 days. These comments cite the fact that dedicated apheresis donations are often used for patients in dire situations who are unable to wait for each donation to be tested. They argue that dedicated apheresis donations tested only once in each 30-day period would not present a safety concern because new tests have substantially increased the reliability of the first donation's test results; because subsequent donations during the 30-day period would create little additional risk to the recipient, since the first donation would expose the recipient to any undetected infection; and because new risk of exposure could be caught by taking the donor's medical history (including health and social history screening) on the day of each subsequent collection. (See 21 CFR 640.3(a).)

Based on the comments submitted and the agency's own evaluation, we have concluded that donations from dedicated apheresis donors must be tested for evidence of infection due to communicable disease agents at the first donation and at a minimum of once at the beginning of each successive 30-day period. This exception from universal testing will provide the recipient of dedicated apheresis donations with adequate protection against disease transfer since the test results would be unlikely to change within the 30-day period. We also believe this exception will limit donor exposure when the patient needs frequent transfusions and will help avoid delaying treatment of patients in need of emergency transfusions.

(Comment 9) One comment suggests that the communicable disease agent testing should be allowed near the time of the first collection to facilitate expedited release of dedicated apheresis donations to patients in need.

We have reviewed the comment and will consider permitting communicable disease agent testing prior to collection of the first dedicated donation in the context of creating specific standards for dedicated donations in future rulemaking.

(Comment 10) Two comments call for use of an abbreviated donor screening questionnaire for dedicated apheresis donors.

Since we are limiting testing for evidence of infection due to communicable disease agents to the first donation in each 30-day period, we believe that the screening process plays an even more important role in evaluating the safety of the blood or blood component being collected from the dedicated donor. The possible implications of an abbreviated screening are not in the scope of this rulemaking, and are under study for future rulemaking.

(Comment 11) Two comments suggest extending this exception from universal testing to other dedicated blood components (e.g. dedicated granulocyte donors; parent to child donations of plasma or red blood cells).

We agree with this comment. We believe that donations from dedicated donors should be treated alike in regards to communicable disease testing. Accordingly, the agency has extended the exception allowing testing for evidence of infection due to communicable disease agents to the first donation in each 30-day period for all donations of blood and blood components from dedicated donors to a single, identified recipient. Syphilis testing is required, at a minimum, for the first donation in each 30-day period in addition to the other communicable disease agents listed in § 610.40(a).

(Comment 12) One comment also calls for extending the exemption to other non-infectious tests required for donations from dedicated apheresis

donors, such as ABO, Rh, red cell antibody screening.

We disagree with this comment. Tests such as ABO, Rh, and red cell antibody screening are part of matching the donation to the donor and, therefore, part of quality assurance processes.

(Comment 13) One comment suggests that subsequent donations from dedicated apheresis donors should not be labeled as untested since the test results from the first donation should apply to subsequent donations.

We agree with this comment. We are requiring that donations subsequent to the first tested donation in each 30-day period from dedicated donors, including apheresis donors, be labeled ''DONOR TESTED WITHIN THE LAST 30 DAYS.''

We are aware that there may be occasions where the dedicated donations are no longer needed by the identified recipient. When an untested donation is to be used for transfusion to another recipient or for further manufacturing, the establishment must assure that all suitability criteria under § 640.3 are met and that testing required under § 610.40 is completed and that the donation tests nonreactive before use.

C. Supplemental Testing

In proposed § 610.40(c), we would require that each donation found to be reactive by a screening test for evidence of infection due to communicable disease agents be further tested whenever a supplemental (additional, more specific) test has been approved for such use by FDA.

(Comment 14) Three comments support our proposal to further test reactive donations whenever a supplemental (additional, more specific) test has been approved for such use by FDA. These comments point out that this information is relevant to the donor and part of the usual and customary business practice for blood centers to provide. One of these comments also suggests that requiring such testing will provide test kit manufacturers with the economic incentive to develop supplemental tests for less common viruses for which donors are screened.

Four comments oppose our mandating supplemental testing. These comments argue that there is not a sufficient public health concern and that the costs are too burdensome. The comments suggest that our regulatory concerns should be limited to deferring reactive donors and labeling positive donations. Several of these comments argue that supplemental testing has no impact on blood safety and is a medical decision to be made by the donor's physician. Others suggest that blood centers do supplemental testing voluntarily if they intend to reenter donors; so supplemental testing should not be required.

Historically, we have recommended in guidance supplemental testing of reactive samples and, for HIV, we have required supplemental testing in § 610.46(b). We consider supplemental testing as part of communicable disease control, necessary in protecting public health. Screening tests are designed to be highly specific for the tested marker. Nevertheless, false positives occur due to sample contamination, cross-reactivity, or nonspecific causes. In § 610.40(e), we are requiring that reactive samples be further tested by a supplemental (additional, more specific) test, when available, that has been approved for such use by FDA. Although a donor must be deferred based on a reactive screening test, the blood and plasma establishment should use the information obtained through supplemental testing to notify and counsel the deferred donor. Providing donors with accurate information about their communicable disease status and deferral as soon as possible helps ensure a healthy donor population. Blood and plasma establishments also can use information from supplemental testing to evaluate the donor for possible reentry into the donor pool. Requalification of donors contributes to blood availability, which also is a public health concern. Therefore, FDA believes supplemental testing has a direct impact on blood safety in preventing communicable disease transmission and in optimizing blood availability.

(Comment 15) Several comments object to HCV supplemental testing in particular because there is currently no requirement for lookback or product retrieval and there is no reentry algorithm in place.

We disagree with the comments. We consider supplemental testing part of blood safety by providing deferred donors with accurate, timely information regarding their deferred status and possible transmission of communicable disease. Currently, we allow reentry of donors who test reactive by a multiantigen screening test for HCV. Reentry into the donor population must follow a method or process approved by FDA. This process includes the use of a supplemental test, e.g., recombinant immunoblot assay 3.0 (RIBA 3.0). We have issued draft guidance on our current thinking on HCV ''lookback'' (see section IV of this document for description on how to access the draft guidance document); we intend to finalize this guidance and to propose new regulations in a future rulemaking for ''lookback'' when donors test reactive for HCV.

(Comment 16) One comment objects to supplemental testing of autologous donations. The comment objected, in part, because of the costs associated with testing each donation from autologous donors.

Under the final rule, we require testing of autologous donations only where there is a public health risk, i.e., where an establishment has a program allowing the use of autologous donations for allogeneic transfusion, or where a collecting establishment ships autologous donations. For those donations of autologous blood and blood components that are required to be tested, we also are requiring blood establishments to further test such donations using supplemental tests. If an autologous donation is reactive in screening tests, blood establishments are required to defer the autologous donor from future allogeneic donations. The deferred autologous donor has the same need as the deferred allogeneic donor for accurate information regarding his or her possible infectious status, and the information from supplemental testing may prevent the donor from spreading the infection. Thus, we believe that supplemental testing of autologous donations is just as necessary to blood safety and public health as supplemental testing of allogeneic donations. For those autologous donors with a record of a positive supplemental test for a specific communicable disease agent, the establishment is not required to perform the supplemental test again.

(Comment 17) Two comments argue that the approved supplemental tests are not always the best method of confirmatory testing, pointing to nucleic-acid-based testing (NAT) for HCV and HIV. The comments also suggest allowing blood establishments to use NAT testing and leave the decision to the donor's physician whether other supplemental tests are warranted medically.

In structuring the proposed rule, we intended to allow for advancements in testing technology without further rulemaking. We built into the requirement for supplemental testing of reactive donations the ability for blood and plasma establishments to use different testing methods as long as those tests have been approved by the agency. NAT is not yet available as a supplemental testing method and cannot now be used in lieu of licensed or approved tests. However, we expect further development in NAT, both as a screening and supplemental test, and intend to issue guidance on the use of such testing in the future.

(Comment 18) Three comments suggest that to reduce costs and delays supplemental tests need be performed only on the first reactive donation in a series of donations.

Supplemental testing, when available, is required for each donation that tests reactive for evidence of infection due to a communicable disease agent(s) listed in § 610.40. We agree with the comments in part, and applied the suggestion to autologous donors. We are making two exceptions to performing supplemental testing on each reactive donation. The first exception requires, at a minimum, that supplemental testing be performed on the first reactive autologous donation in each 30-day period. The second exception is when an autologous donor has a positive supplemental test of record. In that instance, the supplemental test is not required to be performed on subsequent autologous donations.

D. Release or Shipment Prior To Testing

In proposed § 610.40(e), we would allow the use or shipment prior to test results of human blood or blood components under two circumstances: Appropriately documented medical emergency situations; or when approved in writing by FDA. Use or shipment prior to test results may occur, provided the consignee is notified that test results are not available, the tests for evidence of infection due to communicable disease agents are performed as soon as possible after release or shipment, and the results are provided promptly to the consignee.

