Notice to All Users

The *Circular of Information for the Use of Human Blood and Blood Components* (hereafter referred to as *Circular*) is an extension of container labels, as the space on those labels is limited.

Blood and blood components are biological products and living human tissue intended for use in patient treatment. Professional judgment based on clinical evaluation determines the selection of components, dosage, rate of administration, and decisions in situations not covered in this general statement.

This *Circular*, as a whole or in part, cannot be considered or interpreted as an expressed or implied warranty of the safety or fitness of the described blood or blood components when used for their intended purpose. Attention to the specific indications for blood components is needed to prevent inappropriate transfusion.

Because of the risks associated with transfusion, physicians or prescribing health care professionals should be familiar with alternatives to transfusion. Blood banks and transfusion services are referred to the AABB *Standards for Blood Banks and Transfusion Services* for additional information and policies, especially in the areas of recipient sample identification, compatibility testing, issue and transfusion of blood and blood components, investigation of transfusion reactions, and proper record-keeping practices. Transfusionists are referred to the AABB *Technical Manual* for applicable chapters on adult and pediatric transfusion.

The specific product manufacturer's instructions for use should be reviewed for information pertaining to the use of transfusion devices (eg, filters, blood administration sets, and blood warmers).

This *Circular* is supplied to conform with applicable federal statutes and regulations of the Food and Drug Administration (FDA), United States Department of Health and Human Services. The blood components in this *Circular* marked with the symbol "Ω" are blood components for which the FDA currently has not received data to demonstrate that they meet prescribed requirements of safety, purity, and potency, and therefore are not licensed for distribution in interstate commerce.

General Information for Whole Blood and All Blood Components

Donors

Blood and blood components described in this *Circular* are collected from blood donors for use in patients (allogeneic transfusions) or from patients donating for themselves (autologous transfusions). Most allogeneic donations are from volunteer blood donors, and the components are labeled "volunteer donor." If donors receive monetary payment for a blood donation, the components must be labeled as "paid donor."

All blood donors satisfactorily complete a health assessment that includes a medical history questionnaire on past and present illnesses. All donors undergo a physical assessment before donation to satisfy minimum physiologic criteria. Allogeneic donors are assessed for risk factors associated with transmissible infectious agents and instructed to call the blood center after donation if they develop illness or have concerns that their blood may not be safe for transfusion.

Autologous donations are collected from patients who anticipate requiring blood transfusion and elect to donate for their own use. Donor-safety screening criteria and testing procedures applicable to blood collection from allogeneic donors do not always apply to these components. Autologous donations must be labeled accordingly, as described below.

Required Testing of Blood Donations

A sample of donor blood is collected at the time of donation and undergoes required testing before labeling and distribution of the associated blood or blood components for routine transfusion. ABO group and Rh type are determined, including testing for the presence of weak D antigen.

All donations intended for transfusion are tested for evidence of relevant transfusion-transmitted infections. Testing is performed by a qualified laboratory using assays that are licensed, approved, or cleared by FDA. Testing on the current donation (or as indicated, below) must indicate that the results are nonreactive for the following:

1. Antibodies to:
    - human immunodeficiency virus, types 1 and 2 (anti-HIV-1/2)
    - hepatitis C virus (anti-HCV)
    - human T-lymphotropic virus, type I and II (anti-HTLV-I/II)

- hepatitis B core antigen (anti-HBc)
- *Trypanosoma cruzi* either on the current donation or at least one previous donation.

2. Hepatitis B surface antigen (HBsAg).
3. Licensed nucleic acid test (NAT) for:
   - hepatitis B virus (HBV) deoxyribonucleic acid (DNA)
   - hepatitis C virus (HCV) ribonucleic acid (RNA)
   - human immunodeficiency virus (HIV-1) RNA
   - West Nile virus (WNV) RNA.
4. Licensed NAT for *Babesia* (RNA and DNA) for blood collected in states where *Babesia* testing is required by FDA, unless pathogen reduction is performed.
5. Licensed serologic test for *Treponema pallidum* (syphilis).

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

A blood collector may perform additional testing for pathogens; such additional testing may be performed under an FDA-approved investigational new drug (IND) application, using language for component labeling and/or revisions to the *Circular*, as required in the approved IND and provided by the IND sponsor.

