American Association of Tissue Banks®

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Director
Center for Biologics Evaluation and Research (CBER)
Food and Drug Administration
10903 New Hampshire Avenue
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Dear Dr. Prasad,

The American Association of Tissue Banks (AATB) appreciates the opportunity to comment on the Food and Drug Administration (FDA) draft guidance document titled, "Recommendations to Reduce the Risk of Transmission of Mycobacterium tuberculosis (Mtb) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)." AATB appreciates that the agency has taken the important step of reissuing this guidance in draft form rather than as a direct-to-final guidance document for immediate implementation, and we recognize that this document contains important revisions compared to the previous version from January.

AATB understands and supports the agency's classification of Mtb as a relevant communicable disease agent or disease (RCDAD). However, AATB is concerned that current risk mitigation options for Mtb are imperfect and operationally challenging. This concern is particularly true of testing for Mtb, which the guidance document recommends as part of pre-processing product testing. **It is our interpretation that the recommendations around product testing in the guidance are purely advisory in nature rather than as a required step to satisfy current FDA regulations.** If this is not consistent with FDA's interpretation and intent, we urgently request that the agency engage with industry to clarify the intent of the guidance; make significant revisions to the draft guidance document to clarify the actual intent; and indicate how certain elements of the guidance will be enforced by FDA investigators.

In drafting this letter, AATB solicited feedback from dozens of technical, scientific, and medical subject matter experts from accredited tissue banks.

The ideal approach to Mtb risk mitigation would be a reliable and accurate donor screening test to use in addition to exclusion criteria; however, there are a number of unresolved issues and challenges associated with the currently available options for microbiological testing of human tissues for transplantation for Mtb. These include sample issues (size, location and number) to ensure accurate and useful results.

In recognition that the current testing options have limited utility, AATB is leading an industry-wide effort to develop strategies to help tissue establishments determine which products should be tested. The criteria will speak to underlying epidemiology, risk factors, testing considerations, and risk mitigation through product manufacturing choices (e.g., irradiation, terminal sterilization).

Until the challenges associated with currently available microbiological testing options are resolved, such results are unlikely to yield useful information. In recognition of these limitations, AATB will continue to prohibit, through its Standards, the manufacturing of tissues containing viable cells from individuals with certain higher risks.

Finally, we also note that the implementation of targeted product microbiological testing for Mtb will require a long implementation period to address potential challenges, including those related to false negatives; should the agency consider it necessary to expand the approach to testing, we reiterate our request that the agency engage in extensive consultation with industry to ensure that the expectations and timeframes for implementation are appropriate.

AATB appreciates FDA's efforts to address these challenging issues, and we look forward to augmenting these efforts through our own initiatives. We also have a number of more specific questions and concerns, which are detailed in the pages to follow.

I. Concerns with Mtb Testing

These comments outline the challenges of microbiological culture testing of cadaveric human tissue for Mtb with sufficient scientific rigor to reduce the risk of Mtb transmission via human tissue allografts. AATB's Scientific and Technical Affairs Committee is in the process of assessing the many challenges that need to be addressed in order for industry-wide Mtb culture testing to be practicable. In the meantime, AATB feels it is important to highlight the nature of these challenges, which are far more complex than would be the case with instituting standard microbial cultures.

The recommendation to perform Mtb cultures of heart valve, bone, and dura mater - unless processed using a method validated to eliminate Mtb - appears to position culture testing as an interim donor screening tool. While Mtb cultures are recognized for their high specificity and are considered the gold standard for clinical diagnosis of tuberculosis, their sensitivity is limited, particularly in cases where bacterial load is low. This limitation is especially pronounced in the context of random sampling from donors without clinical suspicion of tuberculosis, where the likelihood of detecting Mtb is exceedingly low.

AATB has concerns about the ability to simply adopt the Mtb testing protocols recommended by FDA, as described below. The major concerns include the lack of a currently validated culture testing methodology for use with solid tissue samples, the low-pretest probability of pre-screened donors, challenges with determining and obtaining a suitable sample, and other logistical challenges.

Validity of AFB (Acid Fast Bacilli) Culture Testing of Donated Human Tissue

Section E of the draft guidance references the Clinical Laboratory Standards Institute (CLSI) Standard, M48, Laboratory Detection and Isolation of Mycobacteria for culture detection of mycobacteria (Ref 128). The scope of this standard (M48, 2nd edition)[2] states, "This guideline provides recommendations for laboratories on the total testing process for patients with *suspected mycobacterial infections*." However, as part of the donor eligibility process, potential donors who are suspected of having mycobacterial infections are excluded; therefore, the remaining donor population to be tested by definition is <u>not suspected</u> of having a mycobacterial infection.

