

UPDATE ON STATUS OF BLOOD REGULATIONS

Committee Update

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Bethesda Ramada Inn
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donate blood or blood components for use as a component of a medical device or may donate blood or blood components in the preparation of Hepatitis B Immune Globulin (Human) provided their current donations test nonreactive when tested in accordance with § 610.40(a) and the donor is otherwise determined to be suitable.

(d) Donors with a reactive serologic test for syphilis need not be deferred if found negative by an approved specific treponemal test (confirmatory test for syphilis).

(e) Deferred donors may be found to be suitable as donors of blood or blood components by a method or process found acceptable for such purposes by the Food and Drug Administration.

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

§ 610.42 Restrictions on use for further manufacture of in vitro diagnostic products.

In vitro diagnostic products manufactured from human blood or blood components found to be repeatedly reactive by a screening test performed in accordance with § 610.40(a) shall be labeled in accordance with § 809.10 of this chapter, and shall include a statement of warnings in the label indicating that the product was manufactured from a donation found to be repeatedly reactive by a screening test for evidence of infection due to the identified communicable disease agent.

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

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

When available, a reference panel shall be obtained from the Center for Biologics Evaluation and Research or from a Food and Drug Administration designated source, and shall be used by the manufacturer to verify acceptable sensitivity and specificity of:

(a) Each lot of 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

(b) Each lot of a human immunodeficiency virus (HIV) test approved for use in the diagnosis or monitoring of this communicable disease agent. A lot that is found to be not acceptable for sensitivity and specificity under § 610.44(a) and (b) shall not be released.

§ 610.45 [Removed]

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

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

11. 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]

12. Section 640.2 *General requirements* is amended by removing paragraph (f).

PART 660—ADDITIONAL STANDARDS FOR DIAGNOSTIC SUBSTANCES FOR LABORATORY TESTS

13. The authority citation for 21 CFR part 660 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.

§ 660.42 [Removed]

14. Section 660.42 *Reference panel* is removed.

Dated: April 20, 1999.

Jane E. Henney,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

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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; Notification of Deferred Donors

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to require blood and plasma establishments to notify donors of their deferral due to test results for communicable disease agents or failure to satisfy suitability criteria with the intent of reducing the risk of transmission of communicable disease through the use of blood, blood components, and blood derivatives. Under the proposed rule, blood and plasma establishments would notify the donors that they have been deferred and the reason for the deferral; provide

information concerning appropriate medical followup and counseling; describe the types of donations the donors should not make in the future; and discuss the possibility that the donor may be found suitable in the future, where appropriate. FDA is issuing this rule as part of the agency's "Blood Initiative" in which FDA is reviewing and, when appropriate, revising its regulations, policies, guidance, and procedures related to blood and blood products, including blood derivatives.

DATES: Submit written comments by November 17, 1999. Submit written comments on the information collection provisions by September 20, 1999.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Comments should be identified with the docket number found in brackets in the heading of this document. Submit written comments on the information collection provisions to the Office of Information and Regulatory Affairs (OMB), New Executive Office Bldg., 725 17th St. NW., Washington, DC 20503, Attention: Wendy Taylor, Desk Officer for FDA.

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. Introduction

For a variety of reasons discussed as follows, FDA has decided to comprehensively review and, as necessary, revise its regulations, policies, guidance, and procedures related to the licensing and regulation of blood products. In the *Federal Register* of June 3, 1994 (59 FR 28821 and 59 FR 28822, respectively), FDA issued two documents entitled "Review of General Biologics and Licensing Regulations" (Docket No. 94N-0066) and "Review of Regulations for Blood Establishments and Blood Products" (Docket No. 94N-0080). The documents announced the agency's intent to review biologics regulations (parts 600, 601, 606, 607, 610, 640 and 660 (21 CFR 600, 601, 606, 607, 610, 640 and 660)), and requested written comments from the public. Interested persons were given until August 17, 1994, to respond to the documents. In response to requests for additional time, FDA twice extended the comment period, as announced in the *Federal Register* of August 17, 1994

(59 FR 42193), and November 14, 1994 (59 FR 56448). In addition, FDA responded to requests for a public meeting to allow for the presentation of comments regarding the agency's intent to review the biologics regulations. On January 26, 1995, FDA held a public meeting to provide an opportunity for all interested individuals to present their comments and to assist the agency in determining whether the regulations should be revised, rescinded, or continued without change. Since the time of the regulation review, FDA has implemented a number of changes to its regulations and policies applicable to the general biologics and licensing regulations, some of which have applied to blood products as well as other biological products. (See, e.g., the final rules issued May 14, 1996 (61 FR 24313); August 1, 1996 (61 FR 40153); November 6, 1996 (61 FR 57328); July 24, 1997 (62 FR 39890); and October 15, 1997 (62 FR 53536)).

Because of the importance of a safe national blood supply, the U. S. House of Representatives Committee on Government Reform and Oversight, Subcommittee on Human Resources and Intergovernmental Relations (the Subcommittee) and other groups such as the General Accounting Office (GAO), and the Institute of Medicine (IOM) have reviewed the agency's policies, practices, and regulations. Reports issued following the respective reviews made a number of recommendations as to how FDA might improve the biologics regulations, particularly as they apply to the continued safety of blood products. The relevant reports are: (1) "Protecting the Nation's Blood Supply From Infectious Agents: The Need for New Standards to Meet New Threats," by the Subcommittee (August 2, 1996); (2) "Blood Supply: FDA Oversight and Remaining Issues of Safety," by GAO (February 25, 1997); (3) "Blood Supply: Transfusion-Associated Risk," by GAO (February 25, 1997); and (4) "HIV and the Blood Supply: An Analysis of Crisis Decisionmaking," by IOM (July 13, 1995). These reports are on file with the Dockets Management Branch (address above) under the docket number given in the heading of this document.

FDA has reviewed these reports and agrees with the majority of the recommendations contained within them. However, rather than to only respond specifically to the recommendations from the Subcommittee, GAO, IOM, and the public, FDA has convened a number of internal task forces to review a variety of issues related to the regulation of blood and blood products, including

how to most appropriately update the existing regulations applicable to blood and blood products. In the future, FDA intends to issue a number of blood-related rulemakings that various FDA task groups are currently preparing. FDA is not describing the specific recommendations it has received and the numerous objectives of the Blood Initiative in this document. Future rulemaking and other notices will describe and discuss specific recommendations and regulatory objectives.

II. Background on Notification of Deferred Donors

This rule is proposed in order to reduce the risk of infection due to communicable disease agents to blood product recipients and to individuals handling blood or blood products. The safety of the blood supply is enhanced when donors who may present significant risks of transmitting infectious disease, because of testing results indicating evidence of infection due to communicable disease agents or failure to satisfy suitability criteria associated with the prevention of certain communicable disease agents, are excluded from donating blood and blood components. FDA has issued regulations at parts 610 and 640 on donor testing and suitability in order to help assure the safety of blood products. The Public Health Service (PHS) and FDA, as part of PHS, also have periodically issued guidance on donor testing, suitability, deferral, and notification when new scientific developments warranted. This rule is also being proposed so that donors may be informed of their deferral and seek medical counseling or treatment, if appropriate. Additionally, such notification is expected to improve blood safety by preventing re-donation by individuals at risk for transmitting infectious disease. Also, precautions taken to minimize the risk of transmission by informed donors may reduce the spread of communicable diseases in the population.

FDA has taken a number of actions to provide for the notification of certain deferred donors. Described in the following paragraphs are some of the more significant actions and their impact on donor notification.

In 1983, PHS issued guidelines recommending that individuals at increased risk for Acquired Immune Deficiency Syndrome (AIDS) refrain from donating (Ref. 1).

In 1985, PHS issued guidelines concurrent with the approval of human immunodeficiency virus (HIV) antibody tests that donors testing repeatedly

reactive in screening tests for human immunodeficiency virus, type 1 (HIV-1) be notified. In addition, PHS recommended that the donor be notified if other tests such as the Western blot were positive (Ref. 2).

In 1987, PHS recommended that a person be considered to have serologic evidence of HIV infection only after an enzyme immunoassay screening test was repeatedly reactive and another test such as Western blot had been performed to validate the results (Ref. 3). These recommendations have been updated periodically (Refs. 4 and 5) and extended to include notification of donors testing positive for antibody to human immunodeficiency virus, type 2 (HIV-2) (Ref. 6).

In its 1990 recommendations, FDA recommended to blood establishments that supplemental testing be performed prior to donor notification in its Memorandum to Blood Establishments: Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products.

In 1988, PHS recommended notification of donors who were confirmed positive for human T-lymphotropic virus, type I (HTLV-I) of their test results and that they had been deferred as a donor in Licensure of Screening Tests for Antibody to T-Lymphotropic Virus, Type I (Ref. 7).

In 1991, the Department of Health and Human Services (DHHS), in a PHS Inter-Agency Guideline, recommended notifying donors of the results of tests for hepatitis B surface antigen (HBsAg), antibody to hepatitis C virus (anti-HCV), alanine aminotransferase (ALT) and antibody to hepatitis B core (anti-HBc) in the Public Health Service Interagency Guideline for Screening Donors of Blood, Plasma, Organs, Tissue and Semen for Evidence of Hepatitis B and Hepatitis C (Ref. 8).

In the 1995 Guideline for Quality Assurance in Blood Establishments (60 FR 36290, July 14, 1995), FDA further identified donor notification and counseling as two of the five key elements of donor deferral.

The blood industry has adopted these recommendations as well as developed their own guidance on donor notification. Industry practice includes notifying donors who are permanently deferred due to positive test results for viral markers of their deferred status and providing recommendations for followup testing, counseling, and appropriate medical referral. In the past, however, FDA has not issued regulations on when a deferred donor should be notified. To further enhance the safety of the blood supply, FDA

believes that donors should be notified when they are deferred due to test results or donor suitability criteria. Accordingly, FDA is proposing to require notification of donors who are deferred for evidence of infection due to communicable disease agents as required under proposed § 610.41 and for failure to satisfy suitability criteria associated with the prevention of communicable diseases. The proposed rule would help assure consistency in the blood industry's notification practices, and would provide FDA with clear enforcement authority if compliance problems occur.

GAO, at the request of Congressman John Dingell, Ranking Minority Member, Committee on Commerce, House of Representatives, recently reviewed the FDA's "layers of safety" intended to help ensure the safety of blood products in order "to identify issues that might threaten the nation's blood supply." In its report of February 1997 entitled "Blood Supply: Transfusion Associated Risks," GAO concluded that "the blood supply is safer today than at any time in recent history." Nevertheless, in an accompanying report ("Blood Supply: FDA Oversight and Remaining Issues of Safety"), GAO made several recommendations on improving the safety of our nation's blood supply. GAO recommended that "(FDA) require blood facilities to notify all donors who are permanently deferred that they have been deferred and the medical reason they are deferred." Citing public health concerns, GAO further recommended that:

*** (N)otification be based on positive confirmatory tests for viral markers (for the viruses that have licensed confirmatory tests) and all other medical reasons that result in permanent deferral (for example, the intake of pituitary growth hormone). Notification should include the reason for the permanent deferral, possibilities for re-entry as a donor, and counseling or referral to the donor's physician (including, when pertinent, actions to be taken to minimize transmission of viruses to others).

In its response, DHHS generally agreed with the GAO recommendations. FDA believes the proposed donor notification rule would enhance blood safety by promoting self-exclusion of donors who may present significant risks to the blood supply. FDA believes that donors who are informed of and understand the significance of their deferred status are less likely to attempt to donate again, thus helping to assure a safer blood supply. Donor notification also would enhance the public health by informing donors, as appropriate, of the need to seek treatment and additional medical counseling. Such measures could

benefit the health of the donor and also provide information needed to prevent further spread of infection.

III. The Impact of Other Proposed Rules

FDA intends to issue other proposed rules in conjunction with the proposed donor notification rule. FDA is proposing to revise the donor testing and deferral regulations in part 610, which apply to blood and blood components. The related proposed testing and deferral document is found elsewhere in this issue of the **Federal Register**. FDA also intends to issue in the near future a proposed rule to revise donor suitability requirements.

The related proposed testing and deferral rule would, among other things, add requirements to test blood and blood components for evidence of infection due to hepatitis C virus (HCV), HTLV-I, and HTLV-II, while retaining testing requirements for hepatitis B virus (HBV), HIV-1, and HIV-2. FDA intends that the proposed testing rule would replace the requirements currently found in §§ 610.40 through 610.45. The testing and deferral requirements for a serologic test for syphilis (i.e., evidence of infection due to *Treponema pallidum*) found in §§ 640.5 and 640.65 would remain in part 640. The related proposed testing and deferral rule also would add a requirement in proposed § 610.41 that, except in certain specified circumstances, donors testing repeatedly reactive for evidence of infection due to a communicable disease agent(s) listed in proposed § 610.40(a) be deferred from future donations of blood or blood components. In addition, donors testing reactive for a serologic test for syphilis would also be deferred except as provided in current § 640.65 or proposed § 610.41. Under the proposed donor notification rule, blood and plasma establishments would be required to notify donors who have been deferred under proposed § 610.41.

As mentioned previously, FDA also intends to propose to revise the donor suitability requirements for donors of blood and blood components. FDA intends to identify donor suitability criteria that would cause a donor to be deferred and thus trigger notification under the proposed donor notification document. Among those donor suitability criteria being considered are high risk behavior associated with the transmission of HIV, HBV, and HCV, such as past or present abuse of injectable drugs. A new section identifying donor suitability criteria will be designated in the final rule for donor notification.

IV. Legal Authority

FDA is proposing to issue this new rule under the authority of sections 351 and 361 of the Public Health Service Act (PHS Act) (42 U.S.C. 262 and 264 *et seq.*) and the provisions of the Federal Food, Drug, and Cosmetic Act (the act) that apply to drugs (21 U.S.C. 201 *et seq.*). Under section 361 of the PHS Act, FDA may make and enforce regulations necessary to prevent the introduction, transmission, and spread of communicable disease between the States or from foreign countries into the States (see Sec. I, 1966 Reorg. Plan No. 3 at 42 U.S.C. 202 for delegation of section 361 authority from the Surgeon General to the Secretary of the Department of Health and Human Services (Secretary); see 21 CFR 510.(a)(4) for delegation from the Secretary to the Food and Drug Administration). Intrastate transactions may also be regulated under section 361 of the PHS Act (see *Louisiana v. Mathew*, 427 F. Supp. 174, 176 (E.D.La. 1977)).

Notification of donors that they have been deferred and consequently should not attempt subsequent donations would help prevent unsafe units of blood or blood products from entering the blood supply. The proposed rule targets those donors who may present significant risks of infectious agents; thus, it works directly to prevent the introduction and spread of communicable disease. Moreover, the proposed rule is designed to help ensure that risks of transmitting infectious disease are excluded from the pool of eligible donors. FDA relies on a system of overlapping layers of safety to ensure the safety of the nation's blood products. One of the important layers of safety is the self-exclusion of donors because of high-risk behaviors associated with the risk of HIV, or hepatitis B and C, or signs and symptoms of AIDS and hepatitis. A second crucial layer of safety is the system of donor deferral registries designed to eliminate unsuitable donors from the donor population. Notification of donors who are deferred adds to the protection provided by donor deferral registries by making deferred donors aware that they should not attempt to donate again. Consequently, the screening of unsuitable donors provided by the registries is enhanced by the self-exclusion of donors who have been made aware of their status and the risks their donation may present to the blood supply.

The proposed notification rule also would protect the health of the deferred donor by assuring that the individual is

aware he or she may need further medical evaluation including testing, treatment, and counseling. As FDA has previously made clear "(i)n an indirect but no less important manner, the requirements of donor protection assure * * * that there will be a continuous and healthy donor population" (Additional Standards for Human Blood and Blood Products (41 FR 10762, March 12, 1976)).

FDA's license revocation regulations provide for the initiation of revocation proceedings, among other reasons, if the establishment or the product fails to conform to the standards in the license application or in the regulations designed to ensure the continued safety, purity, or potency of the product (§ 601.5). Section 351 of the PHS Act also provides for criminal penalties for violation of the laws governing biologics. Violations can be punishable by fines or imprisonment, or both.

The act also applies to biological products (42 U.S.C. 262(d)), as amended. Blood and blood components are considered drugs, as that term is defined in section 201(g)(1) of the act (21 U.S.C. 321(g)(1)) (see *United States v. Calise*, 217 F. Supp. 705 (S.D.N.Y. 1962)). Because blood and blood components are drugs under the act, blood and plasma establishments must comply with the substantive provisions and related regulatory scheme of the act. Under section 501(a)(2)(B) of the act, drugs are deemed "adulterated" if the methods used in their manufacturing, processing, packing, or holding do not conform with current good manufacturing practices (CGMP's) (21 U.S.C. 351(a)(2)(B)). Under the proposed donor notification rule, blood and plasma establishments would be required to develop standard operating procedures (SOP's) for notifying deferred donors. A blood or plasma establishment that failed to comply with donor notification procedures would violate CGMP's and, therefore, would be subject to the act's enforcement provisions.

V. Description of the Proposed Rule

FDA is proposing to create a new part 630, General Requirements for Blood, Blood Components, and Blood Derivatives. This part would include the following: (1) Consolidation of the criteria to be used when determining suitability of donors of human blood and blood components; (2) requirements for donor deferral from future donation when a donor fails to satisfy the suitability criteria; and (3) requirements for donor notification and the reason for their deferral due to donor test results or failure to satisfy suitability criteria.

Donor suitability criteria and donor deferral are not the subject of this proposed rule. These proposed requirements will be addressed in a rulemaking to be published in the near future. As necessary, FDA may add other requirements applicable to blood products in the future. The focus of this proposed rulemaking would be to require donor notification when the donor is deferred due to testing results or failure to meet donor suitability criteria and to provide the reason for the deferral.

The proposed rule would require blood and plasma establishments to notify donors who are deferred in accordance with proposed § 610.41 or for failure to satisfy donor suitability criteria that they have been deferred as donors and the reason for their deferral. Deferred donors would be informed, as appropriate, that they should not donate blood or blood components in the future. Donors would also be informed about the need for additional counseling and medical evaluation, as appropriate. Under the proposed rule, blood and plasma establishments would be required to develop SOP's for deferring donors and notifying deferred donors. FDA is not proposing to require blood and plasma establishments to notify donors who the blood or plasma establishments may defer voluntarily for a variety of medical reasons beyond the requirements in proposed § 610.41 and donor suitability criteria associated with the prevention of communicable diseases. FDA recognizes that blood and plasma establishments would need to exercise medical judgment in determining which donors to defer voluntarily and whether to notify such donors. PHS and FDA may periodically issue recommendations on testing, deferral, and notification of donors who may be at risk of infectious disease.

Donors whose blood or blood components test repeatedly reactive for evidence of infection due to a communicable disease agent for which testing would be required by FDA under proposed § 610.40, or as specified for syphilis in current §§ 640.5 or 640.65, would be deferred in accordance with proposed § 610.41. Blood and plasma establishments would notify such deferred donors under the proposed notification rule that they have been deferred, and the reason for their deferral including their screening test results and the results of any approved supplemental (i.e., additional, more specific) tests that were performed. FDA currently requires that supplemental testing for both HIV-1 and HIV-2 antibodies be performed under § 610.46. PHS and FDA have recommended that

HIV notification should occur after the results of the approved supplemental testing are available. Results of supplemental tests are useful in providing additional information for purposes of medical followup and counseling. Therefore, FDA is proposing that blood establishments attempt to obtain the results of supplemental testing proposed under § 610.40(c) prior to notifying donors of their deferral. FDA has included a maximum time period of 8 weeks to notify the donor. If notification occurs prior to receipt of the supplemental test results, blood establishments would be required to renotify the donors with the results of the supplemental testing.

Blood and plasma establishments would be required to notify deferred donors where appropriate, of the possibility for re-entry as donors of blood and blood components if they are found to be suitable using methods or processes approved by FDA in accordance with proposed § 610.41 or current § 640.65, provided that the donor meets all other requirements.

Under § 610.40 of the proposed testing rule, blood and plasma establishments would be required to test blood and blood components, including autologous donations, for evidence of infection due to HIV-1, HIV-2, HBV, HCV, HTLV-I, and HTLV-II using FDA approved tests. Donors whose donations test repeatedly reactive for evidence of those agents required under proposed § 610.40(a) or for syphilis under current §§ 640.5 and 640.65 would be deferred in accordance with proposed § 610.41. This proposed donor notification rule would require that blood and plasma establishments notify the deferred donor of their deferral and of their test results.

In the related proposed § 610.41, FDA is proposing several exceptions to donor deferral that also have an impact on donor notification. Autologous donors testing repeatedly reactive for communicable disease agents would not be deferred. Blood establishments would not be required under this proposed rule to notify autologous donors who test repeatedly reactive for communicable disease agents under proposed § 610.40(a). Nevertheless, FDA recommends that blood establishments notify autologous donors of repeatedly reactive test results and supplemental test results, when applicable, for the purpose of medical followup and counseling. FDA specifically is requesting comments on whether to require notification of autologous donors of repeatedly reactive and supplemental test results even though such donors would not be deferred.

In the related proposed § 610.41(a), donors who test repeatedly reactive for HTLV, types I and II, or anti-HBc on only one occasion, would be permitted to donate again without being deferred from further donation unless there is further testing using an approved supplemental (additional, more specific) test. Should licensed supplemental tests for HTLV, types I and II be approved, donors would be required to be deferred after only a single repeatedly reactive donation similar to most other screening tests. It is FDA's expectation that donor re-entry algorithms would become feasible at that time. However, until such time, upon testing repeatedly reactive a second time for HTLV, types I and II or anti-HBc, the donor would be deferred. Blood establishments would be required to notify donors that they have been deferred from donations of Whole Blood, and transfusable components (including Plasma) only after they had tested repeatedly reactive a second time for HTLV, types I and II or anti-HBc. FDA specifically requests comments on whether to notify donors who test repeatedly reactive for HTLV, types I and II or anti-HBc on only one occasion or to wait to notify donors upon testing repeatedly reactive the second time. Upon the availability of an approved supplemental (additional, more specific) test, a repeatedly reactive donor would be deferred after a single repeatedly reactive donation. At such time, blood establishments would notify donors of the test results of both the approved screening and supplemental tests. As appropriate, blood establishments would notify such deferred donors that they may be eligible for re-entry if determined to be suitable by a method or process approved by FDA in accordance with proposed § 610.41.

In related § 610.41(b), FDA is proposing to exempt from deferral donors testing repeatedly reactive for HTLV, types I and II, or anti-HBc as donors of Source Plasma. However, the agency is requesting comments in the proposed rule "Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents" (hereinafter the "proposed rule on donor testing") on permitting such donors to donate Source Plasma to be used in the manufacture of plasma derivatives as it relates to the exposure to other possible risks, such as through the association of HTLV infection with abuse of intravenous drugs. The agency also includes in the proposed rule on donor testing a discussion on the risk of transmitting HTLV, types I and II.

Related proposed § 610.41(c)(1) would permit deferred donors to donate blood and blood components used in accordance with proposed § 610.40(f). In related proposed § 610.40(f), the agency would require that blood and blood components that test repeatedly reactive when screened for evidence of infection due to communicable disease agents listed in proposed § 610.40(a) would not be shipped or used except for autologous use or for purposes or under conditions approved in writing by FDA. Blood and plasma establishments that collect blood or blood components under conditions approved under proposed § 610.40(f)(2)(ii) or current § 640.65 could notify donors deferred under proposed § 610.41 or current § 640.65 that they would be eligible to donate blood or blood components, as appropriate, for use as a component of an in vitro device or for other approved uses.

In related § 610.41(c)(2), the agency is proposing to restrict the use of blood or blood components from donors showing previous evidence of infection due to hepatitis B virus when tested in accordance with proposed § 610.40(a) and (c). Such blood and blood components may be approved for use only as a source of antibody to hepatitis B surface antigen for the preparation of Hepatitis B Immune Globulin (Human) or as a component of a medical device. Donors with previous evidence of infection with hepatitis B when tested in accordance with proposed § 610.40(a) and (c) may serve as donors of a component of a medical device or as donors of Source Plasma for use as a source of antibody to hepatitis B surface antigen for the preparation of Hepatitis B Immune Globulin (Human). In the proposed rule on donor testing, the agency has requested comments on the use of vaccinated donors for HBV as an alternative to using donors previously showing evidence of infection due to hepatitis B virus in the preparation of Hepatitis B Immune Globulin (Human) provided their current donations test nonreactive when tested in accordance with proposed § 610.40(a) and the donor is otherwise determined to be suitable. Blood and plasma establishments that are approved to collect Source Plasma from such donors under proposed § 610.40(f) could notify deferred donors that they may donate for such purposes.

In related proposed § 610.41, the agency is proposing to defer donors who test reactive for a serologic test for syphilis except as provided under current § 640.65. In related proposed § 610.41(d), the agency would exempt from deferral donors who test reactive on a serologic test for syphilis provided

the donor is found negative by an approved specific treponemal test (confirmatory test for syphilis). Blood and plasma establishments would notify all other donors who test reactive for evidence of syphilis that they have been deferred and of the results of tests including the result of the approved specific treponemal tests. However, as FDA has noted in the preamble to the related proposed rule on donor testing, there is ongoing debate in the scientific community as to the continuing need for a testing requirement for the serological test for syphilis. Therefore, the proposal to defer donors who test reactive for syphilis is subject to change pending the outcome of the request for comments on the value of donor testing for syphilis in the proposed rule on donor testing.

The proposed rule also would require blood and plasma establishments to notify donors who have been deferred because of donor suitability criteria. FDA intends to create in future rulemaking a new section identifying certain donor suitability criteria which are intended to reduce the risk of communicable disease agents that would result in deferral of the donor and require donor notification. Among those donor suitability criteria being considered are high risk behavior associated with the transmission of HIV, HBV, and HCV, such as past or present abuse of injectable drugs. Blood and plasma establishments would notify deferred donors of their deferral and advise them to seek further testing or medical counseling, as appropriate.

Under the proposed rule, blood and plasma establishments would be required to provide information to deferred donors concerning appropriate medical followup and counseling. FDA currently recommends that this information include disease associations and possible modes of transmission as well as actions to be taken to minimize the risk of transmission. FDA believes that such information also would include referral to their own physician, or, where appropriate, the location of public health clinics as well as alternative testing and counseling centers. Blood and plasma establishments should consult current PHS Guidelines and FDA recommendations for more detailed recommendations on the content of donor notification.

A. Timeframe for Notification.

Under § 630.6(c) of the proposed rule, blood and plasma establishments would be required to notify donors within 8 weeks after determining that the donor should be deferred. In many instances

arising under the proposed rule, blood and plasma establishments would be able to fulfill the notification requirements onsite. For example, a donor who is deferred because of donor suitability criteria can be notified at the time of the donor interview or at the first return visit after the information is available, if within 8 weeks. Blood and plasma establishments would be required to have SOP's addressing donor deferral and notification and keep documentation on all deferrals as well as any resulting notification. Some blood and plasma establishments may notify deferred donors by registered mail, return receipt; or may choose to request that the donor return for direct donor notification, so long as notification of deferral occurred within the 8-week period. FDA requests comments on (1) methods of notification that would help assure adequate donor confidentiality and (2) the current application and sufficiency of Federal, State, and local laws that protect the privacy of the individual being notified. FDA believes that at least three attempts should be made within an 8-week period. In all cases, blood and plasma establishments should document their attempts to notify donors and maintain a record of these attempts or of the basis for discontinuing the effort to notify deferred donors.

B. Other Requirements.

Donor notification should be conducted by trained personnel in accordance with the requirements in § 606.20. Blood and plasma establishments would be required to revise their SOP's to include procedures for notification of deferred donors. For the purposes of notification under the proposed rule, blood and plasma establishments would be required to maintain records of the donor's permanent address. Donors should provide proof of a permanent, fixed address. Individuals who do not have evidence of a current address or who merely provide an address of a known or obviously transient nature should not be accepted as donors.