(Comment 19) Several comments support allowing use or shipment of donations prior to testing in medical emergencies and routine shipment for further manufacturing use. One comment opposes any use or shipment prior to testing.

We believe these exceptions are necessary to ensure the continued availability of blood products in emergency situations and when products require rapid preparation, e.g., Source Leukocytes. In either instance, the completion of testing prior to shipment or use may not be feasible. The regulations require the blood or plasma establishment to document the emergency release or shipment of blood or blood components prior to completion of testing. If the blood or plasma establishment ships blood or blood components for further manufacturing use prior to completion of testing, the blood establishment must obtain prior approval from FDA. In either instance, the blood or plasma establishment must complete testing as soon as possible thereafter, and must notify the consignee of test results as soon as they are available.

(Comment 20) One comment argues that a blood establishment should not be required to obtain approval from FDA before shipping untested blood or blood components for further manufacturing use. The comment contends that there is no public health concern since the blood or blood components are not released yet. The comment asserts that a request for FDA approval would delay manufacture of the biological product. The comment asks that any such requests be automatically approved 30 days after submission to FDA.

We believe it is essential as a public health safeguard that blood or plasma establishments shipping blood and blood components for further manufacturing use prior to completion of testing obtain prior approval from FDA and submit their SOP's for review. However, the blood or plasma establishment must submit its SOP's and obtain prior approval only before its first shipment—not, as some comments seem to suggest, before each shipment. This requirement of a single submission will not delay the manufacture of a biological product. We believe that this provision will expedite the manufacturing process by allowing communicable disease testing to be completed after shipment, but before further manufacturing use. Prior approval is necessary to help ensure that a blood or plasma establishment is following proper procedures in shipping potentially infectious blood and blood components for further manufacturing use.

(Comment 21) One comment asks FDA to clarify whether proposed § 610.40(e)(2) addresses the transfer of untested donations within a multifacility manufacturer for labeling purposes.

Requests to ship blood and blood components prior to testing between facilities within a multifacility manufacturer for labeling purposes should be submitted through the license application for that product. FDA will review those applications on a case-by-case basis.

E. Donor Deferral

In proposed § 610.41, we would require donors testing reactive for evidence of infection due to a communicable disease agent or reactive for a serological test for syphilis be deferred from future donations of blood and blood components. Proposed exceptions to this requirement are: (1) Autologous donors; (2) plasmapheresis donors with a reactive serological test for syphilis under § 640.65; (3) donors who test reactive for anti-HTLV, types I or II, or anti-Hepatitis B core (anti-HBc) on only one occasion; (4) donors who test reactive for anti-HTLV, types I or II, or anti-HBc may serve as donors of Source Plasma; (5) deferred donors testing reactive for evidence of infection due to a communicable disease agent may serve as donors for blood or blood components when used following the requirements for restriction on shipment or use; (6) deferred donors showing evidence of infection due to hepatitis B virus when previously tested, may donate blood or blood components in the preparation of Hepatitis B Immune Globulin (Human) provided their current donations test negative for HBsAg and the donor is determined otherwise to be suitable; (7) donors testing reactive with a serological test for syphilis and found negative by an approved specific treponemal test; and (8) previously deferred donors later found to be suitable as donors of blood or blood components by a method or process acceptable for such purposes by FDA.

(Comment 22) One comment supports and one comment opposes allowing donors testing reactive for anti-HTLV, type I or type II, or anti-HBc to serve as donors of Source Plasma.

In the proposed rule, we explained that the communicable disease agents HTLV, types I and II, are highly cell-associated. It is well established that HTLV, types I and II infection may be transmitted to recipients by the transfusion of cellular blood components from infected donors. Conversely, HTLV transmission has not been demonstrated by the transfusion of Plasma or Cryoprecipitate or by the use of products made from Source Plasma. Donors testing reactive for anti-HBc also do not present a risk of transmitting hepatitis B to recipients of plasma derivatives made from Source Plasma. Although blood that is reactive for anti-HBc, even when negative for hepatitis B surface antigen (HBsAg), has a low risk of infectivity for HBV and would not be suitable for transfusion, the plasma from such blood would be suitable for manufacture into plasma derivatives. In most cases, blood that is negative for HBsAg, but is reactive for anti-HBc would be from a donor who has cleared a hepatitis B infection. Such a donor would still have circulating anti-HBc and presumably would also have circulating anti-hepatitis B surface antigen (anti-HB's), which is hepatitis B neutralizing antibody. This neutralizing antibody is thought to contribute to the safety of immune globulin products. Additionally, all licensed human plasma derivatives undergo procedures

that will inactivate HBV and HTLV. In the final rule, therefore, we continue to allow donors testing reactive for anti-HTLV, type I or type II, or anti-HBc to serve as donors of Source Plasma, consistent with the exemption that donors of Source Plasma need not be tested for anti-HTLV, types I and II, and anti-HBc.

(Comment 23) One comment suggests creating a temporary deferral category for donors found reactive with earlier generation EIA/screening test, but negative by more specific tests and reenter those donors if they test negative two times 6 months apart by a later more specific/sensitive test for the same marker.

We disagree with this comment on the basis that it is too specific for a regulation. The final rule contains a provision in § 610.41(b), which allows donors deferred based on reactive screening tests to be reentered into the donor pool if their blood subsequently tests negative for the same communicable disease agent and the donor is shown to be suitable to donate by a method or process approved by FDA. We have identified such donor reentry algorithms in guidance documents for some of the communicable disease agents listed in § 610.40 of the final rule. We expect, in the future, that blood and plasma establishments will submit for approval other reentry algorithms for the listed communicable disease agents.

(Comment 24) One comment requests that FDA explicitly allow the use of newly developed technologies to reenter donors under proposed § 610.40(f)(3).

We are allowing for further advancements in testing methodologies by not identifying specific tests to be performed within this rulemaking. We will continue evaluating new technologies related to reentry of deferred donors. We intend to issue guidance concerning our views on the use of those new technologies in screening and confirmatory communicable disease testing and as part of reentry algorithms for donors deferred based on results of screening tests for infection due to communicable disease agents.

(Comment 25) One comment stated that the exception to deferral in proposed § 610.41(a) should apply to donors who test reactive for anti-HTLV, types I and II, or anti-HBc on only one occasion, unless further testing under proposed § 610.40(c) is positive.

We agree in part with this comment. Once a supplemental test for anti-HTLV, types I and II, or for anti-HBc is approved, deferral will occur after a reactive screening test on one occasion regardless of the outcome of the supplemental (additional, more specific) testing. When a supplemental test is approved, we intend to issue guidance on when donor requalification is appropriate. Until such time, deferral will be based on reactive test results on two occasions.

(Comment 26) One comment requests clarification of the rule's impact on anti-HBc testing of blood and blood components for further manufacturing use.

The final rule does not require blood and plasma establishments to test blood and blood components for further manufacturing use (including Source Plasma) for anti-HBc. The rule does not prohibit establishments that choose to test such products for anti-HBc from using reactive blood or blood components in fractionation products and in in-vitro diagnostic products. A guidance issued to all registered blood establishments addresses labeling for injectable and non-injectable products using anti-HBc reactive blood components. (See the list of documents in section IV of this document (dated September 9, 1991).)

(Comment 27) For the manufacture of Hepatitis B Immune Globulin (Human) (HBIG), one comment supports the use of donors immunized to hepatitis B virus, as an alternative to using donors previously showing evidence of infection due to hepatitis B virus. The comment contends that this change would expand the possible supply. Another comment opposes the sole use of blood from donors immunized to hepatitis B virus in manufacture of HBIG for reasons related to protecting the public health.

We disagree with the first comment, and accept the second. In the final rule, we have permitted deferred donors previously showing evidence of infection due to hepatitis B virus to donate blood or blood components for use in the preparation of HBIG, provided that the current donations test nonreactive for HBsAg and that the donor is otherwise suitable. The agency has concluded that donors with antibodies to HBsAg should not be excluded. Donors having detectable antibodies to HBsAg have a spectrum of antibodies to different epitopes of the hepatitis B virus and, therefore, are acceptable or even desirable as donors for HBIG. Blood or blood components from such donors also may provide better protection against future mutations of the hepatitis B virus. We believe that HBIG prepared from the blood and blood components of donors previously showing evidence of infection would produce a more effective product.

F. Syphilis

In the proposed rule, we requested comments on continuing the requirement for testing each donation of blood and blood components for syphilis. We also requested data supporting their conclusion.

