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

Draft Guidance for Industry

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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
May 2025

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Draft Guidance for Industry

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I. INTRODUCTION

We, FDA, are issuing this guidance to assist you, establishments making donor eligibility (DE) determinations,[1] in understanding the requirements in 21 CFR part 1271, subpart C (21 CFR part 1271, subpart C). The regulations under 21 CFR part 1271, subpart C, set out requirements for determining donor eligibility, including donor screening and testing, for donors of human cells, tissues, and cellular and tissue-based products (HCT/Ps).[2] This guidance provides recommendations for screening donors for evidence of, and risk factors for, infection with *Mycobacterium tuberculosis* (Mtb), the organism that causes tuberculosis. The guidance also recommends additional steps that HCT/P establishments should take to reduce risk of transmission of Mtb until such time as appropriate FDA-licensed, approved, or cleared donor screening tests are available for use to test donors for Mtb infection.

FDA identified a safety concern when investigating reports of Mtb infections in recipients of allograft bone products.[3] These multi-state outbreaks indicated that there is a risk of transmission of Mtb infection by HCT/Ps. This guidance, when finalized, will identify Mtb as a relevant communicable disease agent or disease (RCDAD) as defined in 21 CFR 1271.3(r)(2) and will supplement the recommendations contained in other DE guidance documents for donors of HCT/Ps.[4]

[1] See 21 CFR 1271.50.
[2] HCT/Ps are defined in 21 CFR 1271.3(d) as "articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient."
[3] Centers for Disease Control and Prevention. Second Nationwide Tuberculosis Outbreak Caused by Bone Allografts Containing Live Cells — United States, 2023, MMWR Morb Mortal Wkly Rep. Jan 5, 2024; 72(5253);1385–1389.
[4] See generally https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/tissue-guidances.

When finalized, this guidance will provide specific recommendations to reduce the risk of transmission of Mtb by HCT/Ps.[5]

In general, FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the FDA's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word "should" in FDA's guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. *Mycobacterium tuberculosis* Epidemiology and Public Health Impact

Tuberculosis (TB) is a communicable disease caused by a group of genetically related *Mycobacteria* species collectively referred to as *Mycobacterium tuberculosis* complex. *Mycobacterium tuberculosis* (Mtb) is the most common organism within the Mtb complex to cause TB (Ref. 1). TB is a global health problem with a significant disease burden that can lead to chronic disability, and it is one of the leading causes of death worldwide and the leading cause of death from a single infectious agent (Refs. 1-7). Although the United States (U.S.) has one of the lowest TB rates in the world and has seen a substantial decline in the rate of TB over the last several decades, TB continues to remain a problem causing significant morbidity and mortality. During 2024, 10,347 new cases of TB disease were provisionally reported in the U.S., compared with 9,633 cases during 2022 (Refs. 8-10). Latent tuberculosis infection (LTBI) is estimated to affect a quarter of the world's population and approximately 13.2 million persons, or 4% to 5%, of the U.S. population (Refs. 7-8, 11). People with LTBI do not feel sick and do not have any symptoms. They are infected with Mtb, but do not have TB disease (Refs. 2, 11).

The majority of TB cases in the U.S. are due to reactivation of LTBI in persons who were born in or lived in countries where TB is endemic and the disease burden is moderate to high (e.g., Mexico, the Philippines, Vietnam, India, China, Haiti, Guatemala and other countries) (Refs. 16-19). 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).

[5] This draft guidance was originally published as final guidance in the *Federal Register* on January 7, 2025 (90 FR 1170). That final guidance recommended that establishments making donor eligibility determinations implement the recommendations in the guidance "as soon as feasible, but not later than 4 weeks after the guidance issue date." On February 3, 2025, FDA subsequently announced the availability of a revised version of that final guidance, which recommended implementation on a longer timeframe, by May 4, 2025 (90 FR 8802). FDA has now withdrawn the final guidance "Recommendations To Reduce the Risk of Transmission of *Mycobacterium Tuberculosis* (Mtb) by Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)" and has reissued this draft guidance with certain revisions in response to comments FDA received on the now-withdrawn final guidance issued in January 2025.

