EYE BANK ASSOCIATION OF AMERICA

January 17, 2025

Peter W. Marks, MD, PhD
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 and FDA-2024-D-3067

Dear Dr. Marks,

The Eye Bank Association of America (EBAA) appreciates the opportunity to provide comments in response to the Food and Drug Administration's final 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] and "*Recommendations To Reduce the Risk of Transmission of Disease Agents Associated with Sepsis by Human Cells, Tissues, and Cellular and Tissue-Based Products; Guidance for Industry; Availability*" [Docket No. FDA-2024-D-3067].

The EBAA is the world's oldest transplantation association, established in 1961 by the American Academy of Ophthalmology (AAO) and is 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 2023, U.S. EBAA eye banks provided tissue for 86,986 sight-restoring corneal transplant surgeries.[1]

Corneal transplants performed in 2023 have a lifetime net benefit of nearly $8 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.

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Executive Summary

EBAA appreciates FDA's commitment to protecting public health and reducing the risk of transmission of sepsis and 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 52,000 Americans each year who receive sight-restoring corneal transplant surgeries.

EBAA formally requests that the FDA rescind the final guidance documents, address the areas requiring clarification or revision, and reissue them in draft form. If the FDA is not willing to withdraw the guidance documents, then the agency should suspend implementation or consideration of the guidance during inspections, pending review and revision to address our comments.

While the guidance documents include boilerplate language that "FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities…" and "…should be viewed only as recommendations," in practice, we believe FDA inspectors will begin issuing citations and taking other enforcement actions against entities that do not comply with the new requirements contained in the two guidance, which represent such significant changes to eye banks' processes that they can't reasonably be implemented by February 3.

Given the potential impact to patient's access to cornea and tissue transplants, we believe it is critical for these two documents to be rescinded and, if necessary, reissued in draft form so that interested stakeholders can ask questions, provide feedback, and seek clarity on any new directives from the agency.

Barring a suspension, we will seek an extension of the implementation date to accomplish the same goals and to give us time to update the DRAI, and for eye banks to draft new SOPs, create job aids, train their staff in new procedures, and notify physicians and staff at both their recovery and transplant facilities what to expect under the new requirements.

Comments

The EBAA appreciates this opportunity to provide public comments on existing 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 – Level 1 guidance documents issued for immediate implementation.

The EBAA is astounded and troubled that the FDA issued new or updated guidance documents for immediate implementation, without first providing education to regulated industry describing your current thinking and expectations.

Recommendation: We encourage you to publish draft criteria (with an opportunity for feedback from the public and industry stakeholders) and immediately 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.

Rationale:

FDA identified sepsis as a relevant communicable disease agent or disease (RCDAD) under 21 CFR 1271.3(r)(2) when the August 2007 HCT/P DE Guidance was issued. Additionally, FDA released Important Information for Human Cell, Tissue and Cellular and Tissue-based Product (HCT/P) Establishments Regarding Tuberculosis Outbreaks Linked to a Bone Matrix Product on September 6, 2023. This alert outlined risk mitigation strategies to identify risk factors, conditions, clinical evidence, and physical evidence that can be associated with an increased risk for TB (including active TB and LTBI) and/or an increased risk of sepsis.

In response, EBAA has released recent guidance on screening potential donors for sepsis[3] and Mtb[4] and released updated versions of the Eye-Only DRAI (Donor Risk Assessment Interview) which will be implemented later this month. The final guidances are quite vague and it is unclear what FDA expects. Public education is needed to provide clarity to HCT/P establishments.

Comment 2 – There is no discretion to allow donation by a donor with a medical diagnosis of sepsis or suspicion of sepsis.

Recommendation: Allow for the assessment of a donor with a clinical diagnosis of sepsis during the hospital stay or other healthcare facility stay following consultation with the primary treating physician. This will allow donation when a source of infection was identified that was adequately treated prior to death or when the clinical record indicates that sepsis is resolved. Acknowledge/Allow that a single mention of possible sepsis does not constitute a diagnosis of sepsis.

Rationale

Literature review indicated that a diagnosis of sepsis impacts approximately 35% (at least one third of donors) of the potential in-hospital cadaveric HCT/P donor pool. AATB's pilot

study shows that the total percentage of donors who had either a sepsis diagnosis or met SIRS criteria constituted about 38% of charts reviewed[5]. Eliminating one third of our donor pool will severely reduce the donor supply, and thus patients' access to cornea and tissue transplants.

The CDC reports that, in a typical year, at least 1.7 million adults in America develop sepsis, at least 350,000 adults who develop sepsis die during their hospitalization or are discharged to hospice, and 1 in 3 people who die in a hospital had sepsis during that hospitalization.