(Comment 28) The majority of comments that responded to the issue of testing for syphilis support eliminating such testing. These comments argue that there has been no reported case of transfusion transmitted syphilis in 30 years; that studies show treponemes don't survive in blood stored at 4 ½C and positive treponenemal DNA/RNA is not present in test positive donations based on studies using polymerase chain reaction (PCR) (ARCNET study); that there are no relevant case reports of platelet transfusion transmission; and that recent studies indicate testing for syphilis has limited value as a surrogate marker for other communicable disease agents or high risk behavior. The comments also point out that syphilis testing has unnecessarily constricted the blood supply and eroded donor trust as otherwise qualified donors are deferred based on what turns out to be treated previous infection. Those comments that oppose eliminating the syphilis requirements criticize the recent ARCNET study's methodology and conclusions and argue that there is not sufficient information to eliminate testing requirements.

After reviewing the comments and submitted study in addition to other scientific data, we have determined that the comments did not provide sufficient supporting data to justify eliminating the requirements to test blood and blood components with a serological test for syphilis. Preliminary results from ongoing studies indicate that the infectivity of seroreactive donors remains the subject of scientific debate. (See the transcript of the 67th Blood Product Advisory Committee Meeting, September 15, 2000). We will continue to consider this issue including any further studies that address the issues of transfusion related syphilis infection or testing for syphilis as a surrogate marker for other communicable diseases. We remain interested in receiving data supporting the elimination of the requirement for syphilis testing. Blood and plasma establishments must continue to test donations of blood and blood components for syphilis under §§ 640.5(a), 640.14, 640.23(a), 640.33(a), 640.53(a), and 640.65(b)(2) and references to these sections are inserted into the codified language in §§ 610.40

and 610.41. The final rule requires that blood and plasma establishments defer donors who test reactive for a serologic test for syphilis unless a specific treponemal antibody test is negative or the donation is used for further manufacturing into control serum for a serological test for syphilis.

In § 610.40(h)(2)(vi) and (vii), we added language describing current requirements for the use of human blood, blood components, and Source Plasma with a reactive screening test for syphilis that is determined to be a biological false positive. Human blood and blood components may be used if the reactive screening test is further tested by an adequate and appropriate test demonstrating that the reactive screening test is a biological false positive. (See the list of documents in section IV of this document (dated December 12, 1991)). Such donations must be labeled with both test results. Source Plasma may be used from a donor with a reactive screening test for syphilis if the donor meets the requirements of § 640.65(b)(2).

VI. Effective Date

This final rule becomes effective December 10, 2001. All blood and blood components collected on and after the effective date must be in compliance with the new requirements. Labeling required by §§ 610.40(c)(3)(ii) and (h)(2)(ii), and 610.42 must be submitted to FDA as part of a supplement submission requesting FDA approval prior to distribution of a product under § 601.12(f)(1) (21 601.12(f)(1)). All other labeling changes must be submitted in an annual report under § 601.12(f)(3).

VII. Analysis of Impacts

FDA has examined the impacts of the rule under Executive Order 12866, under the Regulatory Flexibility Act (5 U.S.C. 601–612), and under the Unfunded Mandates Reform Act(2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and equity). The Regulatory Flexibility Act requires agencies to analyze whether a rule may have a significant impact on a substantial number of small entities and, if it does, to analyze regulatory options that would minimize the impact. Section 202(a) of the Unfunded Mandates Reform Act requires that agencies prepare a written statement of anticipated costs and benefits before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of $100 million (adjusted annually for inflation).

The Office of Management and Budget (OMB) has determined that the rule is a significant regulatory action as defined by the Executive Order and so is subject to review. Because the rule does not impose any mandates on State, local, or tribal governments, or the private sector, that will result in any one year of $100 million or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandates Reform Act.

The Regulatory Flexibility Act requires agencies to prepare a Regulatory Flexibility Analysis for each rule unless the agency certifies that the rule will not have a significant economic impact on a substantial number of small entities. Although the rule is not expected to have a significant economic impact on a substantial number of small business entities, a precise impact is uncertain. Therefore, the agency has prepared a Regulatory Flexibility Analysis.

A. Objectives and Basis of the Action

The basis for this rule is to help protect the safety and ensure the quality of the Nation's blood supply, and to promote consistency in the industry. The safety of the Nation's blood supply is enhanced when donors whose test results indicate evidence of infection due to communicable disease agents are excluded from donating blood and blood components. Under the biologics licensing and quarantine provisions of sections 351–361 of the Public Health Service Act (PHS Act) (42 U.S.C. 262–264) and the drug, device, and the general administrative provisions of sections 501–503, 505–519, and 701–704 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 351–353, 355–360i, and 371–374), FDA has the authority to issue regulations designed to protect the public from unsafe or ineffective biological products and to issue regulations necessary to prevent the transmission of communicable diseases into the United States or from one State to another. Under these statutory authorities, the agency is: (1) Requiring supplemental (additional, more specific) testing of all donations that are reactive by screening tests for which there are supplementary tests; and (2) codifying as requirements those recommendations that FDA has issued that are necessary to ensure blood safety, including testing for evidence of infection due to HIV, HBV, HCV, and HTLV.

B. Nature of the Impact

The rule requires that each donation of human blood or blood component, including those intended for use as a component of, or used to prepare, a medical device, but not including those intended for autologous use, unless shipped or used for allogeneic transfusion, be tested for evidence of infection due to HIV, types 1 and 2; HBV; HCV; and HTLV, types I and II. Each donation that is reactive when tested for evidence of infection due to any of the disease agents would be required to be further tested whenever a supplemental (additional, more specific) test has been approved for such use by FDA. FDA is requiring that the testing be done by a laboratory that is registered with FDA and CLIA-certified or meeting equivalent requirements as determined by HCFA. The rule also contains provisions for appropriate deferral of donors based on test results, and exemptions for Source Plasma from being tested for evidence of infection from HTLV, types I and II. Under the rule, allogeneic donations that test reactive shall not be shipped except in situations specifically approved by FDA. Autologous donations may be shipped as long as they are properly labeled.

This rule also requires manufacturers of tests kits, approved for use in testing donations of human blood and blood components for these disease agents, to verify an acceptable sensitivity and specificity of each lot of test kit, using a reference panel obtained from CBER or an FDA designated source, when available.

1. The Type and Number of Entities Affected

The testing of donations from allogeneic and certain autologous donors of blood and blood components will affect all blood and plasma establishments that collect blood and blood components from such donors. FDA's registration database has record of 981 registered blood establishments that collect blood and blood components and 60 licensed plasma centers with approximately 370 locations that collect Source Plasma. Whole Blood donors in the United States are volunteers. By contrast, most Source Plasma centers are commercial establishments with paid donors. Based on information published by the American Association of Blood Banks (AABB) regarding allogeneic donations (Ref. 1), and communications with experts in the blood banking industry

regarding the testing of autologous donations, FDA believes that all of the 12 million blood donations (not including 643,000 autologous donations) currently collected annually by the regional and community blood centers and hospitals are already being tested for the specific disease agents as usual and customary business practice. FDA further estimates that autologous donations that are shipped are already being tested for HIV, types 1 and 2, HBV, HCV, HTLV, types I and II, and syphilis as usual and customary business practice. It is also usual and customary business practice for hospitals to solely use autologous donations for autologous use and not allow autologous donations to be used for allogeneic transfusion. Therefore, we estimate that since industry practices are currently the same as FDA requirements for testing shipped autologous donations, and are more stringent than FDA requirements for use of autologous donations for allogeneic transfusion, then additional costs to blood establishments collecting autologous blood and blood components will be minimal, if any.

In 1997, the Government Accounting Office (GAO) estimated that approximately 12 million donations of Source Plasma were collected by plasma centers (Ref. 2). Although the precise number of those donations currently tested for HIV, types 1 and 2, HBV, and HCV is not reported, FDA assumes that virtually all donations are currently being initially screened for the communicable disease agents specified for plasma donations in the rule. However, based on GAO reported variations in the plasma industry's confirmatory testing of repeat reactive donations, it is also assumed that supplemental testing for HCV is not widely practiced at present.

The requirements for lot testing of approved test kits by manufacturers will entail use of CBER regulatory reference panels to provide verification of the specificity and sensitivity of each lot of test kits approved for use in testing donations of human blood. This release criterion would be applied to lots of test kits produced by licensed manufacturers or lots produced by manufacturers pursuing licensure of such tests. FDA estimates that the number of manufacturers of kits for the four disease agents specified in the rule currently ranges from six to seven establishments per disease agent. It is also possible that some additional number of manufacturers may pursue licensure of such kits in future years, although the total number is likely to remain small because of the expected limits of demand for such tests.

FDA currently has reference panels available for all of the disease agents specified in the rule, and has made the panels available to all currently licensed manufacturers of test kits. To the agency's knowledge, all currently licensed manufacturers covered by the rule are already performing the tests to comply with their own quality assurance standards. The rule is therefore expected to introduce no substantial impact on these establishments.

