# 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)

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# Draft Guidance for Industry

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FDA invites comments on this guidance. Submit one set of either electronic or written comments on this guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to http://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the Federal Register.

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**U.S. Department of Health and Human Services**
**Food and Drug Administration**
**Center for Biologics Evaluation and Research**
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## Draft Guidance for Industry

*This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.*

## I. INTRODUCTION

We, FDA, are issuing this guidance to assist you, establishments making donor eligibility determinations,[1] in understanding the requirements in Title 21 Code of Federal Regulations, 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 updates information regarding sepsis included in the guidance entitled "Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), Guidance for Industry," dated August 2007 (August 2007 HCT/P DE Guidance), and when finalized, will update recommendations for making a donor eligibility determination when screening a donor for clinical evidence of sepsis and clinical signs to consider.

FDA has determined that there is a need for updated recommendations in making donor eligibility determinations to reduce the risk of transmission of infections due to sepsis by HCT/Ps. FDA identified a public health safety concern when investigating reports of *Mycobacterium tuberculosis* (Mtb) infections in recipients of allograft bone products.[3] These multi-state outbreaks indicate that there is a risk of transmission of Mtb infection by HCT/Ps, and Mtb is a disease agent that can cause sepsis.

[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.

When finalized, this guidance will provide specific recommendations to reduce the risk of transmission of disease agents associated with sepsis by HCT/Ps and supersede information in the August 2007 HCT/P DE Guidance regarding sepsis.[4]

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

Sepsis is a clinical syndrome defined as life-threatening organ dysfunction caused by a dysregulated host response to infection (Ref. 1). For the purpose of this guidance, sepsis includes, but is not limited to, bacteremia (which may be associated with a similar risk to recipients as sepsis), septicemia, sepsis syndrome, systemic infection, systemic inflammatory response syndrome (SIRS) when due to infection, or septic shock. Using death certificate data for 2005-2018, a retrospective population-based study found that 6.7% of all deaths were sepsis-related, and sepsis was listed as the underlying cause of death in 21% of these decedents (Ref. 2). A retrospective cohort study involving health care data from over 7 million hospitalizations across 409 hospitals found that the incidence of sepsis did not change significantly between 2009-2014 (Ref. 3). Per the Centers for Disease Control and Prevention (CDC), people are at higher risk for sepsis who are younger than one year old, 65 years or older, have weakened immune systems, chronic medical conditions (e.g., diabetes, lung disease, cancer, kidney disease), recent severe illness or hospitalization, or who are sepsis survivors. In addition, the CDC reports that, in a typical year, sepsis contributes to at least 1.7 million adult hospitalizations, and at least 350,000 deaths annually. (Ref. 4).

The causative agents in sepsis include bacterial, mycobacterial, fungal and viral pathogens. In a study that included data from 2013-2015 involving 225 adult patients and 75 pediatric patients from 4 acute care hospitals in New York, the pathogens causing sepsis were not identified in over 31% of adult patients. However, when a pathogen was identified, the most commonly identified organisms were bacteria, and 97% of the adult patients had at least one comorbidity (Ref. 5). People who survived sepsis are at higher risk for getting sepsis again (Ref. 6).

[4] This draft guidance was originally published as final guidance in the *Federal Register* on January 7, 2025 (90 FR 1141). 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 Disease Agents Associated with Sepsis 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.

## III. DISCUSSION

FDA identified sepsis as a relevant communicable disease agent or disease (RCDAD) under 21 CFR 1271.3(r)(2) when the August 2007 HCT/P DE Guidance was issued. Therefore, for donors of HCT/Ps recovered on or after August 27, 2007,[5] screening for risk associated with sepsis is required (21 CFR 1271.75(a)). Under this guidance, sepsis remains an RCDAD under 21 CFR 1271.3(r)(2). The determination of sepsis as an RCDAD is based on the risk of transmission by HCT/Ps of any agent that could cause sepsis, severity of effect, and availability of appropriate screening measures, as discussed below.

### A. Risk of Transmission

There is a risk of transmission by HCT/Ps of any infectious agent that could cause sepsis. Various bacterial (including mycobacterial), fungal, and viral agents have been shown to be transmissible via use of HCT/Ps (Refs. 7-13), and these agents have sufficient incidence and/or prevalence to affect the potential HCT/P donor population. Bacterial infection potentially resulting in sepsis with associated morbidity and mortality is a recognized risk from transfused blood and blood components[6] (Refs. 14-15) and from transplanted organs (Refs. 16-18).

