



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 606, 610, and 640

[Docket No. FDA-2003-N-0097] (formerly 2003N-0211)

Revisions to Labeling Requirements for Blood and Blood Components, Including Source Plasma

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is revising the labeling requirements for blood and blood components intended for use in transfusion or for further manufacture by combining, simplifying, and updating specific regulations applicable to labeling and circulars of information. These requirements will facilitate the use of a labeling system using machine-readable information that would be acceptable as a replacement for the “ABC Codabar” system for the labeling of blood and blood components. FDA is taking this action as a part of its efforts to comprehensively review and, as necessary, revise its regulations, policies, guidances, and procedures related to the regulation of blood and blood components. This final rule is intended to help ensure the continued safety of the blood supply and facilitate consistency in labeling.

DATES: This rule is effective [INSERT DATE 180 DAYS AFTER DATE OF PUBLICATION IN THE FEDERAL REGISTER].

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SUPPLEMENTARY INFORMATION:

I. Introduction

A. Background

This rule represents FDA's efforts to revise the regulations for blood and blood components. The rule consolidates most labeling requirements for blood and blood components, including Source Plasma, into one section of the Code of Federal Regulations (CFR). The rule also updates the regulations applicable to circulars of information.

In the Federal Register of July 30, 2003 (68 FR 44678), FDA published a proposed rule that proposed revisions to update requirements for storage and shipment of blood and blood components. FDA received numerous comments in response to these proposals, many of which opposed the changes primarily due to economic concerns. FDA has reviewed these comments and appreciates the concerns raised, and is currently reevaluating these proposals. (See discussion in section II.B of this document).

B. Development of the International Society of Blood Transfusion Code (ISBT) 128

In the Federal Register of August 30, 1985 (50 FR 35472), we published a notice of availability entitled "Guideline for the Uniform Labeling of Blood and Blood Components," which described the uniform container label for blood and blood components and recommended labels that incorporated barcode symbology known as "ABC Codabar."

Because the “ABC Codabar” system was becoming outdated, we asked the Blood Products Advisory Committee (BPAC), on March 23, 1995, whether there was persuasive evidence for us to allow conversion from “ABC Codabar” to International Society of Blood Transfusion Code 128 (ISBT 128), according to the International Council for Commonality in Blood Banking Automation (ICCBBA) proposed timetable. The BPAC voted in favor of accepting the proposed timetable by ICCBBA. The BPAC meeting transcript also indicates the Department of Defense’s and the blood industry’s, including America's Blood Centers’ and AABB’s (formerly known as American Association of Blood Banks), support of the move to ISBT 128 for blood and blood components for transfusion.

After the BPAC meeting, ICCBBA developed and submitted to FDA a draft standard entitled “United States Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128,” Version 1.2.0 (draft standard), recommending that ISBT 128 replace “ABC Codabar.” In the Federal Register of November 27, 1998 (63 FR 65600), we announced the availability of the draft standard and requested public comment on both the use of ISBT 128 and timeframes for implementation.

The ICCBBA revised the draft standard in response to public comment and submitted to FDA a revised draft standard entitled “United States Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128,” Version 1.2.0, dated November 1999 (the Version 1.2.0 Standard). We reviewed the new draft standard, the comments received in response to the Federal Register notice of November 27, 1998, and the Version 1.2.0 Standard, and concluded that conformance to the Version 1.2.0 Standard, prepared and reviewed by ICCBBA, would help facilitate the use of a uniform container label for blood and blood components. Thus, in the Federal Register of June 6, 2000 (65 FR 35944), we

announced the availability of a final guidance entitled “Guidance for Industry: Recognition and Use of a Standard for the Uniform Labeling of Blood and Blood Components” dated June 2000, which recognized as acceptable, except where inconsistent with the regulations, use of the Version 1.2.0 Standard and the implementation of the ISBT 128 uniform labeling system. This guidance identified two inconsistencies between the Version 1.2.0 Standard and the requirements in part 606 (21 CFR part 606) at § 606.121; the first inconsistency concerned the requirement that on container labels for Whole Blood the name of the applicable anticoagulant must immediately precede the proper name of the product (§ 606.121(e)(1)(ii)); and the second inconsistency concerned the requirement that the proper name of the product and any appropriate modifiers must be printed in solid red (§ 606.121(d)(2)).

In the Federal Register of August 19, 1999 (64 FR 45366), we published a direct final rule entitled “Revisions to the Requirements Applicable to Blood, Blood Components, and Source Plasma,” which amended § 606.121(d)(2) by adding “or in solid black,” thereby eliminating the inconsistency between the Version 1.2.0 Standard and § 606.121(d)(2), which had previously required that any modifier be printed in solid red.

In the “Guidance for Industry: Recognition and Use of a Standard for Uniform Blood and Blood Component Container Labels” dated September 2006 (<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm079004.pdf>), we recognized as acceptable, except where inconsistent with the regulations, use of the “United States Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128” version 2.0.0, dated November 2005 (the Version 2.0.0 Standard). In the guidance, we noted that the Version 2.0.0 Standard revised the Version 1.2.0 Standard and that there remained an inconsistency between

the Version 1.2.0 Standard, the Version 2.0.0 Standard and the requirements at § 606.121(e)(1)(ii). Since that guidance was issued, we have identified another inconsistency between the requirements under § 606.121(c)(2) and the Version 2.0.0 Standard regarding the requirement to include the FDA assigned registration number on blood and blood component labels. This final rulemaking addresses these inconsistencies by eliminating the existing inconsistencies between the Version 2.0.0 Standard and the requirements at § 606.121(c)(2) and (e)(1)(ii).

(FDA has verified the Web site addresses in this document, but FDA is not responsible for subsequent changes after this document publishes in the Federal Register.)

C. The Proposed Rule

In the Federal Register of July 30, 2003 (68 FR 44678), we published a proposed rule entitled “Revisions to Labeling and Storage Requirements for Blood and Blood Components, Including Source Plasma” (the proposed rule), to combine, simplify and update specific regulations applicable to container labeling and instruction circulars for all human blood and blood components, including Source Plasma. We also proposed to revise the shipping and storage requirements for certain human blood and blood components. Furthermore, we proposed the use of a labeling system using machine-readable information that would be acceptable as a replacement for the “ABC Codabar” system for labeling blood and blood components, and stated that we would also address the existing inconsistencies between the Version 1.2.0 Standard, and the existing regulations as described in section I.B of this document. We also intended to provide more flexibility for inventory management, and to update current requirements designed to ensure potency of the blood components over time by revising the current storage and shipping temperature requirements for frozen noncellular blood components, both for transfusion

and for further manufacture (e.g., Cryoprecipitated Antihemophilic Factor, Fresh Frozen Plasma, and Source Plasma).