Mtb transmission occurs primarily through inhalation of aerosol droplet nuclei containing the bacteria. Individuals who have infectious TB can expel droplet nuclei containing the bacteria through coughing, sneezing, speaking, and singing (Refs. 2, 21-24). 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).

Occupationally acquired TB infections have been reported among individuals exposed to Mtb through aerosol generating procedures (e.g., irrigation of tuberculous infected wounds or abscesses, laboratory processing of infected tissues or other specimens, use of a bone saw on Mtb-infected bone). Healthcare workers acquired TB infections following direct inoculation of nonintact skin (Refs. 44-60), and from exposure to not only contaminated bone allograft products, but also to recipients of these products, during their wound and routine patient care, and to surgical instruments and medical waste associated with use of the bone allograft products (Ref. 61). Cutaneous TB from direct inoculation of skin has also been reported with tattoos, body piercings, acupuncture, autopsies, and surgical procedures that used unsterile equipment (Refs. 48-60, 62).

Risk factors for TB infection and disease include common conditions associated with impaired immunity (e.g., chronic kidney disease, diabetes mellitus, malignancy, immunosuppressive therapy, etc.), behavioral factors including substance abuse, tobacco use, and malnutrition, and environmental factors leading to increased exposure to individuals with infectious tuberculosis (e.g., living or working in crowded facilities such as homeless shelters, long-term care facilities and nursing homes, jails, prisons, correctional facilities, and other congregate settings) (Refs. 11, 26-30).

TB may be underdiagnosed due to the need for a high index of clinical suspicion, inherent diagnostic difficulty, and/or attribution of the clinical syndrome to alternate causes. Persons with LTBI are, by definition, asymptomatic; and a person with TB disease might have symptoms or signs that can mimic or overlap with other medical conditions. 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).

III. DISCUSSION

FDA has identified Mtb as an RCDAD under 21 CFR 1271.3(r)(2). This determination was based on the risk of transmission by HCT/Ps, severity of effect, and availability of appropriate screening and testing measures.

A. Risk of Transmission

There is a risk of transmission of Mtb by HCT/Ps. This is supported by evidence that Mtb can disseminate to organs and tissues via hematogenous, lymphatic, or contiguous spread which may result in infection of bone, ocular tissues, skin, and connected networks such as the central nervous system, and genitourinary tract (Refs. 1-2, 37), and

congenital (perinatal) TB is transmitted in utero (Refs. 38-43).

In addition, because Mtb can be transmitted through inhalation of aerosol droplet nuclei containing the bacteria, there is a risk of transmission to those who may handle or otherwise come in contact with a contaminated HCT/P, such as medical personnel who may be exposed to such products or recipients of those HCT/Ps, or to medical waste or surgical instruments (Refs. 44-61).

1. Potential for Transmission of Mtb by Blood Products and Solid Organs

To date, there have been no documented cases of Mtb in humans transmitted through transfusion of blood or blood components and Mtb is not a relevant transfusion-transmitted infection (RTTI).[6]

Mtb has been transmitted through solid organ transplantation (including lung, liver, kidney, and heart) and has been associated with high morbidity and mortality (Refs. 63-75). All potential transmissions of Mtb reported to the Organ Procurement and Transplantation Network (OPTN) Ad Hoc Disease Transmission Advisory Committee between 2008 and 2018 were analyzed and, among 51 total reports, nine (17%) (9 donors/35 recipients) had 1 or more recipients with proven/probable donor-derived TB transmission, and all of these donors had one or more TB risk factors (i.e., born in a TB-endemic country, travel to a TB-endemic country, incarceration), or had a history of LTBI (Refs. 76-77).

