Association for the Advancement of Blood & Biotherapies

AABB User Guide:

Circular of Information for the Use of Human Blood and Blood Components

June 2024

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Acknowledgements

The *Circular for Information for the Use of Human Blood and Blood Components* (the *Circular)* and the User Guide are made available to you through the important work of the AABB's Circular of Information Task Force, which is comprised of professional AABB member experts including representatives of the Armed Services Blood Program, the American Red Cross, and America's Blood Centers.

FDA's Formal Acceptance and Expectation for Proper Use of the June 2024 *Circular*

- On September 25, 2024 FDA issued guidance formally recognizing the June 2024 *Circular* as an "extension of labeling" which provides specific instructions for the administration and use of blood and blood components intended for transfusion as required in 21 CFR 606.122.
- The *Circular* is a controlled document and must not be revised. Once revised by a facility, the document is no longer recognized by FDA and must be resubmitted to FDA for review.
- The designated pages at the front of the *Circular* permit the addition of facility specific information and FDA required updates in these defined areas only. Additions in these defined areas only are not revisions to the *Circular*.
- During the 2017 Ask the FDA session and again in 2021, FDA stated, ***"the availability of a hard copy Circular should be part of the overall distribution process, in accordance with §606.122, to include distribution on a yearly basis or whenever a change is made to the Circular, or upon request from your customers."***
- As provided above, FDA has clarified their expectations for use of a hard copy with no expressed prohibition on the addition of an electronic version. An electronic version of the *Circular* has been developed and approved by the Circular Task Force to supplement distribution of the hard copy.

About the AABB User Guide

This AABB User Guide for the June 2024 *Circular*, created for AABB members, guides blood collection establishments and transfusion services through the regulatory responsibilities for use of the *Circular.* The AABB User Guide:

- includes numerous links to resources that will assist you with compliance and day-to-day use of the *Circular,*
- is intended to supplement your understanding of FDA's regulatory requirements related to use of the *Circular*,
- explains the role of this "extension of labeling" that is used on a daily basis by blood collection establishments, transfusion services, and health-care providers, and
- provides information on the use of an **electronic version** (USB drive format) of the *Circular*.

Responses provided by FDA at the 2017 (questions 9-12) and 2021 (question 22) Ask the FDA Sessions at the AABB Annual Meeting and language from specific FDA regulations are included throughout the User Guide to assist you in understanding FDA's expectations.

For the purpose of this User Guide, AABB's Circular of Information Task Force is referred to as the "Circular Task Force."

Table of Contents

I. PURPOSE and INTRODUCTION

What is the historical background on the *Circular*?
FDA provided the following historical background at the 2017 Ask the FDA Session at AABB's Annual Meeting:

> "The current circular of information was developed in the 1970's to provide for safe handling and administration of blood components and to provide uniform labeling to facilitate regional and interregional sharing of the Nation's blood supply. In 1974, the Commission for Commonality in Blood Banking Association (CCBBA) was created. It consisted of volunteers from different areasof the medical community and FDA personnel. At the time, labeling varied in format and wording depending on the collector. Blood banking computerization did not yet exist. CCBBA undertook a review of the container label requirements for blood and blood components in order to recommend a revised simplified container label suitable for use by all establishments, to include machine readable code, and to select key information for inclusion on the container label.In support of these efforts, FDA issued a Guideline for the Uniform Labeling of Blood and BloodComponents which described suitable labeling for blood and blood components and then promulgated labeling regulations in 1985. Many of the information elements that were removed from the simplified container label recommended by CCBBA were included in the instruction circular. New cautionary statements and instructions to users were included in the circular when the agency determined that the information was necessary. Because the revised, simplified container label was intended for use with the circular, the instruction circular must be available concurrent with the use of the container label. With that said…**The *Circular of Information for the Use of Human Blood and Blood Components* is considered to be labeling. It was developed as an extension of blood bag container labels, because the space on those labels is limited**."

Is the *Circular* required by FDA?
Yes. In addition to the labeling regulations at 21 CFR 606.121 for the "Container label", you must also comply with the regulations requiring a circular of information in 21 CFR 606.122.

With proper use of the *Circular,* blood collection establishments, as manufacturers of blood products, will:

- Meet the requirements of FDA regulations at 21 CFR 606.122.
- Not need to develop individualized circulars, as they can adopt this FDA recognized *Circular* developed by the Circular Task Force.
- Be able to add their facility information to this formally recognized version of the *Circular*, making it their own extension of labeling for the blood products they distribute to customers.

