July 5, 2025

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, MD 20852

Submitted via http://www.regulations.gov

Re: **Docket No. FDA- FDA-2024-D-3067,** Recommendations to Reduce the Risk of Transmission of Disease Agents Associated with Sepsis by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Draft Guidance for Industry

Dear Dockets Manager:

The Association for the Advancement of Blood and Biotherapies (AABB), America's Blood Centers (ABC), and the American Red Cross (ARC) are pleased to submit joint comments to the U. S. Food and Drug Administration (FDA) in response to the May 2025 draft guidance, Recommendations to Reduce the Risk of Transmission of Disease Agents Associated with Sepsis by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (Draft Guidance)

Our organizations appreciate the opportunity to comment on the Guidance. We support FDA's dedication and mission to enhance the safety of HCT/Ps and to prevent the transmission of communicable disease agents linked to sepsis. These comments closely align with the Joint Comments our organizations submitted to the original January 2025 Final Guidance which has been withdrawn.

COMMENT 1 – Clarification on screening for pathogens that may cause sepsis

Background:

Section III. DISCUSSION, page 3

A. Risk of Transmission

There is a risk of transmission by HCT/Ps of any infectious agent that could cause sepsis. Various bacterial (including mycobacterial), fungal, and viral agents have been shown to be transmissible via use of HCT/Ps, and these agents have sufficient incidence and/or prevalence to affect the potential HCT/P donor population. Bacterial infection potentially resulting in sepsis with associated morbidity and mortality is a recognized risk from transfused blood and blood components and from transplanted organs.

Section IV. RECOMMENDATIONS beginning on page 3 list the following categories:

A. *Screening a Donor for Risk Factors and Conditions of Sepsis*
B. *Screening a Donor for Clinical Evidence of Sepsis*
C. *Screening a Donor for Physical Evidence of Sepsis*
D. *Testing a Donor for Evidence of Sepsis*

For FDA's consideration:

In a February 2021 Japanese study published in the *International Journal of Infectious Diseases*, Current spectrum of causative pathogens in sepsis: A prospective nationwide cohort study in Japan, "a total of 1352 causative pathogens, including 571 gram-positive bacteria, 709 gram-negative bacteria, and 35 fungi, were identified in the 928 patients. A polymicrobial infection with two or more causative pathogens was present in 200 patients."

Requests:

1. Our organizations request clear guidance from FDA on which pathogens, among the hundreds of potential sepsis-causing pathogens, should be prioritized for screening.

2. In addition, we request clarification and detailed recommendations for the use of the most effective and reliable pathogen testing methods, when such methods are available, and their use is appropriate to reduce the risk of sepsis and ensure accurate and timely donor eligibility determinations.

COMMENT 2 – Clarification on what constitutes a "suspicion of sepsis"

Background:

Section IV. RECOMMENDATIONS, page 3:

A. Screening a Donor for Risk Factors and Conditions of Sepsis, page 4

...

In accordance with 21 CFR 1271.75(d), you must determine to be ineligible any potential donor who is identified as having a risk factor for sepsis. The following condition should be considered a risk factor:

1. *Persons who, currently, are known to have a medical diagnosis of sepsis or suspicion of sepsis from their most recent healthcare facility stay or visit preceding HCT/P recovery that is not documented as resolved.*

For FDA's consideration:

Signs and symptoms of sepsis are very complex and overlap with other medical conditions, many of which are not infectious. This can lead to an incorrect donor eligibility determination.

Requests:

1. We ask that FDA establish clear, evidence-based criteria for evaluating an HCT/P donor for systemic infection including well-defined exclusionary criteria.

2. Given the complexity of sepsis and its overlap with noninfectious conditions, please clarify in the recommendations what constitutes a "suspicion of sepsis".

COMMENT 3 – Use of the terms "currently" and "recent history"

Background:

Section IV. RECOMMENDATIONS, page 3:

A. Screening a Donor for Risk Factors and Conditions of Sepsis, page 4

…

In accordance with 21 CFR 1271.75(d), you must determine to be ineligible any potential donor who is identified as having a risk factor for sepsis. The following conditions should be considered a risk factor:

1. *Persons who, currently, are known to have a medical diagnosis of sepsis or suspicion of sepsis from their most recent healthcare facility stay or visit preceding HCT/P recovery that is not documented as resolved.*

AND

Section IV. RECOMMENDATION, page 4:

B. Screening a Donor for Clinical Evidence of Sepsis

…

If a living donor appears healthy and does not have a recent history of sepsis or suspicion of sepsis, the donor is not considered to have risk of sepsis.

For FDA's consideration:

Use of the terms "currently" in Section IV. A. and "recent history" in Section IV. B. is inconsistent and may lead to an inaccurate donor eligibility determination.