2. Estimated Impact of Requirements for Donor Testing

The rule provisions for donation testing, appropriate handling, labeling, and distribution will involve a one-time effort by all blood and plasma establishments to review and modify current blood and plasma donor testing, handling, and recordkeeping protocols to comply with the rule. While the rule does establish test requirements, these are not expected to increase the yearly cost of donor screening testing.

The one-time effort to review and modify current SOP's is expected to take approximately 8 hours of staff time to reconcile the regulations against the facility's current standards. This process could be performed by a technical specialist who works as a regulatory reviewer or manager of quality assurance. Based on the total average hourly compensation of $25.67 for professional specialty and technical occupations in the health services industry, as reported by Bureau of Labor Statistics for March 1997, the cost would be approximately $205, for each of the blood and plasma collecting establishments. Because this final rule does not require that all blood centers test all autologous donations, it is a lesser burden that what was in the proposed rule. FDA assumes that the cost will be the same for all facilities, whether or not they currently test all autologous donations. It is also assumed that all facilities already perform careful labeling and keep records of test results for evidence of infection due to communicable disease agents. Thus, the total one-time cost for the industry is estimated to be $276,955 ((370 + 981 establishments) x $205).

(Comment 29) Ten comments asserted that testing of autologous donations is costly to facilities and patients.

We have considered these comments and we are limiting the requirement to test autologous donations to two occasions when risk of exposure is increased, i.e., when autologous donations are used for allogeneic transfusion or when they are shipped. It is assumed that there will be very little testing that was not already being done, and that the requirement to test autologous donations when used for allogeneic transfusion or shipped will not impose additional cost.

The rule also allows that multiple donations of blood and blood components from single donors dedicated to a single identified recipient be tested once at the beginning of a 30-day period. These dedicated donations, however, are relatively uncommon and are believed to generally undergo testing by all facilities that is at least as frequent as the rule requires.

(Comment 30) Two comments contend that supplemental testing should be required only for HIV and HBsAg. Four additional comments noted that supplemental testing is expensive.

The agency believes that while there are costs to supplemental testing, the costs imposed by this rule are mitigated because a substantial fraction of facilities already perform supplemental testing. In addition, the ability to obtain more precise information on donors testing reactive will improve public health by providing these donors with accurate health information.

Currently, blood and plasma establishments are required under § 610.46(b) to further test donations that test reactive by a screening test for HIV. Anti-HBc and anti-HTLV, types I and II, do not have supplemental (additional, more specific) tests approved for such use by FDA at this time. Therefore, the yearly increase in cost imposed by this final rule is based on the assumption that blood and plasma collecting establishments will need to begin supplemental (additional, more specific) testing on donations that test reactive for HCV and HBsAg. Assuming: (1) An average 0.18 percent (0.0018) rate of HCV reactive donations; (2) an average 0.05 percent (0.0005) rate of HBsAg reactive donations; and (3) an annual volume of approximately 24 million blood and plasma donations, and the cost for a supplemental (additional, more specific) test for HCV and HbsAg is approximately $144.50 and $8.00 respectively (Ref. 3), then the annual cost is estimated to be no greater than $5,946,400 ((24,000,000 x 0.0018) x $114.50 + (24,000,000 x 0.0005) x $8.00).

In summary, the rule would result in an estimated one-time cost of $276,955, and a total annual cost of $5,042,400 to the blood and plasma industries.

3. Expected Benefits of the Rule

The rule is intended to increase the safety of all blood and blood component products by providing recipients with increased protection against communicable disease transmission. The rule addresses exposures that may occur through errors in administration of autologous as well as allogeneic blood units. For example, AABB Anonymous Survey Report included reports of erroneous transfusions (1.2 percent of respondents), untested recovered plasma salvaged (3.7 percent), units lost in transit (12.3 percent), units broken in the lab (33.6 percent), and units broken outside the lab (32.2 percent), as well as other errors (9.8 percent) (Ref. 4). The reduction in communicable disease risk already achieved among allogeneic blood transfusions as a result of infectious disease testing of donors has been quite dramatic. For example, as a result of the expansion of blood donor screening and improved laboratory tests, it is now estimated that the chances of transfusion-related HIV infection have decreased to between 1 in 450,000 to 660,000 per unit of blood (Ref. 5). HCV and HBV transfusion risks have also declined. In 1990, prior to specific testing, HCV was transmitted by 0.2 to 0.5 percent of transfusions, compared with the current rate of approximately 0.0005 percent. The risk of HBV transfusion transmission is currently estimated to be 1 in 500,000 transfused units.

The gravity of the disease risks addressed by the rule is widely recognized. Transfusion of HIV, the virus that causes AIDS, continues to cause great concern. Human T-cell leukemia/lymphoma viruses types I and II ,were identified in the early 1980's. Infection with the virus is associated with tropical spastic paraparesis, adult T-cell leukemia/lymphoma, and some inflammatory disorders (Lapane et al.). Although the virus is primarily transmitted by sexual contact and intravenous drug abuse, it can also be transmitted through blood transfusion.

HBV is a major cause of acute and chronic hepatitis, cirrhosis, and primary hepatocellular carcinoma worldwide. The Centers for Disease Control and Prevention (CDC) estimated that in 1985 approximately 300,000 persons became infected with HBV. Prior to the development of hepatitis screening tests, transfusion-related risks were significant. A retrospective testing of blood donors using first generation tests for the presence of HBsAg found that over half of recipients of HBsAg positive blood developed hepatitis (Ref. 6). Of the current pool of 1 to 1.25 million HBV carriers, approximately 25 percent will develop chronic hepatitis which will progress to cirrhosis and carriers will have a risk of liver cancer that is 12 to 300 times higher than the risk to non-carriers. An estimated 4,000 persons die each year from hepatitis B-related cirrhosis, and more than 800 die from primary hepatocellular carcinoma (PHC). The lifetime medical cost per case of PHC and cirrhosis is estimated to be $96,500 (Ref. 7).

Epidemiologic and experimental studies indicate that HCV is primarily transmitted by the parenteral route. Persons at increased risk of acquiring hepatitis C include parenteral drug users; health-care workers with occupational exposure to blood; hemodialysis patients; and recipients of Whole Blood, blood cellular components, or Plasma. Transfusion of blood or blood products, which accounted for a substantial proportion of HCV infections acquired more than 10 years ago, is now an uncommon means of transmission. CDC estimates that 150,000 to 170,000 new HCV infections occur annually in the United States (Ref. 8). Of patients with transfusion-associated chronic non-A, non-B hepatitis who undergo biopsy within 5 years after onset, at least 40 percent have histological evidence of chronic active hepatitis and 10 to 20 percent have evidence of cirrhosis (Ref. 9). An estimated 30 percent of those infected will eventually die of liver-related causes, an estimated 8,000 patients per year. Although some HCV patients have been found to respond to interferon therapy, the average cost of care per year for persons with liver disease from chronic hepatitis C is estimated to range from $24,600 for patients without interferon-alpha therapy to $26,500 per year for those receiving a 12-month course of therapy. The latter has been estimated to provide patients with an additional 0.37 quality-adjusted life years (Ref. 10). As described previously, the requirement of HIV, types 1 and 2; HBV; HCV; HTLV, types I and II; and syphilis testing for blood and blood component donations significantly reduces the U.S. population's exposure to the morbidity and mortality risks associated with these diseases, and their attendant costs.

4. Small Entity Impact

The information available to characterize the relevant volumes of affected blood and plasma products is limited. Although the rule is not expected to have a significant impact on a substantial number of small entities, the impact on blood and plasma establishments that might qualify as small entities is uncertain. FDA has therefore prepared a Regulatory Flexibility Analysis. The blood and plasma establishments affected by the rule are included under the major Standard Industry Code (SIC) group 80 for providers of health services. According to section 601 of the Regulatory Flexibility Act of 1980, the term ''small entity'' encompasses the terms ''small business,'' ''small organization,'' and ''small governmental jurisdiction.'' ''Small governmental jurisdiction'' generally means governments of cities, counties, towns, townships, villages, school districts, or special districts with a population of less than 50,000.

The extent of the small business impact is uncertain. Although the details of blood collection at hospitals are not available, FDA examined other data to develop a preliminary assessment of small business impact. The size of U.S. hospitals varies substantially. The 1998 American Hospital Association (AHA) survey data (Ref. 11) indicate a total of 5,134 U.S. registered community hospitals grouped into 8 bedsize categories. The average annual revenues for facilities in these bedsize categories range from approximately $5.5 million to $513 million. However, since many hospitals are not-for-profit or are operated by State and local governments, the Small Business Association (SBA) annual receipts criteria for small businesses would not apply to these facilities. Of the 5,134 U.S. community hospitals included in the AHA report, 1,330 are under the control of State and local government, 3,045 are nonprofit institutions, and the remaining 759 are reported to be investor-owned. (Note that while there are over 5,000 community hospitals in this small entity impact analysis, not all 5,000 hospitals are collecting facilities. Therefore, this does not invalidate the estimate of 60 licensed plasma centers with 370 locations and 981 registered blood establishments affected by the rule.)

