

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 606 and 640

[Docket No. 98N-0673]

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Direct final rule.

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and Source Plasma to be more consistent with current practices in the blood industry and to remove unnecessary or outdated requirements.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

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

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

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

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

SUPPLEMENTARY INFORMATION:

I. Blood Initiative

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

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

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

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

II. Legal Authority

FDA is issuing this new rule under the biologics products and

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

III. Highlights of the Direct Final Rule

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

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

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

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

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

collection practices often use more than two cycles for collection.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

IV. Rulemaking Action

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

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

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

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

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

V. Analysis of Impacts

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

FDA has examined the impact of the direct final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U. S. C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Pub. L. 104-4). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impact; and equity). The agency believes that this direct final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. This direct final rule is not a significant regulatory action as defined by the Executive Order and therefore is not subject to review under the Executive Order.

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

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

B. Environmental Impact

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

VI. The Paperwork Reduction Act of 1995

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

VII. Request for Comments

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

List of Subjects

21 CFR Part 606

Blood, Labeling, Laboratories, Reporting and recordkeeping requirements.

21 CFR Part 640

Blood, Labeling, Reporting and recordkeeping requirements.

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

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

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

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

2. Section 606.3 is amended by revising paragraphs (c), (e), (f), and (j) to read as follows:

§ 606.3 Definitions.

* * * * *

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

* * * * *

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

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

* * * * *

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

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

§ 606.100 Standard operating procedures.

* * * * *

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

* * * * *

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

* * * * *

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

* * * * *

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

* * * * *

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

§ 606.121 Container label.

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

* * * * *

(d) * * *

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

* * * * *

(e) * * *

(1) * * *

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

* * * * *

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

§ 606.122 Instruction circular.

* * * * *

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

* * * * *

(n) * * *

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

* * * * *

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

§ 606.151 Compatibility testing.

* * * * *

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

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

* * * * *

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

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

§ 606.160 Records.

* * * * *

(b) * * *

(2) * * *

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

* * * * *

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

§ 606.170 Adverse reaction file.

* * * * *

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

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

PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

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

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

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

§ 640.2 General requirements.

* * * * *

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

(c) * * *

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

* * * * *

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

§ 640.3 Suitability of donor.

* * * * *

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

* * * * *

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

* * * * *

(c) * * *

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

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

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

* * * * *

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

§ 640.4 Collection of the blood.

* * * * *

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

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

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

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

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

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

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

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

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

§ 640.5 Testing the blood.

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

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

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

§ 640.6 [Amended]

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

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

§ 640.13 Collection of the blood.

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

16. Section 640.15 is revised to read as follows:

§ 640.15 Samples for testing.

Samples collected in integral tubing shall meet the following standards:

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

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

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

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

§ 640.16 Processing.

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

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

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

§ 640.22 Collection of source material.

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

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

§ 640.23 Testing the blood.

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

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

§ 640.24 Processing.

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

§ 640.31 [Amended]

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

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

§ 640.32 Collection of source material.

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

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

§ 640.34 Processing.

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

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

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

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

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

(e) * * *

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

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

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

* * * * *

(g) * * *

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

not be issued if there is any evidence of thawing.

* * * * *

§ 640.51 [Amended]

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

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

§ 640.52 Collection of source material.

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

* * * * *

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

§ 640.54 Processing.

(a) * * *

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

* * * * *

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

§ 640.56 Quality control test for potency.

* * * * *

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

* * * * *

28. Section 640.62 is revised to read as follows:

§ 640.62 Medical supervision.

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

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

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

§ 640.63 Suitability of donor.

* * * * *

(c) * * *

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

* * * * *

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

* * * * *

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

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

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

* * * * *

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

§ 640.65 Plasmapheresis.

* * * * *

(b) * * *

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

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

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

* * * * *

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

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

§ 640.69 General requirements.

* * * * *

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

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

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

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

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

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

§ 640.71 Manufacturing responsibility.

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

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

* * * * *

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

§ 640.72 Records.

(a) * * *

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

* * * * *

Dated: April 20, 1999.

Jane E. Henney,
Commissioner of Food and Drugs.

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