American Association of Tissue Banks®

AATB Statement on Ongoing Concerns and Formal Request for Rescission of Sepsis and MTB Guidance Documents Following Meeting with OMB

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Today, the American Association of Tissue Banks (AATB) met with the Office of Management and Budget (OMB) to reiterate our ongoing concerns with two guidance documents issued by the US Food and Drug Administration (FDA) on January 6, 2025, as final:

- *Recommendations to Reduce the Risk of Transmission of Mycobacterium tuberculosis (Mtb) by HCT/Ps*
- *Recommendations to Reduce the Risk of Transmission of Disease Agents Associated with Sepsis by HCT/Ps*

These documents were released by the previous Administration as final guidance on January 6, 2025, with an original implementation date of February 3. Although the current Administration delayed enforcement until May 4, 2025, the FDA has not addressed the many issues AATB raised in an eight-page letter submitted to Dr. Peter Marks on January 15.

AATB is a non-profit, professional, scientific, and educational organization representing more than 120 accredited tissue banks and over 7,000 individual members. Our member establishments manufacture tissue products used in hospitals nationwide every day for patients needing life-transformative tissue implantations. We sincerely appreciate the FDA's mission and share its commitment to safety and public health. However, we believe these guidance documents are deeply flawed.

At today's meeting, I formally requested that the Administration rescind both guidance documents. The recommendations outlined in the guidance are unclear, complex, or in some cases impossible to implement, and will likely lead to significant reductions in the availability of tissue grafts. The sepsis guidance alone could limit access to these products by up to 40%.

We are particularly concerned that these documents were rushed to implementation without sufficient stakeholder engagement, scientific rationale, or practical considerations. Although FDA guidance is technically nonbinding, in practice, FDA investigators often reference guidance documents in their 483 observations and subsequent warning letters, so for our industry, these guidance documents really are de facto regulations.

AATB is not alone in raising these concerns. Leading organizations across healthcare—including AdvaMed, the Medical Device Manufacturers Association, the Society of Thoracic Surgeons, the Eye Bank Association of America, the Association for the Advancement of Blood and Biotherapies, and others—share our views.

AATB's Vice President of Accreditation, Regulatory Affairs, and Standards, Eduardo Nunes, and Chief Medical Officer, Dr. Melissa Greenwald, joined me during the meeting to further articulate our concerns with both guidance documents.

Mtb Guidance

Eduardo Nunes acknowledged two tragic outbreaks of Mtb linked to human tissue transplants in 2021 and 2023. In response to these incidents, AATB acted swiftly and responsibly by issuing educational updates and manufacturing recommendations to reduce the risk of Mtb transmission. In 2023, AATB published interim requirements for excluding donors who may present a risk of Mtb, with a focus on donors aged 65 and older—an evidence-based decision supported by a review of scientific literature and epidemiologic data.

These requirements were developed by a working group of physicians with expertise in tissue safety and donor eligibility. The group stratified risk factors based on whether tissues contained viable cells, as Mtb is an intracellular pathogen requiring living cells for viability. This distinction was critical, as the documented Mtb transmission events have been associated with minimally processed, viable-cell-containing tissues. The exclusion criteria also effectively mitigate sepsis risk, since most donors with sepsis would also be excluded under the age-based requirements.

Despite repeated outreach from AATB, the FDA's Center for Biologics Evaluation and Research (CBER) did not engage in dialogue or participate in AATB's work on these critical safety standards. This lack of collaboration has contributed to problematic elements in the FDA's guidance, particularly concerning treating physician consultation and new product testing expectations.

AATB has significant concerns regarding the FDA's guidance documents' directive for tissue establishments to consult the treating physician in cases of uncertainty about both Mtb and sepsis. In practice, donor eligibility determinations often occur weeks or months after death, making meaningful consultation with a hospitalist, who may have only briefly interacted with the patient, impractical and legally precarious. Such physicians may be reluctant to make postmortem assessments due to liability concerns, and these consultations rarely yield useful information. While consultation with care providers can be valuable, this typically involves outreach to those with long-term knowledge of the patient, such as a primary care provider. The guidance's emphasis on routine consultations with treating physicians reflects a misunderstanding of real-world clinical workflows.

AATB is also concerned about the implications of the FDA's Mtb guidance for new product testing requirements. While infectious disease risk is typically managed through donor screening and testing, no licensed donor screening assay currently exists for Mtb. The expert working group concluded that product testing is not feasible due to the absence of tests designed for this purpose or population. Further, a widespread push for testing would strain the limited capacity of qualified laboratories. Despite these limitations, the FDA guidance cites regulations in footnote 10 (21 CFR 1271.220(a) and 1271.145), suggesting that such testing could be interpreted as mandatory—because we have not received any clarification from the agency, tissue establishments are at the moment wholly unsure of FDA's expectations concerning Mtb testing.