The number of hospitals that would meet at least one of the various SBA definitions for small entities is uncertain. According to the AHA statistics for 1998, the smallest reported hospital size category includes 262 hospitals with 6 to 24 beds, and total gross revenues of $1.43 billion, yielding average revenues of $5.46 million. FDA assumes that the 11 facilities reported to be investor-owned within this bedsize category could qualify as small entities. Although it is possible that all nonprofit hospitals may qualify as small entities, it appears that a number of facilities

might be excluded from that definition because they are reported to be hospitals in a system. According to the AHA survey definition, ''hospitals belonging to a corporate body that owns and/or manages health provider facilities or health-related subsidiaries; the system may also own non-health-related facilities.'' The AHA currently has record of 1,592 hospitals that are nonFederal and nonprofit (including State and local government controlled) that are hospitals in a system. If these facilities were excluded, FDA estimates that 2,783 [1,330 State and local + 3,045 nonprofit—1,592 in-a-system] non-federal, nonprofit hospitals may qualify as small entities. Although, a total of 2,794 [2,783 + 11] hospitals might qualify as small entities, not all such hospitals collect blood and blood components, and some would be transfusion services only.

Approximately 75 of the 981 registered blood establishments that collect blood and blood components are responsible for collecting 65 percent of the blood supply (7.8 million donations). The remaining 906 registered blood establishments assumed to operate as small entities would collect 45 percent of the blood supply (5.4 million donations). If the estimated 5.4 million donations of blood and blood components were evenly distributed over the 906 registered blood collection establishments, each establishment would average 5,960 donations annually, of which approximately 11 (0.0018 x 5,960) might test reactive for HCV and approximately 3 (0.0005 x 5,960) of which might test reactive for HBsAg, and require supplemental testing. The expected cost of the additional testing would then be $1,283.50 (($114.50 x 11) + ($8.00 x 3)) per establishment per year.

The number of plasma facilities that would qualify as small entities is also uncertain. According to the General Accounting Office (Ref. 12) approximately 370 paid plasma collection locations annually collect about 12 million plasma donations, the vast majority of which is processed by 8 companies. FDA estimates that approximately 90 percent of these plasma collection locations are owned by companies that operate multiple facilities. Although the agency is uncertain about the level of revenues for these companies, it is considered likely that most would have annual receipts of $5 million or more per year. The remaining 10 percent of paid plasma collection locations (37 locations) may qualify as small business establishments. The potential impact on these facilities will be a function of the number of donors and the HCV and HBsAg reactive findings among donors at their facility. If the estimated 12 million plasma donations were evenly distributed over the collection centers, each center would average 25,000 donations. Assuming approximately 8 units per plasma donor per year (Ref. 12), each center would average 3,125 donors, approximately 6 (0.0018 x 3,125) of whom might test reactive for HCV and approximately 2 (0.0005 x 3,125) of whom might test reactive for HBsAg, and require supplemental testing. The expected cost of the additional testing would then be $703 (($114.50 x 6) + ($8.00 x 2)) per center per year.

In addition to these for-profit establishments, the remaining plasma collection centers function within blood collection centers that are operated by the American National Red Cross, or are independently operated. The independently operated, not-for-profit blood collection centers would likely qualify as small entities. The added impact of the rule on plasma collection performed at blood collection facilities is expected to be small, however, because the required testing would already be performed for Whole Blood donation.

FDA has considered alternatives for lessening the burden on small entities. The proposed rule proposed that all autologous blood be tested. By choosing this less costly alternative that does not require autologous blood testing, FDA is lessening the burden on small entities.

VIII. The Paperwork Reduction Act of 1995

This final rule contains information collection requirements that are subject to review by OMB under the Paperwork Reduction Act of 1995 (the PRA) (44 U.S.C. 3501–3520). The title, description, and respondent description of the information collection provisions are shown below with an estimate of the annual reporting and recordkeeping burden. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Recordkeeping and Reporting Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents.

Description: FDA is revising the test requirements in part 610 subpart E issued under the authorities of the act and the PHS Act. Section 610.40 of the final rule requires screening tests for evidence of infection due to communicable disease agents, HIV, types 1 and 2; HBV; HCV; HTLV, types I and II, be performed on each donation of human blood and blood component. Certain exceptions to performing screening tests are described elsewhere in this rule.

In § 610.40(c)(1)(ii), each dedicated donation must be labeled as required under § 606.121 and with a label entitled ''INTENDED RECIPIENT INFORMATION LABEL'' containing the name and identifying information of the recipient. Each donation that is untested in the 30-day period must be labeled ''DONOR TESTED WITHIN THE LAST 30 DAYS.''

In § 610.40(d)(4), each autologous donation must be labeled as required under § 606.121 and with the following label, as appropriate. If the donation is: (1) Untested, label with ''UNTESTED;'' (2) negative, label as required under § 606.121; (3) reactive on the current collection or in the last 30 days, label with ''BIOHAZARD'' legend; and (4) tested negative within the last 30 days, label with ''DONOR TESTED WITHIN THE LAST 30 DAYS.''

Under § 610.40(g), each donation that may be released or shipped prior to testing must be labeled as required under § 606.121(h) and the test results must be provided promptly to the consignee. Section 610.40(g)(1) permits release or shipment prior to completion of testing in documented medical emergencies, and § 610.40(g)(2) permits release or shipment prior to completion of testing when FDA provides written approval for the shipment or use.

In § 610.40(h)(2)(ii), human blood or blood components intended for further manufacturing use may be shipped or used under the following conditions.

- When FDA provides written approval for the shipment or use;
- When such human blood and blood components are labeled as required under § 606.121 or § 640.70 and with the ''BIOHAZARD'' legend;
- When such human blood and blood components are labeled reactive for the appropriate screening test for evidence of infection due to the identified communicable disease agent(s);
- When such human blood and blood components are intended for further manufacturing use into injectable products, and a statement indicating the exempted use specifically approved by FDA is included on the container label;
- When such human blood and blood components are intended solely as a component of, or used to prepare, a medical device and the statement ''Caution: For Further Manufacturing Use As a Component of a Medical Device For Which There Are No Alternative Sources;'' and

• When such human blood and blood components are intended for in vitro use and the statement ''Caution: For Further Manufacturing Into In Vitro Diagnostic Reagents For Which There Are No Alternative Sources'' is included.

In § 610.40(h)(2)(vi) and (h)(2)(vii), we added language describing current practice on the use of human blood and blood components, and Source Plasma, with a reactive screening test for syphilis that is determined to be a biological false positive.

In § 610.42(a), medical devices containing or used to prepare human blood or blood components that are reactive for syphilis or by a screening test for evidence of infection due to a communicable disease agent(s) must include, in addition to appropriate labeling requirements in subchapter H (Medical Devices), a statement of warning that the product was manufactured from a donation testing reactive for the identified communicable disease agent(s).

Description of Respondents: Establishments that collect blood and blood components.

As required by section 3506(c)(2)(B) of the PRA, FDA provided an opportunity for public comment on the information collection requirements of the proposed rule (64 FR 67207). In accordance with the PRA, OMB reserved approval of the information collection burden in the proposed rule stating they will make an assessment in light of public comments received on the proposed rule. No letters of comment on the information collection requirements were submitted to OMB or the docket.

Based on current information retrieved from FDA's registration data base, there are approximately 60 licensed plasma collection facilities and approximately 981 registered blood collection facilities for a total of 1,041 establishments. These facilities collect annually an estimated 24.6 million donations: 12 million donations of Source Plasma and 12.6 million donations of Whole Blood, including 643,000 autologous.

Annual Reporting Burden (Table 3)

Section 610.40(c)(1)(ii) requires that each dedicated donation be labeled as required under § 606.121 (OMB No. 0910–0116) and with a label containing the name and identifying information of the recipient. FDA estimates that approximately 5 percent (10,250) of the 205,000 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). FDA estimates that the remaining 95 percent would be tested as allogeneic donations in accordance with § 610.40(a), (b), and (e) because most such donors do not donate more often than once in a 30-day period, and because most establishments choose to test every donation. We estimate that each establishment expends approximately 5 minutes to insert the name of the recipient and identifying information on each label.