As a result, the live-patient standard is incompatible with the cadaveric human tissue donor setting, since a potential donor is <u>not suspected</u> of having a mycobacterial infection, and there is no lesion or target tissue identified to sample and test. USDA testing protocols for Mtb testing also recommend culture testing of suspicious lesions, and for random surveillance testing they recommend PCR to identify presence of Mtb to determine which samples are sent for culture testing.[3–7] The stepwise approach in USDA SOP NVSL-0710.05[3] states that the lab typically receives a paired sample with the formalin fixed samples. SOP NVSL 0696.07[4] describes how routine slaughter surveillance samples are tested by PCR and then, if the PCR is non-negative or at the request of a pathologist, a culture is performed. It further states that high-risk cattle testing is guided by the results of histological analysis to direct how the sample is further tested, i.e., culture or PCR.

The FDA draft guidance also references the Official American Thoracic Society/Infectious Diseases Society of America/Centers for Disease Control and Prevention Clinical Practice Guidelines ("IDSA Guideline" - Ref 130 - Lewinsohn et al 2017)[8] which provides recommendations for the diagnosis of tuberculosis. As any culture testing of a cadaveric human tissue donor would be of an individual not suspected of having a mycobacterial infection (due to donor screening and medical review) and would necessarily be of randomly selected tissue specimens, use of the IDSA guideline as a reference basis for culture testing is similarly challenging. The IDSA guideline makes several recommendations regarding testing to be performed on specimens collected from sites of suspected extrapulmonary TB—acknowledging the limitations of those methodologies to definitively exclude Mtb. However, for patients tested under the IDSA guideline, there would at least be clinical and/or visual evidence guiding a clinician to what specimen types (i.e., lesions, etc.) and what areas of the body of a live patient to test. Such information in tissue banking practice will not be available for a tissue donor, as they would be excluded from the donor eligibility process if they were suspected of having mycobacterial infection. Similarly, both the CDC and the US Preventive Services Task Force recommend only targeted testing of individuals at increased risk for TB.[9,10]

The use of AFB (acid-fast bacilli) culture methodology for recovered tissue samples from non-suspected extrapulmonary sites of non-suspected donors is contrary to the intent and scientific rationale in both the M48 standard, the IDSA guideline, USDA testing protocols,[3–7] and the requirements for samples currently tested by commercial labs for Mtb.[11–15]

AATB acknowledges that these are all clinical recommendations, and this is not a clinical situation. The main reason for recommending against testing the entire US population or pulling random tissue samples from individuals in sites where there are no known signs or symptoms possibly attributable to Mtb is that there is a low pre-test probability of Mtb in the US except in certain higher-risk groups. A low pre-test probability combined with, in this case, testing of as yet unvalidated sample types (bone, heart valves, dura mater) is not likely to yield reliable results without extensive research and method suitability validation prior to initiating testing.

The Negative Predictive Value of Culturing from Donors Screened to be Free of Risk of Mtb Infection

In testing donor tissues for Mtb in order to further ensure the safety of tissue products, it would be ideal to have a high negative predictive value of such testing - meaning that negative results have a high likelihood of being a true negative. The negative predictive value is impacted by pretest probability[16] (in this case, in an already low-prevalence population, the pretest probability will be intentionally lowered further by donor screening efforts), the sensitivity and specificity of the testing method (in this instance, the sensitivity and specificity of culture methods on such tissue samples are not truly known), and sampling methods (if there is no Mtb in the sample tested there is no possibility to detect its presence), all of which will need careful attention. Additionally, inadequate sampling - either by selecting a piece of tissue that is not truly representative or is of insufficient volume - would likely lead to false negative test results, which may provide an unwarranted sense of security in the safety of a product.

Standard Usage and Sampling Challenges

As the M48 standard is geared toward use of clinical laboratory testing methodologies for diagnosing Mtb (and non-tuberculosis mycobacteria (NTM)) within one patient (via defined suspected specimen types), the standard may not provide the usual compendial testing methodology criteria. For instance, the United States Pharmacopeia (USP) compendial methodology for sterility testing as described in USP <71> *Sterility Tests*[17] includes method suitability testing to ensure the validity of the test method to reproducibly yield a positive result when viable bacteria, yeast, and molds are present. USP <71> also includes sampling tables with requirements for the percentage of the lot to test and the volume of sample to be tested. This is an important consideration as the M48 standard (and the IDSA guideline) discusses specimen testing that is oriented toward suspected sites; however, knowledge of suspected extrapulmonary tissue sites from a non-suspected deceased donor will most likely not be available and a

tissue sampling strategy must be more carefully considered than what is outlined in the M48 standard.