We note that the proposed rulemaking inadvertently included proposed changes to § 606.121(c)(13) (68 FR 44678 at 44686), which were inconsistent with a previously proposed amendment to § 606.121(c)(13) in an earlier, related proposed rule entitled “Bar Code Label Requirement for Human Drug Products and Blood” that published in the Federal Register of March 14, 2003 (68 FR 12499). To eliminate any confusion, we published a correction to the proposed rule in the Federal Register of October 27, 2003 (68 FR 61172), and published the related, final rule entitled “Bar Code Label Requirements for Human Drug Products and Blood” in the Federal Register of February 26, 2004 (69 FR 9120). We also note that the proposed rulemaking inadvertently omitted the requirement in current 21 CFR 640.70(a)(7) that requires that for Source Plasma, in the case of immunized donors, the label must state the immunizing antigen. In this final rule, we have corrected this omission and have placed this requirement in redesignated § 606.121(e)(5)(vi).

Regarding the term “communicable disease testing,” used in this final rule, we noted in the proposed rule (68 FR 44678 at 44684) that the terms “infectious agent testing” and “communicable disease testing” (used interchangeably in the proposed rule and in guidance documents) refer to the same testing performed in accordance with § 610.40 (21 CFR 610.40). We also noted that the term “infectious agent” is used rather than “communicable disease agent” for consistency with labeling approved by the Director, Center for Biologics and Evaluation Research (CBER), for the Version 1.2.0 Standard and the “ABC Codabar” System. In this final rule, as well as in the Version 2.0.0 Standard, the terms “infectious agent testing” and

“communicable disease testing” continue to be used interchangeably and refer to the same testing performed in accordance with § 610.40.

II. Revisions to the Proposed Rule

A. Requirements Finalized in This Rule

This rule:

- Finalizes, in part, the proposed requirements for labeling for blood and blood components intended for use in transfusion or further manufacture by all blood establishments, and specific regulations applicable to container labeling and circulars of information;
- Eliminates the two remaining inconsistencies between the Version 2.0.0 Standard and the regulations, described in section I.B of this document;
- Facilitates the use of a labeling system using machine-readable information that would be acceptable as a system for labeling blood and blood components, and the use of new labeling systems that may be developed in the future;
- Consolidates regulations applicable to labeling standards so that most labeling requirements for all blood and blood components, including Source Plasma, found previously in §§ 606.121 and 640.70, can now be found in § 606.121;
- Updates some of the consolidated regulations;
- Replaces “shall” with “must” in all places wherever it appears in the regulations;
- Retitles part 606, subpart G; and
- Makes other, necessary conforming changes, and technical amendments.

B. Requirements Not Finalized in This Rule

At this time, we are not finalizing the proposed requirements for storage and shipping temperatures of certain human blood and blood components, including Source Plasma, because

we are continuing to reevaluate these proposals, taking into account the adverse comments received. Under the proposed rule, we proposed revisions to the labeling requirements regarding storage and shipping temperatures for frozen noncellular blood components in current part 640 (21 CFR part 640) at § 640.70(a)(3) and (b). We also proposed revisions to storage and shipping temperatures in current §§ 600.15 (21 CFR 600.15), 610.53, 640.34, 640.54, 640.69, and 640.76 to help ensure the potency of the frozen noncellular blood components and for consistency between the labeling regulations and the regulations concerning shipping and storage temperatures of frozen noncellular blood components. By updating the storage and shipping temperature requirements and addressing as many labeling changes as possible at one time, we had believed that the proposed rule would limit the number of times establishments would have to revise container labels.

However, we have concluded, based on comments received, that we should reevaluate the proposed revisions to the requirements for storage and shipping temperatures. For example, we received comments from the plasma fractionation industry stating that the proposed freezing/storage temperature of -30°C was below the temperature that would be acceptable to preserve product activity, would be very costly to implement, and would pose a safety hazard to employees working in that environment. In the Federal Register of August 9, 2004 (69 FR 48250), we announced a public workshop entitled “Development of Plasma Standards” that was held August 31 and September 1, 2004. The objective of the workshop was to gather information on current industry practices that are in place for the manufacture of plasma. We also discussed this issue at a March 17, 2005, BPAC meeting and at an April 2, 2009, BPAC meeting.

FDA intends to consider revising storage requirements in the future, based on our review of scientific literature, data from other regulatory authorities and the plasma fractionation industry, and input from BPAC. Based on the information received, we intend to develop standards for the preparation, labeling, storage, and shipping of frozen noncellular blood components for transfusion and for further manufacture.

C. Conforming and Clarifying Changes

This final rule removes § 640.70 from the CFR, and accordingly, we have made conforming changes to § 610.40(h)(2)(ii)(B) and § 640.74(b)(4) both of which currently reference § 640.70. In § 610.40(h)(2)(ii)(B), we have deleted the reference to § 640.70. In § 640.74(b)(4), we have deleted the reference to § 640.70(a) and replaced it with § 606.121 and have deleted the reference to § 640.70(a)(3) and replaced it with § 606.121(e)(5)(ii).

We also made a conforming change to § 610.40(i) to cross-reference another existing requirement for a serological test for syphilis under § 640.65(b)(1)

We also made a conforming change to § 606.121(c)(13)(iii)(D) to cross-reference other existing requirements under § 606.121(c)(9) and § 606.121(i)(5).

We are clarifying proposed § 606.121(i)(4) by removing the phrase “unless exempt under” to “except as provided in.” This clarifying change will not affect the substantive requirements in this regulation.

Further, we made two clarifying changes to § 606.122(f) by changing “statements” to “statement” and replacing the period after “Warning” with a colon, so that the provision now reads in its entirety, “The statement: ‘Warning: The risk of transmitting infectious agents is present. Careful donor selection and available laboratory test do not eliminate the hazard.’”

D. Technical Amendment

We have made a technical amendment to § 606.170 to clarify that reports of the investigation of a fatality must be submitted to CBER either by mail, facsimile, or electronically transmitted mail; and to provide mailing address information for the Director, Office of Compliance and Biologics Quality, CBER.

Further, we have made a technical amendment to § 606.121(e)(2)(i) to require that with the exception of those products listed in § 606.121(e)(2), red blood cell product labels must include the type of additive solution with which the product was prepared.

III. Comments on the Proposed Rule and FDA's Responses

We received approximately 24 comments on the proposed rule. These comments were received from blood establishments, private and public interest groups, and the general public. All of the comments expressed opinions on the proposed revisions to the storage and shipping temperature requirements; about 12 of the comments commented on the proposed labeling requirements. Because we are not finalizing the proposed storage and shipping temperature requirements at this time, this document does not discuss those issues. This document discusses information relevant to and comments concerning the proposed revisions to the labeling requirements. To make it easier to identify comments and our responses, the word "Comment," in parentheses, will appear before the description of comments, and the word "Response," in parentheses, will appear before our responses.

A. General

(Comment 1) Numerous comments supported the proposed revisions to consolidate, simplify and update the regulations applicable to container labeling and the instruction circular; one comment stated that the changes were "long overdue." Several comments applauded our efforts to develop a proposed rule that will facilitate the implementation of "machine-readable"

bar code standards and strongly endorsed the use of ISBT 128 as a unifying bar code standard for blood and blood components, which will improve patient safety. In addition, one of these comments noted that one bar code standard would lower the implementation costs related to the standard and would allow for the exchange of inventories so that the needs of patients everywhere could be more easily met.