VI. Analysis of Impacts and Initial Regulatory Flexibility Analysis

FDA has examined the impacts of the proposed rule under Executive Order 12866, under the Regulatory Flexibility Act (5 U.S.C. 601-612), and under the Unfunded Mandates Reform Act (Public Law 104-4). 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 by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million in any one year (adjusted annually for inflation).

OMB has determined that the proposed 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 1 year of \$100 million or more, FDA is not required to perform a cost-benefit analysis according to the Unfunded Mandate 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. As explained in the following sections of this document, the proposed rule is not expected to have a significant economic impact on a substantial number of small business entities because donor deferral and notification are considered usual and customary business for the affected entities.

A. Objectives and Basis of the Proposed Action

As discussed previously, FDA is considering the proposed action for the purpose of reducing the risk of infection due to communicable disease agents to blood recipients and to individuals handling blood or blood products. The safety of the nation's blood supply is enhanced when donors whose test results indicate evidence of infection due to communicable disease agents or fail to satisfy suitability criteria associated with the prevention of certain communicable disease agents are excluded from donating blood and blood components. Once donors are deferred from donation, such donors would be informed of their deferral and the reason, and advised to seek medical counseling or treatment, as appropriate. Public health would be protected not

only by deferring the donor from future donations and preventing the transmission of communicable disease agents through transfusion, but also by counseling the donor in precautions to minimize the risk of transmitting the disease to others in daily life.

This action is taken under the authority of sections 351 and 361 of the PHS Act and section 501 of the act to prevent the introduction, transmission, and spread of communicable disease, and to ensure that methods used in manufacturing conform with CGMP's. Failure to comply with donor notification procedures would violate CGMP's and, therefore, would be subject to the act's enforcement provisions. FDA has reviewed related Federal rules and has not identified any rules that duplicate, overlap, or conflict with the proposed rule.

B. Nature of the Impact

The proposed rule requires that blood establishments notify deferred donors of their deferral based on either suitability criteria included in the donor screening interview or because of the results of testing for evidence of infection due to disease agents including HIV, HTLV, hepatitis B, or hepatitis C. Under the proposed rule, the donor must be notified that he or she has been deferred, and the reason for deferral. The deferred donor must also be notified of the types of blood or blood components that should not be donated in the future. The notification must also include the results of tests for evidence of infection due to communicable disease including supplemental test results, information concerning appropriate medical followup and counseling, and when applicable, the possibility that the donor may be found suitable for future donations. The donor notification process must include three attempts of notification, completed within 8 weeks of the determination of the donor deferral. In order to implement this notification process, the proposed rule also requires that blood establishments obtain a permanent address for each prospective donor. The establishment must also maintain records of its attempts to notify a deferred donor within the prescribed timeframe.

C. Type and Number of Entities Affected

The proposed deferred donor notification requirements will affect all blood and plasma establishments that collect blood and blood components from allogeneic donors. FDA's Office of Blood Research and Review (OBRR) has record of 2,801 registered blood and plasma establishments, including 487

plasma centers and 2,314 blood centers. The American Association of Blood Banks (AABB) estimates that approximately 14 million blood donations are collected annually. Allogeneic blood donations have recently accounted for an estimated 87.2 percent of that total (Ref. 9). In 1997, GAO estimated that approximately 12 million donations of source plasma were collected by plasma centers (Ref. 10).

D. Estimated Impact of Proposed Requirements for Deferred Donor Notification

The proposed rule is expected to have a minor net impact on blood establishments because the blood industry has already generally implemented deferred donor notification; virtually all establishments include this process within current operational guidelines. FDA expects that the primary impacts of the proposed rule will include a one-time review effort at each facility and a more extensive notification process at those facilities that currently perform deferred donor notification over a longer timeframe or with fewer followup attempts than specified in the rule.

The one-time effort to review and modify current SOP's is expected to vary among establishments depending on the extensiveness of a facility's current protocols for deferred donor notification. For establishments that already keep required donor information and perform the level of notification effort specified by the rule, FDA estimates that it would take approximately 4 hours of staff time to reconcile the proposed regulations against the facility's current standards. This process could be performed by a technical specialist who acts 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 the Bureau of Labor Statistics for March 1997, the cost would be approximately \$103 per facility. For establishments that already perform donor deferral notification but information provided to deferred donors or other aspects of the notification process are not the same as specified in the proposed rule, FDA assumes that approximately 24 hours of staff time would be required to align current SOP's and donor recordkeeping with the provisions of the rule. The cost in this case would be approximately \$616 per facility. FDA does not have the data to estimate the percentage of facilities that will require a minimal effort versus a

more involved review of SOP's; however, it is expected that many facilities have SOP's and recordkeeping standards that are consistent with the rule. Assuming a minimal review is needed at two-thirds of the currently operating establishments, and a more extensive review is conducted by the others, the total one-time cost for the blood and plasma industries is estimated to be \$762,158.

The yearly increase in cost is based on the ongoing notification of deferred donors. FDA assumes that all donors deferred based on the screening interview can be notified onsite at the time of deferral, and provided with the proposed information. FDA assumes that this will introduce no new costs for the blood and plasma establishments. The cost of notifying donors deferred on the basis of blood test findings is based on a proportional extrapolation of the number of donors who would test repeatedly reactive for evidence of infection in tests for HIV, HTLV, HBV, or HCV, and have positive findings in supplemental testing. Assuming a prevalence rate of 121.9 per 100,000 for viral markers for HIV, HTLV, HBV, or HCV among prospective donors (Ref. 11), that approximately 80 percent of donations are made by repeat donors¹, that repeat donors average two donated units per year², and that first time donors contribute one unit, an estimated 8,887 deferred blood donors and 8,861 plasma donors (including first time and repeat donors) would be identified each year.

FDA assumes that all facilities currently make at least one notification attempt for all deferred donors. However, the percentage of facilities that currently make up to three documented attempts within an 8-week period is not known. FDA has therefore estimated the economic impact for two scenarios in which the cost of compliance is based on the assumption that two additional notification attempts are needed, and these notifications are made via registered mail with a return receipt requested, at a cost of \$12.54³ per notified donor. Under the first

¹ This percentage is based on American Red Cross estimates based on donations between January 1996 and June 1997.

² The estimate of an average of two donations per year for repeat blood donors is based on the Center for Disease Control's (CDC's) analysis of blood donations prepared for HCV lookback.

³ This estimate is based on two mailings, at a cost of \$6.27 each. This cost includes \$3.32 first class postage plus \$4.85 fee for registered mail without insurance, plus \$1.10 fee for return receipt requested at the time of mailing showing whom, signature, date and addressee's address (if different) source: USPS 1997 Postal Rates @ "www.usps.gov/consumer".

scenario, FDA assumes half of deferred donors are currently notified through a process like the one specified in the proposed rule. In this case, the cost of compliance, based on the cost of up to two additional notifications to the remaining half of the estimated deferred donors totals \$55,719 for the blood industry, and an estimated \$55,557 for the plasma industry. Under the second scenario, FDA considers that only one-quarter of deferred donors are currently receiving up to three notification attempts. Under this scenario, the cost of up to two additional notifications to the remaining three-quarters of the estimated deferred donors totals \$83,578 for the blood industry, and an estimated \$83,335 for the plasma industry. Thus, the ongoing notification costs for the blood and plasma industries combined are estimated to range from \$111,276 to \$166,913 per year.

E. Expected Benefits of the Proposed Rule

As described in the preamble to this rule, notification of donors that they have been deferred and consequently should not attempt subsequent donations will help prevent unsafe units of blood or blood products from entering the blood supply. Notification of donors who are deferred and can self-defer in the future thus adds to the protection provided by donor deferral registries. In FDA's proposed rule on donor testing found elsewhere in this issue of the *Federal Register*, the agency provides an extensive discussion of the benefits of reducing public exposure to the risks of these infectious diseases. FDA refers the reader to this discussion of the significant public health benefits of minimizing patients' risk of being unwittingly exposed to infection with HIV, HTLV, hepatitis B, and hepatitis C.

F. Small Entity Impact

The proposed rule is not expected to have a significant impact on a substantial number of small entities, however, the impact on blood and plasma establishments that qualify as small entities is uncertain. FDA has therefore prepared an initial regulatory flexibility analysis. The blood and plasma establishments affected by the proposed rule are included under the major standard industrial 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." According to the Small Business Administration (SBA), a small business within the blood industry is an

enterprise with less than \$5 million in annual receipts. A small organization is a not-for-profit enterprise which is independently owned and operated and is not dominant in its field. A "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.

As noted in the foregoing analysis, the proposed rule is expected to have some cost impact on both plasma and blood collection centers. FDA has registered a total of 487 plasma collection facilities. Of that total, the General Accounting Office (GAO) (Ref. 12) has identified approximately 370 for-profit plasma collection centers that primarily collect paid plasma donations. The remaining 100 or so plasma collection facilities function within blood collection centers with volunteer donors, that are either operated by the American Red Cross, or are independently operated. The vast majority of collected source plasma is processed by four companies: Alpha Therapeutic Corp., Baxter Healthcare Corp., Bayer Corp., and Centeon LLC.

FDA estimates that approximately 90 percent of these 370 paid plasma collection centers are owned by companies that operate a number of centers and have annual receipts in excess of \$5 million per year. The remaining 10 percent, or about 37 paid plasma collection centers, may qualify as small business establishments. Of the 100 or so volunteer plasma collection facilities within blood collection centers, the independently operated, not-for-profit blood collection centers would likely qualify as small entities. The potential impact on plasma collection facilities will be a function of the number of donors and the viral marker rates among donors at their facility. The net impact on these facilities, however, is expected to be minor. For example, under cost scenario 1, if the additional yearly cost of \$55,557 were evenly distributed across all 487 registered facilities, this would translate to an added cost of \$114 per facility per year. Under scenario 2, the added cost per facility would be approximately \$171 per year.

The impact on blood collection facilities that qualify as small entities is also uncertain, although it is not expected to be significant. The blood collection facilities that are independent and not-for-profit organizations may qualify as small entities regardless of the size of their operations. The analysis that follows, however, considers the smaller blood collection facilities, because they are expected to experience the greater cost impact. According to the

1996 directory of the AABB, 34 regional and community blood centers have annual revenues of less than \$5 million; and each collect no more than 30,000 donations per year. Because of the pre-existing practice of deferred donor notification at these facilities, and the relatively small number of donors that FDA estimates will be deferred based on blood test findings, the impact on these small facilities is expected to be minor. Based on FDA's calculations, facilities with 30,000 donations or less per year would identify about 22 deferred donors per year through blood testing. At a cost of \$6.27 per notification via registered mail with a return receipt, if all facilities currently need to make two additional notification attempts under this rule, there would be an average small facility notification cost of \$278 (22 x \$12.54) per year. Because the estimated one-time cost for the review and revision of current deferral notification SOP's equaled \$271 (2/3 x \$103 + 1/3 x \$616), or about \$39 when annualized over a 10-year payment period at a 7-percent interest rate, the average annualized cost impact for the smaller collection centers would be about \$317 (\$278 + \$39), or roughly \$0.01 per donation, assuming approximately 30,000 donations per year. It should be noted that blood collection centers that collect both blood and source plasma will not experience a "double" impact, because the same donor pool and donations are used for production of the center's blood and plasma products.

The types of professional staff and skills required to perform the required tasks were described in section VI.D of this document. FDA is confident that the tasks specified in the proposed rule can be readily performed by the type of staff already employed at affected blood and plasma establishments.

To alleviate the impact on small entities while continuing to protect public health, the agency is proposing to recommend, but not require, that autologous donors be notified, if they test repeatedly reactive for evidence of infection; FDA also does not require that these donors be deferred. To minimize facility notification efforts while achieving the public health objectives, FDA proposes that notification should not occur until after the results of the approved supplemental testing are available. The proposed regulations are thus expected to help enhance both public health and public confidence in the safety of the blood and plasma supply, while imposing minimum burden on manufacturers.

As an alternative to this proposal, FDA has considered not requiring donor notification of deferral from future

donation due to communicable disease testing or failure to satisfy suitability criteria associated with the prevention of communicable disease because it is viewed by many as medical practice. However, the agency has rejected this alternative for the following reason. After a lengthy period of time during which the agency published recommendations to establishments on notifying donors of deferral, inconsistency pertaining to information and counseling provided to the deferred donor has been demonstrated among the establishments. Notification of donor deferral has become a public health issue because donors who are not fully informed of their deferral status due to communicable disease testing or failure to meet suitability criteria associated with the prevention of communicable disease may not take precautions to minimize the transmission of communicable disease to others and may not recognize the importance of not attempting to donate blood or blood components in the future.

VII. The Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (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 in this section of this document with an estimate of the annual burden. Included in this estimate is the time for reviewing the instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

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

Title: General Requirements for Blood, Blood Components, and Blood Derivatives; Notification of Deferred Donors.

Description: FDA is proposing requirements for the donor notification process which are intended to prevent further donations from donors who have been deferred for positive test results for evidence of communicable disease agent(s) or for failing to meet the donor suitability criteria intended to reduce the risk of communicable disease agents prior to collection. When a donor is deferred for failing to meet suitability criteria associated with communicable disease agents prior to collection, he or she would be advised not to donate now or in the future and would be provided with information regarding the need for medical followup and counseling. When test results for communicable disease agents are finished, establishment personnel would be required to make at least three attempts to notify donors with positive supplemental (additional, more specific) test results that they are deferred and should have medical followup and counseling. The revisions would require blood and plasma establishments to develop SOP's for deferring donors and for notifying deferred donors and to maintain their permanent address, outline the information that is to be provided to a deferred donor, and to notify deferred donors of positive test results for evidence of infection by communicable disease agent(s) within 8 weeks of the donation initiating deferral, or at their first return visit, whichever is earlier.

FDA is proposing these new requirements to help ensure the nation's blood supply is safe by excluding donors who may present significant risks from donating in the future as well as enhancing the public health by assuring that those donors who have been deferred are advised to seek treatment and counseling.

Description of Respondents: Manufacturers of blood, blood components, and blood derivatives.

There are an estimated 2,800 FDA registered blood and Source Plasma collection facilities in the United States that collect approximately 27,000,000 units of Whole Blood and Source Plasma annually. There are approximately 8 million donors of Whole Blood and 1.5 million donors of plasma for a total of 9.5 million donors per year. From such information as is available to FDA, the agency estimates that approximately 1.2 percent of persons who come to donate annually are deferred prior to donating because of disqualifying answers to the medical history and behavior questionnaire. In addition to the 9.5 million donors per year there would be approximately 115,385 potential donors deferred from donating. It is the customary and usual practice of virtually all registered establishments to explain to a donor why he or she is deferred and excluded from donating. Based on such information as is available to FDA, the

agency estimates that currently two-thirds of registered establishments voluntarily provide additional information and counseling to a deferred donor. Consequently, only one-third or 933 collection facilities would have additional burden related to this proposed rule. Some industry contacts estimated that it takes on average approximately 5 minutes to provide the deferred donor with the appropriate medical health information. FDA estimates that currently 95 percent of the industry that collects 98 percent of the blood and blood components have voluntarily established SOP's for notifying donors who have repeatedly reactive test results that also are positive by supplemental tests for HIV, HBV, or HCV (the number of donors who test and confirm positive for HTLV is so small that this was not included in the estimate). FDA estimates based on 9.5 million donors annually and the viral marker incidence rates for HIV, HBV, and HCV, that 49,591 donors would be deferred annually due to test results. Consequently, 5 percent (140) of the industry collecting 2 percent (992) of the deferred donors would experience new burden related to this proposed rule. FDA estimates on the average it may take 15 minutes to allow for up to three attempts to contact a donor and request that they return for counseling which may take another 15 minutes for a total of 0.5 hours.

TABLE 1.—ESTIMATED ANNUAL REPORTING BURDEN¹

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
630.6(a) and (b) ²	933	41	38,462	.08	3,077
630.6(a), (b), and (c) ³	140	7	992	0.5	496
TOTAL					4,069

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

² Potential donors deferred prior to donation. The number of potential donors deferred annually prior to donation based on failure to meet suitability criteria associated with communicable disease agents is 115,385. Providing information on medical followup and counseling to these deferred donors is estimated to be new burden for approximately one-third of the registered blood and plasma collection facilities.

³ Donors deferred post donation due to test results. Providing information on medical followup and counseling to donors deferred due to test results may be new burden for approximately 5 percent of the industry collecting from 2 percent of such deferred donors. One hundred and forty represents 5 percent of the 2,800 registered establishments and 992 represents 2 percent of the estimated 49,591 donors deferred annually due to test results.

TABLE 2.— ESTIMATED ANNUAL RECORDKEEPING BURDEN¹

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
606.100(b)(20)	2,800	1	2,800	2	5,600
606.160(b)(1)(ix) ²	2,800	59	164,976	3	8,400
606.160(b)(1)(x) ³	2,800	9,643	27,000,000	0	0
TOTAL					14,000

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

² FDA estimates that annually 115,385 potential donors are deferred prior to donation and 49,591 donors are deferred due to test results. Recording the notification of each deferred donor is estimated to require between 2 and 5 minutes (3 minutes on average).

³ Recording the donor's permanent address is customary and usual practice in the industry and is not new or additional burden.

In compliance with section 3507(d) of the Paperwork Reduction Act of 1995 (44 U.S.C. 3507(d)), the agency has submitted a copy of this proposed rule to OMB for review of the information collection provisions. Interested persons are requested to submit written comments regarding information collection by September 20, 1999, to the Office of Information and Regulatory Affairs, OMB (address above), Attention: Desk Officer for FDA.

VIII. Environmental Impact

The agency has determined under 21 CFR 25.31(j) that this action is of a type that not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

IX. Request for Comments and Effective Date

Interested persons may, on or before November 17, 1999, submit to the Docket Management Branch (address above) written comments regarding this proposed rule. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. FDA is proposing that any final rule that may issue based upon this proposed rule become effective 180 days after its date of publication in the *Federal Register*.

X. 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. *Morbidity and Mortality Weekly Report*, vol. 32, pp. 101-103, March 4, 1983.
2. *Morbidity and Mortality Weekly Report*, vol. 34, pp. 1-5, January 11, 1985.
3. *Morbidity and Mortality Weekly Report*, vol. 36, pp. 509-515, August 14, 1987.
4. *Morbidity and Mortality Weekly Report*, vol. 36, pp. 833-840, January 8, 1988.
5. *Morbidity and Mortality Weekly Report*, vol. 38 (No. S-7), July 21, 1989.
6. *Morbidity and Mortality Weekly Report*, vol. 41 (No. RR-2), pp. 1-9, February 28, 1992.
7. *Morbidity and Mortality Weekly Report*, vol. 37, pp. 736-747, December 9, 1988.
8. *Morbidity and Mortality Weekly Report*, vol. 40 (No. RR-4), pp. 1-17, April 19, 1991.
9. Wallace, E. L., W. H. Churchill, D. M. Surgenor, J. An, G. Cho, S. McGurk, and L. Murphy, "Collection and Transfusion of Blood and Blood

Components in the United States, 1992," *Transfusion*, 1995; vol. 35, No. 10, pp. 802-812.

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

11. Glynn, S. A., G. B. Schreiber, M. P. Busch, S. H. Kleinman, A. E. Williams, C. C. Nass, H. E. Ownby, and J. W. Smith, for the Retrovirus Epidemiology Donor Study, "Demographic Characteristics, Unreported Risk Behaviors, and the Prevalence and Incidence of Viral Infections: A Comparison of Apheresis and Whole-Blood Donors," *Transfusion*, April 1998, vol. 38, pp. 350-358.

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

Lists of Subjects

21 CFR Part 606

Blood, Labeling, Laboratories, Reporting and recordkeeping requirements.

21 CFR Part 630

Biologics, Blood, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR Chapter I be 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 606.100 is amended by adding paragraph (b)(20) to read as follows:

§ 606.100 Standard operating procedures.

* * * * *

(b) * * *

(20) Procedures for donor deferral as prescribed in § 610.41 of this chapter and donor notification, including procedures for the appropriate followup if the initial attempt at notification fails, as prescribed in § 630.6 of this chapter.

* * * * *

3. Section 606.160 is amended by adding paragraphs (b)(1)(ix) and (b)(1)(x) to read as follows:

§ 606.160 Records.

* * * * *

(b) * * *

(1) * * *

(ix) Notification of deferred donors, including appropriate followup if the initial attempt at notification fails.

(x) To facilitate the notification of deferred donor, the donor's permanent address.

* * * * *

4. Part 630 is added to read as follows:

PART 630—GENERAL REQUIREMENTS FOR BLOOD, BLOOD COMPONENTS, AND BLOOD DERIVATIVES

Sec.

630.6 Donor notification.

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

§ 630.6 Donor notification.

(a) An establishment that collects blood or blood components shall notify donors who have been deferred based on results of tests for evidence of infection with a communicable disease agent as required by § 610.41 of this chapter or based on deferral for suitability criteria. Blood establishments shall attempt to obtain the results of supplemental testing required under § 610.40(c) of this chapter prior to notifying donors of their deferral. If notification occurs prior to receipt of such results, blood establishments shall renotify donors of the results of the supplemental testing. Blood establishments shall notify donors as described in paragraph (b) of this section.

(b) The notification shall provide the following information to a donor who has been deferred from donating as described in paragraph (a) of this section:

(1) That the donor has been deferred and the reason for deferral;

(2) The types of donations of blood or blood components which the donor should not donate in the future;

(3) Where applicable, the results of tests for evidence of infection due to communicable disease agent(s), that were a basis for deferral under § 610.41 of this chapter, including results of supplemental (i.e. additional, more specific) tests as required in § 610.40(c) of this chapter;

(4) Information concerning appropriate medical followup and counseling; and

(5) Where applicable, the possibility that the donor may be found suitable for future donations.

(c) The notification process shall include a minimum of three attempts to

notify the donor and be completed within 8 weeks after the determination that the donor should be deferred or at the first return visit of the deferred

donor after the determination is made, whichever is earlier.

Dated: April 20, 1999.

Jane E. Henney,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 99-21295 Filed 8-18-99; 8:45 am]

BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES**Food and Drug Administration****21 CFR Part 600**

[Docket No. 98N-0815]

Plasma Derivatives and Other Blood-Derived Products; Requirements for Tracking and Notification**AGENCY:** Food and Drug Administration, HHS.**ACTION:** Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is announcing its intention to propose regulations requiring that certain blood-derived products, including certain plasma derivatives, be tracked from a U.S. licensed manufacturer, through the distribution network, to any patient having custody of the product. Additionally, FDA intends to require notification of consignees and patients having custody of a blood-derived product or an analogous recombinant product in the event the product is associated with a potential increased risk of transmitting a communicable disease, as determined by FDA or by a U.S. licensed manufacturer. The regulations would also apply to any blood-derived product which, in the future, may be routinely dispensed to the patient and held by the patient prior to administration. FDA intends to take this action to help ensure notification of patients having custody of blood-derived products when such products may be associated with a potential increased risk of transmitting a communicable disease so that patients may make informed, appropriate decisions. FDA is soliciting comments and information from interested persons concerning the subject matter of the proposed regulations.

DATES: Submit written comments by November 17, 1999.**ADDRESSES:** Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.**FOR FURTHER INFORMATION CONTACT:** Steven F. Falter, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-827-6210.**SUPPLEMENTARY INFORMATION:****I. Background**

In a July 25, 1996, report entitled "Protecting the Nation's Blood Supply

from Infectious Agents: the Need for New Standards to Meet New Threats," the United States House of Representatives Committee on Government Reform and Oversight provided recommendations to FDA on improvement of the biologics regulations. One of the recommendations concerned the need for the development of a more effective system to notify patients when there are adverse events associated with blood products.

In response to this recommendation, FDA, industry, and patient groups have already taken a number of actions to improve the agency's and industry's response to situations related to concerns about the safety of blood products. FDA has improved its procedures for planning, monitoring, coordinating, and directing FDA investigations for a range of situations including error and accident reports, recalls, and reports of injury or illness, including those related to plasma derivatives. Although primary responsibility for notification of recalls falls to the manufacturer of the product being recalled, FDA uses a variety of electronic communications to make information on recalls and withdrawals available to the public. These include information on the Center for Biologics Evaluation and Research World Wide Web home page, a Fax-on-Demand system, press releases, talk papers (FDA briefing documents), and a "Blood and Plasma Products" hotline. Interested persons may subscribe electronically to the notification system to receive new information automatically. FDA routinely communicates information regarding recalls and withdrawals of plasma derivatives to consumer groups such as the National Hemophilia Foundation and the Committee of Ten Thousand. FDA continues to work with regulated industry to improve the safety of the blood supply, including the development of new, safer products.

FDA has had extensive dialogue with a variety of interested persons in evaluating the current procedures for identifying and notifying recipients in case of safety issues related to blood products. FDA, along with other Government organizations, held a public workshop on November 19, 1996, to obtain public input on notification of the public on recalls and ongoing investigations (see the notice of meeting in the *Federal Register* of November 1, 1996 (61 FR 56549)). Subsequently, FDA has met with numerous consumer groups and industry organizations to discuss notification issues. After extensive discussions with patient communities and within the

Department of Health and Human Services, FDA believes that there is a consensus that persons in custody of a product that may be associated with a potential increased risk of transmitting disease should be so notified; however, it remains unclear as to what specifically would be the most efficient, least burdensome, process that would ensure appropriate notification of all affected persons.

The voluntary programs for notifying recipients in cases of issues related to the quality of blood products are fairly new and efforts continue to recruit participation by patients who are blood product recipients. Thus the success of the voluntary programs cannot yet be fully assessed. However, the success of such voluntary programs will always depend on the continued voluntary support by manufacturers of blood products and the continued vigorous recruitment of patient/recipients to encourage full participation. FDA is concerned that the continued success of patient notification cannot be assured without regulatory standards for the performance of such notification programs and without a clear mechanism of enforcement in the event a notification program is found deficient. FDA intends to continue to monitor progress in the implementation of the voluntary systems and will consider elements of the voluntary systems when developing any regulations resulting from this notice. FDA believes there should be a standardized notification system, clearly understood by industry and by users of blood products, and over which FDA has clear enforcement authority to help ensure that notification consistently and comprehensively takes place.

Accordingly, FDA is considering rulemaking to provide for the prompt notification of patients who may possess certain plasma derivative products for their own use when information indicates a potential for the product to transmit a communicable disease. FDA recognizes that there are several alternatives as to how this notification could best be accomplished. Any such rule would involve the cooperation of a number of entities who must provide information to help ensure that appropriate notification takes place, including the manufacturers of such products, consignees who hold the product for further sale (wholesale distributors), consignees, such as hospitals and pharmacies, who provide the product directly to the patient, and patients. Accordingly, in sections II. and III. of this document FDA outlines the concepts and alternatives it is considering in the development of these

regulations and invites information and comments on the various concepts and alternatives from all interested persons.

II. General Overview of the Regulatory Plan

Under the biologics licensing and quarantine provisions of the Public Health Service Act (42 U.S.C. 262-264) and the drug, device, and general administrative provisions of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 351-353, 355-360, 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. Biological products derived from human plasma have an inherent, potential risk to transmit communicable diseases. Donors of the plasma source material are screened and tested for the potential to transmit a communicable disease. Products made from plasma may be further tested and treated by a process intended to remove or destroy infectious disease agents. However, despite these multiple precautions, there are occasions when problems are identified which may increase the potential risk that the plasma derivative may transmit a communicable disease. Depending on the particular facts, the manufacturer may initiate a recall or market withdrawal of the product so that consignees of the plasma derivative may take appropriate action to prevent the further marketing of the product (see Title 21 of the Code of Federal Regulations (CFR), part 7 (21 CFR part 7) for additional information on the recall and market withdrawal processes).

For some plasma products, generally those that may be chronically administered through the lifetime of the patient, the plasma derivative may be prescribed to the patient and held at the patient's residence until the product is administered. (Note that although FDA is aware only of certain plasma derivative products being routinely held in the patient's custody, FDA intends that any regulations concerning notification would apply to any blood-derived product which may, now or in the future, be released into the custody of a patient.) FDA believes that patients having custody of plasma derivatives are not consistently notified of lot-specific product recalls or withdrawals associated with a potential increased risk of a communicable disease or such notification has not been timely to ensure that appropriate action may be taken by the patient.

