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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 606, 610, 630, 640, 660, and 820

RIN 0910-AG87

[Docket No. FDA-2006-N-0040 (formerly Docket No. 2006N-0221)]

Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the regulations applicable to blood and blood components, including Source Plasma, to make the donor eligibility and testing requirements more consistent with current practices in the blood industry, to more closely align the regulations with current FDA recommendations, and to provide flexibility to accommodate advancing technology. In order to better assure the safety of the nation's blood supply and to help protect donor health, FDA is revising the requirements for blood establishments to test donors for infectious disease, and to determine that donors are eligible to donate and that donations are suitable for transfusion or further manufacture. FDA is also requiring establishments to evaluate donors for factors that may adversely affect the safety, purity, and potency of blood and blood components or the health of a donor during the donation process. Accordingly, these regulations establish requirements for donor education, donor

history, and donor testing. These regulations also implement a flexible framework to help both FDA and industry to more effectively respond to new or emerging infectious agents that may affect blood product safety.

DATES: This rule is effective May 23, 2016.

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SUPPLEMENTARY INFORMATION:

Executive Summary

Purpose of the Final Rule

The final rule helps to protect donors of blood and blood components by requiring establishments to evaluate donors for factors that may cause donation to adversely affect their health. In addition, the final rule is being issued to assure the safety, purity, and potency of the blood and blood component products used for transfusion and for further manufacture.

The final rule applies to establishments that collect and/or process blood and blood components, including transfusion services. This rule requires establishments to assess a donor's medical history to determine that the donor is in good health and to screen the donor for factors that can adversely affect the safety, purity, or potency of blood and blood components. In addition, the rule provides requirements for testing donations for relevant transfusion-transmitted infections. This rule revises and updates existing regulations.

FDA is issuing this rule under the authority of sections 351 and 361 of the Public Health Service Act (PHS Act) (42 U.S.C. 262 and 264), and certain provisions of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) that apply to drugs and devices (21 U.S.C. 201 et seq.).

Summary of the Major Provisions of the Final Rule

Consistent with the proposed rule, in § 630.3(l), we define transfusion-transmitted infection as a disease or disease agent that: (1) Could be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure and (2) for which there may be a risk of transmission by blood or blood components, or by a blood derivative product manufactured from blood or blood components, because the disease or disease agent is potentially transmissible by that blood, blood component or blood derivative product.

Sometimes, a transfusion-transmitted infection will also meet the definition of a relevant transfusion-transmitted infection. We define relevant transfusion-transmitted infection in § 630.3(h) to include two groups of transfusion-transmitted infections. The first group, in § 630.3(h)(1) is a list of 10 named transfusion-transmitted infections: Human immunodeficiency virus, types 1 and 2 (referred to, collectively as HIV); Hepatitis B virus (referred to as HBV); Hepatitis C virus (referred to as HCV); Human T-lymphotropic virus, types I and II (referred to, collectively, as HTLV); Treponema pallidum (referred to as syphilis); West Nile virus; Trypanosoma cruzi (referred to as Chagas disease); Creutzfeldt-Jakob disease (referred to as CJD); Variant Creutzfeldt-Jakob disease (referred to as vCJD); and Plasmodium species (referred to as malaria). In recognition of current industry practices and in response to comments to the proposed rule, we included West Nile virus and Chagas disease in the definition of

relevant transfusion-transmitted infection at § 630.3(h)(1)(vi) and (vii), respectively.

Establishments currently perform donor screening for these relevant transfusion-transmitted infections. Blood establishments other than Source Plasma establishments already perform testing for the first seven listed transfusion-transmitted infections, and Source Plasma establishments already perform testing for HIV, HBV, HCV, and more limited testing for syphilis. Testing requirements for Source Plasma establishments are more limited because Source Plasma undergoes further processing into blood derivative products, and those additional manufacturing steps have been shown to inactivate or remove certain infectious agents. We consider these donor testing and screening practices to meet current standards, and would address any changes in our recommendations for complying with the final rule in guidances issued in accordance with good guidance practice (21 CFR 10.115). The second part of the definition of relevant transfusion-transmitted infections, § 630.3(h)(2), establishes the criteria which will be used to identify other transfusion-transmitted infections that may present risks to the safety, purity, and potency of blood and blood components in the future. A transfusion-transmitted infection will meet the additional criteria for a relevant transfusion-transmitted infection when the following conditions are met: (1) Appropriate screening measures for the transfusion-transmitted infection have been developed and/or an appropriate screening test has been licensed, approved, or cleared for such use by FDA and is available and (2) the disease or disease agent may have sufficient incidence and/or prevalence to affect the potential donor population, or may have been released accidentally or intentionally in a manner that could place potential donors at risk of infection. Under the first prong of these criteria, a transfusion-transmitted infection would become relevant only when an appropriate intervention is available to prevent contamination of the blood supply. Under the second prong, the disease or disease

agent must also meet one of the following two criteria: (1) It may have sufficient incidence and/or prevalence to affect the potential donor population or (2) it may have been released accidentally or intentionally in a manner that could place potential donors at risk of infection.

In the event that circumstances have changed, and that a transfusion-transmitted infection meets the definition of a relevant transfusion-transmitted infection, FDA intends to issue guidance in accordance with good guidance practices to advise stakeholders of FDA's assessment of how the transfusion-transmitted infection now meets the definition of relevant transfusion-transmitted infection. In the same guidance, we would also address appropriate donor screening measures, including medical history assessments, in accordance with § 630.10(e), and any appropriate donor testing in accordance with § 610.40(a)(3) (21 CFR 610.40(a)(3)). We may also address educational materials in accordance with § 630.10(b).

We are finalizing minor changes to the requirements in § 606.100(b) (21 CFR 606.100(b)) to maintain standard operating procedures largely as proposed. In addition, final § 606.100(b)(22) more explicitly requires establishments to have procedures to control the risks of bacterial contamination of platelets, including all steps required under § 606.145.

We address requirements for establishments to take steps to control bacterial contamination of platelets in § 606.145, which is located in the part entitled "Current Good Manufacturing Practice for Blood and Blood Components" instead of in § 630.30(a)(5), as proposed. This placement more clearly reflects the importance of these steps to current good manufacturing practice. Section 606.145 requires establishments to assure that the risks of bacterial contamination of platelets are adequately controlled using FDA approved or cleared devices or other adequate and appropriate methods found acceptable for this purpose by FDA, and explicitly addresses the responsibility of transfusion services to comply with this current

good manufacturing practice. Establishments must take appropriate steps to identify the contaminating organism, and in the event that the organism is identified, the responsible physician for the collection establishment must determine whether that organism is likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor. Such a determination would lead to donor deferral and notification.

In response to comments, we have significantly narrowed the recordkeeping requirement that we proposed in § 606.160(e) (21 CFR 606.160(e)). Instead of requiring collection establishments to share a record of all ineligible donors with appropriate personnel at all locations operating under the same license or under common management, final § 606.160(e) requires establishments to maintain two records: (1) A record of all donors found to be ineligible or deferred at the collection location and (2) a cumulative record of donors deferred from donation at all locations operating under the same license or under common management because their tests were reactive for evidence of infection due to HIV, HBV, or HCV. Establishments other than Source Plasma establishments must include donors deferred for evidence of infection due to HTLV and Chagas disease. A related provision, § 630.10(d), sets out requirements for establishments to consult these records before collection. If a pre-collection review of the cumulative record is not feasible, establishments must review it before releasing blood or blood components.

We maintain current testing requirements in § 610.40, and include additional provisions. In § 610.40(a), we address testing for Chagas disease, West Nile virus, and syphilis. This section would also require testing for additional relevant transfusion-transmitted-infections in the event that donor screening tests are licensed, approved, or cleared, and are available, and that such testing is necessary to reduce adequately and appropriately the risk of transmission of the

relevant transfusion-transmitted infection by blood or blood components. In addition, this section provides that, under appropriate conditions and for certain relevant transfusion-transmitted infections, it may become appropriate to test at a frequency other than at each donation, or, when the conditions in the regulations are met, even to stop testing for that relevant transfusion-transmitted infection. Section 610.40(a)(4) describes types of evidence that may support such a determination.

In § 610.40(e), we are maintaining the existing requirement for further testing when a donation tests reactive for a relevant transfusion-transmitted infection. When a licensed, approved, or cleared supplemental test is not available, the rule provides greater flexibility for the use of licensed, approved, or cleared tests to provide additional information concerning the reactive donor's infection. This section also requires establishments to perform additional testing of a donation found reactive by a non-treponemal donor screening test for syphilis.

Final § 630.5 provides requirements for medical supervision of collection activities, such as determining the eligibility of a donor of blood or blood components, including Source Plasma, collecting blood or blood components, and for performing other donor procedures such as returning red blood cells during apheresis, or immunizing Source Plasma donors as part of an approved immunization program. This section requires establishments to establish, maintain, and follow standard operating procedures for obtaining rapid emergency medical services for donors when medically necessary, and must assure that a person who is currently certified in cardiopulmonary resuscitation is located on the premises whenever collections are performed.

Section 630.10 establishes general donor eligibility requirements and consolidates most donor eligibility requirements for Whole Blood and Source Plasma into a single section. A donor is not eligible and must be deferred if the donor is not in good health or if the

establishment identifies any factor that may cause the donation to adversely affect the health of the donor or the safety, purity, or potency of the blood or blood component. This section requires the establishment to provide the donor with educational material related to a relevant transfusion-transmitted infection when donor education about that infection is necessary to assure the safety, purity, and potency of blood and blood components, to consult records of deferred donors, to assess the donor for risk factors for relevant transfusion-transmitted infections and other factors that might adversely affect the donation or the donor's health, and to obtain proof of the donor's identity and a postal address where the donor may be contacted for 8 weeks after donation.

Section 630.10(f) requires establishments to perform a limited physical assessment of the donor. This assessment must include donor temperature, blood pressure, pulse, minimum weight, condition of the skin at phlebotomy site and on arms, and hemoglobin or hematocrit levels. The rule maintains current requirements for hemoglobin and hematocrit levels for female donors, but since lower levels are also within the normal range for women, the rule would authorize collection from female donors with levels no lower than 12.0 grams of hemoglobin per deciliter of blood, or a hematocrit value no lower than 36 percent, provided that the establishment has taken additional steps to assure that the alternative standard is adequate to assure donor safety, in accordance with a procedure that has been found acceptable for this purpose by FDA. The rule raises the minimum standard for male donors from 12.5 grams of hemoglobin per deciliter of blood, or a hematocrit value that is equal to or greater than 38 percent, to 13 grams and 39 percent, respectively.

Under § 630.10(g)(2) establishments must obtain the donor's acknowledgement that the donor has reviewed educational material required to be provided under this section as well as

information about the risks and hazards of the specific donation procedure. In the proposed rule, this was called the “Donor’s written statement of understanding.”

Section 630.15 establishes additional donor eligibility requirements for the collection of Whole Blood and Red Blood Cells collected by apheresis and Source Plasma and Plasma collected by plasmapheresis. For donors of Whole Blood and Red Blood Cells collected by apheresis, § 630.15(a) requires that donation frequency be consistent with protecting the donor’s health, describes minimum intervals between donations (typically 8 weeks, and 16 weeks for a double Red Blood Cell donation), and addresses donations by donors undergoing therapeutic phlebotomy.

The requirements in § 630.15(b) applicable to donors of Source Plasma and Plasma collected by plasmapheresis are largely consistent with current regulations and practices. The responsible physician, subject to delegation in accordance with § 630.5(c), must conduct an appropriate medical history and physical examination of the donor at least annually, and must defer a donor found to have a medical condition that would place the donor at risk from plasmapheresis, and for red blood cell loss, as described in the rule. This section also addresses informed consent requirements for donors of Source Plasma and Plasma collected by plasmapheresis. These requirements complement other requirements for the collection of plasma by plasmapheresis in parts 630 and 640 (21 CFR parts 630 and 640), including restrictions on frequency of collection specified in §§ 640.32 and 640.65).

Section 630.20 permits, under certain circumstances, the collection of blood and blood components from individuals who are ineligible under one or more of the eligibility requirements under §§ 630.10 and 630.15. This section provides exceptions for autologous donors and donors who are participants in an approved plasmapheresis program for products for which there are no

alternative sources, and for dedicated donations where there is documented exceptional medical need. For all collections authorized under this section, we have clarified the responsible physician's role and responsibilities in these collections.

We are finalizing § 630.25 largely as proposed. This section modifies certain requirements in §§ 630.15(b) and 640.65(b) as they are applicable to the collection of plasma from infrequent plasma donors. For greater clarity, we have included a definition of "infrequent plasma donor" in new § 630.3(e) and we use that defined term in this section.

We have finalized requirements in § 630.30(a) to define when a donation is suitable. Section 630.30(b) expressly prohibits an establishment from releasing an unsuitable donation for transfusion or further manufacturing use unless it is an autologous donation, or an exception is provided. It further requires a blood establishment to defer the donor of an unsuitable donation, although final § 630.30(b)(2) requires deferral of donors of platelets found to be bacterially contaminated only when the establishment determines in accordance with § 606.145 that the bacterial contamination shows evidence of bacteria endogenous to the bloodstream of the donor. This is because we recognize that a frequent cause of bacterial contamination in platelets is due to the passage of the collection needle through the donor's skin, which is not sterile. For this reason, the presence of bacteria that are common skin flora does not warrant deferral of the donor.

We have finalized the donor notification provisions in § 630.40. Consistent with the proposed rule, § 630.40(a) requires establishments to notify donors whose platelet component has tested positive for a bacterial contamination that is likely due to an infection endogenous to the bloodstream of the donor, such as Streptococcus bovis. Identification of this bacterium indicates that the donor may have a serious health condition such as colon cancer.

Section 640.21 addresses eligibility of donors of platelets. Consistent with the proposed rule, § 640.21(b) provides that a plateletpheresis donor must not serve as the source of Platelets for transfusion if the donor has recently ingested a drug that adversely affects platelet function. We have modified this requirement for donors of Whole Blood that is the source of Platelets for transfusion. Section 640.21(c) requires that a Whole Blood donor must not serve as the source of Platelets for transfusion if the donor has recently ingested a drug that adversely affects platelet function unless the unit is labeled to identify the ingested drug that adversely affects platelet function. Section 640.21(g) incorporates existing informed consent requirements.

Based on comments to the proposed rule, we have finalized the requirements for collection of Platelets by plateletpheresis to be consistent with “Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods,” dated December 2007. These provisions address donor platelet counts, frequency and size of plateletpheresis collection, and deferral for red blood cell loss.

We are finalizing the limits on distribution of Source Plasma in § 640.69(e) with minor changes. The final rule now provides that establishments must establish a paid Source Plasma donor’s qualification by determining on at least two occasions in the past 6 months that the donor is eligible under § 630.10(e) and that the donor’s results are negative on all tests required under § 610.40(a). Consistent with current industry standards, we have also finalized the inventory hold provision proposed in § 640.69(f) to require establishments to hold Source Plasma donated by paid donors in quarantine for a minimum of 60 days. In addition, we clarify the conditions that would prevent an establishment from distributing Source Plasma from quarantine.

We are not finalizing proposed § 640.73, “Reporting of donor reactions”, in this rule. Instead, FDA intends to finalize this section when FDA finalizes the proposed Safety Reporting

Requirements for Human Drug and Biologicals (68 FR 12406, March 14, 2003). We will address in that final rule the comments on proposed § 640.73.

We are finalizing § 640.120 largely as proposed. Final § 640.120(b) authorizes the Director of the Center for Biologics Evaluation and Research (CBER) “to respond to a public health need” by issuing an exception or alternative to any requirement in subchapter F of chapter I of title 21 of the CFR if necessary to provide for appropriate donor screening and testing or to assure that blood, blood components, or blood products will be available in a specified location or locations to address an urgent and immediate need for blood, blood components, or blood products. Under these provisions, this authority will be available to FDA to assure the availability of blood and blood components that are safe, pure, and potent.

Analysis of 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 (Pub. L. 104-4). This final rule is not a significant regulatory action under the Executive orders, and it will not have an economic impact, or require expenditures, at magnitudes warranting review under those statutory provisions.

Costs and Benefits

This rule sets forth requirements for donor eligibility and donation suitability to ensure the safety, purity, and potency of the blood and blood components used for transfusion or for further manufacture. Costs estimated in this analysis include costs related to the standard operating procedures and bacterial testing requirements for blood collection establishments and transfusion services. The total upfront costs are \$16,042,628, and include costs related to the review, modification, and creation of standard operation procedures. The mean annual costs of

\$892,233 include costs related to the bacterial testing of single units of Whole Blood-derived platelets and speciation of bacterially contaminated platelets. We anticipate that this final rule will preserve the safety, purity, and potency of blood and blood components by preventing unsafe units of blood or blood components from entering the blood supply, and by providing recipients with increased protection against communicable disease transmission. The requirements set forth in this rule will also help to decrease the number of blood transfusion related fatalities that are associated with the bacterial contamination of platelets. The annual value of additional fatalities averted related by testing of Whole Blood-derived platelets is estimated to be approximately \$27 million to \$90 million and the annual value of averted nonfatal sepsis infections is estimated to be \$3.19 million to \$4.91 million.

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I. Introduction

In the Federal Register of November 8, 2007 (72 FR 63416), FDA published the proposed rule “Requirements for Human Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use” to amend the regulations for blood and blood components, including Source Plasma and Source Leukocytes, by adding donor eligibility and donation suitability requirements that are consistent with current practices in the blood industry, and to more closely align the regulations with current FDA recommendations. We proposed this rule to help ensure the safety of the nation’s blood supply and to help protect the health of donors by requiring establishments to evaluate donors for factors that may adversely affect the safety, purity, and potency of blood and blood components or the health of a donor.

This effort was undertaken as part of the Department of Health and Human Services Blood Action Plan (Ref. 1). The Blood Action Plan was developed in response to recommendations from Congress and other groups including the Government Accountability Office (previously the General Accounting Office) and the Institute of Medicine (Refs. 2, 3). This rulemaking is one of the final remaining action items under the Blood Action Plan.

In response to numerous requests, we extended the comment period for the proposed rule, initially scheduled to close on February 8, 2008, for an additional 180 days to August 4, 2008 (73 FR 1983, January 11, 2008). FDA received 29 letters of comment on the proposed rule, most of which raised multiple issues. Some comments responded to questions that we solicited in the preamble to the proposed rule in order to obtain additional information and data for this rulemaking. For example, we solicited comments on testing for bacterial contamination in platelets (72 FR 63416 at 63421) and requested data addressing the continued need for syphilis

testing to address the risks of transfusion-related syphilis infection, and its value as a surrogate marker for other communicable diseases (72 FR 63416 at 63422).

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

We received 29 letters containing multiple comments from blood establishments, biologics manufacturers, industry trade associations, and other interested persons. In this section, we respond first to general comments and then, in the corresponding section of this preamble, to those on specific provisions of the proposed rule. To make it easier to identify the comments and our responses, the word "Comment," in parentheses, will appear before the comment's description, and the word "Response," in parentheses, will appear before our response. We have also numbered each comment in the order in which we discuss it. The number assigned to each comment is purely for organizational purposes and does not signify the comment's value or importance or the order in which it was received. Certain comments were grouped together because the subject matter of the comments was similar.

A. General

(Comment 1) One comment commended FDA's efforts to update the regulations for blood and blood components to accommodate scientific and industry advances. These advances are vital to assuring the safety, purity and potency of the blood supply. Another comment stated that they fully support the intent of the proposed rule to help assure the safety of the blood supply and to help protect donor health.

(Response) We acknowledge and appreciate these supportive comments.

(Comment 2) One comment applauded and supported FDA efforts to streamline the regulations and bring them up-to-date with current recommendations and current FDA guidance documents. The comment stated that appropriate standards will afford the medical community

the ability to alleviate blood shortages, contribute to the success of public health initiatives, and contribute to quality medical care.

(Response) We appreciate the comment. We revised and updated the regulations applicable to blood and blood components, including Source Plasma and Source Leukocytes, with the goal of ensuring optimal donor safety measures as well as assuring that the public will continue to have access to safe, pure and potent blood and blood components.

B. Definitions (§§ 606.3, 610.39, 630.3, 640.125)

We have combined our discussion of the definitions contained in §§ 606.3, 610.39, 630.3, and 640.125 in this section of the preamble. An understanding of the terms we define is important to an understanding of other sections of this rule that use those terms. We hope to help the reader by discussing these foundational definitions early in this preamble, before we discuss the substantive provisions using those terms.

We are finalizing the definition of blood in §§ 606.3(a) and 630.3(a) as a product that is a fluid containing dissolved and suspended elements which was collected from the vascular system of a human. We received no comments on the proposed definition. The definition in the final rule differs from the proposal only in the reference to “a fluid” instead of “the fluid,” and the substitution of the phrase “was collected from” for “circulates in.” We made these minor changes for accuracy, and to reflect the practical fact that when blood becomes a “product” it is no longer circulating in a human vascular system, but has been collected from the human vascular system. We are finalizing without change the proposed definition of blood component in §§ 606.3(b) and 630.3(b) as “a product containing a part of human blood separated by physical or mechanical means.” We had proposed to modify the definition of blood component in proposed § 1270.3(b) (21 CFR 1270.3(b)). We are not finalizing that provision because, due to

the Agency's issuance of new regulations applicable to human cellular and tissue based products (21 CFR part 1271), the regulations in part 1270 (21 CFR part 1270), including the definition we proposed to amend, now apply only to human tissue recovered before May 25, 2005. (See § 1270.3(j)). For this reason, it is unnecessary to finalize proposed § 1270.3(b).

We are also finalizing as proposed the definitions of donor (§ 630.3(c)), eligibility of a donor (§ 630.3(d)), and suitability of the donation (§ 630.3(j)).

In § 630.3(e), we have added a definition of infrequent plasma donor, which means a donor who has not donated plasma by plasmapheresis or a co-collection of plasma with another blood component in the preceding 4 weeks, and has not donated more than 12.0 liters of plasma (14.4 liters of plasma for donors weighing more than 175 pounds) in the past year. We provided a similar definition in the preamble to the proposed rule, and are adding it to the codified section in order to make the definition more accessible and clear. The preamble described an infrequent plasma donor as a donor: (1) Who has not donated Whole Blood in the preceding 8 weeks or plasma by apheresis in the preceding 4 weeks, or participated in a double Red Blood Cells unit collection program within the preceding 16 weeks; (2) who has not donated more than 12.0 liters of plasma in the past year (14.4 liters of plasma for donors weighing more than 175 pounds); (3) who is determined by the responsible physician to be in good health; and (4) who is not participating in an immunization program for the production of high-titer plasma. Under proposed § 630.25(a), exceptions from certain donor eligibility requirements could apply to such donors who have not donated within the preceding 4 weeks. The definition of infrequent plasma donor in the final rule focuses on the donor's prior donations of plasma and co-collections of plasma because deferral for Whole Blood and Red Blood Cell donation and requirements for donor health are addressed in other sections of this rule (§§ 630.10 and 630.15), and final

§ 630.25 states that the exceptions in § 630.25 are applicable only for infrequent plasma donors who are not participating in an immunization program. The final rule defines an infrequent plasma donor as a donor who has not donated plasma by plasmapheresis or a co-collection of plasma with another blood component in the preceding 4 weeks, and has not donated more than 12.0 liters of plasma (14.4 liters of plasma for donors weighing more than 175 pounds) in the past year. This definition makes clear that for purpose of this exception, co-collection of plasma with another blood component is considered in the same way as collection of plasma. We decided to make this reference to co-collection by apheresis of plasma more explicit in response to comments discussed in comment 115, which asked FDA to harmonize deferral periods after red blood cell loss for apheresis donors of plasma and of apheresis donors of plasma co-collected with platelets.

Due to the addition of this new definition in § 630.3(e), we have redesignated the remaining definitions alphabetically, beginning with intimate contact with risk for a relevant transfusion-transmitted infection (now final § 630.3(f)), through transfusion-transmitted infection (now final § 630.3(l)). Several of these definitions use the term transfusion-transmitted infection, which is alphabetically last. To help the reader understand the definitions that incorporate the term transfusion-transmitted infection, we will first explain the term transfusion-transmitted infection.

Consistent with the proposed rule, we define transfusion-transmitted infection, final § 630.3(l), as a disease or disease agent: (1) That could be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure and (2) for which there may be a risk of transmission

by blood or blood components or by a blood derivative product manufactured from blood or blood components, because the disease or disease agent is potentially transmissible by that blood, blood component or blood derivative product.

Sometimes, a transfusion-transmitted infection will meet the additional criteria established in the definition of a relevant transfusion-transmitted infection. We define relevant transfusion-transmitted infection in § 630.3(h) to include two groups of transfusion-transmitted infections. The first group, in § 630.3(h)(1) is a list of 10 named transfusion-transmitted infections: HIV; HBV; HCV; HTLV; syphilis; West Nile virus; Chagas disease; Creutzfeldt-Jakob disease (CJD); variant Creutzfeldt-Jakob disease (vCJD); and Plasmodium species (malaria). In recognition of current industry practices and in response to comments received on the proposed rule, West Nile virus and Chagas disease are included in the definition of relevant transfusion-transmitted infection at § 630.3(h)(1)(vi) and (vii), respectively. Establishments currently perform donor screening for these relevant transfusion-transmitted infections. Blood establishments other than Source Plasma establishments already perform testing for the first seven listed transfusion-transmitted infections, and Source Plasma establishments already perform testing for HIV, HBV, HCV, and more limited testing for syphilis. Testing requirements for Source Plasma establishments are more limited because Source Plasma undergoes further processing into blood derivative products, and those additional manufacturing steps have been shown to inactivate or remove certain infectious agents. We consider these donor testing and screening practices to meet current standards, and would address any changes in our recommendations for complying with the final rule in guidances issued in accordance with good guidance practice.

The second part of the definition of relevant transfusion-transmitted infections, § 630.3(h)(2), establishes the criteria which will be used to identify other transfusion-transmitted infections that present risks to the safety, purity, and potency of blood and blood components at some time in the future. Under these criteria, a transfusion-transmitted infection will be identified as a relevant transfusion-transmitted infection when the following conditions are met:

(1) Appropriate screening measures for the transfusion-transmitted infection have been developed and/or an appropriate screening test has been licensed, approved, or cleared for such use by FDA and is available and (2) the disease or disease agent may have sufficient incidence and/or prevalence to affect the potential donor population, or may have been released accidentally or intentionally in a manner that could place potential donors at risk of infection.

Under the first prong of these criteria, a transfusion-transmitted infection could be identified as a relevant transfusion-transmitted infection only when an intervention is available to prevent infection of the blood supply. This intervention could be a donor screening measure such as questions during the medical history interview about medical history, travel, or other behaviors, or a donor screening test to detect the disease or disease agent or evidence of the infection.

Under the second prong, the transfusion-transmitted infection must be relevant to the donor population, either because it may have sufficient incidence and/or prevalence to affect the donor population, or because it may have been released in a manner that could place potential donors at risk of infection.

In the event that FDA determines that, under current conditions, a transfusion-transmitted infection now meets the definition of a relevant transfusion-transmitted infection, FDA intends to issue guidance in accordance with good guidance practices to advise stakeholders of FDA's assessment of how the transfusion-transmitted infection now meets the definition of relevant

transfusion-transmitted infection. In the same guidance, we would also address appropriate screening measures, including medical history assessments, in accordance with § 630.10(e), and any appropriate donor testing for relevant transfusion-transmitted infections in accordance with § 610.40(a)(3). We anticipate issuing such guidance initially as a draft for comment, unless, due to urgent circumstances, it is not feasible or appropriate to issue the document first in draft. Under those circumstances we would invite comment on the final guidance, and revise it as appropriate.

We note that members of the Transfusion Transmitted Diseases Committee of AABB, formerly the American Association of Blood Banks, published an article in 2009 identifying 68 emerging infectious disease agents that are potentially transmitted by blood (Ref. 4) and recently updated this list of potential threats (Ref. 5). We recognize the value of such scientific assessments to the recognition and management of emerging infections among blood donors and blood recipients, and note that blood establishments already exercise medical judgment in implementing measures to respond to emerging infectious diseases. However, FDA intends to enforce requirements for screening and/or testing in this final rule with respect to an emerging infectious disease agent that is newly identified as meeting the definition of relevant transfusion-transmitted infection only after FDA issues a final guidance identifying the disease or disease agent as a relevant transfusion-transmitted infection under the criteria in this final rule, and recommends appropriate screening and/or testing measures.

Transfusion-transmitted infections that may, due to changed circumstances, meet the definition of relevant transfusion-transmitted infections in the future include dengue viruses or babesia. These infections meet the definition of transfusion-transmitted infection because they are life-threatening and are known to be transmitted by blood or blood components. We are

continuing to monitor the incidence and prevalence of these infections in the donor population, as well as the development and availability of screening measures and screening tests. As discussed in the previous paragraph, if we determine at a future time that one of these transfusion-transmitted infections meets the criteria for a relevant transfusion-transmitted infection, we would issue guidance to explain our assessment. We would also address in that guidance appropriate screening and/or testing measures under §§ 630.10(e) and 610.40(a)(3).

We revised the defined term intimate contact in the proposed rule to intimate contact with risk for a relevant transfusion-transmitted infection (§ 630.3(f)). This term means having engaged in an activity that could result in the transfer of potentially infectious body fluids from one person to another. By including the phrase “with risk for a relevant transfusion-transmitted infection” in the term, we have clarified that the term applies to only those body fluids potentially infectious for infections that are or have been determined to be relevant transfusion-transmitted infections. Also, in response to several comments, discussed in more detail in comment 7, we deleted the reference to the exchange of “blood or saliva” from the definition.

We define physician substitute in § 630.3(g), responsible physician in § 630.3(i) and trained person in § 630.3(k). These definitions describe the qualifications an individual must possess to perform certain donor eligibility assessments and blood and blood component collection procedures as described in § 630.5. The physician substitute definition is unchanged from the proposed, except that instead of requiring, among other criteria, that the individual be “trained and authorized to perform specified functions under the direction of the responsible physician,” the final rule specifies that the individual be “trained and authorized under State law, and/or local law when applicable, to perform the specified functions under the direction of the responsible physician.” We make this change to clarify that authorization under existing and

applicable state and local law, such as compliance with state practice limitations, is required. The definition of responsible physician is unchanged from the proposed rule. For clarity we substituted the non-plural term trained person, for the term trained personnel, which was used in the proposed rule. We have also specified that a trained person must be “authorized under State law, and/or local law when applicable.”

We did not receive any comments to the proposed definition of you as “an establishment that collects blood and blood components” (proposed § 630.3(l)). However, we are not finalizing that proposed definition. We did not intend to limit the term you to establishments that collect blood and blood components. In fact, we intended the term also to apply to establishments that perform other manufacturing steps, such as testing laboratories and transfusion services. Accordingly, we concluded that including you as a defined term was confusing, and we are not finalizing the proposed definition.

Finally, in new § 610.39, we have added a cross-reference to the definitions in § 630.3 to make clear that when these terms are used in part 610, subpart E (§§ 610.40 through 610.48), the definitions in § 630.3 apply. Although our practice in subpart E has been to cross-reference specific sections, express incorporation of these definitions into the subpart will support the clarity of these provisions. Similarly, we have added new § 640.125 to new subpart M in part 640, entitled “Definitions and Medical Supervision.” Section 640.125 provides a cross-reference to the definitions in § 630.3, making those definitions applicable when those terms are used in part 640. This provision is consistent with the proposed rule, which stated in the introductory paragraph to proposed § 630.3 that the definitions were applicable in part 630 and in part 640.

(Comment 3) One comment recommended that the definition of blood component in proposed §§ 606.3(c) and 630.3(b) should include a cross-reference to the regulations in which

specific blood components (such as Red Blood Cells and Platelets) are defined. The comment stated that the proposed definition fails to impart the complexity of different blood components and their intended uses, that there is little similarity between blood components intended for transfusion and Source Plasma, and that the requirements for donor eligibility and testing are unique for Source Plasma. Another comment proposed that a comprehensive definition be provided for Source Plasma.

(Response) All blood components contain risks for transmission of infectious agents, and collection of donations presents risks for donor safety regardless of the intended use of the donation. There is significant consistency among donor eligibility requirements for all types of blood components; these are addressed in § 630.10. In addition, different types of blood components may present different issues, both for the safety, purity, and potency of the collection, and for the safety of the donor. The regulations have long included requirements specific to Source Plasma, Platelets, Red Blood Cells, and other blood components, and we maintain many of those requirements in the final rule. However, we disagree that the definition of blood component, which includes all products derived from human blood separated by physical or mechanical means, will be improved by cross-references to the sections that address requirements for specific types of blood components. Instead, we address requirements applicable to a specific type of blood component in the sections applicable to those blood components. For example, in part 640, subpart B (§§ 640.10 through 640.17) addresses Red Blood Cells and contains standards for those blood components, as subparts C (§§ 640.20 through 640.27), D (§§ 640.30 through 640.34), and G (§§ 640.60 through 640.76) do for Platelets, Plasma, and Source Plasma, respectively. Finally, we reviewed the current definition of Source Plasma in § 640.60, which states that “the fluid portion of human blood collected by

plasmapheresis and intended as source material for further manufacturing use. The definition excludes single donor plasma products intended for intravenous use.” We conclude that it is sufficiently comprehensive.

(Comment 4) One comment questioned FDA’s inclusion of a person who “presents as a potential candidate for such donation” in the definition of donor. The comment requested clarification on when a person “presents” to donate, and asked whether a donor “presents” simply by walking through the door, or whether a donor “presents” when the blood establishment starts the donor interview to assess the donor’s eligibility under the regulations. The comment stated that certain blood establishments collect blood from donors who have specific characteristics unrelated to donor eligibility, such as a history of a specific disease. The comment stated that preliminary interviews to determine whether an individual has such a characteristic should not be considered to be interviews with a “donor.” The comment asserted that requirements to maintain donor records in § 606.160(b)(1) (21 CFR 606.160(b)(1)) should not apply to records of these preliminary interviews because the specialty centers determine specialty information before assessing the general eligibility of the potential candidate. The comment proposed the following definition, “Donor means a person who: (1) Donates blood or blood components for transfusion or for further manufacturing or (2) a potential candidate who has begun the interactive assessment of eligibility by center personnel.”

(Response) Under the definition of donor in final § 630.3(c), an individual would be a “donor” once the establishment begins any of the interactions that are required under this rule. Accordingly, an individual who has not yet donated, but has received educational material in accordance with § 630.10(b), or started to provide donor information related to medical history under § 630.10(e), would be a donor. For example, questioning of the “donor” regarding travel

history or risk behaviors that could lead to deferral under §§ 630.10(e)(2)(iii) and 630.10(e)(1)(i), respectively, would be considered part of determining donor eligibility. However, other interactions not required under this rule, such as taking a blood sample at a health fair to identify rare blood types or unique antigens or antibodies could be considered preliminary interactions, provided that an interaction required under this rule (such as testing for a relevant transfusion-transmitted infection) was not also initiated during the same encounter. If an establishment's interactions with an individual are only preliminary and are not otherwise required under these regulations, the individual would not yet be considered a "donor."

(Comment 5) One comment recommended that FDA adopt terminology that excludes paid donors from the definition of a donor. The comment stated that people being paid to have their plasma collected are not giving a donation.

(Response) We decline to accept the recommendation. Consistent with the general use of the term in blood collection establishments, FDA uses the term donor to apply to all donors, whether or not they are paid. FDA regulations do not preclude paid donations for blood for transfusion or for further manufacture. We acknowledge that the existing regulations have specific provisions applicable to paid donors. For example, FDA requires the container label of blood and blood components intended for transfusion to include the statement "paid donor" or "volunteer donor." Section 606.121(c)(8)(v)(A) defines a paid donor as a person who receives monetary payment for a blood donation. We do not require that Source Plasma be labeled in this way because it is widely understood that Source Plasma is collected predominantly from paid donors.

(Comment 6) Several comments agreed with the definitions of eligibility of a donor and suitability of the donation in proposed § 630.3(d) and (i), respectively. The comments stated the terms are helpful in clarifying many requirements.

(Response) We agree, and have finalized the definitions as proposed in § 630.3(d) and (j), respectively.

(Comment 7) Several comments stated that the definition of intimate contact, designated in the final rule at § 630.3(f), should be reworded to describe an activity (sexual contact or living with) that could result in an exchange of blood with another individual.

(Response) As stated earlier, we revised the term from intimate contact to intimate contact with risk for a relevant transfusion-transmitted infection. The term means having engaged in an activity that could result in the transfer of potentially infectious body fluids from one person to another. The new definition does not reference blood or saliva specifically; it also does not define the specific activity that could result in the transfer of potentially infectious body fluids. The definition applies only when intimate contact presents risks for transmission of a relevant transfusion-transmitted infection. This definition of intimate contact with risk for a relevant transfusion-transmitted infection and the associated requirement in § 630.10(e)(1)(v) to assess donors for this risk replaces current § 640.3(c)(2), which requires deferral of donors who have a history of close contact within 12 months of donation with an individual having viral hepatitis. The new provisions refine the current requirement, and we note that the donor history questionnaires prepared by AABB and the Plasma Protein Therapeutic Association, which have been recognized as acceptable by FDA for screening donors of blood, blood components and Source Plasma, already address the risk of transmission of HBV and HCV by including

questions about the donor's "sexual contact" and "living with" individuals with hepatitis (Refs. 6, 7, 8).

We also note that FDA has recommended that a donor be deferred on the basis of sexual contact with an individual infected with HIV. Questions related to sexual contact with an individual infected with HIV are also included in the donor history questionnaires found acceptable by FDA (Refs. 6, 7, 8). FDA intends to issue guidance as needed to identify other relevant transfusion-transmitted infections where we consider intimate contact to present significant risks for transmission of such infection.

(Comment 8) Several comments stated that the proposed definition of intimate contact was not consistent with public health messages that the risk of transmission of HIV transmission through kissing is remote.

(Response) We agree with this comment in part and have revised the proposed definition. Public health messages have not identified casual kissing as a risk for HIV. However, CDC has identified open-mouth kissing with an HIV infected person as a risk if there are breaks in the skin or tongue (Ref. 9). FDA's guidance for donor deferral is limited to "having sexual contact with an HIV infected individual" (Ref. 10). It does not recommend deferral for kissing.

(Comment 9) One comment agreed with the proposed definition of physician substitute; however, the comment stated that the term could be misleading for the general public and could imply that physician substitutes can perform all duties of a licensed physician at the Source Plasma establishments.

(Response) We disagree that the term physician substitute implies that physician substitutes can perform all the duties of a licensed physician. We believe the definition in

§ 630.3(g) describes sufficiently the training and qualifications of a physician substitute, who must be a graduate of an education program for healthcare workers that includes clinical training, currently licensed or certified as a health care worker in the jurisdiction where the collection establishment is located, and currently certified in cardiopulmonary resuscitation. Moreover, the definition now makes explicit that a physician substitute must be trained and authorized under State law, and/or local law when applicable, to perform specified functions under the direction of the responsible physician. Finally, § 630.5 describes the activities the responsible physician may delegate to the physician substitute, and those the responsible physician is not authorized to delegate.

(Comment 10) Several comments stated that syphilis and CJD should not be included in the definition of relevant transfusion-transmitted infection.

(Response) We disagree with the comments. Syphilis is a relevant transfusion-transmitted infection which screening tests have long been used to detect. As discussed in our response to comment 31, we continue to review data to determine whether it is still necessary to perform screening tests for this infection. However, data submitted to date do not justify a determination that testing to identify syphilis infection is no longer needed to protect the blood supply. Accordingly, we have included syphilis in the definition of a relevant transfusion-transmitted infection at final § 630.3(h)(1)(v).

We have also determined that CJD and vCJD are relevant transfusion-transmitted infections because of the risks they present. Screening tests are not yet available for CJD and vCJD. It is current practice for establishments to perform screening by means of a medical history interview, and FDA has issued guidance recommending donor screening for these diseases (Ref. 11). Consistent with these current practices, we have included CJD and vCJD in

the definition of a relevant transfusion-transmitted infection at § 630.3(h)(1)(viii) and (ix), respectively.

However, our inclusion of certain transfusion-transmitted infections within the definition of relevant transfusion-transmitted infection does not necessarily mean an establishment will always be required to perform donor history screening, or donor testing for that relevant transfusion-transmitted infection. Specifically, in line with the more flexible testing paradigm and criteria we have adopted in final § 610.40(a), it is possible that testing for syphilis will no longer be necessary to reduce adequately and appropriately the risk of transmission of syphilis by blood or blood components. The same applies to CJD and vCJD, and to relevant transfusion-transmitted infections other than HIV, HBV, and HCV. New § 610.40(a)(4) describes the evidence that may be used to support such a determination.

(Comment 11) One comment recommended the inclusion of West Nile virus, Chagas disease, and bacteria in the definition of relevant transfusion-transmitted infection, noting that blood components are routinely tested for West Nile virus and Chagas disease.

(Response) We agree that West Nile virus and Chagas disease present significant risks to the safety, purity, and potency of the blood supply, and that the performance of screening tests for these transfusion-transmitted infections has become routine. Accordingly, we have added these two infections to the definition of relevant transfusion-transmitted infections in this final rule. However, testing or screening of blood donors to identify specific bacterial infections is not routinely performed for donors of all blood components, although under final § 630.10(e)(2)(i) establishments must assess all donors for symptoms of a recent or current illness. We decline to add bacteria to the definition of relevant transfusion-transmitted infection at this time, but we have addressed bacterial testing of platelets in § 606.145 of this rule.

(Comment 12) One comment recommended that responsible physician be defined to differentiate between the duties of a physician overseeing blood collection at an individual facility and a corporate physician with broader oversight responsibilities. Another comment stated that regional responsible physicians should be responsible for endorsing standard operating procedures (SOPs), and for supervising employees' compliance with those SOPs. Locally based physicians should not control or approve SOPs as this would lead to inconsistency in operations.