(Response) We appreciate these supportive comments. We agree that this rule facilitates the use of the ISBT 128 machine readable labeling system for blood components by eliminating FDA requirements that are inconsistent with the use of the ISBT system. We note that once the this rule is in effect, licensed establishments will no longer need to request a variance from the regulations to fully implement the ISBT system – thus we anticipate that the new rule will save both industry and FDA resources. In addition, the rule updates current labeling requirements to ensure appropriate and complete labeling of all blood and blood components for infectious disease test results, including recovered plasma for further manufacturing. In these ways, the rule will support the safety of the nation’s blood supply.

At the same time, we are preserving for industry the option of using the older labeling system, “ABC Codabar.”

(Comment 2) One comment expressed concern that consolidating the labeling requirements for Source Plasma and other blood components into the same CFR section may make it more difficult to identify the applicable labeling requirements, and suggested as an alternative that we consolidate requirements into a single section with a subsection dedicated to requirements specific to Source Plasma. Another comment noted that consolidating requirements into one section has both advantages and disadvantages. This comment noted that the manufacture of Source Plasma is significantly different from the manufacture of blood

components for transfusion. The comment also noted that other blood products, which are markedly different from blood components for transfusion, have separate labeling requirements in the CFR (e.g., Albumin (part 640, subpart H), Plasma Protein Fraction (part 640, subpart I), and Immune Globulin (part 640, subpart J)). The comment noted that for consistency, we should maintain separate labeling requirements for Source Plasma in part 640, subpart G, and instead revise § 640.70 to require labeling statements based on communicable disease testing.

Two comments noted that a requirement for all test results to be recorded on the product label is not consistent with current industry practice for recovered plasma. See response to comment 8 for further information.

(Response) One purpose of the proposed rule was to consolidate the labeling regulations that apply to blood and blood components in one place in the CFR, including blood components that are used for further manufacture. Not all blood components that are used for further manufacture currently have additional standards in part 640, e.g., recovered plasma. In § 606.121, we have consolidated the labeling requirements for blood and blood components intended for use in transfusion or further manufacture. To clarify this point, in § 606.121(a), we have deleted the phrase “including Source Plasma” from the proposed language and added instead “intended for use in transfusion or further manufacture.” We have also revised § 606.121(c)(11) to require that if the product is intended for further manufacturing use, a statement listing the results of all the tests for communicable disease agents required under § 610.40 for which the donation has been tested and found negative must be on the container label; except that the container label for Source Plasma is not required to list the negative results of serological syphilis testing under § 610.40(i) and § 640.65(b).

In response to comments regarding current industry practice for negative labeling of recovered plasma for further manufacture, we believe that it is current industry practice to include the communicable disease test results for recovered plasma on the container label. See the response to comment 8 for full details.

(Comment 3) One comment requested that in addition to the revisions in this final rule, we make changes to further streamline the labeling submission process for on-demand ISBT 128 labels.

(Response) The comment is beyond the scope of this final rule. However, we will consider the comments on this issue at a later date.

(Comment 4) One comment requested more flexibility on tie-tags used for autologous donations, suggesting that a computer system-generated ABO blood group and Rh type (ABO/Rh) label be applied to the tie-tag as opposed to the current practice of hand writing the ABO/Rh result on the tag and on the “For Autologous Use” label. The comment stated that this change would eliminate the need for handwritten information, thus reducing the likelihood of human error, thereby improving patient safety.

(Response) The comment regarding the use of a computer system-generated ABO/Rh label is beyond the scope of this final rule. However, we note that in the final rule published in the Federal Register of February 26, 2004 (69 FR 9120), entitled “Bar Code Label Requirements for Human Drug Products and Biological Products,” we revised § 606.121(c)(13) to require that the ABO blood group and Rh type of the donor be present in machine-readable format on the container label of all blood and blood components, including autologous units. This requirement is consistent with ISBT 128 standards but requires those manufacturers using “ABC Codabar” to

affix an ABO/Rh bar code label to the “For Autologous Use Only” label on blood and blood components bearing the autologous label. In this final rule, we have amended § 606.121(i)(5) to permit each container label of blood and blood components intended for autologous use and obtained from an unsuitable donor or one who is reactive for evidence of infection due to communicable disease agents under § 610.40 to include the ABO and Rh blood group and type. However, such labeling is not required.

B. 21 CFR 606.121(b)

The proposed rule amended § 606.121(b) by adding the phrase “with any appropriate modifiers and attributes” to clarify that the label provided by the collecting facility may be altered under certain circumstances and may be altered multiple times to adequately identify the contents of a container. Examples of appropriate modifiers include “washed,” “frozen,” and “liquid.” Examples of appropriate attributes include “irradiated” and “divided,” which would indicate a process change. We have finalized these requirements as proposed, including the conforming amendments to §§ 606.121(c)(1) and 606.121(d)(2). In addition, we have added the clarifying phrases “of the product” and “considered finished products” to § 606.121(b). In this section III.B, we describe two examples of circumstances where it is acceptable to alter the label of blood components as finished products after they have been prepared. We note that it is appropriate to revise the label each time, after the finished product has been prepared.

In the preamble of the final rule entitled “Current Good Manufacturing Practice for Blood and Blood Components; Uniform Blood Labeling” published in the Federal Register of August 30, 1985 (50 FR 35458), we responded to a comment (comment number 2) that suggested that the only instance in which labels are permitted to be altered pursuant to § 606.121(b) is when blood components are removed from the product. In the response, we noted, that there are

certain cases when no blood components are removed from a unit, but the unit may nonetheless require relabeling. *Id.* at 35459. For example, such relabeling would be appropriate when the product is further processed by freezing, pooling, washing, or irradiating, provided that the establishments have a validated process for this additional processing. The original label would need to be modified to include the additional information and then reprinted and the product relabeled, i.e., a new label placed over the original label, to accurately identify the product.

Another specific circumstance in which the label of a blood product may be altered under § 606.121(b) is when the original label may need to be recreated because the original bag is destroyed while the product is further processed by, for example, freezing, pooling, washing, or irradiation. The recreated label may be placed on the new bag under applicable regulations and the establishment's standard operating procedures.

C. 21 CFR 606.121(c)(2)

In the proposed rule, we proposed amending § 606.121(c)(2) by replacing “registration number” with “unique facility identifier.” Although, as we discussed in the preamble to the proposed rule (68 FR 44678 at 44683), the FDA-assigned registration number is acceptable as a “unique facility identifier,” we wanted to be able to provide for the use of other recognized donation facility identification numbers, such as the ISBT facility code (which includes machine-readable information). In addition, we proposed removing the requirements of current § 640.70(a)(10) for “name, address, and license number” on the Source Plasma label because they are included in proposed § 606.121(c)(2).

(Comment 5) One comment suggested that this change imposes an additional requirement on collectors of Source Plasma operating multiple sites under a single license.

(Response) FDA believes that the final rule addresses this concern. In consideration of this comment, we are not requiring the container label for blood components for further manufacture to contain a unique facility identifier at this time, because we believe that the blood establishment's FDA approved product label contains sufficient information to permit identification of the collection facility. Regarding Source Plasma, we have learned that most collection facilities include a unique facility identifier on the container label. We agree that this is useful information for identifying the location where the Source Plasma was collected.