2. Potential for Transmission of Mtb by HCT/Ps

Mtb has been transmitted by transplantation of allograft bone, heart valves, and dura mater (Refs. 31, 78-85). In 2021, a national outbreak of TB disease occurred in the U.S. associated with transplantation of a bone allograft product that resulted in significant morbidity and mortality (Ref. 31). A similar outbreak of donor-derived TB transmitted by a bone allograft product occurred in 2023 (Refs. 84-85). Mtb is a risk not only to tissue transplant recipients, but also to healthcare personnel who are exposed to Mtb and may be infected when caring for infected recipients and when handling the tissues.

Transmission of Mtb by HCT/Ps derived from gestational cells and tissues (e.g., amniotic membrane, umbilical cord tissue, umbilical cord blood), and cells and tissues for reproductive use, has not been reported. However, Mtb transmission between sexual partners has been reported (Refs. 86-90). Mtb has been detected in ovaries and semen (Refs. 86, 88, 89), and from related anatomical areas (e.g., cervix, fallopian tubes) (Refs. 88, 90). Mtb has also been identified in placenta in cases of chorioamnionitis and congenital TB (Refs. 38-43, 91-92).

Mtb DNA has been identified in hematopoietic progenitor/stem cells (HPCs) derived from peripheral blood and bone marrow of donors with LTBI, and viable

[6] 21 CFR 630.3(h).

Mtb has been cultured from mesenchymal stem cells in bone marrow of individuals previously considered to be successfully treated for pulmonary TB. Although transmission of Mtb via HPCs used in hematopoietic stem cell transplantation (HSCT) has not been previously reported, there remains a potential risk of transmission (Refs. 93-97). Additionally, typical HSCT recipients are severely immunocompromised which may increase their risk for TB and the severity of an infection.

Mtb infects dermal fibroblasts and can be detected in the skin of individuals with cutaneous TB using mycobacterial cultures or a polymerase chain reaction (PCR) assay for the detection of Mtb DNA (Refs. 48-60, 62). However, Mtb transmission to the recipients of skin or dermal allografts has not been reported.

Mtb transmission via ocular tissue has not been reported; however, Mtb has been detected in ocular tissues (i.e., cornea, sclera, and conjunctival tissues), and in fluids that have contact with ocular tissues, using mycobacterial cultures and/or PCR for Mtb DNA from individuals with systemic TB, LTBI, primary ocular TB, and retinal vasculitis due to Mtb (Refs. 98-101). Surgical procedures used during the recovery of corneas and sclera can potentially lead to cross contamination if Mtb organisms are present in the donor's blood or ocular fluids, particularly when whole globes are enucleated (Ref. 100).

HCT/Ps that are known to have transmitted Mtb are bone, heart valves, and dura mater. Because Mtb organisms have been detected in other HCT/P types, there remains a potential risk of Mtb transmission from HPCs, gestational cells and tissues, reproductive cells and tissues, skin, and corneas or sclera. In addition, TB has sufficient incidence and/or prevalence to affect the potential HCT/P donor population.

B. Severity of Effect

As described earlier, TB is one of the leading causes of death worldwide and the leading cause of death from a single infectious agent (Refs. 1-7). TB disease is associated with a risk for development of several complications including, but not limited to, neurological diseases, pulmonary disease, renal failure, adrenal failure, osteomyelitis, sepsis, infertility, miscarriage, and complications in newborns from perinatal transmission (Refs. 102-126).

Infection with Mtb can be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure.

C. Availability of Appropriate Screening and/or Testing Measures

Appropriate donor screening measures have been developed for reducing the risk of

transmission of Mtb (discussed in section IV. A., B., and C. of this document), and screening measures are in place for evaluating evidence of infection in HCT/P donors to reduce the risk of transmission due to disease agents associated with sepsis,[7] which may be caused by Mtb.