Additionally, the compendial test methods have a defined limit of detection established through method suitability testing. There are no such guidelines for Mtb, and unanswered questions include:

- What is a valid inoculum level for Mtb to result in growth within 42 days?
- Within what length of time must the test become positive relative to the established 42-day incubation period?
    - The USP <71> method suitability testing requires growth within 5 days to support the 14-day routine testing period. This provides a factor of safety in the event there are bacteriostatic/fungistatic elements present in the sample; there is a longer incubation to allow for growth of the adventitious agent. No such methodology exists for Mtb.
- How is sample preparation validated?
    - For example, infected osteocytes are inside the hydroxyapatite matrix; what preparation of the sample must be done to facilitate the release of the osteocytes from the mineralized matrix to support detection without affecting the viability of Mtb in culture?
- What is the reagent (required for both sample preparation and decontamination) impact on the assay validated?

These questions must be addressed before testing for Mtb can be implemented.

The draft guidance refers to testing "appropriate pre-processing donor specimens" for the presence of Mycobacterium tuberculosis (Mtb). Clinical laboratory guidelines define appropriate specimen types for Mtb culture such as sputum, bronchia washings, or lymph nodes, while no such standards currently exist for donor tissues intended for transplantation. Furthermore, it is unclear whether FDA intends that this term refers specifically to portions of tissues such as bone, heart valves, or dura mater, or whether alternative donor specimens may be acceptable or preferable for testing—AATB intends to explore various options, including the utility of bone marrow biopsy samples. All specimen types outlined in the M48 standard are classified as soft tissues and liquid-based sample types, which are easier to handle for culture testing purposes, especially with clinical laboratory sample preparation, culture methodology, and instrumentation. There do not appear to be any sampling recommendations for hard tissue, such as bone, in the M48 standard.

Furthermore, tissues from donors with latent TB infection are likely to contain extremely low and inconsistently distributed bacterial loads, making it nearly impossible to identify a reliable anatomical site for sampling. Without access to a consistent and safe source of Mtb-positive tissue, designing a scientifically robust and reproducible validation study becomes impractical.

Establishing the suitability of donor tissue samples for Mtb culture presents significant challenges. Validation studies would require access to tissues known to be positive for Mtb. Alternatively, the use of samples spiked with viable Mtb organisms may not accurately reflect the biological characteristics of naturally infected tissues, i.e. intracellular presence in the various matrices. AATB plans to lead an industry-wide effort to develop guidelines on this topic.

We understand that the M48 standard is all that is available pertaining to culture testing methodologies for Mycobacteria; however, it must be realized that many scientific and logistical challenges need to be addressed to apply this clinical testing standard to testing in the tissue banking industry.

Time to Appropriately Validate a Culture-Based Assay
Section E. of the guidance document FDA states the following:

> FDA recommends manufacturers evaluate the suitability of both AFB culture methods regarding use of adequate controls to detect inhibition…

Typically, with a validated compendial method such as USP <71> *Sterility Tests*, one only needs to verify absence of inhibition (via method suitability, aka bacteriostasis/fungistasis) prior to implementation. However, with respect to testing for mycobacteria using the M48 standard practices, additional validation efforts beyond testing for inhibition should be performed. Accepted assay validation activities (e.g., limit of detection, specificity, precision, robustness, ruggedness, round robin assessments for interlaboratory variability) would be necessary to allow mycobacterial test methodologies to have high confidence of performance and reliable results.

The FDA guidance goes on to state:

> If a donor specimen selected for testing, as described above, has a positive AFB culture for Mtb (shows growth), you should discard not only the bone, heart valves, or dura mater from that donor that has a positive AFB culture, but also all HCT/P types recovered from that donor. If growth is a mixed culture, an assessment for contamination is recommended (Ref. 128).[2] If the donor has a negative AFB culture (no growth), you should consider the potential for false negative culture results (Refs. 127-129).[2,18,19]

The guidance further states, "If the donor has a negative AFB culture (no growth), you should consider the potential for false negative culture results," which seems to indicate that the AFB culture may not be reliable, and therefore, undermines the utility of the test. It is widely understood that all diagnostic tests carry a risk of false negatives; however, clinical and regulatory decisions must be grounded in the balance of test performance characteristics and public health benefit. The implication that Mtb culture results may be unreliable due to poor sensitivity and negative predictive value raises concerns about the test's practical value. If the test cannot reliably inform donor eligibility decisions, its routine use may not be justified and could lead to unnecessary resource utilization without improving safety outcomes.