Requests:

1. Our organizations request the use of a single term (i.e. "currently") in Section IV. A. and Section IV. B.

2. If use of the term "recent history" is retained in Section IV. B, please define the term.

COMMENT 4 – Cellular starting material (e.g. mononuclear cells or leukocytes) collected from healthy donors – Risk Factors and Conditions of Sepsis

Background:

Section IV. RECOMMENDATIONS

A. Screening a Donor for Risk Factors and Conditions of Sepsis, page 4

Unless an exception identified in 21 CFR 1271.90(a) applies, you must review relevant medical records (21 CFR 1271.3(s)) and ask questions about the donor's medical history and relevant social behavior (21 CFR 1271.3(n)), including risk factors for RCDADs (21 CFR 1271.75(a)). You should also screen the birth mother when an infant donor is less than 1 month of age.

…

1. *Persons who, currently, are known to have a medical diagnosis of sepsis or suspicion of sepsis from their most recent healthcare facility stay or visit preceding HCT/P recovery that is not documented as resolved.*

For FDA's consideration:

These comments are from the perspective of HCT/Ps collected as cellular starting material (e.g. mononuclear cells or leukocytes) from healthy donors. It is reasonable to question a donor about a current diagnosis of sepsis and about whether they are currently undergoing

treatment for sepsis. The additional text, "from their most recent healthcare facility stay or visit preceding HCT/P recovery that is not documented as resolved." seems to be directed toward the recovery of HCT/Ps from a non-living donor who may have had sepsis as a co-morbidity. It also presumes that the donor had a healthcare facility stay or visit, which narrows the scope of the risk factor to be considered. For recovery of organs or tissue it is appropriate to review medical records. It should not be the case for collection of cellular blood components collected from healthy donors.

Requests:

1. For the collection of cellular starting materials (e.g. mononuclear cells or leukocytes) from healthy donors, please reconsider the requirement to review relevant medical records.
2. Please clarify if the term "recovery" includes the collection of cellular starting material from healthy donors.
3. Please clarify if any of the recommendations in Section IV. apply to cadaveric donors only.

COMMENT 5 - Cellular starting material (e.g. mononuclear cells or leukocytes) collected from healthy donors – Physical Evidence of Sepsis

C. Screening a Donor for Physical Evidence of Sepsis, page 5

Unless an exception identified in 21 CFR 1271.90(a) applies, in accordance with 21 CFR 1271.75(d)(1), you must determine to be ineligible any potential donor who has a risk factor for or clinical evidence of sepsis. The following is an example of physical evidence associated with disease agents that can cause sepsis:

1. Unexplained generalized rash or fever.

<u>For FDA's consideration</u>:

These comments are from the perspective of HCT/Ps collected as cellular starting material (e.g. mononuclear cells or leukocytes) from healthy donors. For such donors, rather than performing a physical examination specifically for rash or fever, it would be more appropriate to include a health history question about rash or fever under Section IV. A Screening a Donor for Risk Factors and Conditions of Sepsis.

Requests:

1. For the collection of cellular starting material (e.g. mononuclear cells or leukocytes) from healthy donors, please consider the addition of a health history question to replace the requirement to screen a donor for physical evidence of sepsis.

2. If the requirement is included, please clarify the process by which a cellular starting material (e.g. mononuclear cells or leukocytes) collection facility would perform a physical assessment of these donors to ensure they meet the required criteria for ruling out the risk of sepsis.

AABB (Association for the Advancement of Blood & Biotherapies) is an international, not-for-profit organization representing individuals and institutions involved in the fields of transfusion medicine and biotherapies. The Association works collaboratively to advance the field through the development and delivery of standards, accreditation and education programs. AABB is dedicated to its mission of improving lives by making transfusion medicine and biotherapies safe, available and effective worldwide.

Founded in 1962, America's Blood Centers is North America's largest network of community-based, independent blood programs. The network operates more than 600 blood donor centers providing over half of the U.S., and a quarter of the Canadian blood supply. These blood centers serve more than 150 million people and provide blood products and services to more than 3,500 hospitals and healthcare facilities across North America. America's Blood Centers' U.S. members are licensed and regulated by the U.S. Food and Drug Administration. Canadian members are regulated by Health Canada.

The American Red Cross shelters, feeds and provides emotional support to victims of disasters; supplies about 40 percent of the nation's blood; teaches skills that save lives; provides international humanitarian aid; and supports military members and their families. The Red Cross is a not-for-profit organization that depends on volunteers and the generosity of the American public to perform its mission. About 5.6 million units of whole blood are collected from roughly 3.3 million Red Cross volunteer donors, separated into 8 million transfusable blood products and supplied to approximately 2,700 hospitals and transfusion centers across the country for patients in need.

Thank you for the opportunity to offer these comments.

Sincerely,

[*signatures on file*]

Sharon Carayiannis	Kate Fry	J. Chris Hrouda
Vice President Science and Practice	Chief Executive Officer	President, Biomedical Services
AABB	America’s Blood Centers	American Red Cross