

**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Parts 606 and 640**

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**[Docket No. 98N-0673]**

**Revisions to the Requirements Applicable to Blood, Blood Components, and Source Plasma; Confirmation in Part and Technical Amendment**

**AGENCY:** Food and Drug Administration, HHS.

**ACTION:** Direct final rule; confirmation in part and technical amendment.

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**SUMMARY:** The Food and Drug Administration (FDA) is confirming in part the direct final rule issued in the **Federal Register** of August 19, 1999. The direct final rule amends 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and Source Plasma to be more consistent with current practices in the blood industry and to remove unnecessary or outdated requirements.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 confirming the provisions for which no significant adverse comments were received. The agency received significant adverse comments on certain provisions and is amending Title 21 Code of Federal Regulations to reinstate the former provisions.

**DATES:** The effective date for the amendments to the sections published in the **Federal Register** of August 19, 1999 (64 FR 45366), and listed in table 1 of this document, is confirmed as February 11, 2000. The amendments listed in table 2 of this document are effective [*insert date of publication in the Federal Register*].

**FOR FURTHER INFORMATION CONTACT:** Joseph L. Okrasinski, 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:** Written comments concerning the direct final rule were to be submitted on or before December 3, 1999. FDA stated that the effective date of the direct final rule would be February 11, 2000. If no timely significant comments were submitted to FDA during the comment period, FDA intended to publish a document in the **Federal Register** within 30 days after the comment period ended, confirming the effective date of the final rule. If timely significant comments were received, the agency intended to publish a document in the **Federal Register** withdrawing the direct final rule before its effective date. Because of complex issues related to this rulemaking and because of competing priorities, FDA did not issue a document either confirming or withdrawing the direct final rule before its effective date. Therefore the Code of Federal Regulations was revised as of April 1, 2000, to codify the regulations in the direct final rule.

The agency received significant comments to the docket. If a significant adverse comment applies to an amendment, paragraph, or section of the 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 significant adverse comments.

Thus, FDA is confirming in part the direct final rule (sections listed in table 1 of this document) effective February 11, 2000.

The agency is making technical amendments to 21 CFR 640.25(c), 640.56(c), and 640.71(a) by replacing “Clinical Laboratories Improvement Act of 1967 (CLIA)” with “Clinical Laboratories Improvement Amendments of 1988 (CLIA).” This action is necessary for consistency when referring to CLIA in the regulations.

TABLE 1.—AMENDMENTS EFFECTIVE FEBRUARY 11, 2000

21 CFR Section	Action
606.3(c), (e), and (f)	Revised
606.100(b) and (d)	Revised introductory text
606.100(b)(7) and (b)(18)	Revised
606.121(a), (d)(2), and (e)(1)(ii)	Revised
606.122(f) and (n)(4)	Revised
606.151(e)	Revised
606.160(b)(2)(v)	Revised
606.170(b)	Revised
640.2(b) and (d)	Removed
640.2(c), (e), and (f)	Redesignated as (b), (c), and (d)
640.2(c)(2)	Revised

TABLE 1.—AMENDMENTS EFFECTIVE FEBRUARY 11, 2000—Continued

21 CFR Section	Action
640.3(b)	Revised introductory text
640.3(b)(3), (c)(2), and (c)(3)	Revised
640.3(e)	Removed and reserved
640.4(d)(1) through (d)(4), and (h)	Removed
640.4(i)	Redesignated as paragraph (h)
640.4(b) and (d)	Revised
640.6(c)	Removed
640.13(a)	Revised
640.16(b)	Revised
640.22(a)	Revised
640.25(c)	Revised
640.31(c)	Nomenclature change
640.32(a)	Removed
640.34(e)(2), (e)(3), and (g)(2)	Revised
640.51(c)	Revised
640.52(a)	Removed
640.56(c)	Revised
640.63(c)(3), (c)(5), (c)(12), and (c)(13)	Nomenclature change
640.65(b)(4) and (b)(5)	Revised
640.65(b)(8)	Revised
640.69(d)	Added
640.71(a)	Revised
640.72(a)(1)	Nomenclature change
	Revised

FDA received significant adverse comments on certain provisions of the rule, listed in table 2 of this document. Accordingly in this rulemaking, because these provisions became effective on February 11, 2000, the agency is amending these sections identified in table 2 of this document to reinstate the former provisions.

TABLE 2.—AMENDMENTS EFFECTIVE [insert date of publication in the FEDERAL REGISTER]

21 CFR Section	Action
606.3(j)	Revised
606.151(b) and (c)	Revised
640.2(b)	Revised
640.3(c)(1)	Revised
640.4(g)	Revised
640.4(g)(1), (g)(2), (g)(4), and (g)(5)	Revised introductory text
640.5	Revised
640.5(c)	Revised introductory text
640.15	Revised
640.16(a)	Revised
640.23(a)	Revised
640.24(b)	Revised
640.25(c) introductory text	amended
640.34(a) through (e)(1)	Revised
640.54(a)(2)	Revised
640.56(c) introductory text	Revised
640.62	Revised
640.63(c)(11)	Revised
640.71(a)	amended

Comments received by the agency regarding the reinstated portions of the rule will be applied to the corresponding portion of the companion proposed rule (64 FR 45375, August 19, 1999), and will be considered in developing a final rule using the usual Administrative Procedure Act notice and comment procedures.

