American Association of Tissue Banks®

January 15, 2025

Peter Marks, MD, PhD
Director
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Dear Dr. Marks,

The American Association of Tissue Banks (AATB) appreciates the opportunity to provide comment, as you requested, regarding the following two final guidance documents published by FDA on January 6, 2025:

- Recommendations to Reduce the Risk of Transmission of *Mycobacterium tuberculosis* (Mtb) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps); and

- 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).

AATB is a professional, non-profit, scientific, and educational organization. AATB is the only national tissue banking organization in the United States, and its membership totals more than 120 accredited tissue banks and over 7,000 individual members. These banks recover tissue from more than 70,000 donors and distribute in excess of 3.3 million allografts for more than 2.5 million tissue transplants performed annually in the US. The overwhelming majority of the human tissue distributed for these transplants comes from AATB-accredited tissue banks.

This letter is based on feedback received by AATB from dozens of technical, scientific, and medical subject matter experts from accredited tissue banks. Our industry has significant concerns with the content and timeline of implementation of the two final guidance documents as written and their possible impact on the availability of tissue for patients in need, and we believe there are too many areas requiring clarification or revision to allow for the effective

implementation of the recommendations in these documents. The information in this letter provides a summary of our most salient questions and concerns; where appropriate, we have included our interpretation of the provisions or requests for clarification from the agency.

In light of these concerns, we ask that the agency 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 comments.

While FDA guidance documents generally contain nonbinding recommendations, AATB is aware that these two final guidance documents outline ways to achieve regulatory compliance (e.g., screening for sepsis and Mtb risk factors) and, as such, might serve as the basis for FDA 483 observations and subsequent compliance actions. AATB also believes that these two guidance documents include truly advisory recommendations that the agency does not intend to use as the basis for compliance actions (e.g., Mtb product testing). We request clarification and confirmation from the agency on which recommendations presented in the guidance documents will or will not be the basis for compliance decisions. This clarification will be essential for our ability to understand and plan for the operational impact of the two guidance documents.

Tissue Community Response to Mtb Outbreaks of 2021 and 2023

AATB and our members share FDA's goal of preventing the spread of Mtb, communicable disease agents associated with sepsis, and other communicable diseases. AATB acted after each incident – first, in 2022, providing recommendations on approaches to manufacturing and donor screening intended to reduce the risk of Mtb transmission – and again in 2023, when AATB published interim donor-eligibility requirements. The final requirements were published in 2024 and incorporated into the 15th edition of AATB's *Standards for Tissue Banking*.

Our work was led by the AATB Physicians Council, which recognized the need to establish robust guidance to assist tissue establishments in screening and evaluating tissue donors for evidence of and potential risk factors for Mtb infection. As Mtb appeared to represent the most immediate public health threat, the Physicians Council first convened a working group in January 2023 once details of the first Mtb investigation were made available.[1] The working

[1] Schwartz NG, Hernandez-Romieu AC, Annambhotla P, Filardo TD, Althomsons SP, Free RJ, Li R, Wilson WW, Deutsch-Feldman M, Drees M, Hanlin E, White K, Lehman KA, Thacker TC, Brubaker SA, Clark B, Basavaraju SV, Benowitz I, Burton Glowicz J, Cowan LS, Starks AM, Bamrah Morris S, LoBue P, Stewart RJ, Wortham JM, Haddad MB; Bone Allograft Tuberculosis Investigators. Nationwide tuberculosis outbreak

group comprised tissue establishment medical directors, including infectious disease experts. It received lectures from invited subject matter experts from the Centers for Disease Control and Prevention (CDC) and US Department of Agriculture.

The working group identified several unique challenges posed by Mtb infection that required additional screening measures not currently in place for other infectious disease risks. These challenges included the absence of an FDA approved and effective postmortem screening test, difficulties with microbiological culturing techniques, and the lack of specificity in clinical symptoms. The working group reviewed scientific literature and analyzed epidemiologic data to identify risk factors for both exposure and reactivation of Mtb infection. Considering that Mtb (an intracellular pathogen) organisms require living cells to remain viable in tissue and the differences in tissue processing methods, the group stratified risk factors into those for highly processed tissues and those for tissues containing viable cells.