There are voluntary tracking and notification systems in place for specific plasma derivatives, but these systems require patients to register with the data base administrator in order for the patients to be notified. In order to protect patients and to better prevent the transmission of communicable diseases through plasma derivatives, FDA is considering the issuance of a proposed rulemaking that would require that patients having custody of plasma derivatives be promptly notified of specific lots associated with a potential increased risk of a communicable disease. Because of the importance of such a notification, FDA is considering defining when notification should take place and setting timeframes during which notification must be performed. The proposed rulemaking would also include requirements for tracking of plasma derivatives to patients who have custody of these products for the purpose of permitting identification of such patients for notifying them of recalls and market withdrawals.

III. Concepts of the Proposed Rulemaking

The following discussion is not intended to indicate the specific content of the proposed rulemaking. It is meant only to describe concepts to be covered by the proposed regulations. The discussion identifies a number of specific topics on which the agency is seeking additional information. However, FDA welcomes comments on any aspect regarding the notification of patients relating to the safety of plasma derivative products. Comments received in response to this advance notice of proposed rulemaking (ANPRM) will be used to develop the proposed rule. FDA specifically requests comments on the concepts that follow.

A. Scope of the Regulations—Types of Blood-Derived Products

The intent of the regulations would be to help ensure that patients possessing plasma derivative products are notified of a potential increased risk of communicable disease so that they may take appropriate action, such as returning the product to the distributing establishment. Therefore, FDA intends to limit the scope of the regulations to those plasma derivatives that may be distributed directly to a patient. Such products include Antihemophilic Factor (AHF or Factor VIII) for the treatment of hemophilia A, Factor IX, used for the treatment of hemophilia B, Alpha-1-Proteinase Inhibitor (Human), used for the treatment of alpha-1 antitrypsin deficiency and products analogous to those listed previously, such as porcine

AHF and products made using recombinant technology. The proposed rulemaking would not apply to plasma derivative products, such as albumin, that are not routinely prescribed for home use.

FDA notes that occasionally patients may take custody of Immune Globulin Intravenous (Human) (also known as IGIV) for administration at home. FDA estimates that approximately 5 percent of the IGIV prescribed is taken into the custody of the patient. FDA believes that such patients should be notified in cases when the IGIV is associated with a potential increased risk of transmitting a communicable disease. The agency also recognizes the complexity, expense, and inefficiency of a system which would be needed to track large volumes of product, for the purpose of potentially notifying a small proportion of patients. It may be more efficient to provide specific arrangements for notification at the time the product is prescribed to the limited number of patients who are taking custody of the product for home use. FDA invites comments and recommendations on how appropriate information regarding product safety can be provided to such patients and whether alternative procedures for such a system should be codified as part of the notification rulemaking. FDA also invites comments as to whether other blood products should be included under the regulations, including a discussion of the extent of the increased burdens and public health advantages associated with such an expansion.

Currently, FDA is aware only of plasma derivative products being released into the custody of patients. It is possible that in the future other products, derived from other blood components, such as red blood cells or white blood cells, may be routinely dispensed into the custody of patients. In such a case, FDA intends that the requirements for tracking and notification would also apply to the blood-derived product. Because the information that FDA has so far gathered and the information being sought by FDA pertains primarily to plasma derivative products, this ANPRM will continue to focus upon plasma derivative products. However, FDA invites comments on what additional blood-derived products may be dispensed into the custody of a patient in the future.

As discussed earlier in this document, a number of voluntary efforts are under way to assist in the notification of persons in custody of a plasma derivative product associated with a potential increased risk of transmitting

a communicable disease. Although FDA believes that there may be innate limitations to any voluntary system, little information is available to the agency regarding the effectiveness of the voluntary systems in place. FDA requests data on the effectiveness of such systems in identifying all persons who may have custody of a plasma derivative product and notifying them in case the product is associated with a potential increased risk of transmitting a communicable disease. FDA also requests comments on whether such systems may be improved and, if so, whether regulations establishing a mandatory notification process would remain appropriate.

B. Scope of the Regulations—Reasons for Notification

At this time, FDA intends that the proposed regulations would require notification only for those plasma derivative lots which, within the dating period of the product, may be associated with a potential increased risk of transmitting a communicable disease. In general, FDA believes that notification of end-users should take place in the same instances for which manufacturers are now either recalling or withdrawing plasma derivative products because of a potential increased risk of transmitting disease. A biological product may be unacceptable for human use due to a wide range of reasons, many not related to communicable disease. FDA is inviting comments on how the basis for notification should be defined in the regulations so as to appropriately establish the criteria for determining when notification should be required. FDA is also inviting comments and information on whether the scope should be expanded to cover other instances, which may affect the safety of the product but which may not be associated with a potential increased risk of communicable disease. An established tracking and notification system could be used in the notification of patients having custody of plasma derivatives for all recalls and market withdrawals. FDA invites comments on the adequacy of the current recall process in situations, other than those related to the risk of communicable disease, and the additional benefits that would be provided by requiring patient notification when compared with the additional burdens associated with the notification process.

C. Who Should Be Responsible for Notification and Related Tracking Responsibilities?

In a recall, the manufacturer has primary responsibility for ensuring that

the recall is undertaken promptly and that, based on an assessment of the risk, it extends to an appropriate level, such as to the end-user of the product.

However, other persons, such as the consignees in receipt of the product, play an integral part in the recall process.

FDA is aware of consumer concerns that manufacturers should not know the identity of a patient using its product. Because of concerns about maintaining confidentiality of patients, FDA believes that the manufacturer should not be required to directly contact patients for notification purposes. Such notification could either be accomplished by those consignees who provided the product to the patient or by an independent third party contracted by the manufacturer to notify patients in the case of a notification or withdrawal related to the potential transmission of a communicable disease, while not divulging patient information to the manufacturer. FDA invites comments as to whether the consignees should be held responsible for notification, whether a manufacturer should be required to contract with a third party to perform notification, or whether either option should be permitted under the regulations.

D. Tracking of the Consignment of Applicable Plasma Derivatives

FDA intends that the proposed rule would require that plasma derivatives prescribed to patients for home use be tracked from the manufacturer, to any consignees, and ultimately to such patients for the purpose of permitting identification of such patients when they need to be notified about a product associated with the potential increased risk of transmitting a communicable disease. The tracking of product to intermediate consignees would be necessary for notifying them about the product risk and thus preventing further distribution of the implicated product lot to patients for home use. Depending on the mechanism of notification (see section III.G of this document), required tracking information could be specific for each lot or could simply be the ability to identify all consignees and patients who have received that specific plasma derivative product, regardless of what product lots they may have received. FDA invites comments, data, and other information on the potential recordkeeping burdens that would be associated with tracking such plasma derivative products, including any estimates of the time it would take to prepare such records and of the number of recordkeeping entries that would be necessary each year to maintain these

tracking records. Data are requested both for keeping lot specific tracking information and for product specific information.

E. Initiation of Notification

In most cases the manufacturer would be the first to determine that a plasma derivative may be associated with a potential increased risk of transmitting a communicable disease. However, based, for example, on consumer complaints, laboratory evidence, or information obtained during inspection by FDA or from other public health agencies, FDA anticipates there would be occasions when it is FDA that makes the initial determination that notification is required. In such cases, FDA believes the most efficient means of initiating notification would be for FDA to inform the manufacturer by an appropriate means of rapid communication, such as fax, electronic mail, or telephone, to initiate notification, immediately followed by written information further documenting why the agency deems notification necessary. The previous description is a simplification of the process which would generally take place when problems are perceived with a product. In most cases, there would be considerable discussion among experts, at FDA and at the manufacturer, to evaluate the available information and assess its implications for the safety of the affected products before a decision to notify would be made. Thus, the process described previously would only be the final step in the determination that notification is required.

FDA requests comments on what should be the required elements of the determination that mandatory notification is to take place and what information regarding that determination should be shared between FDA and the manufacturer.

F. Timing for Notification

Because the plasma derivatives held by a patient may be administered at any time, FDA believes that notification of the patient should take place as rapidly as possible after the determination that a notification is necessary. In some cases the first attempt at notifying a patient may not be fruitful; the patient may be away from his or her home or otherwise unavailable. Accordingly, FDA is also considering a regulatory standard for the time by which full notification of patients should be completed (or by when it is determined that the patient cannot be notified with the currently available information). From the time that either the

manufacturer determines notification is appropriate or FDA informs the manufacturer that notification is required, FDA is considering a standard that the initial attempt to notify all persons with custody of the product must take place within 2 days. For those cases when the initial notification attempt fails, FDA is considering requirements that procedures must be in place for two additional attempts for notification; with the final attempt in written form taking place within 1 week from the beginning of the notification process. FDA invites comments and information on how rapidly it is feasible to attempt to contact patients who may possess the product subject to notification and how much time should be allotted to complete the notification process. If possible, the comments should describe in detail the steps which should take place in the notification process and the time which should be allotted for each step. FDA also invites comments on how much time should be permitted to contact consignees, other than the patients with custody of the product, who also may be in possession of the product.

G. Who Should Be Notified

FDA's public health objectives would be met if only those patients are notified who possess the product lot(s) with an increased potential for transmitting a communicable disease. However, a possible alternative would be to notify all patients who have been dispensed the brand of plasma derivative in question during the time period that the product lot subject to the notification has been in distribution. This method would negate the need to track plasma derivative products to the end-user by lot number. FDA invites comments on the comparative advantages and disadvantages of notifying only those patients who may possess the product lot in question versus notifying all patients who may possess the indicated brand of the plasma derivative. Under any system, the information provided to patients would be lot specific.

H. Information Included in a Notification of Patients

Required information to include in a notification of patients could include specific lot information, a statement to describe the risk potentially affecting the product lot, and instructions for further action to be taken by the patients

who have custody of the product lot in question. FDA invites comments on whether the previous information is appropriate and adequately comprehensive for notification.

I. Adequacy of the Notification Process; Quality Assurance

FDA recognizes that, even with a standard mandatory process, notification of every patient may not be successful. For example, the patient may have moved or may be away from his or her home for an extended period of time. FDA is considering a requirement that the manufacturer have a process in place to evaluate, in cooperation with its consignees or any third party involved in notification, the effectiveness of its notification process, such as through the selected sampling of patients who should have been notified, and, with such information, determine how its notification process could be improved. FDA invites comments on the most appropriate means for evaluating the effectiveness of the notification process and who (the manufacturer, consignees, a third party) should be involved in such an evaluation.

J. Relationship of Notification With Product Recalls and Withdrawals

In most, if not all, situations for which FDA is considering requiring notification, manufacturers, under current procedures, would subject the product to recall or market withdrawal. Procedures for product recalls are presented as guidance in 21 CFR part 7. "Market withdrawal" is defined in § 7.3. Product recalls and market withdrawals are similar functions for the removal or correction of a marketed product. In the case of recalls the product is considered to be in violation of the law and may be subject to a regulatory action by FDA, such as seizure of the product. A market withdrawal may be performed for a distributed product associated with a minor violation or for products that are not in violation of the law. Many of the procedures described in this ANPRM as potentially appropriate for the notification process are identical or similar to procedures generally performed in a product recall or market withdrawal (see, for example, the procedures for development of a recall strategy (§ 7.42(a)(1)), conducting effectiveness checks (§ 7.42(b)(3)), and recall communications (§ 7.49)). FDA invites comments on the

interrelationship among product recalls, withdrawals, and the notification process described in this ANPRM. What recall/withdrawal procedures would continue to be appropriate in the event FDA requires patient notification? How may the process best be integrated to ensure effective notification and product removal?

K. Informing Patients of the Notification Process

FDA believes that a patient taking custody of a plasma derivative should be informed that she or he will be notified in the event the plasma derivative is associated with a potential increased risk of transmitting a communicable disease. This information should be provided, in writing, when receiving delivery of the plasma product or before, such as at the time the product is prescribed. FDA invites comments on whether such information can best be provided in the form of patient labeling accompanying the product or should be delivered by other means. FDA also invites comments on whether such information can be standardized for all plasma derivative products and, if so, who should be responsible for preparing such information.

IV. Request for Comments

Interested persons may, on or before November 17, 1999, submit to the Dockets Management Branch (address above) written comments regarding the general and specific issues presented in this ANPRM. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

This ANPRM is issued under section 201 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321 *et seq.*) and under authority of the Commissioner of Food and Drugs.

Dated: June 15, 1999.

Jane E. Henney,
Commissioner of Food and Drugs.
Donna E. Shalala,
Secretary of Health and Human Services.
[FR Doc. 99-21294 Filed 8-18-99; 8:45 am]
BILLING CODE 4160-01-F

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 606 and 640

[Docket No. 98N-0673]

Revisions to the Requirements Applicable to Blood, Blood Components, and Source Plasma; Companion Document to Direct Final Rule

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to amend the biologics regulations by removing, revising, or updating specific regulations applicable to blood, blood components, and Source Plasma to be more consistent with current practices in the blood industry and to remove unnecessary or outdated requirements. FDA is taking this action as part of the agency's "Blood Initiative" in which FDA is reviewing and revising, when appropriate, its regulations, policies, guidance, and procedures related to blood, blood components, and Source Plasma. This proposed rule is a companion document to the direct final rule published elsewhere in this issue of the *Federal Register*. FDA is publishing this companion proposed rule under FDA's usual procedure for notice and comment to provide a procedural framework to finalize the rule in the event the agency receives a significant adverse comment and withdraws the direct final rule.

DATES: Submit written comments on or before December 3, 1999. If FDA receives any significant adverse comment regarding this rule, FDA will publish a document withdrawing the direct final rule within 30 days after the comment period ends. FDA then will proceed to respond to the comments under this proposed rule using the usual notice and comment procedures. Any parties interested in commenting on this document should do so at this time.

If FDA receives no significant adverse comments within the specified comment period, the agency intends to publish a document confirming the effective date of the final rule in the *Federal Register* within 30 days after the comment period on the direct final rule ends. The direct final rule will be effective February 11, 2000.

ADDRESSES: Submit written comments on the proposed rule to the Dockets Management Branch (HFA-305), Food

and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Dano B. Murphy, Center for Biologics Evaluation and Research (HFM-17), Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-827-6210.

SUPPLEMENTARY INFORMATION:

I. Background

This proposed rule is a companion to the direct final rule published in the final rules section of this issue of the *Federal Register*. This companion proposed rule will provide the procedural framework to finalize the rule in the event that the direct final rule receives any adverse comment and is withdrawn. The comment period for this companion proposed rule runs concurrently with the comment period for the direct final rule. Any comments received under this companion rule will also be considered as comments regarding the direct final rule. FDA is publishing the direct final rule because the rule contains noncontroversial changes, and FDA anticipates that it will receive no significant adverse comment.

A significant comment is defined as a comment that explains why the rule would be inappropriate, including challenges to the rule's underlying premise or approach, or would be ineffective or unacceptable without a change. In determining whether a significant adverse comment is sufficient to terminate a direct final rulemaking, FDA will consider whether the comment raises an issue serious enough to warrant a substantive response in a notice-and-comment process. Comments that are frivolous, insubstantial, or outside the scope of the rule will not be considered significant or adverse under this procedure. A comment recommending a rule change in addition to the rule would not be considered a significant adverse comment, unless the comment states why the rule would be ineffective without additional change. In addition, if a significant adverse comment applies to an amendment, paragraph, or section of this rule and that provision can be severed from the remainder of the rule, FDA may adopt as final those provisions of the rule that are not subjects of a significant adverse comment.

If no significant adverse comment is received within the specified comment period, FDA will publish a document within 30 days after the comment period ends confirming that the direct final rule will be effective February 11, 2000. Additional information about

FDA's direct rulemaking procedures is set forth in a guidance published in the *Federal Register* of November 21, 1997 (62 FR 62466).

For a variety of reasons, FDA has decided to comprehensively review and, as necessary, revise its regulations, policies, guidance, and procedures related to the licensing and regulation of blood products. FDA is issuing this companion proposed rule and the direct final rule, published elsewhere in this issue of the *Federal Register*, as part of the agency's "Blood Initiative" in which FDA is reviewing and revising, when appropriate, its regulations, policies, guidance, and procedures related to blood, blood components, and Source Plasma. The "Blood Initiative" is discussed in detail in the preamble to the direct final rule. FDA emphasizes that for many of the changes discussed below, additional issues related to the regulations now being amended continue to be under consideration by the agency. Further, more substantive changes may be proposed at a later date. Accordingly, any comment recommending an additional change to these regulations will not be considered to be an "adverse comment" unless the comment demonstrates that the change being made in the direct final rule represents a major departure from current regulations or accepted industry standards, or cannot be implemented without additional amendments to the regulations.

II. Legal Authority

FDA is proposing to issue this new rule under the biological product and communicable disease provisions of the Public Health Service Act (the PHS Act) (42 U.S.C. 262-264) and the drug, device, and general administrative provisions of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321, 331, 351-353, 355, 360, 360j, 371, and 374). Under these provisions of the PHS Act and the act, FDA has the authority to issue and enforce regulations designed to ensure that biological products are safe, pure, potent, and properly labeled and to prevent the introduction, transmission, and spread of communicable disease.

III. Highlights of the Proposed Rule

FDA is proposing to amend the biologics regulations by removing, revising, or updating specific regulations applicable to blood, blood components, and Source Plasma to be more consistent with current practices and to remove unnecessary or outdated requirements. As previously discussed, FDA is also issuing these amendments as a direct final rule because the agency

has concluded they are noncontroversial and that there is little likelihood that there will be comments opposing the rule. FDA emphasizes that for many of the changes discussed in this document, additional issues related to the regulations now being amended continue to be under consideration by the agency. Further, more substantive changes may be proposed at a later date. Accordingly, any comment recommending additional changes to these regulations will not be considered to be an "adverse comment" unless the comment demonstrates that the change being made in the direct final rule represents a major departure from current regulations or accepted industry standards, or cannot be implemented without additional amendments to the regulation. Below FDA is identifying each of the changes included in the proposed rule.

Part 606 (21 CFR part 606) would be amended as follows:

Section 606.3, Definitions, would be amended to update the definitions provided in the section for consistency with current practice and usages.

The definition of "Component" in proposed § 606.3(c), would be amended to clarify that blood is obtained from a single donor and would no longer include the wording "single-donor unit." This change is to clarify that blood components may be collected by means other than separation from a unit of whole blood, such as by automated plasmapheresis.

The definition of "Plasmapheresis" in proposed § 606.3(e), would be amended by removing the restriction that plasmapheresis may be "immediately repeated, once" because current automated plasmapheresis collection practices often use more than two cycles of collection.

The definition of "Plateletpheresis" in proposed § 606.3(f) would be amended to provide for the common practice of collecting plasma as a by-product of a plateletpheresis procedure in lieu of returning all of the residual plasma to the donor.

The definition of "Compatibility testing" in proposed § 606.3(j) would be amended by removing the reference to serological tests and making the definition more general to apply to all tests performed to establish the matching of a donor's blood or blood components with that of a recipient. This change will provide for current practices used in compatibility testing, such as the electronic crossmatch and the immediate spin crossmatch.

Section 606.100(b) and (d) would be amended to reflect changes in terminology, requirements for testing,

and availability of standard operating procedures (SOP's) to be consistent with current practices. Section 606.100(b) would also be amended by removing the references to homologous and autologous transfusion because subpart F of part 606 applies to all blood products intended for transfusion. In addition, the phrase "unless this is impractical" would be removed because it is current good manufacturing practice (CGMP) to make the applicable SOP's available in all areas where procedures are performed. Section 606.100(b)(7) would be amended by removing "including testing for hepatitis B surface antigen as prescribed in § 610.40 of this chapter" because other tests, in addition to tests for hepatitis B surface antigen, are now required and specific reference to this test is unnecessary. Section 606.100(b)(18) would be amended by removing the bracketed term "salvaged" because its use in § 606.100 is inconsistent with the use of "salvaged plasma" in § 640.76 (21 CFR 640.76). Section 606.100(d) would be amended by removing references to specific organizations because any SOP's meeting FDA requirements would be acceptable, regardless of their source, and because FDA cannot assure that SOP's adopted by particular organizations remain in compliance with FDA regulatory requirements.

Section 606.121(a) would be amended by removing the reference that the "Guideline for Uniform Labeling of Blood and Blood Components" is available from the Docket Management Branch as this is no longer the appropriate office from which to request this document and by removing the reference to the American Blood Commission because the organization no longer exists.

Section 606.121(d)(2) specifies the color requirements for printing the container label and would be amended by adding "or in solid black" because some blood centers use on-demand printers for printing labels that do not have the capability to print in multiple colors.

Section 606.121(e)(1)(ii) prescribes the specific anticoagulants that shall be identified on the container label. Section 606.121(e)(1)(ii) would be amended by removing the references to the names of specific anticoagulants. This change will allow for more flexibility for the acceptance and use of new anticoagulants or changes in nomenclature of existing anticoagulants without requiring amendments to the regulations.

Section 606.122(f) specifies the warning statement required in the

instruction circular and would be amended by removing the reference to "hepatitis" and adding "infectious agents" to include a reference to the additional infectious disease marker tests routinely performed on blood and blood components because the product intended for transfusion carries the risk of transmitting other infectious agents.

Section 606.122(n)(4) specifies that the instruction circular for cryoprecipitated AHF shall contain instructions to thaw the product at a temperature of 37 °C and would be changed to allow instructions for thawing between 30 and 37 °C, permitting more flexibility in the preparation of the component.

Section 606.151(b) would be amended, consistent with current accepted practices, to permit SOP's to include use of recipient serum samples less than 3-days old for compatibility testing if the recipient has been pregnant or transfused within the preceding 3 months.

Section 606.151(c) describes compatibility testing and would be amended by changing "the testing of the donor's cells with the recipient's serum" to "the testing of the donor's cell type with the recipient's serum type" and by replacing "agglutinating, coating, and hemolytic antibodies, which shall include the antiglobulin method" with "incompatibility." This change is intended to accommodate the use of such procedures as an immediate spin crossmatch and an electronic crossmatch.

Section 606.151(e) would be amended by changing "by the physician requesting the procedure" to "by a physician" to take into account that a patient may have more than one physician in attendance at any time.

Section 606.160(b)(2)(v) would be amended by changing "person(s) responsible" to "the person(s) performing the procedure" to clarify that the person(s) performing the labeling procedure is responsible for documenting the performance of that procedure.

Section 606.170(b) would be amended by removing "telegraph" and adding "facsimile, express mail, or electronically transmitted mail" to the possible methods by which the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, shall be notified of a complication of blood collection or transfusion resulting in a fatality.

Part 640 (21 CFR part 640) would be amended as follows:

Section 640.2(b) would be removed because Whole Blood collection in open systems is no longer acceptable or has

it being performed for many years. Section 640.2(d) is removed. In § 640.2 paragraphs (c), (e), and (f) would be redesignated as paragraphs (b), (c), and (d), respectively. Redesignated paragraphs (b) and (c)(2) would be revised by removing references to the original blood container because, to be consistent with current accepted practices such as washing, freezing, deglycerolization, and division of units using sterile connecting devices, the original blood container may, in many cases, no longer be the final container.

Section 640.3(b) would be amended by adding a reference to autologous donations to permit the collection of autologous Whole Blood at intervals of less than 8 weeks, consistent with the current practice of shorter time intervals between collections of blood and blood components from donors participating in autologous collection programs. Section 640.3(b)(3) would be amended to provide hematocrit and hemoglobin values to be used when determining whether a potential donor can donate Whole Blood, by adding to the end of the current paragraph "or a hematocrit value of 38 percent, and for autologous donations, a blood hemoglobin level which shall be demonstrated to be no less than 11.0 g of hemoglobin per 100 mL of blood or a hematocrit value of 33 percent." The acceptable hemoglobin and hematocrit values for autologous donors are consistent with current industry practice and the American Association of Blood Banks technical manual, 12th edition.

Sections 640.3(c)(1) and 640.63(c)(11) would be amended by inserting "after the age of eleven" after the term "hepatitis" because establishments may collect Whole Blood from donors who have a history of hepatitis prior to age eleven to be consistent with recommendations in the FDA memorandum dated April 23, 1992, entitled "Exemptions to Permit Persons with a History of Viral Hepatitis Before the Age of Eleven to Serve as Donors of Whole Blood and Plasma: Alternative Procedure" (21 CFR 640.120). Additional issues concerning donors who have a history of viral hepatitis continued to be reviewed by the agency and may be addressed in future rulemaking objectives.

Sections 640.3(c)(2) and 640.63(c)(12) would be amended by changing the deferral period for donors of Whole Blood who have had close contact with an individual having viral hepatitis from "six months" to "12 months." Similarly, §§ 640.3(c)(3) and 640.63(c)(13) would be amended by changing the deferral period from "six months" to "12 months" for donors of

Whole Blood who received human blood, or any derivative of human blood which the Food and Drug Administration has identified as a possible source of viral hepatitis. These changes are consistent with recommendation made in the FDA memorandum dated April 23, 1992, entitled "Revised Recommendations for the Prevention of Human Immunodeficiency Virus Transmission by Blood and Blood Products and Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV)." In addition, §§ 640.3(c)(3) and 640.63(c)(13) would be amended by changing the reference from a "licensed establishment" to a "blood establishment" to clarify that the regulation applies to all establishments engaged in the collection of blood and blood products.

Sections 640.3(e), 640.31(c), and 640.51(c) would be removed because FDA has concluded that it is no longer necessary to defer donors participating in red blood cell immunization programs. Previously, donors participating in red blood cell immunization programs were deferred for 12 months because fresh red blood cells were used to immunize donors. Red blood cells now used in immunization programs are carefully screened and quarantined thereby minimizing the risk of transmitting known infectious agents. See FDA memorandum dated March 14, 1995, entitled "Revised Recommendations for Red Blood Cell Immunization Programs for Source Plasma Donors" for additional information about current red blood cell immunization practices.

Section 640.4(b) would be amended by removing the word "clinic" and replacing it with the word "center" to reflect current terminology and by changing the word "licensed" to "blood" to clarify that the regulation applies to all blood establishments engaged in the collection of blood and blood products. Section 640.4(d) would be amended by removing the reference to the specific anticoagulant formulae. Section 640.4(d)(1) through (d)(4) would be removed because FDA has determined it is unnecessary to provide specific formulae for anticoagulant solutions in the regulations and that manufacturers should be able to use any anticoagulant approved by FDA for such use.

Sections 640.13(a), 640.22(a), 640.32(a), and 640.52(a) would be amended to delete references to § 640.4(d)(2) and (h), which would be

being removed. Section 640.4(g)(5) would be changed to include the use of different anticoagulants in segments for compatibility testing to be consistent with the use of different approved anticoagulants in the manufacture of blood and blood products. Section 640.4(h) would be removed because heparin anticoagulant solutions are no longer used for the routine collection of blood.

Section 640.5(c) would be amended to be consistent with current Rh factor testing practices by removing "and for other Rh-Hr factors," because these tests are not routinely performed. The section would also be changed to specify that blood testing negative using Anti-D Blood Grouping Reagents may only be labeled "Rh Negative" if the confirmatory testing includes tests for weak expressions of D. These changes would be made to be consistent with current accepted practices which designate that tests for weak expressions of D be performed and the product labeled consistent with the results of those tests.

Sections 640.6(c) and 640.15(c) would be removed because the use of more modern methods of manufacturing and equipment have eliminated the use of pilot tubes attached to the blood units. In § 640.15 paragraph (d) is redesignated as paragraph (c).

Section 640.16(a) would be amended by inserting "or additive solution" after "cryoprotective substance" to reflect an additional procedure for prolonging shelf life now in use in which all the plasma is removed from a unit of blood.

Section 640.16(b) would be amended by removing all but the first sentence. The removed text describes blood collection procedures to be followed when using open vented systems. Use of open vented systems is no longer consistent with CGMP and has not been used for many years.