**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, the direct final rule published on August 19, 1999 (64 FR 45366), is confirmed in part and 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 paragraph (j) to read as follows:

**§ 606.3 Definitions.**

\* \* \* \* \*

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

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

**§ 606.151 Compatibility testing.**

\* \* \* \* \*

(b) The use of fresh recipient serum samples less than 48 hours old for all pretransfusion testing.

(c) The testing of the donor's cells with the recipient's serum (major crossmatch) by a method that will demonstrate agglutinating, coating, and hemolytic antibodies, which shall include the antiglobulin method.

\* \* \* \* \*

**PART 640—ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS**

4. 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.

5. Section 640.2 is amended by revising paragraph (b) to read as follows:

**§ 640.2 General requirements.**

\* \* \* \* \*

(b) *Final container.* The original blood container shall be the final container and 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 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.

\* \* \* \* \*

6. Section 640.3 is amended by revising paragraph (c)(1) to read as follows:

**§ 640.3 Suitability of donor.**

\* \* \* \* \*

(c) \* \* \*

(1) A history of viral hepatitis;

\* \* \* \* \*

7. Section 640.4 is amended by revising the introductory text of paragraph (g) and by revising paragraphs (g)(1), (g)(2), (g)(4) and (g)(5) to read as follows:

**§ 640.4 Collection of the blood.**

\* \* \* \* \*

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

(1) One or more pilot samples shall be provided with each unit of blood when issued or reissued except as provided in § 640.2(c)(2) and all pilot samples 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 pilot samples accompanying a unit of blood shall be collected at the time of filling the final container by the person who collects the unit of blood.

\* \* \* \* \*

(4) All containers for pilot samples accompanying a unit of blood shall be attached to the whole blood container before blood collection in a tamperproof manner that will conspicuously indicate removal and reattachment.

(5) When CPDA-1 is used, pilot samples for compatibility testing shall contain blood mixed with CPDA-1.

\* \* \* \* \*

8. 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 pilot sample 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 pilot 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 may include tests for the Rh<sub>o</sub> variant (D<sup>u</sup>) and for other Rh-Hr factors. Blood may be labeled "Rh Negative" if negative to tests for the Rh<sub>o</sub> (D) and Rh<sub>o</sub> variant (D<sup>u</sup>) factors. If the test using Anti-D Blood Grouping Reagent is negative, but not tested for the Rh<sub>o</sub> variant (D<sup>u</sup>), the label must indicate that this test was not done. 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 serum is specifically designed to be effective.

\* \* \* \* \*

9. Section 640.15 is revised to read as follows:

**§ 640.15 Pilot samples.**

Pilot samples collected in integral tubing or in separate pilot tubes shall meet the following standards:

- (a) One or more pilot samples 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 pilot sample tubes shall be marked or identified so as to relate them to the donor of that unit of red cells.

(c) Before the final container is filled or at the time the final product is prepared, the pilot sample tubes to accompany a unit of cells shall be attached securely to the final container in a tamper proof manner that will conspicuously indicate removal and reattachment.

(d) All pilot sample tubes 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, in each instance by the person who performs the collection or preparation.

10. Section 640.16 is amended by revising paragraph (a) to read as follows:

**§ 640.16 Processing.**

(a) *Separation.* Within 21 days from date of blood collection (within 35 days from date of blood collection when CPDA-1 solution is used as the anticoagulant), 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 blood cells except when a cryoprotective substance is added for prolonged storage.

\* \* \* \* \*

11. 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 shall be tested as prescribed in §§ 610.40 and 610.45 of this chapter and § 640.5 (a), (b), and (c).

\* \* \* \* \*

12. 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 donor clinic 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 4 hours after the collection of the unit of whole blood or plasma.

\* \* \* \* \*

**§ 640.25 [Amended]**

13. Section 640.25 *General requirements* is amended in the introductory text of paragraph (c) by removing “Clinical Laboratories Improvement Act of 1967” and by adding in its place “Clinical Laboratories Improvement Amendments of 1988.”

14. Section 640.34 is amended by revising paragraphs (a) through (e)(1) to read as follows:

**§ 640.34 Processing.**

(a) *Plasma*. Plasma shall be separated from the red blood cells within 26 days after phlebotomy (within 40 days after phlebotomy when CPDA-1 solution is used as the anticoagulant), and shall be stored at -18 °C or colder within 6 hours 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 6 hours after phlebotomy and stored at -18 °C or colder.