The final rule requires a unique facility identifier for the container label of blood and blood components intended for transfusion, to aid in identifying the location where the blood or blood component was collected or processed. We note that the final rule provides flexibility by using the term "unique facility identifier," which may be satisfied by using an establishment's registration number, the FDA establishment identifier, an ISBT facility code, or other designation that will allow identification of the specific location where the blood or blood component was collected or processed. For example, a blood establishment may incorporate its unique facility identifier into the blood component donor, lot, or pool number and use a validated computer or other recordkeeping system that will enable identification of the facility that collected that blood or blood component.

(Comment 6) One comment expressed concern that their current approved labels do not contain a unique site specific identifier that was assigned by FDA, other than the license number, and that the effective date for the final rule should provide adequate time for implementation to allow for label design, acquisition, procedural changes, and depletion of available stock to minimize transition costs.

(Response) Anticipating the need to deplete existing label stock, the effective date for the final rule (refer to section VIII of the proposed rule) (68 FR 44678 at 44685) provides reasonable time for use of the existing label stock. The final rule becomes effective 180 days after the date of publication in the Federal Register.

D. 21 CFR 606.121(c)(10)

The proposed rule combined current § 606.121(c)(11) and part of current § 640.70(a)(2) and redesignated the combined regulations as proposed § 606.121(c)(10). In addition, FDA proposed to revise § 606.121(c)(10) by adding a phrase to the first sentence to clarify that blood and blood components intended for further manufacture are subject to these requirements. Furthermore, FDA proposed to revise § 606.121(c)(10) by adding an alternative warning statement and provided for the use of “other cautionary statements as approved by CBER.” FDA now is finalizing the above amendments as proposed (including deleting current § 606.121(e)(5)(ii)), because it is now redundant in light of new § 606.121(c)(10)).

(Comment 7) Two comments suggested that it is difficult to select the proper cautionary statement to use because information regarding cautionary statements can be found in other sections of the CFR, as well as in certain FDA guidance documents.

(Response) We acknowledge that the circumstances surrounding which cautionary statement to use may vary. We believe that the consolidation of the labeling requirements in this rulemaking for blood and blood components for further manufacture, including Source Plasma, should enhance industry’s ability to select the appropriate cautionary language. We also note that reference 1 and reference 2 to this rulemaking provide general guidelines about the uniform labeling of blood and blood components. Further, we suggest that the commenters may want to pose any specific questions to CBER to obtain further guidance.

E. 21 CFR 606.121(c)(11)

We had proposed to redesignate and combine current §§ 640.70(a)(8) and (a)(11) as § 606.121(c)(11) and to revise redesignated § 606.121(c)(11) to require labeling statements indicating the results of communicable disease tests performed. The proposed change provided that the labeling requirements apply to all blood and blood components for further manufacture, including Source Plasma, and would require establishments to label products for further manufacture with the results of communicable disease testing for which the donation has been tested and found negative.

(Comment 8) Some comments expressed concern regarding the resulting burdens from consolidating previously referenced requirements into § 606.121. One comment requested that § 606.121(c)(11) be re-worded to indicate that communicable disease tests performed on a sample from the donor of the unit are listed in the current circular of information, thus providing a much simpler and more flexible method of meeting labeling requirements without the expense of constantly changing labels. Additionally, the comment stated that use of the circular of information would also address concerns regarding the shipment of positive units for further manufacture, by labeling only the positive units or alternatively recommended continuing the current method of noting “positives” on the shipping form.

In addition, as discussed previously, regarding recovered plasma, two comments stated that a requirement for all test results to be recorded on the product label is not consistent with current industry practice. The comments indicated that to require constant updating of labels to report all negative test results is counterproductive to the positive labeling aspects of the proposed rule, and requested that this requirement be deleted from the final rule.

(Response) FDA disagrees with the comments related to the use of the circular of information to list communicable disease test results. We believe that it is not appropriate to reword proposed § 606.121(c)(11) to require that information on communicable disease testing performed on components intended for further manufacture be included in the circular of information because the circular of information applies only to transfusable products and not to products intended for further manufacture.

We note that we have periodically addressed the uniformity of labeling. For example, we announced the availability of the final guideline entitled “Guideline for Uniform Labeling of Blood and Blood Components” dated August 1985, which described acceptable criteria for labels consistent with current good manufacturing practice regulations for blood and blood components (part 606)

(<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM080974.pdf>). The guideline included illustrated labels for certain blood components used for further manufacture (e.g., Source Plasma, recovered plasma, and Source Leukocytes), that had been reviewed and approved by FDA. We also issued “Guidance for Industry: Recognition and Use of a Standard for Uniform Blood and Blood Component Container Labels” dated September 2006, which recognizes the “United States Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128,” dated November 2005, as an acceptable standard for blood and blood component container labels, except where inconsistent with the regulations.

(<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM079159.pdf>). As discussed in section I.B of this document, we further note that this final rulemaking addresses the inconsistencies that existed.

FDA also disagrees with the comments concerning the labeling of recovered plasma because we believe they are incorrect. We believe it is the usual and customary practice of the blood industry to label the container label of blood and blood components for further manufacture with the negative communicable disease test results of all the tests for communicable disease agents required under § 610.40, except for Source Plasma with respect to serological syphilis testing. We are therefore finalizing the requirement in this rulemaking that the label of blood and blood components for further manufacture must include a statement listing the results of all the tests for communicable disease agents required under § 610.40 for which the donation has been tested and found negative except that the label for Source Plasma is not required to list the negative results of serological syphilis testing under §§ 610.40(i) and 640.65(b).

(Comment 9) One comment noted that consistent with §§ 610.40(i) and 640.65(b)(1), Source Plasma is unique because a serological test for syphilis is performed at intervals of no more than 4 months, rather than at each individual donation. The comment requested clarification on whether syphilis is considered a “communicable disease agent” and if the labeling of serological syphilis testing results is required on units of Source Plasma. This comment also expressed the concern that requiring syphilis test results on each Source Plasma unit would be burdensome for industry because it is current industry practice to pre-label Source Plasma with required communicable disease testing results.

(Response) As noted previously in the response to comment 8, we are not finalizing § 606.121(c)(11) as proposed. We will therefore answer this comment in light of the revised provisions of § 606.121(c)(11). Syphilis is deemed to be a communicable disease agent; the testing requirements for which are included in part 610, subpart E (Testing Requirements for

Communicable Disease Agents), specifically § 610.40(i). Section 610.40(i) incorporates the requirement in § 640.65(b) to test a Source Plasma donor using a serological test for syphilis at the donor's initial examination and at least once every four months thereafter. (More limited testing for Source Plasma reflects the reduced risk presented by syphilis infected collections of Source Plasma. In an FDA Compliance Policy Guide revised in 1995, FDA observed that "the disease-causing spirochetes are destroyed during the storage and/or fractionation of the [source] plasma.")¹

Under § 606.121(c)(11) as finalized, the label for blood and blood components intended for further manufacture must list the results of all the tests for communicable disease agents required under § 610.40 for which the donation has been tested and found negative; except that the container label for Source Plasma is not required to list the negative results of serological syphilis testing under § 610.40(i) and § 640.65(b). This is because the regulations do not require that each Source Plasma donation be tested for syphilis. In the absence of test results for each donation (e.g., in connection with donations made in month three) or where testing for syphilis was performed and the test was negative, the label is silent. When testing is performed and is reactive for syphilis, the label for the unit associated with the positive test and the label for the unit of any donation(s) made after obtaining the test results must appropriately disclose that the Source Plasma tested reactive by a serologic test for syphilis as described in § 606.121(e)(5)(iv).