(Response) We decline to provide distinct definitions for “corporate responsible physician” and “locally based physician”. As discussed in section II.C of this preamble, § 606.100(b) requires blood establishments to establish, maintain, and follow written SOPs for all steps in the collection, processing, compatibility testing, storage, and distribution of blood and blood components. These regulations do not prescribe the roles of corporate and locally based physicians in developing and approving SOPs. In fact, one process for establishing SOPs may be appropriate for one type of blood establishment, such as a licensed blood establishment that collects blood and blood components in multiple states, but inappropriate for a smaller blood establishment that collects and distributes blood and blood components within a limited geographic area.

C. Standard Operating Procedures (§ 606.100)

We are finalizing § 606.100(b), on which we received no comments, largely as proposed. In this section we revised the requirements for SOPs to require more specifically that blood establishments follow those procedures, to distinguish transfusions as either “allogeneic” or “autologous,” and to require more explicitly that establishments establish, maintain, and follow written standard operating procedures for investigating product deviations and for recordkeeping

related to current good manufacturing practice requirements and other applicable requirements and standards. We are also finalizing as proposed § 606.100(b)(20) and (b)(21), which require procedures for donor deferral as prescribed in § 610.41, and procedures, including appropriate follow up, for notification of donors under § 630.40, and, for autologous donors, their referring physicians. We have also added § 606.100(b)(22), which requires establishments to have procedures to control the risks of bacterial contamination of platelets, including all steps required under § 606.145. We are including this provision to clarify that taking steps to control bacterial contamination of platelets is a step in the collection, processing, storage, and distribution of platelets, for which SOPs are required. Our discussion of comments received regarding bacterial testing of platelets can be found at comments 13 through 24 in section II.D.

D. Control of Bacterial Contamination of Platelets (§ 606.145)

We have finalized in new § 606.145 the requirement we proposed as § 630.30(a)(5), which, for platelet components, would have required establishments who collect blood and blood components to “take adequate steps to assure that the donation is tested for bacterial contamination and found negative.” We are finalizing this in part 606 in order to underscore the importance of including methods to control the risk of the proliferation of bacteria in platelets as current good manufacturing practice for blood and blood components.

Unlike other blood components, platelets do not function optimally following refrigeration. They are stored at room temperature, an environment conducive to the growth of bacteria. If the platelet unit is contaminated, bacteria can flourish and grow quickly in the warm, nutrient-rich platelet storage bag. Bacterial contamination is estimated to occur in as many as 1/1,000 to 1/3,000 platelet collections (Refs. 12, 13). The transfusion of bacterially contaminated platelets puts recipients at risk, with reactions varying due to a number of factors,

including the pathogenicity of the bacteria, the quantity of the bacteria transfused, and the immune status of the recipient. Reactions range from no obvious clinical effects to severe and life-threatening infections (Ref. 14). Under current regulations (§ 606.170(b)), blood collection establishments and transfusion services are only required to report to FDA when adverse reactions related to blood collection or transfusion are confirmed to be fatal. Deaths due to bacterial contamination of platelets have been reported to FDA in recent years as follows: in 2008, there were two fatalities reported as complications of platelet transfusions, with subsequent reports of five in 2009, one in 2010, three in 2011, and two in 2012 (Ref. 15).

The final rule requires blood collection establishments and transfusion services to assure that the risks of bacterial contamination of platelets are adequately controlled using FDA approved or cleared devices or other adequate and appropriate methods found acceptable for this purpose by FDA. This final rule requires these manufacturers to meet this standard, and, unlike the language in the proposed rule, does not necessarily require that components be “tested . . . and found negative.” Even though testing of platelet components using an FDA approved or cleared test would currently meet this requirement, the standard setting language used in the final rule would provide for appropriate use of new technologies in the future. For example, if pathogen reduction technology is approved or cleared and available in the future, then use of pathogen reduction technology may also meet the requirements of this provision. We intend to issue guidance addressing how establishments would use FDA approved or cleared devices or methods that FDA has determined to be adequate to assure that the risks of bacterial contamination of platelets are adequately controlled.

Transfusion services are manufacturers that release platelet components for transfusion to an identified recipient but do not routinely collect blood and blood components. Under this rule,

transfusion services may rely on the steps taken by the blood collection establishment to assure that the risks of bacterial contamination of a platelet component are controlled, as long as those methods adequately control risks from the growth of bacteria until the transfusion service releases the product for transfusion. If the collection establishment did not take steps to control the risk of bacterial contamination, then the transfusion service must do so. We note that collection establishments currently take steps to control the risk of bacterial contamination in most platelet components, and expect that transfusion services will have to take steps to control the risk of bacterial contamination only for limited numbers and types of platelet components. For example, a transfusion service may intend to release for transfusion a platelet component derived from a single unit of whole blood. Collection establishments do not typically subject such components to testing by culture-based methods, in part because the volume of the sample required for currently available culture tests would significantly deplete the volume of the component. For such platelet components, § 606.145 would require the transfusion service to take steps, such as the performance of an FDA-cleared rapid test, to assure that the risk of bacterial contamination is adequately controlled.

In the proposed rule (72 FR 63416 at 63421), FDA asked for comments on the following additional points related to testing for bacterial contamination: (1) Whether to require the identification of the species of the bacterial contaminant; (2) whether to require donor deferral and notification when identification of the contaminant indicates possible endogenous bacteremia, and not contamination during collection and processing; and (3) whether to extend bacterial testing requirements to other transfusable blood components. We discuss the first issue at comments 18 through 21, and the second issue at comments 103 through 106, related to

§§ 630.30 and 630.40. With respect to the third issue, as discussed at comment 24, we have decided not to codify a requirement for bacterial testing of other blood components in this rule.

(Comment 13) One comment supported requirements for bacterial testing of platelets prior to transfusion in order to reduce the risk of post-transfusion infection, sepsis, or mortality.

(Response) We appreciate this support for bacterial testing of platelets.

(Comment 14) Several comments opposed a requirement to obtain a negative test result prior to determining a platelet donation to be suitable. Two comments noted that this standard is difficult to apply when a culture-based method is used. The comments stated that in current practice, cultured platelets are released as negative-to-date while incubation is continued. The comments asked FDA not to finalize the proposed requirement.

(Response) We agree that the proposed requirement that platelets be “tested for bacterial contamination and found negative” may have been too prescriptive. Accordingly, § 606.145(a) requires manufacturers to assure that the risks of bacterial contamination of platelets are adequately controlled using FDA approved or cleared devices or other adequate and appropriate methods found acceptable for this purpose by FDA. This could permit release on the basis of an adequate culture test method that is “negative-to-date” on the date of release, even if the establishment continues to incubate the culture. In some circumstances, the culture may later indicate the presence of bacteria in a platelet component that was appropriately released as “negative-to-date”. In that event, the establishment would initiate appropriate action under 21 CFR 606.100(c) and part 7, which may include notifying consignees and retrieving transfusable blood components prepared from that collection.

(Comment 15) Some comments expressed concern that the testing requirement in this provision would be difficult for blood centers to implement because there are currently no

cleared or approved release tests for bacterial testing of platelet products. One of the two cleared quality control tests does not report a single negative result, only a negative-to-date reading. The comment recommended that FDA not finalize these requirements and, instead, provide separate guidance after FDA approves a release test to identify bacteria in platelets.

(Response) We decline to delay establishing a requirement that establishments assure that the risk of bacterial contamination of platelets is adequately controlled. Some manufacturers have been conducting bacterial testing on platelet components for over a decade. We note that the College of American Pathologists has established bacterial testing of platelets as an accreditation standard (Ref. 16). In March 2004, AABB established an accreditation standard requiring accredited blood banks and transfusion services to have methods to limit and detect bacterial contamination in all platelet components (Ref. 17). We have modified the language in the proposed rule so that we require manufacturers to assure that the risks of bacterial contamination of platelets are controlled using FDA approved or cleared devices or other adequate and appropriate methods found acceptable for this purpose by FDA. We intend to issue guidance addressing the use of methods that FDA has determined to be acceptable for this purpose.

(Comment 16) One comment asserted that a requirement for negative test results could become outdated. Methods for bacterial testing continue to evolve and the possibility exists that a pathogen reduction procedure will obviate the need for bacterial screening.

(Response) We recognize that, as technology develops, new methods, including pathogen reduction, may become adequate to satisfy the requirements in § 606.145(a), and may replace testing. We anticipate that, in the future, we will recognize such developments by updating our guidance on the methods that would meet the requirements of § 606.145(a).

(Comment 17) One comment requests that the Agency add a requirement that bacterial contamination testing be performed in a laboratory certified under the Clinical Laboratory Improvement Amendments of 1988 (42 U.S.C. 263a) (CLIA) to perform the testing. The comment asserts that the CLIA requirements complement FDA requirements and lead to higher quality laboratory testing.

(Response) We appreciate the comment. However, we note that final § 606.145(a) requires manufacturers to “assure that the risks of bacterial contamination of platelets are adequately controlled using FDA approved or cleared devices or other adequate and appropriate methods found acceptable for this purpose by FDA.” In the future, technology may develop adequate methods that do not include testing, instead incorporating, for example, pathogen reduction technology. Under these circumstances, laboratory testing may no longer be necessary to assure platelet safety from bacterial contamination. For this reason, we are not specifying a specific requirement to “test” in the final rule, and do not require that “tests” be performed in a laboratory certified under CLIA.

(Comment 18) One comment observed that bacterial speciation may be viewed as an important part of an investigation of a failed product quality control test. Species identification assists in isolating the source of the contamination, such as when the species is associated with environmental contamination, skin flora, or is an enteric organism. Furthermore, species identification permits appropriate investigation and donor counseling to take place. The comment noted that the identification of certain skin bacteria may raise questions about adequate performance of skin preparation procedures, and may support further examination of the donor’s antecubital areas for scarring and pitting at the donor’s next donation. The identification of

enteric organisms such as Streptococcus bovis may be an indication of an underlying illness in the donor.

(Response) We agree with these observations. Bacteria may be introduced into a platelet component by means that do not indicate any illness in the donor, such as passage of the collection needle through the donor's non-sterile skin, or other environmental factors. However, in rare cases, the presence of bacteria is due to its endogenous presence in the donor's bloodstream. This can reveal a serious illness in the donor (Ref. 18). For example, the presence of Streptococcus bovis in the blood is associated with colonic pathology, including malignancy (Refs. 18, 19). Speciation of bacteria can provide information valuable to the processing establishment about deficiencies in platelet collection and processing methods, and may provide information that may be important to the donor's health. To assure blood safety, final § 606.145(b) requires that, in the event that a blood collection establishment identifies platelets as bacterially contaminated, that establishment may not release for transfusion the platelets or any other component prepared from the same collection, and must take appropriate steps to identify the organism. Final § 606.145(c) requires that, in the event that a transfusion service identifies platelets as bacterially contaminated, the transfusion service must not release the platelets, and must notify the blood collection establishment that provided the platelets. The transfusion service must take appropriate steps to identify the organism; these steps may include contracting with the collection establishment or a laboratory to identify the organism. The transfusion service must further notify the blood collection establishment either by providing information about the species of the contaminating organism when the transfusion service has been able to identify it, or by advising the blood collection establishment when the transfusion service has determined that the species cannot be identified. Final § 606.145(d) provides that in

the event that a contaminating organism is identified under § 606.145(b) or (c), the responsible physician for the collection establishment must determine whether the contaminating organism is likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor, in accordance with a standard operating procedure developed under § 606.100(b)(22). This determination may not be further delegated.

Finally, we note that requirements to take appropriate steps to identify contaminating organisms apply only when bacterial contamination is found. In the event that approved or cleared devices or other methods that employ pathogen reduction technology, rather than relying on identifying contamination, are determined to be adequate and appropriate, the use of such technologies may eventually limit the situations where establishments would need to identify the presence of contaminating bacteria. If fewer instances of contamination are identified due to widespread use of pathogen reduction technologies, the instances where establishments are required to identify the contaminating organisms would also be reduced in number.

(Comment 19) Several comments stated that they consider the decision whether to identify the species of the bacterial contaminant to fall within the purview of the collection facility's medical director. Some stated that the standard of care already includes speciation of isolated bacteria and donor notification when felt to be medically appropriate, and regulation is not required in this area. One comment stated that, consistent with the College of American Pathologists and AABB accreditation standards, blood establishments should have a defined policy for how to investigate and handle bacterial contamination. However, this policy represents medical decision making that should not be addressed in regulation.

(Response) Current good manufacturing practices applicable to the manufacture of drugs, including transfusable platelet components, already require a manufacturer to thoroughly

investigate the failure of a batch or any of its components to meet any of its specifications (21 CFR 211.192). Identifying the species of contaminating bacteria can provide information concerning the likely pathway that permitted the bacteria to enter the contaminated component. That information may then permit a manufacturer to determine whether, and how, a deficient manufacturing practice (for example, poor arm preparation, non-sterile docking, or contamination of the collection container) allowed the contamination to occur. Such a determination could enable the manufacturer to take appropriate corrective actions, which may include, for example, additional training of personnel. Because speciation of bacteria provides information that is important to a manufacturer's investigation of the failure of a platelet component to be free of bacteria, a decision concerning whether or not to identify the species of contaminating bacteria is not solely for the medical director to make. Instead, it falls within the province of production and process controls. For this reason, we have included in § 606.145 an explicit current good manufacturing practice requirement for manufacturers to take appropriate steps to identify the organism. In addition, in the event that the contaminating organism is identified, § 606.145(d) requires the responsible physician for the collection establishment to determine whether the contaminating organism is likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor, in accordance with a standard operating procedure developed under § 606.100(b)(22).

(Comment 20) Some comments noted that FDA did not provide a definition of an endogenous bacterial infection, and stated that they are not aware of any bright line dividing an endogenous bacteremia from contamination, since the organisms involved overlap significantly.

(Response) The proposed rule referenced "endogenous" bacteria in proposed § 630.40(a), which would have required notification of a donor "whose platelet component has

tested positive for an endogenous bacterial contamination.” In § 606.145(d), we now require the responsible physician for the collection establishment to determine whether the contaminating organism is likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor, in accordance with a standard operating procedure. Examples of contaminating organisms that the responsible physician, based on his or her medical judgment, may determine to be likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor include Streptococcus bovis, Streptococcus veridins, and Salmonella. We require the responsible physician to make this determination in accordance with a standard operating procedure.

(Comment 21) Another comment stated that FDA should not require testing for a contaminating organism until the Agency approves a test specifically for that purpose. The comment supported the introduction of bacterial screening when assays become available that are accurate, rapid, and economically feasible.

(Response) We believe that, consistent with current standards of the College of American Pathologists and AABB, a majority of collection establishments are currently using bacterial detection methods such as culture to identify the contaminating organism. Section 606.145(b) and (c) require that blood collection establishments and transfusion centers take appropriate steps to identify the organism. To satisfy this requirement, an establishment would use adequate and currently available technologies, which may include appropriate culture methods. As we noted in our response to comment 15, we intend to issue guidance addressing how establishments would use FDA approved or cleared devices or methods that FDA has determined to be adequate to assure that the risks of bacterial contamination of platelets are adequately controlled.

(Comment 22) Some comments noted that, when a transfusion service pools platelets separated from Whole Blood with other units of Whole Blood-derived platelets immediately before releasing the pooled platelet component for transfusion, there is not enough time to use culture methods to assess the pooled unit for bacterial contamination. The comments stated that the proposed rulemaking would, as a practical matter, prohibit the use of components prepared from platelets separated from Whole Blood and then pooled immediately prior to transfusion. The comments further stated that while systems exist that allow Whole Blood-derived platelets to be pooled by a collection facility before storage and tested for bacteria using culture-based methods, these systems are not used by most collection facility component laboratories.

(Response) We disagree that the requirements in final § 606.145 will prohibit the use of platelet components prepared at the transfusion service by pooling units of Whole Blood-derived platelets, and note that practices have evolved since the comment raised these objections. Since the proposed rule published, FDA has cleared rapid bacterial detection devices that detect bacteria in platelets. These devices do not use culture-based methods, and provide a result in less than 1 hour. The transfusion service may use such devices to control the risks of bacterial contamination before releasing a pooled platelet unit for transfusion. We also note that pre-storage pooling has become the prevailing practice for platelet units derived from Whole Blood. Based on data presented at the July 2012 AABB Workshop (Ref. 20), currently about 65 percent of Whole Blood-derived platelets are cultured by collection establishments as pre-stored pools. About 35 percent of those platelet components are tested as pools constituted within 4 hours prior to transfusion using an FDA-cleared rapid test (Ref. 20).

(Comment 23) Some comments stated that the standards requiring testing for platelet contamination, such as those of AABB, do not currently apply to Whole Blood-derived platelets.

Transfusion services may not subject the platelet components they pool to bacterial testing, and instead use, at the time of release for transfusion, surrogate methods such as pH meters, to assess whether bacterial contamination is likely.

(Response) Testing using surrogate methods such as pH meters is inadequate to determine whether platelets are bacterially contaminated. Studies have shown that pH does not constitute an adequate surrogate marker for bacterial contamination in platelets, and has poor sensitivity and poor positive predictive value (Ref. 13). Other FDA cleared devices, including rapid tests, are available for use by a transfusion service to identify the presence of bacterial contamination. The use of such devices can help assure the safety of the platelet component, and protect the recipient from bacterial infections. Accordingly, final § 606.145(a) requires blood collection establishments and transfusion services to assure that the risks of bacterial contamination of platelets are adequately controlled using FDA approved or cleared devices or other adequate and appropriate methods found acceptable for this purpose by FDA.

(Comment 24) Some comments stated that it is not appropriate to extend requirements addressing bacterial contamination of platelets to the manufacture of other transfusable blood components. They note that the rate of reported septic reactions to Red Blood Cells and plasma products is very low, and methods to identify bacterial contamination in these products are not well developed. Furthermore, there appears to be little rationale for requiring bacterial testing of blood products that, unlike platelets, are stored at cold temperatures that do not promote bacterial growth.

(Response) We agree that transfusable blood components other than platelets are stored at cold temperatures that do not promote bacterial growth, and that the rate of septic reactions to these products is very low. The final rule includes requirements specific to bacterial

contamination of platelet components, and also provides that, in the event that a blood collection establishment or transfusion service identifies platelets as bacterially contaminated, that establishment must not release the product or any other component prepared from the same collection. In the event of technological changes, or significant evidence that transfusion recipients are at greater risk from bacterial contamination of Red Blood Cell and Plasma products than is presently considered to exist, we will consider again whether additional requirements specific to blood components other than platelets are necessary.

E. Records (§ 606.160)

The final rule makes the conforming changes described in proposed § 606.160(b)(1)(ix) and (xi), now identified as § 606.160(b)(1)(x) and (xi). These changes relate to the move of the donor notification provisions from § 630.6 to § 630.40. Current § 606.160(b)(1)(x) is redesignated as § 606.160(b)(1)(ix). We also inserted the word “postal” before the word “address” in the current requirement, so that the recordkeeping requirement would closely track the requirement in final § 630.10(g)(1) to obtain a “postal address.”

In response to comments, we have significantly narrowed the requirements we proposed in § 606.160(e). We have not finalized a requirement to share a record of all ineligible donors with appropriate personnel at all locations operating under the same license or under common management. Instead, final § 606.160(e)(1) requires establishments to maintain at each location a record of all donors found to be ineligible or deferred at that location, so that blood and blood components from such individuals are not collected or distributed while they are ineligible or deferred. This provision is related to current § 606.160(e), which requires that “A record shall be available from which unsuitable donors may be identified so that products from such individuals will not be distributed.” Final § 606.160(e)(2) through (4) requires establishments to maintain a

cumulative record of donors deferred from donation under § 610.41 based on their reactive tests for evidence of infection due to HIV, HBV, or HCV. In addition, establishments other than Source Plasma establishments must include in this cumulative record donors deferred from donation for evidence of infection due to HTLV or Chagas disease. Establishments must maintain the cumulative record of deferred donors at all locations operating under the same license or under common management, must update the cumulative record at least monthly, and revise the cumulative record for donors who are requalified under § 610.41(b). Final § 630.10(d) sets out requirements for establishments to consult the cumulative record of deferred donors before collection, or if pre-collection review is not feasible, before release of any blood or blood component prepared from the collection.

(Comment 25) We received several comments objecting to the scope of donor deferrals that would be included in the list of ineligible donors described in the proposed rule.

(Response) We agree that the types of donor deferrals that were proposed to trigger inclusion in the list of ineligible donors were broad, and that requiring extensive deferral records to be updated and consulted at the donation site before collection could be unduly burdensome. The final rule requires establishments to enter into the cumulative list only those donors who were deferred under § 610.41 due to reactive test results for HIV, HBV, or HCV, as well as HTLV or Chagas disease for donors other than Source Plasma donors.

(Comment 26) We received several comments objecting to a requirement for a common donor deferral registry to be used by all donor screening locations operating under a single operating license or common management. Some expressed concern that it would be technologically difficult to make this information available to all locations under a single operating license or under common management.

(Response) Under the final rule establishments must enter into the cumulative list only those donors who were deferred under § 610.41 due to reactive screening test results for HIV, HBV, or HCV, as well as HTLV or Chagas disease for donors other than Source Plasma donors. We believe that it is a current industry practice to maintain such lists (Refs. 21, 22). In the final rule, we have significantly narrowed the scope of information subject to this requirement in a manner that is consistent with this industry practice, and to reduce the technological challenges of making reliable information available.

We disagree with the suggestion that it is technologically difficult for facilities operating under a single license, or under common management, to make this more limited cumulative record of deferred donors available at collection sites for consultation by all facilities operating under a single operating license or under common management. The cumulative record is now required to list only a subset of deferred donors, who are identified by very specific and objective criteria. This information may be made available by providing a copy of the cumulative record of deferred donors at each collection site. Establishments may also comply with this requirement by providing for a pre-collection query of a centrally maintained cumulative record of deferred donors. In the event that pre-collection review is not feasible, § 630.10(d)(1) requires establishments to consult the cumulative record prior to release of any blood or blood component prepared from the collection.

(Comment 27) In the preamble to the proposed rule we also solicited comments on the feasibility of sharing donor deferral lists among licensed and registered establishments. Such shared lists are known as national donor deferral registries, and are already in use among establishments collecting Source Plasma. We received several comments opposing a requirement for a national donor deferral registry. Some described national donor deferral

registries as unnecessary or burdensome. One comment emphasized differences between Source Plasma and collections of Whole Blood and other blood components, and stated that the Source Plasma donor deferral registry would be a poor model for other collection establishments. The comment cited technical limitations such as computer down times and connectivity from remote locations, and stated that the creation of a national donor deferral system for whole blood donors would be burdensome and time-consuming.

(Response) As noted, it is currently the practice of most Source Plasma collection establishments to determine whether a donor is permanently deferred because the donor tested reactive for HIV, HBV, or HCV by accessing a shared list of deferred donors called the National Donor Deferral Registry (NDDR). We recognize that the NDDR is a voluntary, self-regulating initiative by the Source Plasma collection industry that is operated by a third party administrator. We agree it is an important industry practice to ensure the safety of plasma-derived therapies. Moreover, we are aware that, to increase efficiency and to protect donor confidentiality and proprietary information across non-affiliated Source Plasma establishments, information entered into the NDDR is coded as to infectious disease test result. This rule is not intended to interfere with that practice. We believe that the current NDDR goes beyond the requirements in the final rule, since it is a national list of donors deferred by multiple licensed establishments (Ref. 23). For Source Plasma establishments, we believe that participation in the NDDR would meet the requirements under this section. If a Source Plasma establishment does not participate in the NDDR, the establishment must establish its own cumulative record of deferred donors with all other establishments operating under common management or a single license, as required under this section.

We are not requiring blood collection establishments to share donor deferral information in a national donor deferral registry.

(Comment 28) In the preamble of the proposed rule (72 FR 63416 at 63420), we stated that we were considering whether to include, in the final rule, a provision requiring that the donor deferral records be used and disclosed only for purposes consistent with subchapter F of 21 CFR Chapter I. One comment expressed concern about the importance of protecting donor information. Another comment explained why additional protections are not needed. For example, the NDDR used by Source Plasma collectors is never available in its entirety to its users. When an NDDR check is performed, the database is queried to determine whether a record for the potential donor is present. If a record is present, the establishment performing the check is informed that a record exists. No other information is shared. One comment stated confidentiality of information is of extraordinary importance to the industry. The comment stated that each company uses its own best methods for handling confidential information consistent with its operational policies and procedures in submitting relevant information to the NDDR. One comment stated that in their current system, unique donor identifiers such as social security numbers are not available.

(Response) As we discussed earlier in this section, we are not requiring establishments to participate in a national donor deferral registry system, and we are not requiring the sharing of information outside a single license or outside common management.

F. Test Requirements (§§ 610.40, 640.5, 640.71(a))

We have modified proposed § 610.40(a), (b), and (e) in order to address concerns that the proposed rule did not permit an adequately flexible approach to donor testing. Although the testing for HIV, HBV, HCV, and HTLV that is required under current § 610.40(a) would

continue under the new rule, we have also provided additional flexibility for FDA to permit testing less frequently than at every donation, or as appropriate, to stop testing, for relevant transfusion-transmitted infections other than HIV, HBV, and HCV, provided that the practices are supported by evidence related to the risk of transmission of such infection, such as epidemiological data and developments in risk reduction technology. In § 610.40(a), we have clarified requirements for Chagas disease and West Nile virus testing and have continued the existing requirement to test donations for evidence of syphilis. We have also provided requirements for testing for infectious agents that may be identified in the future as relevant transfusion-transmitted infections, in the event that testing becomes necessary to ensure blood safety.

Final § 610.40(b) clarifies that the tests performed to comply with § 610.40(a) must be “licensed, approved, or cleared screening tests”; current § 610.40(b) refers only to “approved screening tests”. We made this change because § 610.40(b) is now applicable to syphilis testing, and syphilis screening tests are generally “cleared,” and not licensed or approved.

The final rule contains a different heading for § 610.40(c). Instead of “Exceptions to testing for allogeneic transfusion or further manufacturing use,” which is used in current § 610.40(c), the heading is now “Exceptions to testing for dedicated donations, medical devices, and samples.” We made this change because the exception from testing for HTLV is now addressed in § 610.40(a)(2)(ii) and (iii), and we are removing the exception for HTLV now found in current § 610.40(c)(2). Since § 610.40(c) no longer addresses Source Plasma (the most commonly identifiable blood component collected for further manufacturing use) the new heading is more accurate.

In § 610.40(e), we are maintaining the existing requirement for further testing when a donation tests reactive for a relevant transfusion-transmitted infection. When a licensed, approved, or cleared supplemental test is not available, the rule provides greater flexibility to allow the use of licensed, approved, or cleared tests, as adequate and appropriate to determine the reactive donor's infection status. We address further testing for donations reactive for syphilis in § 610.40(e)(2).

Under the proposed rule, existing testing practices for HIV, HBV, HCV, and HTLV would continue. In addition, we proposed that, when a test for the disease or disease agent is approved or cleared for donor screening and FDA determines that testing is necessary to reduce the risk of transmission of the relevant transfusion-transmitted infection by the blood or blood component, blood collection establishments would be required to test for CJD, vCJD, and malaria, which were identified as relevant transfusion-transmitted infections in proposed § 630.3(g)(1)(vi) through (viii). We further proposed that, when the conditions concerning the availability and necessity of testing were met, establishments would be required to test for other relevant transfusion-transmitted infections meeting the standard in proposed § 630.3(g)(2).

We also solicited comments with supporting data on whether to discontinue the requirement for testing for syphilis, and we indicated that we might drop the requirement for syphilis testing if sufficient data were submitted (72 FR 63416 at 63422). We stated that testing for a relevant transfusion-transmitted infection may not be required if viral inactivation or removal procedures have been validated to ensure inactivation or removal of the infectious agent and screening for risk factors is available, unless the risk of harm from transmission is too great to rely solely on viral inactivation procedures and screening for risk factors. We are finalizing this provision using the concepts proposed, but have provided greater flexibility to permit

establishments to stop testing, or vary testing frequency, when the evidence shows testing each donation intended for transfusion is no longer necessary to reduce the risk of transmission of the relevant transfusion-transmitted infection by the blood or blood component. Such changes must be made in accordance with procedures found acceptable for this purpose by FDA. We have retained requirements for syphilis testing of blood and blood components for transfusion, since we did not receive data sufficient to support their elimination. However, if such evidence is developed in the future, the rule would allow establishments to change their testing practices in accordance with procedures found acceptable for this purpose by FDA. We have removed existing § 610.40(i), which required testing for syphilis, and address testing transfusable blood and blood components for syphilis in § 610.40(a). To reflect this new citation for the syphilis testing requirement, we made conforming changes to §§ 610.40(d), (g), (h)(1), (h)(2)(vi), and (h)(2)(vii), 610.41 and 610.42.

Current § 640.5 provides additional standards for testing Whole Blood. We did not propose changes to § 640.5 in the proposed rule. However, based on comments received and discussed at comment 29, we recognize that greater flexibility in testing schedules may be appropriate, and that it may be adequate and appropriate to test donors for certain relevant transfusion-transmitted infections less frequently than at every donation, or while observing geographic or seasonal limitations. Accordingly, we are making a related change to the introductory paragraph of § 640.5, which currently provides “All laboratory tests shall be made on a specimen of blood taken from the donor at the time of collecting the unit of blood, and these tests shall include the following.” Because it may be appropriate to perform testing other than on each collection, we are modifying this to state “All laboratory tests shall be made on a specimen of blood taken from the donor, and these tests shall include the following.”

We are also making one other minor conforming change, removing current § 640.5(a) which requires “Whole Blood shall be negative to a serological test for syphilis.” This provision is duplicative of the requirement to test for syphilis in new § 610.40(a)(2), and to avoid confusion we are deleting § 640.5(a).

For similar reasons, we are amending the provisions of current § 640.71(a) which specify certain donor screening tests related to Source Plasma. We are removing the phrase “the following tests” and adding in its place “testing performed in accordance with § 610.40 of this chapter and § 640.65(b)” and we are removing the list of tests set out in current § 640.71(a)(1) through(4). We are making these changes so that § 640.71(a) will conform to final § 610.40.

1. Section 610.40(a)

Final § 610.40(a) addresses testing for the infectious agents already required under current § 610.40(a), and now identified in § 630.3(h)(1) as relevant transfusion-transmitted infections. We continue to require testing of each donation for evidence of infection due to HIV; HBV; and HCV. We also continue to require testing of each donation, except Source Plasma, for evidence of infection due to HTLV and syphilis. We are adding a requirement to test donations, except Source Plasma, for West Nile virus and Chagas disease.

As in the existing regulations, testing requirements for certain relevant transfusion-transmitted infections vary for Source Plasma. For example, we have concluded that, in the absence of testing, the risk of HTLV, a highly cell-associated pathogen, is sufficiently mitigated by plasma derivative manufacturing steps, including validated viral inactivation and removal procedures. These manufacturing procedures therefore obviate the need to test individual donations of Source Plasma for HTLV. We have further determined that these manufacturing procedures obviate the need to test individual donations of Source Plasma for West Nile virus

and Chagas disease. Testing of Source Plasma donors for syphilis must be performed every 4 months in accordance with § 640.65(b).

The final rule allows for the possibility that, in the future, evidence related to the risk of transmission of HTLV, syphilis, West Nile virus, and Chagas disease could support the conclusion that testing of each donation is no longer necessary to reduce adequately and appropriately the risk of transmission of that relevant transfusion-transmitted infection by the blood or blood component. Under final § 610.40(a)(2)(iii)(A), if testing each donation is not necessary to reduce adequately and appropriately the risk of transmission of a relevant transfusion-transmitted infection, an establishment may adopt an adequate and appropriate alternative testing procedure that has been found acceptable for this purpose by FDA. Section 610.40(a)(4) makes clear that an assessment that testing each donation is not necessary could be based on, for example, changing science, or epidemiological or other scientific data. It may also include evidence related to seasonal or regional variations in the activity of the relevant transfusion-transmitted infection. Under final § 610.40(a)(2)(iii)(A), following an assessment that testing each donation is not necessary, establishments may adopt alternative procedures that have been found acceptable for this purpose by FDA such as initial or periodic testing of donations from the same donor due to the epidemiology of the relevant transfusion-transmitted infection.

An example of such an alternative testing paradigm is FDA's current recommendation contained in guidance for one-time testing of a donor for Chagas disease, instead of testing the donor at each donation (Ref. 24). FDA made this recommendation after reviewing comments to the draft guidance and consulting with the Blood Products Advisory Committee (April 2009) (Ref. 25). Consistent with § 610.40(a)(2)(iii)(A), we continue to recognize this testing practice

as an acceptable alternative testing paradigm for Chagas disease. In the future, new epidemiologic or other scientific data could demonstrate that a different testing paradigm, including testing of the donor at each donation, is needed to adequately and appropriately reduce the risk of transmission of Chagas disease.

This rule also provides that establishments may stop testing blood and blood components for HTLV, syphilis, West Nile virus, or Chagas disease in the event that such testing is no longer necessary. Section 610.40(a)(2)(iii)(B) authorizes such an action taken in accordance with procedures found acceptable for this purpose by FDA, when testing is no longer necessary to reduce adequately and appropriately the risk of transmission of such infection by blood or a blood component, based on evidence related to the risk of transmission of that relevant transfusion-transmitted infection. Section 610.40(a)(4) describes the evidence that would support such a finding, such as a change in the epidemiology of the relevant transfusion-transmitted infection, or the implementation of pathogen reduction technology. We note that the rule does not require establishments to test donors of Source Plasma for these relevant transfusion-transmitted infections because of reduced risk of transmission by fractionated products manufactured from Source Plasma.

We recognize that there are no donor screening tests currently licensed, approved, or cleared for the following relevant transfusion-transmitted infections identified in § 610.40(a)(3): CJD, vCJD, or malaria. In the event that a donor screening test is licensed, approved or cleared for one of these infections, the rule would require the use of the test, if testing is necessary to reduce adequately and appropriately the risk of transmission of that relevant transfusion-transmitted infection.

Similarly, FDA has not yet identified any relevant transfusion-transmitted infections under the criteria in § 630.3(h)(2). In the future, if a transfusion-transmitted infection is identified by FDA to meet the criteria for a relevant transfusion-transmitted infection under § 630.3(h)(2), and FDA has licensed, approved or cleared a donor screening test, FDA may seek advice from the Blood Products Advisory Committee on the use of the donor screening test, and seek public comment by issuing guidance in accordance with good guidance practices. When a transfusion-transmitted infection has met both the standards under final § 630.3(h)(2) and § 610.40(a)(3), such that it now meets the criteria for a relevant transfusion-transmitted infection and testing is necessary to reduce adequately and appropriately the risk of transmission of that relevant transfusion-transmitted infection, use of the test would be required. When testing for a particular relevant transfusion-transmitted infection become necessary under final § 610.40(a)(2) or (a)(3), FDA intends to enforce the testing requirements under this regulation only after issuing a final guidance advising establishments and the public of the Agency's assessment of the applicable criteria.

Should testing become necessary to reduce adequately and appropriately the risk of transmission of a relevant transfusion-transmitted infection under § 610.40(a)(3), FDA will also consider the application of § 610.40(a)(3)(ii)(A), which we drafted to parallel § 610.40(a)(2)(iii)(A). Under this provision, if testing each donation is no longer necessary to reduce adequately and appropriately the risk of transmission of a relevant transfusion-transmitted infection, an establishment may adopt an adequate and appropriate alternative testing procedure that has been found acceptable for this purpose by FDA. Under § 610.40(a)(4), such methods may address seasonal or regional variations in the activity of the relevant transfusion-transmitted infection, or where, due to the epidemiology of the relevant transfusion-transmitted infection,

initial or periodic testing of donations from the same donor (instead of testing each donation) would be sufficient. In the event that the standard set forth in § 610.40(a)(3)(ii)(A) and (a)(4) is met, FDA intends to reassess the applicability of alternative testing procedures, and if needed, seek advice from the Blood Products Advisory Committee and issue new guidance in accordance with good guidance practices. Similarly, § 610.40(a)(3)(ii)(B), which we drafted to parallel § 610.40(a)(2)(iii)(B), recognizes that, at some later point in time, if evidence related to the risk of transmission of such infection supports a determination that testing is no longer necessary to adequately and appropriately reduce the risk of transmission of that relevant transfusion-transmitted infection. When testing is not necessary, establishments may stop such testing in accordance with procedures found acceptable for this purpose by FDA. Sections 610.40(a)(3)(ii)(A) and (a)(3)(ii)(B) provide mechanisms for tailoring testing requirements to more accurately address the risks presented by a relevant transfusion-transmitted infection, while assuring that blood establishments perform adequate and appropriate testing of blood donations.

We recognize that greater flexibility in testing schedules may be appropriate, and have incorporated these changes into this final rule. Accordingly, we are making a related change to the introductory paragraph of § 640.5, which currently provides “All laboratory tests shall be made on a specimen of blood taken from the donor at the time of collecting the unit of blood, and these tests shall include the following.” Because it may be appropriate to perform testing other than on each collection, we are modifying this to state “All laboratory tests shall be made on a specimen of blood taken from the donor, and these tests shall include the following.”

(Comment 29) One comment supported a requirement to test for relevant transfusion-transmitted infections that meet the definition under proposed § 630.3(g)(2), when such testing is available and is necessary to reduce the risk of transmission of the relevant transfusion-

transmitted infection by the blood or blood component, because of the need to identify and respond to current and future agents.

(Response) We agree with this comment. We have drafted final § 610.40(a)(3) to provide a framework for applying the rule's testing provisions to infectious agents that may, in the future, meet the standard for relevant transfusion-transmitted infection, as defined in final § 630.3(h)(2). For example, under § 630.3(h)(2), a transfusion-transmitted infection such as babesia or dengue virus may meet the definition of a relevant transfusion-transmitted infection if the disease or disease agent meets criteria for incidence and/or prevalence or may have been accidentally or intentionally released, and if appropriate screening measures have been developed and/or an appropriate screening test has been licensed, approved, or cleared for such use and is available. In the event that such a test has been licensed, cleared, or approved, its use would be required under this section when necessary to reduce the risk of transmission of the relevant transfusion-transmitted infection. Whether testing is necessary would depend on all the relevant circumstances, including, for example, whether screening for travel history or another risk factor would, by itself, adequately reduce the risk of transmission. FDA intends to seek advice on relevant scientific issues from the Blood Products Advisory Committee as appropriate.

(Comment 30) One comment suggested that testing be required for West Nile virus, Chagas disease, and bacteria because testing for those agents is currently conducted.

(Response) We agree that establishments should be required to conduct testing for West Nile virus and Chagas disease for blood and blood components for transfusion. Under the proposed rule, these infectious agents would have been evaluated under the standards for relevant transfusion-transmitted infection in proposed § 630.3(g)(2). To provide greater clarity on this regulation, we have specified these diseases by name in the definition of relevant

transfusion-transmitted infection at § 630.3(h)(1)(vi) and (vii), and testing for these agents is addressed in § 610.40(a)(2). We recognize that bacterial contamination of platelets presents significant issues related to the safety, purity, and potency of platelets. We have addressed the risk presented by bacterial contamination of platelets in §§ 606.145 (see comments 13 through 24), 630.30 (see comments 103 through 106), and 630.40 (see comment 107). We address bacterial contamination of blood components other than platelets in response to comment 24.

(Comment 31) Several comments stated that FDA should not require that blood donors be tested for syphilis. One comment recommended that testing for syphilis continue to be required, but for public health reasons, rather than for its value in protecting blood safety.

(Response) We are continuing to require testing for syphilis at this time. We note that in the proposed rule, FDA requested information on the value of testing for syphilis as a marker of increased risk behavior, as a surrogate test for other infectious diseases, and in preventing the transmission of syphilis through blood transfusion. We stated that if we received adequate data, FDA would eliminate or modify this testing requirement in the final rule. This was the second time we invited the submission of such data; we also invited it in an earlier proposed rule, “Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents” (64 FR 45340, August 19, 1999). Syphilis testing was discussed at the September 2000 Blood Products Advisory Committee meeting and studies that might help determine that such testing would no longer be needed were identified (Ref. 26). We have not received adequate scientific data in response to our solicitations.

However, the final rule recognizes the possibility of discontinuing the requirement for syphilis testing of blood and blood components intended for transfusion. We have moved this requirement from § 610.40(i) to § 610.40(a). The more flexible framework found in

§ 610.40(a)(2)(iii) provides a mechanism under which an establishment could stop testing for syphilis or adopt different testing frequency, provided that evidence related to the risk of transmission demonstrates that testing of each donation is no longer necessary to reduce adequately and appropriately the risk of transmission of syphilis, and provided that the change is made in accordance with procedures found acceptable for this purpose by FDA. In the event that the evidence supports such a determination under § 610.40(a)(2)(iii)(B), FDA intends to issue guidance recognizing procedures for ending syphilis testing of blood and blood components for transfusion.

(Comment 32) Another comment asserted that current syphilis testing practices are deficient, since many confirmed positives are in fact false positives.

(Response) We recognize that syphilis screening tests, like other screening tests, may yield false positive results on some donations. However, § 610.40(h)(2)(vi) permits the use of blood and blood components that test reactive for syphilis if the donation is further tested by an adequate and appropriate test which demonstrates that the reactive screening test is a biologic false-positive. In addition, consistent with the current regulation, the final rule permits the reentry of positive donors who have been successfully requalified under § 610.41(b).

(Comment 33) Several comments stated that testing for CJD and vCJD should not be required.

(Response) There are no currently licensed, approved, or cleared donor screening tests for these agents. If and when donor screening tests for CJD or vCJD become available, testing would be required under this provision only if testing was necessary to adequately and appropriately reduce the risk of transmission of CJD or vCJD, taking into account the risks presented by donated blood and blood components.

(Comment 34) One comment stated that the use of the defined term relevant transfusion-transmitted infection in the proposed rule (§ 630.3(g)) in § 610.40(a) would require testing for agents such as cytomegalovirus (CMV), even though screening of all donors for CMV is not currently thought to be necessary.

(Response) We agree that, currently, it is not necessary to test all donors for CMV. For this reason, donor screening testing for CMV is not now required under § 610.40 of the final rule, which in § 610.40(b) requires testing only “as necessary to reduce adequately and appropriately the risk of transmission” (emphasis added).