There are currently no FDA-licensed, cleared, or approved donor screening tests for use in testing HCT/P donors for evidence of Mtb infection. However, a donor's medical record or medical history may include results of other tests for detection of immune response to or presence of Mtb, which are discussed below.

There are FDA-approved diagnostic products that can detect an immune response to TB antigens; examples include FDA-approved purified protein derivative (PPD) of tuberculin antigens injected intradermally for the tuberculin skin test (TST), and interferon-gamma release assay (IGRA) blood tests (e.g., T-SPOT.TB test and Quantiferon-TB Gold Plus test). Both types of tests measure immune sensitization to mycobacterial protein antigens that occurs following exposure to mycobacteria, and these tests should be used in conjunction with clinical risk assessment, radiography, and other medical and diagnostic evaluations to aid in the diagnosis of Mtb infection. These additional medical and diagnostic evaluations are essential to diagnosing TB disease and LTBI. When using the TST and IGRA tests, the person tested must have viable intact immune cells to produce an accurate result, which makes them impractical for evaluating TB risk for a cadaveric (non-heart beating) donor. A variety of factors can affect TST and/or IGRA test performance, including recent infection (i.e., testing before a cell-mediated immune response has developed), age, receipt of Bacillus Calmette-Guerin (BCG) vaccine (can affect TST but does not affect IGRA), and impaired immunity, specifically, T-lymphocyte mediated cellular immunity (Refs. 130-136). Negative tests results do not exclude LTBI or TB disease.

FDA-cleared diagnostic tests, such as nucleic acid amplification tests (NAAT), including PCR tests, for the detection of Mtb in respiratory specimens (e.g., sputum) are also available. The results of such tests are not intended to be used in isolation and are to be used as an adjunct to other laboratory tests and clinical findings.[8] A negative result does not exclude TB disease (Refs. 17, 31, 127-130). We note that PCR testing of a bone product from an infected donor has not consistently provided the level of sensitivity necessary to identify presence of Mtb (Refs. 31, 85), and FDA has not authorized a PCR test for the detection of Mtb using a bone specimen.

Detection of acid-fast bacilli (AFB) in smears examined microscopically may provide initial bacteriologic evidence of the presence of mycobacteria in clinical specimens. However, AFB smears of respiratory specimens should be collected on three consecutive days to increase sensitivity, AFB smears may produce false negative results due to a variety of reasons (e.g., low levels of Mtb in the specimen, microscope and technologist issues, etc.), and negative results from smears do not exclude TB

[7] In 2007, FDA identified sepsis as a RCDAD, requiring screening of HCT/P donors for risk associated with sepsis).
[8] See, e.g., 21 CFR 866.3372 and Class II Special Controls Guideline: Nucleic Acid-Based In Vitro Diagnostic Devices for the Detection of *Mycobacterium tuberculosis* Complex in Respiratory Specimens.

disease (Refs. 127-130).

Mycobacterial cultures to detect AFB require specific growth media and may take up to 8 weeks to grow the bacilli organism (Ref. 128). CDC considers a positive culture for Mtb to confirm the diagnosis of TB disease (Ref. 130), and clinical practice guidelines for diagnosis of TB suggest that both liquid and solid mycobacterial cultures be performed, rather than either culture method alone, for every specimen obtained from an individual with suspected TB disease (Ref. 130). Mycobacterial cultures are more sensitive for detection of Mtb, particularly when there is a low amount of organism present, than AFB smears or NAAT tests currently available in the Unites States. Although 20% of U.S. TB cases were not culture confirmed (Ref. 127), AFB cultures showed growth when bone product specimens were tested during the investigations of both outbreaks in the U.S., including when PCR testing was negative (Refs. 31, 85).

IV. RECOMMENDATIONS

As noted in sections I. and III. of this document, FDA has identified Mtb as an RCDAD as defined in 21 CFR 1271.3(r)(2). The following recommendations and policies are intended to reduce the risk of transmission of Mtb by HCT/Ps.

