April 7, 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); 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 January 2025 final guidance, Recommendations to Reduce the Risk of Transmission of Mycobacterium tuberculosis (Mtb) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps) (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 spread of Mtb and other communicable disease agents linked to sepsis.

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 Mtb Infection, 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.*

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 more common"

Background:

Section IV. RECOMMENDATIONS

A. Screening a Donor for Risk Factors and Conditions for Mtb Infection, 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, have ever lived in, or ever 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 clearer and more detailed definition of "areas of the world where TB is common".

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

COMMENT 3 – Signs and symptoms of Mtb

Background:

Section IV. RECOMMENDATIONS

B. Screening a Donor for Clinical Evidence of Mtb Infection, page 8

A person with TB disease may have a number of symptoms or signs that can mimic or overlap with other medical conditions. A person with symptoms of TB disease may have one or more of the following types of clinical evidence of Mtb infection that should be considered when making a donor eligibility determination:

- *cough lasting 3 weeks or longer;*
- *chest pain;*
- *coughing up blood (hemoptysis) or sputum (pulmonary TB);*
- *weakness or fatigue;*
- *unexplained weight loss or muscle wasting (cachexia or consumption);*
- *loss of appetite;*
- *fever, chills, night sweats;*
- *generalized or localized lymphadenopathy or lymphadenitis;*
- *blood in the urine (renal TB);*
- *headache or confusion (TB meningitis);*
- *back pain (TB of the spine);*
- *hoarseness (TB of the larynx); or*
- *radiographic imaging (e.g., x-ray or CT scan) suggestive of TB disease.*

When a potential donor has one or more symptoms or signs above, you should document your communication with their primary treating physician to obtain additional information regarding their patient's potential for TB infection or LTBI, unless TB has already been ruled out by the patient's primary treating physician.

As described above, signs and symptoms have overlap with other medical conditions, many of which are not infectious. Without clarity from FDA, various interpretations of signs and symptoms can lead to an incorrect "ineligibility" determination. Contacting the "the primary treating physician" to obtain additional information and documentation is problematic, as many donors, particularly healthy living donors of hematopoietic progenitor/stem cells (HPCs) do not have a "primary treating physician" available. Lack of the availability of a "primary treating physician" should not result in a donor ineligibility determination.

Requests:

1) Please clarify how the specific signs and symptoms listed in the guidance differentiate clinical evidence of Mtb infection from other conditions and identify which of these signs and symptoms of Mtb would be cause for a donor ineligibility determination.

2) Living donors of cellular starting materials (e.g., Leukopaks) who are determined to be healthy, with no history of a positive TB test or a medical diagnosis of TB disease, TB infection, or LTBI, should not be considered at clinical risk for Mtb.

3) In addition, we request that the HCT/P establishment responsible person review and determine donor eligibility in consultation with the "primary treating physician" if applicable and available, when such information would be helpful in making a donor eligibility determination.

COMMENT 4 – Cellular starting material - 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.

Request:

Cellular starting materials intended for further manufacturing are generally collected from healthy living donors. Please clarify the process by which a cellular starting material collection facility (e.g., Leukopak) 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 5 – 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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