AABB User Guide:
Circular of Information for the Use of Human Blood and Blood Components - December 2021
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Use of Human Blood and Blood Components
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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 December 2021 Circular

- On March 22, 2022 FDA issued guidance formally recognizing the December 2021 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 December 2021 Circular, created for AABB members, guides transfusion services and blood collection establishments 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.”
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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 areas of 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 Blood Components 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 has changed and what is new in the December 2021 Circular?**

AABB Regulatory Affairs has prepared a comprehensive Change Table highlighting the significant changes and new information included in the December 2021 Circular. New in this version:

- Whole Blood Section
- Information on Bacterial Risk Control Strategies for Platelets
- Expanded information on Pathogen Reduction Technology
- Pathogen Reduced Cryoprecipitated Fibrinogen Complex Section

**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.”

**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 December 2021. FDA no longer recognizes the October 2017 Circular as acceptable for use.

The December 2021 Circular was formally recognized as acceptable for use by FDA in the March 2022 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 December 2021 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 the 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 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.”

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.

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. The requirement to test blood donations for ZIKV was not included in the October 2017 version of the COI, nor was it included in the December 2021 version (because it is no longer necessary).

Accordingly, for blood centers that continue to have ZIKV tested units in their distributed inventory and to satisfy FDA’s expectations, AABB recommends adding this statement to your Circular at the time testing is discontinued:

“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 by FDA 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 March 2022 guidance describes the reporting requirements of 21 CFR 601.12. In Section IV, Implementation, FDA states:

“Licensed manufacturers must report the implementation of the December 2021 Circular to FDA under 21 CFR 601.12 as follows:

1. If the December 2021 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 December 2021 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 eCircular?

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 December 2021. 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.