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-3863,** Recommendations to Reduce the Risk of Transmission of Mycobacterium tuberculosis (Mtb) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); Draft Guidance for Industry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(ARC) are pleased to submit joint comments to the U. S. Food and Drug Administration (FDA) in response to the May 2025 draft guidance, Recommendations to Reduce the Risk of Transmission of Mycobacterium tuberculosis (Mtb) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (Draft Guidance)

Our organizations appreciate the opportunity to comment on the Draft Guidance. We support FDA's dedication and mission to enhance the safety of HCT/Ps and to prevent the spread of Mtb and other 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align with the Joint Comments our organizations submitted to the original January 2025 Final Guidance which has been withdrawn.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 – Mtb testing has notable limitations and can sometimes produce a false-positive result.

Background:

Section IV. RECOMMENDATIONS

A. Screening a Donor for Risk Factors and Conditions for LTBI and TB Disease,

page 7

Unless an exception identified in 21 CFR 1271.90(a) applies, you must review relevant medical records and ask questions about the donor's medical history and relevant social behavior, including risk factors for RCDADs (21 CFR 1271.3(s), 21 CFR 1271.75(a)). You should also screen the birth mother when an infant donor is less than 1 month of age. In accordance with 21 CFR 1271.75(d), you must determine to be ineligible any potential HCT/P donor who is identified as having a risk factor for Mtb infection. The following should be considered risk factors:

1. *A positive test for TB infection or a medical diagnosis of TB disease, TB infection, or LTBI (regardless of treatment).*

The Centers for Disease Control and Prevention Clinical Testing Guidance for Tuberculosis: Tuberculin Skin Test, Test accuracy lists causes of False-positive results:

> *False-positive results*
>
> *Some persons may have a positive result from a TB skin test even though they are not infected with TB bacteria. The causes of these false-positive results may include, but are not limited to, the following:*
> - *Previous TB vaccination with the bacille Calmette Guérin (BCG) vaccine*
> - *Infection with nontuberculosis mycobacteria (mycobacteria other than M. tuberculosis)*
> - *Incorrect measurement or interpretation of reaction*
> - *Incorrect antigen used*

Requests:

1) Please clarify in the Recommendations section of the guidance that donor testing is not recommended at this time.

2) In cases where a donor reports a false-positive test for TB infection, the test result should be interpreted alongside clinical risk assessment, radiologic findings, vaccination history, and other relevant medical and diagnostic evaluations. Please provide an algorithm which may be used to make a donor eligibility determination for donors that report a false-positive test for TB infection.

COMMENT 2 – Defining "areas of the world where TB is common"

Background:

Section IV. RECOMMENDATIONS

A. Screening a Donor for Risk Factors and Conditions for LTBI and TB Disease, page 7

During review of relevant medical records, including the donor medical history interview, the following information should also be obtained and considered, in light of other information about the donor:

- *Persons who were born in or frequently traveled to areas of the world where TB is common (e.g., most countries in Latin America, the Caribbean, Africa, Asia, Eastern Europe, and Russia);*

Requests:

1) Please provide a definition of "frequently traveled" in order to ensure consistent interpretation and alignment with the intent of the guidance.

2) Please provide a clearer and more detailed definition of "areas of the world where TB is common".

3) Please specify the resources available for identifying countries with TB infection risk to assist organizations in making donor eligibility determinations.

COMMENT 3 – Cellular starting material (e.g. mononuclear cells or leukocytes) collected from healthy donors - Physical evidence of Mtb infection

Background:

Section IV. RECOMMENDATIONS

C. Screening a Donor for Physical Evidence of Mtb Infection, page 9

Relevant medical records (21 CFR 1271.3(s)) include the report of the physical assessment of a cadaveric (non-heart beating) donor (21 CFR 1271.3(o)) or the physical examination of a living donor. 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 HCT/P donor who has risk factors for or clinical evidence of TB infection. The following are examples of physical evidence associated with TB infection:

1. *Generalized lymphadenopathy.*

2. *Unexplained cutaneous lesions that may be consistent with tuberculosis.*

For FDA consideration:

These comments are from the perspective of HCT/Ps collected as cellular starting material from healthy donors. For such donors, rather than performing a physical examination specifically for generalized lymphadenopathy and unexplained cutaneous lesion, it would be more appropriate to include a health history question about swollen lumps in the neck, armpits, or groin that haven't gone away, or an unusual skin rash that cannot be explained under Section IV. A. Screening a Donor for Risk Factors and LTBI and TB Disease.

Request:

1. For the collection of cellular starting material (e.g. mononuclear cells or leukocytes) collected from healthy donors, rather than perform a physical examination specifically for generalized lymphadenopathy or unexplained cutaneous lesions, please consider the addition of a health history question to replace the requirement (as described above under FDA considerations) to screen a donor for physical evidence of LTBI and TB disease.

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 LTBI or TB infection.

COMMENT 4 – Domino transplants

Background:

Section IV. RECOMMENDATIONS includes an interim measure to perform mycobacterium cultures for bone, heart valves, and dura mater:

E. Additional Risk Measures, page 10:

During the investigation of both Mtb outbreaks in the U.S., mycobacterial cultures of bone product specimens showed growth, including when PCR testing was negative. Based on this information and considering the type of HCT/Ps that are known to have transmitted Mtb, performing AFB cultures for bone, heart valves, and dura mater can help mitigate the risk of Mtb transmission. Therefore, as an interim measure, until appropriate FDA-licensed, approved, or cleared donor screening tests for Mtb are available, we recommend:

1. *Manufacturers that process bone, heart valves, or dura mater should select appropriate liquid and solid mycobacterial cultures (AFB cultures) to test for presence of Mtb using appropriate pre-processing donor specimens when the disinfection or sterilization process used has not been validated to demonstrate the capability to eliminate contamination with Mtb. Both liquid and solid*

mycobacterial cultures should be performed, rather than either culture method alone.

The specimen selected for testing should be representative of the HCT/P to be evaluated. FDA recommends manufacturers evaluate the suitability of both AFB culture methods regarding use of adequate controls to detect inhibition and to use voluntary standards from a Standards Development Organization.

Domino Transplant:

The Health Resources & Services Administration (HRSA) organdonor.gov website describes a domino transplant:

> *A domino transplant occurs when patient A needs lungs, but the best treatment is to give that patient a heart and lung combination. Since patient A's heart was good, it can be transplanted into patient B who only needs a heart.*

HRSA's Organ Procurement & Transplantation Network Glossary describes:

> ***Domino Transplant***
>
> *A procedure in which an organ is removed from one transplant candidate and immediately transplanted into a second patient, with the first patient receiving a new organ from a deceased donor.*

The number of domino transplants is increasing. Facilities currently implant heart valves within 72 hours of harvest from domino heart donors who receive a deceased donor heart transplant and donate their own heart for partial transplantation. These living donors are highly screened for infectious disease risks prior to the heart transplantation. Given that mycobacterial cultures take 4 to 8 weeks to grow bacilli organism, the heart valve will have been implanted weeks before results. Heart transplant recipients are routinely screened for Mtb per Guidelines from the American Society of Transplantation Infectious Disease Community of Practice.

Request:

For a domino partial heart transplant, we request donor screening, combined with donor health and travel history and physical exam, to mitigate the risk of Mtb without the need to perform liquid and solid mycobacterial cultures.

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*]

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Vice President Science and Practice	Chief Executive Officer	President, Biomedical Services
AABB	America’s Blood Centers	American Red Cross