EYE BANK ASSOCIATION OF AMERICA

July 1, 2025

Vinayak K. Prasad, MD, MPH
Director
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

In Re: Docket No. FDA-2024-D-3863

Dear Dr. Prasad,

The Eye Bank Association of America (EBAA) appreciates the opportunity to provide comments to the May 2025 draft guidance entitled "*Recommendations to Reduce the Risk of Transmission of Mycobacterium tuberculosis by Human Cells, Tissues, and Cellular and Tissue-Based Products; Guidance for Industry*" [Docket No. FDA-2024-D-3863]

The EBAA is the world's oldest transplantation association, established in 1961 by the American Academy of Ophthalmology (AAO) and the nationally recognized accrediting and standards setting body for eye banks.

The association strives to ensure the superior quality of banked human eye tissue through the adoption and implementation of stringent medical standards, which are scientifically based, and specific to ocular tissue. The association is committed to "the restoration of sight worldwide," and works toward this vision by developing and delivering standards, accreditation, and educational programs that optimize patient and donor care and safety.

EBAA eye banks are non-profit organizations that recover, medically evaluate, process, and distribute ocular tissue for transplant, research, and education. In 2024, U.S. EBAA eye banks provided tissue for 85,926 sight-restoring corneal transplant surgeries.[1]

Corneal transplants performed in 2024 have a lifetime net benefit of $8.24 billion.[2] The Lewin study compared the medical cost of transplant procedures to the direct and indirect lifetime costs of the alternative – living with blindness or severe vision impairment. With a corneal transplant, an individual avoids the direct expenditures that come with vision loss, such as higher routine medical costs, long-term care costs, and the indirect costs of potential years of lost productivity to both the patient and their caregivers.

Executive Summary

EBAA appreciates FDA's commitment to protecting public health and reducing the risk of transmission of Mtb by HCT/Ps. However, we are concerned that FDA's guidance would have

a devastating effect on the availability of ocular tissue and will adversely impact the availability of life transformative tissue products for patients. This includes the over 51,559 Americans each year who receive sight-restoring corneal transplant surgeries. With an estimated 12.7 million people waiting for a corneal transplantation, only 1 donor cornea is available for every 70 people that require one worldwide.[3]

In addition, based on the EBAA's evaluation of annually collected data on all adverse events associated with ocular tissue transplantation and scientific review, there is currently no established risk of Mtb transmission with ocular tissue transplantation with present ocular tissue transplantation quality and safety standards.

Implementation of this guidance as written will require time to update the DRAI, draft new SOPs, create job aids, train staff in new procedures, and notify physicians and staff at both their recovery and transplant facilities what to expect under the new requirements. We will be faced with a decreased supply of ocular tissue, negatively impacting the quality and costs of the corneal grafts that remain available for transplant.

Thank you for rescinding the final guidance published January 7, 2025, and reissuing this draft guidance with an opportunity for feedback from the public and industry stakeholders before beginning work on the final guidance. We hope you will also schedule a public webinar to provide tissue establishments with FDA's regulatory requirements and expectations for donor eligibility determinations and address questions submitted by registrants.

Comments

The EBAA appreciates this opportunity to provide public comments on proposed Center for Biologics Evaluation and Research (CBER) regulatory requirements. On behalf of our member banks, we would like to offer these general comments for consideration:

COMMENT 1 – Agree that *Mycobacterium tuberculosis* (Mtb) is an RCDAD

EBAA agrees with FDA in identifying *Mycobacterium tuberculosis* (Mtb) as a relevant communicable disease agent or disease (RCDAD) as defined in 21 CFR 1271.3(r)(2), and the need for screening donors for evidence of, and risk factors for, infection with Mtb.

Mtb transmission via ocular tissue has not been reported; however, Mtb has been detected in ocular tissues and ocular TB can be a clinical manifestation of extrapulmonary TB. Ocular TB occurs in approximately 1-2% of TB cases, although higher rates have been reported in some areas of the world.[4,5] It is diagnosed based on the presence of characteristic ocular

signs; ancillary evidence of systemic TB (e.g., immunologic or radiologic tests); and the exclusion of alternative etiologies.[7]

Although the cornea is an avascular tissue, Mtb can disseminate via hematogenous spread from pulmonary TB or contiguous spread from more vascular components through the uveal tract.[7]

The Policy & Position Review Subcommittee (PPRS) of the EBAA Medical Advisory Board released an Alert entitled TB and Ocular Tissue Transplantation[6] on September 5, 2023, recommending the following donors be excluded from ocular tissue donation:

1) Individuals with a history (ever) of TB disease (sometimes referred to as "active" or "clinically active" TB)

2) Individuals with a history of latent TB infection initially diagnosed within the prior two (2) years (i.e., the individual has had a positive test for TB)

Donors with active ocular or intraocular inflammation, conjunctivitis, keratitis, scleritis, iritis, uveitis, vitreitis, choroiditis, or retinitis is an EBAA contraindication for transplant, per EBAA Medical Standard D1.110.