Why is an "extension of labeling" needed?
As mentioned, FDA regulations at 21 CFR 606.122 state "A circular of information must be available for distribution if the product is intended for transfusion." The *Circular* will serve as an "extension of labeling" for blood products that are manufactured and distributed. This "extension" of the label is needed because space is limited on the label that is placed on the blood product bag. This *Circular,* similar in purpose to the package insert for drugs, provides important information required in 21 CFR 606.122, including but not limited to:

- General information on product preparation, storage, and testing.

- Contraindications and indications for use.
- Hazards and adverse reactions.
- An overview of specific blood components with detailed information for prescribing and administering blood products.

Does this User Guide provide all the information I need on the *Circular*?
We encourage you to review all sections of this User Guide. This User Guide is intended to supplement your understanding of FDA's requirements and recommendations. It is not intended to replace your review of FDA regulations and guidance.

Additional resources and relevant information can be found in numerous links to assist you with updating your policy and standard operating procedures (SOPs) related to the *Circular*.

What is new and what has changed in the June 2024 *Circular*?
AABB Regulatory Affairs has prepared a comprehensive Change Table highlighting the significant changes and new information included in the June 2024 *Circular*.

New in this version:

- RED BLOOD CELLS, ADENINE SALINE ADDED, LEUKOCYTES REDUCED, O2/CO2 REDUCED are prepared following collection and processing of Leukocyte Reduced Red Blood Cells in a processing system that limits O2 and CO2 levels in the storage environment. The component may be stored under reduced oxygen conditions for up to 42 days at 1-6 C.

Revised in this version:

- The Side Effects and Hazards for Whole Blood and All Blood Components, Nonimmune Complications section was revised:
  - to reflect that there is now an FDA licensed donor screening test for malaria.
  - to include signs and symptoms of TACO
- The Whole Blood section was revised:
  - When preservation of platelet function is required, Whole Blood intended for transfusion should be collected from a donor who has not recently ingested a drug that adversely affects platelet function. (Refer to the current version of the AABB Donor History Questionnaire and the Medication Deferral List.)
  - *Dosage and Administration* includes information on the requirement for serologic compatibility between the recipient and the donor.
- The Cryoprecipitated Antihemophilic Factor and Plasma Cryoprecipitate Reduced sections were revised to reflect that:
  - Cryoprecipitated Antihemophilic Factor (AHF) is prepared by thawing frozen whole-blood-derived or apheresis plasma between 1 and 6 C and recovering the precipitate.
  - "plasma cryoprecipitate reduced is prepared from whole-blood-derived or apheresis-collected plasma after thawing and centrifugation and removal of the cryoprecipitate"
- AABB Note: Cryoprecipitated AHF and plasma cryoprecipitate reduced may be prepared from plasma if the plasma collection set is labeled for the collection of plasma.

- If the collection set is labeled only for the collection of FFP, and the establishment wishes to prepare Cryoprecipitated AHF from other types of plasma such as PF24, the facility should contact FDA to determine what to submit for review. In some instances, blood establishments may need to request an alternative or exception to applicable regulations if the plasma collection set is labeled for the collection of FFP only.

II. REGULATORY REQUIREMENTS and DEVELOPMENT OF THE *CIRCULAR*

Who is responsible for making the *Circular* available?
Each blood collection establishment is responsible for complying with the labeling requirements for the products they manufacture, including making the *Circular* available at distribution, as described in 21 CFR 606.122. Once the *Circular* is distributed to customers by the blood collection establishment, the transfusion service makes the *Circular* available to prescribing physicians and healthcare professionals wherever "questions may arise about transfusion." Environments include, but are not limited to, in-hospital transfusion, out of hospital transfusion, and prehospital transfusion (emergency medical services).

How is the *Circular* developed?
The AABB Board of Directors has tasked the Circular Task Force with preparing the *Circular* for consistency with the FDA requirements of 21 CFR 606.122. The Circular Task Force is comprised of AABB member experts, including representatives from the Armed Services Blood Program, the American Red Cross, America's Blood Centers and the FDA. Once finalized, AABB's Regulatory Affairs Staff submits a formal request to FDA for review and acceptance of the *Circular.* The FDA issues guidance to formally recognize the *Circular* as acceptable for use by all blood collection establishments and transfusion services. AABB's Publications Staff creates the final document that is published.