In § 610.40(g)(2) and (h)(2)(ii)(A), a manufacturer must obtain written approval from FDA when a manufacturer seeks to: (1) Ship human blood or blood components for further manufacturing use prior to completion of testing; or (2) ship human blood or blood components found to be reactive by a screening test for evidence of a communicable disease agent(s) or collect from a donor with a record of a reactive screening test, respectively. The only product currently shipped prior to completion of testing is a licensed product, Source Leukocytes, used in the manufacture of interferon, which requires rapid preparation from blood. Shipment of Source Leukocytes are preapproved under a product license application and each shipment does not have to be reported to the agency. To obtain approval from FDA as described in § 610.40(g)(2), we expect the manufacturer(s) to submit specific procedures for collection, shipment, and quarantine of a product before testing is completed, and the completion of testing as soon as possible after shipping. In addition, the manufacturer must promptly communicate the test results to the consignee. FDA has received two applications from the manufacturers of Source Leukocytes during fiscal year (FY) 95, FY 96, and FY 97. Therefore, we estimate receiving an average of two annually.

According to information from industry, a license application of this type would contain safety and effectiveness information and would take approximately 1,600 hours to prepare. The information that a manufacturer would need to put together for the request is typically part of an Biologics License Application (BLA) submission. Therefore, we estimate that approximately 1 hour of the estimated 1,600 hours would be used in preparing the request for FDA's approval to ship a product prior to completion of testing.

Under § 610.40(h)(2)(ii)(C) and (h)(2)(ii)(D), industry estimates that each manufacturer would ship an estimated 10 blood or blood components per month that would require 2 labels; one as reactive for the appropriate screening test under paragraph (C), and the other stating the exempted use specifically approved by FDA under paragraph (D). According to FDA's database, there are approximately 300 licensed manufacturers that ship known reactive blood or blood components. Industry also estimates that it would take approximately 10 minutes per blood or blood component to affix the labels.

In § 610.40(h)(2)(vi), each donation of human blood or blood component that tests reactive by a screening test for syphilis and is determined to be a biological false positive, must be labeled with both test results. After reviewing information from industry, we estimate that approximately 15,120 donations annually test reactive by a screening test for syphilis, and are determined to be biological false positives by additional testing. We also estimate that the establishment would expend approximately 5 minutes to label the blood or blood component with the results of both tests.

Section 610.42(a) requires a warning statement, including the identity of the communicable disease agent, on medical devices containing human blood or blood components found to be reactive by a screening test for evidence of infection due to a communicable disease agent(s) or syphilis. 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 statement of warning is required to be affixed to the medical device. To account for this rare occasion we estimate that the warning statement would be necessary no more than once a year and we estimate the manufacturer would need to expend 1 hour to complete the labeling requirement.

Annual Recordkeeping Burden (Table 4)

Under § 610.40(g)(1), we are permitting in rare emergency circumstances, the release or shipment of human blood or blood components prior to the completion of testing for evidence of infection due to communicable disease agents. Such emergencies include, e.g., where a patient's need for blood is so acute as to preclude any communicable disease

testing of the blood. We have concluded that the use of untested or incompletely tested blood in such medical emergencies should not be prohibited. Release of blood or blood components due to a medical emergency prior to completion of required testing must be appropriately documented. We estimate the recordkeeping to be minimal with one or less occurrence per year. Documentation of the medical emergency should take a half-hour or less. 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.

TABLE 3.—ESTIMATED ANNUAL REPORTING BURDEN[1]

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
610.40(c)(1)(ii)	1,041	9	10,250	.08	820
610.40(g)(2)	2	1	2	1	2
610.40(h)(2)(ii)(A)	2	1	2	1	2
610.40(h)(2)(ii)(C) and (h)(2)(ii)(D)	300	10	3,000	0.2	600
610.40(h)(2)(vi)	1,041	15	15,120	0.08	1,210
610.42(a)	1	1	1	1	1
Total					2,635

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

TABLE 4.—ESTIMATED ANNUAL RECORDKEEPING BURDEN[1]

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
610.40(g)(1)	981	1	981	0.5	490.5

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

Under section 1320.3(c)(2) of the PRA, the labeling requirements in § 610.40(c)(3)(ii), (d)(4), and (h)(2)(ii)(B) and (h)(2)(ii)(E) do not constitute collection of information because information required to be on the labeling is originally supplied by the Federal Government to the manufacturers for the purpose of disclosure to the public in order to keep the blood supply safe and protect public health.

The information collection provisions of this final rule have been submitted to OMB for review.

Prior to the effective date of this final rule, FDA will publish a notice in the **Federal Register** announcing OMB's decision to approve, modify, or disapprove the information collection provisions in this final rule. An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number.

IX. Environmental Impact

The agency has determined under 21 CFR 25.30(j) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

X. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency has concluded that the rule does not contain policies that have federalism implications as defined in the order and, consequently, a federalism summary impact statement is not required.

XI. References

The following references have been placed on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. American Association of Blood Banks, *Facts About Blood and Blood Banking,* ''http://www.aabb.org''.

2. General Accounting Office, ''Blood Safety: Enhancing Safeguards Would Strengthen the Nation's Blood Supply,'' GAO–HEHS–97–143, June 1997.

3. Lapane, K. L., A. F. Jakiche, D. Sugano, C. S. Wayne Weng, and W. D. Carey, ''Hepatitis C Infection Risk Analysis: Who Should Be Screened? Comparison of Multiple Screening Strategies Based on the National Hepatitis Surveillance Program,'' *The American Journal of Gastroenterology*, vol. 93, no. 4, pp. 591–596, 1998.

4. American Association of Blood Banks (AABB) Association Bulletin No. 95–4: *AABB Position on Testing of Autologous Units. Attachment 1: AABB Anonymous Autologous Survey Request*, May 9, 1999.

5. Podnos, Y. D. and R. A. Williams, Current Risks for Blood Borne Viral Illness in Blood Transfusion, *Western Journal of Medicine*, vol. 168, no. 1, pp. 36–37, January 1998.

6. Public Health Service Inter-Agency Guidelines for Screening Donors of Blood, Plasma, Organs, Tissues, and Semen for Evidence of Hepatitis B and Hepatitis C, *Morbidity and Mortality Weekly Report* 40 (RR–4) April 19, 1991.

7. Margolis, H. S., P. J. Coleman, R. E. Brown, E. E. Mast, S. H. Sheingold, and J. A. Arevalo, ''Prevention of Hepatitis B Virus Transmission by Immunization: an Economic Analysis of Current Recommendations,'' *Journal of the American Medical Association*, vol. 274, no. 15, October 1995.

8. U.S. Centers for Disease Control and Prevention, 1997, ''www.cdc.gov/ncidod/diseases/hepatitis''.

9. *Morbidity and Mortality Weekly Report*, 40 (RR–4) April 19, 1991.

10. Kim, W. R., J. J. Peterucha, J. E. Hermans, T. M. Therneau, E. R. Dickson, R. W. Evans, and J. B. Gross,

''Cost-Effectiveness of 6 and 12 Months of Interferon Therapy for Chronic Hepatitis C,'' *Annals of Internal Medicine*, vol. 127, no. 10, November 1997.

11. Healthcare InfoSource, Inc., a subsidiary of the American Hospital Association, *Hospital Statistics*, 1998 ed., Chicago, IL.

12. General Accounting Office, ''Blood Plasma Safety: Plasma Product Risks Are Low if Good Manufacturing Practices Are Followed.'' GAO–HEHS–98–205, September 1998.

List of Subjects

21 CFR Part 606

Blood, Labeling, Laboratories, Reporting and recordkeeping requirements.

21 CFR Part 607

Blood.

21 CFR Parts 610 and 660

Biologics, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 640

Blood, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 809

Labeling, Medical devices.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act, and under the authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 606, 607, 610, 640, 660, and 809 are amended as follows:

PART 606—CURRENT GOOD MANUFACTURING PRACTICE FOR BLOOD AND BLOOD COMPONENTS

1. The authority citation for 21 CFR part 606 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 355, 360, 360j, 371, 374; 42 U.S.C. 216, 262, 263a, 264.

2. Section 606.121 is amended by revising paragraph (e)(5)(ii), by removing and reserving paragraph (g), and in paragraphs (h)(2) and (h)(3) by removing ''610.45,'' to read as follows:

§ 606.121 Container label.

* * * * *

(e) * * *

(5) * * *

(ii) The statement as applicable: ''Caution: For Manufacturing Use Only''; or ''Caution: For Use in Manufacturing Noninjectable Products Only.'' If the recovered plasma has a reactive screening test for evidence of infection due to a communicable disease agent(s) under § 610.40 of this chapter, or is collected from a donor with a previous record of a reactive screening test for evidence of infection due to a communicable disease agent(s) under § 610.40 of this chapter, the recovered plasma must be labeled as required under § 610.40(h)(2)(ii)(E) of this chapter.