2. Section 610.40(e)

In this section, FDA is maintaining the requirement for further testing when a donation tests reactive for a relevant transfusion-transmitted infection. Consistent with the existing regulation and the proposed rule, establishments must perform further testing using an approved supplemental test when one is available. However, the final rule now recognizes that supplemental tests may be licensed, approved, or cleared. We eliminated the term “additional” as unnecessary. When a supplemental test is not available, the final rule requires the use of other tests as adequate and appropriate to provide additional information concerning the reactive donor’s infection status. This language provides greater clarity concerning the purpose of further testing. Under this paradigm, if an approved supplemental test was not available, or became unavailable, an establishment would conduct further testing using, for example, an alternative algorithm to provide additional information to the establishment concerning the donor’s infection status. For example, a testing algorithm that was adequate and appropriate to determine the reactive donor’s infection status might include the use of multiple approved donor screening tests. We intend to issue guidance on these issues as needed.

Section 610.40(e)(2) requires establishments to perform further testing when a donation is reactive by a non-treponemal donor screening test for syphilis. Previously, we did not require establishments to perform any supplemental testing after a reactive test for syphilis. However, further testing may help to rule out syphilis infection. Additionally, a reactive test result on a non-treponemal syphilis test may be a biologic false-positive result, which may potentially be indicative of a serious illness in the donor, such as lupus erythematosus (Ref. 27). In this setting, further testing will provide important information for donor notification, including information that is appropriate for medical follow up and counseling under § 630.40(b)(4). Blood establishments must perform further testing using a licensed, cleared, or approved supplemental test for syphilis, when available. When no such supplemental test is available, FDA would consider the use of a licensed, approved, or cleared treponemal test to be adequate and appropriate to provide additional information concerning the donor's infection status. Establishments are not required to perform further testing of a donation found to be reactive by a treponemal donor screening test for syphilis, since those tests do not present similar risks of a biological false positive result.

(Comment 35) FDA received several comments raising concern about the lack of availability of supplemental tests for certain infectious agents for which FDA currently requires donor screening.

(Response) FDA recognizes the importance of confirming the infection status of a deferred donor. This information is important to donor notification, and in some instances determines whether a donor should be entered into the cumulative record of deferred donors under § 606.160(e). Accordingly, we have revised this section to require, when a supplemental

test is not available, the use of one or more licensed, approved, or cleared tests as adequate and appropriate to provide additional information concerning the reactive donor's infection status.

G. Donor Deferral (§ 610.41)

We have made conforming changes in final § 610.41(a) to incorporate the “relevant transfusion-transmitted infection” terminology, the inclusion of syphilis testing in § 610.40(a) instead of § 610.40(i), and updated the term from “supplemental” testing to “further” testing, to reflect the change in § 610.40(e). At the same time we clarified the meaning of the second sentence of § 610.41(a)(1), which now states, “However, you must defer the donor if further testing for HBV or HTLV has been performed under § 610.40(e) and the donor is found to be positive, or if a second, licensed, cleared, or approved, screening test for HBV or HTLV has been performed on the same donation under § 610.40(a) and is reactive, or if the donor tests reactive for anti-HBc or anti-HTLV, types I and II on more than one occasion.” Previously this provision stated, “When a supplemental (additional, more specific) test for anti-HBc or anti-HTLV, types I and II has been approved for use under § 610.40(e) by FDA, such a donor must be deferred.” Consistent with current guidance, establishments now defer a donor who tests reactive for anti-HBc or anti-HTLV, types I and II, on more than one occasion, or when further testing on the same donation is positive, or when a second licensed, cleared, or approved screening test for HBV or HTLV has been performed on the same donation and is reactive (Refs. 28, 29).

H. Purpose and Scope (§ 630.1)

Final § 630.1 describes the purpose and scope of the combined subparts of part 630 that require blood establishments to perform the following activities: determine that on the day of donation the donor is in good health and is eligible to donate blood or blood components;

determine the suitability of the donation for use in transfusion or further manufacturing; and notify a donor who is deferred from donating because the donor did not satisfy the eligibility criteria described in part 630 or because the donor's test results revealed a relevant transfusion-transmitted infection as described under § 610.40. This section is consistent with the proposed rule, with one change. Since we are not defining the term "you" in § 630.3, we have finalized § 630.1(b) to describe the scope as "Blood establishments that manufacture blood and blood components, as defined in § 630.3(a) and (b) of this chapter, must comply with subparts A, B, and C of this part." Accordingly, the requirements in part 630 apply to any establishment or facility that collects, or performs other manufacturing steps for, blood or blood components for transfusion, including components for autologous use, for further manufacturing use, or for use as a component of a medical device.

I. Medical Supervision (§§ 630.5, 640.130)

Final § 630.5(a) requires a responsible physician, as defined in § 630.3(i), to determine the eligibility of a donor of blood or blood components, including Source Plasma, in accordance with the regulations in 21 CFR Chapter I, subchapter F. This section describes the activities related to the collection of blood and blood components that the responsible physician may delegate to a physician substitute or other trained person, taking into account the training and medical expertise needed to assess whether the donor's health permits the collection, and to mitigate the risks related to donation. Recognizing that conditions may change, final § 630.5(a)(1)(i)(C) provides that the Director, CBER, may authorize the delegation of additional activities, after determining that delegating the activity would present no undue medical risk to the donor or to the transfusion recipient. The requirements in this section are not intended to preempt State or local laws when those laws require a higher level of medical oversight for

certain blood collection activities. This section combines the existing requirements related to eligibility for donors of Whole Blood (§ 640.3) and Source Plasma (§ 640.63) into a single section.

For the collection of blood and blood components other than Source Plasma and plasma collected by plasmapheresis, § 630.5(b) authorizes the responsible physician to delegate the following activities to a physician substitute or other trained person: Determining the eligibility of a donor and documenting assessments related to that determination; collecting blood and blood components; returning red blood cells to a donor during apheresis procedures; and obtaining the informed consent of a plateletpheresis donor as described in § 640.21(g). Under § 630.5(b)(2), the responsible physician is not required to be present at the collection site when any of these activities are performed, provided that the responsible physician has delegated oversight of these activities to a trained person who is not only adequately trained and experienced in the performance of these activities but also adequately trained and experienced in the recognition of and response to the known adverse responses associated with blood collection procedures.

However, under § 630.5(b)(1)(i)(A), the responsible physician must not delegate the examination and determination that the health of a donor would not be adversely affected by donating, when the donor's systolic blood pressure falls outside the range of 90 to 180 millimeters (mm) of mercury, or when the diastolic blood pressure falls outside the range of 50 to 100 mm of mercury. Additionally, the responsible physician must not delegate the examination and determination that the health of a donor would not be adversely affected by donating Whole Blood or Red Blood Cells more frequently than specified under § 630.15(a)(1).

Under § 630.5(b)(1)(i)(B), the responsible physician must not delegate the following determinations: That the health of a donor whose pulse measurement falls outside the range of 50 to 100 beats per minute, or is irregular, would not be adversely affected by donating; that the health of an ineligible autologous donor permits the collection procedure; and that a dedicated plateletpheresis donor is in good health. The responsible physician may make the determinations addressed in § 630.5(b)(1)(i)(B) by telephonic or other offsite consultation.

Under § 630.5(b)(1)(i)(C), the responsible physician must not delegate the determination of the health of the donor or the determination that the blood or blood component collected would present no undue medical risk to the transfusion recipient, as required for dedicated donations by an ineligible donor for a specific transfusion recipient based on documented exceptional medical need. The responsible physician may make this determination by telephonic or other offsite consultation. In recognition that conditions may evolve in the future, we have added § 630.5(b)(1)(v) to permit the responsible physician to delegate other activities when authorized by the Director, CBER, based on a determination that delegating the activities would present no undue medical risk to the donor or to the transfusion recipient. We anticipate that the Director, CBER, would authorize such delegations under 21 CFR 640.120, or in response to submissions from individual establishments, as appropriate. In addition, such authorizations may be discussed in guidance issued under good guidance practices.

For the collection of Source Plasma and plasma collected by plasmapheresis, § 630.5(c)(1)(i) authorizes the responsible physician to delegate to a physician substitute or other trained person the following activities related to donor eligibility and blood component collection, provided that the responsible physician or a physician substitute is on the premises at the collection site: (1) Determining and documenting donor eligibility, (2) collecting blood and

blood components, (3) returning red blood cells to the donor during apheresis, (4) other activities authorized by the CBER Director, (5) the collection of Source Plasma in an approved collection program from a donor who is otherwise determined to be ineligible, and (6) the collection of a blood sample for testing required under § 640.65(b)(1)(i). Similar to collections of blood and blood components subject to delegations under § 630.5(b), § 630.5(c)(1)(i)(A)(1) through (c)(1)(i)(A)(3) provide that the responsible physician must not delegate specific responsibilities related to the assessment of donor blood pressure, donation frequency after red blood cell loss, donor pulse, and certain plasmapheresis collections from an ineligible donor. Section 630.5(c)(1)(i)(A)(4) and (c)(1)(i)(A)(5) provide that the responsible physician must not delegate the responsible physician's determination related to a donor's false-positive reaction to a serologic test for syphilis, or the responsible physician's determination to permit plasmapheresis of a donor with syphilis. In addition, § 630.5(c)(1)(ii) authorizes the responsible physician, who may or may not be present when these activities are performed, to delegate to a trained physician substitute the approval and signature for a plasmapheresis procedure and review and signature for accumulated laboratory data, the calculated values of each component, and the collection records. However, the responsible physician must not delegate the decision to reinstate a donor in accordance with § 640.65(b)(2)(i). These provisions in § 630.5(c)(1)(ii) were not expressly included in proposed § 630.5. We have included them here in order to state more clearly how the new delegation provisions in § 630.5 affect the existing responsibilities of the responsible physician.

With respect to donor immunization, consistent with the proposed rule, § 630.5(c)(2)(i) authorizes the responsible physician to delegate to a physician substitute or other trained person the administration of an immunizing agent other than red cells to a donor in an approved

immunization program, provided that the responsible physician or physician substitute is on the premises. Section 630.5(c)(2)(ii) authorizes the responsible physician to delegate to a physician substitute the function of donor immunization with red blood cells, provided that the responsible physician has approved the procedure and is on the premises when the procedure is performed. Section 630.5(c)(3) authorizes the responsible physician to delegate to a physician substitute the administration of the medical history, physical examination (including examination before immunization), and informed consent required in § 630.15(b)(1), (b)(2), and (b)(5). The responsible physician is not required to be present at the collection site when the physician substitute performs these activities.

Section 630.5(c)(4) addresses delegations for collections from infrequent plasma donors, as defined in § 630.3(e). This section authorizes the responsible physician to delegate to a trained person the following activities related to collections from infrequent plasma donors: the activities listed in § 630.15(b)(1)(i) through (b)(1)(iii) and (b)(1)(v), and the administration of the informed consent under § 630.15(b)(2). The responsible physician or a physician substitute is not required to be present at the collection site provided that the responsible physician has delegated these activities to a trained person who is also adequately trained and experienced in the recognition of and response to the known adverse responses associated with blood collection procedures. However, if Source Plasma is collected from an infrequent plasma donor and the donor is otherwise ineligible or is participating in an approved immunization program, the responsible physician may only delegate activities as described in § 630.5(c)(1) through (c)(3), as appropriate to that collection.

Section 630.5(d) requires that, for all collections, establishments must establish, maintain, and follow standard operating procedures for obtaining rapid emergency medical services for

donors when medically necessary. In addition, establishments must assure that an individual (responsible physician, physician substitute, or trained person, as defined in § 630.3) who is currently certified in cardiopulmonary resuscitation is located on the premises whenever the establishment is performing collections of blood or blood components.

Finally, we have added § 640.130 to new subpart M of 21 CFR part 640, entitled “Definitions and Medical Supervision.” Section 640.130 clarifies that the requirements for medical supervision established in § 630.5 supplement the regulations in part 640. We are adding this provision to aid the reader in identifying applicable requirements for medical supervision related to the collection of blood and blood components in accordance with part 640.

(Comment 36) One comment agreed that the responsible physician should direct and control the physician substitutes and trained personnel, and supported proposed provisions under which the responsible physician could authorize trained personnel, including physician substitutes, to determine the donor’s eligibility and collect blood and blood components in the absence of a responsible physician.

(Response) We have finalized the proposed rule to permit delegation of blood collection activities to trained persons, including physician substitutes, who are adequately instructed and qualified to perform the delegated functions. This delegation provision is not intended to preempt more restrictive requirements under State or local law. We do not require the responsible physician to be on the premises, except for red blood cell immunizations, although State or local law may provide otherwise. We have also clarified the activities that the responsible physician may not delegate. Delegation is not permitted in these circumstances because the medical expertise of the responsible physician is necessary to assess whether the donor’s health permits the collection.

(Comment 37) One comment requested clarification that designated physician substitutes and trained persons may perform the collection of platelets, Red Blood Cells and plasma (as distinct from Source Plasma) and may return red blood cells during an apheresis collection in the absence of the responsible physician. Another comment criticized a requirement for the presence of a physician substitute in the collection of Source Plasma, noting that red blood cells are now routinely returned by automated equipment during apheresis collections of plasma, Red Blood Cells, and platelets. The comment stated that, since modern apheresis devices return red blood cells to the donor through automated processes, the return of red blood cells does not pose a heightened risk relative to other procedures, and therefore there is no need for a responsible physician or physician substitute to be present during the return of red blood cells to apheresis donors. The comment suggested that the presence of a physician substitute or the responsible physician should only be required in the unlikely event that a Source Plasma establishment was returning red blood cells manually.

(Response) Section 630.5(b)(1)(iii) and (c)(1)(i)(A) of the final rule authorize the responsible physician to delegate to a physician substitute or other trained person the return of red blood cells to the donor during apheresis. Subject to an exception for certain plasmapheresis collections, the regulation does not require the responsible physician to be present at the collection site when red blood cells are returned to the donor during apheresis, provided that the responsible physician has delegated oversight of these activities to a trained person who is also adequately trained and experienced in the recognition of and response to the known adverse responses associated with blood collection procedures. However, when this activity is performed in relation to the collection of plasma by plasmapheresis (other than a collection from an infrequent plasma donor), the regulation requires the responsible physician or physician

substitute to be present at the collection site. We have determined that the presence of the responsible physician or of a physician substitute under the supervision of the responsible physician is necessary to help ensure the continued safety of plasmapheresis donors who are not infrequent donors, as defined in § 630.3(e). This is because such donors are permitted to donate up to two times every week, and larger volumes of fluid may be collected at each donation than from other donors. These factors may increase risks for the donor, and warrant the on-site presence of a physician substitute or the responsible physician.

(Comment 38) One comment noted that § 630.5(c) would permit a collecting establishment to authorize a physician substitute to perform the functions of a responsible physician in the collection of Source Plasma, except the responsible physician would be required to be present for red blood cell immunizations. The comment stated that they assume that FDA is requiring the presence of the responsible physician for the red blood cell immunization to assist the recipient of red blood cells if a life-threatening situation arises during the immunization process. The comment asserted that this is most likely based on the fact that potential life-threatening reactions most commonly occur within 10 to 15 minutes of the start of the transfusion with as little as 10 milliliters (mL) transfused.

The comment said that they understand the potential risks associated with red blood cell immunization. However, the comment stated that having a physician present during the immunization process does not protect against the single greatest risk to recipients of red blood cells, which is human error when identifying the blood product for administration to the recipient of red blood cells. Therefore, in protecting against this risk, the comment stated that it is imperative that plasma establishments have processes and procedures in place to assure that the correct red blood cell product is infused to the intended recipient. The comment reports that this

is currently achieved by adherence to current good manufacturing practices. The comment recommended that FDA remove the requirement of having a physician present during immunization with red blood cells as long as current good manufacturing practices are followed.

(Response) We agree with the description of the risks of red blood cell immunizations. We also agree that Source Plasma establishments must adhere to Current Good Manufacturing Practice for Blood and Blood Components (21 CFR part 606), including § 606.100(b), which require establishments to establish, maintain, and follow written standard operating procedures for all steps in the collection, processing, compatibility testing, storage, and distribution of blood and blood components for allogeneic transfusion, and further manufacturing purposes. However, adherence to current good manufacturing practices does not replace the medical oversight provided by the responsible physician, or the clinical expertise that a responsible physician can provide in the case of an emergency at the establishment. Accordingly, we require that the responsible physician must be present when a donor is immunized with red blood cells. Section 630.5(c)(2)(ii) authorizes the responsible physician to delegate to a physician substitute the function of donor immunization with red blood cells, provided that the responsible physician has approved the procedure and is on the premises at the collection site when the procedure is performed.

(Comment 39) A comment to proposed § 630.5(e) asserted that blood collection personnel should be trained in cardiopulmonary resuscitation and the use of automated external defibrillators, and should call 911 to transport donors to a medical facility for emergency care as soon as possible. Another comment noted that the final rule could require that collection staff be trained in cardiopulmonary resuscitation.

(Response) Final § 630.5(d) requires blood collection establishments to establish, maintain, and follow standard operating procedures for obtaining rapid emergency medical services for donors when necessary. In addition, blood collection establishments must assure that an individual (responsible physician, physician substitute, or trained person) who is currently certified in cardiopulmonary resuscitation is located on the premises whenever collections of blood or blood components are performed. We agree that the availability of such a person on the premises will provide important donor protections in the event they are needed. We are not including in the codified language a requirement for a person also to be trained in the use of automated external defibrillators because such devices are not always available at collection sites. However, we believe that the presence of automated external defibrillators may be helpful, and establishments may choose to provide training on available automated external defibrillators, in addition to assuring that a person currently certified in cardiopulmonary resuscitation is located on the premises during collections. As noted in our response to comment 40, we believe that establishments will incorporate the use of 911 services into their procedures for obtaining rapid emergency medical services for donors when necessary.

(Comment 40) One comment noted that proposed § 630.5(e) would have required establishments to establish, maintain, and follow standard operating procedure for providing emergency medical services for donors within 15 minutes. The comment agreed that SOPs should be established, maintained, and followed for the provision of emergency medical services but stated that ensuring a 15 minute response time would not be feasible in some communities and in any event is beyond the control of the blood establishment. Other comments also noted that local emergency medical service response time is community dependent. Blood centers

cannot control how quickly emergency medical services respond and cannot guarantee a 15 minute response time.

(Response) After considering the comments, we have finalized this provision without referencing a 15 minute timeframe. We recognize that in many instances blood collection facilities must rely on the response time of emergency medical services available through local 911 services. Instead, we are requiring in § 630.5(d) that that establishments establish, maintain, and follow standard operating procedures for obtaining rapid emergency medical services for donors when necessary. In addition, the final rule requires that at least one person (responsible physician, physician substitute, or trained person) on the premises during the collection of blood and blood components be currently certified in cardiopulmonary resuscitation. FDA expects that procedures established by blood collection establishments for obtaining rapid emergency medical services will generally result in the provision of emergency medical services within 15 minutes. However, by not specifying a 15 minute response time (and instead calling only for a “rapid” response), we are recognizing that unanticipated circumstances that are outside the control of the blood establishment may delay such care. Establishments should consider the availability of emergency medical services and local response times, particularly when determining locations for mobile collections.

(Comment 41) One comment responded that proposed § 630.5(e) should be reworded to include public emergency medical services. The comment agreed that the establishment of standard procedures for providing emergency medical services within 15 minutes, if necessary, for donors seems appropriate.

(Response) We decline to include the term “public” prior to emergency medical services in § 630.5(d). We interpret emergency medical services to include an onsite responsible

physician or access to emergency medical services available through 911. If an establishment determines that emergency medical services accessible through 911 may not be available rapidly, due to the location of the collection facility or mobile unit, the establishment should provide for a responsible physician to be present at the collection site.

J. General Donor Eligibility Requirements (§ 630.10)

This section includes requirements to ensure that blood and blood components are safe, pure and potent. It also includes requirements to determine that the donor is in good health and the donor's health will not be adversely affected by the donation. We require the establishment to provide the donor with certain educational material related to infectious disease risk so that the donor can self-defer, to check donor deferral records, to perform a limited physical assessment of the donor, to assess the donor for risk factors for relevant transfusion-transmitted infections and other factors that might adversely affect the donation or the donor's health, to obtain a donor acknowledgement that is signed or otherwise recorded, to defer ineligible donors, and to obtain proof of the donor's identity and a postal address where the donor may be contacted for 8 weeks after donation for purposes of donor notification under § 630.40.

We received comments on this section from individuals, blood establishments and trade organizations. We are finalizing this section largely as proposed, except that we have clarified the language in some sections and combined or revised other sections. We have combined proposed § 630.10(e), (f), and (g) covering various aspects of donor eligibility into one section, § 630.10(e). We have renumbered proposed § 630.10(h) into final § 630.10(f). Final § 630.10(f)(3) provides a modified standard for donor hemoglobin or hematocrit. Proposed § 630.10(i) is final § 630.10(g), and we have clarified proposed § 630.10(i)(2) Donor's written statement of understanding, now titled "Donor's acknowledgement" in § 630.10(g)(2). We also

added § 630.10(h) to state more explicitly what an establishment must do when a donor is ineligible.

1. Section 630.10(a)

Consistent with FDA's long standing requirement that a donor be in good health at the time of donation to assure that blood, blood components and blood products manufactured from their donations will be safe, pure and potent, this section states that an establishment must not collect blood or blood components before determining that the donor is eligible to donate. We received no comments on this provision. We added language to explain that, to be eligible, a donor must be in good health and free from transfusion-transmitted infections as can be determined by the processes in this subchapter. The phrase "as can be determined by the processes in this subchapter" clarifies that blood establishments must assess a donor's eligibility in accordance with these regulations. Like the proposed rule, this section states that a donor is ineligible if the donor is not in good health or if the blood establishment identifies factors that may adversely affect the health of the donor or the safety, purity, or potency of the blood or blood components collected from the donor.

2. Section 630.10(b)

Section 630.10(b) requires that, before determining eligibility, an establishment must provide the donor with educational material in an appropriate format regarding certain relevant transfusion-transmitted infections when providing that information is necessary to assure the safety, purity, and potency of blood and blood components, such as for HIV risk factors.

Currently, the only relevant transfusion-transmitted infection for which FDA has determined that providing such information is necessary to assure blood safety, purity, and potency is HIV. FDA first made this recommendation in 1983 (Ref. 30). The donor history questionnaires and

accompanying materials found acceptable by FDA include blood donor educational material addressing HIV risk behaviors and signs and symptoms of HIV (Refs. 6, 7, 8). Providing this educational information in written or electronic format would meet the requirements of this section. In addition, the provision permits establishments to provide, in the educational material, information concerning the risks and hazards of donation. This provision differs from proposed § 630.10(b) in two significant ways: (1) In response to comments, we have clarified that blood collection establishments must provide information concerning certain, and not all, relevant transfusion-transmitted infections and (2) to provide greater flexibility and to accommodate existing practices, we have revised this section to expressly permit establishments to provide, in this educational material, information regarding the risks and hazards of the donation procedure to meet the requirements under § 630.10(g)(2)(ii)(E).

(Comment 42) Two comments raised concern that the proposal would require establishments to provide the donor with too much information about too many relevant transfusion-transmitted infections. Several comments suggested that the rule should not require the educational material to include signs and symptoms of a relevant transfusion-transmitted infection. Several comments suggested that providing the donor history questionnaire should be sufficient to meet this requirement, while several comments suggested that the donor history questionnaire should not include signs and symptoms of HIV.

(Response) FDA believes that providing educational material to donors protects the safety of the blood supply and donor health. FDA believes that self-deferral by at risk donors because of information provided in the educational materials has helped ensure blood safety (Refs. 6, 7, 8, 31, 32, 33). Blood establishments have voluntarily developed donor educational material in response to potential threats (Refs. 6, 7, 8, 31, 32, 33).

FDA agrees with the comments that educational materials should not describe all relevant transfusion-transmitted infections. Instead, this section requires establishments to provide donor information about a relevant transfusion-transmitted infection when necessary to assure the safety, purity, and potency of blood and blood components. As noted previously, currently HIV is the only relevant transfusion-transmitted infection for which providing such information is necessary. The longstanding practice of providing educational material about HIV, including information about signs and symptoms, would continue as a requirement under this provision.

FDA believes that establishments may choose to include in the donor educational material information to explain the collection procedure and the risks and hazards of the procedure, as required under § 630.10(g)(2)(ii)(E). This section expressly permits the incorporation of that information into the donor educational material, but does not require it.

3. Section 630.10(c)

Section 630.10(c) requires establishments to determine the donor's eligibility on the day of donation and prior to collection. Under § 630.10(c)(1), which is applicable to products that cannot be stored for more than 24 hours, an establishment may determine the donor's eligibility and collect a sample for testing required under § 610.40 no earlier than 2 calendar days before the day of donation. In § 630.10(c)(2), the final rule authorizes blood establishments to clarify a donor's response to a donor history question under § 630.10(e) or (g) in accordance with standard operating procedures and within 24 hours of the time of collection.

(Comment 43) Several comments stated that for components having a shelf life of 24 hours, collecting a sample for testing for infectious diseases one day before donation may not provide enough time to obtain the results. They requested that FDA allow the donor to be tested 3 days prior to collection of the donation or alternatively allowing the donation to be released

under emergency provisions in § 610.40(g) or where appropriately labeled as from a donor who has been previously tested.

(Response) FDA agrees with that there is a need for some flexibility on the timing for collecting a sample for testing and making a donor eligibility determination for donors of blood components that cannot be stored for more than 24 hours. We have decided to finalize the proposed provision, now § 630.10(c)(1), and provide that “when a donor is donating blood components that cannot be stored for more than 24 hours, you may determine the donor’s eligibility and collect a sample for testing required under § 610.40 of this chapter, no earlier than 2 calendar days before the day of donation, provided that your standard operating procedures address these activities.” We believe that this 2 calendar day timeframe will be adequate to accommodate donor testing before collection. We also note that current § 610.40(g) allows release of untested components in appropriately documented medical emergency situations.

(Comment 44) FDA received several comments requesting that FDA permit blood establishments to obtain answers to missing donor information for 24 hours after the collection occurred.

(Response) FDA realizes that sometimes blood establishments become aware that there are missing answers to donor history questions, or they need clarification of answers to certain donor history questions. In response to comments, and consistent with current FDA policy (Ref. 34), we are adding new § 630.10(c)(2) to the final rule. Section 630.10(c)(2) expressly authorizes establishments to clarify donor records after collection under these circumstances, “In the event that, upon review, you find that a donor’s responses to the donor questions before collection were incomplete, within 24 hours of the time of collection, you may clarify a donor’s response or obtain omitted information required under paragraph (e) of this section, provided that

your standard operating procedures (required under 21 CFR 606.100) address these activities.”

This applies only to responses to donor questions, and not to information that establishments are required to obtain as part of the physical assessment of the donor addressed in § 630.10(f).

4. Section 630.10(d)

Section 630.10(d) requires a blood establishment to determine the donor’s eligibility before collection by performing four tasks: (1) Consulting the records of deferred donors maintained under § 606.160(e)(1) and (2). Because it may not be feasible to review the cumulative record described in § 606.160(e)(2) prior to collection at all collection sites, the regulation provides that if pre-collection review is not feasible, the establishment must consult the cumulative record prior to release of any blood or blood component prepared from the collection; (2) assuring that the interval since the donor’s last donation is appropriate; (3) assessing the donor’s medical history; and (4) performing a physical assessment of the donor. We have finalized the description of the last two steps as proposed, and we have clarified the language used to describe the second step by omitting unnecessary language.

The first factor has been changed to reference the “records of deferred donors maintained under § 606.160(e)(1) and (2) of this chapter” instead of the proposed “list of ineligible donors required under § 606.160(e)(2) of this chapter”, and to provide flexibility for consulting the cumulative record before release of blood or blood components when the record cannot be available at the collection site. We discuss final § 606.160(e) at comment 25. The review of the records of deferred donors may be accomplished by making an electronic query of a centralized database.

(Comment 45) One comment questioned the validity of donor deferral registries in ensuring the safety of the blood supply. For example, the comment asserted that requiring

collection facilities to consult the donor deferral registry prior to donation would negatively affect mobile operations and impact other facilities when computer outages occur that would have a significant negative impact on blood availability.

(Response) The requirements in §§ 606.160(e) and 630.10(d)(1) will help assure that blood and blood components that are not suitable for use are not collected or distributed. These provisions protect donors from making donations that should not be collected, protect recipients from the release and use of unsuitable donations, and help establishments to conserve resources used in collecting, testing, and manufacturing blood and blood components. Moreover, since § 630.10(d)(1) helps to prevent the collection of unsuitable units, we believe that it will be feasible for establishments to comply with these requirements while at the same time maintaining adequate supplies of suitable blood and blood components. We believe that the requirements, as finalized, are similar to existing practices within blood establishments. Moreover, § 630.10(d)(1) of the final rule now provides additional flexibility so that if unusual circumstances prevail (for example, at a distant mobile collection, or when an establishment is having temporary technical difficulties), and pre-collection review is not feasible because the establishment cannot consult the cumulative record at the collection site, the establishment may collect from the donor, but must consult the cumulative record before release of any blood or blood component prepared from the collection.

5. Section 630.10(e)

The requirements of proposed § 630.10(e), (f), and (g) are interrelated. We have combined proposed § 630.10(e), (f), and (g) into one section, final § 630.10(e). This section requires establishments to conduct a medical history interview as described in this section to determine if the donor is in good health, to identify risk factors closely associated with exposure

to, or clinical evidence of, a relevant transfusion-transmitted infection, and to determine if there are other conditions that may adversely affect the health of the donor or the safety, purity, or potency of the blood or blood components or any product produced from the blood or blood components. Blood establishments must take a medical history as described in this section.

Section 630.10(e) also contains specific requirements for determining that the donor is in good health and free from risk factors for a relevant transfusion-transmitted infection. This assessment must include the following factors: (1) Factors that make the donor ineligible to donate because of an increased risk for, or evidence of, a relevant transfusion-transmitted infection, including the factors described in § 630.10(e)(1)(i) through (vi) and (2) other factors described in § 630.10(e)(2)(i) through (vii) that may make the donor ineligible, including factors related to donor health or travel history.

Section 630.10(e) is intended to provide explicitly in our regulations for our current donor deferral recommendations and blood establishment practices. We discuss the comments received on that provision. We received no comments on our proposal in § 630.10(g)(7), under which a donor would be ineligible because she was pregnant at the time of, or within 6 weeks of, donation, and have finalized that proposal in § 630.10(e)(2)(v).

(Comment 46) Several organizations requested FDA not to finalize the provision in proposed § 630.10(e) that would have required an establishment to determine whether a health care practitioner ever told the donor not to donate blood.

(Response) We agree. We included this provision, in part, as a result of the anthrax exposures in 2001, where individuals may have been advised not to donate. However, prior advice not to donate blood may be based on a number of factors, including a transient infection, now cured, or blood loss due to an accident, from which the donor has long recovered. We have

not included this provision in the final rule. Instead we require establishments to take a medical history, as described in § 630.10(e). Such a medical history would be focused on eliciting information related to potential and current risks, either to the donor, or to the safety of the donated blood product.

(Comment 47) We received comments stating that FDA has recognized uniform donor history questionnaires and should not add the criteria for deferral in proposed § 630.10(f).

(Response) FDA believes that use of a current and acceptable donor history questionnaire, such as the donor history questionnaires and accompanying materials found acceptable by FDA in guidance (Refs. 6, 7, 8), would meet these requirements. If the need arises, FDA will describe how to comply with these provisions in guidance documents issued in accordance with good guidance practices.

(Comment 48) One comment suggested that we abandon the term “social” in proposed § 630.10(f)(1), “social behaviors associated with relevant transfusion-transmitted infections.”

(Response) We agree and have dropped the term “social.” Section 630.10(e)(1)(i) now refers simply to “behaviors.”

(Comment 49) Other comments stated that FDA should not consider the behavior of men who have had sex with another man even one time since 1977 to be “behaviors associated with relevant transfusion-transmitted infections” under proposed § 630.10(f)(1).

(Response) This rule does not specify the circumstances under which FDA would consider men who have sex with another man to be a behavior associated with relevant transfusion-transmitted infections. Instead, that is an issue FDA has addressed in previous guidance related to the issue (Ref. 10). We are currently reviewing this policy. If we determine

that modifications of any behavior-based donor deferral recommendations are warranted, we will issue new guidance to blood establishments in accordance with good guidance practices.

(Comment 50) We received several comments suggesting that FDA change the following phrase in proposed § 630.10(f)(2), “Medical treatments and procedures associated with exposure to relevant transfusion-transmitted infections.” The comments stated that this criterion was too vague and suggested that the donor history questionnaire would provide a sufficient basis for determining whether the donor had risk exposures from medical procedures.

(Response) We agree with the comment in part and have made this criterion, now contained in § 630.10(e)(1)(ii), more specific. FDA recognizes that many medical procedures present some risk, which cannot be specifically quantified. Consequently, final § 630.10(e)(1)(ii) states, “Receipt of blood or blood components or other medical treatments and procedures associated with possible exposure to a relevant transfusion-transmitted infection.” In any event, we agree with comments that an acceptable donor history questionnaire, such as the donor history materials that are currently recognized in FDA guidances (Refs. 6, 7, 8), may be used to elicit information adequate to satisfy these provisions.

(Comment 51) One comment asked FDA to clarify how establishments would gather information related to signs and symptoms of relevant transfusion-transmitted infections under proposed § 630.10(f)(3).

(Response) In final § 630.10(e)(1)(iii), we require establishments to assess “Signs and/or symptoms of a relevant transfusion-transmitted infection.” For example, FDA has issued guidance on signs and symptoms of HIV (Refs. 10, 30). If a donor exhibits signs or symptoms of HIV, they would be deferred under this provision. We believe that an establishment would meet this requirement by determining that the donor is in good health, and using a currently

acceptable donor history questionnaire. FDA has periodically issued new guidance recommending assessment for signs and symptoms of a new infectious agent or disease (Refs. 35, 36). FDA will issue guidance in accordance with good guidance practices in the event that different information is needed to satisfy the requirements of this section.

(Comment 52) Several comments asked FDA to reconsider the longstanding requirement for deferral of donors with a “history of viral hepatitis.”

(Response) Neither the proposed nor the final rule refers to a “history of viral hepatitis” as a factor in determining donor eligibility. We are finalizing the donor eligibility requirements without reference to a requirement to defer donors with a history of viral hepatitis after the age of 11. Instead, under new § 630.3(h)(1)(ii) and (iii), HBV and HCV are relevant transfusion-transmitted infections. Under § 630.10(e)(1)(iii), an establishment must defer a donor exhibiting signs and/or symptoms of relevant transfusion-transmitted infections, including HBV and HCV. Reactive test results for these relevant transfusion-transmitted infections would result in donor deferral as described in § 610.41(a).

(Comment 53) One comment requested that that we not finalize the requirement in proposed § 630.10(f)(4) to determine whether a donor has been institutionalized in a correctional institution, preferring that this be addressed in guidance, not regulation. Another comment recommended that FDA clarify that deferral would be for institutionalization in a correctional institute for 3 days or more.

(Response) We have finalized a requirement in § 630.10(e)(1)(iv) that establishments determine whether a donor has been institutionalized in a correctional institution. We have rejected the suggestion that we leave this deferral to guidance because we concluded that this deferral is readily described and unlikely to change due to technological developments. We

agree with the second comment and have further clarified that the deferral applies to donors who were institutionalized in a correctional institution for 72 consecutive hours or more in the 12 months before donation.

(Comment 54) We received comments asking us to revise the definition for “intimate contact” provided in proposed § 630.3(e), which was applicable to proposed § 630.10(f)(5), and to clarify that the deferral for “intimate contact” would only apply to those relevant transfusion-transmitted infections where such transmission occurs through intimate contact.

(Response) We agree in part with the comment. We have modified the defined term in § 630.3(f) so that it is now “intimate contact with risk for a relevant transfusion-transmitted infection” and clarified that this term refers to conduct that could result in the transfer of potentially infectious body fluids from one person to another. The provision that is now finalized in § 630.10(e)(1)(v) incorporates this clarified definition, and requires inquiry concerning such intimate contact with risk for a relevant transfusion-transmitted infection, which is defined in § 630.3(f) as having engaged in an activity that could result in the transfer of potentially infectious body fluids from one person to another. We have issued guidance when we believed that deferral for intimate contact with an individual infected with a relevant transfusion-transmitted infection or exposed to a relevant transfusion-transmitted infection was appropriate (Refs. 11, 37). FDA will issue a future guidance document as necessary for deferral of donors because of specific intimate contact with risk for a relevant transfusion-transmitted infection.

(Comment 55) One comment requested that we state that nonsterile percutaneous inoculation, as proposed in § 630.10(f)(6), be considered a basis for deferral only when the inoculation took place within 4 months of the donation.

(Response) We did not specify in the proposed regulation a timeframe for this deferral, stating that the blood establishment should defer the donor if the factor was “still applicable” at the time of donation, and we have not specified a timeframe in the final rule codifying this factor at § 630.10(e)(1)(vi). FDA’s 1992 guidance entitled, “Revised Recommendations for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products,” recommends a 1year deferral for nonsterile percutaneous exposure, and this recommendation is still current (Ref. 10).

(Comment 56) We received several comments asking FDA to modify proposed § 630.10(g)(1), which identified “Medical or dental treatment, or symptoms of a recent or current illness” as a basis for ineligibility. These comments asked FDA to delete the reference to dental treatment.

(Response) We agree with these comments in part. In finalizing proposed § 630.10(g)(1), we have revised this provision and separated it into two sections. Section 630.10(e)(2)(i) now requires establishments to assess donors for symptoms of a recent or current illness. Section 630.10(e)(2)(ii) now requires establishments to assess donors for certain medical treatments or medications, such as a major surgical procedure, that indicates that the donor should not donate. We have omitted the requirement to defer donors for recent dental treatment.

(Comment 57) We received several comments asking FDA to delete the provision in proposed § 630.10(g)(1) through (g)(3) which refer to ineligibility because of medical treatment, medication, or major surgical procedure. One comment suggested that the deferral be limited to the criteria and medications enumerated in current FDA guidance documents. Several comments asked FDA to identify major medical procedures.

(Response) We have finalized § 630.10(e)(2)(ii) to require blood establishments to assess donors for certain medical treatments or medications, such as a major surgical procedure, that indicate that the donor should not donate. This provision is intended to protect the health of the donor and ensure the safety and purity of the blood product. We note that we have issued guidance on donor deferral criteria for certain medications (Ref. 38). We believe that establishments can meet the requirements of this section by using current donor history questionnaire materials recognized as acceptable by FDA, or other approved donor history questionnaire. If our recommendations for deferral for medical procedures or specific medications change, we would issue guidance in accordance with good guidance practices.

(Comment 58) We received several comments asking FDA not to finalize proposed § 630.10(g)(4), under which a donor would be ineligible on the basis of travel to, or residence in, an area endemic for a transfusion-transmitted infection. The comments criticized the provision as vague and more appropriately dealt with in FDA guidance documents.

(Response) In finalizing this provision in § 630.10(e)(2)(iii), we have provided additional clarity by stating that a donor would be ineligible on the basis of such travel or residence only when such screening is necessary to assure the safety, purity, and potency of blood and blood components due to the risks presented by donor travel and the risk of transmission of that transfusion-transmitted infection by such donors. For example, in the future we may determine that screening donors under this provision for the Chickungunya virus, a transfusion-transmitted infection that is transmitted by mosquitoes, is necessary to assure the safety, purity, and potency of blood and blood components. If so, we would address deferral of donors with a travel history to an area endemic for Chickungunya in accordance with good guidance practices.

(Comment 59) Several comments suggested that we delete the provision in proposed § 630.10(g)(6), which would have required a determination of ineligibility due to exposure or possible exposure to a released disease or disease agent relating to a transfusion-transmitted infection, if it was known or suspected that such a release has occurred. The comments suggested that this provision was vague and better addressed in guidance when an event occurs.

(Response) In § 630.10(e)(2)(iv), we have finalized this provision as proposed. This factor only becomes relevant when a disease or disease agent for a transfusion-transmitted infection has been released. We expect this to apply in rare circumstances, such as after a serious accident or bioterrorism attack involving the release of such agents. FDA intends to issue guidance, as practicable, when a released disease or disease agent is identified and is of a nature or type that donor deferral would be warranted. We note that we previously issued guidance on the deferral of donors with possible exposure to anthrax due to a possible bioterrorism event (Ref. 39).

(Comment 60) We received several comments on proposed § 630.10(g)(8), which would have required blood establishments to determine to be ineligible donors who gave answers to medical history questions that appeared unreliable due to the apparent influence of drugs or alcohol, or due to another reason affecting the reliability of the donor's answers. The comments agreed with the deferral, but stated that blood establishment procedures were adequate to address this issue.

(Response) We combined donor suitability requirements from existing regulations for Whole Blood donations (§ 640.3) and Source Plasma donations (§ 640.63) in the final rule. Source Plasma regulations have had a longstanding requirement (§ 640.63(d)) that "any donor who, in the opinion of the interviewer, appears to be under the influence of any drug, alcohol, or

for any reason does not appear to be providing reliable answers to medical history questions, shall not be considered a suitable donor.” Until now, there has not been a corresponding provision in the requirements for Whole Blood donors, even though a donor who does not provide reliable answers presents similar risks in that venue. We are finalizing this requirement for all donations in § 630.10(e)(2)(vi).

In the preamble to the proposed rule we gave, as an example of an unreliable answer, a donor who states that he or she is donating in order to be tested for infectious agents. This is because of our concern that the donor may be aware of some additional, undisclosed, risk factor that leads him or her to seek information on their infection status by presenting at a blood donation center. Such undisclosed risk factors endanger blood safety, particularly when the donor is in the “window period” when the donor is infected and infectious, but the infection cannot yet be detected by donor screening tests. We did not receive comments on this example. We have decided to expressly require the deferral of a donor who states they are seeking testing for a relevant transfusion-transmitted infection. We expect that blood establishments may then refer the donors to public health testing clinics and other venues providing testing.

