



Association for the  
Advancement of  
Blood & Biotherapies

**AABB Resources to Support  
FDA's Voluntary Tuberculosis  
Risk Mitigation Strategies for  
HCT/P Establishments and  
Transfusion Services**

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## Purpose and Overview

As described in FDA's Sep 6, 2023 Safety & Availability Communication, [Important Information for Human Cell, Tissue and Cellular and Tissue-based Product \(HCT/P\) Establishments Regarding Tuberculosis Outbreaks Linked to a Bone Matrix Product](#):

*"In 2021, a multi-state outbreak of Mtb in the United States was linked to transplantation of a bone allograft product and resulted in significant morbidity and mortality. A new, similar outbreak is currently under investigation."*

- The [2021 outbreak investigation](#) involved the implantation of allograft contaminated with Mycobacterium tuberculosis (Mtb) into 113 patients in 18 states resulting in significant morbidity and mortality. The lack of use of a system to track donated human tissue to individual recipients posed a challenge during the investigation. As described in the Jan 2024 *American Journal of Transplantation* publication, [Incomplete tissue product tracing during an investigation of a tissue-derived tuberculosis outbreak](#):

*"This investigation highlights the critical need to improve tissue-tracking systems to ensure unbroken traceability, facilitating investigations of recipient adverse events and enabling timely public health responses to prevent morbidity and mortality."*

- The [2023 outbreak investigation](#) involved a total of 36 patients who had surgery or dental procedures. The products were linked to a single lot, shipped to thirteen facilities in seven states. Two deaths have been reported. All patients involved were contacted and all unused lots were recalled.

### This Toolkit:

- Describes AABB's [longstanding](#) Standards for Blood Bank and Transfusion Services and Standards for Cellular Therapy Product Services and requirements for traceability of blood and blood products and cellular therapy products which, if implemented, provide robust support for product identification and traceability necessary to swiftly identify and locate products with potential risk for disease transmission or other safety and quality concerns.
- Is intended to supplement your understanding of FDA's September 6, 2023, Safety & Availability Communication, "[Important Information for Human Cell, Tissue and Cellular and Tissue-based Product \(HCT/P\) Establishments Regarding Tuberculosis Outbreaks Linked to a Bone Matrix Product](#)" (Sept 6<sup>th</sup> Safety Communication)

- Provides an overview of the important information from FDA on the investigation of an outbreak caused by Mycobacterium Tuberculosis (Mtb) and voluntary risk mitigation strategies.

**NOTE:**

- 1) To support our members with questions, AABB reached out to FDA to confirm that we correctly understand FDA to be providing risk mitigation strategies applicable to all donors of [HCT/Ps](#), as defined in [21 CFR 1271.3\(d\)](#), [including](#) hematopoietic stem/progenitor cells (HPCs) derived from peripheral and cord blood.
- 2) FDA's Sept 6<sup>th</sup> Safety Communication:
  - Provides risk mitigations strategies that may be considered by the HCT/P establishment's responsible person for voluntary implementation and are not issued as formal recommendations in FDA guidance.
  - Focuses on the evaluation of risk and does not mention donor deferral.
- 3) Mtb has not been identified as a relevant transfusion-transmitted infection, and as such would not be captured in AABB's [Emerging Infectious Disease Fact Sheets](#).

➤ **AABB standards for Cellular Therapy Services focused on Requirements for Traceability**

AABB Standards for Cellular Therapy Services have long required traceability of each product from source through final disposition (implant/transplant/infusion). These essential safety measures allow for effective, rapid traceability of each product to:

- Quickly identify at-risk patients following receipt of potentially infected products.
- Allow for prompt treatment of at-risk patients.
- Seamlessly track and recall all unused cellular therapy products.
- Address [gaps in traceability](#) identified during the 2021 Mtb outbreak investigation.
- Provide a means for notification of the manufacturer of a non-conforming product.

The following standards from AABB's Standards for Cellular Therapy Services (11<sup>th</sup> edition) include, but are not limited to, these applicable standards:

**Standard 5.7 Product Identification and Traceability**

The facility shall establish and maintain policies, processes, and procedures that ensure the chain of identity and chain of custody for identification and traceability of each cellular therapy product and all related samples from their initial source, through all processing and testing steps, to their final disposition. Policies, processes, and procedures shall also allow the identification and traceability of each cellular therapy product and all related samples from their final disposition, through all processing and/or testing steps, to their source.

**5.7.1 Traceability and Unique Identification**

A numeric or alphanumeric system shall be used that will make it possible to trace any cellular therapy product or sample from donor/source to recipient/final disposition and back to the donor/source and to review records applying to the specific cellular therapy product or sample, including those related to reported adverse events. Unique identifiers shall not be obscured, altered, or removed.

**5.18.1 Management of Stored Noncryopreserved Inventory**

**5.18.1.4** The facility shall have processes to ensure traceability for any given product (and aliquots if applicable) from donation to final disposition.