These risk factors, along with recommendations for donor screening, were published in 2024.[2] The recommendations were incorporated into the aforementioned updated AATB S*tandards* to be implemented on January 31, 2025. Furthermore, the AATB Scientific and Technical Affairs Committee (STAC) has been working to evaluate the applicability of tissue radiation methods to eliminate Mtb and is in the process of submitting a manuscript for peer review.

The Physicians Council is also aware that sepsis has been identified by the FDA as a relevant communicable disease agent or disease (RCDAD) and is a risk factor for Mtb infection. However, Mtb infection rarely presents as clinical sepsis, and clinical sepsis is rarely caused by Mtb. The working group believes the evidence-based approach presented in the manuscript provides the most effective measures for reducing Mtb risk while maintaining a balance between safety and tissue availability. Furthermore, given the many overlapping risks for Mtb and sepsis, the working group believes AATB's new Mtb exclusion criteria would already lead to a winnowing of donors at risk of sepsis, such that there would be fewer sepsis rule-out cases not already excluded by the new Mtb exclusionary criteria.

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in the USA linked to a bone graft product: an outbreak report. Lancet Infect Dis. 2022 Nov;22(11):1617-1625. doi: 10.1016/S1473-3099(22)00425-X. Epub 2022 Aug 4. PMID: 35934016; PMCID: PMC9605268.

[2] Greenwald MA, Edwards N, Eastlund DT, Gurevich I, Ho AP, Khalife G, Lin-Torre J, Thompson HW, Wilkins RM, Alrabaa SF. The American Association of Tissue Banks tissue donor screening for Mycobacterium tuberculosis-Recommended criteria and literature review. Transpl Infect Dis. 2024 Nov;26 Suppl 1(Suppl 1):e14294. doi: 10.1111/tid.14294. Epub 2024 Jun 9. PMID: 38852068; PMCID: PMC11578281.

Upon completion of the Mtb criteria, AATB convened a working group of tissue establishment medical directors to develop additional guidance and recommendations in evaluating tissue donors for sepsis. The working group recognizes the particularly complex challenge associated with sepsis, as it is a physiological syndrome with significant overlap of signs and symptoms with many noninfectious disease states. Given the high risk of morbidity and mortality associated with sepsis and to expedite testing and empiric treatment, many clinicians have a low threshold for considering possible sepsis in their differential diagnosis.

It is the opinion of the Physicians Council that it is not the presence of organ dysfunction per se but rather systemic infection that poses the risk for infectious disease transmission. The working group believes that tissue bank medical directors are well-positioned to assess systemic infection risk, as they usually have more objective data available than the treating clinician had prior to the donor's death. The goal of the working group is to establish clear, meaningful, and objective criteria that will allow medical directors to use an evidence-based approach to evaluate donors for the presence of or risk factors for systemic infection.

AATB has been awaiting the FDA's publication of these related guidance documents, which we had hoped would complement AATB's published requirements. We are disappointed to note that both guidance documents would have benefitted significantly from more robust and collaborative dialogue with the industry, as many of the recommendations in the guidance documents are impractical or unclear. Despite these tragic events, the Mtb risk posed by tissues to recipients remains low and has been further reduced by AATB's recent actions. The approach outlined in the guidance documents is particularly concerning because, if interpreted broadly, it may result in making otherwise safe tissue unavailable to patients in need.

Cross-cutting Issues in Both Guidance Documents

There are two cross-cutting issues of concern in these documents. The first is that they appear to recommend extensive consultation with the donor's "primary treating physician" in order to rule out the possibility of Mtb or sepsis. Second, both guidance documents recommend implementing the changes within four weeks (i.e., by February 3, 2025). Given the significant impact on tissue establishments and the broad need to clarify many issues, only a small number of which are raised in this letter, this timeline is not feasible.