(Comment 61) We received comments requesting that we not finalize the proposed requirement to determine a donor to be ineligible due to receipt of a xenotransplantation product, or intimate contact with such a recipient (proposed § 630.10(g)(5)).

(Response) In final § 630.10(e)(2)(vii), we require establishments to assess the eligibility of a donor on the basis of receipt of a xenotransplantation product. We finalized this provision to protect the health of the donor who received the xenotransplantation product and to address the risk of transmission of animal infectious agents by blood and blood products collected from such a donor. In 2002, we discussed those risks in a draft guidance entitled “Guidance for Industry:

Precautionary Measures to Reduce the Possible Risk of Transmission of Zoonoses by Blood and Blood Products from Xenotransplantation Product Recipients and Their Intimate Contacts” (Ref. 37). We have not finalized the proposed requirement to require screening for intimate contact with a xenotransplantation recipient. If, in the future, we determine that donation by an individual who has had intimate contact with a recipient of a xenotransplantation product may affect that donor’s health, or the safety, purity, or potency of the blood or blood component, or product produced from the blood or blood component collected from that donor, we will issue guidance to address these risks.

6. Section 630.10(f)

As we described earlier, we combined proposed § 630.10(e) through (g) into § 630.10(e) in the final rule. We have finalized proposed § 630.10(h) as final § 630.10(f).

The physical assessment criteria set forth in § 630.10(f)(1) through(6) in this final rule requires establishments to determine that a donor is in good health which helps to assure that blood and blood components collected are safe, pure, and potent. This section requires establishments to determine on the day of donation and prior to collection of blood or blood components that the donor is in good health, indicated in part by a normal temperature, a blood pressure within acceptable limits, an acceptable hemoglobin or hematocrit level, a regular pulse, and a minimum weight requirement. Blood establishments are also required to perform an examination of the donor’s phlebotomy site and the donor’s arms and forearms.

a. Temperature (§ 630.10(f)(1)).

(Comment 62) We received no comments objecting to the requirement for measuring a donor’s temperature. We received one comment asking whether we would specify a subnormal temperature.

(Response) We are finalizing the proposed requirement to determine that the donor's oral body temperature does not exceed 37.5 °C (99.5 °F), or the equivalent if measured at another body site, since an elevated temperature indicates that the donor is not in good health and may be a symptom of infection or other adverse condition. On the other hand, a temperature that is a few degrees lower than 37.5 °C (99.5 °F), is not necessarily indicative of poor health. We decline to specify a subnormal temperature at this time. Instead, we leave assessment of an apparently healthy donor who presents for donation with an unusually low temperature for blood establishments to address in their standard operating procedures.

b. Blood pressure (§ 630.10(f)(2)).

(Comment 63) Several comments recommended that FDA should not finalize a requirement for determining the donor's blood pressure, while others recommended not specifying limits for systolic and/or diastolic blood pressure measurements, or addressing such bounds only in guidance. One comment stated that a baseline blood pressure for all donors at each donation is needed in the event of a reaction.

(Response) Current § 640.3(b)(2) requires that donors be in good health, as demonstrated by systolic and diastolic blood pressure within normal limits, unless the examining physician is satisfied that an individual with blood pressure outside these limits is an otherwise qualified donor. In the preamble to the proposed rule we had solicited comments requesting supporting scientific data regarding the necessity, or lack of necessity of requiring specific upper and lower blood pressure limits for a donor (72 FR 63416 at 63426 and 63427). We did not receive significant data. In November 2009, we asked the Blood Products Advisory Committee whether available data support the utility of obtaining pre-donation blood pressure measurements as predictors of risk of an adverse response to donation, and the majority responded that data did

not establish pre-donation blood pressure as a predictor of risk of an adverse response. However, even though the vote did not support blood pressure measurement as a predictor of risk, many members of the committee stated that blood pressure measurement should be retained as part of the donor assessment. The committee members noted that studies examining adverse events and blood pressure have been restricted to donors with currently acceptable blood pressure levels. Several committee members were concerned that it was not safe for donors with blood pressures above 180 mm of mercury to donate. They noted the lack of data on the safety of blood donations in hypertensive donors and the potential for severe adverse events in such donors. Other committee members noted that low blood pressure could be predictive of adverse events in young female donors who have low blood volume.

We are finalizing a requirement to measure the donor's blood pressure before donation. If a donor's systolic blood pressure is outside the range of 90 to 180 mm of mercury, or if the donor's diastolic blood pressure is outside the range of 50 to 100 mm of mercury, establishments may permit the donor to donate only when the responsible physician has examined the donor and determined that the health of the donor would not be adversely affected by donating. Note that under § 630.5(b)(1)(i)(A) and (c)(1)(i)(A)(1), the responsible physician is not authorized to delegate this examination and determination of the health of the donor, and must personally perform this examination and determination. Final § 630.10(f)(2) is consistent with the proposed rule and largely consistent with the current requirement in § 640.3(b)(2), and will assure that donors who present with either unusually high, or unusually low, blood pressure will be examined by the responsible physician before they are permitted to donate. We are establishing these criteria in the regulation, rather than providing a flexible standard, because we have determined that establishing clear criteria will be more protective of donor health. We note that,

under the limits provided in § 630.10(f)(2), donors with blood pressure readings above 140/90 would be eligible to donate, even though such donors may be hypertensive (Ref. 40). However, experience to date indicates that donors with blood pressures in the range provided in this rule may safely donate (Refs. 41, 42).

(Comment 64) In response to our request for comments on the accuracy of blood pressure measurements, one comment stated that “Many factors can influence blood pressure along with pulse such as stress, exercise, and caffeine intake. In addition, interobserver differences are found with measurements that rely on sphygmomanometers and stethoscopes. Therefore, a general preference for automated devices is found not only among donor centers but also among clinics, hospitals, and for use at home. These devices are commercially available and approved for sale. We recommend that FDA acknowledge the acceptance of automated devices in either the preamble to the final rule or in guidance. FDA also notes that an isolated measurement of blood pressure may not reliably assess acceptability for donation.”

(Response) We are not requiring that a specific type of device to be used to measure blood pressure. Establishments may use manual or automated devices as long as such use is consistent with the applicable standards or current good manufacturing practices, and their own standard operating procedures.

(Comment 65) The comment recommended that FDA provide the following, or similar, guidance: “Firms should have a procedure for re-measuring the vital signs if there is reason to believe stress or other factors have affected the initial measurement.”

(Response) We are not issuing guidance on this issue at this time. We recognize that stress and other factors may affect initial measurements of the donor’s blood pressure and pulse, required under § 630.10(f)(2) and (f)(4). In accordance with § 606.100(b)(2), establishments

must have standard operating procedures for taking a donor's blood pressure and pulse before collection. However, these requirements do not prevent a blood collection establishment from providing in those standard operating procedures for taking and relying upon a second measurement of blood pressure if there is reason to believe stress or another factor affected the initial measurement and taking a second measurement is consistent with medical practice.

c. Hemoglobin or hematocrit determination (§ 630.10(f)(3)).

We proposed to require that a donor's hemoglobin level or hematocrit value be determined using a sample of blood obtained by fingerstick, venipuncture or by a method that provides equivalent results. Blood obtained from the earlobe is not acceptable. We received no comments on this provision and are finalizing this provision as proposed. This section was proposed as § 630.10(h)(3)(i); we now finalize it as the first paragraph of § 630.10(f)(3). We further proposed to retain the existing requirement for autologous donations that a donor's hemoglobin level be no less than 11 grams of hemoglobin per deciliter of blood or a hematocrit value of 33 percent. We received no comments on this provision and are finalizing this provision as proposed. In addition, for allogeneic donations, we proposed to retain existing requirements that a donor's hemoglobin level be no less than 12.5 grams of hemoglobin per deciliter of blood or a hematocrit value of no less than 38 percent. We also solicited comments (72 FR 63416 at 63427) on:

- Changing the minimum acceptable hemoglobin level to 12.0 grams per deciliter of blood or hematocrit of 36 percent for female allogeneic donors, or whether a decision to collect from donors with such levels should be left to the discretion of the medical director of the collecting establishment on a case-by-case basis;

- The possibility of adverse effects caused by the collection of blood and blood components from female allogeneic donors with a minimum level of 12.0 grams of hemoglobin per deciliter of blood or a hematocrit value of 36 percent;
- The possibility of adverse effects caused by the collection of blood and blood components from allogeneic donors with a minimum level of 12.5 grams of hemoglobin per deciliter of blood or a hematocrit value of 38 percent;
- Establishing a more stringent interdonation interval; and
- The use of copper sulfate solution based methods as an appropriate method to determine acceptable hemoglobin levels.

Since the proposed rule was published, FDA has brought up issues related to blood donation, hemoglobin levels, and iron depletion in donors for discussion at two Blood Products Advisory Committee meetings on September 10, 2008 and July 27, 2010 (Refs. 43, 44). In addition, the Department of Health and Human Services, Public Health Service, Advisory Committee on Blood Safety and Availability discussed iron depletion and donor informed consent at its December 17, 2008 meeting (Ref. 45). In co-sponsorship with the Department of Health and Human Services, National Heart, Lung and Blood Institute, AABB, America's Blood Centers and Plasma Protein Therapeutics Association, FDA held a workshop entitled "Public Workshop: Hemoglobin Standards and Maintaining Adequate Iron Stores in Blood Donors" on November 8-9, 2011 (November 2011 Workshop) (Ref. 46).

At the July 2010 Blood Products Advisory Committee meeting, following the discussion of hemoglobin qualification standards and iron depletion in donors, the committee voted unanimously (10 yes votes, 0 no votes, 1 abstention) in support of raising the hemoglobin level for men, but did not support a change in the hemoglobin level for women (10 no votes and 1

abstention) (Ref. 44). The shortcomings of relying solely on hemoglobin measurement and the need to study measures to mitigate iron deficiency in blood donors were discussed at both meetings of the Blood Products Advisory Committee (Refs. 43, 44) and at the November 2011 Workshop (Ref. 46). After reviewing those discussions and the data presented at those meetings, we have decided to promulgate different standards for male and female donors, but not to alter the current 8 week interval between donations of Whole Blood and single donations of apheresis Red Blood Cells. Recognizing that research in this area continues and that data may be developed to support a change in donor hemoglobin standards, we have provided for greater flexibility in donor hemoglobin standards.

Section 630.10(f)(3)(i) now requires that allogeneic donors must have a hemoglobin level or hematocrit value that is adequate to assure donor safety. In addition, we establish minimum standards. The minimum standard established for female allogeneic donors in § 630.10(f)(3)(i)(A) is consistent with the current standard: A hemoglobin level that is equal to or greater than 12.5 grams per deciliter of blood, or a hematocrit value that is equal to or greater than 38 percent. However, we recognize that a lower hemoglobin/hematocrit level is also within the normal range for female donors. Since hemoglobin levels are influenced by the male hormone testosterone, female donors typically have lower hemoglobin levels than male donors. The fact that a female donor's hemoglobin/hematocrit level is lower than that of a male of similar age does not necessarily mean that the female donor has low iron stores, which the body uses to replace hemoglobin lost to blood donation (Refs. 47, 48). For this reason, in the preamble to the proposed rule we specifically requested comment on whether to permit collections from female allogeneic donors with a hemoglobin level of 12.0 grams per deciliter of blood or a hematocrit value of 36 percent. We are not establishing that minimum level at this

time. However, § 630.10(f)(3)(i)(A) provides that an establishment may collect blood from female allogeneic donors who have a hemoglobin between 12.0 and 12.5 grams per deciliter of blood, or hematocrit value between 36 and 38 percent, provided that the establishment takes additional steps to assure that the lower value is adequate with respect to donor safety, in accordance with a procedure that has been found acceptable for this purpose by FDA. FDA has not yet recognized any such procedures, and awaits the development of data related to these issues. Conceivably, these steps might include a pre-donation measure of iron stores by means of a ferritin test, or iron replacement therapy and monitoring of iron stores. We have determined that standard collections from a donor with a hemoglobin level as low as 12.0 grams per deciliter of blood or hematocrit value of 36 percent would meet minimum potency levels based on calculated hemoglobin content.

Section 630.10(f)(3)(i)(B) of the final rule establishes a minimum standard for male allogeneic donors of 13.0 grams of hemoglobin per deciliter of blood, or a hematocrit value that is equal to or greater than 39 percent. This standard aligns more closely with the low range of normal levels for men, and is higher than the current regulation's minimum standard of 12.5 grams of hemoglobin per deciliter of blood, or a hematocrit value that is equal to or greater than 38 percent (Ref. 48). We requested comment in the preamble to the proposed rule on the possibility of adverse effects on male donors with a minimum hemoglobin level of 12.5 grams per deciliter of blood or a hematocrit value of 38 percent. We solicited these comments, in part, because of our concern about possible adverse effects of collecting blood from male donors with below normal hemoglobin or hematocrit levels, and reports about iron depletion resulting from blood donation (Refs. 46, 49, 50). Males with below normal hemoglobin or hematocrit levels may have a higher incidence of iron deficiency due to frequent blood donations or undiagnosed

conditions such as gastrointestinal bleeding due to colon cancer. Since the proposed rule published, the results of a study sponsored by the Department of Health and Human Services, National Heart, Lung and Blood Institute, the Retrovirus Epidemiology Donor Study-II (REDS-II) Donor Iron Status Evaluation Study (REDS-II-RISE study) on hemoglobin levels in donors have become available (Refs. 49, 50). The results of the REDS-II-RISE study amplified existing concern about frequent donation and iron depletion. In this rule, we are establishing higher minimum hemoglobin/hematocrit levels for male donors after reviewing that study and considering the comments submitted.

(Comment 66) We received numerous comments asking FDA not to make changes in acceptable hemoglobin and hematocrit levels for male and female donors until the REDS-II-RISE study on hemoglobin levels in donors was completed.

(Response) We are finalizing this rule after reviewing the results of the REDS-II-RISE study. Preliminary results of the REDS-II-RISE study were presented at the July 2010 Blood Products Advisory Committee meeting. At the conclusion of that discussion, the advisory committee voted unanimously that the available scientific evidence supported raising the minimum hemoglobin/hematocrit levels for male donors. The committee did not support lowering minimum standards for female donors (Ref. 44). The REDS-II-RISE study published on October 10 and 24, 2011, and the results were discussed at a November 2011 Workshop (Ref. 46). Results from the REDS-II-RISE study were published in an article entitled, "Iron deficiency in blood donors: the REDS-II Donor Iron Status Evaluation (RISE) Study," (Ref. 50). The authors reported a high prevalence of iron depletion in frequent blood donors. As recommended by the comments, FDA has considered the results of the REDS-II-RISE study in determining appropriate hemoglobin standards for this rule. We agree that the study provides important new

information on hemoglobin levels in donors, and supports increasing the minimum hemoglobin/hematocrit requirements for male donors. We recognize that this is an important donor safety issue, and we will continue to review the scientific data as we consider these issues in the future.

(Comment 67) We received one comment supporting lowering the hemoglobin level for women and one opposing lowering the hemoglobin level for women. The comment supporting a lower minimum hemoglobin level stated that a hemoglobin level of 12.0 grams per deciliter of blood was normal for women, and allowing such donors to donate would improve blood availability. The comment opposing lowering the minimum hemoglobin level stated that this practice would make more women susceptible to anemia and iron deficiency.

(Response) For female allogeneic donors, the current minimum hemoglobin/hematocrit levels remain the default minimum levels under this rule. In the event that an establishment takes additional steps that are adequate to assure donor safety an establishment may collect from female donors with normal, but lower, hemoglobin levels, between 12.0 and 12.5 grams per deciliter of blood, or a hematocrit value between 36 and 38 percent, provided the establishment has taken additional steps to assure that this alternative standard is adequate to ensure that the health of the donor will not be adversely affected due to the donation, in accordance with a procedure that has been found acceptable for this purpose by FDA. We have not yet found such a procedure adequate for this purpose. However, we recognize that, in the future, new data may support revised hemoglobin/hematocrit standards for female allogeneic donors, particularly if it becomes possible to measure other values, including iron stores, before donation. In determining or recognizing an alternative measure, FDA intends to consider other evidence related to donor health, including iron stores. Until then, establishments must follow the current standard for

female allogeneic donors: a hemoglobin level of 12.5 grams per deciliter of blood or a hematocrit value of 38 percent.

(Comment 68) One comment stated that changing the hemoglobin level could affect cleared devices as some are cleared based on a specified hemoglobin/hematocrit lower limit.

(Response) We recognize that some operator's manuals for apheresis devices describe the minimum hemoglobin level of 12.5 grams per deciliter of blood, or a hematocrit value of 38 percent, and that these references would need to be updated to reflect the new minimum standard for male donors. In addition, related changes to apheresis device software may be needed.

d. Pulse (§ 630.10(f)(4)).

Current regulations require that a donor of Source Plasma have a normal pulse, but do not specify a related requirement for donors of Whole Blood or other blood components. We proposed in § 630.10(h)(4) to require that all donors have a regular pulse that measures between 50 and 100 beats per minute. A donor with an irregular pulse or measurements outside these limits would be permitted to donate only when the responsible physician has examined the donor and determines and documents that the health of the donor would not be adversely affected by donating. We have finalized this provision in § 630.10(f)(4) with one change. The final rule provides that a donor with an irregular pulse or measurements outside these limits may be permitted to donate only when the responsible physician determines and documents that the health of the donor would not be adversely affected by donating. This determination may be made by the responsible physician on the basis of an assessment of the donor's information (for example, the responsible physician may conclude that the donor's low pulse rate is due to regular marathon running). This provision thus does not require that the responsible physician personally examine the donor. Note that under final § 630.5(b)(1)(i)(B) and (c)(1)(i)(A)(2), the

responsible physician cannot delegate this determination that the donor's health would not be adversely affected by donating.

(Comment 69) Several comments opposed adding a requirement for determining that the donor has a regular pulse between 50 and 100 beats per minute. One comment indicated that the physician should examine the donor for any irregularity in their pulse, not just a pulse outside the proposed limits.

(Response) To assure that donors are in good health and will not be adversely affected by donating, we are finalizing the requirement to measure the donor's pulse and assess eligibility based on pulse rate and regularity. In November 2009, FDA asked the Blood Products Advisory Committee if available data support the utility of obtaining pre-donation pulse measurements as predictors of risk of adverse response to donation. The majority of the committee agreed (10 yes votes, 8 no votes) that pulse measurement was a predictor of risk of adverse response to donation. In particular, high pulse rates may be associated with higher rates of vasovagal reactions. We also agree with the comment that an irregular pulse can indicate that a donor is not in good health (Ref. 51). Therefore, final § 630.10(f)(4) requires that the donor's pulse must be regular and between 50 and 100 beats per minute--no less than 50 beats per minute, and no more than 100 beats per minute. A donor with an irregular pulse or measurements outside these limits is ineligible unless the responsible physician determines and documents that the health of the donor would not be adversely affected by donating.

(Comment 70) One comment asserted that a phone consultation between the blood collection center and the responsible physician should be sufficient to determine whether a donor with an irregular pulse can donate, rather than the proposed requirement that responsible physician actually "examine" the donor. For example, the comment stated that their blood

collection center routinely permits the responsible physician on-call to give phone authorization for donors with pulse rates between 40 and 50 beats per minute to donate, when it is ascertained by the donor's history that the donor is an athlete.

(Response) We agree with the comment. A donor with an irregular pulse or measurements outside the limits provided in final § 630.10(f)(4) may be permitted to donate when the responsible physician has determined that the health of the donor would not be adversely affected by donating. We have not finalized a requirement that the responsible physician must examine the donor, and we provide that in appropriate circumstances the responsible physician may make a determination of whether a donor's health would be adversely affected by donating blood or blood components. Such a determination may be reached by a phone consultation between the establishment and the responsible physician, though under § 630.5(b)(1)(i)(B) and (c)(1)(i)(A)(2), the responsible physician cannot delegate the determination that the donor's health would not be adversely affected by donating.

e. Weight (§ 630.10(f)(5)).

We proposed in § 630.10(h)(5) that a donor weigh a minimum of 50 kilograms (110 pounds) and not have any unexplained loss of greater than 10 percent of body weight within the past 6 months. We are finalizing the requirement that donors weigh at least 110 pounds, but have not finalized the requirement related to unexplained weight loss.

(Comments 71) Several comments suggested deleting the requirement to assess the donor's weight because most blood establishments do not currently weigh donors. Several comments said there was no justification for the 110 pounds lower weight limit and that deferrals based on the overall health of the donor were better addressed through the donor history questionnaire.

(Response) Section 630.10(f)(5) does not require blood establishments to weigh Whole Blood donors. Blood establishments may make this determination by asking a donor whether the donor weighs at least 110 pounds.

f. Skin examination (§ 630.10(f)(6)).

In proposed § 630.10(h)(6) we proposed requirements that: (1) The donor's phlebotomy site be free of evidence of infection, inflammation, lesions, and pitted skin and (2) the donor's arms and forearms be free of punctures and scars indicative of injected drugs of abuse. We have finalized these provisions, except that we have deleted the reference to "pitted skin".

(Comment 72) One comment recommended that FDA not include the term "pitted skin" from the final rule. The comment stated frequent plasmapheresis donors would be expected to have pitted areas of their skin due to the needle punctures for their donations as frequently as twice per week. The comments asserted that a close examination for pitted skin could lead to deferral of committed donors.

(Response) We agree with the comment that frequent donors often have pitted areas of their skin due to needle punctures. Therefore, we do not include the term pitted skin in § 630.10(f)(6) of the final rule, and require only that the donor's arms must be free of infection, inflammation, and lesions. We note that pitted skin may be more difficult to decontaminate, which may affect the choice of the phlebotomy site.

7. Section 630.10(g)

a. Proof of identity and postal address (§ 630.10(g)(1)).

We proposed in § 630.10(i)(1) that collection establishments obtain, before donation, proof of the donor's identity and a mailing address where the donor may be contacted for 8 weeks following donation. Establishments are currently required to maintain a record of this

address in the donor record as required under § 606.160(b)(1)(x) (redesignated in this rule as § 606.160(b)(1)(ix)). Establishments may use this information to contact the donor to communicate regarding test results for evidence of infection, as required under § 630.40. We are finalizing this provision as proposed, except that the final rule specifies that the donor's mailing address must be a postal address.

(Comment 73) One comment suggested that the donor's name and last four digits of their Social Security Number (United States) or Social Insurance Number (Canada), with proof of an address, would be adequate proof of a donor's identification. Another comment stated that it is not always possible to obtain photographic identification, stating that members of certain groups are reluctant to have their photographs taken. The comment stated that FDA should allow for other means of identifying the donor.

(Response) We have finalized the rule to require that blood establishments obtain proof of identity of the donor prior to donation. However, we have not specified the means of establishing proof. We believe that photographic identification, a valid driver's license, validated biometric means, or other means can be useful in establishing the donor's identity. Establishments must include procedures for establishing donor identity in their standard operating procedures under § 606.100(b). We also note that, while this provision establishes a requirement for Whole Blood donors, § 640.65(b)(3) has long required Source Plasma establishment to have a donor identification system in place. For Source Plasma establishments, § 630.10(g)(1) does not add new requirements.

(Comment 74) We received several comments objecting to the requirement to obtain an address where the donor may be contacted for 8 weeks after donation. One comment stated that this provision would have an impact on blood collection on college campuses due to the

movement of college students to other addresses for the summer. One comment referenced information from the United States Postal Service, indicating that most individuals who move do leave a forwarding address. The comment suggested that donors can be contacted through this mechanism. The comment further suggested that newer communication technologies such as email and cell phones can be used for notification purposes when necessary.

(Response) We have finalized the rule to require that blood establishments obtain a postal address where the donor may be contacted for 8 weeks after donation. This provision supports effective communication on issues that may be important to the donor and his or her contacts. We recognize that, when the donors are found ineligible prior to collection, they are deferred and notified of the reasons for their deferral at the blood center. However, communication with the donor becomes necessary after donation due to reactive or positive test results obtained on the donation. We believe that most establishments invite the donor back to the donor center to inform the donor of reactive or positive infectious disease test results on the donation. We do not believe that the provision improperly burdens blood establishments because of college students and other mobile populations. Student donors would provide the postal address where they expect to be in residence if they plan to leave school during the 8 weeks following donation. We recognize that other means of contact, such as email or telephone, may permit more rapid communication. Establishments may also request an email address or telephone number, although the rule does not require establishments to collect this information. If the donor has been successfully contacted by other means, then we do not require that contact be made using the postal service.

b. Donor acknowledgement (§ 630.10(g)(2)).

In proposed § 630.10(i)(2), we proposed to require establishments to provide the donor with a written statement of understanding to be read and signed by the donor. The establishment would be required to use procedures to assure that the donor understands the material provided in the statement, which must not include language that would waive any of the donor's legal rights and must address seven elements: (1) The donor statement that he or she has reviewed the educational material required by § 630.10(b); (2) the donor's agreement not to donate if the donation could put the blood supply at risk; (3) testing of the donor's blood; (4) additional testing of the donor's blood if initial tests are reactive; (5) the consequences if the donation is determined not to be suitable, or if the donor is ineligible; (6) the risks and hazards of the specific donation procedure or of immunization, if applicable; and (7) the donor's opportunity to ask questions and withdraw consent at any time.

We have modified the provision after considering comments received to the proposed rule and the recommendations made from the Blood Products Advisory Committee at the April 28-29, 2011, meeting (Ref. 52). For clarity, we now call this "Donor's acknowledgement," instead of the proposed "Donor's written statement of understanding." The statement does not have to be in a written form only, although it must provide for a signature or other documented acknowledgement.

In proposed § 630.10(i)(2)(iv), we proposed to require that the donor be informed that a blood sample will be tested for specified relevant transfusion-transmitted infections and that the further testing might be required for reactive donations. Although we are finalizing the requirement that the donor be informed of infectious disease testing, following the recommendation of the Blood Products Advisory Committee at the April 2011 meeting (Ref.

52), we are not finalizing a requirement that the donor acknowledge that infectious disease testing may include additional testing of reactive samples (proposed § 630.10(i)(2)(iv)). We are not including this detailed requirement in the final rule, and are finalizing 6 out of the 7 proposed requirements.

We have also clarified the requirement that the donor be informed of the risks and hazards of the donation procedure. We now require in § 630.10(g)(2)(ii)(E) that the donor acknowledgement include acknowledgment that the donor has been provided and reviewed information regarding the risks and hazards of the specific donation procedure that the donor will undergo. This is required for every donation of blood and blood components, including Source Plasma and other donations by apheresis. We are finalizing this section with the additional modifications discussed in our responses to comments.

(Comment 75) One comment questioned the use of the term “understanding” as used in “written statement of understanding” in proposed § 630.10(i)(2).

(Response) We have revised the provision to require that the donor acknowledge that the donor has read the material provided. Accordingly, we now designate this as “Donor’s acknowledgement”.

(Comment 76) We were also asked how this section relates to other sections of the existing Source Plasma regulations on informed consent.

(Response) For collections of plasma and platelets for apheresis, §§ 630.15(b) and 640.21(g) require establishments to engage the donor at least annually in an informed consent dialogue. See discussion in comments 86 and 117. The requirement to obtain a donor acknowledgement applies to every collection of blood and blood components, including

apheresis collections of plasma and platelets. The donor's acknowledgement must be obtained at each donation.

(Comment 77) Several comments objected to a requirement that the donor "sign" a statement and urged FDA to allow an electronic signature.

(Response) We agree that this requirement can be satisfied by an electronic signature. Final § 630.10(g)(2)(i) requires that the donor's acknowledgement be provided by signature or other documented acknowledgement.

8. Section 630.10(h)

We have added § 630.10(h) to make explicit a requirement in the proposed regulation. Section 630.10(h) provides that a blood establishment must not collect from a donor found, before collection, to be ineligible, unless an exception exists. In addition, we incorporated existing requirements to defer donors found to be ineligible and to notify the donors of their deferral as required in § 630.40(a).

K. Donor Eligibility Requirements Specific to Whole Blood, Red Blood Cells and Plasma Collected by Apheresis (§ 630.15)

Section 630.15(a) establishes donor eligibility requirements for the collection of Whole Blood and Red Blood Cells collected by apheresis, and § 630.15(b) establishes donor eligibility requirements for collections of Source Plasma and plasma collected by plasmapheresis. These requirements are in addition to those in § 630.10.

For donors of Whole Blood and Red Blood Cells collected by apheresis, this rule requires that donation frequency be consistent with protecting the donor's health, describes minimum intervals between donations, and addresses donations by donors undergoing therapeutic phlebotomy. We have added references to Red Blood Cells collected by apheresis to the heading

and at several points in this section to clarify the applicability of § 630.15(a) to Red Blood Cells collected by apheresis.

For donors of Source Plasma and plasma collected by plasmapheresis, the rule requires the responsible physician, subject to § 630.5(c), to conduct an appropriate medical history and physical examination of the donor. Additionally, blood establishments are required to weigh the donor before each plasmapheresis procedure and to assess the donor's total protein level prior to each donation. This provision includes a requirement in § 630.15(b)(1)(ii) to defer a plasmapheresis donor found to have a medical condition that would place the donor at risk from plasmapheresis, and to defer a donor because of red blood cell loss as described in the rule. This section also contains informed consent requirements for donors of Source Plasma and plasma collected by plasmapheresis. These provisions complement other requirements for the collection of plasma by plasmapheresis in part 640 and part 630, including restrictions on frequency of collection as specified in §§ 640.32 and 640.65. In addition § 630.15(b)(1) cross-references certain exceptions provided for plasmapheresis collections from infrequent plasma donors in § 630.25.

1. Section 630.15(a)

Consistent with the proposed rule, final § 630.15(a)(1) requires that for a collection resulting in a single unit of Whole Blood or Red Blood Cells collected by apheresis, the donation frequency must be no more than once in 8 weeks. For an apheresis collection resulting in two units of Red Blood Cells, the donor must not donate more than once in 16 weeks. These limitations on donation frequency reflect long standing donation interval practices established to protect the donor from potential health risks associated with frequent donations of Whole Blood or Red Blood Cells. The purpose of these provisions is to protect the health of the donor and

allow time for red blood cell recovery. In § 630.15(a)(1)(ii), we provide two exceptions to the donation interval: (1) The donation is for autologous use as prescribed by the donor's physician and the responsible physician determines and documents that the donation may proceed or (2) the donation is a dedicated donation based on the intended recipient's documented exceptional medical need and the responsible physician determines and documents that the health of the donor would not be adversely affected by donating. In the final rule, we added the term "exceptional" to clarify that this exception to donation frequency should apply only in those rare situations where the recipient's need for a component from a donor with particular characteristics is exceptional. For example, it may be appropriate to rely on this exception in the event that a recipient needs a blood component that is negative for a rare blood cell antigen. Under this exceptional medical need provision, the responsible physician must examine the donor and determine and document that the health of the donor would not be adversely affected by donating. Under § 630.5(b)(1)(i), the responsible physician is not authorized to delegate the examination of the donor or the determination that the health of the donor would not be adversely affected by donating.

For clarity, the requirements regarding therapeutic phlebotomy have been consolidated in the final rule in § 630.15(a)(2).

(Comment 78) One comment stated that the applicability of proposed § 630.15 to Red Blood Cells collected by apheresis was unclear. The comment stated that "double unit collection programs," often have additional and different donor eligibility requirements, as described in proposed § 630.15(a)(1).

(Response) Final § 630.15(a) now more expressly includes Red Blood Cells collected by apheresis. Final § 630.15(a)(1) establishes minimum time intervals between collections of

Whole Blood, and single and double units of Red Blood Cells by apheresis. These time intervals are consistent with existing regulations and guidance. This addition makes explicit what was less directly stated in the proposed rule. Proposed § 630.15(a)(1) referred to “double unit collection programs,” which are double Red Blood Cell collections by apheresis. Moreover, proposed § 640.12 required establishments to determine the eligibility of donors of Red Blood Cells in accordance with §§ 630.10 and 630.15.

(Comment 79) One comment stated that FDA should not specify 8 and 16 week donation intervals. Instead, the comment recommended that a blood establishment determine donation frequency without reference to a specific donation interval, taking into account the donor history, the results of a limited physical examination, the participation of a medical director or his or her designee, and the blood center’s procedures. Another comment recommended that a physician be allowed to authorize more frequent collection by certifying that the prospective donor has recovered from the prior donation without evidence of residual effects or to allow the physician to simply certify that the prospective donor meets his/her requirements for a repeat donation on the day of the examination.

(Response) FDA regulations have long specified a minimum interval of 8 weeks between Whole Blood donations, unless a physician examines the donor and certifies the donor to be in good health. FDA is finalizing minimum donation intervals in this rule to protect the health of donors of Whole Blood and Red Blood Cells collected by apheresis because too frequent donation may adversely affect a donor’s health (Refs. 47, 48). In the final rule at § 630.15(a)(1), we are retaining a minimum requirement for an 8 week interval between the donation of a unit of Whole Blood or donation of a single unit of Red Blood Cells by apheresis, and requiring a 16 week interval after a double collection of Red Blood Cells. A 16 week

interval following a double collection of Red Blood Cells is recommended in current FDA guidance (Ref. 53). Blood establishments are free to establish longer donation intervals.

We have provided a limited exception to these donation intervals to allow for more frequent collections for: (1) An autologous donation as prescribed by the donor's physician only when the donor has been examined by the responsible physician who determines and documents that the donation may proceed and (2) a dedicated donation based on the intended recipient's documented exceptional medical need, only when the responsible physician examines the donor and determines and documents that the health of the donor would not be adversely affected by donating.

(Comment 80) Several comments requested that we clarify in the final rule that donors with hereditary hemochromatosis can donate more frequently than the 8 week interval set forth in proposed § 630.15(a)(1) and also to clarify that more frequent donations from such donors may be collected more frequently without an exception or alternative under § 640.120.

(Response) Final § 630.15(a)(2) states clearly that a donation may be collected from a donor more frequently than once in 8 weeks for collections resulting in a single unit of Whole Blood or Red Blood Cells, or 16 weeks for apheresis collections resulting in a double collection of Red Blood Cells, when the donor is determined to be eligible under § 630.10 and the collection is a physician-ordered therapeutic phlebotomy of a donor, including a donor with hereditary hemochromatosis. Establishments do not need an exception or alternative under § 640.120 to make a collection under this provision if the requirements set forth in § 630.15(a)(2) are met.

(Comment 81) One comment recommended that the term "iron overload" should be substituted for the term "hereditary hemochromatosis" in the provision providing an exception to

the requirement to label a collection with the disease state of a donor undergoing therapeutic phlebotomy.

(Response) We decline to substitute the term “iron overload” for the term “hereditary hemochromatosis” in final § 630.15(a)(2). The term, “iron overload” describes imprecisely the donors for whom establishments would perform phlebotomies without charge. However, we agree with the comment that this provision may, at some time in the future, appropriately be applied to collections from donors whose therapeutic phlebotomy is necessitated by a disease or condition other than hereditary hemochromatosis. Accordingly, final § 630.15(a)(2) provides that no labeling for the disease or condition is required if: (i) The donor meets all eligibility criteria; (ii) the donor undergoes a therapeutic phlebotomy as prescribed by a licensed health care provider treating the donor for (A) hereditary hemochromatosis; or (B) another disease or condition, when the health of a donor with that disease or condition will not be adversely affected by donating, the donor’s disease or condition will not adversely affect the safety, purity, and potency of the blood and blood components collected, or any products manufactured from them, and the collection is in accordance with a procedure that has been found acceptable for this purpose by FDA; and (iii) the establishment performs without charge therapeutic phlebotomies for all individuals with that disease or condition. Labeling to identify the disease state or condition that necessitated the therapeutic phlebotomy is still required when these criteria are not met.

(Comment 82) Another comment suggested that the final rule should not require a physical examination by a responsible physician at the time of donation for individuals presenting a prescription for therapeutic phlebotomy for medical reasons. The comment observed that the 2001 guidance document entitled, “Guidance for Industry: Variances for

Blood Collection from Individuals with Hereditary Hemochromatosis,” (Ref. 54) did not provide for such a physical examination for exceptions or alternatives granted in accordance with that guidance document.

(Response) We agree with this suggestion. The final rule does not require that an individual undergoing a prescribed therapeutic phlebotomy to promote the donor’s health be examined by a responsible physician at the time of donation. The physical assessment required for all donors under § 630.10(f) still applies, however.

(Comment 83) One comment supported the proposal that disease labeling would not be required for blood and blood components donated by an individual with hereditary hemochromatosis if the donor meets all eligibility criteria and the collecting establishment performs therapeutic phlebotomies without charge for all individuals with hereditary hemochromatosis, including those who need therapeutic phlebotomy but do not wish or are not eligible to donate. However, the comment recommended that the final rule authorize blood establishments to accept grants and gifts from third parties, including partial insurance coverage, related to the costs of phlebotomy.

(Response) The final rule provides that blood establishments do not have to label donations from a donor with hereditary hemochromatosis with the donor’s disease state if the donor is eligible and the establishment does not charge anyone with hereditary hemochromatosis (or another disease or condition, if the conditions in the regulation are met) for therapeutic phlebotomy. This provision is intended to remove the incentive for an individual with hereditary hemochromatosis to provide untruthful answers to donor eligibility questions for a blood donation in order to receive the benefit of a phlebotomy without charge. If a blood establishment charged a fee for an ineligible donor to undergo a therapeutic phlebotomy, but not for an eligible

donor with hereditary hemochromatosis, the ineligible hereditary hemochromatosis donor would have an incentive to deny risk conditions that might preclude cost-free donation (Ref. 55). This policy is in part based on recommendations of the Advisory Committee on Blood Safety and Availability (Ref. 56). We decline to modify this provision to address the acceptance of grants, gifts, or insurance payments. We note that we did not propose such a provision, and we believe that a reference to grants, gifts, or insurance payments could confuse patients seeking a therapeutic phlebotomy.

(Comment 84) One comment suggested that hospitals that transfuse suitable blood and blood components labeled with the donor's iron overload disease state should include a statement to that effect in their informed consent for transfusion.

(Response) This rule does not address the content of hospital discussions related to informed consent for transfusion. Final § 630.15(a)(2) authorizes blood establishments to collect blood and blood components only from donors, including donors with hereditary hemochromatosis, determined to be eligible. Blood from hereditary hemochromatosis donors has been used for transfusion in other countries without reports of adverse events in recipients (Refs. 57, 58, 59).

1. Section 630.15(b)

We revised proposed § 630.15(b)(1), formerly entitled "Physical examination and informed consent," by dividing it into two sections. This clarifies that separate requirements apply for the medical history and physical examination (final § 630.15(b)(1)) and for obtaining informed consent (final § 630.15(b)(2)). As a result, proposed § 630.15(b)(2) through (b)(7) are finalized as § 630.15(b)(3) through (b)(8).

a. Medical history and physical examination (§ 630.15(b)(1)).

This section, titled “Physical examination and informed consent” in the proposed rule, is now titled “Medical history and physical examination.” Informed consent requirements are now addressed in § 630.15(b)(2). The new heading more accurately describes the assessment required under this section. As proposed, we would have required the responsible physician to examine the donor for medical conditions that would place the donor at risk during plasmapheresis. We intended for this physical examination to include conducting an appropriate medical history and physical examination to identify medical conditions that may place the donor at risk from plasmapheresis.

(Comment 85) One comment stated that FDA should not require a responsible physician to examine the donor before the initial donation and at least annually thereafter. The comment asserted that plasmapheresis collection has been in place for years without risk to donors. The comment also stated that an annual and initial exam is unnecessary for infrequent plasma donors and donors not participating in immunization programs.

(Response) Examination by a qualified licensed physician is already required under current § 640.63(b) for all Source Plasma donors, and we believe that the requirement to conduct a medical history and physical examination before the first donation, and at least annually thereafter, contributes to the safety record of these collections. We have modified this requirement by authorizing the responsible physician in § 630.5(c)(3) to delegate this activity to a physician substitute, as defined in § 630.3(g). During the annual physical, donors may be examined for a variety of conditions, such as heart disease, seizures, trouble breathing, allergies, recent medical operations, or medications, in order to ensure that donating will not adversely affect the health of the donor. Such evaluations would include a physical examination and

medical history which might identify medications or underlying medical conditions that would lead to donor deferral. Because frequent donation by plasmapheresis of plasma for transfusion raises similar donor safety concerns, this requirement now applies to collections from frequent plasmapheresis donors, and not only to Source Plasma donors.

However, we agree with the comment that an annual and initial examination is unnecessary for an infrequent plasma donor, as defined in § 630.3(e). Final § 630.25 provides certain exceptions from donor eligibility requirements for infrequent plasma donors, including the requirement for an enhanced medical history and physical examination under § 630.15. These donors remain subject to the requirements for medical history and physical assessment under § 630.10.

b. What requirements apply to obtaining informed consent? (§ 630.15(b)(2)).

(Comment 86) Several comments stated that for plasmapheresis donors, the distinction between the written statement of understanding and informed consent should be clarified.

(Response) We have clarified that the written statement of understanding, renamed and revised as the donor's acknowledgement in final § 630.10(g)(2), applies to the collection of all blood and blood components, including Source Plasma and plasmapheresis collections. Informed consent for Source Plasma donation has long been required under current § 640.61, and this rule continues those requirements for Source Plasma and plasmapheresis collections. In recognition that the donation of Source Plasma and plasma by plasmapheresis may present additional and potentially greater risks to the donors, § 630.15(b)(2) requires the responsible physician to obtain the informed consent of such a donor on the first day of donation or no more than 1 week before the first donation. Section 630.5 addresses the authority of the responsible physician to delegate this task. The responsible physician must explain the risks and hazards of

the procedure to the donor. The explanation must be made in such a manner that the donor may ask questions of the responsible physician. The explanation must also give the donor a clear opportunity to refuse the procedure. This informed consent process involves a dialogue between the donor and the responsible physician. The establishment must obtain informed consent from these donors at least once every year. If a donor does not return for 6 months, the establishment must obtain informed consent again. If new risks and hazards are identified, or if the donor is enrolled in a new program such as an immunization or special collection program, then a new informed consent, addressing the specific risks and hazards of that program, must be obtained. The informed consent requirements in § 630.15(b)(2) are in addition to the donor acknowledgement, which under § 630.10(g)(2), must be obtained from the donor at each donation.

c. Weight (§ 630.15(b)(3)).