Although not recognized by FDA as a tissue establishment function, tissue evaluation is an essential eye banking function, which must be performed on all ocular tissue. Eyes are examined with a pen light or portable slit lamp prior to recovery. Corneal tissue is examined by slit lamp biomicroscopy and specular microscopy to identify infiltrates, scars, foreign bodies, or endothelial disease. This may help explain why Mtb transmission via ocular tissue has never been reported despite corneal transplants being performed globally, including Mtb endemic countries.

COMMENT 2: The guidance as written does not provide recommendations for interpretation of false positive results in diagnostic testing.

Section A - Screening a Donor for Risk Factors and Conditions for Mtb Infection
The guidance states that tissue establishments must determine to be ineligible any potential HCT/P donor who is identified as having a risk factor for Mtb infection. A positive test for TB infection or a medical diagnosis of TB disease, TB infection, or LTBI (regardless of treatment) should be considered risk factors.

Section B. Screening a Donor for Clinical Evidence of LTBI and TB Disease

In accordance with 21 CFR 1271.75(d), you must determine to be ineligible any potential HCT/P donor who exhibits clinical evidence of LTBI or TB. Examples of clinical evidence of LTBI or TB disease:

2. Persons who have ever had a positive test for LTBI or TB disease. For example, a positive blood test such as Interferon Gamma Release Assay (IGRA) (e.g., T-SPOT.TB, QuantiFERON-TB Gold Plus, QuantiFERON TB Gold In-Tube), a positive tuberculin skin test (TST) (also known as PPD, Mantoux, or tine test), or a positive test for TB infection on any specimen (i.e., mycobacterial culture, NAAT or PCR for Mtb DNA).

The Centers for Disease Control and Prevention Clinical Testing Guidance for Tuberculosis: Tuberculin Skin Test, Test accuracy[8] lists causes of false-positive results, including:

- 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

Your guidance acknowledges that BCG vaccine "can affect TST but does not affect IGRA" but does not allow for eligibility in donors who report a false-positive skin test for TB infection, in the absence of a positive IGRA test[9].

We are particularly concerned by the implication that a donor with a positive PPD test and a known history of BCG vaccination "shall" be deemed ineligible, despite the absence of any symptoms, exposure history, or radiographic findings. This does not enhance safety and risks excluding healthy donors without scientific justification; it will actually rule out a large portion of the population that may have been vaccinated.

Recommendation:
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.

Revise language regarding positive tuberculin skin test (TST, PPD, Mantoux, or tine test) results to allow eligibility in donors with:

- a known history of BCG vaccination,
- negative IGRA test
- no symptoms of active or latent TB, and

- no known Mtb exposure

COMMENT 3: FDA needs to define "frequently" with regard to travel history to TB endemic countries.

The guidance document directs tissue establishments to collect information about whether the donor was "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).

The donor might be eligible provided there is no clinical or physical evidence, or suspicion of LTBI or TB disease, and no communicable disease risks have been identified.

Recommendation:

EBAA recommends assessing donors for prolonged or repeated travel within a defined timeframe We recommend "within the past 2 years, a donor traveled for ≥ 3 months to a country with high TB incidence", as opposed to the wording currently listed in the guidance. The word frequently could be interpreted differently by eye banks and FDA inspectors.

COMMENT 4: We question the need to screen donors for occupational and residence histories and certain medical conditions in the absence of clinical or physical evidence or suspicion of LTBI or TB disease.

The guidance document also directs eye establishments to collect information about potential Mtb exposure risks, including:

> "Persons who have ever lived in or worked in high-risk congregate settings (e.g., jails, prisons, correctional facilities, long-term care facilities, homeless shelters); occupational exposure risks and past residence in high-risk congregate settings."
>
> "Persons who have certain medical conditions (e.g., diabetes, chronic kidney disease/end stage renal disease with or without dialysis), or are on medication, that can impair immune function."

These donors might be eligible provided there is no clinical or physical evidence, or suspicion, of LTBI or TB disease, and no communicable disease risks have been identified.

These Mtb risk factors are not included in the current UDRAI[10] and are inconsistent with current time-based deferral periods, such as the 12-month deferral for history of juvenile detention, lock up, jail or prison for more than 72 consecutive hours.[11] This would also

necessitate adding questions about the donor's occupational history and residence in long-term care facilities and homeless shelters.

Furthermore, eye banks are asked to consider persons who have certain medical conditions (e.g., diabetes, chronic kidney disease/end stage renal disease with or without dialysis), or are on medication, that can impair immune function to be at risk. These Mtb risk factors were not included in the recently released Eye-Only DRAI[12], as these medical conditions are not considered contraindications for ocular donors. We ask the FDA to provide evidence that there is any sensitivity to detection of TB infection by asking these questions in the absence of other known TB risks factors or symptoms.