### B. Severity of Effect

Sepsis could be fatal or life-threatening, result in permanent impairment of a body function or permanent damage to a body structure, and/or necessitate medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

### C. Availability of Appropriate Screening and/or Testing Measures

Appropriate screening measures have been developed for detection of sepsis (see below). Sepsis is a clinical diagnosis and, as such, there are no specific testing measures to detect sepsis that serve to prevent the transmission of a pathogen that causes sepsis. However, testing for pathogens that may cause sepsis is available.

## IV. RECOMMENDATIONS

The HCT/P establishment's responsible person (21 CFR 1271.3(t)) must determine and document the eligibility of a cell or tissue donor (21 CFR 1271.50). The responsible person(s) who is (are) authorized to perform designated functions for which he or she is trained and

[5] The August 2007 HCT/P DE Guidance states: "We recommend that you implement the recommendations in this guidance as soon as feasible, but not later than 6 months after the original issuance date of this guidance (February 27, 2007)." https://www.fda.gov/media/73072/download.

[6] See Guidance for Industry, *Bacterial Risk Control Strategies for Blood Collection Establishments and Transfusion Services to Enhance the Safety and Availability of Platelets for Transfusion* (December 2020), https://www.fda.gov/media/123448/download.

qualified (i.e., related to making a donor eligibility determination) should have appropriate medical training and be qualified to identify risk factors and conditions, clinical evidence, and physical evidence consistent with higher risk for sepsis.

### A. Screening a Donor for Risk Factors and Conditions of Sepsis

Unless an exception identified in 21 CFR 1271.90(a) applies, you must review relevant medical records (21 CFR 1271.3(s)) and ask questions about the donor's medical history and relevant social behavior (21 CFR 1271.3(n)), including risk factors for RCDADs (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 donor who is identified as having a risk factor for sepsis. The following condition should be considered a risk factor:

1. Persons who, currently, are known to have a medical diagnosis of sepsis or suspicion of sepsis from their most recent healthcare facility stay or visit preceding HCT/P recovery that is not documented as resolved. (Refs. 1-6).

### B. Screening a Donor for Clinical Evidence of Sepsis

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

Except as noted in this section, and in accordance with 21 CFR 1271.75(d), you must determine to be ineligible any potential donor who exhibits clinical evidence of sepsis. Examples of clinical evidence of sepsis may include:

1. medical records of a potential donor from their current healthcare facility stay preceding HCT/P recovery, that document sepsis, bacteremia, septicemia, sepsis syndrome, systemic infection, systemic inflammatory response syndrome (SIRS) due to infection, or septic shock, that is not resolved. (Refs. 1-6, 19-22);

2. clinical evidence of current systemic infection exhibited by a potential donor whose immune system was weakened and unable to respond to infection (i.e., immunocompromised or immunosuppressed, such as due to age, a medical condition, or medication), or who is a recent sepsis survivor. In this scenario, when feasible and appropriate, you should communicate (and document your communication) with the patient's primary treating physician to obtain additional information regarding their patient's potential for higher risk of sepsis (Refs. 1-6, 19-22).

If a living donor appears healthy and does not have a recent history of sepsis or suspicion of sepsis, the donor is not considered to have risk of sepsis.

If available medical records did not document sepsis risk as described in listing 1. above, and any applicable communication with the patient's primary treating physician in listing 2. above was not conclusive, you should consider the following indicators of higher risk for sepsis when making a donor eligibility determination (Refs. 1, 19-25):

- Possible signs of sepsis may include altered mentation, hypoxemia, elevated lactate, oliguria, hypotension, renal dysfunction, elevated bilirubin, and/or multi-system organ failure.
- Prolonged stays (>7 days) in an intensive care unit.
- Positive blood cultures, although sepsis may be present without a positive blood culture.

### C. Screening a Donor for Physical Evidence of Sepsis

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 donor who has a risk factor for or clinical evidence of sepsis. The following is an example of physical evidence associated with disease agents that can cause sepsis:

1. Unexplained generalized rash or fever (Refs. 26-27).

### D. Testing a Donor for Evidence of Sepsis

As stated previously, there are no specific testing measures that detect sepsis that serve to prevent the transmission of a pathogen that causes sepsis. However, testing for pathogens that may cause sepsis is available and results of testing should be considered when making a donor eligibility determination.

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