What version of the *Circular* is currently in use and how can I verify it has been accepted by FDA? The current version of the *Circular* is dated June 2024. FDA no longer recognizes the December 2021 *Circular* as acceptable for use.

The June 2024 *Circular* was formally recognized as acceptable for use by FDA in the September 2024 guidance. We encourage you to review the recommendations in this guidance and all relevant regulations to ensure you understand FDA's expectations.

At the request of FDA, the June 2024 *Circular* is posted on the AABB website to enable the public to view the current version, verify the date of the current version, as well as review the contents. This posted version is locked to protect the document content.

Why can't I copy or download the pdf version posted on AABB's website?
AABB has posted the *Circular* as a locked and watermarked pdf document. This controlled document can be viewed by the public but not copied or printed. This safety measure is necessary to:

- Protect the content approved by the Circular Task Force and formally accepted by FDA by preventing inadvertent or intended modifications.
- Protect transfusion recipients by controlling the information on intended use, dosing, administration and other considerations that directly impact patient safety.
- Ensure transfusion services are provided a current *Circular* from their blood supplier. The posted

Circular does not provide blood supplier information, nor FDA required updates.

III. PROPER USE OF THE *CIRCULAR*

The following information is based on FDA's responses during the 2017 and 2021 Ask the FDA sessions.

Does FDA require blood collection establishments to use hard copies?
Yes. When asked to clarify FDA's expectation for the frequency of and method for distribution of the *Circular,* FDA gave three criteria for use of the hard copy *Circular*. FDA stated that "We believe availability of a **hard copy** circular should be part of your overall distribution process inaccordance with §606.122, to include:

- Distribution on a **yearly basis**, or
- whenever **a change is made** to the *Circular*, or
- **upon request** from your customers."

Who are the intended users of the *Circular*?
Blood establishments manufacturing blood products use the *Circular* as an extension of labeling to provide specific instructions for the administration and use of blood and blood components intended for transfusion (as required in 21 CFR 606.122). The *Circular* must be available for review by Transfusion Services, prescribing physicians and staff anywhere blood is issued and transfused. FDA was asked if the *Circular* should be "made available at the time of issue for transfusions in a private practice or other setting, and for emergency use if needed during patient transport by air or ground etc." FDA clarified that:

> "FDA believes that the *Circular* should be available for distribution to physicians, transfusionists, caregivers, and other health care professionals in any setting in which questions may arise regarding blood transfusion. If the environment includes blood transfusion, the *Circular* should be available."

When is the *Circular* updated and who is responsible?
Each blood collection establishment is responsible for updating their *Circular* and sending the updated *Circular* to customers, as noted above.

The Circular Task Force works with FDA to develop updates as new products and tests are licensed by FDA. Each blood collection establishment is responsible for adding the updated information to their *Circular*. A list of the FDA required updates is maintained on AABB's Circular of Information web page. Consistent with long-standing practices, the FDA approved language can be added using an ink stamp or a pre-printed adhesive label. See Section IV, page 8 for updates to the *eCircular*. Refer to AABB's web page for detailed information. As described above, these FDA required updates and not "revisions' to the *Circular*.

Why are there "blank" pages at the front of the *Circular*?
The *Circular* includes blank pages where the updates can be added. Blank pages appear prior to the Table of Contents to make it easy for you to add your facility information and FDA required updates.

What language should be added to the Circular by blood centers that manufacture licensed COVID-19 Convalescent Plasma (CCP)?

CCP manufacturing processes, including the criteria used to qualify the donor and product, may differ among blood establishments and include unique manufacturing considerations. Therefore, FDA will work individually with each manufacturer during the Blood License Application process to review and approve appropriate language to be added to the facility *Circular*.

Which blood centers should continue to add the "Alternative Procedures for the Manufacture of Cold-Stored Platelets" Language Update to the "blank" pages at the front of the Circular?
On June 23, 2023, FDA issued a guidance, for immediate implementation, Alternative Procedures for the Manufacture of Cold-Stored Platelets Intended for the Treatment of Active Bleeding when Conventional Platelets Are Not Available or Their Use Is Not Practical that permits blood establishments to adopt exceptions and alternatives to certain requirements to support the manufacture of cold-stored platelets (CSP) without submitting a variance request to the agency under 21 CFR 640.120. FDA noted that maintaining platelet availability in the face of logistical challenges (e.g., in military, prehospital or austere settings) or other threats to blood availability (e.g., mass casualty events or public health emergencies) is critical to assure that platelets are available to patients with active bleeding.