More generally, concerning the pre-labeling of Source Plasma, it is FDA's expectation that tests for required infectious disease tests are completed prior to shipment of the Source Plasma for further manufacture to the fractionator or for distribution. However, we also recognize that in certain circumstances, nucleic acid test (NAT) testing of Source Plasma may take an extended period to resolve positive NAT pools to identify an individual positive unit.

¹ <http://www.fda.gov/ICECI/ComplianceManuals/CompliancePolicyGuidanceManual/ucm073876.htm>.

Additionally, we recognize the difficulty of placing a “label” on a frozen product. We note that Source Plasma may be labeled and then may be shipped for pre-release storage at another facility while still under the manufacturer’s control due to the manufacturer’s storage limitations. This raises the question of whether it is acceptable for a manufacturer to pre-label (at the time of collection) Source Plasma as “tested and found negative” while performing NAT testing and shipping such products under quarantine (i.e., while still under the manufacturer’s control) and delaying release and distribution until all the test results are obtained.

Under the revised regulation, if the product is intended for further manufacturing use, a statement listing the results of all the tests for communicable disease agents required under § 610.40 for which the donation has been tested and found negative must be listed on the container label; except that the container label for Source Plasma is not required to list the negative results of serological syphilis testing under § 610.40(i) and § 640.65(b). In addition, blood and blood components intended for further manufacture must be labeled in accordance with § 610.40, when the donation has been tested and demonstrates evidence of infection due to a communicable disease agent(s).

Under § 606.121(c)(11) as finalized, it is acceptable for Source Plasma manufacturers to place the label indicating negative communicable disease test results on the product prior to completion of communicable disease testing (pre-label) as long as either (1) The unit is shipped to a storage facility and remains under quarantine control by the collection establishment until all testing is completed and accurately reflected on the label or (2) the unit is not released and distributed into interstate commerce until the results from all communicable disease tests are obtained and accurately reflected on the label. Thus, the requirements under §§ 606.121(c)(11) and 610.40 are not fulfilled until the container label accurately lists the results obtained from all

communicable disease testing required under § 610.40. At that time, the product is ready for distribution and release into interstate commerce.

In the event that a shipped unit is pre-labeled with a negative test result but is later found positive upon completed testing, that unit must be relabeled in accordance with § 610.40, including obliteration of the negative result.

F. 21 CFR 606.121(e)(2)(i) and 21 CFR 606.121(e)(5)(vi)

In finalizing this rulemaking, we have amended § 606.121(e)(2)(i) to require that with the exception of those products listed in § 606.121(e)(2), red blood cell product labels must include the type of additive solution with which the product was prepared as this information is useful when making determinations in connection with the shelf life of the product. For example, red cell additive solutions (e.g., AS-1, AS-3, AS-5) provide nutrients to the blood components which in turn allows for an extended shelf life. We note that the labeling of the container with the additive solution is also industry practice.

We proposed to redesignate current § 640.70(a)(7) as § 606.121(e)(5)(vi). We also proposed to update redesignated § 640.70(a)(7) to broaden the labeling requirements to include collections from donors who are not immunized but are in specific collection programs. The proposal replaced the term “normal donor” with the term “nonimmunized donor.” After consideration, we have determined that “nonimmunized donor” is not a recognized term, and we will continue to use the term “normal donor.”

G. 21 CFR 606.122

We proposed to amend § 606.122 by revising the introductory paragraph and paragraphs (e), (f), and (m). We received comments only on the heading of this regulation, “Instruction circular,” which we did not propose to change, and paragraphs (e) and (m).

1. Title for § 606.122

(Comment 10) A few comments desired consistency between § 606.121(c)(8)(ii), which refers to the “Circular of Information,” and § 606.122, which refers to the “Instruction circular.” One comment suggested revising § 606.121(c)(8)(ii) to use the same language in the AABB “Standards for Blood Banks and Transfusion Services”: “See Circular of Information for the Use of Human Blood and Blood Components.”

(Response) We agree that there should be consistency between §§ 606.121(c)(8)(ii) and 606.122. We are therefore revising the title of § 606.122 and the corresponding language in §§ 606.122(k), (l), (m), and (n) by replacing “Instruction circular” with “Circular of Information” to be consistent with the wording required on labels of blood and blood components for transfusion, as illustrated in the “Guideline for the Uniform Labeling of Blood and Blood Components” and the “United States Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128,” dated November 2005, (<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM079159.pdf>). However, although it is a common industry practice for blood establishments to refer to the "Circular of Information for the Use of Human Blood and Blood Components," we decline to change § 606.121(c)(8)(ii) as suggested because existing regulations do not preclude blood establishments from creating their own circulars of information to address the labeling standards required in § 606.122. Moreover, § 606.121(c)(8)(ii) is consistent with labeling approved by the Director, CBER, i.e., ISBT 128 and “ABC Codabar.”

2. 21 CFR 606.122(e) and 21 CFR 606.122(f)

We proposed that the instruction circular contain statements regarding the results of each infectious agent for which the blood was tested, including all FDA required tests, and found negative. We have decided to clarify that under § 606.122(e), a product intended for transfusion must include a statement that the product was prepared from blood that was found negative when tested for communicable disease agents as required under § 610.40 (include each test that was performed). We also proposed to amend § 606.122(f) by updating the warning statement to reflect the risk associated with the communicable disease agents for which testing is currently performed. We have decided to keep the currently required statement but note that we have made two clarifying changes to this statement by changing “statements” to “statement” and replacing the period after “Warning” with a colon, so that the provision now reads in its entirety, “The statement: ‘Warning: The risk of transmitting infectious agents is present. Careful donor selection and available laboratory tests do not eliminate the hazard.’” to be consistent with the warning statements reflected in the current Circular of Information.

(Comment 11) One comment supported the change if they correctly interpreted “name each infectious agent” as requiring a list of infectious agents, and opined that it is not necessary to “name” each type of test that is performed for each infectious agent. For example, according to the comment, it is not necessary to list both antibody tests and nucleic acid tests. Another comment recommended that either § 606.121(c)(11) or § 606.121(c)(8)(ii) should be revised to require the label to bear a statement “See Circular of Information *** results of infectious agent testing.”