All references to "pilot tubes" and "pilot samples" would be replaced with the words "sample(s)" or "segment(s)" to reflect current terminology for various testing specimens. The following sections would be amended by replacing "pilot tubes," "pilot samples," or "pilot sample tubes" with "segments" or "samples" as appropriate in §§ 640.2(e)(1), 640.4(g) introductory text, and paragraphs (g)(1), (g)(2), (g)(4), and (g)(5), 640.5, 640.15(a) through (c), and 640.69(d) introductory text, and paragraphs (d)(1) through (d)(4).

Section 640.23(a) would be amended to include the preparation of Platelets prepared by automated collection procedures and to allow the group and typing tests performed on Platelets prepared by apheresis to be valid for a

period not to exceed 3 months, thereby, eliminating the necessity of repeat testing of blood samples from donors participating in frequent plasmapheresis collection procedures.

Section 640.24(b) would be amended by changing the time period for separation of the platelet concentrate from "4 hours" to "within the time period specified in the directions for use for the specific device." Similar changes would be made to the timeframe for the storage of plasma that is set forth in § 640.34(a) through (d) and (e)(1) and the freezing of plasma set forth in § 640.54(a)(2). These changes, consistent with current accepted practices, permit more flexibility by permitting different timeframes depending on the particular blood collection device being used.

Sections 640.25(b) and 640.56(a) would be amended to require testing only in those months in which blood products would be prepared for use. This eliminates the need for performing quality control procedures during those months when product is not being manufactured.

Sections 640.25(c), 640.56(c), and 640.71(a) would be amended to update references to cite the "Clinical Laboratories Improvement Amendments of 1988 (CLIA)" consistent with nomenclature in the regulations implementing CLIA in 42 CFR part 493.

Section 640.34(d) would be amended by removing the reference to storing platelet rich plasma at temperatures between 1 and 6 °C because storage at such temperatures adversely affects platelet function.

Section 640.34(e)(2) and (e)(3) would be amended to include the proper name of the product "Plasma, Cryoprecipitate Reduced" as per recommendations of the Blood Products Advisory Committee at the meeting of September 18 and 19, 1997. Section 640.34(g)(2) would be amended to permit for proof of continuous monitoring of the temperature to be within acceptable ranges for the product as an alternative to requiring the storing of the product in a manner to show evidence of thawing. FDA believes that, with current technology, monitoring systems of freezers used for storage are adequately sensitive and reliable to detect any significant rise in storage temperature.

Section 640.62 requiring that a qualified licensed physician be on the premises when donor suitability is being determined would be amended to require a qualified licensed physician to be physically available on the premises, or be available to attend to the donor within 15 minutes, when a pheresis procedure is being performed, for consultation and management of donor

adverse reactions, except that the qualified licensed physician shall be physically available on the premises when red blood cell immunizations are being performed. FDA has determined that a qualified licensed physician must always be readily available, if needed, and shall be on the premises for red blood cell immunizations.

Section 640.63(c)(3) would be amended by adding at the end of the sentence "or a hematocrit level of 38 percent," which is equivalent to a hemoglobin level of 12.5 grams per 100 milliliters of blood, to be consistent with current accepted practices.

Section 640.63(c)(5) would be amended by adding "or total plasma" after "A total serum" to be consistent with current accepted practice of using a capillary tube coated with anticoagulant for fingerstick sample collection.

Section 640.65(b)(4) would be amended by changing "in any 48-hour period" to "2-day" to permit more flexibility in scheduling donor appointments and by adding the word "manual" to the phrases "during a plasmapheresis procedure" to clarify that the regulation applies to a manual plasmapheresis collection procedure, but does not apply to automated apheresis.

Section 640.65(b)(5) would be amended by adding "during a manual plasmapheresis procedure" after the phrases "removed from the donor" to clarify that the regulation applies to a manual plasmapheresis collection procedure, but does not apply to automated apheresis.

Section 640.65(b)(8) would be added to address the collection of Source Plasma using automated collection devices. The regulation describes the frequency of collection consistent with § 640.65(b)(4) and (b)(5) and the volume of plasma to be collected during such procedures consistent with the plasma collection volumes approved for each device and with recommendations included in the FDA memorandum to all plasma establishments dated November 4, 1992, entitled "Volume Limits for Automated Collection of Source Plasma."

Section 640.72(a)(1) would be amended by replacing "compiled every 3 months" with "shall be available" to eliminate the necessity of compiling documents for review at specified periods of time.

IV. Analysis of Impacts

A. Review Under Executive Order 12866 and the Regulatory Flexibility Act and the Unfunded Mandates Reform Act of 1995

FDA has examined the impact of the companion proposed rule under Executive Order 12866 and the Regulatory Flexibility Act (5 U. S. C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). 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 impact; and equity). The agency believes that this proposed rule is consistent with the regulatory philosophy and principles identified in the Executive Order. This proposed rule is not a significant regulatory action as defined by the Executive Order and therefore is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options to minimize any significant impact of a rule on small business entities. Because the proposed rule amendments have no compliance costs and do not result in any new requirements, the agency certifies that the proposed rule will not have a significant negative economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required. This proposed rule also does not trigger the requirement for a written statement under section 202(a) of the Unfunded Mandates Reform Act because it does not impose a mandate that results in an expenditure of \$100 million or more by State, local, and tribal governments in the aggregate, or by the private sector in any 1 year.

B. Environmental Impact

The agency has determined under 21 CFR 25.31(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.

V. Paperwork Reduction Act of 1995

FDA tentatively concludes that this proposed rule contains no collections of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VI. Request for Comments

Interested persons may, on or before December 3, 1999, submit to the Docket Management Branch (address above) written comments regarding this proposal. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects**21 CFR Part 606**

Blood, Labeling, Laboratories, Reporting and recordkeeping requirements.

21 CFR Part 640

Blood, Labeling, Reporting and recordkeeping requirements.

Therefore under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and authority delegated by the Commissioner of Food and Drugs, it is proposed that 21 CFR parts 606 and 640 be 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 606.3 is amended by revising paragraphs (c), (e), (f), and (j) to read as follows:

§ 606.3 Definitions.

* * * * *

(c) *Component* means that part of a single-donor's blood separated by physical or mechanical means.

* * * * *

(e) *Plasmapheresis* means the procedure in which blood is removed from the donor, the plasma is separated from the formed elements and at least the red blood cells are returned to the donor.

(f) *Plateletpheresis* means the procedure in which blood is removed from a donor, a platelet concentrate is separated, and the remaining formed elements are returned to the donor along with a portion of the residual plasma.

* * * * *

(j) *Compatibility testing* means the tests performed to establish the matching of a donor's blood or blood

components with that of a potential recipient.

3. Section 606.100 is amended by revising the introductory text of paragraphs (b) and (d), and by revising paragraphs (b)(7) and (b)(18) to read as follows:

§ 606.100 Standard operating procedures.

* * * * *

(b) Written standard operating procedures shall be maintained and shall include all steps to be followed in the collection, processing, compatibility testing, storage, and distribution of blood and blood components for transfusion and further manufacturing purposes. Such procedures shall be available to the personnel for use in the areas where the procedures are performed. The written standard operating procedures shall include, but are not limited to, descriptions of the following, when applicable:

* * * * *

(7) All tests and repeat tests performed on blood and blood components during manufacturing.

* * * * *

(18) Procedures for preparing recovered plasma, if performed, including details of separation, pooling, labeling, storage, and distribution.

* * * * *

(d) In addition to the requirements of this subpart and in conformity with this section, any facility may utilize current standard operating procedures such as the manuals of the organizations, as long as such specific procedures are consistent with, and at least as stringent as, the requirements contained in this part.

* * * * *

4. Section 606.121 is amended by revising paragraphs (a), (d)(2), and (e)(1)(ii) to read as follows:

§ 606.121 Container label.

(a) The container label requirements are designed to facilitate the use of a uniform container label for blood and blood components (except Source Plasma) by all blood establishments.

* * * * *

(d) * * *

(2) The proper name of the product, any appropriate modifier(s), the donor classification statement, and the statement "properly identify intended recipient" shall be printed in solid red or in solid black.

* * * * *

(e) * * *

(1) * * *

(ii) The name of the applicable anticoagulant immediately preceding

and of no less prominence than the proper name approved for use by the Director, Center for Biologics Evaluation and Research.

* * * * *

5. Section 606.122 is amended by revising paragraphs (f) and (n)(4) to read as follows:

§ 606.122 Instruction circular.

* * * * *

(f) The statements: "Warning. The risk of transmitting infectious agents is present. Careful donor selection and available laboratory tests do not eliminate the hazard."

* * * * *

(n) * * *

(4) Instructions to thaw the product for no more than 15 minutes at a temperature between 30 and 37 °C.

* * * * *

6. Section 606.151 is amended by revising paragraphs (b), (c), and (e) to read as follows:

§ 606.151 Compatibility testing.

* * * * *

(b) The use of fresh recipient serum samples less than 3-days old for all pretransfusion testing if the recipient has been pregnant or transfused within the previous 3 months.

(c) The testing of the donor's cell type with the recipient's serum type by a method that will demonstrate incompatibility.

* * * * *

(e) Procedures to expedite transfusion in life-threatening emergencies. Records of all such incidents shall be maintained, including complete documentation justifying the emergency action, which shall be signed by a physician.

7. Section 606.160 is amended by revising paragraph (b)(2)(v) to read as follows:

§ 606.160 Records.

* * * * *

(b) * * *

(2) * * *

(v) Labeling, including initials of the person(s) performing the procedure.

* * * * *

8. Section 606.170 is amended by revising paragraph (b) to read as follows:

§ 606.170 Adverse reaction file.

* * * * *

(b) When a complication of blood collection or transfusion is confirmed to be fatal, the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, shall be notified by telephone,

facsimile, express mail, or electronically transmitted mail as soon as possible; a written report of the investigation shall be submitted to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, within 7 days after the fatality by the collecting facility in the event of a donor reaction, or by the facility that performed the compatibility tests in the event of a transfusion reaction.

(Information collection requirements approved by the Office of Management and Budget under control number 0910-0116)

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

9. 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.

10. Section 640.2 is amended by removing paragraphs (b) and (d), by redesignating paragraphs (c), (e), and (f) as paragraphs (b), (c), and (d), respectively, and by revising newly redesignated paragraphs (b) and (c)(2) to read as follows:

§ 640.2 General requirements.

(b) *Blood container* The blood container shall not be entered prior to issue for any purpose except for blood collection. Such container shall be uncolored and transparent to permit visual inspection of the contents and any closure shall be such as will maintain an hermetic seal and prevent contamination of the contents. The container material shall not interact with the contents under the customary conditions of storage and use, in such a manner as to have an adverse effect upon the safety, purity, or potency of the blood.

(c) * * *

(2) A segment is properly attached and has not been removed, except that blood lacking a properly attached segment may be reissued in an emergency provided it is accompanied by instructions for sampling and for use within 6 hours after entering the container for sampling;

11. Section 640.3 is amended by revising the introductory text of paragraph (b), by revising paragraphs (b)(3), (c)(1), (c)(2), and (c)(3) and by removing and reserving paragraph (e) to read as follows:

§ 640.3 Suitability of donor.

(b) *Qualifications of donor; general.* Except as provided in paragraph (f) of this section and for autologous donations, a person may not serve as a source of Whole Blood more than once in 8 weeks. In addition, donors shall be in good health, as indicated in part by:

(3) For allogeneic donors, a blood hemoglobin level which shall be demonstrated to be no less than 12.5 grams (g) of hemoglobin per 100 milliliters (mL) of blood; or a hematocrit value of 38 percent, and for autologous donors, a blood hemoglobin level which shall be demonstrated to be no less than 11.0 g of hemoglobin per 100 mL of blood or a hematocrit value of 33 percent.

(c) * * *
(1) A history of viral hepatitis after the age of eleven;

(2) A history of close contact within 12 months of donation with an individual having viral hepatitis;

(3) A history of having received within 12 months of donation, human blood or any derivative of human blood which the Food and Drug Administration has advised the blood establishment is a possible source of viral hepatitis.

12. Section 640.4 is amended by removing paragraphs (d)(1) through (d)(4) and (h), by redesignating paragraph (i) as paragraph (h), and revising paragraphs (b) and (d), the introductory text of paragraph (g), and paragraphs (g)(1), (g)(2), (g)(4), and (g)(5) to read as follows:

§ 640.4 Collection of the blood.

(b) *The donor center* The pertinent requirements of §§ 600.10 and 600.11 of this chapter shall apply at both the blood establishment and at any other place where the bleeding is performed.

(d) *The anticoagulant solution.* The anticoagulant solution shall be sterile and pyrogen-free. Anticoagulant solutions shall be compounded and used according to a formula approved by the Director, Center for Biologics Evaluation and Research.

(g) *Samples for laboratory tests.* Samples for laboratory tests shall meet the following standards:

(1) One or more segments shall be provided with each unit of blood when issued or reissued except as provided in § 640.2(e)(2) and all segments shall be from the donor who is the source of the unit of blood.

(2) All samples for laboratory tests performed by the manufacturer and all segments accompanying a unit of blood shall be collected at the time of filling the original blood container.

(4) All segments accompanying a unit of blood shall be attached to the whole blood container before blood collection, in a tamper proof manner that will conspicuously indicate removal and reattachment.

(5) Segments for compatibility testing shall contain blood mixed with the appropriate anticoagulant.

13. Section 640.5 is amended by revising the introductory text and paragraph (c) to read as follows:

§ 640.5 Testing the blood.

All laboratory tests shall be made on a specimen of blood taken from the donor at the time of collecting the unit of blood, and these tests shall include the following:

(c) *Determination of the Rh factors.* Each container of Whole Blood shall be classified as to Rh type on the basis of tests done on the sample. The label shall indicate the extent of typing and the results of all tests performed. If the test, using Anti-D Blood Grouping Reagent, is positive, the container may be labeled "Rh Positive". If this test is negative, the results shall be confirmed by further testing which shall include tests for the Rh₀ variant (D^u). Blood may be labeled "Rh Negative" if further testing is negative. Units testing positive after additional more specific testing shall be labeled as "Rh Positive." Only Anti-Rh Blood Grouping Reagents licensed under, or that otherwise meet the requirements of, the regulations of this subchapter shall be used, and the technique used shall be that for which the reagent is specifically designed to be effective.

§ 640.6 [Amended]

14. Section 640.6 *Modifications of Whole Blood* is amended by removing paragraph (c).

15. Section 640.13 is amended by revising paragraph (a) to read as follows:

§ 640.13 Collection of the blood.

(a) The source blood shall be collected as prescribed in § 640.4.

16. Section 640.15 is revised to read as follows:

§ 640.15 Samples for testing.

Samples collected in integral tubing shall meet the following standards:

(a) One or more segments of either the original blood or of the Red Blood Cells being processed shall be provided with each unit of Red Blood Cells when issued or reissued.

(b) Before they are filled, all segments shall be marked or identified so as to relate them to the donor of that unit of red cells.

(c) All segments accompanying a unit of Red Blood Cells shall be filled at the time the blood is collected or at the time the final product is prepared.

17. Section 640.16 is amended by revising paragraphs (a) and (b) to read as follows:

§ 640.16 Processing.

(a) *Separation.* Within the timeframe specified in the directions for the use of the specific devices, Red Blood Cells may be prepared either by centrifugation, done in a manner that will not tend to increase the temperature of the blood, or by normal undisturbed sedimentation. A portion of the plasma sufficient to insure optimal cell preservation shall be left with the red cells except when a cryoprotective substance or additive solution is added for prolonged storage.

(b) *Sterile system* All surfaces that come in contact with the red cells shall be sterile and pyrogen-free.

18. Section 640.22 is amended by revising paragraph (a) to read as follows:

§ 640.22 Collection of source material.

(a) Whole blood used as the source of Platelets shall be collected as prescribed in § 640.4.

19. Section 640.23 is amended by revising paragraph (a) to read as follows:

§ 640.23 Testing the blood.

(a) Blood from which plasma is separated for the preparation of Platelets or Platelets, Pheresis shall be tested as prescribed in §§ 610.40 and 610.45 of this chapter and § 640.5(a), (b), and (c). Results of tests performed in accordance with § 640.5(b) and (c) for Platelets, Pheresis products shall be valid for a period not to exceed 3 months.

20. Section 640.24 is amended by revising paragraph (b) to read as follows:

§ 640.24 Processing.

(b) Immediately after collection, the whole blood or plasma shall be held in

storage between 20 and 24 °C, unless it must be transported from the collection center to the processing laboratory. During such transport, all reasonable methods shall be used to maintain the temperature as close as possible to a range between 20 and 24 °C until it arrives at the processing laboratory where it shall be held between 20 and 24 °C until the platelets are separated. The platelet concentrate shall be separated within the timeframe specified in the directions for use for the specific device used for the collection of the unit of whole blood or plasma.

§ 640.31 [Amended]

21. Section 640.31 *Suitability of donors* is amended by removing paragraph (c).

22. Section 640.32 is amended by revising the first sentence of paragraph (a) to read as follows:

§ 640.32 Collection of source material.

(a) Whole blood shall be collected, transported, and stored as prescribed in § 640.4.

23. Section 640.34 is amended by revising paragraphs (a) through (d), (e)(1) through (e)(3), and (g)(2) to read as follows:

§ 640.34 Processing.

(a) *Plasma.* Plasma shall be separated from the red blood cells and shall be stored at -18 °C or colder within the timeframe specified in the directions for use for the specific device after transfer to the final container, unless the product is to be stored as Liquid Plasma.

(b) *Fresh Frozen Plasma.* Fresh Frozen Plasma shall be prepared from blood collected by a single uninterrupted venipuncture with minimal damage to and minimal manipulation of the donor's tissue. The plasma shall be separated from the red blood cells, frozen solid within the timeframe specified in the directions for use for the specific device, and stored at -18 °C or colder.

(c) *Liquid Plasma.* Liquid Plasma shall be separated from the red blood cells and shall be stored at a temperature of 1 to 6 °C within the timeframe specified in the directions for use for the specific device after filling the final container.

(d) *Platelet Rich Plasma* Platelet Rich Plasma shall be prepared from blood collected by a single uninterrupted venipuncture with minimal damage to and manipulation of the donor's tissue. The plasma shall be separated from the red blood cells by centrifugation within

the timeframe specified in the directions for use for the specific device after completion of the phlebotomy. The time and speed of centrifugation shall have been shown to produce a product with at least 250,000 platelets per microliter. The plasma shall be stored at a temperature between 20 and 24 °C, immediately after filling the final container. A gentle and continuous agitation of the product shall be maintained throughout the storage period, if stored at a temperature of 20 to 24 °C.

(e) * * *

(1) Platelets shall be separated as prescribed in subpart C of part 640, prior to freezing the plasma. The remaining plasma may be labeled as "Fresh Frozen Plasma," if frozen within the timeframe specified in the directions for use for the specific device after filling the final container.

(2) Cryoprecipitated AHF shall be removed as prescribed in subpart F of part 640. The remaining plasma shall be labeled "Plasma, Cryoprecipitate Reduced."

(3) Plasma remaining after both Platelets and Cryoprecipitated AHF have been removed may be labeled "Plasma, Cryoprecipitate Reduced."

(g) * * *

(2) With the exception of Platelet Rich Plasma and Liquid Plasma the final product shall be inspected for evidence of thawing or breakage at the time of issuance, however, the containers need not be stored in a manner that shows evidence of thawing if records of continuous monitoring of the storage temperature establish that the temperature remained at -18 °C or colder. If continuous monitoring of the product is not available, the final product shall be stored in a manner that will show evidence of thawing and shall not be issued if there is any evidence of thawing.

§ 640.51 [Amended]

24. Section 640.51 *Suitability of donors* is amended by removing paragraph (c).

25. Section 640.52 is amended by revising paragraph (a) to read as follows:

§ 640.52 Collection of source material.

(a) Whole blood used as a source of Cryoprecipitated AHF shall be collected as prescribed in § 640.4. Whole blood from which both Platelets and Cryoprecipitated AHF is derived shall be maintained as required under § 640.24 until the platelets are removed.

26. Section 640.54 is amended by revising paragraph (a)(2) to read as follows:

§ 640.54 Processing.

(a) * * *

(2) The plasma shall be frozen solid after blood collection within the timeframe specified in the directions for use for the specific device. A combination of dry ice and organic solvent may be used for freezing; *Provided*, That the procedure has been shown not to cause the solvent to penetrate the container or leach plasticizer from the container into the plasma.

* * * * *

27. Section 640.56 is amended by revising the introductory text of paragraph (c) to read as follows:

§ 640.56 Quality control test for potency.

* * * * *

(c) The quality control test for potency may be performed by a clinical laboratory which meets the standards of the Clinical Laboratories Improvement Act of 1988 (CLIA) (42 U.S.C. 263a) and is qualified to perform potency tests for antihemophilic factor. Such arrangements must be approved by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration. Such testing shall not be considered as divided manufacturing, as described in § 610.63 of this chapter, provided the following conditions are met:

* * * * *

28. Section 640.62 is revised to read as follows:

§ 640.62 Medical supervision.

A qualified licensed physician shall be available to attend to the donor within 15 minutes when donor suitability is being determined, immunizations are being made, whole blood is being collected, and red blood cells are being returned to the donor, except that during the administration of immunization red blood cells a qualified licensed physician shall be on the premises.

29. Section 640.63 is amended by revising paragraphs (c)(3), (c)(5), (c)(11), (c)(12), and (c)(13) to read as follows:

§ 640.63 Suitability of donor.

* * * * *

(c) * * *

(3) A blood hemoglobin level of no less than 12.5 grams of hemoglobin per 100 milliliters of blood or a hematocrit level of 38 percent;

* * * * *

(5) A total serum or total plasma protein of no less than 6.0 grams per 100 milliliters of blood;

* * * * *

(11) A history of viral hepatitis after the age of eleven;

(12) Freedom from a history of close contact within 12 months of donation with an individual having viral hepatitis;

(13) Freedom from a history of having received, within 12 months, human blood or any derivative of human blood which the Food and Drug Administration has advised the blood establishment is a possible source of viral hepatitis, except for specific immunization performed in accordance with § 640.66.

* * * * *

30. Section 640.65 is amended by revising paragraphs (b)(4) and (b)(5) and by adding paragraph (b)(8) to read as follows:

§ 640.65 Plasmapheresis.

* * * * *

(b) * * *

(4) The amount of whole blood, not including anticoagulant, removed from a donor during a manual plasmapheresis procedure or in any 2-day period shall not exceed 1,000 milliliters unless the donor's weight is 175 pounds or greater, in which case the amount of whole blood, not including anticoagulant, removed from the donor during a manual plasmapheresis procedure or in any 2-day period shall not exceed 1,200 milliliters.

(5) The amount of whole blood, not including anticoagulant, removed from a donor during a manual plasmapheresis procedure within a 7-day period shall not exceed 2,000 milliliters unless the donor's weight is 175 pounds or greater, in which case the amount of whole blood, not including anticoagulant, removed from a donor during a manual plasmapheresis procedure within a 7-day period shall not exceed 2,400 milliliters.

* * * * *

(8) The volume of plasma collected during an automated plasmapheresis collection procedure shall be consistent with the volumes specifically approved by the Director, Center for Biologics Evaluation and Research, and collection shall not occur less than 2 days apart or more frequently than twice in a 7-day period.

31. Section 640.69 is amended by revising paragraph (d) to read as follows:

§ 640.69 General requirements.

* * * * *

(d) *Samples*. If samples are provided, they shall meet the following standards:

(1) Prior to filling, all samples shall be marked or identified so as to relate them directly to the donor of that unit of plasma.

(2) All samples shall be filled at the time the final product is prepared by the person who prepares the final product.

(3) All samples shall be representative of the contents of the final product or be collected from the donor at the time of filling the collection container.

(4) All samples shall be collected in a manner that does not contaminate the contents of the final container.

32. Section 640.71 is amended by revising the introductory text of paragraph (a) to read as follows:

§ 640.71 Manufacturing responsibility.

(a) All steps in the manufacturing of Source Plasma, including donor examination, blood collection, plasmapheresis, laboratory testing, labeling, storage, and issuing shall be performed by personnel of the establishment licensed to manufacture Source Plasma, except that the following tests may be performed by personnel of an establishment licensed for blood and blood derivatives under section 351(a) of the Public Health Service Act, or by a clinical laboratory that meets the standards of the Clinical Laboratories Improvement Act of 1988 (CLIA) (42 U.S.C. 263a): *Provided*, The establishment or clinical laboratory is qualified to perform the assigned test(s).

* * * * *

33. Section 640.72 is amended by revising paragraph (a)(1) to read as follows:

§ 640.72 Records.

(a) * * *

(1) Documentation shall be available to ensure that the shipping temperature requirements of § 600.15 of this title and of § 640.74(b)(2) are being met for Source Plasma intended for manufacture into injectable products.

* * * * *

Dated: April 20, 1999.

Jane E. Henney,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 99-21293 Filed 8-18-99; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 606 and 640

[Docket No. 98N-0673]

Revisions to the Requirements Applicable to Blood, Blood Components, and Source Plasma

AGENCY: Food and Drug Administration, HHS.

ACTION: Direct final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the biologics regulations by removing, revising, or updating specific regulations applicable to blood, blood components, and Source Plasma to be more consistent with current practices in the blood industry and to remove unnecessary or outdated requirements. FDA is issuing these amendments directly as a final rule because they are noncontroversial and there is little likelihood that FDA will receive any significant comments opposing the rule. Elsewhere in this issue of the *Federal Register*, FDA is publishing a proposed rule under FDA's usual procedures for notice and comment in the event the agency receives any significant adverse comments. If FDA receives any significant adverse comment sufficient to terminate the direct final rule, FDA will consider such comments on the proposed rule in developing the final rule. FDA is issuing this rule as part of the agency's "Blood Initiative" in which FDA is reviewing and revising, when appropriate, its regulations, policies, guidance, and procedures related to blood, blood components, and Source Plasma.

DATES: This rule is effective February 11, 2000. Submit written comments on or before December 3, 1999. If no timely significant comments are received, the agency will publish a document in the *Federal Register* within 30 days after the comment period on this direct final rule ends, confirming the effective date of the final rule. If timely significant adverse comments are received, the agency will publish a document in the *Federal Register* withdrawing the direct final rule before its effective date.

ADDRESSES: Submit written comments on the direct final rule to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852.

FOR FURTHER INFORMATION CONTACT: Dano B. Murphy, Center for Biologics Evaluation and Research (HFM-17),

Food and Drug Administration, 1401 Rockville Pike, Rockville, MD 20852-1448, 301-827-6210.

SUPPLEMENTARY INFORMATION:

I. Blood Initiative

For a variety of reasons, FDA has decided to comprehensively review and, as necessary, revise its regulations, policies, guidance and procedures related to the licensing and regulation of blood products. In the *Federal Register* of June 3, 1994 (59 FR 28821 and 59 FR 28822, respectively), FDA issued two documents entitled "Review of General Biologics and Licensing Regulations" (Docket No. 94N-0066) and "Review of Regulations for Blood Establishments and Blood Products" (Docket No. 94N-0080). The documents announced the agency's intent to review biologics regulations, 21 CFR parts 600, 601, 606, 607, 640, and 660 and requested written comments from the public. Interested persons were given until August 17, 1994, to respond to the documents. In response to requests for additional time, FDA twice extended the comment period, as announced in the *Federal Register* of August 17, 1994 (59 FR 42193), and November 14, 1995 (59 FR 56448). In addition, FDA responded to requests for a public meeting to allow for the presentation of comments regarding the agency's intent to review the biologics regulations. On January 26, 1995, FDA held a public meeting to provide an opportunity for all interested individuals to present their comments and to assist the agency in determining whether the regulations should be revised, rescinded, or continued without change. Since the time of the regulation review, FDA has implemented a number of changes to its regulations and policies applicable to blood products as well as other biological products. (See, e.g., the final rules issued on May 14, 1996 (61 FR 24313); August 1, 1996 (61 FR 40153); November 6, 1996 (61 FR 57328); July 24, 1997 (62 FR 39890); and October 15, 1997 (62 FR 53536).)