Section 630.15(b)(2) of the proposed rule would have required that establishments determine a donor's weight at each donation of plasma by plasmapheresis. We received several comments regarding this provision, which we address in this rule, and are finalizing this provision in § 630.15(b)(3) as proposed.

(Comment 87) Two comments asserted that weighing a donor at each donation is not useful. One comment further stated that donors are not weighed prior to plateletpheresis procedures, and there is no evidence that asking the donor to state their weight, as opposed to weighing donors, has been unsafe. The comment further asserted that it would not make sense to require a donor to be weighed prior to a co-collection of plasma and platelets by apheresis as donors are currently not weighed prior to triple plateletpheresis procedures, and there have been no adverse events.

(Response) We are finalizing this provision as proposed, and require establishments to weigh a donor before collecting plasma by plasmapheresis. A current weight measurement permits the collecting establishment to calculate accurately the plasma volumes to be collected based on a weight specific nomogram. The need for accurate measurement applies to all collections by plasmapheresis, whether Source Plasma, or frequent or infrequent plasmapheresis collection. We have not included a requirement to weigh plateletpheresis donors. The instructions for use for the apheresis devices used for such collections vary concerning whether they require the user to weigh the donor. Instead, establishments would address donor weight in their standard operating procedures for plateletpheresis collection in a manner that is consistent with the instructions for use (operator's manual) for the apheresis devices used by the establishment to collect platelets.

When there is a co-collection including plasma by apheresis, this provision requires the establishment to weigh the donor because the collection of plasma by apheresis will be based on the donor's weight. In addition, the instruction for use, including the operator's manual of the device used to collect platelets by apheresis, may include an instruction to determine the donor's weight for co-collections with plasma.

(Comment 88) One comment also recommended that in addition to weighing donors at Source Plasma establishments, the donor's height be taken once a year. The comment suggested that conversion of the measurement of height and weight to lean body mass should be the basis for the quantity of plasma removed.

(Response) Measuring the donor's height combined with measuring a donor's weight may be useful in identifying and using a more accurate nomogram to determine the maximum quantity of plasma that should be collected from the donor by plasmapheresis. However, we

believe donors are able to accurately report their height, which is less likely to fluctuate over time than their weight. Therefore, § 630.15(b)(3) requires establishments to weigh each donor prior to each donation, while permitting reliance on a donor's self-reported height when needed to determine an accurate nomogram for the maximum quantity of plasma that should be collected. We note that under current § 606.65(e) establishments must follow the device instructions for use and operators manual of the apheresis collection device.

d. Total protein level (§ 630.15(b)(4)).

We are finalizing the requirement for collection establishments to test the donor's blood sample for total plasma protein, and that the donor have a value of no less than 6.0 grams per deciliter and no more than 9.0 grams per deciliter. Consistent with current § 640.63(c)(5) and proposed § 630.15(b)(4), this section requires establishments to continue the practice of assessing protein levels before each plasmapheresis procedure. In addition, we are maintaining the existing requirement in current § 640.65(b)(1)(i), which requires establishments to assess a Source Plasma donor's total protein levels, and to perform a plasma or serum protein electrophoresis or quantitative immuno-diffusion test or an equivalent test to determine immunoglobulin composition of the plasma or serum, on the day of the first medical examination or plasmapheresis, and at least every 4 months thereafter. Final § 640.65(b)(2)(i) requires the responsible physician to review the accumulated laboratory data, including any tracings of the plasma or serum protein electrophoresis pattern, the calculated values of the protein composition of each component, and the collection records within 14 calendar days after the sample is drawn to determine whether or not the donor should be deferred from further donation. Comments on § 640.65(b)(2)(i) are discussed at comment 118.

(Comment 89) Several comments questioned the validity of the proposal to require 9.0 grams protein per deciliter value for the upper limit for total plasma protein. One comment stated the requirement for total protein should specify that the donor's total plasma or serum protein must have a value of no less than 6.0 grams per deciliter and that the acceptable upper limit may be established based on applicable statistical analysis of test results on their donors.

(Response) After further consideration, we are finalizing these limits largely as proposed. We consider the lower limit, no less than 6.0 grams protein per deciliter, and the total upper limit of 9.0 grams protein per deciliter in a plasma or serum sample, as appropriate measurement parameters to ensure the donor's health. We have determined that the reference ranges for testing protein in serum and plasma are comparable (Ref. 60); the final rule now applies these lower and upper limits whether testing is performed on either a plasma or serum sample. Although the comments questioned the value of an upper limit, we consider an upper limit to be necessary to ensure donor health, because high protein levels can be associated with adverse health conditions, such as plasma cell dyscrasias (Ref. 61).

(Comment 90) Another comment suggested FDA should consider a flexible regulation to allow for the development of an acceptable alternative to the current procedures.

(Response) We have not identified a need to provide for a variable standard in this rule. An establishment that proposes to use a different standard may submit a request for an exception or alternative under § 640.120.

e. Examination before immunization (§ 630.15(b)(5)).

We have finalized § 630.15(b)(5) to be consistent with proposed § 630.15(b)(4), but we have revised the language for clarity. This section requires the responsible physician, subject to § 630.5, to conduct an appropriate medical history and physical examination of the donor no

more than 1 week before the first immunization injection of a donor for the production of high-titer antibody plasma. This requires that the responsible physician conducts an appropriate medical history and physical examination, as described in § 630.15(b)(1), before the first immunization. It further provides an opportunity to obtain an informed consent specific for participation in an immunization program, as required in § 630.15(b)(2)(iv) (Ref. 62). However, it is not necessary to repeat the medical history and physical examination required in § 630.15(b)(1) if the immunized donor's plasma is collected within 3 weeks of the first immunization injection. Under § 630.15(b)(5)(ii), establishments are not required to re-examine a donor before immunizing the donor for the production of high-titer antibody plasma if the donor is currently participating in a plasmapheresis collection program and is eligible under § 630.10.

f. Deferral of donors due to red blood cell loss (§ 630.15(b)(6)).

For the safety of the donor, we are requiring establishments to defer donors from donating Source Plasma and plasma collected by plasmapheresis following red blood cell loss due to a donation of Whole Blood or Red Blood Cells collected by apheresis. Establishments must also ensure that the cumulative red blood cell loss resulting from previous donations does not adversely affect the health of the donor.

Under final § 630.15(b)(6)(i), establishments must defer a donor from donating plasma by plasmapheresis for 8 weeks following a donation of Whole Blood or a single unit of Red Blood Cells by apheresis. However, establishments may collect Plasma by plasmapheresis 48 hours after a donation of Whole Blood or a single unit of Red Blood Cells, provided the extracorporeal volume of the apheresis collection device is less than 100 mL (§ 630.15(b)(6)(i)). We authorize collection under these circumstances because the risk of red blood cell loss in the

donor is lower. The limited volume of the extracorporeal circuit limits the donor's potential red blood cell loss in routine apheresis collection. In addition, under § 630.15(b)(6)(ii), plasma donors must be deferred for 16 weeks if the donor donates two units of Red Blood Cells during a single apheresis procedure. Final § 630.15(b)(6)(iii) requires deferral for 8 weeks or more if the cumulative red blood cell loss in any 8 week period could adversely affect donor health.

We have not finalized the provisions in the proposed rule that would have required deferral after red blood cell loss of equal to or greater than 200 mL (proposed § 630.15(b)(5)(i) and (b)(5)(iii)). We recognize that it is difficult to measure the amount of blood lost in order to determine whether the volume is equal to or greater than 200 mL. Instead, we are finalizing the requirement in § 630.15(b)(6)(iii) to defer the donor if the donor's cumulative red blood cell loss in any 8 week period could adversely affect donor health. We have addressed deferral due to red blood cell loss in guidance (Ref. 63) and intend to issue future guidance on the impact of the cumulative red blood cell loss following frequent apheresis procedures.

(Comment 91) One comment noted that FDA's guidance, "Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods," which published in December 2007 during the comment period for the proposed rule, contained recommendations for 16 week deferral of platelet donors who experienced losses of red blood cells of 300 mL or more. The comment recommended that 16 week deferrals for larger red blood cell loss should be included for plasma donors in this final rule.

(Response) We agree with this comment about the relevance of FDA's recommendations in "Guidance for Industry and FDA Review Staff: Collection of Platelets by Automated Methods," hereafter, referred to as the "2007 Guidance" (Ref. 64). Because the risks associated with red blood cell loss are comparable for donors of plasma and platelets by apheresis,

§ 630.15(b)(6)(iii) requires establishments to defer for 16 weeks plasma donors who donate two units of Red Blood Cells during a single apheresis procedure.

(Comment 92) Another comment stated that specific deferral periods are unnecessarily restrictive, and that there should be a provision similar to that in the proposed rule at § 640.21(e), to the effect that collection of plasma by apheresis should be permitted following a donation of Whole Blood or other red cell loss, if the extracorporeal red blood cell volume for the apheresis device is less than or equal to 100 mL. The comment noted that most of the plasma collected by apheresis from volunteer blood donors is plasma collected concurrently with apheresis platelets. The comment stated that since FDA recognizes that plateletpheresis collection is safe in this circumstance, it does not make sense to have more restrictive criteria for the collection of plasma by apheresis during plateletpheresis, as the red blood cell loss would be the same for these procedures.

(Response) We recognize that a co-collection of Plasma and Platelets may occur and we agree that the risks associated with red blood cell loss for collections of Source Plasma and Plasma by apheresis are similar to those for collections of Platelets by apheresis. The requirements for deferral of Plasma donors due to red blood cell loss following Whole Blood or Red Blood Cell donation or inadvertent red blood cell loss are addressed in this section. Separately, we are finalizing a corresponding provision for the deferral of Platelet donors due to Whole Blood or Red Blood Cell donation or red blood cell loss in § 640.21. We intend for the deferrals for red blood cell loss to be the same for all collections of Plasma and Platelets by apheresis, including co-collections, because we consider the risks of red blood cell loss to be the same.

In the final rule, we require the deferral of plasmapheresis donors following the donation of Whole Blood and Red Blood Cells, and because of cumulative red blood cell loss over time. Consistent with the final requirements for Platelets in § 640.21, § 630.15(b)(6)(i) permits the collection of Source Plasma and Plasma by plasmapheresis 2 days after a donation of Whole Blood or a single unit of Red Blood Cells, provided the extracorporeal volume of the apheresis collection device is less than 100 mL.

g. Exceptions to deferral due to red blood cell loss (§ 630.15(b)(7)).

Final § 630.15(b)(7) provides an exception to deferral due to red blood cell loss for certain Source Plasma donors. While the introductory paragraph of proposed § 630.15(b)(6) referred to participation in a plasmapheresis program instead of to Source Plasma collections, we finalized this exception using the more explicit term “Source Plasma.” In proposed § 630.15(b)(6)(i), the responsible physician would have been required to conduct an examination and “certify” the donor’s good health; final § 630.15(b)(7)(i) requires that the responsible physician examine the donor at the time of the current donation and determine and document that the donor is in good health and the donor’s health permits the plasmapheresis. Under § 630.5(c)(1)(i)(A), the responsible physician is not authorized to delegate this examination and determination. In proposed § 630.15(b)(6)(ii), this exception would apply when the “donor possesses an antibody that is transitory, of a highly unusual or infrequent specificity, or of an unusually high titer.” In final § 630.15(b)(7)(ii), the exception is reserved for donors whose plasma possesses a property such as an antibody, antigen, or protein deficiency, that is transitory, of a highly unusual or infrequent specificity, or of an unusually high titer. This reference to the donor’s plasma, instead of the narrower reference to an “antibody” in the plasma is repeated in final § 630.15(b)(7)(iii), which requires the establishment to document the special characteristics

of the donor's plasma and the need for plasmapheresis of that donor. We altered this provision to refer more generally to the unusual characteristics of the plasma, rather than to a specific antibody, because we recognized that this exception should be available under appropriate circumstances where the donor's plasma has other unusual characteristics, such as a rare antigen. As additional protection against additional red blood cell loss in a collection under this provision, final § 630.15(b)(7)(iv) provides that the extracorporeal volume of the apheresis device used to collect plasma under this provision must be less than 100 mL. We note that donors who donate subject to this exception must be advised of the risks and hazards related to this donation under §§ 630.10(g)(2) and 630.15(b)(2), or under § 630.15(b)(2)(iv), if the donor is newly enrolled in the program.

(Comment 93) One comment asserted that the statement in the proposed rule at § 630.15(b)(6)(ii), "the donor possesses an antibody that is transitory..." requires modification. The comment stated that the usual antibody characterized this way would be anti-Jka or -Jkb. The comment continued that it would be difficult to determine whether the plasma was collected from someone who has an antibody that is transitory before it is collected. The comment recommended the language be changed to state, "donor's plasma contains an antibody..."

(Response) We are retaining the word "transitory" in final § 630.15(b)(7), although it now refers to a transitory property in the donor's plasma, rather than specifically to a transitory antibody. This provision is meant to apply to collections of plasma from individuals with specific transitory properties. These provisions apply only when an establishment knows that the donor's plasma has a particular property that is transitory.

h. Malaria (§ 630.15(b)(8)).

Consistent with proposed § 630.15(b)(7), final § 630.15(b)(8) does not require Source Plasma donors to be free from risk of malaria (for example, based on residence in or travel history to a malaria endemic area). We do not require establishments to screen Source Plasma donors for malaria risk factors because Source Plasma undergoes further manufacturing steps to effectively remove or inactivate pathogens such as the malaria parasite, and licensed plasma derivatives manufactured from Source Plasma have not transmitted malaria.

(Comment 94) Several comments agreed with our proposal to not require freedom from malaria risk for Source Plasma donors.

(Response) We are finalizing this provision as proposed.

(Comment 95) In response to our request for comments with supporting data concerning whether this provision should be expanded to donors of plasma for transfusion (72 FR 63416 at 63429), one comment supported not requiring an assessment of malaria risk, but did not provide supporting data. The comment stated that there is very low residual red blood cell contamination in a plasmapheresis product, and that the thawing process renders the malaria parasite non-viable. The comment also cited the lack of historical malaria transmission from Fresh Frozen Plasma.

(Response) The malaria parasite resides in red blood cells, and we recognize most red blood cells are removed from plasma collected by apheresis. There are limited data on the viability of malaria parasites in plasma and the residual red blood cells contained in plasma. However, plasma intended for transfusion, unlike Source Plasma used to manufacture plasma derivatives, does not undergo further manufacturing steps to remove or inactivate pathogens. Absent data demonstrating that the risk of transfusion-transmitted malaria is eliminated with

plasma products intended for transfusions as well as a licensed test for malaria, we require that all donors, except Source Plasma donors, be assessed for risk of malaria.

(Comment 96) Two comments responded to our request for comments concerning whether Source Plasma donors should be screened for other parasitic diseases. The comments recommended that Source Plasma donors not be screened for other parasitic diseases, since, due to the nature of Source Plasma donation and the manufacturing process, these have no impact on product quality or safety. One comment urged FDA to distinguish between plasma collected for transfusion and plasma collected for further manufacture, and consider the intended final use of the products. The comment recommended that donors should not be screened for any pathogen that can be removed by filtration.

(Response) We are not including in this final rule a specific exemption for assessing Source Plasma donors for risk of all parasitic diseases; nor are we eliminating donor screening for pathogens that can potentially be removed by filtration or other manufacturing methods. Insufficient data were submitted in support of these proposals. We intend to address recommendations for donor screening and testing for specific new diseases identified as relevant transfusion-transmitted infections on a case by case basis. We recently chose not to recommend screening or testing of Source Plasma donors for Chagas disease, another parasitic infection (Ref. 24). We intend to continue such individual assessments and issue appropriate recommendations in the future.

L. Exceptions for Certain Ineligible Donors (§ 630.20)

Section 630.20 permits, under certain circumstances, the collection of blood and blood components from individuals who do not meet one or more of the eligibility requirements under §§ 630.10 or 630.15, or are deferred under § 610.41. In finalizing this provision, we made

several changes. In the first sentence, we make clear a requirement that was implicit in the proposed rule: that collection authorized under this provision may proceed only after the establishment performs the required donor assessments and determines a donor to be ineligible under any provision of §§ 630.10(e) and (f) or 630.15(a). We have not included the reference to donors deferred under § 610.41 because of a reactive screening test for a relevant transfusion-transmitted infection in final § 630.20. We determined that the provision was unnecessary to include here because §§ 610.40(h)(2)(i) and 610.41(a)(5) already authorize autologous collections from reactive donors, and §§ 610.40(h)(2)(ii) and 610.41(a)(2) and (3) authorize plasmapheresis collections under a special collection program. For a collection from a reactive donor outside these provisions, a blood establishment would first file a request under § 640.120. We expect that such requests would occur only in extraordinary medical circumstances. We also reorganized the section and clarified the responsible physician's role and responsibilities for all collections authorized under § 630.20.

Final § 630.20(a) permits establishments to collect from certain ineligible donors donating only for autologous use, as prescribed by the donor's physician. Autologous donors have long been permitted to donate blood for their own use even though they do not meet eligibility criteria, including a reactive result on a donor screening test. This section provides additional protections for an ineligible, autologous donor who may not be in good health: The donor must have a hemoglobin level no less than 11.0 grams of hemoglobin per deciliter of blood or a hematocrit value no less than 33 percent, and the responsible physician must determine and document before the collection that the health of the donor permits the collection. Under § 630.5(b)(1)(ii), the responsible physician must not delegate the determination of the donor's health. Note that § 630.20(c)(1) of the proposed rule stated that this exception would be

available when “[t]he donation is for autologous use ... and is not for allogeneic transfusion or for further manufacturing use.” Final § 630.20(a) defines the scope of this exception in fewer words that are intended to have the same meaning, “The donation is for autologous use only” (emphasis added).

Also consistent with the proposed rule, final § 630.20(b) permits the collection of plasma from donors participating in an approved Source Plasma program to collect plasma for further manufacturing use into in vitro products for which there are no alternative sources. One example of such products is plasma collected from donors with relevant transfusion-transmitted infection(s) or other diseases; the plasma may be used to develop positive controls for infectious disease test kits. The collection must take place under the medical oversight specified in the approved plasmapheresis program, and for each collection the donor must meet the criteria in § 630.10(f)(1) through (6) and the responsible physician must determine and document that the donor’s health permits the collection procedure. Under § 630.5(c)(1)(i)(A)(2), the responsible physician must not delegate the determination that the donor’s health permits the collection procedure.

Final § 630.20(c) provides an exception when the donation is restricted for use solely by a specific transfusion recipient based on documented exceptional medical need, and the responsible physician determines and documents that the donor’s health permits the collection procedure, and that the donation presents no undue risk to the transfusion recipient. This is similar to proposed § 630.20(c)(3), but we have clarified that this applies to the collection of blood components for transfusion (not further manufacturing use), and that the medical need of the transfusion recipient must be exceptional. Consistent with final § 630.15(a)(1)(ii)(B), we added the term “exceptional” to clarify that this exception to donor eligibility should apply only

in those rare situations where the recipient's need for a component from a donor with particular characteristics is exceptional.

(Comment 97) Two comments recommended that the language throughout this section refer to "responsible physician or physician substitute" instead of to "responsible physician."

(Response) We decline to add the extra words requested here. Section 630.5 addresses the activities which the responsible physician may delegate.

(Comment 98) Two comments asserted that it was unnecessary and burdensome to require the responsible physician to examine and certify the good health of an autologous donor before allowing a collection under this exception. The comments noted that autologous donors are under the care of their personal physicians, and these collections take place pursuant to prescription or physician's order. Autologous donors may wish to donate at facilities geographically distant from the facility where the blood establishment's responsible physician is located. The comments stated that the rule should therefore not require examination by the responsible physician. Some comments also criticized the proposed requirements that the responsible physician examine the donor and certify in writing that the donor's health permits the collection procedure for special collection programs and directed donations.

(Response) We have revised proposed § 630.20. For collections under these exceptions, the final rule requires that the responsible physician determine and document that the donor's health permits the collection procedure, and additionally for directed donations under § 630.20(c), that the donation presents no undue medical risk to the transfusion recipient. We note that this determination will be made after the applicable donor eligibility assessments required under § 630.10 and § 630.15 are performed. The responsible physician can make these determinations based on information developed during the donor eligibility assessments, rather

than during an additional examination of the donor, and, consistent with § 630.5(b)(1)(i)(B) through (b)(1)(i)(C) and (c)(1)(i)(A)(2) through (c)(1)(i)(A)(3), can make this determination from another geographic location. The responsible physician's determination must be documented. In accordance with § 606.100, blood establishments must have written standard operating procedures for collections under these provisions.

We also note that establishments must have prior written approval from the Director, CBER for special collections under § 630.20(b). FDA will review donor selection criteria for these programs, as well as the provision for medical oversight of collections, and must approve the procedures before such collections may proceed. In some circumstances, FDA may require additional donor protections to be in place. For example, FDA may determine that collections from donors with clotting factor deficiencies may proceed only if the responsible physician examines the donor before each donation and is present to oversee the collection. These terms would be addressed in FDA's review and approval of the special collection program. In addition, final § 630.20(b) requires that ineligible donors who are permitted to donate under this section must meet the criteria in § 630.10(f)(1) through (6).

For collections under § 630.20(c), the responsible physician is not authorized to delegate the determination that the donor's health permits the collection procedure, or that the donation presents no undue medical risk to the transfusion recipient. Because the collection and transfusion of blood and blood components from such collections may present risks to both the donor and the transfusion recipient, we have determined that these determinations must be made by the responsible physician, who may make these determinations from an offsite location.

(Comment 99) One comment emphasized the importance of directed platelet donations, and urged FDA to rely on the blood establishment to determine whether to collect platelets from

a donor with a hematocrit value of 37 percent (just below the value of 38 percent referenced in current regulations) when the collection is intended for a specific recipient based on documented medical need.

(Response) We agree that dedicated platelet donations are important. Final § 630.20(c) would permit dedicated donations based on documented exceptional medical need, provided that the responsible physician determines and documents that the donor's health permits the collection procedure, and that the donation presents no undue medical risk to the transfusion recipient.

M. Exceptions from Certain Donor Eligibility Requirements for Infrequent Plasma Donors

(§ 630.25)

We are finalizing this provision largely as proposed. For greater clarity, we have included a definition of "infrequent plasma donor" in new § 630.3(e), and we use that defined term in this section. An infrequent plasma donor is a donor who has not donated plasma by plasmapheresis or a co-collection of plasma with another blood component in the preceding 4 weeks, and who has not donated more than 12.0 liters of plasma (14.4 liters of plasma for donors weighing more than 175 pounds) in the past year. Final § 630.25 provides exceptions for collections from infrequent plasma donors who are not participating in an immunization program. This reflects our determination that, for these collections, it is not necessary for establishments to assess infrequent plasma donors using the medical history and physical examination required in § 630.15(b)(1); to perform the test for total protein required to be performed prior to collection under § 630.15(b)(4) and periodically under § 640.65(b)(1)(i); or to perform a plasma or serum protein electrophoresis or quantitative immuno-diffusion test or an equivalent test to determine immunoglobulin composition of the plasma or serum, as required

under § 640.65(b)(1)(i). Further, it is not necessary for the responsible physician to review the laboratory data as required in § 640.65(b)(2)(i).

We have added the term “medical history” in the first sentence of final § 630.25(a), to make clear that this provision may provide an exception to the requirements in § 630.15(b)(1) to conduct both the medical history and physical examination required for Source Plasma or frequent plasma collection. However, blood establishments are still required to perform the medical history and physical assessment required under § 630.10. In addition, as discussed in response to comment 102, we have directly addressed the applicability of this exception to donors who previously donated a co-collection of plasma and another blood component by apheresis.

(Comment 100) One comment stated that the donor eligibility requirements for frequent plasma donors are unnecessary for infrequent donors.

(Response) Our regulations have long provided additional donor eligibility requirements for Source Plasma donors (see current § 640.63) to address potential risks associated with frequent plasmapheresis donation, and this rule incorporates those long-standing provisions. However, we agree that infrequent plasma donors are not exposed to the same risks as frequent donors. In final § 630.25, we provide exceptions from certain donor eligibility requirements for infrequent plasma donors.

(Comment 101) One comment recommended that the exceptions in § 630.25 should be applicable to donors who donate plasma more frequently than once in 4 weeks if the donor’s physician determines the donor to be in good health.

(Response) We decline to accept this comment. The conduct of a medical history and physical exam, the pre-collection review of total protein levels, and the periodic review of

protein composition and other laboratory data as required by §§ 630.15(b)(1), (b)(4), and 640.65(b) are necessary to protect the health of plasma donors who are not infrequent plasma donors, as defined in § 630.3(e) (Refs. 65, 66).

(Comment 102) One comment requested clarification concerning whether the exceptions proposed in § 630.25 should be available when a donor made a recent platelet donation by apheresis. Another comment stated that this provision would unnecessarily restrict infrequent plasma collections after red blood cell loss. The comment noted that proposed § 630.25 did not address the applicability of this exception after recent donation of platelets by apheresis. The comment noted that most of the plasma collected by apheresis from volunteer blood donors is plasma collected at the same time as apheresis platelets. The comment stated that the criteria for the collection of plasma at the same time as collection of platelets by apheresis should be similar.

(Response) Final § 630.25 provides exceptions for infrequent plasma donors, as defined in § 630.3(e), who are not participating in an immunization program. In response to the comment, we have not included in final § 630.25 the references to red blood cell loss due to apheresis and Whole Blood collections, which we included in proposed § 630.25(a). Instead, final § 630.25 provides for more narrow exceptions to the provisions that relate to the risks of frequent plasmapheresis. We address the deferral of plasma donors for red blood cell loss in § 630.15(b)(6) and (7), and the deferral of platelet donors for red blood cell loss in § 640.21(f).

We agree with the comment that the effects of a recent co-collection of plasma with platelets or another blood component by apheresis should be considered in determining whether the exceptions in § 630.25 are available. Accordingly, § 630.25 applies only to infrequent plasma donors, and § 630.3(e) excludes from the definition of infrequent plasma donor a donor who has donated a co-collection of plasma with another blood component by apheresis in the

preceding 4 weeks. This reflects our determination that, like donations of plasma by plasmapheresis, co-collections of plasma and platelets or another blood component by apheresis during the previous 4 weeks should not be subject to these exceptions. In this way, FDA provides protection to donors from the risks associated with frequent donation of plasma by apheresis (Ref. 64).

N. Donation Suitability Requirements (§ 630.30)

We have finalized requirements in § 630.30(a) to define when a donation is suitable, and in § 630.30(b) to state what an establishment must do when a donation is not suitable.

Under final § 630.30(a)(1) through (4), a donation is suitable when: (1) The establishment determines that the donor is not currently deferred from donation as determined by review of the records of deferred donors described in § 606.160(e); (2) the results in accordance with §§ 630.10 through 630.25 indicate that the donor is in good health and procedures were followed to ensure that the donation would not adversely affect the health of the donor; (3) the results in accordance with § 630.10(e) indicate that the donor is free from risk factors for, or evidence of, relevant transfusion-transmitted infections and other factors that make the donor ineligible to donate; (4) the donor's blood has been tested in accordance with § 610.40 and, unless an exception applies, is negative or nonreactive; and (5) the donation meets other requirements in subchapter F. The final rule now specifies in § 630.30(a)(1) that an establishment must determine that the donor is not currently deferred from donation by reviewing the donor records described in § 606.160(e). Final § 630.30(a)(2) clarifies that the determination of the donor's good health must also include a finding that procedures were followed to ensure that the donation would not adversely affect the health of the donor.

Proposed § 630.30(a)(5) would have required an establishment to determine as part of its review of the suitability of platelet components that “you have taken adequate steps to assure that the donation is tested for bacterial contamination and found negative.” After further consideration we have determined that this provision, which concerns a current good manufacturing practice, should be codified in part 606, which is titled “Current Good Manufacturing Practice for Blood and Blood Components.” Accordingly, we discuss comments to proposed § 630.30(a)(5) at comments 13 through 24 (discussing final § 606.145). Consistent with proposed § 630.30(a)(6), § 630.30(a)(5) in the final rule states that a donation is suitable when the donation meets other requirements in subchapter F.

We have made several changes from the proposal in finalizing § 630.30(b), titled “What must you do when the donation is not suitable?” Final § 630.30(b)(1) now provides “You must not release the donation for transfusion or further manufacturing use unless it is an autologous donation, or an exception is provided in this chapter.” This provision is revised to state more explicitly a clear consequence of finding that a donation is not suitable.

Final § 630.30(b)(2), consistent with the proposed rule, requires a blood establishment to defer the donor of an unsuitable donation. However, although the proposed rule would have required deferral of all donors of platelets found to be bacterially contaminated, § 630.30(b)(2) of the final rule requires deferral only when the establishment determines in accordance with new § 606.145 that the bacterial contamination is likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor. We made this change in response to comments, which are discussed at comment 103. In addition, we discuss the requirement to determine whether contaminating bacteria are likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor at comment 103.

We are not finalizing the provision (proposed § 630.30(b)(3)) that would have required establishments to enter information about deferred donors into the cumulative record of deferred donors. As discussed at comments 25 through 28, we are finalizing the requirements related to the cumulative record of deferred donors more narrowly and new § 606.160(e)(2), not this section, specifies the information required to be included in that record.

Consistent with the proposed rule, we require establishments to notify deferred donors in accordance with final § 630.40. However, although we reiterated the reasons for deferral and notification in the language of proposed § 630.30(b)(4), in final § 630.30(b)(4) we are taking the simpler approach of cross-referencing the donor notification requirements in § 630.40. This is not a substantive change.

(Comment 103) Several comments opposed a broad requirement to defer and notify donors when their platelet component is identified as bacterially contaminated. Some comments observed that the presence of bacteria on a donor's skin is expected and typically is not an indication of illness in the donor. Most instances of bacterial contamination of platelets occur due to the limitations of collection facility practices, which may permit the introduction of skin flora or other contaminants into the collection. On the other hand, in some instances, the presence of certain bacterial contaminants in a platelet component could indicate an underlying bacteremia, and potentially a serious illness in the donor. One comment also asserted that donor deferral based on a bacterial culture positive result may be appropriate if: (1) The positive culture is an indication of an underlying donor pathology that may be cause for deferral (for example, a donor who cultured positive for Streptococcus bovis who later was found to have colonic pathology) or (2) the positive culture may indicate a higher risk of future contaminated collections.

One comment would support notification only when a local investigation completely ruled out collection facility practices as the source of contamination. Another comment asserted that while identification of the bacterial contaminant is likely to be performed to aid the medical director in evaluating the potential risk to transfusion recipient or donor, the extent of this identification may be limited to “coagulase negative Staphylococcus” or “Bacillus species, not anthracis.” The comment went on to state that further identification of the species of the bacterial contaminant should not be required.

(Response) We agree that most instances of bacterial contamination of platelets occur because of limitations to aseptic methods of collection. If we were to require deferral and notification of all donors who donated platelets that subsequently tested positive for bacterial contamination, we would unnecessarily alarm many fully qualified donors. We further agree with the comments noting that a subset of the findings of contamination are linked to bacteria-associated illness in the donor, such as a colonic malignancy which may be signaled by the presence of Streptococcus bovis in the donated platelets (Ref. 19). Accordingly, we have narrowed the proposal related to donor deferral and notification. Under § 630.30(b)(3), a collection establishment must defer the donor of bacterially contaminated platelets when the contaminating organism is identified in accordance with § 606.145 as likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor. This reference to endogenous infection is intended to refer to bacteria that originate from the bloodstream of an asymptomatic donor, and not to bacteria that are typically found on the surface of the skin.

This rule does not require donor deferral when the presence of bacteria is due to contamination with the skin flora, or other contamination at the collection site. We have similarly limited donor notifications related to platelet contamination. Final § 630.30(b)(4)

requires establishments to notify donors in accordance with § 630.40. As noted at comment 107, § 630.40(a) now requires an establishment to make reasonable attempts to notify any donor whose donated platelets have been determined under § 606.145(d) to be contaminated with an organism that is identified as likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor.

(Comment 104) Several comments stated that they consider the decision whether to defer and notify the donor to fall within the purview of the collection facility's medical director. They stated that regulation is not required in this area. Another comment stated that blood establishments already have a defined policy for how to investigate situations where a blood component contains a contaminant in the unit that might suggest the presence of a systemic infection in the donor, and that the donor should be notified and then investigated, counseled and/or treated as appropriate by a knowledgeable physician. The comment asserted that AABB has in place a logical and medically sound approach to these issues and that current procedures set forth by the industry organization and establishments are sufficient.

(Response) We recognize that numerous blood establishments already defer and notify donors in accordance with the policies embodied in this regulation. However, others do not, and donors at those facilities may not receive information that is important to their health. In order to protect these donors, we are requiring donor deferral and notification when the responsible physician for the collection establishment determines that the contaminating organism is likely to be associated with bacterial infection that is endogenous to the bloodstream of the donor.

(Comment 105) Another comment recommended that FDA not finalize these donor deferral and notification provisions. The comment urged FDA to instead provide separate

guidance after FDA approves a bacterial release test. The comment asserted that guidance was needed to address the deferral period and the reason for deferral.

(Response) Since the proposed rule was published, the tools for bacterial testing of platelets have improved and notification practices have evolved. FDA has cleared several devices for quality control testing of platelets, including two culture-based systems and two non-culture-based rapid tests. One test has also been cleared as a safety measure following testing with an early culture. In the United States, culture of apheresis platelets by collection centers is virtually universal. Approximately 65 percent of Whole Blood-derived platelets are pooled early in storage (pre-storage pooling) at the collection center and are all cultured; the remaining 35 percent are pooled just prior to transfusion by the transfusion service and are typically tested with a rapid test (information obtained at the AABB July 2012 workshop) (Ref. 20). In addition, AABB published industry standards requiring follow-up of positive samples to identify the organism (Ref. 17). A practice of notifying donors after finding endogenous bacteria with clinical consequences, such as Streptococcus bovis, has been reported by the American Red Cross, among others (Refs. 18, 19). These circumstances support even more strongly the donor deferral and notification provisions we proposed. Accordingly, we decline the comments' request that we delay finalizing these provisions. We will issue additional guidance as appropriate.

(Comment 106) Another comment stated that a lookback procedure with respect to all cases of bacterial contamination would not be appropriate; rather, reasonable medical judgment should be applied in these instances.

(Response) We are not requiring a lookback procedure in this rule.

O. Requalification of Previously Deferred Donors (§ 630.35)

We received no comments on proposed § 630.35. On our own initiative, we have restructured this provision to more clearly identify situations where a prior deferral will not prevent future donations by an eligible donor. This section continues to provide that a previously deferred donor may donate again if that donor meets donor eligibility criteria at the time of the current collection, and if the collecting establishment determines that the basis for the previous deferral is no longer applicable.

In final § 630.35(a), we make clear that the basis for a previous deferral is no longer applicable if the deferral was for a defined period of time and that time period has passed, or if the deferral was otherwise temporary, such as those deferrals based on eligibility criteria described in final § 630.10(f)(1) through (5) or § 630.15(b)(4). These sections require deferral for individual donor conditions that may change over time: temperature, blood pressure, hemoglobin or hematocrit, pulse, weight, and for plasmapheresis donors, total protein levels.

Final § 630.35(b) makes clear that when the basis for the deferral is no longer applicable, donors who were deferred for reasons other than under § 610.41(a) may be found to be eligible to donate under a requalification method or process found acceptable for such purpose by FDA. For example, donors who were deferred under § 630.10(e)(1)(vi) for tattooing involving nonsterile percutaneous skin inoculation could be requalified after 12 months if they meet all other donor eligibility criteria (Ref. 67). FDA intends to recognize additional methods and processes in guidance documents issued in accordance with good guidance practices. In addition, to respond to individual requests or a public health need, FDA may also authorize alternative procedures related to donor requalification under § 640.120. We note that reentry of

donors deferred under § 610.41(a) is already addressed in current § 610.41(b), which remains in effect.

P. Requirements for Notifying Deferred Donors (§ 630.40)

We have finalized § 630.40(a) consistently with the proposed rule, in which we proposed to move the existing donor notification provision from §§ 630.6 to 630.40, and to add a requirement for notifying donors whose platelet component has tested positive for a bacterial contamination that is likely due to an infection endogenous to the bloodstream of the donor. In addition, the proposed and final rules incorporate updated references to notification after deferral due to ineligibility under new §§ 630.10 and 630.15. While existing § 630.6(a) requires notification of a donor determined not to be suitable based on suitability criteria under § 640.3 or § 640.63, those provisions are being replaced by the donor eligibility criteria in §§ 630.10 and 630.15. Throughout final § 630.40, we also made conforming changes to certain terminology to be consistent with terms used elsewhere in this final rule.

(Comment 107) Several comments, discussed at comments 104 through 106, raised concerns about deferral and notification of donors whose platelet component has tested positive for bacterial contamination that is likely due to an infection endogenous to the bloodstream of the donor. A few comments stated that it would be difficult to notify donors whose platelets indicate evidence of bacterial infection in the donor because FDA has not issued guidance regarding how to identify such situations.

(Response) As noted at Comment 20, we now require in § 606.145(d) that the responsible physician for the collection establishment determine whether the contaminating organism is likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor. Donor deferral and notification are required only after the responsible

physician has made this determination, based on medical judgment, in accordance with the blood collection establishment's SOP.

Q. Platelets: Eligibility of Donors (§ 640.21)

In this final rule, we have revised requirements for collection of Platelets based on comments. We published the proposed rule in November 2007 and subsequently in December 2007 issued the 2007 Guidance (Ref. 64), as we discussed in comment 91. Many of the comments criticized provisions of the proposed rule, while supporting recommendations made in the 2007 Guidance. We have finalized this section to be more consistent with our recommendations in the 2007 Guidance document.

Consistent with proposed § 640.21(a)(1), final § 640.21(a) requires establishments to determine the eligibility of platelet donors in accordance with §§ 630.10 and 630.15, except as expressly modified in § 640.21. We received no comments on this provision and are finalizing it as proposed.

Proposed § 640.21(b) stated that a donor must not serve as the source of Platelets for transfusion if the donor has recently ingested a drug that adversely affects platelet function. We have finalized this provision in two sections. Final § 640.21(b) states that a plateletpheresis donor must not serve as the source of Platelets for transfusion if the donor has recently ingested a drug that adversely affects platelet function. This is because a donor of platelets collected by plateletpheresis will typically be the sole source of platelets provided in a therapeutic transfusion, and the effects of any drugs on platelet function will not be mitigated by pooling the affected platelets with platelets from other donors who have not taken the drug. Final § 640.21(c) states that a Whole Blood donor must not serve as the source of Platelets for transfusion if the donor has recently ingested a drug that adversely affects platelet function, unless the platelet unit is

labeled to identify the ingested drug. We made this change because we recognize that establishments frequently pool multiple units of Whole Blood platelets in order to mitigate the effects of a single unit collected from a donor who ingested a drug that adversely affects platelet function.

In final § 640.21(d), we require establishments to assess and monitor the donor's platelet count. Establishments: (1) Must take adequate and appropriate steps to assure that the donor's platelet count is at least 150,000 platelets/ μ L before plateletpheresis begins. If an establishment does not have records of a donor's platelet count from prior donations and is not able to assess the donor's platelet count either prior to or immediately following the initiation of the collection procedure, the establishment must not collect 9.0×10^{11} or more platelets in that donation; (2) must defer from platelet donation a donor whose pre-donation platelet count is less than 150,000 platelets/ μ L until a subsequent pre-donation platelet count indicates that the donor's platelet count is at least 150,000 platelets/ μ L; and (3) must take appropriate steps to assure that the donor's intended post-donation platelet count will be no less than 100,000 platelets/ μ L. We revised these provisions in response to comments that proposed § 640.21(c) was too prescriptive.

Final § 640.21(e) addresses frequency of plateletpheresis collection in a manner that is largely consistent with the proposed rule. Consistent with proposed § 640.21(c)(4)(i), final § 640.21(e)(1) provides that a donor may donate no more than a total of 24 plateletpheresis collections during a 12-month rolling period. Proposed § 640.21(c)(4)(ii) authorized no more than 2 single component collections of platelets by plateletpheresis within a 7 calendar day period, with a minimum of 2 calendar days between procedures, and proposed § 640.21(c)(4)(iii) would have authorized no more than one double or triple component collection procedure within a 7 calendar day period. However, the proposed rule did not provide numerical values to

distinguish among single, double, and triple collections. Final § 640.21 provides one value, 6×10^{11} platelets, to identify collections that warrant a longer deferral period between donations. Final § 640.21(e)(2) provides that when an establishment collects fewer than 6×10^{11} platelets, the establishment must wait at least 2 days before any subsequent plateletpheresis collection. The establishment must not attempt to collect more than 2 collections within a 7 day period. Final § 640.21(e)(3) provides that when an establishment collects 6×10^{11} or more platelets, the establishment must wait at least 7 days before any subsequent plateletpheresis collection (proposed § 640.21(c)(4)(iii)).

Consistent with proposed § 640.21(d), final § 640.21(e)(4) provides an exception to these limits. For a period not to exceed 30 days, a donor may serve as a dedicated plateletpheresis donor for a single recipient as often as is medically necessary, provided that the donor is in good health, as determined and documented by the responsible physician, and the donor's platelet count is at least 150,000 platelets/ μ L, as measured at the conclusion of the previous donation or before initiating plateletpheresis for the current donation. Current § 610.40(c)(1) addresses the frequency of donor testing for such dedicated plateletpheresis donors.