The 2007 donor eligibility guidance[6] permits medical directors to accept donors when there was a clinical diagnosis of sepsis during the hospital stay when a source of infection was identified that was adequately treated prior to death or the clinical record indicates that sepsis is resolved. Additionally, the 2007 DE guidance permits medical directors to accept donors meeting SIRS/ SOFA criteria if they believe the symptoms are explained by an alternative diagnosis.

Electronic medical records (EMR) often produce exceedingly long, occasionally inaccurate notes with redundancy, inconsistency, and outdated information due to the use of copy and paste functions used by an overwhelming number of clinicians. This can result in the passive repetition of patient problem lists, even when some of the patient problems may have been completely resolved, resulting in discharge diagnosis lists which are not updated.

Eye banks have been under increased inspectional scrutiny regarding screening donors for risk factors and conditions of sepsis which has already led to a significant decrease in donors and cancelled surgeries. Reaching out to the responsible physician to identify donors with adequately treated infections and resolved sepsis has had some limited success and is the current recommendation from the EBAA Sepsis Working Group.

The guidance states that tissue establishments "must determine to be ineligible" any donor "known to have a medical diagnosis of sepsis or suspicion of sepsis," but provides no direction on what constitutes a "suspicion" of sepsis or who should be responsible for determining that there is a suspicion of sepsis.

We interpret this to mean that the reviewing medical director or designee must decide if there is a suspicion of sepsis after thoroughly reviewing the available medical records, laboratory testing, donor risk assessment interview, and autopsy findings. Furthermore, EBAA does not interpret that a single notation in the patient's electronic health records of possible sepsis, including the obtaining of cultures of blood and other bodily fluids to exclude infection as a cause of observed symptoms, is sufficient to trigger a finding of ineligibility.

Comment 3 – Unrealistic expectation of conferring with primary treating physician prior to making donor eligibility determination

B. Screening a Donor for Clinical Evidence of Sepsis

2. clinical evidence exhibited by a potential donor that is consistent with risk of systemic infection and whose immune system was weakened and unable to respond to infection (i.e., immunocompromised or immunosuppressed, such as due to age, a medical condition, or medication), or who is a sepsis survivor. In this scenario, you should document your communication with the patient's primary treating physician to obtain additional information regarding their patient's potential for higher risk of sepsis**.**

Recommendation:

Allow for the assessment of a donor with clinical evidence of sepsis during the hospital stay or other healthcare facility stay by qualified designees when the eye bank maintains and follows established protocols and/or algorithms as defined in approved standard operating procedures without consultation with the responsible physician.

Rationale

We agree that documentation of sepsis, bacteremia, septicemia, sepsis syndrome, systemic infection, systemic inflammatory response syndrome (SIRS) due to infection, or septic shock should make the donor ineligible. However, a single notation in the patient's electronic health records of possible sepsis, including the obtaining of blood cultures to exclude infection as a cause of observed symptoms, should be insufficient to trigger a finding of ineligibility.

The requirement to document your communication with the primary treating physician when the patient has a potential for higher risk of sepsis is not feasible for ocular tissue, when tissue must be recovered and donors' eligibility determined in a matter of days. Attending physicians and/or hospitalists are busy treating their living patients and will not respond to our calls to discuss the deceased potential donor. Formally consulting the primary treating physician on their perception of the risk of sepsis (or Mtb) beyond what was documented in the medical record can inadvertently expose those physicians to liability risks. This will strain our relationship with healthcare providers and cause an unnecessary burden on the healthcare system.

Furthermore, the examples listed for potential higher risk of sepsis due to weakened immune system would require consultation with the "primary treating physician" on *all*

immunocompromised donors. This includes criteria which are not currently rule outs for ocular tissue donors and will severely decrease the supply of corneal tissue.

A total of 56% of ocular donors are older than 60 years of age[1]. The Cornea Donor Study[7] showed that graft survival over a 5-year follow-up period using corneal tissue from donors 66 to 75 years of age is similar to graft survival using corneas from younger donors. Last year, 16.7% of ocular donors have cancer listed as their cause of death[1]. CDC reports that the prevalence of diabetes was 15.8% in all adults. Although eye banks do ask about diabetes in the DRAI, they do so for processing decisions, not for donor eligibility. The Eye-Only DRAI eliminated questions about renal dysfunction, as our PPRS did not consider this significant for ocular donors. Adding these new criteria to the DRAI is a process that would require months of planning and execution and are not scientifically based for ocular tissue.