Until CSP collection devices are approved, variances are no longer needed, and such information has been included in the next version of the *Circular*, blood establishments that manufacture CSP must update their June 2024 Circular to provide adequate directions for the use of CSP. FDA recommends including the following statements and information:

a. "CSP are intended for the treatment of active bleeding when conventional platelets are not available, or their use is not practical."
b. "CSP must be stored continuously at 1-6°C to control the risk of bacterial contamination for up to 14 days."
c. "Transfusion services should establish procedures for examining CSP for visible aggregates before transfusion."

Which blood centers should continue to add the Zika Virus Language Update to the "blank" pages at the front of the *Circular*?
On May 12, 2021, the FDA's July 2018 Zika virus (ZIKV) Testing Guidance was withdrawn because the agency determined that testing for ZIKV or pathogen reduction as an alternative to testing for ZIKV is not necessary to comply with the requirements of 21 CFR 610.40(a)(3) because ZIKV is no longer a Relevant Transfusion-Transmitted Infection.

Accordingly, the recommendation was not included in the December 2021 *Circular*. For blood centers that continue to have ZIKV tested units in their distributed inventory, AABB recommends adding this statement to your *Circular*:

> "Blood components collected between [insert date-date] were tested with a licensed nucleic acid test (NAT) for Zika Virus RNA and found to be nonreactive."

At the time your blood center no longer has ZIKV-tested units in your distributed inventory, you can opt to delete this statement from your *Circular of Information*.

How often is a new version published?
The Circular Task Force determines when a new version should be developed and submitted to FDA based on new information related to dosing and prescribing, and licensing of new products and tests. When the new version is accepted by FDA, as announced in an FDA guidance, AABB publishes the new version. At that time, all FDA required updates are incorporated in the new version of the *Circular*.

How will I know when an update is needed?
There are several ways we can help you stay informed. The Circular Task Force works with the AABB's Regulatory Affairs staff to monitor new recommendations and product approvals that require an update. To

stay informed, you should know that:

- AABB routinely publishes **Regulatory Updates** in the Weekly Report to ensure members receive
- important regulatory information. AABB's Weekly Report is sent each Wednesday.
- All updates to the *Circular* (and other important regulatory information) are announced in the Regulatory Updates.
- If you are not receiving the Weekly Report, you can contact AABB for assistance.
- The Accreditation Contact for each AABB Accredited facility also receives the Weekly Report.
- AABB will send a News Flash to alert members of important Regulatory news prior to the Wednesday release of the Weekly Report when necessary.
- FDA guidance specifies when new recommendations will require updates to the *Circular.* Your facility can also monitor FDA activities, including new recommendations and product approvals,by subscribing to FDA's email update system.

IV. ADDING AN OPTIONAL ELECTRONIC VERSION OF THE *CIRCULAR*

Is it possible to use an electronic version of the *Circular*?
Yes. The decision to add an electronic version of the *Circular* (also referred to as an *eCircular* in this User Guide) resides with each blood collection establishment. This optional electronic version can be added to your overall distribution plan for the *Circular*. FDA has clarified their expectations for use of a hard copy with no expressed prohibition on the addition of an electronic version. An electronic version of the *Circular* has been developed and approved by the Circular Task Force to supplement distribution of the hard copy.

As noted earlier, FDA has stated:

> "We believe availability of a hard copy circular should be part of your overall distribution process in accordance with §606.122, to include distribution on a yearly basis, or whenever a change is made to the circular, or upon request from your customers."

How would we use the electronic version?
As mentioned, the electronic version is optional. Each blood collection establishment must determine how best to incorporate the use of the *eCircular*– such as whether to make it available to your customers/transfusion services via a link posted on your website or sent as an attachment. Your facility must develop a policy and SOPs for safe and effective use of the document - if you decide to use the electronic version.

Does the information or content of the electronic version differ from the hard copy of the *Circular*?

No. The version date, cover, format, and content approved by the Circular Task Force and accepted by FDA are exactly the same in both versions. Revisions made to the electronic *Circular* would result in a version not recognized by FDA in guidance which would require resubmission to FDA for review.