We further encourage FDA to consider the timeframe necessary for performing appropriate assay validation with clinical laboratory culturing practices, as the agency references in the guidance document, so that tissue establishments can practicably and confidently apply such practices (especially considering result sharing between tissue recovery and processors, including eye banks).

Other considerations as a function of validation may include:

- Impact of initial donor storage and specimen shipping and storage (freezing, refrigeration, ambient, etc.) on the test article and Mtb viability.
- Different specimen type considerations and the multitude of Mtb culturing methods that may arise from different processors vs. a universal / general testing approach for a tissue donor.
- Impact of specimen processing reagents used for decontamination procedure to minimize other confounding bacterial/ fungal contaminants and for required intracellular liberation of Mtb.

As mentioned in the preceding section, we understand the M48 standard accounts for a considerable amount of available and relevant testing information for tissue banks, but not all of the standard is adoptable in its current form. Thus, additional validation work is required to make mycobacterial culture testing reliable and applicable for tissue banking within the context of validated processes.

General Culturing Practices and Laboratory Testing / Capacity Considerations

In addition to time considerations needed to establish and perform culture-based assay validations, there are practical issues that must be addressed with microbiological laboratories who would be performing such testing. It is important to acknowledge that the amount of time required for liquid and solid media incubation, culture growth evaluation, any sub-culture requirements (for isolation and identification), and result reporting is significantly longer than any other cultures performed within tissue banking. Incubation required for Mtb culturing can span 6-8 weeks alone with additional time, most likely additional weeks, for any colony isolation for false-positive contamination assessment and/or true mycobacterial identification.

Tissues that have a short shelf-life (<8 weeks) that are stored in a refrigerated state, for instance, will have to be released before results of culture are available. Such products otherwise could not be provided for clinical use unless they are released under a utility-based release where any untoward late arriving results are conveyed to the implanting surgeon after the fact. The result of this is that most likely the riskiest tissues, i.e., those with a short shelf-life in order to maintain cell viability, are those that would most likely be released prior to completing the full incubation time for the test specimens, while it is the highly-processed / sterilized tissues that are held long enough prior to processing and distribution to await final culture results.

Laboratory testing and capacity considerations could also be quite impactful to the tissue banking industry for the following reasons:

- The amount of testing specimen required to test a donor is anticipated to be quite high, which would mean the sample count for testing laboratories would also be high.
- Specimens must be held in culture up to 8 weeks rather than 2 weeks, so the required incubator space or culture instrumentation needed for samples would also be high.
- The volume of testing and the storage capacity required both present significant operational challenges for laboratories.
- Current commercial mycobacteria-based media from media manufacturers mainly target clinical laboratory needs rather than the larger sample sizes and tissue types that would be necessary to meet the needs of a tissue establishment; the development of new commercial media options will also take time.

Culture Result Reporting and Sharing

Tissue establishments will also have significant workflow adjustments, including:

- To obtain the relevant specimen sample and volume of sample to yield the most confident culture results, *the tissue sample will most likely need to be obtained from initially processed tissue*, as a normal recovery swab sample would not be able to detect Mtb.
- Current processing workflows largely do not contemplate the need to obtain “preprocessing” tissue samples for culturing in the processing environment, nor such lengthy culture times.
- The longer Mtb culture incubation time will put a logistical strain on the industry when recovered tissues are sent to multiple processors, given that current procedures anticipate provision of all pre-processing culture results within 2-3 weeks. If for instance, Establishment A receives cardiovascular tissue and Establishment B receives musculoskeletal tissue, both processors would need to perform some sort of Mtb testing, and the timing may likely be different based on when processing begins post-recovery. This means that Mtb cultures are anticipated to be information in the “late arriving results” category - i.e., known to be pending, but not available until after distribution of the product. For example, this could mean that bone tissue that is processed beginning a year after collection could have Mtb culture results a year or more after heart valves from the same donor have already been distributed.