A. Screening a Donor for Risk Factors and Conditions for LTBI and TB Disease

Unless an exception identified in 21 CFR 1271.90(a) applies, you must review relevant medical records and ask questions about the donor's medical history and relevant social behavior, including risk factors for RCDADs (21 CFR 1271.3(s), 21 CFR 1271.75(a)). You should also screen the birth mother when an infant donor is less than 1 month of age. In accordance with 21 CFR 1271.75(d), you must determine to be ineligible any potential HCT/P donor who is identified as having a risk factor for Mtb infection. The following should be considered a risk factor:

1. 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).

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 (Refs. 11, 16-20, 23, 26-31):

- Persons who were 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);
- 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);
- Persons who have ever lived with, or have been a close contact with, another

person who has TB; or

- 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.

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).

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

Unless an exception identified in 21 CFR 1271.90(a) applies, you must review relevant medical records for clinical evidence of RCDADs (21 CFR 1271.75).

For cadaveric (non-heart beating) donors, establishments should:

- Determine whether an autopsy was not performed due to a perceived risk of transmission of a communicable disease, including TB, or,
- If an autopsy was performed, whether any special precautions were taken that would suggest there was special concern regarding the risk of transmission of TB from the donor.

If an autopsy was performed, you should wait for the final autopsy report unless it would compromise the utility of the tissue, for example, because your HCT/P (e.g., cornea) needs to be released within a limited timeframe.

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 disease (Refs. 17, 31-36, 38-43, 48-62, 78-101, 127-136). Examples of clinical evidence of LTBI or TB disease:

1. Persons who have ever had a medical diagnosis of TB disease or LTBI or TB disease (regardless of treatment); or

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).

A person with TB disease may have a number of signs or symptoms that can mimic or overlap with other medical conditions. If a person falls into any of the categories described in the bullets in section IV. A., or if there is physical evidence, or suspicion of LTBI or TB disease, the presence of any of the following symptoms or signs of TB

disease should be considered when making a donor eligibility determination. (Refs. 2-3, 43-46, 98-127):

- 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); or
- 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).

If a living donor appears healthy and there is no suspicion or medical history of LTBI or TB disease (including no prior medical diagnosis of TB disease or LTBI, and no positive test for TB infection), the donor is not considered to have a risk of TB infection.

C. Screening a Donor for Physical Evidence of Mtb Infection

Relevant medical records (21 CFR 1271.3(s)) include the report of the physical assessment of a cadaveric (non-heart beating) donor (21 CFR 1271.3(o)) or the physical examination of a living donor. Unless an exception identified in 21 CFR 1271.90(a) applies, in accordance with 21 CFR 1271.75(d)(1), you must determine to be ineligible any potential HCT/P donor who has risk factors for or clinical evidence of TB infection. The following are examples of physical evidence associated with TB infection:

1. Generalized lymphadenopathy (Refs. 111-112).

2. Unexplained cutaneous lesions that may be consistent with tuberculosis (Refs. 44-52).

D. Testing a Donor for Evidence of Mtb infection

Under 21 CFR 1271.80(c), establishments must use appropriate FDA-licensed, approved, or cleared donor screening tests in accordance with the manufacturer's instructions to adequately and appropriately reduce the risk of transmission of RCDADs, such as Mtb. As discussed above, FDA-approved and -cleared products for the detection of immune response to or presence of Mtb are available. However, there are currently no FDA-licensed, cleared, or approved donor screening tests for use in testing HCT/P donors for evidence of Mtb infection.