(Response) We do not agree that the infectious agent need only be listed once on the labeling for both transfusable products and products for further manufacturing if the blood or blood component was tested by different tests for the same infectious agent. We have revised § 606.122(e) to clarify that the circular of information must list the results of all donor screening tests for communicable disease agents required under § 610.40 for which the blood or blood component was tested and found negative (e.g., negative for antibodies to HIV and Non-reactive for HIV-1 RNA). We interpret “negative” to include “Non-reactive.” In response to the suggestion to revise § 606.121(c)(11), we refer to our response to comment 8. As noted in that response, we are not finalizing § 606.121(c)(11) as proposed. We also believe that it is not practical to revise § 606.121(c)(8)(ii) to require a statement of all negative test results on the container label of blood and blood components for transfusion, due to space limitations on the container label. We believe that the circular of information is the best place to list this type of information.

3. 21 CFR 606.122(m)(3)

The proposed rule proposed to clarify that the instruction circular must contain, when applicable, instructions to begin administration of plasma within “a specified time” after thawing.

(Comment 12) One comment requested clarification of § 606.122(m)(3) and suggested that the current statement in the Circular of Information for the Use of Human Blood and Blood Components, “Transfusion should be completed within four hours and prior to component expiration,” could be used.

(Response) We do not want to establish in regulation a specified time to begin or complete the transfusion of a plasma component. Instead, we believe that it is appropriate to

provide industry with increased flexibility for developing and specifying timeframes for which thawed plasma components can still be used for transfusions if stored at appropriate temperatures per industry standards. We are therefore finalizing the amendment to § 606.122(m)(3) as proposed.

H. Concerns About Labeling for Transfusable Products

(Comment 13) One comment asked if manufacturers of licensed products will have to resubmit labels for approval, citing that such a requirement would add to the cost of compliance and impact the ability of some centers to support out-of-state regions in need of blood during FDA label review/approval process time.

(Response) This rulemaking, in part, updates existing regulations to be consistent with current practice. Under the final rule, licensed manufacturers who have FDA approved container labels that meet the requirements of the final rule do not have to resubmit their labels for approval. If a manufacturer wishes to make labeling changes, a supplement submission must be submitted to FDA consistent with the requirements under § 601.12(f)(1) (21 CFR 601.12(f)(1)).

(Comment 14) One comment expressed concern that the proposed revision to § 606.121(c)(2) will change the commenter's current FDA approved labels and will cost blood establishments approximately \$40,000 annually in registration and licensing fees if ISBT or a similar system is utilized. A substantial additional cost will be involved in the purchase of printers, scanners, bar code readers, validation, and training.

(Response) We are not requiring blood establishments to utilize the ISBT labeling system. Blood establishments may continue to use the "ABC Codabar" system. Both of these systems are acceptable labeling under the bar code requirements.

IV. Legal Authority

FDA is issuing this rulemaking under the biological products provisions and the communicable diseases provisions of the Public Health Service Act (PHS Act) (42 U.S.C. 216, 262, 263, 263a, 264, 300aa-25), and the drugs, devices, and general administrative provisions of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 360, 360c, 360d, 360h, 360j, 371, 372, 374 and 381). Under these provisions of the PHS Act and the Federal Food, Drug, and Cosmetic Act, we have 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.

V. Analysis of Economic Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612), and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct 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 Agency believes that this final rule is not a significant regulatory action under Executive Order 12866.

The Regulatory Flexibility Act requires Agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. Because the requirements of the final rule are either consistent with industry practice or would be industry practice absent existing prohibitions, the Agency certifies that the final rule will not have a significant economic impact on a substantial number of small entities.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that Agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100,000,000 or more (adjusted annually for inflation) in any one year.” The current threshold after adjustment for inflation is \$136 million, using the most current (2010) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in any 1-year expenditure that would meet or exceed this amount.

A purpose of the final rule is to simplify and unify the existing labeling standards. Labeling standards are currently found in multiple sections of the regulations and these amendments would move these standards to one section of the regulations. Through our revising, consolidating, and redesignating these regulations, parties wishing to understand the labeling requirements will be able to refer to a single source. This final rule also includes provisions that add flexibility to the regulations that should lower the cost of compliance.

In the proposed rule, we asserted that the new labeling requirements were consistent with current industry practice and did not impose an additional burden. We received comments stating that the proposed labeling requirements for including all communicable disease test results and a unique facility identifier on the product label did not conform to current industry practice for certain blood and blood components intended for further manufacture. In the final rule, as a result of these comments, we revised these requirements. We have also amended § 606.121(e)(2)(i) to require that certain red blood cell product labels must include the type of additive solution with which the product was prepared. We believe that the labeling requirements of the final rule conform to current industry practice.

The final rule requires a change in the circular of information to reflect current testing practices. Existing labeling regulations do not allow the circular to reflect current required testing or to adjust to future changes in required testing or plasma thawing procedures. We believe the circular of information would already be in compliance with the final rule amendments and reflect current requirements and practices if compliance were permitted by existing regulations. As the circular is updated regularly, we believe any required changes can be made in the ordinary revision cycle at a cost too small to reliably quantify.

Overall, because the requirements of this final rule are either industry practice or would be industry practice absent existing prohibitions, estimated costs are negligible. We believe this action to be beneficial as it increases flexibility and lowers compliance costs. Because we believe costs to any entity will be too small to reliably quantify, we certify that this final rule will not have a significant impact on a substantial number of small entities.

VI. Environmental Impact

The Agency has determined under 21 CFR 25.30(h) 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.

VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the final rule does not contain policies that have substantial direct effect on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, FDA has concluded that the final rule does not contain policies that

have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VIII. The Paperwork Reduction Act of 1995

This final 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 (44 U.S.C. 3501-3520). The title, description, and respondent description of the information collection provisions are shown in this section VIII with a discussion of the information collection burden.

Title: Revisions to Labeling Requirements for Blood and Blood Components, Including Source Plasma.

Description: FDA is consolidating the regulations related to labeling blood and blood components. Regulations for labeling of all blood and blood components would be consolidated in §§ 606.121(Container label) and 606.122 (Circular of information).

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

Burden Estimate: Section 606.121(c)(11) requires that if the product is intended for further manufacturing use, a statement listing the results of all the tests for communicable disease agents required under § 610.40 for which the donation has been tested and found negative must be on the container label; except that the label for Source Plasma is not required to list the negative results of serological syphilis testing under §§ 610.40(i) and 640.65(b). The Agency believes that as a part of industry's usual and customary labeling business practices, industry currently labels blood and blood components for further manufacture with the results of required testing found in § 610.40. In addition, § 606.121(e)(2)(i) requires that certain red blood

cell product labels must include the type of additive solution with which the product was prepared. The Agency believes that this labeling requirement of the final rule also is part of usual and customary industry practice.

Because the Agency believes the rule amendments and the information collection provisions under § 606.121(c)(11) and (e)(2)(i) in the final rule are part of usual and customary business practice and do not create any new burden for respondents, FDA is not estimating the burden associated with the information collection provisions in this final rule.

The collection of information requirements under §§ 606.121 and 606.122 are approved under OMB control number 0910-0116; in § 640.70 have been approved under OMB control number 0910-0338.