With respect to the role of the primary treating physician, absent additional clarification from FDA, AATB intends to interpret both guidance documents to mean that the medical director of the tissue establishment 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.

The licensed medical director at the tissue establishment, after thoroughly reviewing the available medical records, laboratory testing, tissue culture results, donor risk assessment interview, and autopsy findings, is better positioned to accurately assess the donor's risk for infectious disease transmission.

Issues Specific to the Sepsis Guidance Document

The sepsis guidance document includes a number of provisions in section IV, Recommendations, that can be applied very broadly, resulting in significant hurdles to the determination of eligibility for any previously hospitalized donor.

Section A – Screening a Donor for Risk Factors and Conditions of Sepsis

The guidance reflects the regulations in that tissue establishments "must determine to be ineligible" any donor with a risk factor for sepsis. It goes on to state that individuals "known to have a medical diagnosis of sepsis or suspicion of sepsis" should be considered to have a risk factor, 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.

AATB interprets this to mean that the reviewing medical director must decide if there is a suspicion of sepsis based on their review of all clinical records, final culture results, pre-processing culture results, and other relevant medical records. Furthermore, AATB 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.

As previously noted, AATB is in the process of developing educational resources that include criteria for what constitutes a "suspicion of sepsis." In the meantime, AATB anticipates that accredited banks will rely on their own internal criteria and procedures to ascertain a "suspicion of sepsis."

Section B – Screening a Donor for Clinical Evidence of Sepsis

This section indicates that establishments "must determine to be ineligible" potential donors who exhibit clinical evidence of sepsis (citing 21 CFR 1271.75(d)), with two examples provided in a separate sentence. The lead-in to those two examples states, "[e]xamples of clinical evidence of sepsis may include:..." In contrast, the 2007 donor eligibility guidance leads into the examples of clinical evidence of sepsis by stating, "[e]xcept as noted in this section and in accordance with §1271.75(d), you should determine to be ineligible any potential donor who

exhibits one or more of the following examples of clinical evidence of relevant communicable disease."

The different language used in the two guidance documents – shifting from a clear description of clinical evidence that provides the basis for a finding of ineligibility to the current wording, which provides two examples of clinical evidence only - creates ambiguity in the interpretation of the new final guidance. Absent further information provided by FDA, AATB interprets both examples to be illustrative and that the tissue establishment medical director continues to have final decision-making authority as to what constitutes clinical evidence of sepsis.

Of the two examples provided in this section, the second advisory example is difficult to interpret. That second example notes that examples of clinical evidence of sepsis may include "clinical evidence…consistent with risk of systemic infection" among immunocompromised individuals, rather than providing specific clinical signs or symptoms that are indicative of sepsis. Furthermore, there appears to be a recommendation to consult with the "primary treating physician" on *all* immunocompromised donors, which is not consistent with current industry practice and has several troubling implications. One principal concern would be that 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. In the event of increased liability risks, real or perceived, treating physicians may be unwilling to share information or insights with tissue establishments.

In addition to the unresolved issues around assessing the donor's sepsis risk, we note that the previous donor eligibility guidance sepsis criteria included a provision for the possibility that a donor may be found eligible when there is a subsequent "rule-out" of sepsis in the medical records.[3] AATB strongly believes that this provision is appropriate, and medical directors intend to continue to find eligible donors who have clinical evidence that sepsis was appropriately "ruled out" through review of the relevant medical records.

Issues Specific to the Mtb Guidance Recommendations

This guidance seems to introduce a new expectation for product testing in section IV.E. Although this expectation is stated as a recommendation, the regulations cited in footnote 10 (21 CFR 1271.220(a) and 1271.145) leave ambiguity as to whether FDA intends to cite tissue establishments upon inspection if they have not performed the extensive design control and

[3] IV.E. 12. Persons who are deceased and have a documented medical diagnosis of sepsis or have documented clinical evidence consistent with a diagnosis of sepsis that is not explained by other clinical conditions at the time of death. *For example, if a statement such as "rule-out sepsis" is noted in the medical records, and subsequent notations indicate a diagnosis other than sepsis, a potential donor might still be eligible.*

validation for such testing to be implemented. The timeframe needed to implement Mtb product testing would range from several months to a year or longer, especially if all tissue establishments in the US are simultaneously trying to arrange for testing services from a limited number of qualified laboratories. As such, absent further clarification from FDA, accredited tissue establishments will consider this to be advisory in nature, and the decision to implement product testing will remain an establishment-specific determination. AATB will also continue to evaluate the feasibility of implementing and the appropriateness of requiring product testing, which is under discussion with our Scientific and Technical Affairs Committee.