Following investigations of TB outbreaks linked to HCT/Ps, FDA recognizes the public health need to reduce risk of Mtb transmission by HCT/Ps, given the morbidity and mortality experienced after recent, multistate outbreaks. We also recognize that, with the current absence of FDA-licensed, cleared, or approved donor screening tests for Mtb, HCT/P establishments may wish to use products described in section III.C, such as FDA-cleared diagnostic tests, to test HCT/P donors to help reduce risk of transmission, particularly if the potential donor presents with symptoms or signs of TB disease, falls into any of the categories described in the bullets in section IV. A., or if there is physical evidence, or suspicion, of LTBI or TB disease, unless the patient's primary treating physician has excluded TB disease and an alternative diagnosis has been established. In light of these considerations, FDA does not intend to object if an establishment chooses to collect a specimen from a living donor of HCT/Ps (or while the donor's heart is still beating) and test for evidence of Mtb infection using a test discussed in section III.C, even though such tests are not FDA-licensed, cleared, or approved as donor screening tests.[9] FDA would not consider a negative or nonreactive test result obtained from such testing to override other clinical and physical evidence of, and risk factors for, TB disease discussed in section IV. A., B., and C. of this guidance. In addition, when making a donor eligibility determination, you should consider any negative or nonreactive test result obtained using the tests described above along with such clinical and physical evidence, and risk factors. You should follow your procedures for sharing with other establishments information pertaining to possible contamination or potential for transmission of communicable disease, and you are responsible for sharing this information with other establishments that recovered or received HCT/Ps from the same donor (21 CFR 1271.160(b)(2)(i)).

FDA expects establishments to use appropriate licensed, approved, or cleared Mtb donor screening tests once such tests are available.

E. Additional Risk Reduction Measures

During the investigation of both Mtb outbreaks in the U.S., mycobacterial cultures of bone product specimens showed growth, including when PCR testing was negative

[9] FDA also generally does not intend to take action against a manufacturer of a test described in section III.C. where the manufacturer offers such a test to an HCT/P establishment to test donors for evidence of Mtb infection while there are no FDA-licensed, approved, or cleared donor screening tests available. This policy does not otherwise change FDA's expectations regarding these manufacturers' compliance with applicable device requirements, such as submission of medical device reports in accordance with 21 CFR part 803.

(Refs. 31, 85). 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:

1. Manufacturers that process bone[10], heart valves, or dura mater should select appropriate liquid and solid mycobacterial cultures (AFB cultures) to test for presence of Mtb using appropriate pre-processing donor specimens when the disinfection or sterilization process used has not been validated to demonstrate the capability to eliminate contamination with Mtb. Both liquid and solid mycobacterial cultures should be performed, rather than either culture method alone (Refs. 127-130).

   The specimen selected for testing should be representative of the HCT/P to be evaluated. FDA recommends manufacturers evaluate the suitability of both AFB culture methods regarding use of adequate controls to detect inhibition and to use voluntary standards from a Standards Development Organization (Ref. 128).

2. 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). If the donor specimen has a negative AFB culture (no growth), you should consider the potential for false negative culture results (Refs. 127-129).

While we do not consider these additional steps to be part of the donor testing required under 21 CFR 1271.80 and 21 CFR 1271.85, FDA believes that performing AFB culture, as recommended above, is an important interim measure to address safety concerns regarding TB transmission from HCT/Ps.[11] You should follow your procedures for sharing with other establishments information pertaining to possible contamination or potential for transmission of communicable disease, and you are responsible for sharing this information with other establishments that recovered or received HCT/Ps from the same donor (21 CFR 1271.160(b)(2)(i)).

[10] For clarity, this does not include minimally manipulated bone marrow for homologous use and not combined with another article, which is excepted from the definition of an HCT/P under 21 CFR 1271.3(d)(4).

[11] We also note that an establishment that processes HCT/Ps "must process each HCT/P in a way that does not cause contamination or cross-contamination during processing, and that prevents the introduction, transmission, or spread of communicable disease through the use of the HCT/P" (21 CFR 1271.220(a)). In addition, establishments "must recover, process, store, label, package, and distribute HCT/Ps, and screen and test cell and tissue donors, in a way that prevents the introduction, transmission, or spread of communicable diseases" (21 CFR 1271.145).

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