To comply with section 3506(c)(2)(A) of the PRA (44 U.S.C. 3506(c)(2)(A)), elsewhere in this Federal Register, FDA is publishing a notice of the proposed collection of information set forth in this document. The collection of information provisions of this final rule have been submitted to OMB for review. Prior to the effective date of this final rule, FDA will publish a notice in the Federal Register announcing OMB's decision to approve, modify, or disapprove the new collection of information provisions in this final rule. An Agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

IX. References

The following references have been placed on display in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m.,

Monday through Friday. FDA has verified the Web site addresses in this document, but FDA is not responsible for subsequent changes after this document publishes in the Federal Register.

1. “Guideline for the Uniform Labeling of Blood and Blood Components,” August 1985, <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM080974.pdf>.

2. “United States Industry Consensus Standard for the Uniform Labeling of Blood and Blood Components Using ISBT 128,” November 2005, <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM079159.pdf>.

3. “Guidance for Industry: Recognition and Use of a Standard for Uniform Blood and Blood Component Container Labels,” September 2006, <http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm079004.pdf>.

List of Subjects

21 CFR Part 606

Blood, Labeling, Laboratories, Reporting and recordkeeping requirements.

21 CFR Part 610

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 authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 606, 610, 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. Revise the heading for subpart G to read as follows:

Subpart G--Additional Labeling Standards for Blood and Blood Components

3. Section 606.121 is revised 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 intended for use in transfusion or further manufacture by all blood establishments.

(b) The label provided by the collecting facility and the initial processing facility must not be removed, altered, or obscured, except that the label may be altered to indicate the proper name of the product, with any appropriate modifiers and attributes, and other information required to identify accurately the contents of a container after blood components considered finished products have been prepared.

(c) The container label must include the following information, as well as other specialized information as required in this section for specific products:

(1) The proper name of the product in a prominent position, with any appropriate modifiers and attributes.

(2) The name, address, unique facility identifier, and, if a licensed product, the license number of each manufacturer; except the container label for blood and blood components for further manufacture is not required to include a unique facility identifier.

(3) The donor or lot number relating the unit to the donor. If pooled, all donor numbers, all donation numbers, or a pool number that is traceable to each individual unit comprising the pool.

(4)(i) The expiration date, including the day, month, and year, and, if the dating period for the product is 72 hours or less, including any product prepared in a system that might compromise sterility, the hour of expiration.

(ii) If Source Plasma intended for manufacturing into noninjectable products is pooled, the expiration date for the pool is determined from the collection date of the oldest unit in the pool, and the pooling records must show the collection date for each unit in the pool.

(5) For Whole Blood, Plasma, Platelets, and partial units of Red Blood Cells, the volume of the product, accurate to within ± 10 percent; or optionally for Platelets, the volume or volume range within reasonable limits.

(6) Where applicable, the name and volume of source material.

(7) The recommended storage temperature (in degrees Celsius).

(8) If the product is intended for transfusion, the statements:

(i) "Rx only."

(ii) "See circular of information for indications, contraindications, cautions, and methods of infusion."

(iii) "Properly identify intended recipient."

(iv) "This product may transmit infectious agents."

(v) The appropriate donor classification statement, i.e., “paid donor” or “volunteer donor,” in no less prominence than the proper name of the product.

(A) A paid donor is a person who receives monetary payment for a blood donation.

(B) A volunteer donor is a person who does not receive monetary payment for a blood donation.

(C) Benefits, such as time off from work, membership in blood assurance programs, and cancellation of nonreplacement fees that are not readily convertible to cash, do not constitute monetary payment within the meaning of this paragraph.

(9) If the product is intended for transfusion or as is otherwise appropriate, the ABO group and Rh type of the donor must be designated conspicuously. For Cryoprecipitated Antihemophilic Factor (AHF), the Rh type may be omitted. The Rh type must be designated as follows:

(i) If the test using Anti-D Blood Grouping Reagent is positive, the product must be labeled: “Rh positive.”

(ii) If the test using Anti-D Blood Grouping Reagent is negative, but the test for weak D (formerly D_u) is positive, the product must be labeled: “Rh positive.”

(iii) If the test using Anti-D Blood Grouping Reagent is negative and the test for weak D (formerly D_u) is negative, the product must be labeled: “Rh negative.”

(10) If the product is not intended for transfusion, a statement as applicable: “Caution: For Manufacturing Use Only,” or “Caution: For Use in Manufacturing Noninjectable Products Only,” or other cautionary statement as approved by the Director, Center for Biologics Evaluation and Research (CBER).

(11) If the product is intended for further manufacturing use, a statement listing the results of all the tests for communicable disease agents required under § 610.40 of this chapter for which the donation has been tested and found negative; except that the container label for Source Plasma is not required to list the negative results of serological syphilis testing under §§ 610.40(i) and 640.65(b) of this chapter.

(12) The blood and blood components must be labeled in accordance with § 610.40 of this chapter, when the donation is tested and demonstrates evidence of infection due to a communicable disease agent(s).

(13) The container label of blood or blood components intended for transfusion must bear encoded information in a format that is machine-readable and approved for use by the Director, CBER.

(i) Who is subject to this machine-readable requirement? All blood establishments that manufacture, process, repack, or relabel blood or blood components intended for transfusion and regulated under the Federal Food, Drug, and Cosmetic Act or the Public Health Service Act.

(ii) What blood products are subject to this machine-readable requirement? All blood and blood components intended for transfusion are subject to the machine-readable information label requirement in this section.

(iii) What information must be machine-readable? Each label must have machine-readable information that contains, at a minimum:

- (A) A unique facility identifier;
- (B) Lot number relating to the donor;
- (C) Product code; and

(D) ABO and Rh of the donor, except as described in paragraphs (c)(9) and (i)(5) of this section.

(iv) How must the machine-readable information appear? The machine-readable information must:

(A) Be unique to the blood or blood component;

(B) Be surrounded by sufficient blank space so that the machine-readable information can be scanned correctly; and

(C) Remain intact under normal conditions of use.

(v) Where does the machine-readable information go? The machine-readable information must appear on the label of any blood or blood component which is or can be transfused to a patient or from which the blood or blood component can be taken and transfused to a patient.

(d) Unless otherwise approved by the Director, CBER, the container label for blood and blood components intended for transfusion must be white and print must be solid black, with the following additional exceptions:

(1) The ABO and Rh blood groups must be printed as follows:

(i) Rh positive: Use black print on white background and use solid black or other solid color for ABO.

(ii) Rh negative: Use white print on black background for Rh and use black outline on a white background for ABO.

(2) The proper name of the product, with any appropriate modifiers and attributes, the donor classification statement, and the statement “properly identify intended recipient” may be printed in solid red or in solid black.

(3) The following color scheme may be used for differentiating ABO Blood groups:

Blood Group	Color of Label
O	Blue
A	Yellow
B	Pink
AB	White

(4) Special labels, such as those described in paragraphs (h) and (i) of this section, may be color-coded.

(e) Container label requirements for particular products or groups of products.

(1) Whole Blood labels must include:

(i) The name of the applicable anticoagulant approved for use by the Director, CBER.

(ii) The volume of anticoagulant.