Final § 640.21(f) addresses the deferral of plateletpheresis donors due to red blood cell loss in a manner that is generally consistent with proposed § 640.21(e). Proposed § 640.21(e) referred to deferral "for a period of 8 weeks after donating a unit of Whole Blood or after losing a volume of whole blood equal to or greater than 450 mL, or red blood cells equal to or greater than 200 mL, cumulatively over an 8 week period; or ... for a period of 16 weeks after donating a double Red Blood Cells unit collection." Final § 640.21(f)(1) finalizes a requirement to defer a donor from donating plateletpheresis or a co-collection of platelets and plasma by apheresis for 8 weeks following donation of a unit of Whole Blood or a single unit of Red Blood Cells by

apheresis. Consistent with proposed § 640.21(e), and in recognition that certain apheresis collection devices limit potential losses of red blood cells and whole blood, the rule provides an exception to this 8 week deferral, this section permits such apheresis collections 2 calendar days after a donation of Whole Blood or a single unit of Red Blood Cells, provided that the extracorporeal volume of the device is less than 100 mL. While proposed § 640.21(e) did not reference the collection of Platelets with Plasma in this exception, we are responding to comments by addressing that collection in final § 640.21(f)(1). Final § 640.21(f)(2) finalizes a 16 week deferral after a donation of a double Red Blood Cells collection. We have not finalized the proposed requirement to defer a donor based on cumulative loss of whole blood or red blood cells over an 8 week period, because it may be difficult for the establishment to assess cumulative blood loss. Instead, final § 640.21(f)(3) requires an establishment to defer a donor for 8 weeks or more if the cumulative red blood cell loss in any 8 week period could adversely affect donor health.

Proposed § 640.21(a)(2) would have required blood collection establishments to include a statement that the “long-term effects of frequent apheresis are unknown” in the platelet donor’s statement of understanding (finalized as the donor acknowledgement in § 630.10(g)(2)). Instead of finalizing that provision, we have incorporated the informed consent requirements found in current § 640.21(c), into final § 640.21(g). As with Source Plasma donation, the responsible physician must obtain the informed consent of a plateletpheresis donor on the first day of donation, and at subsequent intervals no longer than 1 year. Informed consent for plateletpheresis would involve a dialogue between the plateletpheresis donor and the responsible physician. The responsible physician must explain the risks and hazards of the procedure to the donor; that explanation must be made in such a manner that the donor may give consent, but also

has a clear opportunity to refuse the procedure. Authorization to delegate this task to a trained person is addressed in § 630.5(b)(1)(iv). This requirement is different from and is in addition to the requirement in § 630.10(g) to obtain a donor's acknowledgement at every donation.

(Comment 108) One comment suggested that we use the term "platelet apheresis" throughout this provision.

(Response) We use the term "plateletpheresis" in this rule to describe the process of using automated methods to collect Platelets while returning other blood components to the donor. The use of this term is consistent with our current regulations and the 2007 Guidance.

(Comment 109) Two comments stated that proposed § 640.21(b) should be finalized consistently with the recommendations on deferring donors of apheresis platelets who have ingested drugs that inhibit platelet function.

(Response) The recommendations for deferring plateletpheresis donors for ingesting platelet-inhibiting drugs that are contained in the 2007 Guidance are consistent with this final rule (Ref. 64).

(Comment 110) One comment stated that donors of Whole Blood-derived platelets should not be deferred for ingesting platelet-inhibiting drugs. The comment stated that a Whole Blood-derived platelet component collected from a donor who has ingested platelet inhibitory drugs would not be given as a single unit dose, and platelet-inhibiting effects of the ingested drugs would be very limited.

(Response) Final § 640.21(b) states that a plateletpheresis donor must not serve as a source of platelets for transfusion if the donor has recently ingested drugs that adversely affect platelet function. Final § 640.21(c) now states that a Whole Blood donor must not serve as the source of Platelets for transfusion if the donor has recently ingested a drug that adversely affects

platelet function unless the labeling of the unit identifies the ingested drug that adversely affects platelet function. This information will enable the transfusion service to make an informed decision when selecting a single unit of Whole Blood platelets for a small dose transfusion (for example, to a neonate), and will provide useful information to collection establishments and transfusion services when selecting units to pool for a standard dose for the transfusion of platelets. We are not prescribing a specific method for labeling these units. Currently available methods include providing the information on the unit label, as a sticker placed on the unit, or in labeling such as a tie-tag attached to the unit.

(Comment 111) Several comments observed that the proposal in § 640.21(c)(1) applicable to frequent platelet collections, which would require a platelet count before commencing a collection by apheresis, is not consistent with the 2007 Guidance, which recommended that historic averages or default counts may be used in lieu of an actual platelet count. The comments supported those alternatives to a requirement to obtain an actual platelet count, which might not be available at mobile collection sites. Other comments suggested that the regulation should permit reliance on platelet counts taken at other times, including an average of the donor's last three venous platelet counts, the donor's last post-donation platelet count, the platelet count obtained from a pre-collection venous blood sample from the donor's previous donations, the average pre-platelet counts for local donor populations, and the default count for the collection equipment being used. One comment noted that first time donors at mobile collection sites would not have a record of previous platelet counts, but should still be permitted to donate.

(Response) Although we recommend that blood establishments obtain a pre-donation sample from a donor for a platelet count when feasible, we agree that under some conditions it

may not be possible to measure a donor's platelet count before commencing the collection of platelets by apheresis. We have revised the final rule accordingly. Final § 640.21(d) requires the collecting establishment to assess and monitor the donor's platelet count for all collections of Platelets by plateletpheresis. However, we do not require an actual measurement of the donor's platelet count before initiating an apheresis collection of Platelets, unless the establishment suspects that the donor's platelet count is less than 150,000 platelets/ μ L. Instead, § 640.21(d)(1) requires establishments to take adequate and appropriate steps to assure that the donor's platelet count is at least 150,000 platelets/ μ L before initiating plateletpheresis collection. We believe that the recommendations in the 2007 guidance (Ref. 64), which address the use of historic values or the default machine setting when an actual platelet count cannot be obtained in advance of a donation, would currently satisfy the requirement in § 640.21(d)(1) to take such adequate and appropriate steps. If an establishment does not have records of a donor's platelet count from prior donations and is not able to assess the donor's platelet count either prior to or immediately following the initiation of the collection procedure, the establishment may collect platelets by plateletpheresis, but must not collect 9.0×10^{11} or more platelets from that platelet donor. Final § 640.21(d)(2) requires establishments to defer a donor whose pre-donation platelet count is less than 150,000 platelets/ μ L until a subsequent pre-donation count indicates that the donor's platelet count is at least 150,000 platelets/ μ L. This provision requires an actual measurement of the donor's platelet count before initiating another collection of platelets.

(Comment 112) One comment asked whether the proposal that the post-donation count be no less than 100,000 platelets/ μ L would require blood centers to perform a post-donation platelet count. The comment stated that performing a post-donation count is burdensome. Another comment said that post-collection counts should never be required. The comment stated

that apheresis collection device settings can be validated to reliably avoid post-collection counts below 100,000 platelets/ μ L.

(Response) Final § 640.21(d)(3) requires a collecting establishment to take appropriate steps to assure that the donor's intended post-donation platelet count will be no less than 100,000 platelets/ μ L. We expect that establishments will implement this requirement by validating the settings on their apheresis collection devices to avoid post-collection counts below 100,000 platelets/ μ L.

(Comment 113) One comment suggested that FDA specify that in the event the donor's post-donation platelet count is less than 100,000 platelets/ μ L, the donation should be reviewed by the Medical Director, who, based on the donor's history, may deem the donor to be eligible for future donations.

(Response) Because § 640.21(d)(3) requires establishments to take appropriate steps to assure that a platelet donor's intended post-donation platelet count will be no less than 100,000 platelets/ μ L, we believe that this situation will occur rarely. If the donor returns to donate platelets, § 640.21(d) would require the establishment to assess and monitor the donor's platelet count, and, under § 640.21(d)(1), would require the establishment to take adequate and appropriate steps to assure that the donor's platelet count is at least 150,000 platelets/ μ L before initiating plateletpheresis collection. A donor whose pre-donation count is less than 150,000 platelets/ μ L must be deferred under § 640.21(d)(2).

(Comment 114) Several comments suggested that limitations on frequency of plateletpheresis collections should not be finalized. They criticized as unnecessary the limitations to 24 collections in a 1 year period and the requirement for a 2 day interval between each collection. Some comments stated that there is no evidence to support a requirement for a 7

day donation interval following the donation of a double or triple component. One comment asserted that other protections (such as following instructions for use on apheresis collection devices) are adequate to protect the donor.

(Response) We have finalized these requirements in § 640.21(e). Some studies have demonstrated a higher incidence of iron deficiency in frequent plateletpheresis donors. In a United Kingdom study of serum ferritin levels of frequent plateletpheresis donors, there was a direct correlation between plateletpheresis donation frequency and iron depletion. The authors suggested that the iron depletion in these donors is due to blood loss that can occur with each plateletpheresis donation (Ref. 68). In addition, frequency of donation may affect the donor's ability to replace platelets adequately (Ref. 69). For this reason, in order to protect the health of the donor, we have finalized limits on the frequency of platelet donation in § 640.21(e). We agree that collection of more than a single replacement dose of platelets is generally safe. However, the specified interdonation intervals are prescribed to assure that plateletpheresis donors have time to recover their platelet counts between collections.

We also note that § 640.21(e)(4) provides an exception that may be available when a donor serves as a dedicated plateletpheresis donor for a single recipient. Under this exception a healthy donor may donate more frequently during a 30 day period, in order to provide platelets for a recipient in need of multiple transfusions of platelets.

(Comment 115) One comment noted that the proposed deferrals of plasma donors for red blood cell loss contained in proposed § 630.15(b)(5) were different from the deferrals for platelet donors for red blood cell loss in proposed § 640.21(e).

(Response) We have harmonized the deferrals for red blood cell loss in final § 640.21(f) based on comments regarding co-collection of Platelets and Plasma by apheresis, discussed at comment 92.

(Comment 116) One comment recommended that a Whole Blood donor should have to wait 8 weeks before donating by plateletpheresis, unless the instrument used is designed to collect less than 100 mL of red blood cells, regardless of the donor's hematocrit, when the donor is not fully re-infused. The comment stated that there is a potential for plateletpheresis donors to lose more than 100 mL of red blood cells based on the type of machine used and the donor's hematocrit, and identified one apheresis device with an extracorporeal blood volume greater than 200 mL.

(Response) Final § 640.21(f)(1) allows an establishment to collect either platelets by apheresis or platelets with Plasma by apheresis 48 hours after a donation of Whole Blood or Red Blood Cells, only if the extracorporeal volume of the apheresis collection device is less than 100 mL. An establishment could not collect platelets by apheresis using the device with an extracorporeal volume greater than 200 mL identified by the comment under this provision.

(Comment 117) Two comments criticized proposed § 640.21(a)(2), which would have required the statement of understanding to include a statement that the long-term effects of frequent apheresis are unknown. One comment suggested that there is adequate published literature that would indicate that the effects of long-term frequent apheresis are known. Another similar comment asserted that no long-term adverse effects have been reported with frequent apheresis, and it is not necessary to include a statement with information provided to the donor.

(Response) Final § 640.21(g) requires the responsible physician to explain the risks and hazards of the procedure to the donor as part of the informed consent process. In addition,

§ 630.10(g)(2)(ii)(E) requires that, at every donation, the donor acknowledge that the donor has been provided and reviewed information regarding the risks and hazards of the specific donation procedure. These regulations do not require that the donor be informed that the long term effects of frequent apheresis are unknown; we recognize that, as knowledge improves, such a statement may no longer be accurate. However, even though the current literature does not answer all questions concerning the long term consequences of frequent plateletpheresis (Ref. 70), the informed consent must address long term risks and hazards associated with frequent apheresis, such as iron depletion (Refs. 71, 72). The donor's informed consent is required before the first plateletpheresis donation, and at least yearly thereafter.

R. Source Plasma: Plasmapheresis (§ 640.65(b))

We have finalized these sections largely as proposed. Final § 640.65(b)(1)(i) and (b)(2)(i) now reference § 630.25, incorporating those exceptions related to collections from infrequent plasma donors. This reflects our determination, as described in the section addressing § 630.25, certain provisions are not necessary for these collections. Final § 640.65(b)(2)(i) also requires that plasmapheresis donors be tested every 4 months to assure that they have a total protein of no less than 6.0 grams per deciliter, and no more than 9.0 grams per deciliter in a plasma sample or a serum sample. We received comments on this protein standard, which is also incorporated in § 630.15(b)(4). We discuss those comments at comment 89. Final § 640.65(b)(2)(i) further requires the responsible physician to review the accumulated laboratory data, including any tracings of the plasma or serum protein electrophoresis pattern, the calculated values of the protein composition of each component, and the collection records to determine if the donor should be deferred from further donation. This section further requires that if the review is not completed within 14 calendar days after the sample is drawn, the collection

establishment must defer the donor pending the review. This will assure that establishments do not take additional collections from an ineligible donor in the event that this review is delayed.

(Comment 118) A few comments to proposed § 640.65(b)(2)(i) recommended that the review time for determining whether a donor would be deferred from further donation should remain at 21 days, not 14 days as proposed. The comment stated that the current 21 day allowance is needed to ensure adequate time for testing, return of test results to the laboratory and medical review. The comment stated that FDA should note that Canadian health authorities recently changed their requirement to 21 days.

(Response) We decline to provide a 21 day timeframe for review. This change from 21 days to 14 days reflects changes on how samples are submitted for testing, and how test results are transmitted. These changes permit faster receipt and review of test results. As we noted in the proposed rule, current § 640.65(b)(2)(i) requires this review to take place within 21 days; we are reducing the time period to 14 calendar days because results are typically transmitted and recorded electronically, permitting faster access. Requiring medical review of these laboratory test results within 14 days is one of the important protections this rule provides to Source Plasma donors.

S. Source Plasma: General Requirements (§ 640.69)

We have finalized two sections as final § 640.69(e) and (f). These provisions incorporate industry practices known as the Qualified Donor Standard and Inventory Hold. Final § 640.69(e) provides that establishments must ensure that Source Plasma donated by paid donors is not used for further manufacturing into injectable products until the donor has a record of being found eligible to donate in accordance with § 630.10, and a record of negative test results on all tests required under § 610.40(a), on at least two occasions in the past 6 months. Because the

regulation requires the establishment to determine a paid donor to be eligible on at least two occasions, but does not require that a unit be collected at the time of the initial eligibility determination, the regulation permits establishments that prefer to establish a donor's qualification by screening the donor and collecting a blood sample, but not a full donation, for testing in accordance with § 610.40(a).

We have finalized the inventory hold provision proposed in § 640.69(f) to require establishments to hold Source Plasma donated by paid donors in quarantine for a minimum of 60 days before it is released for further manufacturing use to make an injectable product. In addition, we now state explicitly the conditions that would prevent an establishment from distributing Source Plasma from quarantine. Under final § 640.69(f), an establishment must not distribute quarantined donations if the donor is subsequently deferred under § 610.41 because of a reactive screening test for evidence of infection due to a relevant transfusion-transmitted infection, or if the establishment subsequently determines the donor to be ineligible under § 630.10 due to risk factors closely associated with exposure to, or clinical evidence of, infection due to a relevant transfusion-transmitted infection. Since Source Plasma would be placed in quarantine under this section after the donation has been determined to be suitable under § 630.30, this section describes the information, typically obtained in connection with a subsequent Source Plasma donation by the donor, which would disallow the distribution from quarantine of that donor's prior donations. We added this language so that establishments would understand that, under this section, post-donation information would prevent the distribution of quarantined donations if that information consisted of a reactive screening test on a subsequent donation or a subsequent donor deferral due to risk factors associated with relevant transfusion-transmitted infection. Other donor information would not prevent distribution of previously

quarantined units, even if it led to deferral of the donor from current collections. For example, information related to a donor's health on the day of a future donation (see, for example, § 630.10(f)(1) through (f)(6)) would not affect the distribution from quarantine of previously collected units.

(Comment 119) Two comments noted that proposed § 640.69(e) and (f) would codify existing, voluntary practices used in Source Plasma establishments. The comments urged FDA not to mandate voluntary industry standards. The comments noted that the Qualified Donor Standard and Inventory Hold were developed before nucleic acid testing was available to identify HIV as well as certain other relevant transfusion-transmitted infections, and that the use of nucleic acid testing significantly improves the identification of recent infections in the donor. According to the comments, incorporating these industry standards in regulation could inhibit the development of new practices based on new technology, and otherwise limit flexibility in the future.

(Response) As we explained in the proposed rule, these provisions are intended to provide additional mitigations of the risk of infectious disease transmission presented by collections from paid Source Plasma donors. Since the 1970s, it has been documented that paid Source Plasma donors are at higher risk than volunteer blood donors for certain relevant transfusion-transmitted infections (Ref. 73). In a 1998 report, the General Accounting Office (GAO) compared the incidence rates (positives per 100,000 person years) between paid and volunteer plasma donors, reporting "we found that the incidence rates for HIV, HBV, and HCV were much higher for paid donors. HIV incidence rates were 19 times higher among paid donors (61.8 versus 3.3 for volunteer donors), while HBV and HCV rates were 31 times (245.5 versus 8.0) and 4 times higher (63.5 versus 14.9), respectively." The GAO concluded, "there is a

consistent pattern of higher marker rates among paid donors than among volunteer donors.” The GAO further recognized the Qualified Donor Standard and Inventory Hold help to mitigate the risks of infection from plasma pools used for manufacturing plasma derivative products. Accordingly, in consideration of the additional risks presented by the paid Source Plasma donors, both industry and the GAO have recognized the importance of these practices in increasing the safety of products manufactured from Source Plasma. Although donor testing has improved with the advent of nucleic acid testing, Source Plasma collectors have continued to incorporate the Qualified Donor Standard and Inventory Hold into their quality standards, as reflected, for example, by the Plasma Protein Therapeutics Association, Quality Standards of Excellence, Assurance and Leadership (QSEAL) Certification Program (Ref. 74).

We solicited comments and supporting data in the proposed rule on whether other requirements would achieve the same results as these practices. We did not receive responsive comments and data. FDA appreciates that, in the future, new standards and practices may develop, which could replace the Qualified Donor Standard and Inventory Hold. However, such alternatives have not yet been identified. If appropriate alternative standards become available in the future, FDA could allow the use of those appropriate alternative standards as alternative procedures under § 640.120, as well as revise this regulation when warranted.

(Comment 120) One comment asked that the wording in § 640.69(e) be revised to state that Source Plasma may be released once a donor has two sets of negative/non-reactive/not implicated viral marker test results. The comment further asserted that it should not be a requirement that the samples sent for testing be drawn at the same time the donor donates Source Plasma.

(Response) Under the final rule, an establishment may draw samples for testing under § 610.40(a) without collecting Source Plasma at the same time.

(Comment 121) One comment questioned the requirements in § 640.69(f), asserting that a proposal to require Source Plasma collectors to store the plasma at the collection center during the 60-day Inventory Hold would be unduly burdensome. The comment noted that the voluntary industry standard for the 60-day hold gives the manufacturer the flexibility to determine the most appropriate place for storage. Moreover, the comment stated that a requirement to use interim “quarantine” labeling on individual Source Plasma collections would add cost. The comment also stated that the term “Quarantine” should not be used because it implies that the plasma being placed in the 60-day hold is violative, when the product is simply held in inventory as part of the standard routine process.

(Response) The language of the proposed rule would not have required that Source Plasma be stored at the collection site, nor did it require establishments to label individual collections of Source Plasma as “Quarantined.” Rather the proposed rule simply required that the product be “held in quarantine.” The final rule requires that Source Plasma be held for a minimum of 60 days and prohibits distribution of certain units “after placing a donation in quarantine.” Final § 640.69(f) does not specify where an establishment must store the product. The establishment is not required to store the product at the collection site, and an establishment may store the product at an appropriate off site facility during the 60-day Inventory Hold. Nor does this provision require individual labeling of units. Instead, it simply requires that the establishment be able to identify any units that may not be distributed because of post-donation information received during the 60-day hold, and to identify when the 60-day hold has expired for a unit. We believe that establishments can meet these requirements by employing a variety

of methods, including physical segregation, labeling (units, cases, or other packing units), or by electronic means (such as by computerized inventory). Finally, we disagree that the use of the term “quarantine” in this context suggests that the product subject to the Inventory Hold is violative. Rather, the term merely implies that the establishment is restricted from distributing the quarantined product while it is subject to the Inventory Hold.

(Comment 122) One comment objected to the use of “paid” to describe donors of Source Plasma subject to this provision. The comment asserted that paid Source Plasma donors are compensated for the time it takes to fulfill their commitment to donate. The comment stated that donating blood and plasma should be encouraged and that it is often necessary to reward donors for their donation.

(Response) We have finalized the rule incorporating the term “paid donor.” This usage is consistent with current § 606.121(c)(8)(v)(A), which is applicable to transfusable blood and blood components. That section defines a paid donor as a person who receives monetary payment for a blood donation.

T. Source Plasma: Records (§ 640.72)

In proposed § 640.72(a)(2) through (a)(4), we proposed several changes to current § 640.72 in order to conform to changes in this rule. We have finalized this section largely as proposed.

(Comment 123) One comment asked FDA to authorize establishments under § 640.72(a)(3) to maintain as an electronic record the records of the plasma donor’s informed consent to participate in the plasmapheresis program, and where applicable, to participate as an immunized donor. This informed consent is required under § 630.15(b)(2). The comment stated

that informed consent requirements should be consistent with proposed § 630.10(i)(2), which allows for a “signature or acceptable substitute for a signature to indicate that understanding”.

(Response) We note that the donor acknowledgement, which the establishment is required under final § 630.10(g)(2) to obtain at each donation, requires a signature or other documented acknowledgement. The donor acknowledgement record is required to be maintained in accordance with § 606.160(a). For informed consent, obtained at the intervals specified in § 630.15(b)(2), final § 640.72(a)(3) now requires establishments to maintain the original or a clear copy or other durable record which may be electronic, of the donor’s consent for participation in the plasmapheresis program or immunization.

(Comment 124) Several comments questioned the reference in proposed § 640.72(a)(4) to documentation by the responsible physician that the donor is in good health under §§ 630.10 and 630.15 on the day of examination. The comments stated that trained persons would be capable of making assessments under §§ 630.10 and 630.15.

(Response) We agree with the comment that reference to §§ 630.10 and 630.15 in proposed § 640.72(a)(4) was misplaced. Instead, under final § 640.72(a)(4) we require that records of the medical history and physical examination of the donor, conducted in accordance with § 630.15(b)(1) and, where applicable, § 630.15(b)(5), must address the eligibility of the donor as a plasmapheresis donor and, if applicable, an immunized donor. Delegation of this examination and determination is addressed in § 630.5(c)(3).

U. Source Plasma: Reporting of Donor Reactions (§ 640.73)

We are not finalizing § 640.73 in this rule. Instead, FDA intends to finalize this section when FDA finalizes the proposed rule, “Safety Reporting Requirements for Human Drug and Biologicals” (68 FR 12406, March 14, 2003) (Ref. 75). We will address in that final rule the

comments received on proposed § 640.73 in this docket. By doing so, we intend to consolidate the safety and reporting requirements of all human drugs and biologicals under this chapter into one comprehensive regulation.

V. Alternative Procedures (§ 640.120)

We are finalizing proposed § 640.120 which separates and revises current § 640.120(a) into proposed § 640.120(a) and (b), and revises and redesignates current § 640.120(b) as § 640.120(c). Under proposed § 640.120(a), a blood establishment could request that the Director, CBER, approve a proposed exception or alternative to any requirement in Title 21 of the CFR, Chapter I, subchapter C (21 CFR parts 200 through 299; these include drug regulations, such as current good manufacturing practice regulations, that are applicable to blood products) and F (21 CFR parts 600 through 680), regarding blood, blood components, or blood products. Current § 640.120(a) authorizes exceptions or alternatives to regulations in subchapter F but omits reference to subchapter C; proposed § 640.120(a) addressed this omission. Under proposed § 640.120(a)(1), an establishment could request an exception or alternative in writing, or, if there are difficult circumstances and submission of a written request is not feasible, as an oral request under proposed § 640.120(a)(2). We also proposed in § 640.120(b) to permit the CBER Director to issue an exception or alternative to these regulations in the event of a public health emergency which impacts blood and blood product establishments or blood availability. We proposed to redesignate current § 640.120(b) as § 640.120(c), and to revise it to state that FDA would publish alternative procedures and exceptions periodically on the CBER Web site rather than in the Federal Register, as our current regulations provide.

We are finalizing this provision largely as proposed, while making some clarifying changes. In final § 640.120(a), we no longer refer to our approval of an exception or alternative

procedure. Instead, we refer to issuing an exception or alternative. This is consistent with the use of the term “issue” in proposed § 640.120(b).

In § 640.120(b), we proposed that the Director be authorized “in a public health emergency” to issue exceptions or alternatives if “necessary to assure that blood, blood components, or blood products will be available in a specified location to respond to an unanticipated immediate need for blood, blood components or blood products.” Final § 640.120(b) authorizes the Director “to respond to a public health need” by issuing a notice of exception or alternative if an exception or alternative is “necessary to assure that blood, blood components, or blood products will be available in a specified location or locations to address an urgent and immediate need for blood, blood components, or blood products or to provide for appropriate donor screening and testing.” We made these two changes to emphasize that this authority will be available to address urgent and immediate needs for blood, blood components, and blood products. The use of this provision is not contingent on whether that need could have been anticipated. In addition, we made explicit the Director’s authority to issue exceptions or alternatives to provide for appropriate donor screening and testing. In recent years, we have confronted shortages and near-shortages of important donor tests. These situations have caused us to recognize the importance of being able to protect donors and recipients by permitting the use of alternative, but adequate, testing algorithms.

(Comment 125) FDA received two comments on proposed § 640.120. Both comments concerned § 640.120(b), relating to alternative procedures during a public health emergency. The comments urged FDA to be more specific about which regulatory provisions in subchapters C and F of Title 21 of the CFR would potentially be the subject of exceptions or alternative procedures during a public health emergency. One comment further indicated that blood

establishments would be better able to prepare facilities and train staff if CBER provided more specific information about exceptions and alternative procedures which may be used during a public health emergency.

(Response) The Agency does not agree that potential variances should be listed within the regulation. Whether or not an exception or alternative is appropriate will depend on the specific situation. The scope, duration, and nature of a specific situation, how it impacts blood establishments, and the extent to which blood and blood products continue to be available, will determine whether a particular provision in subchapter F of title 21 of the CFR would be an appropriate subject for an exception or alternative procedure to address the public health need. Current § 610.40(g) authorizes release or shipment of blood or blood components prior to testing in appropriately documented medical emergency situations. Moreover, CBER has posted on its Web site a document entitled “Exceptions and Alternative Procedures Approved Under 21 CFR 640.120” (Ref. 76), which provides examples of exceptions and alternatives permitted under current § 640.120(a). Blood establishments may find this information to be useful for emergency planning purposes. In addition, FDA intends to continue to work with stakeholders on how to assure the continued availability of safe, pure, and potent blood and blood products during emergencies and other situations that may warrant a variance under this section.

W. Reagent Red Blood Cells (§§ 660.31, 660.32)

We are not finalizing proposed § 660.31, which proposed that donors of peripheral blood for Reagent Red Blood Cells, used as diagnostic substances for laboratory tests, must meet all the criteria for donor eligibility under §§ 630.10 and 630.15, and we are deleting current § 660.31. We are also deleting § 660.32, which addressed the collection of blood for Reagent Red Blood Cells from donors of peripheral blood. We are taking this action because blood

collection establishments in the United States are fully subject to the requirements for donor eligibility, testing, and donation suitability discussed at length in this rulemaking, and these requirements are duplicative for such collections. Moreover, Reagent Red Blood Cells are licensed products subject to licensing standards to assure that the product is safe, pure, and potent. FDA assures that all licensed Reagent Red Blood Cells meet standards for safety, purity, and potency.

(Comment 126) One comment asked FDA not to reference in § 660.31 the criteria for donor eligibility in §§ 630.10 and 630.15. The comment stated that Reagent Red Blood Cells are not used for transfusion and are further processed for reagent use only; it is not necessary for donors of these products to meet the criteria in §§ 630.10 and 630.15.

(Response) We do not agree that donor eligibility provisions should not apply to donors of Red Blood Cells to be manufactured into Reagent Red Blood Cells. Blood collection establishments in the United States must comply with §§ 630.10 and 630.15, and we will require manufacturers of licensed Reagent Red Blood Cells to comply with applicable standards. However, we are deleting §§ 660.31 and 660.32 from the final rule as duplicative.

X. Quality System Regulation: Scope (§ 820.1)

We did not receive any comments on this section and we are finalizing the section as proposed.

Y. Technical Amendments

As has been noted elsewhere in this document, we are making a number of technical changes. These include changes in terminology in certain provisions as follows:

- We are removing the terms “communicable disease agent”, “communicable disease agents”, and “communicable disease agent(s)” wherever they appear and adding in their

place “relevant transfusion-transmitted infection”, “relevant transfusion-transmitted infections”, and “relevant transfusion-transmitted infection(s)” to be consistent with the new definition of “relevant transfusion-transmitted infection” in § 630.3(h). These changes occur throughout 21 CFR part 610 subpart E, as well as in the following provisions: §§ 606.121(c)(11), (c)(12), and (i)(5), 606.122(e), 630.40(b)(3), (d)(1), (d)(1)(i), (d)(1)(iii), 640.5(f), and 640.67;

- We are removing the terms “qualified licensed physician”, “licensed physician”, and “physician on the premises” and adding in their place “responsible physician” to be consistent with the new definition of “responsible physician” in § 630.3(i). These changes occur in the following provisions: §§ 606.110(a), 640.65(b)(1)(i), (b)(1)(ii), (b)(2)(i), (b)(2)(iii), and (b)(2)(iv), 640.66, and 640.71(b)(1);
- We are removing the terms “suitable” or “suitability” and adding in their place “eligible” or “eligibility” to be consistent with the new definition of “eligibility of a donor” in § 630.3(d). These changes occur in the following provisions: §§ 606.40(a)(1), 606.100(b)(1), 606.121(i)(5), 606.160(b)(1)(x), 610.40(h)(2)(iv)(A), 610.41(a)(3), (a)(4), and (b), 630.40(a), (b), (b)(1), and (c), 640.12, 640.31, and 640.51;
- We also are removing “supplemental test” and “supplemental (additional, more specific) test”, or similar wording, and adding in their place “further testing” to be consistent with the further testing requirements in § 610.40(e). These changes occur in the following provisions: §§ 610.40(e)(2), 610.46(a)(2), (a)(3), (a)(4), (b)(2), and (b)(3), 610.47(a)(2), (a)(3), (a)(4), (b)(2), and (b)(3), 630.40(a), (b)(3), and (d)(1)(iii);

- We are removing the term “certified in writing” and adding in its place “determined and documented” to be consistent with the requirement to determine and document in § 640.21(e)(4). This change occurs in § 606.110(a); and
- We are removing the reference to “Health Care Financing Administration” and replacing the reference with this Federal Agency’s current name, “Centers for Medicare and Medicaid Services” in § 610.40(f).

As part of this final rule, we also are removing certain provisions from the CFR because the provisions are superseded or replaced by provisions in the final rule. These include: §§ 610.40(c)(2) and (i), 640.3, 640.27, 640.61, 640.62, and 640.63. For the same reasons, we are removing and reserving §§ 640.4(a), 640.5(a), and 640.64(a). With these changes, we need to make conforming changes when these removed provisions are referenced elsewhere in the CFR.

- § 610.40(i): The final rule removes from the CFR § 610.40(i), which addresses syphilis testing, because syphilis testing is now addressed in § 610.40(a). Accordingly, as part of this final rule, we are removing references to § 610.40(i) that appear in: §§ 610.40(d), (g), and (h)(1), 610.41(a) and (a)(5), and 610.42(a). In removing the reference to § 610.40(i) from §§ 610.40(d), 610.41(a) and (a)(5), and 610.42(a), we are also removing the text “or by a serological test for syphilis”, which modifies the reference to § 610.40(i). In removing the reference to § 610.40(i) in § 610.40(h)(2)(vi), we are adding in its place a reference to § 610.40(a), and, because of the changes to § 640.5, we are removing the related reference to performing syphilis testing under § 640.5. In § 610.40(h)(2)(vii), we are removing the reference to § 610.40(i), and replacing it with references to §§ 640.65(a)(2)(ii) and (b)(1)(i), which address syphilis testing for Source

Plasma donors. We are also removing § 640.65(b)(2), and replacing it with the more precise citation to § 640.65(b)(2)(ii) through (b)(2)(iv).

- § 640.3: The final rule removes from the CFR § 640.3, which addresses suitability requirements for Whole Blood donors. This subject is now addressed in part 630. Accordingly, as part of this final rule, we are removing the reference to § 640.3 that appears in § 606.121(i)(5) and adding in its place a reference to § 630.10. We are removing the reference to § 640.3 that appears in § 640.4(e) and adding in its place a reference to § 630.10. We are removing the references to § 640.3 that appear in §§ 640.12, 640.31(a) and 640.51(a), and substituting references to §§ 630.10 and 630.15. We are removing the reference to § 640.3 as part of our changes to newly designated § 630.40(a), and adding in its place the reference to §§ 630.10 and 630.15.
- § 640.62: The final rule removes from the CFR § 640.62, which addresses medical supervision in Source Plasma situations. This subject is now addressed in part 630. Accordingly, as part of this final rule, we are removing references to § 640.62 that appear in §§ 640.22(c), 640.32(b), and 640.52(b). To clarify that § 630.5 applies to medical supervision for the collection of Source Plasma and other collections addressed in part 640, we have added § 640.130 in new subpart M. This section states that the requirements for medical supervision established in § 630.5 supplement the regulations in part 640.
- § 640.63: The final rule removes from the CFR § 640.63, which addresses suitability requirements for Source Plasma donors. This subject is now addressed in part 630. Accordingly, as part of this final rule, we are removing the reference to § 640.63 that appears in § 606.110(b) and adding in its place a reference to §§ 630.10 and 630.15. We

also are removing the reference to § 640.63 as part of our revisions to newly designated § 630.40(a), and adding in its place a reference to §§ 630.10 and 630.15. As part of our changes to §§ 640.31(b) and 640.51(b), we also are removing references to § 640.63 and adding in their place a references to §§ 630.10 and 630.15. Similarly, as part of our revisions to § 640.72, we are removing the reference to § 640.63 in § 640.72(a)(2) and adding in its place a reference to §§ 630.10 and 630.15. We also are removing the reference to § 640.63(b)(3) in § 640.72(a)(4) and adding in its place references to § 630.15(b)(1) and (b)(5), among other changes.

III. Legal Authority

FDA is issuing this rule under the authority of sections 351 and 361 of the Public Health Service Act (PHS Act) (42 U.S.C. 262 and 264), and certain provisions of the FD&C Act (21 U.S.C. 201 et seq.).

The establishment of these criteria for determining the eligibility of a donor of blood and blood components and the suitability of blood and blood components for transfusion or for further manufacturing is intended to assure that donations are safe, pure, and potent including preventing unsafe units of blood or blood components that may transmit a relevant transfusion-transmitted infection from entering the blood supply, while safeguarding the health of donors.

FDA has been delegated authority under section 361 of the PHS Act to make and enforce regulations necessary to prevent the introduction, transmission, or spread of communicable disease from foreign countries into the States or possessions, or from one State or possession into any other State or possession. Intrastate transactions affecting communicable disease transmission may also be regulated under section 361 of the PHS Act (Independent Turtle

Farmers of Louisiana, Inc. v. United States, 703 F.Supp.2d 604, 620-21 (W.D. La. 2010); Louisiana v. Mathews, 427 F. Supp. 174, 176 (E.D. La. 1977)).

It is important to recognize that, in the past, blood transfusion and manufacturing of blood derivatives presented significant risks of transmission of communicable diseases such as HBV and HIV. Risks of transmission of infectious diseases still remain from emerging infectious agents. As FDA has previously noted, section 361 of the PHS Act, “is designated to eliminate the introduction of communicable disease, such as hepatitis, from one state to another. Of necessity, therefore, this authority must be exercised upon the disease causing substance within the state where it is collected, manufactured, or otherwise found. Thus, the Commissioner of Food and Drugs may promulgate current good manufacturing practice regulations for intrastate blood banking, pursuant to the [PHS Act], as hepatitis is a communicable disease. Without proper controls, it is likely to spread on an interstate basis.” (39 FR 18614, May 28, 1974). These statements are equally true today, where the spectrum of diseases transmitted by blood has increased to include, for example, HIV agents that cause AIDS, and HCV, an additional cause of hepatitis as well as emerging infectious agents. We understand communicable diseases to include those transmitted by viruses, bacteria, fungi, parasites, and transmissible spongiform encephalopathy agents. Preventing the spread of communicable disease is the important purpose underlying the comprehensive regulations for blood establishments now in place, which this final rule modifies and modernizes.

Under section 361 of the PHS Act, FDA is authorized to enforce the regulations it issues to prevent the introduction, transmission, or spread of communicable disease interstate through such means as inspection, disinfection, sanitation, destruction of animals or articles found to be so infected or contaminated as to be sources of dangerous infection in human beings, and other

measures that may be necessary. In addition, under section 368(a) of the PHS Act, any person who violates a regulation prescribed under section 361 of the PHS Act may be punished by imprisonment for up to 1 year. Individuals may also be punished for violating such a regulation by a fine of up to \$100,000 if death has not resulted from the violation or up to \$250,000 if death has resulted. For organizational defendants, fines range up to \$200,000 and \$500,000.

Individuals and organizations also face possible alternative fines based on the amount of gain or loss (18 U.S.C. 3559 and 3571(b) through (d)). Federal District Courts also have jurisdiction to enjoin individuals and organizations from violating regulations implementing section 361 of the PHS Act. (See Califano v. Yamasaki, 442 U.S. 682, 704-05 (1979); United States v. Beatrice Foods Co., 493 F.2d 1259, 1271-72 (8th Cir. 1974), cert. denied, 420 U.S. 961 (1975).)

Blood and blood components introduced or delivered for introduction into interstate commerce are subject to section 351 of the PHS Act, which requires that such products be licensed (42 U.S.C. 262). Section 351 of the PHS Act further authorizes FDA, by delegation, to establish requirements for such biologics licenses (42 U.S.C. 262(a)(2)(A)). In addition to its authority under section 361 of the PHS Act, FDA relies on this authority when the final regulations are applied to products subject to biologics license. To obtain a license, applicants must show that the biological product is safe, pure, and potent and that the manufacturing establishment meets all applicable standards designed to assure the continued safety, purity, and potency of the blood and blood components. FDA license revocation regulations provide for the initiation of revocation proceedings if, among other reasons, the establishment or the product fails to conform to the standards in the license application or in the regulations designed to ensure the continued safety, purity, or potency of the product (§ 601.5).

Violations of section 351 are punishable by a 1-year term of imprisonment, a fine as described in the preceding paragraph, or both (42 U.S.C. 262(f), 18 U.S.C. 3571). Blood and blood components are also drugs or devices, as those terms are defined in sections 201(g)(1) and (h) of the FD&C Act (21 U.S.C. 321(g)(1) and (h); see United States v. Calise, 217 F. Supp. 705, 708-09 (S.D.N.Y. 1962)); 42 U.S.C. 262(j) (“The Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) applies to a biological product subject to regulation under this section, except that a product for which a license has been approved ... shall not be required to have an approved [new drug] application”). Since blood and blood components are drugs or devices generally subject to the FD&C Act, in issuing these regulations, FDA relies on the FD&C Act’s grant of authority to issue regulations for the efficient enforcement of the FD&C Act (21 U.S.C. 371(a)). The FD&C Act requires blood establishments to comply with the FD&C Act’s current good manufacturing practice provisions and related regulatory scheme. Under section 501 of the FD&C Act (21 U.S.C. 351), drugs, including blood and blood components, are deemed “adulterated” if the methods used in their manufacturing, processing, packing, or holding do not conform with current good manufacturing practice (21 U.S.C. 351(a)(2)(B)). Devices are deemed “adulterated” if the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with current good manufacturing practice requirements established by FDA in regulations (21 U.S.C. 351(h) and 360j(f)(1)). The provisions of this rule are critical aspects of current good manufacturing practice. The regulation requires collection establishments to assure that donors of blood and blood components meet the essential criteria for eligibility, and that blood and blood components are suitable for transfusion or further manufacturing. Blood and blood components not manufactured in accordance with current good manufacturing practice, including the provisions

of this rule, and other provisions in the CFR, would be considered adulterated under 21 U.S.C. 351(a)(2)(B) or 21 U.S.C. 351(h) and 360j(f)(1), and collection establishments and blood and blood components would be subject to the FD&C Act's enforcement provisions for violations of the FD&C Act. These include seizure of violative products (21 U.S.C. 332), injunction against ongoing and future violations, and criminal penalties (21 U.S.C. 333 and 18 U.S.C. 3571). The FD&C Act punishes both misdemeanor and felony violations of the FD&C Act. Misdemeanor violations are punishable by a term of imprisonment of up to 1 year, a fine as described previously, or both. (21 U.S.C. 333(a)(1), 18 U.S.C. 3571). Individuals convicted of felony violations may be sentenced to a term of imprisonment of up to 3 years, a fine of up to \$250,000, or both. Organizations convicted of felony violations may be sentenced to a fine of up to \$500,000. Individuals and organizations also face possible alternative fines based on the amount of gain or loss (18 U.S.C. 3571(b) through (d)).

IV. Analysis of 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 (Pub. L. 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 as defined by 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 costs associated

with this rule are expected to be minimal, the Agency certifies that this 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 \$141 million, using the most current (2013) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in a 1-year expenditure that would meet or exceed this amount.

This rule sets forth requirements for donor eligibility and donation suitability to ensure the safety, purity, and potency of the blood and blood components used for transfusion or for further manufacture. Costs estimated in this analysis include costs related to the SOPs and bacterial testing requirements for blood collection establishments and transfusion services. The total upfront costs are \$16,042,628, and include costs related to the review, modification, and creation of standard operation procedures. The mean annual costs of \$892,233 include costs related to the bacterial testing and speciation of platelets. We anticipate that this final rule will preserve the safety, purity, and potency of blood and blood components by preventing unsafe units of blood or blood components from entering the blood supply, and by providing recipients with increased protection against communicable disease transmission. The requirements set forth in this rule will also help to decrease the number of blood transfusion related fatalities that are associated with the bacterial contamination of platelets. The annual value of additional fatalities averted related by testing of Whole Blood-derived platelets is estimated to be

approximately \$27 million to \$90 million and the annual value of averted nonfatal sepsis infections is estimated to be \$3.19 million to \$4.91 million.