Because of the importance of a safe national blood supply, the U.S. House of Representatives Committee on Government Reform and Oversight, Subcommittee on Human Resources and Intergovernmental Relations (the Subcommittee) and other groups such as the General Accounting Office (GAO), and the Institute of Medicine (IOM) have reviewed the agency's policies, practices, and regulations. Reports issued following the respective reviews contained a number of

recommendations as to how FDA might improve the biologics regulations, particularly as they apply to the continued safety of blood products. The relevant reports are: (1) "Protecting the Nation's Blood Supply From Infectious Agents: The Need for New Standards to Meet New Threats," by the Subcommittee (August 2, 1996); (2) "Blood Supply: FDA Oversight and Remaining Issues of Safety," by GAO (February 25, 1997); (3) "Blood Supply: Transfusion-Associated Risks," by GAO (February 25, 1997); and (4) "HIV and the Blood Supply: An Analysis of Crisis Decisionmaking," by IOM (July 13, 1995). These reports are on file with the Dockets Management Branch (address above) under the docket number found in brackets in the heading of this document.

FDA has reviewed these reports and agrees with the majority of the recommendations contained within them. However, rather than to only respond specifically to the recommendations from the Subcommittee, GAO, IOM, and the public, FDA has convened a number of internal task forces to review a variety of issues related to the regulation of blood and blood products, including how to most appropriately update the existing regulations applicable to blood and blood products. In the future, FDA intends to issue a number of blood-related regulations that various FDA task groups are preparing. FDA emphasizes that for many of the changes discussed in section III of this document, additional issues related to the regulations now being amended continue to be under consideration by the agency. Further, more substantive changes may be proposed at a later date. Accordingly, any comment recommending an additional change to these regulations will not be considered to be an "adverse comment" unless the comment demonstrates that the change being made in the direct final rule represents a major departure from current regulations or accepted industry standards, or cannot be implemented without additional amendments to the regulations.

FDA is not describing the specific recommendations it received and the numerous objectives of the Blood Initiative in this document. Future rulemaking and other notices will describe and discuss specific recommendations and regulatory objectives as they apply to each rulemaking.

II. Legal Authority

FDA is issuing this new rule under the biologics products and

communicable disease provisions of the Public Health Service Act (the PHS Act) (42 U.S.C. 262-264) and the drug, device, and general administrative provisions of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321, 331, 351-353, 355, 360, 360j, 371, and 374). Under these provisions of the PHS Act and the act, FDA has the authority to issue and enforce regulations designed to ensure that biological products are safe, pure, potent, and properly labeled and to prevent the introduction, transmission, and spread of communicable disease.

III. Highlights of the Direct Final Rule

FDA is amending the biologics regulations by removing, revising, or updating specific regulations applicable to blood, blood components, and Source Plasma to be more consistent with current practices and to remove unnecessary or outdated requirements. FDA is issuing these amendments as a direct final rule because the agency has concluded they are noncontroversial and that there is little likelihood that there will be comments opposing the rule. FDA emphasizes that for many of the following changes, additional issues related to the regulations now being amended continue to be under consideration by the agency. Further, more substantive changes may be proposed at a later date. Accordingly, any comment recommending additional changes to these regulations will not be considered to be an "adverse comment" unless the comment demonstrates that the change being made in the direct final rule represents a major departure from current regulations or accepted industry standards, or cannot be implemented without additional amendments to the regulation. In the following paragraphs, FDA discusses each of the rule changes in the direct final rule.

Part 606 (21 CFR part 606) is amended as follows:

Section 606.3, Definitions, is amended so that the definitions provided in the section are consistent with current meanings and usages.

The definition of "Component" in § 606.3(c) is amended to apply to blood obtained from a single donor and no longer includes the wording "single-donor unit." This change is to clarify that blood components may be collected by means other than separation from a unit of whole blood, such as by automated plasmapheresis.

The definition of "Plasmapheresis" in § 606.3(e) is amended by removing the restriction that plasmapheresis may be "immediately repeated, once" because current automated plasmapheresis

collection practices often use more than two cycles for collection.

The definition of "Plateletpheresis" in § 606.3(f) is amended to provide for the common practice of collecting plasma as a by-product of a plateletpheresis procedure in lieu of returning all of the residual plasma to the donor.

The definition of "Compatibility testing" in § 606.3(j) is amended by removing the reference to serological tests and making the definition more general to apply to all tests performed to establish the matching of a donor's blood or blood components with that of a potential recipient. This change will provide for current practices used in compatibility testing, such as the electronic crossmatch and the immediate spin crossmatch.

Section 606.100(b) and (d) are amended to reflect changes in terminology, requirements for testing, and availability of standard operating procedures (SOP's) to be consistent with current practices. Section 606.100(b) is also amended by removing the references to homologous and autologous transfusion because subpart F of part 606, applies to all blood products intended for transfusion. In addition, the phrase "unless this is impractical" is removed because it is current good manufacturing practice (CGMP) to make the applicable SOP's available in all areas where procedures are performed. Section 606.100(b)(7) is amended by removing "including testing for hepatitis B surface antigen as prescribed in § 610.40 of this chapter" because other tests, in addition to tests for hepatitis B surface antigen, are now required and specific reference to this test is unnecessary. Section 606.100(b)(18) is amended by removing the bracketed term "salvaged" because its use in § 606.100 is inconsistent with the use of "salvaged plasma" in § 640.76. Section 606.100(d) is amended by removing references to specific organizations because any SOP's meeting FDA requirements would be acceptable, regardless of their source, and because FDA cannot assure that SOP's adopted by particular organizations remain in compliance with FDA's regulatory requirements.

Section 606.121(a) is amended by removing the reference that the "Guideline for the Uniform Labeling of Blood and Blood Components" is available from Dockets Management Branch as this is no longer the appropriate office from which to request this document and by removing the reference to the American Blood Commission because the organization no longer exists.

Section 606.121(d)(2) specifies the color requirements for printing the container label and is amended by adding "or in solid black" because some blood centers use on-demand printers for printing labels, that do not have the capability to print in multiple colors.

Section 606.121(e)(1)(ii) prescribes the specific anticoagulants that shall be identified on the container label. Section 606.121(e)(1)(ii) is amended by deleting the references to the names of specific anticoagulants. This change will allow for more flexibility for the acceptance and use of new anticoagulants or changes in nomenclature of existing anticoagulants without requiring amendments to the regulations.

Section 606.122(f) specifies the warning statement required in the instruction circular and is amended by removing the reference to "hepatitis" and adding "infectious agents" to include a reference to the additional infectious disease marker tests routinely performed on blood and blood components because the product intended for transfusion carries the risk of transmitting other infectious agents.

Section 606.122(n)(4) specifies that the instruction circular for cryoprecipitated AHF shall contain instructions to thaw the product at a temperature of 37 °C and is amended to allow instructions for thawing between 30 and 37 °C, permitting more flexibility in the preparation of the component.

Section 606.151(b) is amended, consistent with current accepted practices, to permit SOP's to include use of recipient serum samples less than 3-days old for compatibility testing if the recipient has been pregnant or transfused within the preceding 3 months.

Section 606.151(c) describes compatibility testing and is amended by changing "the testing of the donor's cells with the recipient's serum" to "the testing of the donor's cell type with the recipient's serum type" and by replacing "agglutinating, coating, and hemolytic antibodies, which shall include the antiglobulin method" with "incompatibility." This change is intended to accommodate the use of such procedures as an immediate spin crossmatch and an electronic crossmatch.

Section 606.151(e) is amended by changing "by the physician requesting the procedure." to "by a physician." to take into account that a patient may have more than one physician in attendance at any time.

Section 606.160(b)(2)(v) is amended by changing "person(s) responsible" to "the person(s) performing the

procedure" to clarify that the person(s) performing the labeling procedure is responsible for documenting the performance of that procedure.

Section 606.170(b) is amended by deleting "telegraph" and adding "facsimile, express mail, or electronically transmitted mail" to the possible methods by which the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, shall be notified of a complication of blood collection or transfusion resulting in a fatality.

Part 640 (21 CFR part 640) is amended as follows:

Section 640.2(b) is removed because Whole Blood collection in open systems is no longer acceptable nor has it been performed for many years. Section 640.2(d) is revised. In § 640.2 paragraphs (c), (e), and (f) are redesignated as paragraphs (b), (c), and (d), respectively. Redesignated § 640.2(b) and (c)(2) are revised by removing references to the original blood container because, consistent with current accepted practices such as washing, freezing, deglycerolization, and division of units using sterile connecting devices, the original blood container may, in many cases, no longer be the final container.

Section 640.3(b) is amended by adding a reference to autologous donations to permit the collection of autologous Whole Blood at intervals of less than 8 weeks, consistent with the current practice of shorter time intervals between collections of blood and blood components from donors participating in autologous collection programs. Section 640.3(b)(3) is amended to provide hematocrit and hemoglobin values to be used when determining whether a potential donor can donate Whole Blood, by adding to the end of the current paragraph "or a hematocrit value of 38 percent, and for autologous donations, a blood hemoglobin level which shall be demonstrated to be no less than 11.0 g of hemoglobin per 100 mL of blood or a hematocrit value of 33 percent." The acceptable hemoglobin and hematocrit values for autologous donors are consistent with current industry practice and the American Association of Blood Banks technical manual, 12th edition.

Sections 640.3(c)(1) and 640.63(c)(11) are amended by inserting "after the age of eleven" after the term "hepatitis" because establishments may collect Whole Blood from donors who have a history of hepatitis prior to age eleven to be consistent with recommendations in the FDA memorandum dated April 23, 1992, entitled "Exemptions to Permit Persons with a History of Viral

Hepatitis Before the Age of Eleven to serve as Donors of Whole Blood and Plasma: Alternative Procedure" (21 CFR 640.120). Additional issues concerning donors who have a history of viral hepatitis continued to be reviewed by the agency and may be addressed in future rulemaking objectives.

Sections 640.3(c)(2) and 640.63(c)(12) are amended by changing the deferral period for donors of Whole Blood who have had close contact with an individual having viral hepatitis from "six months" to "12 months." Similarly, §§ 640.3(c)(3) and 640.63(c)(13) are amended by changing the deferral period from "six months" to "12 months" for donors of Whole Blood who received human blood, or any derivative of human blood which FDA has identified as a possible source of viral hepatitis. These changes are consistent with recommendations made in the FDA memoranda dated April 23, 1992, entitled "Revised Recommendations for the Prevention of Human Immunodeficiency Virus Transmission by Blood and Blood Products and Revised Recommendations for Testing Whole Blood, Blood Components, Source Plasma and Source Leukocytes for Antibody to Hepatitis C Virus Encoded Antigen (Anti-HCV)." In addition, §§ 640.3(c)(3) and 640.63(c)(13) have been amended by changing the reference from a "licensed establishment" to a "blood establishment" to clarify that the regulation applies to all establishments engaged in the collection of blood and blood products.

Sections 640.3(e), 640.31(c), and 640.51(c) are removed because FDA has concluded that it is no longer necessary to defer donors participating in red blood cell immunization programs. Previously, donors participating in red blood cell immunization programs were deferred for 12 months because fresh red blood cells were used to immunize donors. Red blood cells now used in immunization programs are carefully screened and quarantined thereby minimizing the risk of transmitting infectious agents. See FDA memorandum dated March 14, 1995, entitled "Revised Recommendations for Red Blood Cell Immunization Programs for Source Plasma Donors" for additional information about current red blood cell immunization practices.

Section 640.4(b) is amended by removing the word "clinic" and replacing it with the word "center" to reflect current terminology and by changing the word "licensed" to "blood" to clarify that the regulation applies to all blood establishments

engaged in the collection of blood and blood products. Section 640.4(d) is amended by removing the reference to the specific anticoagulant formulae. Section 640.4(d)(1) through (d)(4) is removed because FDA has determined it is unnecessary to provide specific formulae for anticoagulant solutions in the regulations and that manufacturers should be able to use any anticoagulant approved by FDA for such use. Sections 640.13(a), 640.22(a), 640.32(a), and 640.52(a) are amended to remove references to § 640.4(d)(2) and (h), which are being removed.

Section 640.4(g)(5) has been changed to include the use of different anticoagulants in segments for compatibility testing to be consistent with the use of different approved anticoagulants in the manufacture of blood and blood products. Section 640.4(h) is removed because heparin anticoagulant solutions are no longer used for the routine collection of blood.

Section 640.5(c) is amended to be consistent with current Rh factor testing practices by removing "and for other Rh-Hr factors," because these tests are not routinely performed. The section is also changed to specify that blood testing negative using Anti-D Blood Grouping Reagents may only be labeled "Rh Negative" if the confirmatory testing includes tests for weak expressions of D. These changes have been made to be consistent with current accepted practices which designate that tests for weak expressions of D be performed and the product labeled consistent with the results of those tests.

Sections 640.6(c) and 640.15(c) are removed because the use of more modern methods of manufacturing and equipment have eliminated the use of pilot tubes attached to blood units. In § 640.15 paragraph (d) is redesignated as paragraph (c).

Section 640.16(a) is amended by inserting "or additive solution" after "cryoprotective substance" to reflect an additional procedure for prolonging shelf life now in use in which all the plasma is removed from a unit of blood.

Section 640.16(b) is amended by removing all but the first sentence. The removed text describes blood collection procedures to be followed when using open vented systems. Use of open vented systems is no longer consistent with CGMP and has not been used for many years.

All references to "pilot tubes" and "pilot samples" have been replaced with the words "sample(s)" or "segment(s)" to reflect current terminology for various testing specimens. The following sections are amended by replacing "pilot tubes,"

"pilot samples," or "pilot sample tubes" with "segments" or "samples" as appropriate: §§ 640.2(e)(2), 640.4(g) introductory text, and paragraphs (g)(1), (g)(2), (g)(4), and (g)(5), 640.5, 640.15(a) through (c), and 640.69(d) introductory text, and paragraphs (d)(1) through (d)(4).

Section 640.23(a) is amended to include the preparation of Platelets prepared by automated collection procedures and to allow the group and typing tests performed on Platelets prepared by apheresis to be valid for a period not to exceed 3 months, thereby, eliminating the necessity of repeat testing of blood samples from donors participating in frequent plateletpheresis collection procedures.

Section 640.24(b) is amended by changing the time period for separation of the platelet concentrate from "4 hours" to "within the time period specified in the directions for use for the specific device." Similar changes are made to the timeframe for the storage of plasma that is set forth in § 640.34(a) through (d) and (e)(1) and the freezing of plasma set forth in § 640.54(a)(2). These changes, consistent with current accepted practices, permit more flexibility by permitting different timeframes depending on the particular blood collection device being used.

Sections 640.25(b) and 640.56(a) are amended to require testing only in those months in which blood products are prepared for use. This eliminates the need for performing quality control procedures during those months when product is not being manufactured.

Sections 640.25(c), 640.56(c), and 640.71(a) are amended to update references to cite the "Clinical Laboratories Improvement Amendments of 1988 (CLIA)" consistent with nomenclature in the regulations implementing CLIA in 42 CFR part 493.

Section 640.34(d) is amended by deleting the reference to storing platelet rich plasma at temperatures between 1 and 6 °C because storage at such temperatures adversely affects platelet function.

Section 640.34(e)(2) and (e)(3) are amended to include the proper name of the product "Plasma, Cryoprecipitate Reduced" as per recommendations of the Blood Products Advisory Committee at its September 18 and 19, 1997 meeting. Section 640.34(g)(2) is amended to permit proof of continuous monitoring of the temperature to be within acceptable ranges for the product as an alternative to requiring the storing of the product in a manner to show evidence of thawing. FDA believes that, with current technology, monitoring systems of freezers used for storage are

adequately sensitive and reliable to detect any significant rise in storage temperature.

Section 640.62 requiring that a qualified licensed physician be on the premises when donor suitability is being determined is amended to require a qualified licensed physician to be physically available on the premises, or be available to attend to the donor within 15 minutes, when a pheresis procedure is being performed, for consultation and management of donor adverse reactions, except that the qualified licensed physician shall be physically available on the premises when red blood cell immunizations are being performed. FDA has determined that a qualified licensed physician must always be readily available, if needed, and shall be on the premises for red blood cell immunizations.

Section 640.63(c)(3) is amended by adding at the end of the sentence "or a hematocrit level of 38 percent," which is equivalent to a hemoglobin level of 12.5 g per 100 mL of blood, to be consistent with current accepted practices.

Section 640.63(c)(5) is amended by adding "or total plasma" after "A total serum" to be consistent with current accepted practice of using a capillary tube coated with anticoagulant for fingerstick sample collection.

Section 640.65(b)(4) is amended by changing "in any 48-hour period" to "2-day" to permit more flexibility in scheduling donor appointments and by adding the word "manual" to the phrases "during a plasmapheresis procedure" to clarify that the regulation applies to a manual plasmapheresis collection procedure, but does not apply to automated apheresis.

Section 640.65(b)(5) is amended by adding "during a manual plasmapheresis procedure" after the phrases "removed from the donor" to clarify that the regulation applies to a manual plasmapheresis collection procedure, but does not apply to automated apheresis.

Section 640.65(b)(8) is added to address the collection of Source Plasma using automated collection devices. The regulation delineates the frequency of collection consistent with § 640.65(b)(4) and (b)(5) and the volume of plasma to be collected during such procedures consistent with the plasma collection volumes approved for each device and with recommendations included in the FDA memorandum dated November 4, 1992, entitled "Volume Limits for Automated Collection of Source Plasma."

Section 640.72(a)(1) is amended by replacing "compiled every 3 months"

with "shall be available" to eliminate the necessity of compiling documents at specified time intervals.

IV. Rulemaking Action

In the **Federal Register** of November 21, 1997 (62 FR 62466), FDA described its procedures on when and how FDA will employ direct final rulemaking. FDA has determined that this rule is appropriate for direct final rulemaking because FDA views this rule as including only noncontroversial amendments and anticipates no significant adverse comments. Consistent with FDA's procedures on direct final rulemaking, FDA is publishing elsewhere in this issue of the **Federal Register**, a companion proposed rule to amend the biologics regulations by removing, revising, and updating existing regulations to be more consistent with current accepted practices. The companion proposed rule provides a procedural framework within which the rule may be finalized in the event the direct final rule is withdrawn because of any significant adverse comment. The comment period for the direct final rule runs concurrently with the companion proposed rule. Any comment received under the companion proposed rule will be considered as comments regarding the direct final rule.

FDA has provided a comment period on the direct final rule of 75 days after August 19, 1999. If the agency receives any significant adverse comment, FDA intends to withdraw this direct final rule action by publication of a document in the **Federal Register** within 30 days after the comment period ends. A significant adverse comment is defined as a comment that explains why the rule would be inappropriate, including challenges to the rule's underlying premise or approach, or would be ineffective or unacceptable without a change. In determining whether a significant adverse comment is sufficient to terminate a direct final rulemaking, FDA will consider whether the comment raises an issue serious enough to warrant a substantive response in a notice-and-comment process. Comments that are frivolous, insubstantial, or outside the scope of the rule will not be considered significant or adverse under this procedure. A comment recommending a rule change in addition to the rule would not be considered a significant adverse comment, unless the comment states why the rule would be ineffective without additional change. In addition, if a significant adverse comment applies to an amendment, paragraph, or section of this rule and

that provision can be severed from the remainder of the rule, FDA may adopt as final those provisions of the rule that are not subjects of a significant adverse comment.

If any significant adverse comment is received during the comment period, FDA will publish, within 30 days after the comment period ends, a document withdrawing the direct final rule. If FDA withdraws the direct final rule, any comments received will be applied to the proposed rule and will be considered in developing a final rule using the usual Administrative Procedure Act notice-and-comment procedures.

If FDA receives no significant adverse comments during the specified comment period, FDA intends to publish a confirmation document within 30 days after the comment period ends confirming the effective date.

V. Analysis of Impacts

A. Review Under Executive Order 12866 and the Regulatory Flexibility Act and Unfunded Mandates Reform Act of 1995

FDA has examined the impact of the direct final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U. S. C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). 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 impact; and equity). The agency believes that this direct final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. This direct final rule is not a significant regulatory action as defined by the Executive Order and therefore is not subject to review under the Executive Order.

The Regulatory Flexibility Act requires agencies to analyze regulatory options to minimize any significant impact of a rule on small business entities. Because the direct final rule amendments have no compliance costs and do not result in any new requirements, the agency certifies that the direct final rule will not have a significant negative economic impact on a substantial number of small entities. Therefore, under the Regulatory Flexibility Act, no further analysis is required. This direct final rule also does not trigger the requirement for a written statement under section 202(a) of the Unfunded Mandates Reform Act

because it does not impose a mandate that results in an expenditure of \$100 million or more by State, local, and tribal governments in the aggregate, or by the private sector in any 1 year.

B. Environmental Impact

The agency has determined under 21 CFR 25.31(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.

VI. The Paperwork Reduction Act of 1995

This direct final rule contains no collection of information. Therefore, clearance by the Office of Management and Budget under the Paperwork Reduction Act of 1995 is not required.

VII. Request for Comments

Interested persons may, on or before December 3, 1999, submit to the Docket Management Branch (address above) written comments regarding this final rule. Two copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects

21 CFR Part 606

Blood, Labeling, Laboratories, Reporting and recordkeeping requirements.

21 CFR Part 640

Blood, Labeling, Reporting and recordkeeping requirements.

Therefore under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and authority delegated by the Commissioner of Food and Drugs, 21 CFR parts 606 and 640 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 606.3 is amended by revising paragraphs (c), (e), (f), and (j) to read as follows:

§ 606.3 Definitions.

* * * * *

(c) *Component* means that part of a single-donor's blood separated by physical or mechanical means.

* * * * *

(e) *Plasmapheresis* means the procedure in which blood is removed from the donor, the plasma is separated from the formed elements and at least the red blood cells are returned to the donor.

(f) *Plateletpheresis* means the procedure in which blood is removed from a donor, a platelet concentrate is separated, and the remaining formed elements are returned to the donor along with a portion of the residual plasma.

* * * * *

(j) *Compatibility testing* means the tests performed to establish the matching of a donor's blood or blood components with that of a potential recipient.

3. Section 606.100 is amended by revising the introductory text of paragraphs (b) and (d), and by revising paragraphs (b)(7) and (b)(18) to read as follows:

§ 606.100 Standard operating procedures.

* * * * *

(b) Written standard operating procedures shall be maintained and shall include all steps to be followed in the collection, processing, compatibility testing, storage, and distribution of blood and blood components for transfusion and further manufacturing purposes. Such procedures shall be available to the personnel for use in the areas where the procedures are performed. The written standard operating procedures shall include, but are not limited to, descriptions of the following, when applicable:

* * * * *

(7) All tests and repeat tests performed on blood and blood components during manufacturing.

* * * * *

(18) Procedures for preparing recovered plasma, if performed, including details of separation, pooling, labeling, storage, and distribution.

* * * * *

(d) In addition to the requirements of this subpart and in conformity with this section, any facility may utilize current standard operating procedures such as the manuals of the organizations, as long as such specific procedures are consistent with, and at least as stringent as, the requirements contained in this part.

* * * * *

4. Section 606.121 is amended by revising paragraphs (a), (d)(2), and (e)(1)(ii) to read as follows:

§ 606.121 Container label.

(a) The container label requirements are designed to facilitate the use of a uniform container label for blood and blood components (except Source Plasma) by all blood establishments.

* * * * *

(d) * * *

(2) The proper name of the product, any appropriate modifier(s), the donor classification statement, and the statement "properly identify intended recipient" shall be printed in solid red or in solid black.

* * * * *

(e) * * *

(1) * * *

(ii) The name of the applicable anticoagulant immediately preceding and of no less prominence than the proper name approved for use by the Director, Center for Biologics Evaluation and Research.

* * * * *

5. Section 606.122 is amended by revising paragraphs (f) and (n)(4) to read as follows:

§ 606.122 Instruction circular.

* * * * *

(f) The statements: "Warning. The risk of transmitting infectious agents is present. Careful donor selection and available laboratory tests do not eliminate the hazard."

* * * * *

(n) * * *

(4) Instructions to thaw the product for no more than 15 minutes at a temperature between 30 and 37 °C.

* * * * *

6. Section 606.151 is amended by revising paragraphs (b), (c), and (e) to read as follows:

§ 606.151 Compatibility testing.

* * * * *

(b) The use of fresh recipient serum samples less than 3-days old for all pretransfusion testing if the recipient has been pregnant or transfused within the previous 3 months.

(c) The testing of the donor's cell type with the recipient's serum type by a method that will demonstrate incompatibility.

* * * * *

(e) Procedures to expedite transfusion in life-threatening emergencies. Records of all such incidents shall be maintained, including complete documentation justifying the emergency action, which shall be signed by a physician.

7. Section 606.160 is amended by revising paragraph (b)(2)(v) to read as follows:

§ 606.160 Records.

* * * * *

(b) * * *

(2) * * *

(v) Labeling, including initials of the person(s) performing the procedure.

* * * * *

8. Section 606.170 is amended by revising paragraph (b) to read as follows:

§ 606.170 Adverse reaction file.

* * * * *

(b) When a complication of blood collection or transfusion is confirmed to be fatal, the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, shall be notified by telephone, facsimile, express mail, or electronically transmitted mail as soon as possible; a written report of the investigation shall be submitted to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, within 7 days after the fatality by the collecting facility in the event of a donor reaction, or by the facility that performed the compatibility tests in the event of a transfusion reaction.

(Information collection requirements approved by the Office of Management and Budget under control number 0910-0116)

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

9. 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.

10. Section 640.2 is amended by removing paragraphs (b) and (d), by redesignating paragraphs (c), (e), and (f) as paragraphs (b), (c), and (d), respectively, and by revising newly redesignated paragraphs (b) and (c)(2) to read as follows:

§ 640.2 General requirements.

* * * * *

(b) *Blood container* The blood container shall not be entered prior to issue for any purpose except for blood collection. Such container shall be uncolored and transparent to permit visual inspection of the contents and any closure shall be such as will maintain an hermetic seal and prevent contamination of the contents. The container material shall not interact with the contents under the customary conditions of storage and use, in such a manner as to have an adverse effect upon the safety, purity, or potency of the blood.

(c) * * *

(2) A segment is properly attached and has not been removed, except that blood lacking a properly attached segment may be reissued in an emergency provided it is accompanied by instructions for sampling and for use within 6 hours after entering the container for sampling;

* * * * *

11. Section 640.3 is amended by revising the introductory text of paragraph (b), by revising paragraphs (b)(3), (c)(1), (c)(2), and (c)(3) and by removing and reserving paragraph (e) to read as follows:

§ 640.3 Suitability of donor.

* * * * *

(b) *Qualifications of donor; general.* Except as provided in paragraph (f) of this section and for autologous donations, a person may not serve as a source of Whole Blood more than once in 8 weeks. In addition, donors shall be in good health, as indicated in part by:

* * * * *

(3) For allogeneic donors, a blood hemoglobin level which shall be demonstrated to be no less than 12.5 grams (g) of hemoglobin per 100 milliliters (mL) of blood; or a hematocrit value of 38 percent, and for autologous donors, a blood hemoglobin level which shall be demonstrated to be no less than 11.0 g of hemoglobin per 100 mL of blood or a hematocrit value of 33 percent.

* * * * *

(c) * * *

(1) A history of viral hepatitis after the age of eleven;

(2) A history of close contact within 12 months of donation with an individual having viral hepatitis;

(3) A history of having received within 12 months of donation, human blood or any derivative of human blood which the Food and Drug Administration has advised the blood establishment is a possible source of viral hepatitis.

* * * * *

12. Section 640.4 is amended by removing paragraphs (d)(1) through (d)(4) and (h), by redesignating paragraph (i) as paragraph (h), and revising paragraphs (b) and (d), the introductory text of paragraph (g), and paragraphs (g)(1), (g)(2), (g)(4), and (g)(5) to read as follows:

§ 640.4 Collection of the blood.