(iii) If tests for unexpected antibodies are positive, blood intended for transfusion must be labeled: “Contains (name of antibody).”

(2) Except for frozen, deglycerolized, or washed Red Blood Cell products, Red Blood Cell labels must include:

(i) The type of anticoagulant, and if applicable, the volume of Whole Blood and type of additive solution, with which the product was prepared.

(ii) If tests for unexpected antibodies are positive and the product is intended for transfusion, the statement: “Contains (name of antibody).”

(3) If tests for unexpected antibodies are positive, Plasma intended for transfusion must be labeled: “Contains (name of antibody).”

(4) Recovered plasma labels must include:

(i) In lieu of an expiration date, the date of collection of the oldest material in the container.

(ii) For recovered plasma not meeting the requirements for manufacture into licensable products, the statement: “Not for Use in Products Subject to License Under Section 351 of the Public Health Service Act.”

(iii) The type of anticoagulant with which the product was prepared.

(5) Source Plasma labels must include the following information:

(i) The cautionary statement, as specified in paragraph (c)(10) of this section, must follow the proper name with any appropriate modifiers and attributes and be of similar prominence as the proper name.

(ii) The statement “Store at -20 °C or colder,” provided, that where plasma is intended for manufacturing into noninjectable products, this statement may be replaced by a statement of the temperature appropriate for manufacture of the final product to be prepared from the plasma.

(iii) The total volume or weight of plasma and total quantity and type of anticoagulant used.

(iv) When plasma collected from a donor is reactive for a serologic test for syphilis, a statement that the plasma is reactive and must be used only for the manufacturing of positive control reagents for the serologic test for syphilis.

(v) Source Plasma diverted for Source Plasma Salvaged must be relabeled “Source Plasma Salvaged” as prescribed in § 640.76 of this chapter. Immediately following the proper name of the product, with any appropriate modifiers and attributes, the labeling must prominently state as applicable, “STORAGE TEMPERATURE EXCEEDED -20 °C” or “SHIPPING TEMPERATURE EXCEEDED -5 °C.”

(vi) A statement as to whether the plasma was collected from normal donors, or from donors in specific collection programs approved by the Director, CBER. In the case of specific

collection programs, the label must state the defining characteristics of the plasma. In the case of immunized donors, the label must state the immunizing antigen.

(f) Blood and blood components determined to be unsuitable for transfusion must be prominently labeled “NOT FOR TRANSFUSION,” and the label must state the reason the unit is considered unsuitable. The provision does not apply to blood and blood components intended solely for further manufacture.

(g) [Reserved]

(h) The following additional information must appear on the label for blood and blood components shipped in an emergency prior to completion of required tests, in accordance with § 610.40(g) of this chapter:

(1) The statement: “FOR EMERGENCY USE ONLY BY _____.”

(2) Results of any tests prescribed under §§ 610.40 and 640.5(a), (b), or (c) of this chapter completed before shipment.

(3) Indication of any tests prescribed under §§ 610.40 and 640.5(a), (b), or (c) of this chapter not completed before shipment.

(i) The following additional information must appear on the label for blood and blood components intended for autologous transfusion:

(1) Information adequately identifying the patient, e.g., name, date of birth, hospital, and identification number.

(2) Date of donation.

(3) The statement: “AUTOLOGOUS DONOR.”

(4) The ABO and Rh blood group and type, except as provided in paragraph (c)(9) of this section.

(5) Each container of blood and blood component intended for autologous use and obtained from a donor who fails to meet any of the donor suitability requirements under § 640.3 of this chapter or who is reactive to or positive for one or more tests for evidence of infection due to communicable disease agents under § 610.40 of this chapter must be prominently and permanently labeled “FOR AUTOLOGOUS USE ONLY” and as otherwise required under § 610.40 of this chapter. Such units also may have the ABO and Rh blood group and type on the label.

(6) Units of blood and blood components originally intended for autologous use, except those labeled as prescribed under paragraph (i)(5) of this section, may be issued for allogeneic transfusion provided the container label complies with all applicable provisions of paragraphs (b) through (e) of this section. In such case, the special label required under paragraphs (i)(1), (i)(2), and (i)(3) of this section must be removed or otherwise obscured.

(j) A tie-tag attached to the container may be used for providing the information required by paragraphs (e)(1)(iii), (e)(2)(ii), and (e)(3), (h), or (i)(1), (i)(2), and (i)(3) of this section.

4. Section 606.122 is amended by:

- a. Revising the section heading;
- b. Revising the introductory text;
- c. Revising paragraphs (e), (f), (m)(2), (m)(3), and (m)(5); and
- d. Revising the introductory text in paragraphs (k), (l), (m), and (n).

The revisions read as follows:

§ 606.122 Circular of information.

A circular of information must be available for distribution if the product is intended for transfusion. The circular of information must provide adequate directions for use, including the following information:

* * * * *

(e) A statement that the product was prepared from blood that was found negative when tested for communicable disease agents, as required under § 610.40 of this chapter (include each test that was performed).

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

* * * * *

(k) For Red Blood Cells, the circular of information must contain:

* * * * *

(l) For Platelets, the circular of information must contain:

* * * * *

(m) For Plasma, the circular of information must contain:

(1) * * *

(2) Instructions to thaw the frozen product at a temperature appropriate for the product.

(3) When applicable, instructions to begin administration of the product within a specified time after thawing.

* * * * *

(5) A statement that this product has the same risk of transmitting infectious agents as Whole Blood; other plasma volume expanders without this risk are available for treating hypovolemia.

(n) For Cryoprecipitated AHF, the circular of information must contain:

* * * * *

6. 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, CBER, must be notified by telephone, facsimile, express mail, or electronically transmitted mail as soon as possible. A written report of the investigation must be submitted to the Director, Office of Compliance and Biologics Quality, CBER, by mail, facsimile, or electronically transmitted mail (for mailing addresses, see § 600.2 of this chapter), 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.

PART 610--GENERAL BIOLOGICAL PRODUCTS STANDARDS

7. The authority citation for 21 CFR part 610 continues to read as follows:

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

8. Section 610.40 is amended by revising paragraphs (h)(2)(ii)(B) and (i) to read as follows:

§ 610.40 Test requirements.

* * * * *

(h) * * *

(2) * * *

(ii) * * *

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

* * * * *

(i) Syphilis testing. In addition to the testing otherwise required under this section, you must test by a serological test for syphilis under §§ 640.5(a), 640.14, 640.23(a), 640.33(a), 640.53(a), and 640.65(b)(1) and (b)(2) of this chapter.

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.

§ 640.70 [Removed]

10. Section 640.70 is removed.

11. Section 640.74 is amended by revising paragraph (b)(4) to read as follows:

§ 640.74 Modification of Source Plasma

* * * * *

(b) * * *

(4) The label affixed to each container of Source Plasma Liquid shall contain, in addition to the information required by § 606.121 of this chapter, but excluding § 606.121(e)(5)(ii) of this

chapter, the name of the manufacturer of the final blood derivative product for whom it was prepared.

* * * * *

Dated: December 22, 2011.

Leslie Kux,

Acting Assistant Commissioner for Policy.

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