The full discussion of economic impacts is available in Docket No. FDA-2006-N-0040 (formerly Docket No. 2006N-0221) and at

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>

(Ref. 77).

V. Environmental Impact

FDA 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.

VI. 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.

VII. 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 the following paragraphs with an estimate of the annual

reporting, recordkeeping, and disclosure burdens. Included in the estimate is the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing each collection of information.

Title: Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use.

Description: FDA is amending the regulations applicable to blood and blood components, including Source Plasma, to make donor eligibility and testing requirements more consistent with current practices in the blood industry, to more closely align the regulations with current FDA recommendations, and to provide flexibility to accommodate advancing technology. The following information collection provisions are for recordkeeping, and third party disclosure.

In this final rule, under § 606.100(b), FDA requires establishments to establish, maintain, and follow written SOPs for all steps in the collection, processing, compatibility testing, storage, and distribution of blood and blood components for allogeneic transfusion, autologous transfusion, and further manufacturing purposes. Under this provision, FDA also clarifies that establishments must establish, maintain, and follow written SOPs for all steps in the investigation of product deviations related to § 606.171; and for all steps in recordkeeping related to current good manufacturing practice and other applicable requirements and standards. FDA has separated the requirements for procedures for donor deferral and donor notification, previously provided under § 606.100(b)(20), into the requirement for procedures for donor deferral under § 606.100(b)(20) and the procedures for donor notification under § 606.100(b)(21). In addition, under § 606.100(b)(22), blood collection establishments and

transfusion services must have procedures to control the risk of bacterial contamination of platelets, including all steps required under § 606.145.

FDA continues to require, under § 606.160(b)(1)(i), collection establishments to maintain donor records that include donor selection, including medical interview and examination and where applicable, informed consent. The regulations in this final rule that pertain to the requirements to maintain donor records under § 606.160(b)(1)(i), are as follows:

- § 606.110(a)(2) allows for the use of plateletpheresis and leukapheresis procedures provided that the procedure is performed under the supervision of a responsible physician who is aware of the health status of the donor, and the physician has determined and documented that the donor's health permits plateletpheresis or leukapheresis.
- § 630.5(b)(1)(i) allows the responsible physician to delegate to a physician substitute or other trained person the activity of determining the eligibility of a donor and documenting assessments related to that determination (with certain specified exceptions).
- § 630.10(f)(2) allows a donor with blood pressure measurements outside of the established limits to donate only when the responsible physician determines and documents that the health of the donor would not be adversely affected by donating.
- § 630.10(f)(4) allows a donor with an irregular pulse or measurements outside of the established limits to donate only when the responsible physician determines and documents that the health of the donor would not be adversely affected by donating.
- § 630.10(g)(2)(i) requires that prior to each donation, collection establishments must provide information to the donor addressing the elements specified in § 630.10

(g)(2)(ii)(A) through (g)(2)(ii)(E) and obtain the donor's acknowledgement that the donor has reviewed the information.

- § 630.15(a)(1)(ii)(A) requires that when a donation is for autologous use, the responsible physician must determine and document that the donation may proceed.
- § 630.15(b)(2) requires that: (1) The responsible physician must obtain the informed consent of a plasma donor on the first day of donation or no more than 1 week before the first donation, and at subsequent intervals of no longer than 1 year; (2) the responsible physician must obtain the informed consent of a plasma donor who does not return within 6 months of the last donation; (3) the responsible physician must explain the risks and hazards of the procedure to the donor; (4) if a donor is enrolled in a new program, such as an immunization or special collection program, the responsible physician must again obtain an informed consent specific for that program.
- § 630.15(b)(7)(i) requires that the responsible physician determines and documents that the donor is in good health and the donor's health permits the plasmapheresis.
- § 630.15(b)(7)(iii) requires that special characteristics of the donor's plasma and the need for plasmapheresis of the donor under § 630.20(b) are documented at the establishment.
- § 630.20(a) allows for the collection of blood and blood components from a donor who is determined to be not eligible to donate under any provision of § 630.10(e) and (f) or § 630.15(a), if the donation is for autologous use only as prescribed by the donor's physician, and the donor has a hemoglobin level no less than 11.0 grams of hemoglobin per deciliter of blood or a hematocrit value no less than 33 percent, and the responsible physician determines and documents that the donor's health permits the collection procedure.

- § 630.20(b) allows for plasma to be collected under a Source Plasma collection program for further manufacturing use into in vitro products for which there are no alternative sources from a donor who is determined to be not eligible to donate under any provision of § 630.10(e) and (f) or § 630.15(a), if the donor meets the criteria in § 630.10(f)(1) through (6) and the responsible physician determines and documents for each donation that the donor's health permits the collection procedure, and the collection takes place under the medical oversight specified in the approved plasmapheresis program.
- § 640.21(e)(4) allows, for a period not to exceed 30 calendar days, a donor to serve as a dedicated plateletpheresis donor for a single recipient, in accordance with § 610.40(c)(1), as often as is medically necessary, provided in part, that the donor is in good health, as determined and documented by the responsible physician.

FDA redesignated § 606.160(b)(1)(ix) to § 606.160(b)(1)(x), and redesignated § 606.160(b)(1)(x) to § 606.160(b)(1)(ix). Also, FDA replaced previous cross-reference to § 630.6 with new cross-reference to § 630.40 in § 606.160(b)(1)(x) and (b)(1)(xi).

FDA revised § 606.160(e) to require establishments to maintain two records to include the following sections: (1) A record of all donors found to be ineligible or deferred at that location; so that blood and blood components from an ineligible donor are not collected and/or released while the donor is ineligible or deferred and (2) establishments must maintain at all locations operating under the same license or under common management a cumulative record of donors deferred from donation were reactive for evidence of infection due to HIV, HBV, or HCV. In addition, establishments other than Source Plasma establishments must include in this cumulative record donors deferred for evidence of infection due to HTLV or Chagas disease; (3) the cumulative record must be updated at least monthly to add donors newly deferred for the

reasons described herein; (4) in addition, establishments must revise the cumulative record to remove donors who have been requalified under § 610.41(b).

Under final § 606.145(c), in the event a transfusion service identifies platelets as bacterially contaminated, the transfusion service must not release the product and must notify the blood collection establishment that provided the platelets. In addition, the transfusion service must take appropriate steps to identify the organism; these steps may include contracting with the collection establishment or a laboratory to identify the organism. The transfusion service must further notify the blood collection establishment either by providing information about the species of the contaminating organism when the transfusion service has been able to identify it, or by advising the blood collection establishment when the transfusion service has determined that the species cannot be identified.

Under final § 630.5(d), collection establishments must establish, maintain, and follow SOPs for obtaining rapid emergency medical services for donors when medically necessary. Under final § 630.10(b), collection establishments must provide educational material concerning relevant transfusion-transmitted infections to donors before donation when donor education about that relevant transfusion-transmitted infection is necessary to assure the safety, purity, and potency of blood and blood components.

Under § 630.10(c)(1) and (2), collection establishments may perform certain activities, provided that these activities are addressed in their SOPs.

FDA requires under § 630.15(a)(1)(ii)(B), that for a dedicated donation based on the intended recipient's documented exceptional medical need, the responsible physician determines and documents that the health of the donor would not be adversely affected by donating.

Under § 630.15(a)(2) collection establishments may collect more frequently than once in 8 weeks for collections resulting in a single unit of Whole Blood or Red Blood Cells, or once in 16 weeks for apheresis collections resulting in two units of Red Blood Cells, when the donor is determined under § 630.10 to be eligible to undergo a therapeutic phlebotomy, provided that the container label conspicuously states the disease or condition of the donor that necessitated phlebotomy. However, no disease state labeling is required when the conditions under § 630.15(a)(2)(i) through (iii) are met.

Under § 630.20(c), a collection establishment may collect blood and blood components from a donor who is determined to be not eligible to donate under any provision of § 630.10(e) and (f) or § 630.15(a), if the donation is restricted for use solely by a specific transfusion recipient based on documented exceptional medical need, and the responsible physician determines and documents that the donor's health permits the collection procedure, and that the donation presents no undue medical risk to the transfusion recipient.

FDA redesignated § 630.6 to § 630.40, which requires collection establishments under § 630.40(a) to make reasonable attempts to notify any donor, including an autologous donor, who has been deferred based on the results of tests for evidence of infection with a relevant transfusion-transmitted infection(s), as required under § 610.41(a); or any donor who has been deferred as required under § 630.30(b)(3) because their donated platelets have been determined under § 606.145(d) to be contaminated with an organism that is identified as likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor; and any donor who has been determined not to be eligible as a donor based on eligibility criteria under §§ 630.10 and 630.15.

Under § 640.21(c), a Whole Blood donor must not serve as the source of platelets for transfusion if the donor has recently ingested a drug that adversely affects platelet function, unless the unit is labeled to identify the ingested drug that adversely affects platelet function.

FDA separated § 640.72(a)(2) into § 640.72(a)(2)(i) and (ii), and redesignated the cross-reference previously provided in § 640.72(a)(2) from § 640.63 to § 630.10, and added cross-reference to § 630.15. Final § 640.72(a)(2)(i) requires establishments that collect plasma to maintain records, including a separate and complete record of initial and periodic examinations, tests, laboratory data, and interviews etc., as required in §§ 630.10, 630.15, 640.65, 640.66, and 640.67, except as provided in § 640.72(a)(2)(ii). Final § 640.72(a)(2)(ii) provides that negative results for testing for evidence of infection due to relevant transfusion-transmitted infections required in § 610.40, and the volume or weight of plasma withdrawn from a donor need not be recorded on the individual donor record if such information is maintained on the premises of the plasmapheresis center where the donor's plasma has been collected.

Under § 640.72(a)(4), collection establishments must maintain records of the medical history and physical examination of the donor conducted in accordance with § 630.15(b)(1) and, where applicable, § 630.15(b)(5), and must document the eligibility of the donor as a plasmapheresis donor, and, when applicable, as an immunized donor.

Description of Respondents: Licensed and unlicensed, registered blood establishments that collect blood and blood components for transfusion, licensed blood establishments that collect Source Plasma, and registered and unregistered transfusion services.

As required by section 3506(c)(2)(B) of the Paperwork Reduction Act, FDA provided an opportunity for public comment on the information collection requirements of the proposed rule (72 FR 63416 at 63434).

Based on information received from FDA's database systems, there are approximately 1,265 licensed blood collection establishments and approximately 416 licensed Source Plasma establishments, for a total of 1,681 licensed blood collection establishments. Also, there are approximately 680 total unlicensed, registered blood collection establishments. The approximate total of 2,361 collection establishments, includes the 1,265 licensed blood collection establishments, 416 licensed Source Plasma establishments, and 680 total unlicensed, registered blood collection establishments. FDA estimates that there are 4,961 total transfusion services. Most of these transfusion services are not required to register with FDA.

The recordkeeping and third party disclosure estimates are based on information provided by industry, CMS, GAO, HHS, and FDA experience. Based on this information, FDA estimates that collection establishments annually collect approximately 40 million units of Whole Blood and blood components, which includes approximately 25 million donations of Source Plasma from approximately 2 million donors, and approximately 15 million¹ donations of Whole Blood and apheresis Red Blood Cell donations from approximately 10.9 million donors, including approximately 225,000 (1.5 percent of 15 million) autologous donations. Assuming each autologous donor makes an average of 2 donations, FDA estimates that there are approximately 112,500 autologous donors.

FDA estimates the information collection burden as follows:

¹ These estimates are based on the 2011 National Blood Collection and Utilization Survey Report, which estimated that a total of 15,721,000 Whole Blood and Red Blood Cell units were collected in 2011. The 2011 report noted a decline in the numbers of Whole Blood and Red Blood Cell units collected and transfused.

Table 1.--Estimated Annual Recordkeeping Burden¹

21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Average Burden per Recordkeeping	Total Hours
606.100(b) (Maintenance of SOPs) ²	2,361	1	2,361	24	56,664
606.100(b) (Maintenance of SOPs) ³	4,961	1	4,961	10	49,610
606.160(b)(1)(i) ⁴	2,361	16,942	40,000,000	0.17	6,800,000
630.15(a)(1)(ii)(B)	1,945	1	1,945	1	1,945
630.20(c)	1,945	1	1,945	1	1,945
640.72(a)(4)	416	4,808	2,000,000	0.08	160,000
Total					7,070,164

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

² The recordkeeping requirements in §§ 606.171, 630.5(d), and 630.10(c)(1) and (2) are included in the estimate for § 606.100(b).

³ The recordkeeping requirements in § 606.100(b)(22) is included in the estimate for § 606.100(b).

⁴ The recordkeeping requirements in §§ 606.110(a)(2); 606.160(e); 630.5(b)(1)(i); 630.10(f)(2) and (4); 630.10(g)(2)(i); 630.15(a)(1)(ii)(A) and (a)(1)(ii)(B); 630.15(b)(2), (b)(7)(i) and (b)(7)(iii); 630.20(a) and (b); and 640.21(e)(4), are included in the estimate for § 606.160(b)(1)(i).

Table 2.-- Estimated One-Time Recordkeeping Burden¹

21 CFR Section	No. of Recordkeepers	No. of Records per Recordkeeper	Total Annual Records	Hours per Record	Total Hours
606.100(b) (Review and Modify SOPs) ²	1,574	1	1,574	40	62,960
606.100(b) (Review and Modify SOPs) ²	787	1	787	60	47,220
606.100(b) (Review and Modify SOPs)	4,961	1	4,961	16	79,376
606.100(b)(22) (Establish SOPs)	1,488	1	1,488	16	23,808
Total					213,364

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

² The recordkeeping requirements in §§ 606.171; 630.5(d); and 630.10(c)(1) and (2), are included in the estimate for § 606.100(b).

Table 3.--Estimated Annual Third-Party Disclosure Burden¹

21 CFR Section	No. of Respondents	No. of Disclosures per Respondent	Total Annual Disclosures	Average Burden per Disclosure (in hours)	Total Hours
606.145(c)	4,961	0.28	1,400	0.02	28

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

Recordkeeping: As shown in table 1, under § 606.100(b), FDA estimates that for the 2,361 recordkeepers, which includes approximately 1,265 licensed blood collection establishments, approximately 416 licensed Source Plasma establishments, and approximately 680 total unlicensed, registered blood collection establishments, it will take approximately 24

hours annually to review and maintain SOPs. The recordkeeping requirements in §§ 606.171, 630.5(d), and 630.10(c)(1) and (2) are included in the estimate for § 606.100(b).

In addition, the information collection burden under § 606.100(b)(22), for the transfusion services to maintain their SOPs is included in the information collection burden estimate under § 606.100(b).

The information collection burden for §§ 606.110(a)(2); 606.160(e); 630.5(b)(1)(i); 630.10(f)(2) and (4); 630.10(g)(2)(i); 630.15(a)(1)(ii)(A) and(B); 630.15(b)(2), (b)(7)(i) and (b)(7)(iii); 630.20(a) and (b); and 640.21(e)(4), refer to the requirement to maintain records for donor selection under § 606.160(b)(1) specifically § 606.160(b)(1)(i) and are included in the information collection burden estimate under this regulation.

In table 1, under § 630.15(a)(1)(ii)(B) and § 630.20(c), FDA calculates the information collection burden that for the 1,945 recordkeepers, which includes approximately 1,265 licensed blood collection establishments and approximately 680 registered blood collection establishments. The donation would be used solely by a specified recipient based on documented medical need, and thus would occur rarely. Consequently, the burden to collection establishments is minimal.

The revisions to § 606.160(b)(1)(ix) through (xi) are technical amendments and do not result in any new information collection burden. The information collections for these sections have been approved under OMB control number 0910-0116.

FDA is not calculating the information collection burden for final § 606.100(b)(20) and (21) because these regulations have not been changed only redesignated. The information collection for final § 606.100(b)(20) and (21) have been approved under OMB control number 0910-0116.

Under § 606.160(e), FDA is not calculating the information collection burden specifically for establishments to maintain donor records because there is either minimal or no additional burden associated with the final § 606.160(e) because establishments have either been maintaining these records or providing access to these records at locations operating under the same license or under common management under current regulation(s) or guidance(s), or as part of their usual and customary business practice. In addition, the number of ineligible donors for which the establishments must maintain records has been decreased from the proposed rule in this final rule, which reduces the information collection burden for this requirement. The information collection for § 606.160(e) have been approved as part of § 606.160 under OMB control number 0910-0116.

FDA is not calculating the information collection burden for § 640.72(a)(2)(i), because the information collection for maintaining a complete record of all initial and periodic examinations, tests, laboratory data, interviews, etc., for final § 630.10 (redesignated from § 640.63) and §§ 640.65, 640.66, and 640.67 have been approved under OMB control number 0910-0116. In addition, the information collection cross-referenced under § 630.15, is included in the information collection burden estimate for § 606.160(b)(1)(i). FDA is not calculating the information collection burden for § 640.72(a)(2)(ii), because there is no additional burden and is covered under OMB control number 0910-0116.

As shown in table 2, under § 606.100(b), FDA estimates that for the 2,361 recordkeepers, two-thirds or 1,574 of the collection establishments will each expend, as a one-time burden, to reconcile their SOPs with the requirements. FDA estimates for the remaining one-third or 787 of the collection establishments each will expend additional time to establish and reconcile their

SOPs with the requirements. The one-time recordkeeping requirements in §§ 606.171, 630.5(d), and 630.10(c)(1) and (2) are included in the estimate for § 606.100(b).

In table 2, under § 606.100(b)(22), FDA estimates that for the 4,961 transfusion services potentially impacted by this rule, 40 percent are following the voluntary standards for testing, speciation, and notifying the blood establishment, as usual and customary practice. For the remaining 60 percent (2,977) transfusion services, approximately one-half (1,488) would be impacted by the rule and each of these would expend, as a one-time burden, and to create SOPs consistent with the requirements.

Third Party Disclosure: In table 3, under § 606.145(c), FDA estimates that for the approximate 4,961 transfusion services, there would be 1,400 total notifications per year to blood collection establishments (700 notifications per year that platelets are bacterially contaminated and 700 notifications per year concerning the identity or non-identity of the species of the contaminating organism).

The labeling requirements under § 630.15(a)(2), are consistent with the current requirement under § 640.3(d) that donations from a donor “shall not be used as a source of Whole Blood unless the container label conspicuously indicates the donor's disease that necessitated withdrawal of blood.” FDA is not calculating the information collection burden for § 630.15(a)(2) because the burden is included in the calculation for § 640.3(d). In addition, § 630.15(a)(2) reduces the information collection burden by not requiring labeling under the conditions specified in the regulation. The information collection burden in § 630.40(d) is approved under OMB control number 0910-0116.

Under § 630.10(b), FDA requires collection establishments to provide the donor with educational material. FDA is not calculating the information collection burden for this

regulation because establishments collecting blood and blood components perform this activity as a usual and customary business practice and there is minimal new information collection burden for this requirement.

The information collection burden in final § 630.40 resulting from the redesignation of § 630.6 has been approved under OMB control number 0910-0116. Under final § 630.40, FDA considers the changes in text from “communicable disease” to “relevant transfusion-transmitted infection(s)”, “suitable” to “eligible”, and “suitability” to “eligibility”, to be technical amendments that do not confer any new burden. FDA is not calculating the information collection burden under § 606.145(d) for the additional requirement that establishments that collect blood or blood components make reasonable attempts to notify any donor whose donated platelets have been determined to be contaminated with an organism that is identified as likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor, because establishments perform this activity as a usual and customary business practice and there is minimal new information collection burden for this requirement. The third party disclosure burden under § 630.30(b)(4), is covered under § 630.40.

Under § 640.21(c), FDA requires the establishments to label donations received from platelet donors who have recently ingested a drug that adversely affects platelet function to identify the ingested drug. FDA is not calculating the information collection burden for this regulation as there is minimal additional burden for this requirement because establishments collecting blood and blood components perform this activity as a usual and customary business practice.

The collections of information under § 640.120 has been approved under OMB control number 0910-0338. FDA is not calculating information collection burden for § 640.120, because the changes that were made will not have an impact on the current burden estimated for industry.

The information collection provisions in this final rule have been submitted to OMB for review as required by section 3507(d) of the Paperwork Reduction Act of 1995.

Before 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 information collection 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.

VIII. References

The following references have been placed on display in the Division of Dockets Management (see ADDRESSES) 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, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the Federal Register.)

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74. Plasma Protein Therapeutics Association, Quality Standards of Excellence, Assurance and Leadership (QSEAL), Certification Program.

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<http://www.fda.gov/OHRMS/DOCKETS/98fr/03-5204.pdf>.

76. FDA, Exceptions and Alternative Procedures Approved Under 21 CFR 640.120,

<http://www.fda.gov/BioLogicsBloodVaccines/BloodBloodProducts/RegulationoftheBloodSupply/ExceptionsandAlternativeProcedures/default.htm>.

77. Final Regulatory Impact Analysis, Final Regulatory Flexibility Analysis, and Unfunded Mandates Reform Act Analysis for Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use,

<http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/EconomicAnalyses/default.htm>.

List of Subjects

21 CFR Part 606

Blood, Labeling, Laboratories, Reporting and recordkeeping requirements.

21 CFR Parts 610 and 660

Biologics, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 630

Blood, Reporting and recordkeeping requirements.

21 CFR Part 640

Blood, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 820

Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and under authority delegated to the Commissioner of Food and Drugs, 21 CFR Chapter I is 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. In § 606.3, revise paragraphs (a) and (c) to read as follows:

§ 606.3 Definitions.

* * * * *

(a) Blood means a product that is a fluid containing dissolved and suspended elements which was collected from the vascular system of a human.

* * * * *

(c) Blood component means a product containing a part of human blood separated by physical or mechanical means.

* * * * *

§ 606.40 [Amended]

3. In § 606.40(a)(1), remove “suitability” and add in its place “eligibility”.

4. Amend § 606.100 as follows:

- a. Revise paragraph (b) introductory text;
- b. In paragraph (b)(1), remove “suitability” and add in its place “eligibility”;
- c. Revise paragraph (b)(20); and
- d. Add paragraphs (b)(21) and (b)(22).

The revisions and additions read as follows:

§ 606.100 Standard operating procedures.

* * * * *

(b) Establishments must establish, maintain, and follow written standard operating procedures for all steps in the collection, processing, compatibility testing, storage, and distribution of blood and blood components for allogeneic transfusion, autologous transfusion, and further manufacturing purposes; for all steps in the investigation of product deviations related to § 606.171; and for all steps in recordkeeping related to current good manufacturing practice and other applicable requirements and standards. Such procedures must be available to the personnel for use in the areas where the procedures are performed. The written standard operating procedures must include, but are not limited to, descriptions of the following, when applicable:

* * * * *

(20) Procedures for donor deferral as prescribed in § 610.41 of this chapter.

(21) Procedures for donor notification and notification of the referring physician of an autologous donor, including procedures for the appropriate followup if the initial attempt at notification fails, as prescribed in § 630.40 of this chapter.

(22) Procedures to control the risks of bacterial contamination of platelets, including all

steps required under § 606.145.

* * * * *

§ 606.110 [Amended]

5. Amend § 606.110 as follows:

a. In paragraph (a), remove “qualified licensed physician” and add in its place “responsible physician” and remove “certified in writing” and add in its place “determined and documented”; and

b. In paragraph (b), remove “640.63” and add in its place “630.10, 630.15”.

§ 606.121 [Amended]

6. Amend § 606.121 as follows:

a. In paragraph (c)(11) remove “communicable disease agents” and add in its place “relevant transfusion-transmitted infections”; and remove “§§ 610.40(i) and 640.65(b)” and add in its place “§ 640.65(b)”;

b. In paragraph (c)(12) remove “communicable disease agent(s)” and add in its place “relevant transfusion-transmitted infection(s)”;

c. In paragraphs (h)(2) and (3), remove “640.5(a), (b),” and add in its place “640.5(b)”;

and

d. In paragraph (i)(5), remove “suitability” and add in its place “eligibility”; remove “§ 640.3” and add it its place “§ 630.10”; and remove “communicable disease agents” and add in its place “relevant transfusion-transmitted infections”.

§ 606.122 [Amended]

7. In § 606.122(e), remove “communicable disease agents” and add in its place “relevant transfusion-transmitted infections”.

8. Add § 606.145 to subpart H to read as follows:

§ 606.145 Control of bacterial contamination of platelets.

(a) Blood collection establishments and transfusion services must assure that the risk of bacterial contamination of platelets is adequately controlled using FDA approved or cleared devices or other adequate and appropriate methods found acceptable for this purpose by FDA.

(b) In the event that a blood collection establishment identifies platelets as bacterially contaminated, that establishment must not release for transfusion the product or any other component prepared from the same collection, and must take appropriate steps to identify the organism.

(c) In the event that a transfusion service identifies platelets as bacterially contaminated, the transfusion service must not release the product and must notify the blood collection establishment that provided the platelets. The transfusion service must take appropriate steps to identify the organism; these steps may include contracting with the collection establishment or a laboratory to identify the organism. The transfusion service must further notify the blood collection establishment either by providing information about the species of the contaminating organism when the transfusion service has been able to identify it, or by advising the blood collection establishment when the transfusion service has determined that the species cannot be identified.

(d) In the event that a contaminating organism is identified under paragraph (b) or (c) of this section, the collection establishment's responsible physician, as defined in § 630.3(i) of this chapter, must determine whether the contaminating organism is likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor, in accordance with a

standard operating procedure developed under § 606.100(b)(22). This determination may not be further delegated.

9. In § 606.160, revise paragraphs (b)(1)(ix) through (xi), and (e) to read as follows:

§ 606.160 Records.

* * * * *

(b) * * *

(1) * * *

(ix) The donor's postal address provided at the time of donation where the donor may be contacted within 8 weeks after donation.

(x) Records of notification of donors deferred or determined not to be eligible for donation, including appropriate followup if the initial attempt at notification fails, performed under § 630.40 of this chapter.

(xi) Records of notification of the referring physician of a deferred autologous donor, including appropriate followup if the initial attempt at notification fails, performed under § 630.40 of this chapter.

* * * * *

(e) Records of deferred donors. (1) Establishments must maintain at each location a record of all donors found to be ineligible or deferred at that location so that blood and blood components from an ineligible donor are not collected and/or released while the donor is ineligible or deferred; and

(2) Establishments must maintain at all locations operating under the same license or under common management a cumulative record of donors deferred from donation under § 610.41 of this chapter because their donation tested reactive under § 610.40(a)(1) of this

chapter for evidence of infection due to HIV, HBV, or HCV. In addition, establishments other than Source Plasma establishments must include in this cumulative record donors deferred from donation under § 610.41 of this chapter because their donation tested reactive under § 610.40(a)(2) of this chapter for evidence of infection due to HTLV or Chagas disease.

(3) The cumulative record described in paragraph (e)(2) of this section must be updated at least monthly to add donors newly deferred under § 610.41 of this chapter due to reactive tests for evidence of infection due to HIV, HBV, or HCV, and, if applicable, HTLV or Chagas disease.

(4) Establishments must revise the cumulative record described in paragraph (e)(2) of this section to remove donors who have been requalified under § 610.41(b) of this chapter.

PART 610--GENERAL BIOLOGICAL PRODUCTS STANDARDS

10. 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.

11. Revise the heading for subpart E to read as follows:

Subpart E--Testing Requirements for Relevant Transfusion-Transmitted Infections

12. Add § 610.39 to subpart E to read as follows:

§ 610.39 Definitions.

The definitions set out in § 630.3 of this chapter apply to this subpart.

13. Amend § 610.40 as follows:

- a. Revise paragraph (a);
- b. Revise paragraph (b);
- c. Revise paragraph (c) heading;

d. Remove paragraph (c)(2) and redesignate paragraphs (c)(3) and (4) as paragraphs (c)(2) and (3);

e. In redesignated paragraph (c)(2)(i), remove “communicable disease agents listed in paragraphs (a)(5) and (a)(6) of this section” and add in its place “relevant transfusion-transmitted infections listed in § 630.3(h)(iv) of this chapter”;

f. In paragraph (d), remove “communicable disease agents” and add in its place “relevant transfusion-transmitted infections”; and remove “or by a serological test for syphilis under paragraph (i) of this section”;

g. Revise paragraph (e);

h. In paragraph (f), remove “Health Care Financing Administration” and add in its place “Centers for Medicare and Medicaid Services”;

i. In paragraph (g) introductory text, remove “communicable disease agents” in both places it appears and add in each place “relevant transfusion-transmitted infections”; and remove “paragraphs (a) and (i)” and add in its place “paragraph (a)”;

j. In paragraph (h)(1), remove “a communicable disease agent(s) designated in paragraphs (a) and (i)” in both places it appears and add in each place “relevant transfusion-transmitted infection(s) designated in paragraph (a)”;

k. In paragraphs (h)(2)(ii) introductory text, (h)(2)(ii)(C), and (h)(2)(iv) introductory text, remove “communicable disease agent(s)” wherever it appears and add in its place “relevant transfusion-transmitted infection(s)”;

l. In paragraph (h)(2)(iv)(A), remove “suitable” and add in its place “eligible”;

m. In paragraph (h)(2)(vi), remove “paragraph (i)” and add in its place “paragraph (a)”;

and remove “consistent with § 640.5 of this chapter.”;

n. In paragraph (h)(2)(vii), remove “§ 610.40(i)” and add in its place “§ 640.65(a)(2)(ii) and (b)(1)(i)”; and remove “§ 640.65(b)(2)” and add in its place “§ 640.65(b)(2)(i) through (b)(2)(iv)”; and

o. Remove paragraph (i).

The revisions read as follows:

§ 610.40 Test requirements.

(a) Human blood and blood components. Except as specified in paragraphs (c) and (d) of this section, you, an establishment that collects blood and blood components for transfusion or for use in manufacturing a product, including donations intended as a component of, or used to manufacture, a medical device, must comply with the following requirements:

(1) Test each donation for evidence of infection due to the relevant transfusion-transmitted infections described in § 630.3(h)(1)(i) through (iii) of this chapter (HIV, HBV, and HCV).

(2) Test each donation for evidence of infection due to the relevant transfusion-transmitted infections described in § 630.3(h)(1)(iv) through (vii) of this chapter (HTLV, syphilis, West Nile virus, and Chagas disease). The following exceptions apply:

(i) To identify evidence of infection with syphilis in donors of Source Plasma, you must test donors for evidence of such infection in accordance with § 640.65(b) of this chapter, and not under this section.

(ii) You are not required to test donations of Source Plasma for evidence of infection due to the relevant transfusion-transmitted infections described in § 630.3(h)(1)(iv), (vi), and (vii) of this chapter (HTLV, West Nile virus, and Chagas disease).

(iii) For each of the relevant transfusion-transmitted infections described in § 630.3(h)(1)(iv) through (vii) of this chapter (HTLV, syphilis, West Nile virus, and Chagas disease):

(A) If, based on evidence related to the risk of transmission of that relevant transfusion-transmitted infection, testing each donation is not necessary to reduce adequately and appropriately the risk of transmission of such infection by blood or a blood component, you may adopt an adequate and appropriate alternative testing procedure that has been found acceptable for this purpose by FDA.

(B) If, based on evidence related to the risk of transmission of that relevant transfusion-transmitted infection, testing previously required for that infection is no longer necessary to reduce adequately and appropriately the risk of transmission of such infection by blood or a blood component, you may stop such testing in accordance with procedures found acceptable for this purpose by FDA.

(3) For each of the relevant transfusion-transmitted infections described in § 630.3(h)(1)(viii) through (x) of this chapter (CJD, vCJD, malaria) and § 630.3(h)(2) of this chapter (other transfusion-transmitted infections):

(i) You must test for evidence of infection when the following conditions are met:

(A) A test(s) for the relevant transfusion-transmitted infection is licensed, approved or cleared by FDA for use as a donor screening test and is available for such use; and

(B) Testing for the relevant transfusion-transmitted infection is necessary to reduce adequately and appropriately the risk of transmission of the relevant transfusion-transmitted infection by blood, or blood component, or blood derivative product manufactured from the collected blood or blood component.

(ii) You must perform this testing on each donation, unless one of the following exceptions applies:

(A) Testing of each donation is not necessary to reduce adequately and appropriately the risk of transmission of such infection by blood, blood component, or blood derivative product manufactured from the collected blood or blood component. When evidence related to the risk of transmission of such infection supports this determination, you may adopt an adequate and appropriate alternative testing procedure that has been found acceptable for this purpose by FDA.

(B) Testing of each donation is not necessary to reduce adequately and appropriately the risk of transmission of such infection by blood, blood component, or blood derivative product manufactured from the collected blood or blood component. When evidence related to the risk of transmission of such infection supports this determination, you may stop such testing in accordance with procedures found acceptable for this purpose by FDA.

(4) Evidence related to the risk of transmission of a relevant transfusion-transmitted infection that would support a determination that testing is not necessary, or that testing of each donation is not necessary, to reduce adequately and appropriately the risk of transmission of such infection by blood or blood component, as described in paragraphs (a)(2)(iii)(A) and (B) of this section, or by blood, blood component, or blood derivative, as described in paragraphs (a)(3)(ii)(A) and (B) of this section, includes epidemiological or other scientific evidence. It may include evidence related to the seasonality or geographic limitation of risk of transmission of such infection by blood or blood component, or other information related to when and how a donation is at risk of transmitting a relevant transfusion-transmitted infection. It may also include evidence related to the effectiveness of manufacturing steps (for example, the use of

pathogen reduction technology) that reduce the risk of transmission of the relevant transfusion-transmitted infection by blood, blood components, or blood derivatives, as applicable.

(b) Testing using one or more licensed, approved, or cleared screening tests. To perform testing for evidence of infection due to relevant transfusion-transmitted infections as required in paragraph (a) of this section, you must use screening tests that FDA has licensed, approved, or cleared for such use, in accordance with the manufacturer's instructions. You must perform one or more such tests as necessary to reduce adequately and appropriately the risk of transmission of relevant transfusion-transmitted infections.

(c) Exceptions to testing for dedicated donations, medical devices, and samples. * * *

* * * * *

(e) Further testing. You must further test each donation, including autologous donations, found to be reactive by a donor screening test performed under paragraphs (a) and (b) of this section using a licensed, approved, or cleared supplemental test, when available. If no such supplemental test is available, you must perform one or more licensed, approved, or cleared tests as adequate and appropriate to provide additional information concerning the reactive donor's infection status. Except:

(1) For autologous donations:

(i) You must further test under this section, at a minimum, the first reactive donation in each 30 calendar day period; or

(ii) If you have a record for that donor of a positive result on further testing performed under this section, you do not have to further test an autologous donation.

(2) You are not required to perform further testing of a donation found to be reactive by a treponemal donor screening test for syphilis.

* * * * *

14. Amend § 610.41 as follows:

a. In paragraph (a) introductory text, remove “communicable disease agent(s) listed in § 610.40(a) or reactive for a serological test for syphilis under § 610.40(i)” and add in its place “relevant transfusion-transmitted infection(s) under § 610.40(a)”;

b. Revise paragraph (a)(1);

c. In paragraph (a)(2), remove “communicable disease agent(s) listed in” and add in its place “relevant transfusion-transmitted infection(s) under”;

d. In paragraphs (a)(3) and (4), remove “suitable” and add in its place “eligible”;

e. In paragraph (a)(5), remove “communicable disease agent(s) described under § 610.40(a) or reactive with a serological test for syphilis under § 610.40(i)” and add in its place “relevant transfusion-transmitted infections(s) under § 610.40(a)”;

f. In paragraph (b), remove “suitable” and add in its place “eligible”.

The revisions read as follows:

§ 610.41 Donor deferral.

(a) * * *

(1) You are not required to defer a donor who tests reactive for anti-HBc or anti-HTLV, types I and II, on only one occasion. However, you must defer the donor if further testing for HBV or HTLV has been performed under § 610.40(e) and the donor is found to be positive, or if a second, licensed, cleared, or approved screening test for HBV or HTLV has been performed on the same donation under § 610.40(a) and is reactive, or if the donor tests reactive for anti-HBc or anti-HTLV, types I and II, on more than one occasion;

* * * * *

§ 610.42 [Amended]

15. In § 610.42(a), remove “or reactive for syphilis under § 610.40(i)”; and remove “communicable disease agent(s)” and add in its place “relevant transfusion-transmitted infection(s)”.

§ 610.44 [Amended]

16. In paragraph (a)(1) remove “communicable disease agents listed in” and add in its place “relevant transfusion-transmitted infections under”; and in paragraph (a)(2) remove “communicable disease agent” and add in its place “relevant transfusion-transmitted infection”.

§ 610.46 [Amended]

17. Amend § 610.46 as follows:

a. In paragraph (a)(2), remove “a supplemental (additional, more specific) test” and add in its place “further testing”;

b. In paragraph (a)(3), remove “supplemental (additional, more specific) test results” and add in its place “results of further testing”; and remove “there is no available supplemental test that is approved for such use by FDA” and add in its place “further testing under paragraph (a)(2) of this section is not available”;

c. In paragraph (a)(4), remove “supplemental (additional, more specific) test” and add in its place “further testing”; and remove “there is no available supplemental test that is approved for such use by FDA” and add in its place “further testing is not available”; and

d. In paragraph (b)(2), remove “supplemental (additional, more specific) test” and add in its place “further testing”; and remove “there is no available supplemental test that is approved for such use by FDA” and add in its place “further testing is not available”; and

e. In paragraph (b)(3), remove in the first sentence “the supplemental (additional, more specific) test” and add in its place “further testing”; remove in the first sentence “there is no available supplemental test that is approved for such use by FDA,” and add in its place “further testing is not available”; remove in the last sentence “supplemental (additional, more specific) test results” and add in its place “results of further testing”; and remove in the last sentence “there is no available supplemental test that is approved for such use by FDA” and add in its place “further testing is not available”.

§ 610.47 [Amended]

18. Amend 610.47 as follows:

a. In paragraph (a)(2), remove “a supplemental (additional, more specific) test” and add in its place “further testing”;

b. In paragraph (a)(3), remove in the first sentence “supplemental (additional, more specific) test results” and add in its place “results of further testing”; and remove in the first sentence “there is no available supplemental test that is approved for such use by FDA” and add in its place “further testing is not available”;

c. In paragraph (a)(4), remove “supplemental (additional, more specific) test” and add in its place “further testing”; and remove “there is no available supplemental test that is approved for such use by FDA” and add in its place “further testing is not available”; and

d. In paragraph (b)(2), remove “supplemental (additional, more specific) test” and add in its place “further testing”; and remove “there is no available supplemental test that is approved for such use by FDA” and add in its place “further testing is not available”; and

e. In paragraph (b)(3), remove in the first sentence “supplemental (additional, more specific) test” and add in its place “further testing”; remove in the first sentence “there is no

available supplemental test that is approved for such use by FDA” and add in its place “further testing is not available”; remove in the last sentence “supplemental (additional, more specific) test results” and add in its place “results of further testing”; and remove in the last sentence “there is no available supplemental test that is approved for such use by FDA” and add in its place “further testing is not available”.

PART 630--REQUIREMENTS FOR BLOOD AND BLOOD COMPONENTS INTENDED FOR TRANSFUSION OR FOR FURTHER MANUFACTURING USE

19. The authority citation for part 630 continues to read as follows:

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

20. Revise the heading for part 630 to read as set forth above.

21. Add subpart C with the heading to read as follows:

Subpart C--Donor Notification

22. Redesignate § 630.6 as § 630.40, and further redesignate newly designated § 630.40 to subpart C.

23. Amend newly designated § 630.40 as follows:

a. Revise the section heading;

b. In paragraph (a), revise the first sentence; and remove the word “supplemental” from the second and third sentences and add in its place “further”;

c. In paragraphs (b) introductory text and (b)(1), remove “suitable” and add in its place “eligible”;

d. In paragraph (b)(3), remove “communicable disease agent(s)” and add in its place “relevant transfusion-transmitted infection(s)”; and remove “supplemental (i.e., additional, more specific) tests” and add in its place “further testing”;

- e. In paragraph (c), remove “suitable” and add in its place “eligible”;
- f. In paragraph (d)(1) introductory text, remove “communicable disease agent(s)” and add in its place “relevant transfusion-transmitted infection(s) or whose platelets indicate evidence of a bacterial infection that is endogenous to the bloodstream of the donor”;
- g. In paragraph (d)(1)(i), remove “communicable disease agent(s)” and add in its place “relevant transfusion-transmitted infection(s)”; and
- h. In paragraph (d)(1)(iii), remove “communicable disease agent(s)” and add in its place “relevant transfusion-transmitted infection(s)”; and remove “supplemental (i.e., additional, more specific) tests” and add in its place “further testing”;

The revisions read as follows:

§ 630.40 Requirements for notifying deferred donors.

(a) Notification of donors. You, an establishment that collects blood or blood components, must make reasonable attempts to notify any donor, including an autologous donor, who has been deferred based on the results of tests for evidence of infection with a relevant transfusion-transmitted infection(s) as required by § 610.41(a) of this chapter; any donor who has been deferred as required under § 630.30(b)(3) because their donated platelets have been determined under § 606.145(d) of this chapter to be contaminated with an organism that is identified as likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor; and any donor who has been determined not to be eligible as a donor based on eligibility criteria under §§ 630.10 and 630.15. * * *

* * * * *

24. Add subparts A and B to part 630 to read as follows:

Subpart A--General Provisions

Sec.

630.1 Purpose and scope.

630.3 Definitions.

Subpart B--Donor Eligibility Requirements

Sec.

630.5 Medical supervision.

630.10 General donor eligibility requirements.

630.15 Donor eligibility requirements specific to Whole Blood, Red Blood Cells and Plasma collected by apheresis.

630.20 Exceptions for certain ineligible donors.

630.25 Exceptions from certain donor eligibility requirements for infrequent plasma donors.

630.30 Donation suitability requirements.

630.35 Requalification of previously deferred donors.

Subpart A--General Provisions

§ 630.1 Purpose and scope.