This ambiguity has already caused confusion and the potential for regulatory risk within the tissue banking community. AATB believes the FDA's decision to issue guidance without engaging with industry stakeholders, including AATB, resulted in missed opportunities for clarity, collaboration, and scientifically sound policymaking. The FDA's failure to distinguish between exposure and reactivation

risk, or to recognize the critical differences between tissues with viable cells and those without, has undermined the effectiveness and practicality of their guidance.

AATB's criteria, which are more comprehensive than the FDA's guidance, were developed transparently and with expert consensus. We maintain that many of these concerns could have been addressed preemptively if the FDA had collaborated with AATB and the broader community.

Sepsis Guidance

Dr. Melissa Greenwald highlighted that following the completion of work on Mtb, AATB convened an expert working group of tissue establishment medical directors to develop additional requirements for evaluating tissue donors for sepsis. This group recognized the complexity of assessing sepsis risk, given that it is a physiological syndrome with overlapping symptoms seen in many noninfectious conditions. The working group emphasized that the genuine concern for tissue donation is the presence of a systemic infection, not the clinical syndrome of sepsis itself.

Due to the potentially severe consequences of sepsis and the urgency it demands in clinical settings, many physicians adopt a low threshold for considering it in their differential diagnosis. However, the FDA has addressed industry concerns about the number of individuals evaluated for sepsis syndrome, referencing a retrospective study of claims data from 2009–2014 that showed no increase in sepsis diagnoses among hospitalized individuals. AATB believes this study does not address the subset of patients who might be candidates for tissue donation. Furthermore, the study acknowledged challenges in accurately diagnosing sepsis, citing limitations of claims data, changes in diagnosis and coding practices, and the impact of evolving epidemiology—issues that directly mirror AATB's concerns.

To better understand the potential impact of more conservative sepsis screening criteria, AATB reviewed additional literature and conducted its own pilot study. The results suggested that such criteria could significantly reduce the number of eligible tissue donors by as much as 40%. These findings were shared with the FDA in 2024. However, it remains unclear how the implementation of the sepsis guidance would affect donor availability because it is not yet known which elements of the 2025 guidance are considered mandatory versus advisory.

The working group asserts that tissue establishment medical directors are better equipped than treating physicians to evaluate sepsis risk in potential donors, as they often have access to comprehensive post-mortem data, including final culture results and autopsy findings. The medical director's role is distinct from that of the treating physician, who is not responsible for assessing tissue donor eligibility.

AATB calls for an evidence-based approach allowing medical directors to evaluate donors for systemic infection. The current FDA guidance does not provide this. Instead, it introduces broad provisions that could lead to the unnecessary exclusion of donors, especially those who had been hospitalized. The guidance instructs establishments to rule out donors with either a diagnosis or a "suspicion" of sepsis. Yet, it does not clarify what constitutes a suspicion or who is qualified to make that judgment. To date, the agency has not provided any clarification on this issue.

AATB strongly objects to the idea that routine notations in medical records—such as documentation of a sepsis concern or the ordering of cultures—should automatically disqualify a donor. The guidance also states that potential donors showing "clinical evidence" of sepsis must be deemed ineligible, referencing regulatory language (21 CFR 1271.75(d)) but offering vague examples. One example refers to immunocompromised individuals with signs "consistent with risk of systemic infection." It would be

clearer if the FDA provided specific clinical signs or symptoms indicative of sepsis among immunocompromised individuals, or stated that special attention should be paid to that population when evaluating donors for systemic infections.

Additionally, the guidance appears to suggest consulting with the donor's primary treating physician in all cases involving immunocompromised individuals. This is not standard practice in the industry and raises concerns about increased liability for those physicians, which could discourage their cooperation with tissue banks.

Overall, AATB is concerned that the current language and lack of clarity in the FDA's sepsis guidance will increase operational costs and unnecessarily reduce the availability of otherwise safe tissue for transplant.

Conclusion

Tissue donation—like blood or organ donation—is a profoundly altruistic act, often made by donors or their families during moments of profound personal loss. Each tissue graft is a one-of-a-kind biological product, generously offered by a single donor to help a patient in need. Because these donations are human-derived, they carry inherent risks, making rigorous safety measures essential to protect recipients.

While the impact of tissue donation is extraordinary, transforming and even saving lives, we must also remain aware of our responsibility. Despite our best efforts, mistakes can happen. Acknowledging this is not a sign of failure but a call to continually strive for better, safer practices in honoring the generosity of donors and the trust of recipients.

In summary, we respectfully urge the Administration to rescind these two guidance documents and instruct the FDA to work collaboratively with the tissue banking community to develop practical, evidence-based strategies to protect patient safety and tissue access.

Our members remain ready and willing to work in good faith with regulators to achieve our shared goal: a safe, reliable, and accessible tissue supply for all who need it.