* * * * *

(b) *The donor center* The pertinent requirements of §§ 600.10 and 600.11 of this chapter shall apply at both the

blood establishment and at any other place where the bleeding is performed.

(d) *The anticoagulant solution* The anticoagulant solution shall be sterile and pyrogen-free. Anticoagulant solutions shall be compounded and used according to a formula approved by the Director, Center for Biologics Evaluation and Research.

(g) *Samples for laboratory tests* Samples for laboratory tests shall meet the following standards:

(1) One or more segments shall be provided with each unit of blood when issued or reissued except as provided in § 640.2(e)(2) and all segments shall be from the donor who is the source of the unit of blood.

(2) All samples for laboratory tests performed by the manufacturer and all segments accompanying a unit of blood shall be collected at the time of filling the original blood container.

(4) All segments accompanying a unit of blood shall be attached to the whole blood container before blood collection, in a tamper proof manner that will conspicuously indicate removal and reattachment.

(5) Segments for compatibility testing shall contain blood mixed with the appropriate anticoagulant.

13. Section 640.5 is amended by revising the introductory text and paragraph (c) to read as follows:

§ 640.5 Testing the blood.

All laboratory tests shall be made on a specimen of blood taken from the donor at the time of collecting the unit of blood, and these tests shall include the following:

(c) *Determination of the Rh factors* Each container of Whole Blood shall be classified as to Rh type on the basis of tests done on the sample. The label shall indicate the extent of typing and the results of all tests performed. If the test, using Anti-D Blood Grouping Reagent, is positive, the container may be labeled "Rh Positive". If this test is negative, the results shall be confirmed by further testing which shall include tests for the Rh₀ variant (D^o). Blood may be labeled "Rh Negative" if further testing is negative. Units testing positive after additional more specific testing shall be labeled as "Rh Positive." Only Anti-Rh Blood Grouping Reagents licensed under, or that otherwise meet the requirements of, the regulations of this subchapter shall be used, and the

technique used shall be that for which the reagent is specifically designed to be effective.

§ 640.6 [Amended]

14. Section 640.6 *Modifications of Whole Bloods* amended by removing paragraph (c).

15. Section 640.13 is amended by revising paragraph (a) to read as follows:

§ 640.13 Collection of the blood.

(a) The source blood shall be collected as prescribed in § 640.4.

16. Section 640.15 is revised to read as follows:

§ 640.15 Samples for testing.

Samples collected in integral tubing shall meet the following standards:

(a) One or more segments of either the original blood or of the Red Blood Cells being processed shall be provided with each unit of Red Blood Cells when issued or reissued.

(b) Before they are filled, all segments shall be marked or identified so as to relate them to the donor of that unit of red cells.

(c) All segments accompanying a unit of Red Blood Cells shall be filled at the time the blood is collected or at the time the final product is prepared.

17. Section 640.16 is amended by revising paragraphs (a) and (b) to read as follows:

§ 640.16 Processing.

(a) *Separation.* Within the timeframe specified in the directions for the use of the specific devices, Red Blood Cells may be prepared either by centrifugation, done in a manner that will not tend to increase the temperature of the blood, or by normal undisturbed sedimentation. A portion of the plasma sufficient to insure optimal cell preservation shall be left with the red cells except when a cryoprotective substance or additive solution is added for prolonged storage.

(b) *Sterile system* All surfaces that come in contact with the red cells shall be sterile and pyrogen-free.

18. Section 640.22 is amended by revising paragraph (a) to read as follows:

§ 640.22 Collection of source material.

(a) Whole blood used as the source of Platelets shall be collected as prescribed in § 640.4.

19. Section 640.23 is amended by revising paragraph (a) to read as follows:

§ 640.23 Testing the blood.

(a) Blood from which plasma is separated for the preparation of Platelets or Platelets, Pheresis shall be tested as prescribed in §§ 610.40 and 610.45 of this chapter and § 640.5(a), (b), and (c). Results of tests performed in accordance with § 640.5(b) and (c) for Platelets, Pheresis products shall be valid for a period not to exceed 3 months.

20. Section 640.24 is amended by revising paragraph (b) to read as follows:

§ 640.24 Processing.

(b) Immediately after collection, the whole blood or plasma shall be held in storage between 20 and 24 °C, unless it must be transported from the collection center to the processing laboratory. During such transport, all reasonable methods shall be used to maintain the temperature as close as possible to a range between 20 and 24 °C until it arrives at the processing laboratory where it shall be held between 20 and 24 °C until the platelets are separated. The platelet concentrate shall be separated within the timeframe specified in the directions for use for the specific device used for the collection of the unit of whole blood or plasma.

§ 640.31 [Amended]

21. Section 640.31 *Suitability of donors* is amended by removing paragraph (c).

22. Section 640.32 is amended by revising the first sentence of paragraph (a) to read as follows:

§ 640.32 Collection of source material.

(a) Whole blood shall be collected, transported, and stored as prescribed in § 640.4.

23. Section 640.34 is amended by revising paragraphs (a) through (d), (e)(1) through (e)(3), and (g)(2) to read as follows:

§ 640.34 Processing.

(a) *Plasma.* Plasma shall be separated from the red blood cells and shall be stored at -18 °C or colder within the timeframe specified in the directions for use for the specific device after transfer to the final container, unless the product is to be stored as Liquid Plasma.

(b) *Fresh Frozen Plasma.* Fresh Frozen Plasma shall be prepared from blood collected by a single uninterrupted venipuncture with minimal damage to and minimal manipulation of the donor's tissue. The plasma shall be

separated from the red blood cells, frozen solid within the timeframe specified in the directions for use for the specific device, and stored at -18°C or colder.

(c) *Liquid Plasma*. Liquid Plasma shall be separated from the red blood cells and shall be stored at a temperature of 1 to 6°C within the timeframe specified in the directions for use for the specific device after filling the final container.

(d) *Platelet Rich Plasma*. Platelet Rich Plasma shall be prepared from blood collected by a single uninterrupted venipuncture with minimal damage to and manipulation of the donor's tissue. The plasma shall be separated from the red blood cells by centrifugation within the timeframe specified in the directions for use for the specific device after completion of the phlebotomy. The time and speed of centrifugation shall have been shown to produce a product with at least 250,000 platelets per microliter. The plasma shall be stored at a temperature between 20 and 24°C , immediately after filling the final container. A gentle and continuous agitation of the product shall be maintained throughout the storage period, if stored at a temperature of 20 to 24°C .

(e) * * *

(1) Platelets shall be separated as prescribed in subpart C of part 640, prior to freezing the plasma. The remaining plasma may be labeled as "Fresh Frozen Plasma," if frozen within the timeframe specified in the directions for use for the specific device after filling the final container.

(2) Cryoprecipitated AHF shall be removed as prescribed in subpart F of part 640. The remaining plasma shall be labeled "Plasma, Cryoprecipitate Reduced."

(3) Plasma remaining after both Platelets and Cryoprecipitated AHF have been removed may be labeled "Plasma, Cryoprecipitate Reduced."

* * * * *

(g) * * *

(2) With the exception of Platelet Rich Plasma and Liquid Plasma the final product shall be inspected for evidence of thawing or breakage at the time of issuance, however, the containers need not be stored in a manner that shows evidence of thawing if records of continuous monitoring of the storage temperature establish that the temperature remained at -18°C or colder. If continuous monitoring of the product is not available, the final product shall be stored in a manner that will show evidence of thawing and shall

not be issued if there is any evidence of thawing.

* * * * *

§ 640.51 [Amended]

24. Section 640.51 *Suitability of donors* is amended by removing paragraph (c).

25. Section 640.52 is amended by revising paragraph (a) to read as follows:

§ 640.52 Collection of source material.

(a) Whole blood used as a source of Cryoprecipitated AHF shall be collected as prescribed in § 640.4. Whole blood from which both Platelets and Cryoprecipitated AHF is derived shall be maintained as required under § 640.24 until the platelets are removed.

* * * * *

26. Section 640.54 is amended by revising paragraph (a)(2) to read as follows:

§ 640.54 Processing.

(a) * * *

(2) The plasma shall be frozen solid after blood collection within the timeframe specified in the directions for use for the specific device. A combination of dry ice and organic solvent may be used for freezing: *Provided*, That the procedure has been shown not to cause the solvent to penetrate the container or leach plasticizer from the container into the plasma.

* * * * *

27. Section 640.56 is amended by revising the introductory text of paragraph (c) to read as follows:

§ 640.56 Quality control test for potency.

* * * * *

(c) The quality control test for potency may be performed by a clinical laboratory which meets the standards of the Clinical Laboratories Improvement Act of 1988 (CLIA) (42 U.S.C. 263a) and is qualified to perform potency tests for antihemophilic factor. Such arrangements must be approved by the Director, Center for Biologics Evaluation and Research, Food and Drug Administration. Such testing shall not be considered as divided manufacturing, as described in § 610.63 of this chapter, provided the following conditions are met:

* * * * *

28. Section 640.62 is revised to read as follows:

§ 640.62 Medical supervision.

A qualified licensed physician shall be available to attend to the donor within 15 minutes when donor

suitability is being determined, immunizations are being made, whole blood is being collected, and red blood cells are being returned to the donor, except that during the administration of immunization red blood cells a qualified licensed physician shall be on the premises.

29. Section 640.63 is amended by revising paragraphs (c)(3), (c)(5), (c)(11), (c)(12), and (c)(13) to read as follows:

§ 640.63 Suitability of donor.

* * * * *

(c) * * *
(3) A blood hemoglobin level of no less than 12.5 grams of hemoglobin per 100 milliliters of blood or a hematocrit level of 38 percent;

* * * * *

(5) A total serum or total plasma protein of no less than 6.0 grams per 100 milliliters of blood;

* * * * *

(11) A history of viral hepatitis after the age of eleven;

(12) Freedom from a history of close contact within 12 months of donation with an individual having viral hepatitis;

(13) Freedom from a history of having received, within 12 months, human blood or any derivative of human blood which the Food and Drug Administration has advised the blood establishment is a possible source of viral hepatitis, except for specific immunization performed in accordance with § 640.66.

* * * * *

30. Section 640.65 is amended by revising paragraphs (b)(4) and (b)(5) and by adding paragraph (b)(8) to read as follows:

§ 640.65 Plasmapheresis.

* * * * *

(b) * * *

(4) The amount of whole blood, not including anticoagulant, removed from a donor during a manual plasmapheresis procedure or in any 2-day period shall not exceed 1,000 milliliters unless the donor's weight is 175 pounds or greater, in which case the amount of whole blood, not including anticoagulant, removed from the donor during a manual plasmapheresis procedure or in any 2-day period shall not exceed 1,200 milliliters.

(5) The amount of whole blood, not including anticoagulant, removed from a donor during a manual plasmapheresis procedure within a 7-day period shall not exceed 2,000 milliliters unless the donor's weight is 175 pounds or greater, in which case the amount of whole blood, not including

anticoagulant, removed from a donor during a manual plasmapheresis procedure within a 7-day period shall not exceed 2,400 milliliters.

* * * * *

(8) The volume of plasma collected during an automated plasmapheresis collection procedure shall be consistent with the volumes specifically approved by the Director, Center for Biologics Evaluation and Research, and collection shall not occur less than 2 days apart or more frequently than twice in a 7-day period.

31. Section 640.69 is amended by revising paragraph (d) to read as follows:

§ 640.69 General requirements.

* * * * *

(d) *Samples.* If samples are provided, they shall meet the following standards:

(1) Prior to filling, all samples shall be marked or identified so as to relate them directly to the donor of that unit of plasma.

(2) All samples shall be filled at the time the final product is prepared by the person who prepares the final product.

(3) All samples shall be representative of the contents of the final product or be collected from the donor at the time of filling the collection container.

(4) All samples shall be collected in a manner that does not contaminate the contents of the final container.

32. Section 640.71 is amended by revising the introductory text of paragraph (a) to read as follows:

§ 640.71 Manufacturing responsibility.

(a) All steps in the manufacturing of Source Plasma, including donor examination, blood collection, plasmapheresis, laboratory testing, labeling, storage, and issuing shall be performed by personnel of the establishment licensed to manufacture Source Plasma, except that the following tests may be performed by personnel of an establishment licensed for blood and blood derivatives under section 351(a) of the Public Health Service Act, or by a clinical laboratory

that meets the standards of the Clinical Laboratories Improvement Act of 1988 (CLIA) (42 U.S.C. 263a): *Provided*, The establishment or clinical laboratory is qualified to perform the assigned test(s).

* * * * *

33. Section 640.72 is amended by revising paragraph (a)(1) to read as follows:

§ 640.72 Records.

(a) * * *

(1) Documentation shall be available to ensure that the shipping temperature requirements of § 600.15 of this title and of § 640.74(b)(2) are being met for Source Plasma intended for manufacture into injectable products.

* * * * *

Dated: April 20, 1999.

Jane E. Henney,
Commissioner of Food and Drugs.

Donna E. Shalala,
Secretary of Health and Human Services.

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Part IV

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 600 et al.

**Requirements for Testing Human Blood
Donors for Evidence of Infection Due to
Communicable Disease Agents and
Requirements for Blood, Blood
Components, and Blood Derivatives;
Rules and Proposed Rules**

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 607, 610, 640, and 660

[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: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to revise the general biological product standards 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 licensed supplemental (i.e., additional, more specific) testing when a donation is found to be repeatedly reactive for any of the required screening tests for evidence of infection due to communicable disease agents. The agency is also proposing to require manufacturers of test kits approved for use in testing donations of human blood and blood components for evidence of infection due to communicable disease agents to use reference panels, when available, to verify the acceptable sensitivity and specificity of each lot. FDA is taking this action as part of the agency's "Blood Initiative" in which FDA is reviewing and revising, when appropriate, its regulations, policies, guidance, and procedures related to blood and blood products, including plasma derivatives. This proposed rule is intended to help protect the safety and ensure the quality of the nation's blood supply and to promote consistency in the industry.

DATES: Submit written comments on the proposed rule by November 17, 1999. Submit written comments on the information collection provisions by September 20, 1999. The agency is proposing that any final rule that may issue based upon this proposed rule become effective 180 days after its date of publication in the *Federal Register*.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit written comments on the information collection provisions to the Office of Information and Regulatory Affairs, OMB, New Executive Office Bldg., 725

17th St. NW., Washington, DC 20503, Attn: Wendy Taylor, Desk Officer for FDA.

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. Introduction

A. The Blood Initiative

For a variety of reasons, discussed as follows, FDA has decided to comprehensively review and, as necessary, revise its regulations, policies, guidance, and procedures related to the licensing and regulation of blood products. In the *Federal Register* of June 3, 1994 (59 FR 28821 and 59 FR 28822, respectively), FDA issued two documents entitled "Review of General Biologics and Licensing Regulations" (Docket No. 94N-0066) and "Review of Regulations for Blood Establishments and Blood Products" (Docket No. 94N-0080). The documents announced the agency's intent to review biologics regulations in parts 600, 601, 606, 607, 610, 640, and 660 (21 CFR parts 600, 601, 606, 607, 610, 640, and 660) and requested written comments from the public. Interested persons were given until August 17, 1994, to respond to the documents. In response to requests for additional time, FDA twice extended the comment period, as announced in the *Federal Register* of August 17, 1994 (59 FR 42193), and November 14, 1994 (59 FR 56448). In addition, FDA responded to requests for a public meeting to allow for the presentation of comments regarding the agency's intent to review the biologics regulations. On January 26, 1995, FDA held a public meeting to provide an opportunity for all interested individuals to present their comments and to assist the agency in determining whether the regulations should be revised, rescinded, or continued without change. Since the time of the regulation review, FDA has implemented a number of changes to its regulations and policies applicable to the general biologics and licensing regulations, some of which applied to blood products as well as other biological products. (See, e.g., the final rules issued on May 14, 1996 (61 FR 24313); August 1, 1996 (61 FR 40153); November 6, 1996 (61 FR 57328); July 24, 1997 (62 FR 39890); and October 15, 1997 (62 FR 53536).)

Because of the importance of a safe national blood supply, the U.S. House of Representatives Committee on Government Reform and Oversight,

Subcommittee on Human Resources and Intergovernmental Relations (the Subcommittee) and other groups such as the General Accounting Office (GAO), and the Institute of Medicine (IOM) have reviewed the agency's policies, practices, and regulations. Reports issued following the respective reviews made a number of recommendations as to how FDA might improve the biologics regulations, particularly as they apply to the continued safety of blood products. The relevant reports are: (1) "Protecting the Nation's Blood Supply From Infectious Agents: The Need for New Standards to Meet New Threats" by the Subcommittee (August 2, 1996); (2) "Blood Supply: FDA Oversight and Remaining Issues of Safety" by GAO (February 25, 1997); (3) "Blood Supply: Transfusion-Associated Risks" by GAO (February 25, 1997); and (4) "HIV and the Blood Supply: An Analysis of Crisis Decisionmaking" by IOM (July 13, 1995). These reports are on file with the Dockets Management Branch (address above) under the docket number given in the heading of this document.

FDA has reviewed these reports and agrees with the majority of the recommendations contained within them. However, rather than to only respond specifically to the recommendations from the Subcommittee, GAO, IOM, and the public, FDA has convened a number of internal task forces to review a variety of issues related to the regulation of blood and blood products, including how to most appropriately update the existing regulations applicable to blood and blood products. In the future, FDA intends to issue a number of blood-related rulemakings that various FDA task groups are currently preparing. FDA is not describing the specific recommendations it has received and the numerous objectives of the Blood Initiative in this document. Future rulemaking and other notices will describe and discuss specific recommendations and regulatory objectives.

B. Requirements and Recommendations for Testing Donors of Blood and Blood Components

Requirements for testing blood donors for hepatitis B surface antigen and antibody to HIV are currently codified in part 610. The agency has issued various guidance documents to registered blood and plasma establishments providing recommendations for testing for antibody to hepatitis B core antigen, antibody to human T-lymphotropic virus types I and II, antibody to hepatitis

C virus, and HIV-1 p24 antigen. The purposes of the guidance documents are to assist blood 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, FDA has determined that blood 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, FDA is proposing to require testing consistent with its current recommendations and industry practice. This will help ensure consistency in the blood industry's testing practices, and provide FDA with clear enforcement authority if compliance problems should occur.

The guidance documents referenced in this document or otherwise applicable to the testing of blood donors may be obtained from the Office of Communication, Training, and Manufacturers Assistance (HFMA-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 obtain the documents by using the World Wide Web (WWW). For WWW access, connect to CBER at "http://www.fda.gov/cber/publications.htm".

As part of the Blood Initiative, the agency is proposing to revise part 610 subpart E. Currently, subpart E requires testing for HBV and HIV and the development and administration of a product quarantine and recipient notification ("Lookback") program when donors test repeatedly reactive for antibody to HIV, or otherwise are determined to be unsuitable when tested in accordance with § 610.45. In response to the recommendations made in various reports addressing the safety of the nation's blood supply mentioned previously, FDA is proposing to: (1) Require screening tests for evidence of infection due to communicable disease agents for autologous donations (blood

donations intended to be later reinfused into the donor) in order to reduce the risk of transmission of communicable disease by untested units inadvertently entering the blood supply; (2) require supplemental (additional, more specific) testing of all donations that are repeatedly reactive by screening tests for which there are supplemental (additional, more specific) tests; and (3) codify 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. FDA is considering proposing a general testing regulation for blood and blood components in the future that would require blood establishments to test for additional relevant communicable diseases. Such a rule could impose testing obligations as additional relevant communicable disease agents are identified and FDA approves tests for such agents.

II. Legal Authority

FDA is proposing to issue this new rule under the authority of sections 351 and 361 of the Public Health Service Act (PHS Act) (42 U.S.C. 262 and 264 *et seq.*), and the provisions of the Federal Food, Drug, and Cosmetic Act (the act) that apply to drugs (21 U.S.C. 201 *et seq.*). Under section 361 of the PHS Act, FDA may make and enforce regulations necessary to prevent the introduction, transmission, and spread of communicable disease between the States or from foreign countries into the States (see Sec. I, 1966 Reorg. Plan No. 3 at 42 U.S.C. 202 for delegation of section 361 authority from the Surgeon General to the Secretary of the Department of Health and Human Services (Secretary); see 21 CFR 5.10(a)(4) for delegation from the Secretary to the Food and Drug Administration). Intrastate transactions may also be regulated under section 361 of the PHS Act (see *Louisiana v. Mathew*, 427 F. Supp. 174, 176 (E.D.La. 1977)). Testing each donation for evidence of infection due to communicable disease agents would help prevent unsafe units of blood or blood components from entering the blood supply. The focus of the proposed rule is preventing the introduction and spread of communicable disease through transfusion.

All blood and blood components introduced or delivered for introduction into interstate commerce also are subject to section 351 of the PHS Act (42 U.S.C. 262). Section 351(a) of the PHS Act requires that manufacturers must have a license which has been issued upon showing that the manufacturing

establishment meets all applicable standards, prescribed in the biologics regulations, designed to insure the continued safety, purity, and potency of the blood and blood components, and that the product is safe, pure, and potent. FDA's license revocation regulations provide for the initiation of revocation proceedings, if, among other reasons, the establishment or the product fails to conform to the standards in the license application or in the regulations designed to ensure the continued safety, purity, or potency of the product (§ 601.5). Section 351 of the PHS Act provides for criminal penalties for violation of the laws governing biologics. Violations can be punishable by fines or imprisonment, or both.

The act also applies to biological products (42 U.S.C. 262(d), as amended). Blood and blood components are considered drugs, as that term is defined in section 201(g)(1) of the act (21 U.S.C. 321(g)(1)) (see *United States v. Calise*, 217 F. Supp. 705 (S.D.N.Y. 1962)). Because blood and blood components are drugs under the act, blood establishments must comply with the substantive provisions and related regulatory scheme. Under section 501 of the act (21 U.S.C. 351), drugs are deemed "adulterated" if the methods used in their manufacturing, processing, packing, or holding do not conform with current good manufacturing practices (21 U.S.C. 351(a)(2)(B)). Under the proposed rule, blood establishments would be required to test each donation of blood and blood components for evidence of infection due to communicable disease agents. Blood and blood components manufactured from donations that are not tested in accordance with this proposed rule would be considered adulterated under 21 U.S.C. 351(a)(2)(B), and blood establishments, and blood and blood components would be subject to the act's enforcement provisions for violations of the act.

III. Description of the Proposed Rule

This rule is proposed in order to reduce the risk of infection due to communicable disease agents to blood product recipients and to individuals handling blood or blood products including components of a medical device. FDA proposes to require that each donation of human blood or blood component, including those intended for autologous use or as a component of a medical device, 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 repeatedly reactive when screened for evidence of infection due to any of the

communicable disease agents would be required to be further tested whenever a supplemental (additional, more specific) test has been approved for such use by FDA. Testing would be required to be performed by a laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA) and registered with FDA in accordance with part 607. When donors test repeatedly reactive, the agency would require deferral of such donors from future donations. Criteria are proposed for release or shipment of human blood or blood components prior to completion of testing, and restrictions on shipment or use of human blood or blood components that test repeatedly reactive when screened for evidence of infection. The proposed rule would also require manufacturers of approved test kits to test human blood donors for evidence of infection due to communicable disease agents to verify an acceptable sensitivity and specificity of each lot of test kit using a reference panel obtained from CBER, when available.

A. Required Testing for Communicable Disease Agents

Proposed § 610.40(a) would require testing for evidence of infection due to the communicable disease agents HIV, types 1 and 2; HBV; HCV; and HTLV, types I and II using screening tests approved for such use by FDA in accordance with the manufacturers' instructions. The agency is not proposing to specify the marker(s) to be tested for, such as a specific antigen or antibody. The purpose of testing is to adequately and appropriately reduce the risk of transmission of communicable disease agents. Thus, one or more tests that would fulfill proposed § 610.40 should be chosen for this purpose.

Historically, tests for new or different markers of infection due to a communicable disease agent have changed as they become more appropriate or the technology in testing has become more sensitive or specific. Therefore, FDA is structuring the proposed regulations so that manufacturers may adopt adequate and appropriate methodologies to protect the safety of the nation's blood supply, without necessitating rulemaking by the agency with the development or advancement of each test method, e.g., FDA recognizes the possibility that nucleic-acid-based screening could replace some current methods of testing. FDA believes that such nucleic-acid-based screening, including "in-house" or "home brew" screening of blood or blood components for communicable disease agents required under this

regulation should be regulated under section 351 of the PHS Act when the blood or blood components are intended for use in preparing a product, including donations for autologous use or as a component of a medical device. Several manufacturers have begun to conduct nucleic-acid-based screening of plasma pools for HIV and HCV under investigational new drugs (IND). FDA considers such nucleic acid testing of plasma pools used to manufacture blood products to be donor screening. FDA intends to issue draft guidance and request public comment on nucleic acid testing in the near future.

As technology advances, FDA intends to regularly issue guidance describing those tests that it believes are adequate and appropriate in reducing the risk of transmission of communicable disease agents. The agency would issue such guidance in draft, giving the opportunity for public comment and for manufacturers to prepare to use any appropriate new testing technologies. In some circumstances, when it is necessary to protect the public health, the agency may, as described under its current Good Guidance Practices (62 FR 8961, February 27, 1997), recommend immediate implementation of the guidance. Consistent with FDA guidance, as discussed in section I.B of this document, it is current practice by the blood industry to test blood donations intended for transfusion or for further manufacture for antibody to HIV, types 1 and 2; HIV-1 p24 antigen; hepatitis B surface antigen (HBsAg); antibody to hepatitis C; and by a serologic test for syphilis. Blood donations intended for transfusion routinely are additionally tested for antibody to HTLV, types I and II, and antibody to hepatitis B core antigen (anti-HBc).

Although blood that is repeatedly reactive for anti-HBc would not be suitable for transfusion even when negative for HBsAg, the plasma from such blood (viz., recovered plasma) 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-HBs, which is hepatitis B neutralizing antibody.

In a small percentage of "window-period" cases, the blood could be from a donor who only recently became infected with hepatitis B virus such that the number of viruses in the blood are below detectable limits via antigen testing. While a unit of blood from a donor in window period could be

infectious, use of plasma from such a donor, after pooling with plasma from many donors and manufacturing into plasma derivatives, does not present a risk of transmitting hepatitis B to recipients of the plasma derivatives. On the basis of our present knowledge, this safety results from several factors. First, plasma that is negative for HBsAg, even if it is reactive for anti-HBc, would have only a low titer of hepatitis B virus. This titer is further lowered by pooling with many "true-negative" units of plasma. Second, virtually all plasma derivatives undergo validated virus removal and/or inactivation procedures in the course of manufacture. Third, there is a high probability that some units of plasma in the pool will be reactive for anti-HBs. This can have the added benefit both of neutralizing any hepatitis B virus present and potentially aiding in its removal during the process of purifying plasma derivatives. For this last reason, present knowledge suggests that excluding plasma that is negative for HBsAg but reactive for anti-HBc could reduce the safety of plasma derivatives because it would reduce the level of anti-HBs in pooled plasma and thereby reduce protection against any contaminating hepatitis B virus present in the pooled plasma.

For the same reasons, FDA does not currently believe that Source Plasma (which is not obtained from Whole Blood donations and is used only for further manufacture) that is negative for HBsAg needs to be tested for anti-HBc.