**Reference Standard 6.2.1A – Retention of Records**

Item No.	Relevant Standard	Record to be Retained	Retention After Creation (C) or Final (F) Disposition of Related Product
115	5.7.1	Unique identification and traceability of cellular therapy products and samples from source to final disposition	C

**7.2 Control of Nonconforming Products or Services**

The facility shall establish and maintain policies, processes, and procedures to prevent the unintended use or release of nonconforming materials, products, or services. This control shall provide for identification, documentation, evaluation, segregation (when appropriate), and disposition of nonconforming materials and products.

### **7.2.1 Product Review, Investigation, and Look-Back**

The facility shall have policies, processes, and procedures to identify nonconforming products and the initiation of an investigation, including look-back as applicable, as soon as possible.

#### **7.2.1.1 Customer Notification**

The facility shall report to the customer:

- 1) Any cellular therapy products lost, damaged, or otherwise unsuitable for use.
- 2) Released products or delivered services that are determined to be nonconforming, as soon as possible.

#### **7.2.1.2**

Products identified as nonconforming following distribution shall be reported to the FDA or relevant Competent Authority in accordance with written policies, processes, and procedures.

#### **7.2.1.3**

Customers shall be notified when the nonconforming products can impact the purity, potency, safety or efficacy of the product.

### **7.2.3 Microbially Contaminated Products**

The facility shall have policies, processes, and procedures addressing the management of cellular therapy products with positive microbial culture results, including:

- 1) Product labeling.
- 2) Investigation of cause.
- 3) Notification of other facilities and/or departments involved in procurement, processing, and distribution of the product.
- 4) Notification of the donor's physician, if it affects the donor's health.
- 5) Notification of recipient's physician.
- 6) Recipient follow-up and outcome analysis.
- 7) Reporting to regulatory agencies, if appropriate.

## **➤ AABB Standards for Blood Banks and Transfusion Services focused on Requirements for Traceability**

AABB also provides longstanding tissue traceability requirements for blood banks and transfusion services accredited under AABB's Standards for Blood Banks and Transfusion Services. These include hospital transfusion services that store and

issue tissue. These essential safety measures allow for effective, rapid traceability of each product to:

- Quickly identify at-risk patients following receipt of potentially infected products.
- Allow for prompt treatment of at-risk patients.
- Seamlessly track and recall all unused cellular therapy products.
- Address [gaps in traceability](#) identified during the 2021 Mtb outbreak investigation.
- Provide a means for notification of the manufacturer of a non-conforming product.

The following standards from AABB's Standards for Blood Banks and Transfusion Services include, but are not limited to, these applicable standards:

#### **5.1.8.2 Traceability**

The BB/TS shall ensure that all blood, blood components, tissue, derivatives, and critical materials used in their processing, as well as laboratory samples and donor and patient records, are identified and traceable.

#### **5.1.8.5 Unit or Tissue Identification**

The labeling system shall make it possible to trace any unit of blood, blood component (including those in a pool), or tissue from source to final disposition. The system shall allow recheck of records applying to the specific unit or tissue, including investigation of reported adverse events.

#### **5.1.9 Handling, Storage, and Transportation**

The organization shall ensure that products or services are handled, stored, and transported in a manner that prevents damage, limits deterioration, and provides traceability.

#### **6.2.1.1 Records**

The record system shall make it possible to trace any unit of blood, blood component, tissue, or derivative from its source to final disposition; to review the records applying to the specific component; and to investigate adverse events manifested by the recipient.

<b>Reference Standard 6.2.9A-Retention of Records</b>					
<b>Standard</b>	<b>Record to Be Maintained</b>	<b>Donor/ Unit</b>	<b>Patient</b>	<b>Tissue</b>	<b>Derivative</b>
5.1.8.2	Traceability of blood, blood components, tissue, derivatives, and critical materials	X	X	X	X
7.3.9	Investigation of adverse effects, disease transmission, or other suspected adverse events of tissue and derivatives and reporting of such cases to the tissue supplier or manufacturer, and outside agencies as required	NA	X	X	X

**Recall for purposes of recipient tracing:**

**7.2.3** The organization shall:

- 1) Identify, quarantine, retrieve, recall, and determine the disposition of nonconforming products or services.
- 2) Identify and manage nonconforming products or services.
- 3) Notify users, suppliers, and outside agencies as required.

**7.2.4 Released Nonconforming Products or Services**

Products or services that are determined after release not to conform to specified requirements shall be evaluated to determine the effect of the nonconformance on the quality and/or safety of the product or service.

**7.3.9 Adverse Events Related to Tissue or Derivatives**

The BB/TS shall have a process for investigating adverse effects, disease transmission, or other suspected adverse events related to the use of tissue and derivatives and for promptly reporting such cases to the supplier, manufacturer, and outside agencies as required.



