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 (HFM–40), Center for Biologics Evaluation and Research (CBER), Food and Drug Administration, 1401 Rockville Pike, suite 200N, Rockville, MD 20852–1448. Send one self-addressed adhesive label to assist that office in processing your requests. The guidance documents may also be obtained by mail by calling the CBER Voice Information system at 1–800–835–4709 or 301–827–1800, or by FAX by calling the FAX Information System at 1–888–CBER–FAX or 301–827–3844. Persons with access to the Internet may 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 § 640.120–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 § 610.45

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

Bedsize 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

Bedsize 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 BURDEN[1]

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 BURDEN[1]

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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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