In January 1995, as part of a National Institutes of Health Consensus Development Conference, a panel of non-federal, nonadvocate experts met to provide physicians and other transfusion medicine professionals with a consensus on infectious disease testing for blood transfusions. One of the issues reviewed was the value of testing for syphilis in protecting the safety of the blood supply. The serologic test for syphilis was introduced in 1938 to prevent the transmission of syphilis through blood transfusions. In the early AIDS era it was thought to have additional value as a marker of high risk behavior, although this benefit has been challenged. The serologic test for syphilis has a high rate of false positives, leading to further supplemental (additional, more specific) testing using specific treponemal confirmatory tests. After discussion, the panel agreed "Because the contribution of serologic tests for syphilis in preventing transfusion-transmitted syphilis is not understood, the panel concludes that testing of donors for syphilis should continue." FDA regulations continue to require the

serologic test for syphilis (see §§ 640.5(a) and 640.65(b)). However, the agency recognizes that many scientists, including some members of the blood banking community, continue to advocate the elimination of the serologic test for syphilis as a testing requirement. The agency is soliciting comments, with supporting data, from the public in regard to the value of donor testing for syphilis as a marker of high risk behavior, as a surrogate test for other infectious diseases, and in preventing the transmission of syphilis through blood transfusion. If the agency receives comments with adequate data supporting the removal of the requirement for a serologic test for syphilis, FDA may proceed with rulemaking to remove the requirements for a serologic test for syphilis, including treponemal and nontreponemal based tests, from part 640.

B. Affected Products

Each donation of human blood or blood components, i.e., whole blood, red blood cells, plasma, sera, platelets, and leukocytes, intended for transfusion or for further manufacturing, would be required to be tested for evidence of infection due to communicable disease agents. For the purpose of this proposed rule, any reference to "blood or blood components" will include Source Leukocytes and Source Plasma unless specifically addressed. This proposal includes testing requirements for donations intended for autologous use or as a source material or component of a medical device. Inclusion of testing requirements for donations intended solely for use in a medical device is a safeguard for persons who may be exposed to infectious blood products used in such devices.

Despite the reduced risk of infection when using autologous blood, FDA is concerned that the increased demand to use autologous donations may compromise transfusion safety for both autologous and allogeneic recipients. Recent data from an industry conducted survey show that errors and accidents involving autologous blood occur with sufficient frequency to compromise the safety of both autologous and allogeneic transfusions. Examples of these errors and accidents include the erroneous transfusion of an autologous unit to an unintended recipient; the inappropriate salvage of plasma for further manufacture from untested or infectious disease marker positive autologous units; the breakage of autologous units during laboratory processing or product transport; and clerical errors in inventory management, including

inadvertent crossover of autologous units to the allogeneic inventory. Proposed § 610.40 would require uniform testing for both autologous and allogeneic donations, thus significantly reducing any risk to the public health posed by the inadvertent improper use of potentially infectious products.

Unlicensed blood and blood components are often used as components or source material in the manufacture of certain medical devices, including in vitro diagnostic test kits. To apply the current good manufacturing practice (CGMP) for blood and blood components to such products used in the manufacture of unlicensed blood products that are device components or device raw materials, FDA issued a final rule on June 9, 1989 (54 FR 24706), requiring manufacturers of such products to follow the blood CGMP's in 21 CFR part 606. The preamble to that final rule stated that blood products that are device components or device raw materials excluded from the scope of the device CGMP's under § 820.1 (the quality system regulation) are subject to the blood CGMP's in part 606. Violations of part 606 involving such device components or raw materials are subject to enforcement action under section 501(h) of the act.

Accordingly, FDA is proposing in this rule to clarify the applicability of testing for evidence of infection due to communicable disease agents to human blood or blood components used in the manufacture of a medical device.

C. Exceptions

Proposed § 610.40(b)(1) and (b)(2) would exempt Source Plasma, and donations of human blood and blood components intended solely as a component of an in vitro medical device unless they contain viable leukocytes, from being tested for evidence of infection with HTLV, types I and II. Donations of Source Plasma, i.e., the fluid portion of human blood collected by plasmapheresis and intended as source material for further manufacturing use, would not be required to be tested for evidence of infection with HTLV, types I and II because HTLV is highly cell-associated in humans and HTLV transmission has not been demonstrated by the transfusion of plasma or by the use of products made from Source Plasma. Currently, in FDA's existing guidance, testing for antibodies to HTLV, types I and II is recommended for donors only if blood components, including plasma, are intended for transfusion.

Under proposed § 610.40(b)(3), FDA would not apply the requirements under

§ 610.40(a) to certain cases when the human blood or blood components are not intended for commercial distribution or for use in preparing a product. This proposal would be consistent with the current requirements in § 610.45 *Human Immunodeficiency Virus (HIV) requirements*. Such cases include the in-house use (i.e., use within the same establishment) or distribution of samples of blood, blood components, plasma, or sera for: (1) Clinical laboratory testing; and (2) research purposes, provided that it is not intended for administration to humans or use in manufacturing a product. FDA believes that the proposed exceptions would help ensure the continued public health while not impeding continuing research efforts and the ability to ship blood samples for purposes of clinical laboratory testing.

FDA is requesting comment on whether to exempt from testing for evidence of infection due to communicable disease agents listed in proposed § 610.40(a) each donation of dedicated apheresis donors. Specifically, FDA seeks comments on whether the proposed rule, when finalized, should be revised to permit testing proposed in § 610.40(a) to be completed only once at the beginning of a 30-day period of donation by a dedicated apheresis donor for a single recipient. This procedure is currently practiced in specific clinical situations such as a human leukocyte antigen (HLA) matched or family donor donating as a dedicated donor for a patient being treated for diseases such as aplastic anemia, bone marrow, transplant candidate, or leukemia. The agency is requesting comments on the testing of dedicated apheresis platelet donors, at a minimum, at the beginning of a 30-day period during which other donations may continue without further testing. The agency is also requesting comments on alternatives (including the rationale) to testing each donation that may be applied to autologous donations as well as dedicated apheresis donors for a single recipient. For example, could the added safety resulting from mandatory testing of autologous donations be similarly achieved by both improving procedures or requirements for clearly and permanently marking autologous units to distinguish them from allogeneic units and requiring that they be labeled as untested for infectious disease agents, and if so, what additional factors would favor the choice of one approach over the other.

D. Further Testing

Under § 610.40(a), each donor blood sample would be tested by a screening test approved for such use by FDA, according to the directions supplied by the manufacturer of the test kit. As described in the directions, each tested sample would be determined to be reactive or nonreactive. A reactive result on initial testing (initial reactivity) indicates the possible presence of a marker in the sample. According to the manufacturers' instructions, initially reactive samples are to be tested again, generally in duplicate, and a sample that is found to be reactive on any single retest (i.e., on one or more of the duplicate retests), is considered to be repeatedly reactive. Screening tests are designed to be highly sensitive for the marker specific to the test kit. Because of this sensitivity, the possibility of false positives due to sample contamination, cross reactivity or nonspecific binding exists. In § 610.40(c), the agency proposes to require that repeatedly reactive samples be further tested by a supplemental (additional, more specific) test, when available, that has been approved for such use by FDA. In the past, FDA has issued guidances, discussed previously, that recommend the supplemental testing of repeatedly reactive samples. Although a donor may be deferred from donating based on a repeatedly reactive screening test alone, the supplemental testing would be required so that the following information could be ascertained: (1) Medical information useful in notification and counseling as soon as possible for the donor; and (2) Additional information to be used in evaluating the donor for possible reentry into the donor pool at a future time.

E. Testing Responsibility

Under the regulations, testing of donor blood samples is considered a step in the manufacture of blood products (see § 607.3(d)). Appropriate testing is critical to the continued safety of the nation's blood supply. FDA believes that it is important that FDA know which laboratories are performing such testing and that such laboratories can perform testing adequately. Accordingly, FDA is proposing in § 610.40(d) to require that testing for evidence of infection due to the communicable disease agents designated in § 610.40(a) be performed by a laboratory registered with FDA in accordance with part 607, and certified to perform testing on human specimens under the CLIA (see 42 CFR part 493). In addition, FDA is proposing to remove § 607.65(g), which exempts from

registration clinical laboratories that are approved for Medicare reimbursement and which are engaged in the testing of blood products in support of other registered establishments. As a result, such laboratories would need to register with FDA.

F. Release or Shipment Prior to Testing

Under § 610.40(e), FDA proposes to permit, in specified situations, the release or shipment of human blood or blood components before the completion of testing required under § 610.40(a). Section 640.2(f) would be removed. The agency recognizes that there are rare medical emergencies, e.g., where a patient's need for blood is so acute that transfusion is necessary before knowing the results of any communicable disease testing of the blood. FDA believes that the use of untested or incompletely tested blood in such medical emergencies should not be prohibited. Because products other than Whole Blood may need to be released in medical emergency situations, FDA is proposing to place the provision for medical emergency situations in § 610.40(e), which is applicable to all blood products, and to remove § 640.2(f), which is applicable to Whole Blood only.

FDA is proposing in § 610.40(e) to permit, with FDA approval, routine shipment of certain blood components for further manufacturing before testing is completed and the tests results are received by the collection facility. To obtain approval from FDA, the agency would expect the collection facility and the manufacturing facility to whom the blood product is being shipped, to submit with their request specific procedures for collection, shipment, and quarantine of a product before testing is completed. Once the procedures have been approved, manufacturers may then begin to ship products prior to the completion of testing. This proposal is intended to ensure the continued availability of biological products, such as interferon, that are important to the medical community and which require rapid preparation from blood.

The provisions for emergency release and shipment prior to completion of testing would require appropriate documentation, that testing would be performed as soon as possible, and that the results would be provided promptly to the consignee.

G. Restrictions on Shipment or Use

In § 610.40(f)(1), FDA is proposing to require that blood and blood components testing repeatedly reactive when screened for evidence of infection due to a communicable disease agent

designated in proposed § 610.40(a), or collected from a donor with a record of a repeatedly reactive test result, shall not be shipped or used to prepare any product, including products not subject to licensure, except as described in section III of this document. FDA believes that inappropriate handling, labeling, or use of such blood could be hazardous to the public health. Therefore, FDA is proposing to restrict the shipment or use of such blood and blood components.

Under proposed § 610.40(f)(2)(i), the restriction on shipment or use of blood or a blood component that tests repeatedly reactive when screened for evidence of infection due to a communicable disease agent listed in proposed § 610.40(a) would not apply to units intended for autologous use. Autologous blood or blood components would be required to be appropriately labeled in accordance with § 606.121(i) and with the Biohazard legend demonstrated in the codified section. Under proposed § 610.40(f)(2)(ii), blood establishments intending to ship or use human blood or blood components for further manufacture that test repeatedly reactive when screened for evidence of infection due to a communicable disease agent listed in proposed § 610.40(a) would apply for approval by FDA. Application for approval would be submitted as part of the license application or a supplement to the approved license. For unlicensed products, application for approval would be submitted in accordance with § 640.120 as discussed in section K of this document. The written application would describe the intended use of the blood or blood component, and the procedures for collecting, handling, labeling, and shipping the blood. Blood and blood components are required to be labeled in accordance with §§ 606.121 and 640.70, as appropriate. Repeatedly reactive blood or blood components would be required to be labeled as repeatedly reactive for the applicable marker for the identified communicable disease agent and display the Biohazard legend. If repeatedly reactive blood or blood components are to be used for further manufacturing into injectable products, the blood or blood component would be required to be labeled with the exempted use specifically approved by FDA. For manufacturing into noninjectable products, such as in vitro diagnostic products when there is no alternative source such as monoclonal antibody, repeatedly reactive blood or blood components would be required to be labeled with the statement "Caution:

For Further Manufacturing Into Non-Injectable Products For Which There Are No Alternative Sources". Distribution may not commence until approval is granted.

Under proposed § 610.40(f)(3), FDA would permit the use of blood or blood components from a donor who was deferred as a result of testing repeatedly reactive on a screening test(s) for specified communicable disease agent(s) if the blood or blood components test negative for those same disease agent(s) and the donor has been shown to be suitable to donate blood by a method or process described in a supplement to the establishment's license and approved for that purpose by FDA. (Such methods are called "donor reentry" algorithms.) FDA has identified such methods or processes in the agency's guidance documents, discussed previously, in the format of algorithms, or step-by-step procedures designed to reenter the donor into the donor pool, when appropriate.

There are occasions when human blood or blood components that test repeatedly reactive when screened for evidence of infection due to a communicable disease agent listed in proposed § 610.40(a) are needed for further manufacture, e.g., when used in the manufacture of certain in vitro diagnostic products. The agency proposes in § 610.42 to require that a repeatedly reactive unit used for further manufacturing into an in vitro diagnostic product be labeled as repeatedly reactive for the applicable marker of infection due to the identified communicable disease agent. For an in vitro diagnostic product manufactured from a repeatedly reactive unit, the agency would require in § 610.42 that the manufacturer label the product in accordance with 21 CFR 809.10 and that a warning be included stating that the product was manufactured from a donation that tested repeatedly reactive for the appropriate marker of infection for the identified communicable disease agent. This would be required to help prevent the spread of communicable disease in those handling the product, (i.e., such labeling should result in handlers taking appropriate precautions for their and other's safety).

H. Compliance with §§ 610.46 and 610.47 ("Lookback" requirements for HIV)

Current § 610.45(d) requires the blood establishment to comply with §§ 610.46 and 610.47 and perform testing, quarantine, consignee notification and recipient notification when a blood donor tests repeatedly reactive for HIV or when the blood establishment has

been made aware of other test results indicating HIV infection. The agency is not proposing to include this requirement in this proposed rule. However, in future rulemaking, the agency will propose new regulations for "Lookback" when donors test repeatedly reactive for HCV, comparable to those requirements currently applicable for donors testing repeatedly reactive for HIV. The new "Lookback" proposed regulations will consolidate in one section the current requirements for HIV "Lookback" and the proposed HCV "Lookback" requirements. In the event that finalization of the new proposed "Lookback" rule is delayed, the agency intends to issue the current language in § 610.45(d) as § 610.40(g) with specific paragraph and section cites revised.

I. Donor Deferral

Once the donor (except for autologous donors or other donors as discussed in section III.I of this document), at the time of donation, tests repeatedly reactive by a screening test(s) performed in accordance with proposed § 610.40(a), the blood or blood components from that donation are to be quarantined and either destroyed or excluded from use in transfusion; and, based on the particular marker that tests repeatedly reactive, the donor will then be either deferred from donating in the future or deferred if a similar result is obtained on any subsequent donation. Similar provisions under §§ 640.5 and 640.65 apply to donations reactive for syphilis, however, some additional exceptions apply. Blood establishments are currently required under § 606.160 to maintain records of results and interpretation of all tests and retests, and a record from which unsuitable donors may be identified so that products from such individuals will not be distributed. Proposed § 610.41 explicitly would require the deferral of donors based on testing. FDA is issuing elsewhere in this issue of the **Federal Register**, notice and comment rulemaking proposing to require the notification of donors of their deferral from donating in the future and the reason for the deferral (such as health history or test results). FDA also intends to issue notice and comment rulemaking in the near future proposing donor suitability criteria.

In proposed § 610.41(a), donors who test repeatedly reactive for HTLV, types I and II, or anti-HBc only once, would be permitted to donate again without being deferred from further donation unless there is further testing using an approved supplemental (additional, more specific) test. This proposal is consistent with FDA's guidance to all

registered blood establishments dated August 19, 1997, entitled "Donor Screening for Antibodies to HTLV-II." Once supplemental tests for HTLV, types I and II are approved, donors would be deferred after only a single repeatedly reactive donation similar to most other screening tests. It is FDA's expectation that donor reentry algorithms would become feasible at that time. However, until such time, upon testing repeatedly reactive a second time for HTLV, types I and II or anti-HBc, the donor would be deferred.

FDA is proposing in § 610.41(b) to permit donors testing repeatedly reactive for HTLV, types I and II or anti-HBc to serve as donors of Source Plasma (See section III.C of this document for discussion on the risk of transmitting HTLV, types I and II through Source Plasma; see section III.A of this document for discussion on the use of plasma from donors who test repeatedly reactive for anti-HBc). However, the agency is requesting comments on this proposal that permits such donors to donate Source Plasma to be used in the manufacture of plasma derivatives as it relates to exposure to other possible risks, such as the association of HTLV infection with abuse of intravenous drugs.

Proposed § 610.41(c)(1) permits deferred donors to donate blood and blood components when used in accordance with § 610.40(f). In proposed § 610.40(f), the agency proposes that blood and blood components that test repeatedly reactive when screened for evidence of infection due to communicable disease agents listed in proposed § 610.40(a) would not be shipped or used except for autologous use or for purposes or under conditions approved in writing by FDA. Such approval may also be obtained under current § 640.120.

The agency is proposing in § 610.41(c)(2) to restrict the use of blood or blood components from donors showing evidence of infection due to hepatitis B virus when tested in accordance with § 610.40(a) and (c). Such blood and blood components may be approved for use only as a source of antibody to hepatitis B surface antigen (anti-HBs, Hepatitis B neutralizing antibody) for the preparation of Hepatitis B Immune Globulin (Human) or as a component of a medical device. Use of such blood or blood components would be prohibited in the manufacture of other biological products. The agency requests comments on the use of vaccinated donors for HBV as an alternative to using donors previously showing evidence of infection due to

hepatitis B virus in the preparation of Hepatitis B Immune Globulin (Human).

In proposed § 610.41(d), the agency would not defer donors of blood and blood components from further donations, if the donor was found negative by an approved specific treponemal test (confirmatory test for syphilis) despite a reactive screening test. Accordingly, if the donor tests positive by the more specific test, then the donor would be deferred and reentered into the donor pool only in accordance with proposed § 610.41(e). Donors of Source Plasma testing reactive for the serologic test for syphilis, shall follow the procedure provided in § 640.65(b)(2)(ii), (b)(2)(iii), and (b)(2)(iv).

J. Use of Reference Panels by Manufacturers of Test Kits

For a number of years, FDA has made available reference panels (also known as lot release panels) of known reactivity to a marker of infection due to a communicable disease agent. These reference panels are used by manufacturers in the qualitative and semi-quantitative evaluations of their in vitro tests to detect a defined marker of infection due to the identified communicable disease agent. FDA is proposing to move the requirements for reference panels for hepatitis B test kits to proposed § 610.44 and add that reference panels be used when available for all the test kits for communicable disease agents identified in proposed § 610.40(a) and for all approved HIV tests. The agency would require the use of these regulatory reference panels obtained from the Center for Biologics Evaluation and Research (CBER) or from an FDA designated source, when available, to provide a verification by the manufacturer of the sensitivity and specificity of each lot of test kit approved for use in testing donations of human blood and blood components. 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. Once a reference panel is assembled and available for use in lot release testing, the Director, CBER, would send a letter informing all licensed manufacturers of the appropriate test kit of the availability of the reference panel and of the date the agency believes the new reference panel should be put into use for lot release testing. This will usually be followed by a notice in the **Federal Register**. Lots of test kits found to be not acceptable for sensitivity and specificity would be prohibited from release. By inserting the requirement in this section, FDA is

attempting to emphasize the need for reference panels to manufacturers of blood and blood components so that they may use the appropriately released lot of test kits. Accordingly, the agency is proposing to remove § 660.42, a requirement for a reference panel for hepatitis B surface antigen, and include the use of reference panels by manufacturers of test kits in proposed § 610.44 for better consolidation.

K. Use of § 40.120-Alternative Procedures

FDA recognizes that as technology and scientific knowledge advance, there will continue to be instances when a regulation will become outdated or where unanticipated circumstances may warrant a departure from an approach detailed in the regulations. In order to be more responsive to improved technologies, increased scientific knowledge, and concerns about the continued availability of blood and blood products, the agency has issued a regulation at § 640.120, which allows the Director, CBER, to approve an exception or alternative to any requirement in subchapter F of chapter I of title 21 of the Code of Federal Regulations regarding blood, blood components, or blood products. The Director, CBER, would approve such an exception or alternative only if, in the judgment of the Director, CBER, the safety, purity, potency, and effectiveness of the final product is adequately ensured. The Director, CBER, may request additional data or information from the person who has requested permission for an exception or alternative before granting the request. Any exception or alternative to the proposed rule, once finalized, would proceed under § 640.120.

L. Removal of § 10.45

With the reconstruction and streamlining of the regulations in regard to testing requirements for communicable disease agents, the agency is proposing to remove § 610.45, human immunodeficiency virus (HIV) requirements, because it has been incorporated into the revision of proposed § 610.40.

IV. Analysis of Impacts and Initial Regulatory Flexibility Analysis

FDA has examined the impacts of the proposed rule under Executive Order 12866, under the Regulatory Flexibility Act (5 U.S.C. 601-612), and under the Unfunded Mandates Reform Act (Public Law 104-4). 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).

OMB has determined that the proposed 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 Mandate 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 proposed 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 an Initial Regulatory Flexibility Analysis.

A. Objectives and Basis of the Proposed Action

FDA is taking this action as part of the agency's "Blood Initiative" in which FDA is reviewing and revising, when appropriate, its regulations, policies, guidance, and procedures related to blood and blood products, including plasma derivatives. The basis for this proposed rule is to help protect the safety and ensure the quality of the nation's blood supply, and to promote consistency in the industry. Under the biologics licensing and quarantine provisions of the PHS Act (42 U.S.C. 262-264) and the drug, device, and the general administrative provisions of the act (21 U.S.C. 351-353, 355-360, 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 proposing to: (1) Require screening tests for evidence of infection due to communicable disease agents for autologous donations in order to reduce the risk of transmission of communicable disease by untested units entering the blood supply inadvertently; (2) require supplemental (additional, more specific) testing of all donations that are repeatedly reactive by screening tests for which there are supplemental tests; and (3) codify 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 proposed rule requires that each donation of human blood or blood component, including those intended for autologous use or as a component of a medical device, 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 repeatedly reactive when tested for evidence of infection due to any of the disease agents would be required to be further tested whenever a supplemental, more specific test has been approved for such use by FDA. FDA is proposing to require that the testing be done by a laboratory that is registered with FDA and CLIA-certified. The proposed 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. FDA is proposing to permit shipping of units prior to testing if appropriate procedures are developed for collection, shipment and quarantine to protect against unnecessary communicable disease risks from use of shipped units later found to test repeatedly reactive. Under the proposed rule, allogeneic donations that test repeatedly reactive shall not be shipped except in situations specifically approved by FDA; however, repeatedly reactive autologous units may be shipped with labeling to indicate biohazard.

The rule would also require manufacturers of test 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 proposed testing of donations from allogeneic and 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 Office of Blood Research and Review (OBRR) has record of 2,801 registered blood and plasma establishments, including 487 plasma centers and 2,314 blood centers. Most Source Plasma centers are commercial establishments with paid plasma donors. By contrast, whole blood donors in the United States are volunteers. The most recently published survey of the blood industry was conducted in 1992 (Ref. 1), and the aggregate figures for blood collection reported in the 1992 survey are generally consistent with the aggregate numbers (i.e., 14 million blood donations) currently provided by the American Association of Blood Banks (AABB) (Ref. 2), although the number of registered facilities is now somewhat higher. The 1992 survey of U.S. blood establishments reported on 2,093 entities, including 157 distinct regional and community blood centers. Data on activities of the regional and community blood centers were obtained as responses to the AABB's 1993 Institutional Membership Questionnaire, directly from the American Red Cross, or in the case of non-AABB centers, from responses to questionnaires mailed from the Center for Blood Research. According to the 1992 survey, 1,936 hospitals listed as members of the AABB, are involved in blood collection. These hospitals are a subset of the American Hospital Association (AHA) list of 5,288 hospitals presumed to transfuse blood.

According to the 1992 survey, all U.S. blood establishments were estimated to collect a total of 13,794,000 units of blood. Allogeneic donations accounted for 87.2 percent (12,035,000 units), directed donations accounted for 3.2 percent (436,000 units) and autologous donations comprised 8.1 percent (1,117,000 units) of the total. Regional and community blood centers report receiving 702,000 of the total autologous units, and hospital blood centers collected an estimated 415,000 units. Based on information published by the AABB and the American Red Cross regarding allogeneic donations, and communications with experts in the blood banking industry regarding the testing of autologous donations, FDA believes that all blood donations currently collected by the regional and community blood centers, and all of the

allogeneic donations collected by hospitals are already being tested for the specified disease agents. FDA also estimates that approximately one-third to one-half of the autologous donations currently collected by hospitals are already being tested for HIV, types 1 and 2, HBV, HCV, and HTLV, types I and II. In the following analysis, an approximate midpoint of 40 percent is used as the assumed percentage of hospital-collected autologous donations already being tested for the specified disease agents.

In 1997, the Government Accounting Office (GAO) estimated that approximately 12 million donations of Source Plasma were collected by plasma centers (Ref. 3). 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 proposed rule. However, based on GAO reported variations in the plasma industry's confirmatory testing of repeat reactive donations, it is also assumed that supplemental confirmatory testing for HCV is not widely practiced at present.

The proposed requirements for manufacturer testing of approved test kits will entail manufacturers' use of CBER regulatory reference panels to provide verification of the specificity and sensitivity of each lot of test kit 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 proposed 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 proposed rule are already performing the proposed tests to comply with their own quality assurance standards. The proposed rule is therefore expected to introduce no substantial impact on these establishments.

2. Estimated Impact of Proposed Requirements for Donor Testing

The proposed rule provisions for donation testing, appropriate handling, labeling, and distribution will involve a one-time effort by all blood establishments to review and modify current blood donor testing, handling, and recordkeeping protocols to comply with the proposed rule. The rule will also involve a yearly increase in donor testing for establishments that currently do not test both allogeneic and autologous blood and blood component donations.

The one-time effort to review and modify current standard operating procedures (SOP's) is expected to vary among establishments, depending on whether the establishment already engages in testing and labeling both autologous and allogeneic blood donations for the specified set of disease agents. For establishments that already perform testing and labeling of both autologous and allogeneic donations (i.e., all plasma centers collecting only for allogeneic use, regional and community blood centers, and 40 percent of hospital collection sites), FDA estimates that it would take approximately 8 hours of staff time to reconcile the proposed regulations against the facility's current standards. This process could be performed by a technical specialist who acts 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 centers and an estimated 40 percent of the hospital blood centers. For establishments that already perform the proposed testing on allogeneic, but do not test autologous donations, FDA assumes that approximately 16 hours of staff time would be required to reconcile and expand the current facility standards to comply with the requirements of the proposed regulation. The cost in this case would be \$411 per facility. It is also assumed that all facilities perform careful labeling and recordkeeping on autologous units donations, and that recordkeeping will include more infectious disease information but will not require substantially more time than is already allocated. Thus, the total one-time cost for the industry is estimated to be \$813,554 (2,800 establishments - 1,936 hospital blood centers) x \$205 + (1,936 x 0.40 x \$205) + (1,936 x 0.60 x \$411).

The yearly increase in cost of testing for the 1,162 hospitals assumed not to currently test all donations is based on a proportional extrapolation (60 percent of donors) from the estimated number of autologous donations collected in hospital blood centers, as reported in the 1992 blood collection survey (415 units); the estimated cost per required test; and an estimated rate of 0.19 percent HCV repeat-reactive donations reported by the American Red Cross, based on donations received between January 1996 and June 1997. The cost for HIV, types 1 and 2 is estimated to be approximately \$5 per test (Ref. 4); the cost per test for HBV, i.e., HBsAg and anti-HBc, are respectively estimated to be \$39.20 (Ref. 5) and \$38.59; the cost of HCV-EIA and supplemental assay are respectively estimated to be \$49.90 and \$114.50 (Ref. 6) per test; and the cost of HTLV, types I and II is estimated to be \$5.00 per test (Ref. 7). The total yearly increase in cost for the industry, based on these factors, is estimated to be \$34,316,570 (415,000 x .60 x [(\$5.00 + \$39.20 + \$38.59 + \$49.90 + \$5.00) + 0.0019 x \$114.50]).

The yearly increase in cost for the plasma industry is based on the assumption that potentially all plasma centers will need to begin routine followup testing on donations that test repeatedly reactive for hepatitis C. Assuming an average 0.18 percent (0.0018) rate of HCV repeatedly reactive donations, an annual volume of 12 million donations and the cost of \$114.50 per supplemental HCV test, the annual cost is estimated to be no greater than \$2,514,420. FDA recognizes that the cost may actually be less if a substantial fraction of HCV repeatedly reactive donations collected by the plasma centers already undergo confirmatory testing.