(a) What is the purpose of subparts A, B, and C of this part? The purpose of these subparts, together with §§ 610.40 and 610.41 of this chapter, is to provide certain minimum criteria for each donation of blood and blood components, for:

- (1) Determining the eligibility of a donor of blood and blood components;
- (2) Determining the suitability of the donation of blood and blood components; and
- (3) Notifying a donor who is deferred from donation.

(b) Who must comply with subparts A, B, and C of this part? Blood establishments that manufacture blood and blood components, as defined in § 630.3(a) and (b), must comply with subparts A, B, and C of this part.

§ 630.3 Definitions.

As used in this part and in part 610, subpart E, and part 640 of this chapter:

(a) Blood means a product that is a fluid containing dissolved and suspended elements which was collected from the vascular system of a human.

(b) Blood component means a product containing a part of blood separated by physical or mechanical means.

(c) Donor means a person who: (1) Donates blood or blood components for transfusion or for further manufacturing use; or

(2) Presents as a potential candidate for such donation.

(d) Eligibility of a donor means the determination that the donor is qualified to donate blood and blood components.

(e) Infrequent plasma donor means a donor who has:

(1) Not donated plasma by plasmapheresis or a co-collection of plasma with another blood component in the preceding 4 weeks; and

(2) Not donated more than 12.0 liters of plasma (14.4 liters of plasma for donors weighing more than 175 pounds) in the past year.

(f) Intimate contact with risk for a relevant transfusion-transmitted infection means having engaged in an activity that could result in the transfer of potentially infectious body fluids from one person to another.

(g) Physician substitute means a trained and qualified person(s) who is:

(1) A graduate of an education program for health care workers that includes clinical training;

(2) Currently licensed or certified as a health care worker in the jurisdiction where the collection establishment is located;

(3) Currently certified in cardiopulmonary resuscitation; and

(4) Trained and authorized under State law, and/or local law when applicable, to perform the specified functions under the direction of the responsible physician.

(h) Relevant transfusion-transmitted infection means:

(1) Any of the following transfusion-transmitted infections:

(i) Human immunodeficiency virus, types 1 and 2 (referred to, collectively, as HIV);

(ii) Hepatitis B virus (referred to as HBV);

(iii) Hepatitis C virus (referred to as HCV);

(iv) Human T-lymphotropic virus, types I and II (referred to, collectively, as HTLV);

(v) Treponema pallidum (referred to as syphilis);

(vi) West Nile virus;

(vii) Trypanosoma cruzi (referred to as Chagas disease);

(viii) Creutzfeldt-Jakob disease (referred to as CJD);

(ix) Variant Creutzfeldt-Jakob disease (referred to as vCJD); and

(x) Plasmodium species (referred to as malaria).

(2) A transfusion-transmitted infection not listed in paragraph (h)(1) of this section when the following conditions are met:

(i) Appropriate screening measures for the transfusion-transmitted infection have been developed and/or an appropriate screening test has been licensed, approved, or cleared for such use by FDA and is available; and

(ii) The disease or disease agent:

(A) May have sufficient incidence and/or prevalence to affect the potential donor population; or

(B) May have been released accidentally or intentionally in a manner that could place potential donors at risk of infection.

(i) Responsible physician means an individual who is:

(1) Licensed to practice medicine in the jurisdiction where the collection establishment is located;

(2) Adequately trained and qualified to direct and control personnel and relevant procedures concerning the determination of donor eligibility; collection of blood and blood components; the immunization of a donor; and the return of red blood cells or other blood components to the donor during collection of blood component(s) by apheresis; and

(3) Designated by the collection establishment to perform the activities described in paragraph (i)(2) of this section.

(j) Suitability of the donation means a determination of whether the donation is acceptable for transfusion or for further manufacturing use.

(k) Trained person means an individual, including a physician substitute, who is authorized under State law, and/or local law when applicable, and adequately instructed and qualified to perform the specified functions under the direction of the responsible physician.

(l) Transfusion-transmitted infection means a disease or disease agent:

(1) That could be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to a body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure; and

(2) For which there may be a risk of transmission by blood or blood components, or by a blood derivative product manufactured from blood or blood components, because the disease or disease agent is potentially transmissible by that blood, blood component, or blood derivative product.

Subpart B--Donor Eligibility Requirements

§ 630.5 Medical supervision.

(a) Who must determine the eligibility of a donor? The responsible physician must determine the eligibility of a donor of blood or blood components in accordance with this subchapter.

(b) Which activities related to the collection of blood and blood components, other than Source Plasma and plasma collected by plasmapheresis, may the responsible physician delegate?

(1) The responsible physician may delegate the following activities to a physician substitute or other trained person:

(i) Determining the eligibility of a donor and documenting assessments related to that determination, except the responsible physician must not delegate:

(A) The examination and determination of the donor's health required in § 630.10(f)(2) for donors with blood pressure measurements outside specified limits, or for certain more frequent donations under § 630.15(a)(1)(ii);

(B) The determination of the health of the donor required in §§ 630.10(f)(4), 630.20(a), and 640.21(e)(4) of this chapter. The responsible physician may make this determination by telephonic or other offsite consultation; or

(C) The determination of the health of the donor and the determination that the blood or blood component collected would present no undue medical risk to the transfusion recipient, as required in § 630.20(c). The responsible physician may make these determinations by telephonic or other offsite consultation.

(ii) Collecting blood or blood components;

(iii) Returning red blood cells to the donor during apheresis;

(iv) Obtaining the informed consent of a plateletpheresis donor as described in § 640.21(g) of this chapter; or

(v) Other activities provided that the Director, Center for Biologics Evaluation and Research, determines that delegating the activities would present no undue medical risk to the donor or to the transfusion recipient, and authorizes the delegation of such activities.

(2) The responsible physician need not be present at the collection site when activities delegated under paragraph (b)(1) of this section are performed, provided that the responsible physician has delegated oversight of these activities to a trained person who is adequately trained and experienced in the performance of these activities and is also adequately trained and experienced in the recognition of and response to the known adverse responses associated with blood collection procedures.

(c) Which activities related to the collection of Source Plasma and plasma collected by plasmapheresis may the responsible physician delegate?

(1) Donor eligibility and blood component collection activities. (i) The responsible physician may delegate to a physician substitute or other trained person any of the activities described in paragraph (c)(1)(i)(A) of this section, provided that the responsible physician or a physician substitute is on the premises at the collection site:

(A) The activities listed in paragraphs (b)(1)(i) through (iii) and (b)(1)(v) of this section, with respect to Source Plasma and plasma collected by plasmapheresis. However, the responsible physician must not delegate:

(1) The examination and determination of the donor's health required in § 630.10(f)(2) for donors with blood pressure measurements outside specified limits, or in § 630.15(b)(7) for certain donors who have experienced red blood cell loss;

(2) The determination of the health of the donor required in §§ 630.10(f)(4) and 630.20(a) and (b). The responsible physician may make this determination by telephonic or other offsite consultation;

(3) The determination of the health of the donor and the determination that the blood component would present no undue medical risk to the transfusion recipient, as required in § 630.20(c). The responsible physician may make this determination by telephonic or other offsite consultation.

(4) The determination related to a donor's false-positive reaction to a serologic test for syphilis in accordance with § 640.65(b)(2)(iii) of this chapter; and

(5) The determination to permit plasmapheresis of a donor with a reactive serological test for syphilis in accordance with § 640.65(b)(2)(iv) of this chapter.

(B) The collection of Source Plasma in an approved collection program from a donor who is otherwise determined to be ineligible.

(C) The collection of a blood sample in accordance with § 640.65(b)(1)(i) of this chapter.

(ii) The responsible physician, who may or may not be present when these activities are performed, may delegate to a physician substitute the following activities:

(A) Approval and signature for a plasmapheresis procedure as provided in § 640.65(b)(1)(ii) of this chapter; and

(B) Review and signature for accumulated laboratory data, the calculated values of each component, and the collection records in accordance with § 640.65(b)(2)(i) of this chapter.

However, the responsible physician must not delegate the decision to reinstate the deferred donor in accordance with that provision.

(2) Donor immunization. The responsible physician must not delegate activities performed in accordance with § 640.66 of this chapter, except that:

(i) The responsible physician may delegate to a physician substitute or other trained person the administration of an immunization other than red blood cells to a donor in an approved collection program, provided that the responsible physician or a physician substitute is on the premises at the collection site when the immunization is administered.

(ii) The responsible physician may delegate to a physician substitute the administration of red blood cells to a donor in an approved collection program, provided that the responsible physician has approved the procedure and is on the premises at the collection site when the red blood cells are administered.

(3) Medical history, physical examination, informed consent, and examination before immunization. Provided that such activities are performed under the supervision of the responsible physician, the responsible physician may delegate to a physician substitute the activities described in § 630.15(b)(1), (2), and (5). The responsible physician is not required to

be present at the collection site when the physician substitute performs these activities under supervision.

(4) Infrequent plasma donors. (i) For infrequent plasma donors other than those described in paragraph (c)(4)(ii) of this section, the responsible physician may delegate to a trained person the activities listed in paragraphs (b)(1)(i) through (iii) and (b)(1)(v) of this section and the informed consent requirements described in § 630.15(b)(2). The responsible physician or a physician substitute need not be present at the collection site when any of these activities are performed, provided that the responsible physician has delegated oversight of these activities to a trained person who is not only adequately trained and experienced in the performance of these activities but also adequately trained and experienced in the recognition of and response to the known adverse responses associated with blood collection procedures.

However, the responsible physician must not delegate:

(A) The examination and determination of the donor's health required in § 630.10(f)(2) for donors with blood pressure measurements outside specified limits, or in § 630.15(b)(7) for certain donors who have experienced red blood cell loss; or

(B) The determination of the health of the donor required in § 630.10(f)(4).

(ii) For infrequent plasma donors who are otherwise ineligible or are participating in an approved immunization program, the responsible physician may delegate only in accordance with paragraphs (c)(1) through (3) of this section.

(d) Must rapid emergency medical services be available? Establishments that collect blood or blood components must establish, maintain, and follow standard operating procedures for obtaining rapid emergency medical services for donors when medically necessary. In addition, establishments must assure that an individual (responsible physician, physician

substitute, or trained person) who is currently certified in cardiopulmonary resuscitation is located on the premises whenever collections of blood or blood components are performed.

§ 630.10 General donor eligibility requirements.

(a) What factors determine the eligibility of a donor? You, an establishment that collects blood or blood components, must not collect blood or blood components before determining that the donor is eligible to donate or before determining that an exception to this provision applies. To be eligible, the donor must be in good health and free from transfusion-transmitted infections as can be determined by the processes in this subchapter. A donor is not eligible if the donor is not in good health or if you identify any factor(s) that may cause the donation to adversely affect:

- (1) The health of the donor; or
- (2) The safety, purity, or potency of the blood or blood component.

(b) What educational material must you provide to the donor before determining eligibility? You must provide educational material concerning relevant transfusion-transmitted infections to donors before donation when donor education about that relevant transfusion-transmitted infection, such as HIV, is necessary to assure the safety, purity, and potency of blood and blood components. The educational material must include an explanation of the readily identifiable risk factors closely associated with exposure to the relevant transfusion-transmitted infection. You must present educational material in an appropriate form, such as oral, written or multimedia, and in a manner designed to be understood by the donor. The educational material must instruct the donor not to donate blood and blood components when a risk factor is present. When providing educational material to donors under this section, you may include in those materials the information required to be provided to donors under paragraph (g)(2)(ii)(E) of this section.

(c) When must you determine the eligibility of a donor? You must determine donor eligibility on the day of donation, and before collection. Except:

(1) When a donor is donating blood components that cannot be stored for more than 24 hours, you may determine the donor's eligibility and collect a sample for testing required under § 610.40 of this chapter, no earlier than 2 calendar days before the day of donation, provided that your standard operating procedures address these activities.

(2) In the event that, upon review, you find that a donor's responses to the donor questions before collection were incomplete, within 24 hours of the time of collection, you may clarify a donor's response or obtain omitted information required under paragraph (e) of this section, provided that your standard operating procedures address these activities.

(d) How must you determine the eligibility of a donor? You must determine the donor's eligibility before collection of blood or blood components, by the following procedures:

(1) You must consult the records of deferred donors maintained under § 606.160(e)(1) and (2) of this chapter. Exception: if pre-collection review of the record described in § 606.160(e)(2) of this chapter is not feasible because you cannot consult the cumulative record at the collection site, you must consult the cumulative record prior to release of any blood or blood component prepared from the collection.

(2) Assure that the interval since the donor's last donation is appropriate;

(3) Assess the donor's medical history; and

(4) Perform a physical assessment of the donor.

(e) How do you assess the donor's medical history? Before collection you must conduct a medical history interview as described in this section to determine if the donor is in good health; to identify risk factors closely associated with exposure to, or clinical evidence of a

relevant transfusion-transmitted infection; and to determine if there are other conditions that may adversely affect the health of the donor or the safety, purity, or potency of the blood or blood components or any product manufactured from the blood or blood components. Your assessment must include each of the following factors:

(1) Factors that make the donor ineligible to donate because of an increased risk for, or evidence of, a relevant transfusion-transmitted infection. A donor is ineligible to donate when information provided by the donor or other reliable evidence indicates possible exposure to a relevant transfusion-transmitted infection if that risk of exposure is still applicable at the time of donation. Information and evidence indicating possible exposure to a relevant transfusion-transmitted infection include:

- (i) Behaviors associated with a relevant transfusion-transmitted infection;
- (ii) Receipt of blood or blood components or other medical treatments and procedures associated with possible exposure to a relevant transfusion-transmitted infection;
- (iii) Signs and/or symptoms of a relevant transfusion-transmitted infection;
- (iv) Institutionalization for 72 hours or more consecutively in the past 12 months in a correctional institution;
- (v) Intimate contact with risk for a relevant transfusion-transmitted infection; and
- (vi) Nonsterile percutaneous inoculation.

(2) Other factors that make the donor ineligible to donate. A donor is ineligible to donate when donating could adversely affect the health of the donor, or when the safety, purity, or potency of the blood or blood component could be affected adversely. Your assessment of the donor must include each of the following factors:

- (i) Symptoms of a recent or current illness;

(ii) Certain medical treatments or medications;

(iii) Travel to, or residence in, an area endemic for a transfusion-transmitted infection, when such screening is necessary to assure the safety, purity, and potency of blood and blood components due to the risks presented by donor travel and the risk of transmission of that transfusion-transmitted infection by such donors;

(iv) Exposure or possible exposure to an accidentally or intentionally released disease or disease agent relating to a transfusion-transmitted infection, if you know or suspect that such a release has occurred;

(v) Pregnancy at the time of, or within 6 weeks prior to, donation;

(vi) Whether, in the opinion of the interviewer, the donor appears to be under the influence of any drug, alcohol or for any reason does not appear to be providing reliable answers to medical history questions, or if the donor says that the purpose of donating is to obtain test results for a relevant transfusion-transmitted infection; and

(vii) The donor is a xenotransplantation product recipient.

(f) How do you perform a physical assessment of the donor? You must determine on the day of donation, and before collection that the donor is in good health based on the following, at a minimum:

(1) Temperature. The donor's oral body temperature must not exceed 37.5 °C (99.5 °F), or the equivalent if measured at another body site;

(2) Blood pressure. The donor's systolic blood pressure must not measure above 180 mm of mercury, or below 90 mm of mercury, and the diastolic blood pressure must not measure above 100 mm of mercury or below 50 mms of mercury. A donor with measurements outside these limits may be permitted to donate only when the responsible physician examines the donor

and determines and documents that the health of the donor would not be adversely affected by donating.

(3) Hemoglobin or hematocrit determination. You must determine the donor's hemoglobin level or hematocrit value by using a sample of blood obtained by fingerstick, venipuncture, or by a method that provides equivalent results. Blood obtained from the earlobe is not acceptable.

(i) Allogeneic donors must have a hemoglobin level or hematocrit value that is adequate to assure donor safety and product potency. The following minimum standards apply.

(A) Female allogeneic donors must have a hemoglobin level that is equal to or greater than 12.5 grams of hemoglobin per deciliter of blood, or a hematocrit value that is equal to or greater than 38 percent. Recognizing that lower levels are also within normal limits for female donors, you may collect blood from female allogeneic donors who have a hemoglobin level between 12.0 and 12.5 grams per deciliter of blood, or a hematocrit value between 36 and 38 percent, provided that you have taken additional steps to assure that this alternative standard is adequate to ensure that the health of the donor will not be adversely affected due to the donation, in accordance with a procedure that has been found acceptable for this purpose by FDA.

(B) Male allogeneic donors must have a hemoglobin level that is equal to or greater than 13.0 grams of hemoglobin per deciliter of blood, or a hematocrit value that is equal to or greater than 39 percent.

(ii) An autologous donor must have a hemoglobin level no less than 11.0 grams of hemoglobin per deciliter of blood, or a hematocrit value no less than 33 percent.

(4) Pulse. The donor's pulse must be regular and between 50 and 100 beats per minute. A donor with an irregular pulse or measurements outside these limits may be permitted to donate

only when the responsible physician determines and documents that the health of the donor would not be adversely affected by donating.

(5) Weight. The donor must weigh a minimum of 50 kilograms (110 pounds).

(6) Skin examination. (i) The donor's phlebotomy site must be free of infection, inflammation, and lesions; and

(ii) The donor's arms and forearms must be free of punctures and scars indicative of injected drugs of abuse.

(g) Are there additional requirements for determining the eligibility of the donor? You must obtain the following from the donor on the day of donation:

(1) Proof of identity and postal address. You must obtain proof of identity of the donor and a postal address where the donor may be contacted for 8 weeks after donation; and

(2) Donor's acknowledgement. (i) Prior to each donation, you must provide information to the donor addressing the elements specified in paragraphs (g)(2)(ii)(A) through (E) of this section and obtain the donor's acknowledgement that the donor has reviewed the information. You must establish procedures in accordance with § 606.100 of this chapter to assure that the donor has reviewed this material, and provide for a signature or other documented acknowledgement.

(ii) The donor acknowledgement must not include any exculpatory language through which the donor is made to waive or appear to waive any of the donor's legal rights. It must, at a minimum clearly address the following:

(A) The donor has reviewed the educational material provided under paragraph (b) of this section regarding relevant transfusion-transmitted infections;

(B) The donor agrees not to donate if the donation could result in a potential risk to recipients as described in the educational material;

(C) A sample of the donor's blood will be tested for specified relevant transfusion-transmitted infections;

(D) If the donation is determined to be not suitable under § 630.30(a) or if the donor is deferred from donation under § 610.41 of this chapter, the donor's record will identify the donor as ineligible to donate and the donor will be notified under § 630.40 of the basis for the deferral and the period of deferral;

(E) The donor has been provided and reviewed information regarding the risks and hazards of the specific donation procedure; and

(F) The donor has the opportunity to ask questions and withdraw from the donation procedure.

(h) What must you do when a donor is not eligible? You must not collect blood or blood components from a donor found to be ineligible prior to collection based on criteria in §§ 630.10 or 630.15, or deferred under § 610.41 of this chapter or § 630.30(b)(2), unless this subchapter provides an exception. You must defer donors found to be ineligible and you must notify the donor of their deferral under § 630.40.

§ 630.15 Donor eligibility requirements specific to Whole Blood, Red Blood Cells and Plasma collected by apheresis.

(a) What additional donor eligibility requirements apply when you, an establishment that collects blood or blood components, collect Whole Blood or Red Blood Cells by apheresis?

(1) Donation frequency must be consistent with protecting the health of the donor.

(i) For a collection resulting in a single unit of Whole Blood or Red Blood Cells collected by apheresis, donation frequency must be no more than once in 8 weeks, and for apheresis collections resulting in two units of Red Blood Cells, the donor must not donate more than once in 16 weeks.

(ii) The limitations in paragraph (a)(1)(i) of this section apply unless the responsible physician examines the donor at the time of donation and one of the following conditions exists:

(A) The donation is for autologous use as prescribed by the donor's physician and the responsible physician determines and documents that the donation may proceed; or

(B) The donation is a dedicated donation based on the intended recipient's documented exceptional medical need and the responsible physician determines and documents that the health of the donor would not be adversely affected by donating.

(2) Therapeutic phlebotomy. When a donor who is determined to be eligible under § 630.10 undergoes a therapeutic phlebotomy under a prescription to promote the donor's health, you may collect from the donor more frequently than once in 8 weeks for collections resulting in a single unit of Whole Blood or Red Blood Cells, or once in 16 weeks for apheresis collections resulting in two units of Red Blood Cells, provided that the container label conspicuously states the disease or condition of the donor that necessitated phlebotomy. However, no labeling for the disease or condition is required under this section if:

(i) The donor meets all eligibility criteria;

(ii) The donor undergoes a therapeutic phlebotomy as prescribed by a licensed health care provider treating the donor for:

(A) Hereditary hemochromatosis; or

(B) Another disease or condition, when the health of a donor with that disease or condition will not be adversely affected by donating, and the donor's disease or condition will not adversely affect the safety, purity, and potency of the blood and blood components, or any products manufactured from them, and the collection is in accordance with a procedure that has been found acceptable for this purpose by FDA; and

(iii) You perform without charge therapeutic phlebotomies for all individuals with that disease or condition.

(b) What additional donor eligibility requirements apply when you, an establishment that collects blood or blood components, collect Source Plasma or plasma by plasmapheresis?

(1) Medical history and physical examination. Except as provided in § 630.25:

(i) The responsible physician must conduct an appropriate medical history and physical examination of the donor on the day of the first donation or no more than 1 week before the first donation and at subsequent intervals of no longer than 1 year.

(ii) The responsible physician must examine the donor for medical conditions that would place the donor at risk from plasmapheresis. If the donor is determined to be at risk, you must defer the donor from donating.

(iii) The responsible physician must conduct a new medical history and physical examination of a donor who does not return for 6 months.

(2) What requirements apply to obtaining informed consent?

(i) The responsible physician must obtain the informed consent of a plasma donor on the first day of donation or no more than 1 week before the first donation, and at subsequent intervals of no longer than 1 year.

(ii) The responsible physician must obtain the informed consent of a plasma donor who

does not return within 6 months of the last donation.

(iii) The responsible physician must explain the risks and hazards of the procedure to the donor. The explanation must include the risks of a hemolytic transfusion reaction if the donor is given the cells of another donor and the risks involved if the donor is immunized. The explanation must be made in such a manner that the donor may give their consent and has a clear opportunity to refuse the procedure.

(iv) If a donor is enrolled in a new program, such as an immunization or special collection program, the responsible physician must again obtain an informed consent specific for that program.

(3) Weight. You must weigh a donor at each donation.

(4) Total protein level. You must determine the donor's total plasma protein level before each plasmapheresis procedure. The donor must have a total plasma protein level of no less than 6.0 grams per deciliter and no more than 9.0 grams per deciliter in a plasma sample or a serum sample.

(5) Examination before immunization. (i) No more than 1 week before the first immunization injection for the production of high-titer antibody plasma, the responsible physician must conduct an appropriate medical history and physical examination, as described in paragraph (b)(1) of this section, in addition to assessing the general donor eligibility requirements under § 630.10. It is not necessary to repeat the medical history and physical examination requirement in paragraph (b)(1) of this section, if the immunized donor's plasma is collected within 3 weeks of the first immunization injection.

(ii) You are not required to repeat the medical history and physical examination required under paragraph (b)(1) of this section for a donor currently participating in a plasmapheresis

collection program and determined to be eligible under § 630.10 unless the medical history and physical examination are due under paragraph (b)(1)(i) or (b)(1)(iii) of this section.

(6) Deferral of donors due to red blood cell loss. (i) You must defer a donor from donating plasma by plasmapheresis for 8 weeks if the donor has donated a unit of Whole Blood, or a single unit of Red Blood Cells by apheresis. However, you may collect plasma by plasmapheresis after a donation of Whole Blood or a single unit of Red Blood Cells by apheresis after at least 2 calendar days have passed, provided that the extracorporeal volume of the apheresis device is less than 100 milliliters.

(ii) You must defer a donor from donating plasma by plasmapheresis for a period of 16 weeks if the donor donates two units of Red Blood Cells during a single apheresis procedure;

(iii) You must defer a donor for 8 weeks or more if the cumulative red blood cell loss in any 8 week period could adversely affect donor health.

(7) Exceptions to deferral due to red blood cell loss. You are not required to defer a Source Plasma donor from donating plasma by plasmapheresis due to red blood cell loss if the following conditions are met:

(i) The responsible physician examines the donor at the time of the current donation and determines and documents that the donor is in good health and the donor's health permits the plasmapheresis;

(ii) The donor's plasma possesses a property, such as an antibody, antigen, or protein deficiency that is transitory, of a highly unusual or infrequent specificity, or of an unusually high titer;

(iii) The special characteristics of the donor's plasma and the need for plasmapheresis of the donor under § 630.20(b) are documented at your establishment; and

(iv) The extracorporeal volume of the apheresis device is less than 100 milliliters.

(8) Malaria. Freedom from risk of malaria is not required for a donor of Source Plasma.

(9) You must comply with other requirements for collection of plasma in part 640 of this chapter and this part including restrictions on frequency of collection as specified in §§ 640.32 and 640.65 of this chapter.

§ 630.20 Exceptions for certain ineligible donors.

After assessing donor eligibility under §§ 630.10 and 630.15, an establishment may collect blood and blood components from a donor who is determined to be not eligible to donate under any provision of § 630.10(e) and (f) or § 630.15(a) if one of the following sets of conditions are met:

(a) The donation is for autologous use only as prescribed by the donor's physician, the donor has a hemoglobin level no less than 11.0 grams of hemoglobin per deciliter of blood or a hematocrit value no less than 33 percent, and the responsible physician determines and documents that the donor's health permits the collection procedure; or

(b) The donation is collected under a Source Plasma collection program which has received prior written approval from the Director, Center for Biologics Evaluation and Research, to collect plasma for further manufacturing use into in vitro products for which there are no alternative sources, the donor meets the criteria in § 630.10(f)(1) through (6), and the responsible physician determines and documents for each donation that the donor's health permits the collection procedure, and the collection takes place under the medical oversight specified in the approved plasmapheresis program.

(c) The donation is restricted for use solely by a specific transfusion recipient based on documented exceptional medical need, and the responsible physician determines and documents

that the donor's health permits the collection procedure, and that the donation presents no undue medical risk to the transfusion recipient.

§ 630.25 Exceptions from certain donor eligibility requirements for infrequent plasma donors.

For an infrequent plasma donor who is not participating in an immunization program, establishments are not required to:

- (a) Perform a medical history and physical examination of the donor under § 630.15(b)(1);
- (b) Perform a test for total protein under § 630.15(b)(4);
- (c) Determine the total plasma or serum protein and immunoglobulin composition under § 640.65(b)(1)(i) of this chapter; or
- (d) Review the data and records as required in § 640.65(b)(2)(i) of this chapter.

§ 630.30 Donation suitability requirements.

- (a) When is a donation suitable? A donation is suitable when:
 - (1) The donor is not currently deferred from donation as determined by review of the records of deferred donors required under § 606.160(e) of this chapter;
 - (2) The results in accordance with §§ 630.10 through 630.25 indicate that the donor is in good health and procedures were followed to ensure that the donation would not adversely affect the health of the donor;
 - (3) The results in accordance with § 630.10(e) indicate that the donor is free from risk factors for, or evidence of, relevant transfusion-transmitted infections and other factors that make the donor ineligible to donate;
 - (4) The donor's blood is tested in accordance with § 610.40 of this chapter, and is negative or nonreactive, unless an exception applies under § 610.40(h) of this chapter; and

(5) The donation meets other requirements in this subchapter.

(b) What must you do when the donation is not suitable? (1) You must not release the donation for transfusion or further manufacturing use unless it is an autologous donation, or an exception is provided in this chapter.

(2) You must defer the donor when a donation is determined to be unsuitable based on the criteria in paragraphs (a)(1) through (4) of this section.

(3) You must defer the donor of bacterially contaminated platelets when the contaminating organism is identified in accordance with § 606.145(d) of this chapter as likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor.

(4) You must notify the deferred donor in accordance with the notification requirements in § 630.40.

§ 630.35 Requalification of previously deferred donors.

Establishments may determine a deferred donor to be eligible as a donor of blood and blood components if, at the time of the current collection, the donor meets the eligibility criteria in this part, except for the record of the previous deferral, and you determine that the criteria that were the basis for the previous deferral are no longer applicable. Criteria for the previous deferral are no longer applicable if the following conditions are met:

(a) The previous deferral was for a defined period of time and that time period has passed, or the deferral was otherwise temporary, such as a deferral based on eligibility criteria described in §§ 630.10(f)(1) through (5) or 630.15(b)(4); or

(b) For a donor deferred for reasons other than under § 610.41(a) of this chapter, you determine that the donor has met criteria for requalification by a method or process found acceptable for such purpose by FDA.

PART 640--ADDITIONAL STANDARDS FOR HUMAN BLOOD AND BLOOD PRODUCTS

25. 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.

§ 640.3 [Removed]

26. Remove § 640.3.

§ 640.4 [Amended]

27. In § 640.4, remove and reserve paragraph (a); and in paragraph (e), remove “§ 640.3” and add in its place “§ 630.10 of this chapter”.

§ 640.5 [Amended]

28. Amend § 640.5 as follows:

- a. In the introductory text, remove “at the time of collecting the unit of blood”;
- b. Remove and reserve paragraph (a); and
- c. In heading and text of paragraph (f), remove “communicable disease agents” wherever it appears and add in its place “relevant transfusion-transmitted infections”.

29. Revise § 640.12 to read as follows:

§ 640.12 Eligibility of donor.

Establishments must determine the eligibility of donors of the source blood for Red Blood Cells in accordance with §§ 630.10 and 630.15 of this chapter.

§ 640.14 [Amended]

30. In 640.14, remove “§ 640.5(a), (b),” and add in its place “§ 640.5(b)”.

31. Revise § 640.21 to read as follows:

§ 640.21 Eligibility of donors.

(a) Establishments must determine the eligibility of donors of platelets derived from Whole Blood and donors of platelets collected by plateletpheresis in accordance with §§ 630.10 and 630.15 of this chapter, except as provided in this section.

(b) A plateletpheresis donor must not serve as the source of platelets for transfusion if the donor has recently ingested a drug that adversely affects platelet function.

(c) A Whole Blood donor must not serve as the source of platelets for transfusion if the donor has recently ingested a drug that adversely affects platelet function unless the unit is labeled to identify the ingested drug that adversely affects platelet function.

(d) If you are collecting platelets by plateletpheresis, you must assess and monitor the donor's platelet count.

(1) You must take adequate and appropriate steps to assure that the donor's platelet count is at least 150,000 platelets per microliter ($/\mu\text{L}$) before plateletpheresis begins. Exception: If you do not have records of a donor's platelet count from prior donations and you are not able to assess the donor's platelet count either prior to or immediately following the initiation of the collection procedure, you may collect platelets by plateletpheresis, but you must not collect 9.0×10^{11} or more platelets from that donor.

(2) You must defer from platelet donation a donor whose pre-donation platelet count is less than 150,000 platelets/ μL until a subsequent pre-donation platelet count indicates that the donor's platelet count is at least 150,000 platelets/ μL ; and

(3) You must take appropriate steps to assure that the donor's intended post-donation platelet count will be no less than 100,000 platelets/ μL .

(e) Frequency of plateletpheresis collection. (1) The donor may donate no more than a total of 24 plateletpheresis collections during a 12-month rolling period.

(2) When you collect fewer than 6×10^{11} platelets, you must wait at least 2 calendar days before any subsequent plateletpheresis collection. You must not attempt to collect more than 2 collections within a 7 calendar day period.

(3) When you collect 6×10^{11} or more platelets, you must wait at least 7 calendar days before any subsequent plateletpheresis collection.

(4) Exception. For a period not to exceed 30 calendar days, a donor may serve as a dedicated plateletpheresis donor for a single recipient, in accordance with § 610.40(c)(1) of this chapter, as often as is medically necessary, provided that the donor is in good health, as determined and documented by the responsible physician, and the donor's platelet count is at least 150,000 platelets/ μ L, measured at the conclusion of the previous donation or before initiating plateletpheresis for the current donation.

(f) Deferral of plateletpheresis donors due to red blood cell loss. (1) You must defer a donor from donating platelets by plateletpheresis or a co-collection of platelets and plasma by apheresis for 8 weeks if the donor has donated a unit of Whole Blood, or a single unit of Red Blood Cells by apheresis unless at least 2 calendar days have passed and the extracorporeal volume of the apheresis device is less than 100 milliliters.

(2) You must defer a donor from donating platelets for a period of 16 weeks if the donor donates two units of Red Blood Cells during a single apheresis procedure.

(3) You must defer a donor for 8 weeks or more if the cumulative red blood cell loss in any 8 week period could adversely affect donor health.

(g) The responsible physician must obtain the informed consent of a plateletpheresis donor on the first day of donation, and at subsequent intervals no longer than 1 year.

(1) The responsible physician must explain the risks and hazards of the procedure to the donor; and

(2) The explanation must be made in such a manner that the donor may give consent, and has a clear opportunity to refuse the procedure.

32. Revise § 640.22(c) to read as follows:

§ 640.22 Collection of source material.

* * * * *

(c) If plateletpheresis is used, the procedure for collection must be as prescribed in §§ 640.21, 640.64 (except paragraph (c)), and 640.65, or as described in an approved biologics license application (BLA) or an approved supplement to a BLA.

* * * * *

§ 640.23 [Amended]

33. In § 640.23(a), remove “§ 640.5(a), (b),” and add in its place “§ 640.5(b)”.

§ 640.27 [Removed]

34. Remove § 640.27.

35. Revise § 640.31 to read as follows:

§ 640.31 Eligibility of donors.

(a) Whole Blood donors must meet the criteria for donor eligibility prescribed in §§ 630.10 and 630.15 of this chapter.

(b) Collection establishments must determine the eligibility of plasmapheresis donors in accordance with §§ 630.10 and 630.15 of this chapter.

§ 640.32 [Amended]

36. In § 640.32(b), remove “§§ 640.62, 640.64” and add in its place “§640.64”.

§ 640.33 [Amended]

37. In § 640.33(a), remove “§ 640.5(a), (b),” and add in its place “§ 640.5(b)”.

38. Revise § 640.51 to read as follows:

§ 640.51 Eligibility of donors.

(a) Whole blood donors must meet the criteria for eligibility prescribed in §§ 630.10 and 630.15 of this chapter.

(b) Collection establishments must determine the eligibility of plasmapheresis donors in accordance with §§ 630.10 and 630.15 of this chapter.

§ 640.52 [Amended]

39. In § 640.52(b), remove “§§ 640.62, 640.64” and add in its place “§640.64”.

§ 640.53 [Amended]

40. In § 640.53(a), remove “§ 640.5(a), (b),” and add in its place “§ 640.5(b)”.

§ 640.61 [Removed]

41. Remove § 640.61.

§ 640.62 [Removed]

42. Remove § 640.62.

§ 640.63 [Removed]

43. Remove § 640.63.

§ 640.64 [Amended]

44. In § 640.64, remove and reserve paragraph (a).

45. Amend § 640.65 as follows:

a. In paragraph (b)(1)(i), revise the first sentence;

- b. In paragraph (b)(1)(ii), remove “physician on the premises” and add its place “responsible physician”;
- c. Revise paragraph (b)(2)(i); and
- d. In paragraphs (b)(2)(iii) and (iv) remove “physician on the premises” and add in its place “responsible physician”.

The revisions read as follows:

§ 640.65 Plasmapheresis.

* * * * *

(b) * * *

(1)(i) Except as provided under § 630.25 of this chapter, the responsible physician must draw a sample of blood from each donor on the day of the initial physical examination or plasmapheresis, whichever comes first, and at least every 4 months thereafter. * * *

* * * * *

(2)(i) Except as provided under § 630.25 of this chapter, the responsible physician must review the accumulated laboratory data, including any tracings of the plasma or serum protein electrophoresis pattern, the calculated values of the protein composition of each component, and the collection records within 14 calendar days after the sample is drawn to determine whether or not the donor should be deferred from further donation. If a determination is not made within 14 calendar days, the donor must be deferred pending such a determination. The responsible physician must sign the review. If the protein composition is not within normal limits established by the testing laboratory, or if the total protein level is less than 6.0 grams per deciliter or more than 9.0 grams per deciliter in a plasma sample or serum sample, the donor must be deferred from donation until the protein composition returns to acceptable levels.

Reinstatement of the donor into the plasmapheresis program when the donor's protein composition values have returned to an acceptable level must first be approved by the responsible physician.

* * * * *

46. In § 640.66, revise the first sentence and remove the second sentence. The revisions read as follows:

§ 640.66 Immunization of donors.

If specific immunization of a donor is to be performed, the selection, scheduling and administration of the antigen, and the evaluation of each donor's clinical response, shall be by the responsible physician. * * *

§ 640.67 [Amended]

47. In § 640.67, remove "communicable disease agents" and add in its place "relevant transfusion-transmitted infections".

48. In § 640.69, add paragraphs (e) and (f) to read as follows:

§ 640.69 General requirements.

* * * * *

(e) Restrictions on distribution. Establishments must ensure that Source Plasma donated by paid donors not be used for further manufacturing into injectable products until the donor has a record of being found eligible to donate in accordance with § 630.10 of this chapter and a record of negative test results on all tests required under § 610.40(a) of this chapter on two occasions in the past 6 months.

(f) Hold. Source Plasma donated by paid donors determined to be suitable for further manufacturing into injectable products must be held in quarantine for a minimum of 60 calendar

days before it is released for further manufacturing. If, after placing a donation in quarantine under this section, the donor is subsequently deferred under § 610.41 of this chapter, or you subsequently determine a donor to be ineligible under § 630.10 of this chapter due to risk factors closely associated with exposure to, or clinical evidence of, infection due to a relevant transfusion-transmitted infection, you must not distribute quarantined donations from that donor for further manufacturing use to make an injectable product.

§ 640.71 [Amended]

49. Amend § 640.71 as follows:

a. In paragraph (a) introductory text, remove “the following tests” and add in its place “testing performed in accordance with § 610.40 of this chapter and § 640.65(b)”;

b. Remove paragraphs (a)(1) through (4); and

c. In paragraph (b)(1), remove “licensed physician” and add in its place “responsible physician”.

50. In § 640.72, revise paragraphs (a)(2) through (4) to read as follows:

§ 640.72 Records.

(a) * * *

(2)(i) For each donor, establishments must maintain records including a separate and complete record of initial and periodic examinations, tests, laboratory data, and interviews, etc., as required in §§ 630.10 and 630.15 of this chapter and §§ 640.65, 640.66, and 640.67, except as provided in paragraph (a)(2)(ii) of this section.

(ii) Negative results for testing for evidence of infection due to relevant transfusion-transmitted infections required in § 610.40 of this chapter, and the volume or weight of plasma withdrawn from a donor need not be recorded on the individual donor record if such information

is maintained on the premises of the plasmapheresis center where the donor's plasma has been collected.

(3) The original or a clear copy or other durable record which may be electronic of the donor's consent for participation in the plasmapheresis program or for immunization.

(4) Records of the medical history and physical examination of the donor conducted in accordance with § 630.15(b)(1) of this chapter and, where applicable, § 630.15(b)(5) of this chapter must document the eligibility of the donor as a plasmapheresis donor and, when applicable, as an immunized donor.

* * * * *

51. Revise § 640.120 to read as follows:

§ 640.120 Alternative procedures.

(a) The Director, Center for Biologics Evaluation and Research, may issue an exception or alternative to any requirement in subchapter F of chapter I of title 21 of the Code of Federal Regulations regarding blood, blood components, or blood products. The Director may issue such an exception or alternative in response to:

(1) A written request from an establishment. Licensed establishments must submit such requests in accordance with § 601.12 of this chapter;

(2) An oral request from an establishment, if there are difficult circumstances and submission of a written request is not feasible. Establishments must follow up such oral request by submitting written requests under paragraph (a)(1) of this section within 5 working days.

(b) To respond to a public health need, the Director may issue a notice of exception or alternative to any requirement in subchapter F of chapter I of title 21 of the Code of Federal Regulations regarding blood, blood components, or blood products, if a variance under this

section is necessary to assure that blood, blood components, or blood products will be available in a specified location or locations to address an urgent and immediate need for blood, blood components, or blood products or to provide for appropriate donor screening and testing.

(c) If the Director issues such an exception or alternative orally, the Director will follow up by issuing a written notice of the exception or alternative. Periodically, FDA will provide a list of approved exceptions and alternative procedures on the FDA Center for Biologics Evaluation and Research Web site.

52. Add subpart M, consisting of §§ 640.125 and 640.130, to part 640 to read as follows:

Subpart M--Definitions and Medical Supervision

Sec.

640.125 Definitions.

640.130 Medical supervision.

§ 640.125 Definitions.

The definitions set out in § 630.3 of this chapter apply to the use of those defined terms in this part.

§ 640.130 Medical supervision.

The requirements for medical supervision established in § 630.5 of this chapter supplement the regulations in this part.

PART 660--ADDITIONAL STANDARDS FOR DIAGNOSTIC SUBSTANCES FOR
LABORATORY TESTS

53. The authority citation for 21 CFR part 660 continues to read as follows:

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

54. Revise § 660.31 to read as follows:

§ 660.31 Eligibility of donor.

Donors of peripheral blood for Reagent Red Blood Cells must meet all the criteria for donor eligibility under §§ 630.10 and 630.15 of this chapter.

PART 820--QUALITY SYSTEM REGULATION

55. The authority citation for 21 CFR part 820 continues to read as follows:

Authority: 21 U.S.C. 351, 352, 360, 360c, 360d, 360e, 360h, 360i, 360j, 360l, 371, 374, 381, 383; 42 U.S.C. 216, 262, 263a, 264.

§ 820.1 [Amended]

56. In § 820.1(a)(1), remove “Manufacturers of human blood and blood components are not subject to this part, but are subject to part 606 of this chapter” and add in its place “Manufacturers of blood and blood components used for transfusion or for further manufacturing are not subject to this part, but are subject to subchapter F of this chapter”.

Dated: May 15, 2015.

Leslie Kux,

Associate Commissioner for Policy.

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