The guidance document also directs tissue establishments to collect information about two potential Mtb exposure risks, occupational exposure risk and current residence in a nursing home, as part of the DRAI process. These Mtb risk factors were not included in AATB's recently updated and already published donor screening requirements and, therefore, were not included as questions within the soon-to-be-implemented DRAI. Adding these new criteria to the DRAI is a process that would require months of planning and execution.

We are particularly disappointed that the FDA Mtb guidance does not incorporate any of the criteria advanced by AATB in response to the tragic Mtb transmissions, including clarity on exposure versus reactivation risk criteria and a delineation of risk between products that contain viable cells and those that do not. To our knowledge, there have not been any cases of Mtb transmission through tissues that do not contain viable cells since the FDA began regulating HCT/Ps in 1993.

AATB's Next Steps

While we await clarification on the issues raised in this letter, AATB will continue to activate its councils and working groups to address communicable disease risks associated with sepsis. We believe that the most effective approach to evaluating donors for these risks will mirror current clinical practice, which relies on a matrix of factors such as age, history and physical examination, risk factors for exposure to various specific infectious agents, social, behavioral, and epidemiological exposures, host immune system, and evaluation of the completeness of infectious disease workup done. These criteria will then be stratified by tissue type, where tissues containing viable cells or those that are minimally processed will have the strictest criteria as opposed to those that are irradiated and terminally sterilized. As an example, a 20-year-old who suffers head trauma in a motor vehicle accident and develops fever and tachycardia while in the ICU will automatically trigger sepsis workup. If the workup during the hospital stay is negative for infection, such donor, in an abundance of caution, may still not be eligible for viable tissue donation but could instead be eligible for irradiated tissues such as bone, tendons, and skin. This approach to sepsis evaluation will be informed by

recommendations from the CDC, Infectious Disease Society of America, and European Society of Clinical Microbiology and infectious Diseases.

With respect to Mtb, AATB has already required the adoption of a number of evidence-based exclusionary criteria that are likely to significantly reduce the risk of Mtb from tissues. We will continue to engage our members on this topic and will monitor the adoption and impact of these new criteria on tissue safety and availability.

Conclusion

AATB's Standards and Accreditation programs are an important resource for the industry, and we are committed to the safety and quality of transplanted tissue. Historically, AATB has incorporated FDA regulations and guidance documents into our *Standards*. We are concerned that the lack of clarity in these guidance documents presents a real barrier to consideration of these new criteria, and **we are unable to incorporate either the FDA Mtb or sepsis final guidance into the *Standards for Tissue Banking* until these issues are resolved.**

Given the issues we have identified, we reiterate our request that the agency rescind the final guidance documents, resolve the issues raised in this letter and in other comments, and reissue the recommendations in draft form. Doing so would provide affected stakeholders working in good faith sufficient time to implement the recommendations and allow the agency to resolve the aforementioned issues to ensure the documents are clear, well understood by users and investigators, and carefully tailored to ensure the safety of transplanted tissue.

We appreciate the FDA's demonstrated willingness to issue and revise final guidance documents for immediate implementation as necessary, including during the COVID-19 public health emergency. However, we believe the magnitude of issues identified in these documents necessitates that the agency rescind the final guidance documents, address the areas requiring clarification or revision, and reissue them in draft form. We look forward to working with the FDA to resolve the issues of concern in these two final guidance documents in order to ensure safety and preserve the availability of tissue for transplantation in the US.

Regards,

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