Request for Congressional Sign-On Letter

The Association for Advancing Tissue and Biologics (AATB) urges members to write to the Food and Drug Administration expressing concerns with the agency's current approach to screening human tissue donors for sepsis. The current approach could lead to an approximately 25 percent reduction in tissue donors which would threaten the availability of allograft tissue products for patients in need. A template letter is below. For more information or a clean copy of this letter, please contact Andy Vogt (vogta@aatb.org).

Marty Makary, MD, MPH
Commissioner
Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993-0002

Dear Commissioner Makary:

We write today regarding the Food and Drug Administration (FDA) policy on screening human tissue donors for sepsis. We share the agency's goal of reducing infectious disease transmission via contaminated human cells, tissues, and cellular or tissue-based products (HCT/Ps), as evidenced by the House of Representatives passage of H.R. 1082, the *Shandra Eisenga Human Cell and Tissue Product Safety Act* last year. As we continue to meet with experts and constituents in this field, we have heard that screening for *systemic infection* (meaning evidence of an active, disseminated infection with potential for communicable disease transmission), rather than a sepsis diagnosis, may be a more effective strategy for mitigating disease transmission. We therefore urge the FDA to consider adopting this approach prior to finalizing the draft guidance document *"Recommendations to Reduce the Risk of Transmission of Disease Agents Associated with Sepsis by Human Cells, Tissues, and Cellular and Tissue-Based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)"* ("sepsis guidance"). Assessment for systemic infection, rather than sepsis, more directly aligns with our and FDA's goal of reducing communicable disease transmission by targeting actual infection risk.

When the FDA finalized its most recent guidance on donor eligibility (DE), in 2007, it was reasonable to classify sepsis as a relevant communicable disease agent or disease (RCDAD) as a surrogate measure for infection risk. However, it is now clear, given the evolution of "sepsis" in clinical practice since the 2007 DE guidance, that a sepsis diagnosis is not a scientifically valid surrogate for communicable disease risk in tissue donation. As detailed below, reliance on sepsis as a surrogate may both unnecessarily exclude otherwise suitable donors and potentially fail to identify donors with true potential for disease transmission.

A primary concern is that multiple sepsis definitions remain in use, and experts continue to disagree on how the term should be applied in clinical practice as it relates to the presence of an

infection. A sepsis diagnosis in a potential donor's medical record may reflect an infection that warrants exclusion under donor eligibility criteria, or it may simply indicate a condition that requires additional clinical assessment. Some infections, even those that could contribute to a sepsis diagnosis (such as a urinary tract infection), are easy to treat and should not in and of themselves be disqualifying for potential tissue donors. Absent careful, case-specific evaluation, such an approach would seem to unnecessarily disqualify otherwise eligible donors. A study conducted by the American Association of Tissue Banks suggests categorical exclusion based on a prior sepsis diagnosis could result in an approximately 25 percent reduction in tissue donors, which will most likely have an adverse effect on the availably of tissue products for patients in need.

An additional concern is that sepsis does not seem to meet the three conditions provided by FDA to qualify as an RCDAD (i.e., risk of transmission, severity of effect, and availability of appropriate screening measures or tests). In particular, sepsis is not itself a transmissible disease and may not even be the result of an infectious disease. In cases where sepsis is the result of an infection, that infection may or may not pose a risk of transmission to a tissue recipient. In short, the designation of sepsis as an RCDAD conflates clinical severity with communicable disease risk and incentivizes formulaic decision-making that is not reflective of the true risk of disease transmission. By contrast, designating systemic infection as an RCDAD—rather than relying on the presence or absence of a sepsis diagnosis—could more consistently identify potential donors who present a meaningful risk of infectious disease transmission, particularly those with objective evidence of systemic infection but that were not septic and had no mention of sepsis in their medical record.

Finally, coding, payment, and reimbursement practices have further contributed to concerns about the accuracy and consistency of sepsis diagnoses. We understand that the Office of the Inspector General (OIG) plans to release a report this year on *"Medicare Inpatient Hospital Billing for Sepsis,"* which will examine the sepsis definitions in use today. In their description of the forthcoming report, OIG notes that the Centers for Medicare and Medicaid Services (CMS) and Centers for Disease Control and Prevention (CDC) "recognize an older, broader definition," and that "there are concerns that hospitals may be taking advantage of this broader definition, as they have a financial incentive to do so." We encourage the agency to consider the OIG findings prior to finalizing the sepsis guidance to better understand if the definition used by CDC and CMS has contributed to an excessive number of sepsis diagnoses in the United States.

We appreciate your continued commitment to ensuring the highest standards of safety and oversight for human cells, tissues, and cellular or tissue-based products (HCT/Ps) and to minimizing the risk of infectious disease transmission. We stand ready to work with you on these issues, and we encourage you to consult with stakeholders and experts in this area as you consider an appropriate path forward.

Sincerely,