How would we update the electronic version of the *Circular*?
Similar to the hard copy *Circular*, facility information, FDA required updates and approved language may be added to the 2 blank pages prior to the Table of Contents. Large editable text boxes permit additions.

How can we be sure the content of the electronic version won't be altered or modified?
The *eCircular* is created as a controlled pdf document. The pages designated for facility information and updates will permit additions in these defined areas only. With the exception of the defined areas (editable text boxes), the remaining content must not be revised. Once revised, the document is no longer recognized by FDA and must be submitted to FDA for review. The Covers, Table of Contents and all pages that follow are "locked" to protect the content and to prevent intentional or inadvertent modification. This ensures that the content approved by the AABB Task Force and formally accepted byFDA cannot be revised. The blood collection establishment is responsible for controlling modifications to its *eCircular.*

V. IMPLEMENTATION OF THE *CIRCULAR*

What is required for implementation of the *Circular*?
FDA's September 2024 guidance describes the reporting requirements of 21 CFR 601.12. In Section IV, Implementation, FDA states:

"Licensed manufacturers must report the implementation of the June 2024 Circular to FDA under 21 CFR 601.12 as follows:

1. If the June 2024 Circular is implemented **without modification and in its entirety**, the change is considered to be minor. You must report such changes to FDA in your annual report,consistent with 21 CFR 601.12(f)(3) and noting the date the process was implemented.

2. If the June 2024 Circular is implemented **with modification**, the change is considered to be major. You must report such changes as a Prior Approval Supplement, consistent with 21 CFR 601.12(f)(1)."

What are some examples of acceptable and unacceptable use of the hard copy and e*Circular*?

ACCEPTABLE:

- A hard copy *Circular* with Blood Center information and FDA required updates added to designated pages as described above, is sent each year AND whenever the *Circular* is updated with new information or upon request from your customer.
- Following distribution of a hard copy *Circular* with Blood Center information and FDA required updates added to designated pages as described above, an electronic version of the *Circular* with Blood Center information and FDA required updates added to designated pages as described above, is sent by the blood collector to the hospital blood bank.
- Following distribution of a hard copy *Circular* with Blood Center information and FDA required

updates added to designated pages as described above, an electronic version of the *Circular* with Blood Center information and FDA required updates added to designated pages as described above, is downloaded and printed by the blood collector.

- Following distribution of a hard copy *Circular* with Blood Center information and FDA required updates added to designated pages as described above, a link to an electronic version of the *Circular* with Blood Center information and FDA required updates added to designated pages as described above, is posted on the blood collector's website.
- A transfusion service requests additional copies of the *Circular* from the blood collector for distribution to a provider of emergency transport services.
- The watermarked version without local modifications, posted on AABB's website, is used as a reference or teaching tool rather than an extension of container labeling.

UNACCEPTABLE:

- A hard copy or electronic version of the *Circular* without Blood Center information and FDA required updates added to designated pages as described above, is provided to a transfusion service as part of the extension of labeling as required under 21 CFR 606.122.
- The electronic version of the *Circular* is revised to change the content approved by the AABB Task Force and formally accepted by FDA.
- The electronic version of the *Circular* is revised to remove or replace logos or information on the front or back cover.
- A transfusion service purchases and distributes the hard copy *Circular,* to serve as an extension of container labeling for blood products they did not manufacture.
- A hard copy of the *Circular* with Blood Center information and FDA required updates added to designated pages dated October 2017 is used to meet the labeling requirements under 21 CFR 606.122.
- A blood collection establishment decides to use only the electronic version of the *Circular* without distribution of a hard copy version first.
- A blood collector does not provide an additional copy of the *Circular* when requested by a customer.

VI. ORDERING THE *CIRCULAR*

How can I purchase the *Circular?*
Please visit the AABB Store to order the current version of the *Circular of Information for the Use of Human Blood and Blood Components*, dated June 2024. The *Circular* can be ordered as:

- A hard copy brochure (in bundles of 50 copies) or as
- A brochure/electronic bundle (hard copy/USB drive format) for blood collection centers that elect to use the optional electronic version in addition to the hard copy.

Do I have to be an AABB member to order the *Circular* from AABB?
No. The *Circular* can be ordered by **all** blood collection establishments.

How can a Transfusion Service get additional copies?
Transfusion Services should contact their blood supplier to request copies of the *Circular.*

CONTACT AABB REGULATORY AFFAIRS AT regulatory@aabb.org for assistance.