- Some eye banks do not currently receive tissue pre-processing results, and it is not clear whether receipt of Mtb testing results would be considered optional—although it appears that it would not be optional to receive such results, and changes to current contracts would need to be updated.
- There is concern that with multiple establishments running respective AFB culturing among multiple laboratories may create potentially unintended consequences of requiring the discarding all donor tissues if one laboratory makes an error (dropped sample, unable to obtain identification, etc.) and is unable to provide a result.

Additional Concerns
The table that follows includes a number of other specific concerns and questions based on our review of this guidance document.

Conclusion
Thank you again for rescinding the previously issued final guidance document and for reissuing this guidance in draft form. We appreciate your review of our recommendations and stand ready to assist the FDA in any way that you deem appropriate.

Regards,

Marc Pearce, MBA
President and CEO
American Association of Tissue Banks

II. Other Areas of Concern

Location	Text	Comments
II.A.	One study estimated the prevalence of LTBI in the U.S. among this group to be 15.9% overall and ranged from 2.6% in persons aged 6-14 years to 32.1% in ages ≥ 65 years (Refs. 19-20).	AATB was unable to verify those percentage values in either of the two references cited, although it may have come from this 2012 reference (Miramontes, R., Hill, A. N., Woodruff, R. S. Y., Lambert, L. A., Navin, T. R., Castro, K. G., & LoBue, P. A. (2015). Tuberculosis infection in the United States: Prevalence estimates from the national health and nutrition examination survey, 2011-2012. *PLoS ONE*, *10*(11). https://doi.org/10.1371/journal.pone.0140881). Please verify or provide further information.
II.A.	Whether or not an individual develops TB infection or disease following an exposure is in part a function of their immune response to the inoculum of Mtb bacilli, and might lead to latent infection, a state in which Mtb bacteria survive in the body in a dormant state and there is no evidence of clinical disease (i.e., LTBI) (Refs. 1-2, 25).	AATB suggests editing this statement with the following (or something similar) for clarity: Primary infection after exposure to TB could lead to a number of different outcomes. Those include TB infection (otherwise known as latent TB infection), TB disease, or clearance of the infection, depending on the immune response. Latent TB infection (i.e., TB infection) is a state in which Mtb bacteria survive in the body in a dormant state and there is no evidence of clinical disease (i.e., LTBI/ TBI) (Refs. 1-2, 25).
II.A.	Sepsis due to Mtb in hospitalized patients might not be identified during their admission and blood cultures and other specimen cultures may be negative (Refs. 31-36).	This statement is true, but Mtb is an uncommon cause of sepsis, and sepsis is not an effective tool for identifying Mtb infection.
IV.A.	A positive test for TB infection or a medical diagnosis of TB disease, TB infection, or LTBI (regardless of treatment) (Refs. 31-36, 38-43, 62, 78-86, 91-97).	As noted above, we believe AATB's approach of prohibiting accredited establishments from the manufacturing of higher-risk tissues from donors with risk factors beyond those of having TB infection or TB disease to be a more effective approach to limit the risk of Mtb transmission while also reducing the potential for disruptions to the availability of tissue products. We will continue to require that our members rely on this tactic, which we believe is complimentary to FDA's approach described in this guidance document. AATB agrees that we should further address donors with a positive TB test greater than two years ago, which would further strengthen tissue establishments' donor

Location	Text	Comments
		screening efforts, and we intend to make changes to AATB's Standards to bring them in line with this element of the guidance. Furthermore, AATB feels that taking a careful and proactive approach to donor screening for Mtb is a more effective approach to excluding donors with Mtb than the nonspecific sepsis diagnosis.
IV.A.	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 [… goes on to list multiple risk factors, some for exposure some for reactivation]… A donor who falls into any of the categories described in the bullets above 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 (discussed in section IV. B. and C. of this guidance).	Some of the information described in this element is not currently collected as part of routine donor screening. AATB intends to continue to work to address the collection of the additional donor screening information suggested in the Mtb draft guidance document. We interpret the information requested here to be advisory and educational in nature, in that it contributes to an assessment of the Mtb risk presented by the donor. Through revisions to the UDRAI, AATB will work toward making the collection of this information part of the donor evaluation.
IV.E.	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:	As noted above, AATB takes this language to be advisory rather than an enforceable provision. For the reasons mentioned above, current testing options are lacking, and the high rate of false negatives may provide an unwarranted sense of security in the safety of a product. A reliable testing strategy for Mtb will require the availability of new test options, and a long timeframe for the validation and implementation of such testing. If and when new testing methodologies become available, we look forward to engaging with CBER about the feasibility and logistical considerations that will be necessary to support widespread adoption of any test.

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