* * * * *

PART 607—ESTABLISHMENT REGISTRATION AND PRODUCT LISTING FOR MANUFACTURERS OF HUMAN BLOOD AND BLOOD PRODUCTS

3. The authority citation for 21 CFR part 607 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 355, 360, 371, 374; 42 U.S.C. 216, 262.

§ 607.65 [Amended]

4. Section 607.65 *Exemption for blood product establishments* is amended by removing paragraph (g).

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

5. The authority citation for 21 CFR part 610 is revised to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360c, 360d, 360h, 360i, 371, 372, 374, 381; 42 U.S.C. 216, 262, 263, 263a, 264.

6.–7. The heading of subpart E is revised to read as follows:

Subpart E—Testing Requirements for Communicable Disease Agents

8. Section 610.40 is revised to read as follows:

§ 610.40 Test requirements.

(a) *Human blood and blood components.* Except as specified in paragraphs (c) and (d) of this section, you, an establishment that collects blood or blood components, must test each donation of human blood or blood component intended for use in preparing a product, including donations intended as a component of, or used to prepare, a medical device, for evidence of infection due to the following communicable disease agents:

(1) Human immunodeficiency virus, type 1;

(2) Human immunodeficiency virus, type 2;

(3) Hepatitis B virus;

(4) Hepatitis C virus;

(5) Human T-lymphotropic virus, type I; and

(6) Human T-lymphotropic virus, type II.

(b) *Testing using one or more approved screening tests.* To test for evidence of infection due to communicable disease agents designated in paragraph (a) of this section, you must use screening tests that the Food and Drug Administration (FDA) has approved for such use, in accordance with the manufacturer's instructions. You must perform one or more such tests as necessary to reduce adequately and appropriately the risk of transmission of communicable disease.

(c) *Exceptions to testing for allogeneic transfusion or further manufacturing use.*

(1) *Dedicated donations.* (i) You must test donations of human blood and blood components from a donor whose donations are dedicated to and used solely by a single identified recipient under paragraphs (a), (b), and (e) of this section; except that, if the donor makes multiple donations for a single identified recipient, you may perform such testing only on the first donation in each 30-day period. If an untested dedicated donation is made available for any use other than transfusion to the single, identified recipient, then this exemption from the testing required under this section no longer applies.

(ii) Each donation must be labeled as required under § 606.121 of this chapter and with a label entitled ''INTENDED RECIPIENT INFORMATION LABEL'' containing the name and identifying information of the recipient. Each donation must also have the following label, as appropriate:

Donor Testing Status	Label
Tests negative Tested negative within the last 30 days	Label as required under § 606.121 ''DONOR TESTED WITHIN THE LAST 30 DAYS''

(2) *Source Plasma.* You are not required to test donations of Source Plasma for evidence of infection due to the communicable disease agents listed in paragraphs (a)(5) and (a)(6) of this section.

(3) *Medical device.* (i) You are not required to test donations of human blood or blood components intended solely as a component of, or used to prepare, a medical device for evidence of infection due to the communicable disease agents listed in paragraphs (a)(5) and (a)(6) of this section unless the final device contains viable leukocytes.

(ii) Donations of human blood and blood components intended solely as a component of, or used to prepare, a medical device must be labeled ''Caution: For Further Manufacturing Use as a Component of, or to Prepare, a Medical Device.''

(4) *Samples.* You are not required to test samples of blood, blood components, plasma, or sera if used or distributed for clinical laboratory testing or research purposes and not intended for administration to humans or in the manufacture of a product.

(d) *Autologous donations.* You, an establishment that collects human blood or blood components from autologous donors, or you, an establishment that is a consignee of a collecting establishment, are not required to test donations of human blood or blood components from autologous donors for evidence of infection due to communicable disease agents listed in paragraph (a) of this section or by a serological test for syphilis under paragraph (i) of this section, except:

(1) If you allow any autologous donation to be used for allogeneic transfusion, you must assure that all autologous donations are tested under this section.

(2) If you ship autologous donations to another establishment that allows autologous donations to be used for allogeneic transfusion, you must assure that all autologous donations shipped to that establishment are tested under this section.

(3) If you ship autologous donations to another establishment that does not allow autologous donations to be used for allogeneic transfusion, you must assure that, at a minimum, the first donation in each 30-day period is tested under this section.

(4) Each autologous donation must be labeled as required under § 606.121 of this chapter and with the following label, as appropriate:

Donor Testing Status	Label
Untested	''DONOR UNTESTED''
Tests negative	Label as required under § 606.121
Reactive on current collection/reactive in the last 30 days	''BIOHAZARD'' legend in § 610.40(h)(2)(ii)(B)
Tested negative within the last 30 days	''DONOR TESTED WITHIN THE LAST 30 DAYS''

(e) *Further testing.* You must further test each donation, including autologous donations, found to be reactive by a screening test performed under paragraphs (a) and (b) of this section, whenever a supplemental (additional, more specific) test has been approved for such use by FDA, except:

(1) For autologous donations, you must further test under this paragraph, at a minimum, the first reactive donation in each 30-day period; or

(2) If you have a record for that donor of a positive result on a supplemental (additional, more specific) test approved for such use by FDA, you do not have to further test an autologous donation.

(f) *Testing responsibility.* Required testing under this section, must be performed by a laboratory registered in accordance with part 607 of this chapter and either certified to perform such testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) under 42 CFR part 493 or has met equivalent requirements as determined by the Health Care Financing Administration in accordance with those provisions.

(g) *Release or shipment prior to testing.* Human blood or blood components that are required to be tested for evidence of infection due to communicable disease agents designated in paragraphs (a) and (i) of this section may be released or shipped prior to completion of testing in the following circumstances provided that you label the blood or blood components under § 606.121(h) of this chapter, you complete the tests for evidence of infection due to communicable disease agents as soon as possible after release or shipment, and that you provide the results promptly to the consignee:

(1) Only in appropriately documented medical emergency situations; or

(2) For further manufacturing use as approved in writing by FDA.

(h) *Restrictions on shipment or use*—(1) *Reactive screening test.* You must not ship or use human blood or blood components that have a reactive screening test for evidence of infection due to a communicable disease agent(s) designated in paragraphs (a) and (i) of this section or that are collected from a donor with a previous record of a reactive screening test for evidence of infection due to a communicable disease agent(s) designated in paragraphs (a) and (i) of this section, except as provided in paragraphs (h)(2)(i) through (h)(2)(vii) of this section.

(2) *Exceptions.* (i) You may ship or use blood or blood components intended for autologous use, including reactive donations, as described in paragraph (d) of this section.

(ii) You must not ship or use human blood or blood components that have a reactive screening test for evidence of infection due to a communicable disease agent(s) designated in paragraph (a) of this section or that are collected from a donor deferred under § 610.41(a) unless you meet the following conditions:

(A) Except for autologous donations, you must obtain from FDA written approval for the shipment or use;

(B) You must appropriately label such blood or blood components as required under § 606.121, or § 640.70 of this chapter, and with the ''BIOHAZARD'' legend;

BIOHAZARD

(C) Except for autologous donations, you must label such human blood and blood components as reactive for the appropriate screening test for evidence of infection due to the identified communicable disease agent(s);

(D) If the blood or blood components are intended for further manufacturing

use into injectable products, you must include a statement on the container label indicating the exempted use specifically approved by FDA.

(E) Each blood or blood component with a reactive screening test and intended solely as a component of, or used to prepare a medical device, must be labeled with the following label, as appropriate:

Type of Medical Device	Label
A medical device other than an in vitro diagnostic reagent	''Caution: For Further Manufacturing Use as a Component of a Medical Device For Which There Are No Alternative Sources''
An in vitro diagnostic reagent	''Caution: For Further Manufacturing Into In Vitro Diagnostic Reagents For Which There Are No Alternative Sources''

(iii) The restrictions on shipment or use do not apply to samples of blood, blood components, plasma, or sera if used or distributed for clinical laboratory testing or research purposes, and not intended for administration in humans or in the manufacture of a product.

(iv) You may use human blood or blood components from a donor with a previous record of a reactive screening test(s) for evidence of infection due to a communicable disease agent(s) designated in paragraph (a) of this section, if:

(A) At the time of donation, the donor is shown or was previously shown to be suitable by a requalification method or process found acceptable for such purposes by FDA under § 610.41(b); and

(B) tests performed under paragraphs (a) and (b) of this section are nonreactive.

(v) Anti-HBc reactive donations, otherwise nonreactive when tested as required under this section, may be used for further manufacturing into plasma derivatives without prior FDA approval or a ''BIOHAZARD'' legend as required under paragraphs (h)(2)(ii)(A) and (h)(2)(ii)(B) of this section.