Infectious disease testing requirements for autologous donation vary, depending on whether the unit will be drawn in one facility and infused in another facility and whether the units might be made available for allogeneic transfusion. Infectious disease testing is not required for autologous units drawn, stored, and infused at the same facility if the facility does not allow autologous donations to be used for allogeneic transfusion. Autologous units for which testing has not been performed are labeled "DONOR UNTESTED." Autologous units with reactive test results may be transfused to the donor with appropriate physician authorization. The "BIOHAZARD" label and "FOR AUTOLOGOUS USE ONLY" label will be applied to all autologous units that are tested for evidence of relevant transfusion-transmitted infections as listed above and determined to be reactive. If units labeled "AUTOLOGOUS DONOR" are transfused at a different facility that does not allow autologous donations to be used for allogeneic transfusions, at a minimum the first donation in each 30-day period is tested for evidence of infection as listed above. If testing results are nonreactive, subsequent units not tested within the same 30-day period following initial tests will be labeled as "DONOR TESTED WITHIN THE LAST 30 DAYS." A "BIOHAZARD" label is required if autologous units have a reactive relevant transfusion-transmitted infection test result within the last 30 days.

In addition, if these units are untested, they must be labeled as "DONOR UNTESTED." If a facility allows for autologous units to be crossed over for inclusion in the general blood inventory, the donors and units must be subjected to the same donor eligibility and donation suitability requirements and test requirements as allogeneic donors and units.

Tests for unexpected antibodies against red blood cell (red cell) antigens are performed on donor samples for every donation. The results of these tests are negative or have been determined to be clinically insignificant unless otherwise indicated on the label. Other tests may have been performed on donor blood as indicated by information that has been provided by the blood bank or transfusion service on an additional label or tie tag, or in a supplement to this *Circular*.

Bacterial Risk Control Strategies for Platelets

To control the risk of bacterial contamination, platelet components stored at room temperature have been either:

1. tested and found negative for bacterial contamination using FDA-recommended bacterial risk control strategies and FDA-cleared or approved devices, or
2. treated using FDA-approved pathogen reduction technology.

Note: Certain bacterial testing strategies include secondary culture or rapid testing performed prior to transfusion.

Blood and Component Labeling

All **Components Available** identified in this *Circular* are listed using the Information Standard for Blood and Transplant 128 (ISBT 128) product name.

Blood and blood component labels will contain the following information:

1. The proper name, Whole Blood or blood component, including any appropriate qualifications, modifiers, and attributes.
2. The method by which the blood component was prepared, either by whole blood or apheresis collection.
3. The storage temperature range (in degrees Celsius).
4. The preservatives and anticoagulant used in the preparation of the blood or blood components, when appropriate.
5. The standard contents or volume is assumed unless otherwise indicated on the label or in *Circular* supplements.
6. The number of units in pooled blood components.
7. The name, address, registration number, and US license number (if applicable) of the collection and processing location.
8. The expiration date, including the day, month, and year, and, if the dating period for the product is 72 hours or less, including any product prepared in a system that might compromise sterility, the hour of expiration. When the expiration time is not indicated, the product expires at midnight.
9. The donation (unit or pool) identification number.
10. The donor category (paid or volunteer, and autologous, if applicable).
11. ABO group and Rh type, if applicable.
12. Special handling information, as required.
13. Statements regarding proper recipient identification, this *Circular*, infectious disease risk, and prescription requirement.
14. Any sedimenting agent used during cytapheresis, if applicable.

Instructions for Use

The following general instructions pertain to Whole Blood and all the blood components described in this *Circular*:

1. All blood and blood components must be maintained in a controlled environment and stored under appropriate conditions as described in the current version of the AABB *Standards for Blood Banks and Transfusion Services*.
2. The intended recipient and the blood container must be properly identified before the transfusion is started.
3. Aseptic technique must be employed during administration. If the container is entered in a manner that violates the integrity of the system, the component expires 4 hours after entry if maintained at room temperature (20-24 C) or 24 hours after entry if refrigerated (1-6 C).
4. All blood components must be transfused through a sterile, pyrogen-free filter designed to remove clots and aggregates (generally a standard 150- to 260-micron filter).
5. Blood and blood components should be mixed thoroughly before use.
6. Blood and blood components must be inspected immediately before use. If, upon visual inspection, the container is not intact or the appearance is abnormal (presence of excessive hemolysis, a significant color change in the blood bag as compared with the tubing segments, floccular material, cloudy appearance, or other problems), the blood or blood component must not be used for transfusion, and appropriate follow-up with the transfusion service must be performed.
7. No medications or solutions may be added to or infused through the same tubing simultaneously with blood or blood components, with the exception of 0.9% Sodium Chloride, Injection, United States Pharmacopeia (USP), unless: 1) they have been approved for this use by FDA, or 2) there is documentation available to show that the addition is safe and does not adversely affect the blood or blood component.
8. Lactated Ringer's Injection USP or other solutions containing calcium should never be added to or infused through the same tubing with blood or blood components containing citrate.
9. Blood components should be warmed, if clinically indicated, for situations such as exchange or massive transfusions, or for patients with cold-reactive antibodies. Warming must be accomplished using an FDA-cleared warming device.
10. Life-threatening reactions may occur after the infusion of only a small volume of blood or blood components; therefore, unless otherwise indicated by the patient's clinical condition, the rate of infusion should initially be slow.
11. Periodic observation and recording of vital signs should occur before, during, and after the transfusion to identify suspected adverse reactions. If a transfusion reaction occurs, the transfusion must be discontinued

immediately, and appropriate therapy initiated. The infusion should not be restarted unless approved by transfusion service protocol.

12. Specific information and instructions concerning possible adverse reactions shall be provided to the patient or a responsible caregiver when direct medical observation or monitoring of the patient will not be available after transfusion.
13. Transfusion of blood or blood components should start before expiration and finish within 4 hours after entering the container.
14. All adverse events related to transfusion, including possible bacterial contamination of blood or a blood component or suspected disease transmission, must be reported to the transfusion service according to its local protocol.

Refer to the section on **Further Processing** for additional information on:
- Pathogen Reduction Technology
- Leukocyte Reduction
- Irradiation
- Washing and Volume Reduction

Refer to the section on **Additional Testing** for additional information on:
- Identification of CMV-Seronegative Blood
- Identification of Low-Titer Anti-A and/or Anti-B Blood Products

Side Effects and Hazards for Whole Blood and All Blood Components

Transfusion-related adverse events may be voluntarily reported to the National Healthcare Safety Network (NHSN) hemovigilance program (https://www.cdc.gov/nhsn/biovigilance/index.html) unless there is a state requirement to report. The NHSN Biovigilance Component Hemovigilance Module Surveillance Protocol (https://www.cdc.gov/nhsn/pdfs/biovigilance/bv-hv-protocol-current.pdf) provides case classification criteria for Centers for Disease Control and Prevention-defined transfusion-associated adverse reactions.

Immunologic Complications, Immediate

1. *Hemolytic transfusion reaction*, the immune destruction of red cells, most commonly occurs from exposure of transfused red cells to incompatible recipient plasma. The transfusion of blood components containing plasma which is incompatible with the recipient's red cells rarely results in clinically relevant hemolysis. Further details are discussed in the section on components containing red cells and in the platelets section.
2. *Immune-mediated platelet destruction*, one of the causes of refractoriness to platelet transfusion, is the result of alloantibodies in the recipient to human leukocyte antigen (HLA) or platelet-specific antigens on transfused platelets. This is described in more detail in the section on platelets.
3. *Febrile nonhemolytic reaction* is manifested by a temperature elevation of ≥1 C or ≥1.8 F or chills/rigors occurring during or within 4 hours after a transfusion and in the absence of any other pyretic stimulus or active warming. This may reflect the action of antibodies against white cells or the action of cytokines either present in the transfused component or generated by the recipient in response to transfused elements. Febrile reactions may occur in less than 1% of transfusions of leukocyte-reduced red cell components and about 5% of leukocyte-reduced apheresis platelet components. Febrile reactions occur more frequently in patients receiving non-leukocyte-reduced components and those previously alloimmunized by transfusion or pregnancy. No routinely available pre- or posttransfusion tests are helpful in predicting or preventing these reactions. Antipyretics usually provide effective symptomatic relief. Patients who experience repeated, severe febrile reactions may benefit from receiving leukocyte-reduced components. If these reactions are caused by cytokines in the component, prestorage leukocyte reduction may be beneficial.
4. *Allergic reactions* frequently occur (ie, with 1-3% of plasma-containing components) as mild or self-limiting urticaria or wheezing that usually responds to antihistamines. More severe manifestations, including respiratory and cardiovascular symptoms, are more consistent with anaphylactoid/anaphylactic reactions and may require more aggressive therapy (see below). No laboratory procedures are available to predict these reactions.