(c) *Liquid Plasma*. Liquid Plasma shall be separated from the red blood cells within 26 days after phlebotomy (within 40 days after phlebotomy when CPDA-1 solution is used as the anticoagulant), and shall be stored at a temperature of 1 to 6 °C within 4 hours 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 4 hours after 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 to 24 °C or between 1 and 6 °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) *Modifications of Plasma.* It is possible to separate Platelets and/or Cryoprecipitated AHF from Plasma. When these components are to be separated, the plasma shall be collected as described in § 640.32 for Plasma.

(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 solid within 6 hours after phlebotomy.

\* \* \* \* \*

15. 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 within 6 hours after blood collection. 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.

\* \* \* \* \*

**§ 640.56 [Amended]**

16. Section 640.56 *Quality control test for potency* is amended in the introductory text of paragraph (c) by removing “Clinical Laboratories Improvement Act of 1988” and by adding in its place “Clinical Laboratories Improvement Amendments of 1988”.

17. Section 640.62 is revised to read as follows:

**§ 640.62 Medical supervision.**

A qualified licensed physician shall be on the premises 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.

18. Section 640.63 is amended by revising paragraph (c)(11) to read as follows:

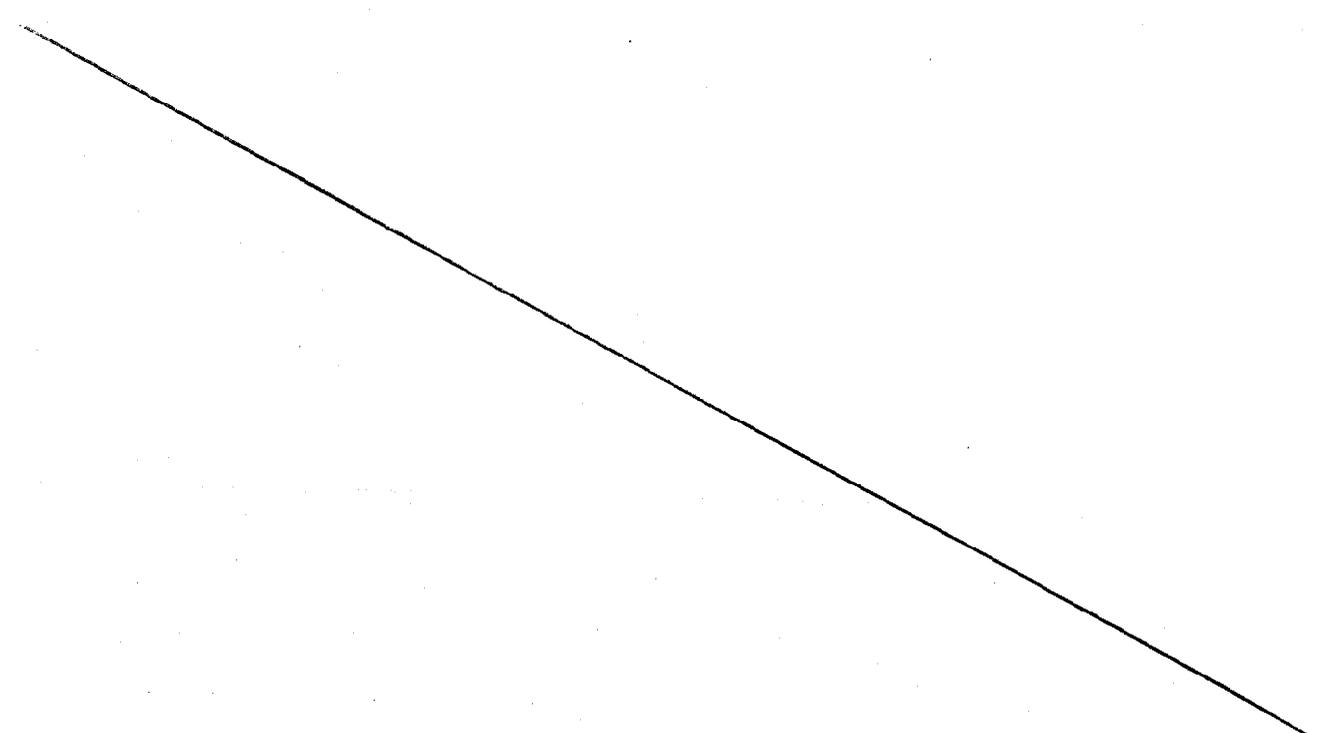
**§ 640.63 Suitability of donor.**

\* \* \* \* \*

(c) \* \* \*

(11) Freedom from a history of viral hepatitis;

\* \* \* \* \*



Jan 5, 2001  
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E. ...

§ 640.71 [Amended]

19. Section 640.71 *Manufacturing responsibility* is amended in the introductory text of paragraph (a) by removing “Clinical Laboratories Improvement Act of 1967” and by adding in its place “Clinical Laboratories Improvement Amendments of 1988”.

Dated: 12/29/00  
December 29, 2000.

Margaret M. Dotzel,  
Associate Commissioner for Policy.

CERTIFIED TO BE A TRUE  
COPY OF THE ORIGINAL

[FR Doc. 00-???? Filed ??-??-00; 8:45 am]

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