The much more stringent donor screening requirements will increase eye banks' time, effort, and expense while sharply reducing the supply of corneal tissue in the United States, leading to inevitable delays and cancelations of surgeries due to a lack of tissue.

Sepsis, being neither specific nor diagnostic of transmissible infections by tissues, is taken into consideration as one item among many and is not the sole determinant of eligibility. Other factors evaluated include the medical, social, and behavioral history of the donor which determines epidemiologic exposures, immune status, susceptibility to infections and potential of harboring certain transmissible infections. The physical exam findings, laboratory, microbiological and imaging data are also evaluated.

Donor screening criteria for "sepsis" would best be aligned with the presence of a true systemic infection transmissible by tissues, not the physiologic response to an infection. Although there is a risk of transmission of ocular infections with corneal transplantation, there is currently no evidence to suggest that septic donors increase the risk of transmission of infections associated with corneal transplants.

Chu *et* al[8] compared outcomes of keratoplasty among 697 corneas from 356 donors, 70 of which were from bacteremic donors. Corneoscleral rim cultures showed similar microbial growth rates in grafts, 7.1% in bacteremic donors vs 9.1% in nonbacteremic donors (p=0.30). None of the contaminated corneas grew the same bacterial strains as those from their blood cultures. The most common contaminant was normal skin flora, supporting previous reports that bacterial contamination of donor corneas likely originates from external sources rather than internal infection. Furthermore, corneas from bacteremic donors had similar endothelial cell density (ECD) compared to those from non-bacteremic donors, and both groups had transplant success rates greater than 98%.

Spelsberg *et al*[9] conducted a similar study examining outcomes of transplantation of corneas from 91 donors with multiorgan failure secondary to sepsis and 809 from non-

septic donors. They showed similar rates of graft contamination between grafts taken from septic and non-septic donors (8% vs 11%), with the same finding that no microbes isolated from the contaminated grafts matched any pathogens isolated from the cadaver's blood. They also reported no cases of endophthalmitis in recipients from both groups, as well as similar rates of graft failure.

Vasiliauskaite *et al*[10] examined outcomes from septic versus non-septic donor grafts for Descemet membrane endothelial keratoplasty and found similar discard and contamination rates. They also reported that studies that showed higher contamination rates in grafts from septic donors did not find any matches between the pathogen of the graft culture contaminant and the septic donor.

In response to the recent FDA inspectional focus on donor eligibility with regard to sepsis, the EBAA released our May 17, 2024 Regulatory Alert[3] and formed a Sepsis Working Group to study the issue more closely. The Medical Review Subcommittee (MRS) reviewed[11] all 2023 infectious adverse reaction reports in OARRS (16 endophthalmitis and 13 keratitis cases). The MRS was asked to review the appropriateness of accepting the donor, whether the donor was septic prior to recovery, and the likelihood that sepsis was related to the recipient infection.

All but one donor was accepted consistent with existing protocols and FDA regulations. This donor had clinical evidence and a diagnosis of sepsis a few hours before death and should have been determined to be ineligible. One donor had pneumonia, and another had UTI as a source of infection, but did not fulfill the criteria for SIRS and consequently sepsis. However, there was no evidence to suggest that SIRS transmitted infection to the recipient, as there was no match in cultures between donor and recipient, including the septic donor associated with an ocular infectious adverse event.

Comments Specific to the Mtb Guidance Recommendations

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.

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 should be considered risk factors.

The Policy & Position Review Subcommittee (PPRS) of the EBAA Medical Advisory Board released an Alert entitled TB and Ocular Tissue Transplantation[4] 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)

While the recently released Eye-Only DRAI specifically asks whether the donor EVER had tuberculosis or a positive skin or blood test for tuberculosis, the new FDA guidance does not consider whether the donor had been adequately treated for their LTBI.

The guidance document also directs eye establishments to collect information about potential Mtb exposure risks, including occupational exposure risk and current residence in a nursing home, as part of the DRAI process. 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. Adding these new criteria to the DRAI is a process that would require months of planning and execution.

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.

B. Screening a Donor for Clinical Evidence of Mtb Infection

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

- 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.

Most of these symptoms are included in the Eye-only DRAI, but some others are too general and nonspecific (i.e., back pain, hoarseness, and blood in urine).

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.

Conclusion

EBAA appreciates FDA's dedication to protecting public health and ensuring quality and safety of tissues for transplantation. However, we believe the magnitude of issues identified in these documents necessitates that the agency rescinds the final guidance documents, address the areas requiring clarification or revision, and reissue them in draft form. 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

EYE BANK ASSOCIATION OF AMERICA

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