Adding these new criteria to the DRAI is a process that would require months of planning and execution and increased costs. This is certainly not in keeping with Executive Order 14192 requirement for incremental costs significantly less than zero .

COMMENT 5: Clarification needed regarding autopsy concerns.

Regarding autopsy concerns for cadaveric donors, it is reasonable to defer potential donors who were denied an autopsy due to concerns over TB transmission. However, the process for identifying such rare cases requires clarification. Without this, inspectors might interpret the guidelines to mandate a documented inquiry with hospital pathology, Medical Examiner, or coroner for every donor to confirm that deferral for an autopsy was not linked to TB transmission concerns.

Recommendation:

To avoid unnecessary procedural burdens, we propose that the final language clearly state: "Donors who were deferred for an autopsy due to perceived risk of TB should be determined ineligible."

COMMENT 6: FDA needs to refine the criteria for screening donors for clinical evidence of TB disease.

B. Screening a Donor for Clinical Evidence of LTBI and TB Disease

The TB guidance lists a myriad of symptoms of TB disease that should be considered for DE determination, including:

- radiographic imaging (e.g., x-ray or CT scan) suggestive of TB disease,
- 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;
- Sterile pyuria (presence of white blood cells in the urine) with or without hematuria (blood in the urine) (renal TB);
- headache or confusion (TB meningitis);
- back pain (TB of the spine);
- hoarseness (TB of the larynx).

If a person has any of the signs or symptoms listed above and either (1) falls into any of the categories described in the bullets in section IV.A., or (2) there is physical evidence or a suspicion of LTBI or TB disease, when feasible and appropriate, you should communicate (and document your communication) with the potential donor's primary treating physician to obtain additional information regarding their patient's potential for TB infection or LTBI (unless TB has already been excluded and an alternative diagnosis has been established by the patient's primary treating physician).

The guidance acknowledges that these signs and symptoms can mimic or 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.

FDA needs to refine its criteria to focus on key indicative symptoms (e.g., radiographic imaging suggestive of MTB, hemoptysis, prolonged cough, night sweats, unexplained weight loss) which are included in the DRAI already to screen for Mtb, rather than these general, nonspecific symptoms (i.e., back pain, hoarseness, fatigue, and blood in urine).

The current Donor Risk Assessment Interview (DRAI) includes multiple screening questions to identify risk of Mtb, including many of these key indicative signs and symptoms. Adding these new criteria to the DRAI is a process that would require months of planning and execution and increased costs, for little benefit.

The recommendation to document your communication with the primary treating physician when a potential donor has one or more symptoms or signs above, to obtain additional information regarding their patient's potential for TB infection or LTBI, unless TB has already been ruled out has several troubling implications and exposes the physician to liability risks. Once again, this is not feasible for ocular tissue when tissue must be recovered, and donors' eligibility determined in a matter of days.

EBAA intends to interpret this recommendation to mean that the eye bank should contact the primary treating physician if clarification would be helpful to the donor eligibility determination, as is currently the standard practice within the industry.

Recommendation:

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 a cause for a donor ineligibility determination.
2. The guidance gives no usable framework for how to apply risk factors (Section IV .A.) during screening in the context of symptoms or medical history. This absence will lead to variability and confusion during implementation.
3. Add to the document an acknowledgment that conditions, explained by unrelated, definitive, or noninfectious diagnoses, should not result in a conclusion of MTB contraindication.

COMMENT 7: There are no donor screening tests for evidence of Mtb infection

There are currently no FDA-licensed, cleared, or approved donor screening tests for use in testing HCT/P donors for evidence of Mtb infection. Requiring extensive new testing protocols, including those that may not yet exist, risks imposing unreasonable burdens on eye banks and reducing the availability of safe tissue.

Even when ocular TB is suspected, attempts at microbiological detection of Mtb in ocular tissue via PCR and/or culture have shown variable results, with an inability to detect Mtb being common. This may be due, in part, to cases in which there is ocular inflammation without the presence of viable Mtb in ocular tissue.

Requiring manufacturers that process bone, heart valves, or dura mater to perform AFB cultures will do nothing to improve the safety and availability of corneal tissue, as these results would not be available on shared donors until months after corneal transplantation.

Conclusion

EBAA appreciates FDA's dedication to protecting public health and ensuring quality and safety of tissues for transplantation. However, we believe that issues identified in this draft guidance require clarification or revision, prior to release as a final guidance. We are committed to working with the Agency to ensure that its approach is evidence-based, risk-based, and does not inadvertently interfere with patients' access to cornea and tissue transplants.

Sincerely,

Kevin P. Corcoran, CAE
President & CEO
Eye Bank Association of America

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