➤ **Mtb Risk in HCT/Ps:**

From FDA's [Safety & Availability Communication](#), dated September 6, 2023:

*“Based on our emerging awareness of Mtb transmission risks, establishments may wish to consider whether an HCT/P donor has:*

- *ever had a diagnosis of TB, treatment for suspected TB, or a positive test for TB (i.e., a skin test, blood test, or sputum test).*
- *an increased risk for TB infection due to any of the following:*
  - *was born in, has lived in, or ever traveled to areas of the world where TB is endemic (refer to [https://worldhealthorg.shinyapps.io/tb\\_profiles/External Link Disclaimer](https://worldhealthorg.shinyapps.io/tb_profiles/External_Link_Disclaimer))*
  - *ever lived with another person who has TB or is currently or has been a close contact of a person with TB*
  - *ever worked or resided in congregate settings (e.g., correctional facility, long-term care facility, homeless shelter)*
  - *has certain medical conditions, or is on medication, that can impair immune function.”*

➤ **Responsible Person (training and/or retraining):**

FDA begins by noting that the HCT/P establishment's responsible person should have appropriate medical training and be qualified to review clinical evidence consistent with risks for sepsis and tuberculosis (TB) infection and must verify and document that, on the basis of record review, release criteria have been met and they have determined that an HCT/P is available for distribution ([21 CFR 1271.265\(c\)\(1\)](#)).

*“Maintaining knowledge and awareness of these outbreaks and seeking additional training and/or re-training will help enable responsible persons to identify risk factors, conditions, clinical evidence, and physical evidence that can be associated with an increased risk for TB (including active TB and latent tuberculosis infection (LTBI) and/or an increased risk of sepsis.”*

➤ **Donor Screening Considerations:**

Based on FDA's Sept 6<sup>th</sup> Safety Communication, the HCT/P establishment's responsible person ([21 CFR 1271.3\(t\)](#)) who has authority for determining and

documenting the **eligibility of a cell or tissue donor** ([21 CFR 1271.50](#)) may wish to consider adding HCT/P donor screening to address the risk for TB.

The following example questions have been developed for those who wish to consider screening HCT/P donors.

1. Have you ever had a diagnosis of TB?
2. Have you ever been treated for suspected TB?
3. Have you ever had a positive test for TB (including a positive skin test, blood test, or sputum test)?
4. Were you born in an area of the world where TB is endemic?
5. Have you ever lived in an area of the world where TB is endemic?
6. Have you ever traveled to an area of the world where TB is endemic?
7. Have you ever lived with another person who has TB?
8. Are you currently a close contact of a person with TB?
9. In the past, have you been a close contact of a person with TB?
10. Have you ever worked in a correctional facility, long-term care facility, or homeless shelter?
11. Have you ever lived in a correctional facility, long-term care facility, or homeless shelter?
12. Do you have a medical condition that can impair your immune system?
13. Are you taking medications that can impair your immune system?

### ➤ Donor Testing Considerations:

FDA notes that:

- There are currently no FDA-licensed, cleared, or approved donor screening tests available with an indication to screen HCT/P donors for evidence of active TB or LTBI, and
- The agency is actively evaluating the risks and appropriate mitigation strategies, including testing.

### ➤ Supporting Resources:

AABB's encourages members to:

- Review relevant publications:
  - Wortham JM, Haddad MB, Stewart RJ, et al. Second Nationwide Tuberculosis Outbreak Caused by Bone Allografts Containing Live Cells — United States, 2023. MMWR Morb Mortal Wkly Rep 2024;72:1385–1389. DOI: <http://dx.doi.org/10.15585/mmwr.mm725253a1>
  - Marshall KE, Free RJ, Filardo TD, et al. Incomplete tissue product tracing during an investigation of a tissue-derived tuberculosis outbreak. Am J Transplant 2023. Epub September 15, 2023. <https://doi.org/10.1016/j.ajt.2023.09.005>
  - Schwartz NG, Hernandez-Romieu AC, Annambhotla P, et al.; Bone Allograft Tuberculosis Investigators. Nationwide tuberculosis outbreak in

the USA linked to a bone graft product: an outbreak report. *Lancet Infect Dis* 2022;22:1617–25. [https://doi.org/10.1016/S1473-3099\(22\)00425-X](https://doi.org/10.1016/S1473-3099(22)00425-X)

- Visit the CDC website for additional information. A few of CDC's many resources are linked here:
  - Tuberculosis <https://www.cdc.gov/tb/default.htm>
  - Basic TB Facts <https://www.cdc.gov/tb/topic/basics/default.htm>
  - Tuberculosis – [CDC Yellow Book 2024](#)
  - CDC Map – [Estimated incidence rates per 100,000 population](#)
  - CDC Table 5-06 - [Estimated proportion of multidrug-resistant \(MDR\) TB cases in countries with high MDR TB burden, 2019](#)
  
- Review the Additional Resources listed at the end of the [Sept 6<sup>th</sup> Safety Communication](#).
  
- Review AABB Weekly Report Articles
  - [REGULATORY UPDATE: FDA Outlines Risk Mitigation Strategies Concerning TB and HCT/P Donation; AABB Releases Accompanying Toolkit](#) – Sep 13, 2023
  - [Two Tuberculosis Deaths Linked to Bone Matrix Material](#) – Aug 16, 2023