In summary, the proposed rule would result in an estimated one-time cost of \$813,554, and a total annual cost of \$36,830,990 (\$34,316,570 + \$2,514,420) to the blood and plasma industries.

3. Expected Benefits of the Proposed Rule

The proposed 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 accidents and 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. 17). 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 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. 8). HCV and HBV transfusion risks have also declined. In 1994, 4.3 percent of all HCV infections were transfusion-related, compared to the current rate of 0.02 percent to 0.05 percent. Similarly, although 5.7 percent of the general population is estimated to be seropositive for HBV, the risk of HBV transfusion transmission is currently estimated to be 1 in 200,000 transfused units.

Although the impetus for autologous donation is often the donor's desire to avoid risk of infection from other donors' blood, studies comparing the prevalence of disease markers in autologous donations compared to allogeneic donations have found the incidence of positive disease markers for first time donations among autologous donors to be similar to that among first-time allogeneic donors. Moreover, the rate among first-time autologous donors was generally higher than that found among repeat allogeneic donors (Ref. 9). The finding of positive markers for an allogeneic donation, however, would result in a blood bank's rejection of the donor unit. By contrast, the disease-positive autologous unit would be retained and potentially stored in the same freezer as the screened allogeneic units. Without the proposed requirement for infectious disease testing and labeling, the label of a disease-positive autologous unit may not indicate that the unit presents a potentially infectious disease risk. The accidental and inadvertent use of such units may expose unwitting recipients to a higher than acceptable risk.

The gravity of the disease risks addressed by the proposed rule are 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 sexually

transmitted, 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 B 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. 10). 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 have a risk of liver cancer that is 12 to 300 times higher than noncarriers. 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. 11).

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. 12). Of patients with transfusion-associated chronic non-A, non-B hepatitis who undergo biopsy within 5 years after onset, at least 40 percent have histologic evidence of chronic active hepatitis and 10 to 20 percent have evidence of cirrhosis (Ref. 13). 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. 14). As described previously, the requirement of HIV, types 1 and 2; HBV; HCV; and

HTLV, types I and II testing for all blood and blood component donations, including those for autologous 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 proposed 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. The FDA has therefore prepared an Initial Regulatory Flexibility Analysis. The blood and plasma establishments affected by the proposed rule are included under the major Standard Industrial 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." According to the Small Business Administration (SBA), a small business within the blood industry is an enterprise with less than \$5 million in annual receipts. A small organization is a not-for-profit enterprise which is independently owned and operated and is not dominant in its field. A "small governmental jurisdiction" generally means governments of cities, counties, towns, townships, villages, school districts, or special districts with a population of less than fifty thousand.

As described in the foregoing analysis, hospitals that do not currently test autologous donations for HIV types 1 and 2, HBV, HCV, and HTLV types I and II are expected to be the primary entity affected by the proposed rule. However, 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. 15) 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 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.

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 in a system" refer to those "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 non-federal 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. Thus, a total of 2,794 [2,783 + 11] hospitals might qualify as small entities.

The agency does not know how many of the estimated total of 415,000 autologous units would be collected at hospitals qualifying as a "small entity," nor how many of those establishments are already performing the proposed testing for autologous donors (as noted in the earlier cost analysis, an estimated 40 percent of all hospital-based autologous collections already include blood testing). Some of the hospitals that would be classified as small entities will already be testing autologous donors as required by the proposed rule, and are therefore expected to incur an estimated one-time cost of \$205, as described earlier. Other small establishments, that begin autologous donor testing in compliance with the proposed rule, will incur an estimated \$411 one-time cost, and yearly costs of new testing based on the number of autologous donors at their facility. The following analysis of potential impact focuses on the annual blood testing costs, which represent the largest

component of cost impact. The analysis assumes that the collections of autologous units may be distributed across hospitals of different size in proportion to the hospitals' share of all reported inpatient surgeries. Table 1 estimates the percentage of all inpatient hospital surgeries, based on the number

of inpatient surgeries reported to AHA as performed by hospitals in different bedsize categories. This percentage is used to estimate a share of the total of 415,000 autologous units collected by hospitals in each bedsize category, for which testing would be newly required under the proposed rule. The number of

autologous units per hospital within a bedsize category is based on the total estimated autologous units per bedsize category divided by the total number of hospitals reported for that size category. These estimates (rounded to the nearest whole unit) are presented in the rightmost column of the Table 1.

TABLE 1.—ESTIMATED AUTOLOGOUS BLOOD UNITS PER HOSPITAL BASED ON ESTIMATED SHARE OF INPATIENT SURGERIES BY BEDSIZE CATEGORY AND TOTAL HOSPITAL COLLECTIONS OF AUTOLOGOUS UNITS

Bedsizes Category	Non-federal Hospitals	Estimated percent inpatient surgeries	Estimated share of 415,000 collected autologous units	Estimated autologous units per hospital
6 to 24	262	0.21	857	3
25 to 49	906	2.02	8,364	9
50 to 99	1,128	6.03	25,029	22
100 to 199	1,338	19.38	80,407	60
200 to 299	692	20.99	87,095	126
300 to 399	361	16.24	67,398	187
400 to 499	196	12.17	50,506	258
500 +	251	22.97	95,343	380

The cost impact of testing autologous blood collections is based on the above estimates of autologous units per hospital, and the earlier estimated average HIV, HCV, HTLV, and HBV testing cost per donation of \$137.82

[\$5.00 + \$49.90 + \$5.00 \$38.50 + \$39.20] + [0.0019 x \$114.50]. The estimated annual cost impact per hospital, by bedsize category, is shown in the Table 2. To provide some perspective on relative impact, the newly-incurred cost

for autologous unit testing is also shown as a percentage of average annual gross revenues per hospital. The notification cost is estimated to be approximately 0.01 percent of the average annual gross revenues for every size category.

TABLE 2.— ESTIMATED DOLLAR COST PER HOSPITAL FOR AUTOLOGOUS BLOOD TESTING AND ESTIMATED COST AS A PERCENTAGE OF AVERAGE ANNUAL REVENUES

Bedsizes Category	Estimated Cost per Hospital at \$138 per Newly Tested Unit	Gross Annual Revenue per Hospital (Millions)	Autologous Blood Testing Cost as Percent of Gross Annual Revenue
6 to 24	\$451	\$5.459	0.01
25 to 49	\$1,272	\$12.606	0.01
50 to 99	\$3,058	\$27.711	0.01
100 to 199	\$8,282	\$74.803	0.01
200 to 299	\$17,346	\$153.988	0.01
300 to 399	\$25,731	\$236.917	0.01
400 to 499	\$35,514	\$329.161	0.01
500 +	\$52,351	\$513.066	0.01

These findings of this analysis suggest that the relative cost impact may be fairly consistent across hospitals of different sizes, if the number of affected autologous units per bedsize category is proportionate to the number of inpatient surgeries performed by hospitals in different size categories. However, the distribution of affected autologous units across hospitals of different size and types of ownership is currently unknown. Because this information is essential for the estimation of the economic impact on small entities, FDA requests industry comment on the anticipated numbers of affected units of autologous blood and their distribution across hospitals in the industry, particularly those units collected by

hospitals that can be classified as small entities.

Regardless of size, the net cost impact for hospitals that must begin testing autologous units may be limited because the cost of the require testing may generally be shifted to patients or to third-party payers, including Medicare. For example, the cost of units or packed red blood cells or blood components, including costs of processing and administration, are covered under both Medicare Part A and Part B (Ref. 16). Currently, Medicare pays for all but the first 3 pints of blood per calendar year. A Medicare beneficiary may choose to pay for or replace the first three units of blood, the annual blood deductible.

The specific requirements and anticipated costs for changes in SOP's for donation collection, testing, labeling, quarantine, and distribution are described previously. All blood establishments are already engaged in a substantial amount of donation testing, recordkeeping, unit labeling, and control. For some hospital blood centers, these activities may be expanded. However, as indicated previously, it is not clear whether the establishments most affected could be characterized as small business entities.

The number of plasma facilities that would qualify as small entities is also uncertain. According to the General Accounting Office (Ref. 16) approximately 370 paid plasma

collection centers annually collect about 11 million liters of plasma, the vast majority of which is processed by four companies: Alpha Therapeutic Corp., Baxter Healthcare Corp., Bayer Corp., and Centeon LLC. FDA estimates that approximately 90 percent of these plasma collection centers are owned by companies that operate a number of centers. 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 centers may qualify as small business establishments. The potential impact on these facilities will be a function of the number of donors and the HCV repeatedly reactive findings among donors at their facility. If the estimated 12 million plasma donations were evenly distributed over the 487 registered facilities, each facility would average 25,000 donations. Assuming approximately 8 units per plasma donor per year (Ref. 16) each facility would average 3,125 donors, approximately 6 [0.0018 x 3,125] of whom might test repeatedly reactive for HCV and require supplemental testing. The expected cost of the additional testing would then be \$687 [\$114.50 x 6] per facility per year.

In addition to these for-profit entities, the remaining 100 or so plasma collection facilities, of the total of 487 registered facilities, function within blood collection centers that are operated by the American 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 proposed 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 several alternatives for lessening burden on small entities. The first alternative would be to not issue additional requirements for testing of allogeneic or autologous donations for evidence of infection due to communicable disease agents and continue with the recommendations for testing in addition to the required tests for HIV and HBV. FDA considers this alternative to be ineffective because it does not promote consistency in testing and related procedures among entities, does not provide FDA with clear enforcement authority, and is converse to the agency's and industry's mission, i.e., the safety of the blood supply. A second alternative would be to continue to specify in the regulations the marker to

be tested for, such as a specific antigen or antibody. Tests for new or different markers of infection due to a communicable disease agent have changed as they become more appropriate or the technology in testing has become more sensitive or specific. FDA believes this alternative would not provide for the continued improvement in the testing regimen and would limit flexibility not only in testing, but in controlling cost to the different entities performing testing. Finally, FDA has requested industry comment and suggestions for alternatives to autologous unit testing, as discussed earlier under section "C. Exceptions."

V. The Paperwork Reduction Act of 1995

This proposed rule contains information collection provisions that are subject to review by the Office of Management and Budget (OMB) under the Paperwork Reduction Act of 1995 (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 this estimate is the time for reviewing the instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

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

Title: Requirements for Testing Human Blood Donors for Evidence of Infection due to Communicable Disease Agents.

Description: FDA is proposing to revise the testing requirements in part 610 subpart E issued under the authorities of the act and the PHS Act. Currently, subpart E in part 610 requires testing for HBV and HIV and the development and administration of product quarantine and recipient notification ("Lookback") program when donors test repeatedly reactive for antibody to HIV, or otherwise are

determined to be unsuitable when tested in accordance with § 610.45. FDA is proposing to: (1) Require screening tests for evidence of infection due to communicable disease agents for autologous donations; (2) require supplemental (additional, more specific) testing of all repeatedly reactive screening test results for which there is a supplemental test; and (3) codify 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.

FDA proposes to require that each donation of human blood or blood component, including those intended for autologous use or as a component of a medical device, 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 repeatedly reactive when screened for evidence of infection due to any of the communicable disease agents would be required to be further tested whenever a supplemental (additional, more specific) test has been approved for such use by FDA. Testing would be required to be performed by a laboratory certified under CLIA and registered with FDA in accordance with part 607. Deferral of donors testing repeatedly reactive from future donations would be required. Criteria are proposed for release or shipment of human blood or blood components prior to completion of testing, and restrictions on use of human blood or blood components that test repeatedly reactive when screened for evidence of infection. The proposed rule would also require manufacturers of test kits approved to test human blood donors for evidence of infection due to communicable disease agents to verify an acceptable sensitivity and specificity of each lot of test kit using a reference panel obtained from CBER of other FDA designated source, when available.

Description of Respondents:

Manufacturers of blood and blood components and clinical testing laboratories.

Based on June 1998 registration records, there are approximately 2,801 FDA registered blood collection facilities in the United States that collect approximately 27,000,000 units of Whole Blood and Source Plasma annually. To ensure consistency in the blood industry's testing practices, FDA is proposing to require testing consistent with its current recommendations and industry practice. Laboratories that perform testing of donor blood samples must be registered with FDA in accordance with part 607. Currently,

§ 607.65(g) provides an exemption from FDA registration to clinical laboratories that are approved for Medicare reimbursement and which are engaged in the testing of blood products in support of other registered establishments. FDA is proposing to remove this exemption and require such clinical labs to register. Because laboratories that currently perform testing of donor blood samples are already registered, FDA anticipates that the number of new registrants from clinical labs that will no longer be exempt from registration will be one or less per year. Under part 607 the burden for registrants not previously exempt is approved under OMB 0910-0052. Under that OMB package, FDA estimated the time required to prepare and send in the information for a new registration is approximately 1 hour.

FDA proposes to permit the emergency release or shipment of human blood or blood components prior to the completion of testing for evidence of infection due to communicable disease agents. The agency recognizes that there are rare medical emergencies, e.g., where a patient's need for blood is so acute as to preclude any communicable disease testing of the blood. FDA believes that the use of untested or incompletely tested blood in such medical emergencies should not be prohibited. FDA is proposing to remove § 640.2(f), which provides for emergency release of Whole Blood prior to completion of required testing and to place the provision for medical emergency situations in § 610.40(e), which will be applicable to all blood products, including Whole Blood.

Release of blood or blood components due to a medical emergency prior to completion of required testing must be appropriately documented and the results of required testing provided to the consignees as soon as possible. Because such a medical emergency is a rare occurrence, FDA expects the recordkeeping and reporting burden to be very minimal with one or less occurrence per year. Documentation of the medical emergency should take a half hour or less and the reporting of test results to consignees is considered under section 1320.3(b)(2) of the PRA to be part of usual and customary practice or procedures to finish the testing and provide the results.

FDA is proposing in § 610.40(e) to permit, with FDA approval, shipment of certain blood components for further manufacturing before testing is completed and the test results are received by the collection facility. The only product currently shipped prior to completion of hepatitis B 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 the shipment does not have to be reported to the agency). To obtain approval from FDA, the agency would expect the manufacturer(s) to submit specific procedures for collection, shipment, and quarantine of a product before testing is completed, completion of testing as soon as possible after shipping, and prompt communication of test results to the consignee. Based on the number of applications for the manufacture of

Source Leukocytes received during fiscal year (FY) 95, FY 96, and FY 97, the agency anticipates two applications may be received 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. FDA estimates 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.

According to information retrieved from FDA's database on licensed establishments, there are approximately 145 manufacturers producing licensed Source Leukocytes. Under § 610.40(e)(2), the agency estimates, based on information provided by industry, that each manufacturer would ship approximately three units of blood or blood components prior to testing the donor and that it would take an estimated 15 minutes to provide the completed test results to the consignee.

Under § 610.40(f)(2)(ii), according to FDA's database, there are approximately 343 licensed manufacturers that would ship known repeatedly reactive units. Industry estimates that each manufacturer would ship an estimated 10 units per month that would require two labels: one as repeatedly reactive for the appropriate screening test, and the other stating the exempted use specifically approved by FDA. Industry also estimates that it would take approximately 10 minutes per unit to affix the labels.

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

TABLE 3.—ESTIMATED ANNUAL REPORTING BURDEN¹

21 CFR Section	No. of Respondents	Annual Frequency per Response	Total Annual Responses	Hours per Response	Total Hours
607.20	1	1	1	1	1
610.40(e)(2)	145	36	5,220	0.25	1,305
610.40(f)(2)(ii)	343	120	41,160	0.2	8,232
Total					9,538

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

TABLE 4.—ESTIMATED ANNUAL RECORDKEEPING BURDEN¹

21 CFR Section	No. of Recordkeepers	Annual Frequency per Recordkeeping	Total Annual Records	Hours per Recordkeeper	Total Hours
610.40	1	1	1	1	1

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 21 CFR 610.40(f)(2) and 610.42 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 reporting of test results to the consignee in § 610.40(e) does not constitute collection of information burden because it is the customary and usual practice or procedure to finish the testing and provide the results to the manufacturer responsible for labeling the blood products.

In compliance with section 3507(d) of the PRA of 1995 (44 U.S.C. 3507(d)), the agency has submitted a copy of this proposed rule to OMB for review of the information collection provisions. Interested persons are requested to submit written comments regarding information collection by September 20, 1999 to the Office of Information and Regulatory Affairs, OMB (address above).

VI. Environmental Impact

The agency has determined under 21 CFR 25.31(j) that this action is of a type that does not individual or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

VII. Request for Comments

Interested persons may, on or before November 17, 1999, submit to the Dockets Management Branch (address above) written comments regarding this proposal, except that comments regarding information collection provisions should be submitted in accordance with the instructions in section V. of this document. Two copies of any comments on issues other than information collection are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

VIII. 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. Wallace, E. L., W. H. Churchill, D. M. Surgenor, J. An, G. Cho, S. McGurk, and L. Murphy, "Collection and Transfusion of Blood and Blood Components in the United States, 1992," *Transfusion*, 35, 802-812, 1995.

2. American Association of Blood Banks, *Facts About Blood and Blood Banking*, "http://www.aabb.org/docs/facts.html".

3. General Accounting Office, "Blood Safety: Enhancing Safeguards Would

Strengthen the Nation's Blood Supply," GAO-HEHS-97-143, June 1997.

4. AuBuchon, J. P., J. D. Birkmeyer, and M. P. Busch, "Cost-effectiveness of Expanded Human Immunodeficiency Virus Testing Protocols for Donated Blood," *Transfusion*, 37:45-51, 1997.

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6. 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, 4:591-596, 1998.

7. Tynell, E., S. Andersson, E. Lithander, M. Arneborn, J. Blomberg, H. Bertil Hansson, A. Krook, M. Nomberg, K. Ramstedt, A. Shanwell, and A. Bjorkman, "Screening for Human T-Cell Leukaemia/Lymphoma Virus Among Blood Donors in Sweden: Cost Effectiveness Analysis," *British Medical Journal*, vol. 316, 1417-1422, May 1998.

8. Podnos, Y. D., and R. A. Williams, Current Risks for Blood Borne Viral Illness in Blood Transfusions, *Western Journal of Medicine*, vol. 168, 1:36-37, January 1998.

9. Myhre, B. A., and P. I. Figueroa, "Infectious Disease Markers in Various Groups of Donors," *Annals of Clinical and Laboratory Science*, vol. 25, 1:39-43, 1995.

10. 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.

11. 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.

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

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

14. Kim, W. R., J. J. Poterucha, 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.

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

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

17. American Association of Blood Banks (AABB) Association Bulletin No. 95-4: AABB

Position on Testing of Autologous Units. Attachment 1: AABA Anonymous Autologous Survey Request, May 9, 1999.

List of Subjects

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.

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, it is proposed that 21 CFR parts 607, 610, 640, and 660 be amended as follows:

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

1. 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]

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

PART 610—GENERAL BIOLOGICAL PRODUCTS STANDARDS

3. The authority citation for 21 CFR part 610 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.

4. The Table of Contents for subpart E of part 610 is revised to read as follows:

Subpart E—Testing Requirements for Communicable Disease Agents

Sec.

610.40 Test requirements.

610.41 Donor deferral.

610.42 Restrictions on use for further manufacture of in vitro diagnostic products.

610.44 Use of reference panels by manufacturers of test kits.

610.46 "Lookback" requirements.

610.47 "Lookback" notification requirements for transfusion services.

5. The heading of subpart E is revised to read as follows:

Subpart E—Testing Requirements for Communicable Disease Agents

6. Section 610.40 is revised to read as follows:

§ 610.40 Test requirements.

(a) *Human blood and blood components.* Except as specified in paragraph (b) of this section, each donation of human blood or blood components intended for use in preparing a product, including donations intended for autologous use or as a component of a medical device, shall be tested for evidence of infection due to the following communicable disease agents by using screening tests approved for such use by the Food and Drug Administration (FDA) in accordance with the manufacturer's instructions. One or more such tests shall be performed as necessary to adequately and appropriately reduce the risk of transmission of communicable disease.

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

(b) *Exceptions.* (1) Donations of Source Plasma are not required to be tested for evidence of infection due to the communicable disease agents listed in paragraphs (a)(5) and (a)(6) of this section.

(2) Donations of human blood or blood components intended solely as a component of an in vitro medical device are not required to be tested for evidence of infection due to the communicable disease agents listed in paragraphs (a)(5) and (a)(6) of this section unless they contain viable leukocytes.

(3) Requirements in this subpart shall not apply to the in-house use or distribution of samples of blood, blood components, plasma, or sera if intended for clinical laboratory testing or research purposes, and not for administration to humans or use in the manufacture of a product.

(c) *Further testing.* Each donation found to be repeatedly reactive by a screening test performed in accordance with paragraph (a) of this section shall be further tested whenever a supplemental (additional, more specific) test has been approved for such use by FDA.

(d) *Testing responsibility.* Testing for evidence of infection due to the

communicable disease agents designated in paragraph (a) of this section shall be performed by a laboratory registered in accordance with part 607 of this chapter and certified to perform testing on human specimens under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) in accordance with 42 CFR part 493.

(e) *Release or shipment prior to testing.* Human blood or blood components that are required to be tested for evidence of infection due to the communicable disease agents designated in paragraph (a) of this section may be:

(1) Released for shipment or use before test results are available only in appropriately documented medical emergency situations; or

(2) Shipped for further manufacturing as approved in writing by FDA, provided the tests for evidence of infection due to communicable disease agents are performed as soon as possible after release or shipment and the results provided promptly to the consignee.

(f) *Restrictions on shipment or use.* (1) Human blood or blood components that have a repeatedly 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 with a record of a repeatedly reactive screening test for evidence of infection due to a communicable disease agent designated in paragraph (a) of this section shall not be shipped or used, except as provided in paragraph (f)(2) or (f)(3) of this section.

(2) The restrictions shall not apply to:

(i) Blood or blood components intended for autologous use, provided that such units shall be appropriately labeled in accordance with § 606.121 (i) of this chapter and with the following Biohazard legend:



BIOHAZARD

(ii) Blood or blood components may be shipped or used under conditions specifically approved in writing by FDA, provided that such blood or blood components are appropriately labeled in accordance with § 606.121 or § 640.70 of

this chapter and display the Biohazard legend. Such blood or blood components shall be labeled as repeatedly reactive for the appropriate screening test for evidence of infection due to the identified communicable disease agent. For blood or blood components intended for further manufacturing into injectable products, labeling shall include a statement indicating the exempted use specifically approved by FDA. For blood or blood components intended for in vitro use, labeling shall include the statement "Caution: For Further Manufacturing Into Non-Injectable Products For Which There Are No Alternative Sources".

(iii) Samples for in-house use or distribution if intended for clinical laboratory testing or research purposes, and not intended for administration in humans or use in the manufacture of a product.

(3) Human blood or blood components testing negative for evidence of infection due to a communicable disease agent(s) designated in paragraph (a) of this section from a donor with a record of a repeatedly reactive result for the same screening test for evidence of infection due to a communicable disease agent(s) designated in paragraph (a) of this section may be used if the donor has been subsequently shown to be suitable by a requalification method or process found acceptable for such purposes by FDA.

7. Section 610.41 is revised to read as follows:

§ 610.41 Donor deferral.

Except for autologous donors and as provided in § 640.65(b)(2)(ii), (b)(2)(iii), and (b)(2)(iv) of this chapter, donors testing repeatedly reactive for evidence of infection due to a communicable disease agent(s) listed in § 610.40(a) or reactive for a serologic test for syphilis shall be deferred from future donations of blood and blood components except:

(a) Donors who test repeatedly reactive for HTLV, types I or II, or anti-HBc on only one occasion, unless further tested under § 610.40(c).

(b) Donors testing repeatedly reactive for HTLV, types I and II or anti-HBc may serve as donors of Source Plasma.

(c)(1) Deferred donors testing repeatedly reactive for evidence of infection due to a communicable disease agent listed in § 610.40(a) may serve as donors for blood or blood components when used in accordance with § 610.40(f).

(2) Deferred donors previously showing evidence of infection due to hepatitis B virus when tested in accordance with § 610.40(a) and (c) may

donate blood or blood components for use as a component of a medical device or may donate blood or blood components in the preparation of Hepatitis B Immune Globulin (Human) provided their current donations test nonreactive when tested in accordance with § 610.40(a) and the donor is otherwise determined to be suitable.

(d) Donors with a reactive serologic test for syphilis need not be deferred if found negative by an approved specific treponemal test (confirmatory test for syphilis).

(e) Deferred donors may be found to be suitable as donors of blood or blood components by a method or process found acceptable for such purposes by the Food and Drug Administration.

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

§ 610.42 Restrictions on use for further manufacture of in vitro diagnostic products.

In vitro diagnostic products manufactured from human blood or blood components found to be repeatedly reactive by a screening test performed in accordance with § 610.40(a) shall be labeled in accordance with § 809.10 of this chapter, and shall include a statement of warnings in the label indicating that the product was manufactured from a donation found to be repeatedly reactive by a screening test for evidence of infection due to the identified communicable disease agent.

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

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

When available, a reference panel shall be obtained from the Center for Biologics Evaluation and Research or from a Food and Drug Administration designated source, and shall be used by the manufacturer to verify acceptable sensitivity and specificity of:

(a) Each lot of 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

(b) Each lot of a human immunodeficiency virus (HIV) test approved for use in the diagnosis or monitoring of this communicable disease agent. A lot that is found to be not acceptable for sensitivity and specificity under § 610.44(a) and (b) shall not be released.

§ 610.45 [Removed]

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

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

11. 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]

12. Section 640.2 *General requirements* is amended by removing paragraph (f).

PART 660—ADDITIONAL STANDARDS FOR DIAGNOSTIC SUBSTANCES FOR LABORATORY TESTS

13. The authority citation for 21 CFR part 660 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.

§ 660.42 [Removed]

14. Section 660.42 *Reference panel* is removed.

Dated: April 20, 1999.

Jane E. Henney,

Commissioner of Food and Drugs.

Donna E. Shalala,

Secretary of Health and Human Services.

[FR Doc. 99-21296 Filed 8-18-99; 8:45 am]

BILLING CODE 4160-01-F

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; Notification of Deferred Donors

AGENCY: Food and Drug Administration, HHS.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is proposing to require blood and plasma establishments to notify donors of their deferral due to test results for communicable disease agents or failure to satisfy suitability criteria with the intent of reducing the risk of transmission of communicable disease through the use of blood, blood components, and blood derivatives. Under the proposed rule, blood and plasma establishments would notify the donors that they have been deferred and the reason for the deferral; provide

information concerning appropriate medical followup and counseling; describe the types of donations the donors should not make in the future; and discuss the possibility that the donor may be found suitable in the future, where appropriate. FDA is issuing this rule as part of the agency's "Blood Initiative" in which FDA is reviewing and, when appropriate, revising its regulations, policies, guidance, and procedures related to blood and blood products, including blood derivatives.

DATES: Submit written comments by November 17, 1999. Submit written comments on the information collection provisions by September 20, 1999.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Comments should be identified with the docket number found in brackets in the heading of this document. Submit written comments on the information collection provisions to the Office of Information and Regulatory Affairs (OMB), New Executive Office Bldg., 725 17th St. NW., Washington, DC 20503, Attention: Wendy Taylor, Desk Officer for FDA.

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. Introduction

For a variety of reasons discussed as follows, FDA has decided to comprehensively review and, as necessary, revise its regulations, policies, guidance, and procedures related to the licensing and regulation of blood products. In the *Federal Register* of June 3, 1994 (59 FR 28821 and 59 FR 28822, respectively), FDA issued two documents entitled "Review of General Biologics and Licensing Regulations" (Docket No. 94N-0066) and "Review of Regulations for Blood Establishments and Blood Products" (Docket No. 94N-0080). The documents announced the agency's intent to review biologics regulations (parts 600, 601, 606, 607, 610, 640 and 660 (21 CFR 600, 601, 606, 607, 610, 640 and 660)), and requested written comments from the public. Interested persons were given until August 17, 1994, to respond to the documents. In response to requests for additional time, FDA twice extended the comment period, as announced in the *Federal Register* of August 17, 1994