(vi) You may use human blood or blood components, excluding Source Plasma, that test reactive by a screening test for syphilis as required under paragraph (i) of this section if, consistent with § 640.5 of this chapter, the donation is further tested by an adequate and appropriate test which demonstrates that the reactive screening test is a biological false positive. You must label the blood or blood components with both test results.

(vii) You may use Source Plasma from a donor who tests reactive by a screening test for syphilis as required under § 610.40(i) of this chapter, if the donor meets the requirements of § 640.65(b)(2) of this chapter.

(i) *Syphilis testing.* In addition to the testing otherwise required under this section, you must test by a serological test for syphilis under §§ 640.5(a), 640.14, 640.23(a), 640.33(a), 640.53(a), and 640.65(b)(2) of this chapter.

9. Section 610.41 is revised to read as follows:

§ 610.41 Donor deferral.

(a) You, an establishment that collects human blood or blood components, must defer donors testing reactive by a screening test for evidence of infection due to a communicable disease agent(s) listed in § 610.40(a) or reactive for a serological test for syphilis under § 610.40(i), from future donations of human blood and blood components, except:

(1) You are not required to defer a donor who tests reactive for anti-HBc or anti-HTLV, types I or II, on only one occasion. When a supplemental (additional, more specific) test for anti-HBc or anti-HTLV, types I and II, has been approved for use under § 610.40(e) by FDA, such a donor must be deferred;

(2) A deferred donor who tests reactive for evidence of infection due to a communicable disease agent(s) listed in § 610.40(a) may serve as a donor for blood or blood components shipped or used under § 610.40(h)(2)(ii);

(3) A deferred donor who showed evidence of infection due to hepatitis B surface antigen (HBsAg) when previously tested under § 610.40(a), (b), and (e) subsequently may donate Source Plasma for use in the preparation of Hepatitis B Immune Globulin (Human) provided the current donation tests nonreactive for HBsAg and the donor is otherwise determined to be suitable;

(4) A deferred donor, who otherwise is determined to be suitable for donation and tests reactive for anti-HBc or for evidence of infection due to HTLV, types I and II, may serve as a donor of Source Plasma;

(5) A deferred donor who tests reactive for a communicable disease agent(s) described under § 610.40(a) or reactive with a serological test for syphilis under § 610.40(i), may serve as an autologous donor under § 610.40(d).

(b) A deferred donor subsequently may be found to be suitable as a donor of blood or blood components by a requalification method or process found acceptable for such purposes by FDA. Such a donor is considered no longer deferred.

10. Section 610.42 is added to subpart E to read as follows:

§ 610.42 Restrictions on use for further manufacture of medical devices.

(a) In addition to labeling requirements in subchapter H of this chapter, when a medical device contains human blood or a blood component as a component of the final device, and the human blood or blood component was found to be reactive by a screening test performed under § 610.40(a) and (b) or reactive for syphilis under § 610.40(i), then you must include in the device labeling a statement of warning 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).

(b) FDA may approve an exception or alternative to the statement of warning required in paragraph (a) of this section based on evidence that the reactivity of the human blood or blood component in the medical device presents no significant health risk through use of the medical device.

11. Section 610.44 is added to subpart E to read as follows:

§ 610.44 Use of reference panels by manufacturers of test kits.

(a) When available and appropriate to verify acceptable sensitivity and specificity, you, a manufacturer of test kits, must use a reference panel you obtain from FDA or from an FDA designated source to test lots of the following products. You must test each lot of the following products, unless FDA informs you that less frequent testing is appropriate, based on your consistent prior production of products of acceptable sensitivity and specificity:

(1) A test kit approved for use in testing donations of human blood and blood components for evidence of

infection due to communicable disease agents listed in § 610.40(a); and

(2) Human immunodeficiency virus (HIV) test kit approved for use in the diagnosis, prognosis, or monitoring of this communicable disease agent.

(b) You must not distribute a lot that is found to be not acceptable for sensitivity and specificity under § 610.44(a). FDA may approve an exception or alternative to this requirement. Applicants must submit such requests in writing. However, in limited circumstances, such requests may be made orally and permission may be given orally by FDA. Oral requests and approvals must be promptly followed by written requests and written approvals.

§ 610.45 [Removed]

12. Section 610.45 *Human Immunodeficiency Virus (HIV) requirements* is removed.

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

13. The authority citation for 21 CFR part 640 continues to read as follows:

Authority: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371; 42 U.S.C. 216, 262, 263, 263a, 264.

§ 640.2 [Amended]

14. Section 640.2 *General requirements* is amended by removing paragraph (d).

15. Section 640.5 is amended by revising paragraph (f).

§ 640.5 Testing the blood.

* * * * *

(f) *Test for communicable disease agents.* Whole Blood shall be tested for evidence of infection due to communicable disease agents as required under § 610.40 of this chapter.

§ 640.14 [Amended]

16. Section 640.14 *Testing the blood* is amended by removing ''§§ 610.40 and 610.45'' and by adding in its place '' § 610.40''.

§ 640.23 [Amended]

17. Section 640.23 *Testing the blood* is amended in paragraph (a) by removing ''§§ 610.40 and 610.45'' and by adding in its place ''§ 610.40''.

§ 640.33 [Amended]

18. Section 640.33 *Testing the blood* is amended in paragraph (a) by removing ''§§ 610.40 and 610.45'' and by adding in its place ''§ 610.40''.

§ 640.53 [Amended]

19. Section 640.53 *Testing the blood* is amended in paragraph (a) by removing ''§§ 610.40 and 610.45'' and by adding in its place ''§ 610.40''.

20. Section 640.67 is revised to read as follows:

§ 640.67 Laboratory tests.

Each unit of Source Plasma shall be tested for evidence of infection due to communicable disease agents as required under § 610.40 of this chapter.

21. Section 640.70 is amended by revising paragraph (a)(2).

§ 640.70 Labeling.

(a) * * *

(2) The statement ''Caution: For Manufacturing Use Only'' for products intended for further manufacturing into injectable products, or the statement, ''Caution: For Use In Manufacturing Noninjectable Products Only'', for products intended for further manufacturing into noninjectable products. The statement shall follow the proper name in the same size and type of print as the proper name. If the Source Plasma has a reactive screening test for evidence of infection due to a communicable disease agent(s) under § 610.40 of this chapter, or is collected from a donor with a previous record of a reactive screening test for evidence of infection due to a communicable disease agent(s) under § 610.40 of this chapter, the Source Plasma must be labeled under § 610.40(h)(2)(ii)(E) of this chapter.

* * * * *

PART 660—ADDITIONAL STANDARDS FOR DIAGNOSTIC SUBSTANCES FOR LABORATORY TESTS

22. The authority citation for 21 CFR part 660 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360c, 360d, 360h, 360i, 371, 372; 42 U.S.C. 216, 262, 263, 263a, 264.

§ 660.42 [Removed]

23. Section 660.42 *Reference panel* is removed.

PART 809—IN VITRO DIAGNOSTIC PRODUCTS FOR HUMAN USE

24. The authority citation for 21 CFR part 809 continues to read as follows:

Authority: 21 U.S.C. 331, 351, 352, 355, 360b, 360c, 360d, 360h, 360i, 360j, 371, 372, 374, 381.

25. Section 809.20 is amended by revising paragraph (b).

§ 809.20 General requirements for manufacturers and producers of in vitro diagnostic products.

* * * * *

(b) *Compliance with good manufacturing practices.* In vitro diagnostic products shall be manufactured in accordance with the good manufacturing practices requirements found in part 820 of this chapter and, if applicable, with § 610.44 of this chapter.

Dated: June 1, 2001.

Bernard A. Schwetz,

Acting Principal Deputy Commissioner.

[FR Doc. 01–14408 Filed 6–8–01; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 606 and 630

[Docket No. 98N–0607]

General Requirements for Blood, Blood Components, and Blood Derivatives; Donor Notification

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the biologics regulations to require blood and plasma establishments to notify donors, including autologous donors, whenever the donor is deferred or determined not to be suitable for current or future donations of blood and blood components. A donor is deferred based on results of tests for communicable disease agents or determined not to be suitable for donation based on failure to satisfy suitability criteria. Blood and plasma establishments also are required to notify the referring physician of an autologous donor when the autologous donor is deferred based on tests for evidence of infection with a communicable disease agent(s). A standard operating procedure (SOP) and recordkeeping also are required. This final rule is intended to help protect public health and to promote consistency in the industry. Elsewhere in this issue of the **Federal Register**, FDA is publishing a final rule on the requirements for testing human blood donors for evidence of infection due to communicable disease agents.

DATES: This rule is effective December 10, 2001.

FOR FURTHER INFORMATION CONTACT: Paula S. McKeever, Center for Biologics Evaluation and Research (HFM–17), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448, 301–827–6210.

SUPPLEMENTARY INFORMATION: