American Society of Transplant Surgeons®

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December 20, 2021

Janet Woodcock, MD
Acting Commissioner
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Docket No. FDA-2012-N-0559 for Proposed Collection; Comment Request; PHS Guideline on Infectious Disease Issues in Xenotransplantation

Dear Commissioner Woodcock:

The American Society of Transplantation Surgeons (ASTS) is pleased to have the opportunity to comment on the request for information regarding the Public Health Service (PHS) Guideline on Infectious Disease Issues in Xenotransplantation. ASTS is a medical specialty society representing approximately 1,900 professionals dedicated to excellence in transplantation surgery. Our mission is to advance the art and science of transplant surgery through patient care, research, education, and advocacy.

Given the growing success in xenotransplant translational studies and the ever-closer clinical application of solid organ and cell-based xenotransplantation, we believe the discussion is timely and important. We have carefully reviewed the Guidelines posted 20 years ago and the Agency's recent briefing document. There are four areas about which we have specific comments: **1) optimal selection of xenograft recipients, 2) surveillance for infectious disease of xenograft recipients and other persons at risk of exposure, 3) safe handling of donor and recipient tissues post-mortem, and 4) creation and management of a central database and sample repository.**

The goal of these comments is to enhance clinical safety and the quality of care for patients, clinical staff and the community, while allowing clinical investigation to move forward. The risk for infection will, of course, be related to the intensity and duration of immunosuppression deployed in a specific xenotransplantation regimen that will be defined for each specific protocol. For all xenotransplant trials, it is expected that Universal Precautions will be employed that have provided a high level of safety in the care of individuals infected with other pathogens. For aerosol-generating procedures and/or respiratory infections, airborne precautions can be employed during hospitalization. Otherwise, routine personal protective equipment will be utilized.

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I. Selection of Xenograft Recipients

A. Factors Influencing Patient Selection

1. Pig organ transplantation should ***not*** be offered to patients who have underlying immune deficiency or who have immunocompromised or otherwise debilitated close family members or social contacts.
2. The patient and his/her immediate family and close social/sexual contacts should be required to provide baseline samples of blood for storage against future epidemiologic investigations.

B. Surveillance for Infectious Disease of Xenograft Recipients and Other Persons at Risk of Exposure

Any hospital personnel who are pregnant (or might become pregnant while they are participating in the care of the xenograft recipient) should ***not*** participate in the direct care of the patient or be exposed to source animal or recipient body fluids, cells, or tissues. Care providers who are themselves immunodeficient should ***not*** participate in the direct care of the patient or be exposed to source animal or recipient body fluids, cells, or tissues without a full understanding of potential risks.

1. Operating room personnel who may possibly be exposed to pig tissues, cells, blood, or other bodily fluids or to the xenograft recipient's tissues, blood or bodily fluids should have baseline blood samples drawn at the time of exposure. Although most personnel will be protected from direct contact, there is a possibility that they may be exposed by a needle stick or laceration or unanticipated failure of the protective clothing. The blood samples drawn from the personnel would be stored (see below).

2. Supportive personnel, e.g., those who do ***not*** come into direct contact with pig tissues, cells, or blood, or recipient's blood or other bodily fluids, would ***not*** need to provide a blood sample for storage.

3. In the event that an accident occurs that exposes them directly to pig or recipient plasma, serum, blood, cells, or other bodily fluids, medical, nursing, and auxiliary staff caring for the patient should then be required to provide a sample of their blood for storage or testing immediately and again at 3-4 weeks and at 3 and 6 months after the event.

4. Personnel working in a laboratory with pig or recipient plasma, serum, blood, cells, or other bodily fluids, e.g., saliva, sputum, urine, should only be required to provide a sample of blood for storage in the event of an accident that exposes them directly to pig or recipient plasma, serum, blood, cells, or other bodily fluids.

II. Storage of Blood Samples

Immunosuppressed allotransplant recipients generally manifest either donor-derived or opportunistic infections in the first-year post-transplantation.[1] Malignancies and uncommon infections may manifest later, but generally within 5-10 years. Patient survival post-organ transplantation is generally less than 20 years. Source animals will be intensively screened for xenotransplantation studies. Frozen storage (e.g., -80 degrees) of serum, cells, and tissues is costly and cumbersome. Storage beyond 20 years for initial studies should not be necessary. Practically, unless regulatory authorities will provide storage capability, it seems unlikely that investigators, patients or corporate entities will be available to monitor storage beyond 20 years.

Although it should be the responsibility of the sponsor of the clinical trial to provide the required blood samples for long-term storage, storage should be the responsibility of a recognized government authority or institution (or an FDA-designated organization), and not be made the responsibility of the sponsor of the clinical trial or the hospital in which the trial is carried out.

III. Handling of Donor and Recipient Tissues Post-Mortem

Cadavers and tissues that have been in circulatory contact (via blood) with a xenograft require special handling until further information is known about their actual infectious risks. In general, all individuals who are in close contact with blood or body fluids from recipients of xenografts should exercise universal precautions and wear proper PPE. Donor pig herd-specific infectious control protocols for zoonotic pathogen risk stratification with development of testing and sample storage protocols will be an essential component of reducing the risk of transmission from the xenograft to recipient and close contacts. Recipients should be tested for porcine endogenous retrovirus (PERV) A, B, and C mRNA production by reverse transcriptase-PCR (RT-PCR) and DNA integration by quantitative real-time PCR. Baseline blood should be collected for individuals in close contact with the recipient's blood and body fluids. Should at any time the recipient's PERV screening become positive, testing should be performed on those with the highest risk contact with the recipient. Should the recipient of a xenograft in the early phase studies expire in or outside of the hospital, a postmortem should be conducted with tissue, blood, and fluids sampled, tested and stored. Immediate on-site embalming or cremation is suggested as well as appropriate disposal of any tissue removed and not stored.

In conclusion, risk mitigation protocols including standard infection control measures, active surveillance for PERV in the recipient, and passive storage of samples assessed to have been at potential risk of exposure to transmissible zoonotic pathogens from the recipient should be implemented premortem. The recipient should be engaged in an active surveillance testing protocol and those with intimate contact with blood and body fluids need only a passive surveillance approach with collection of baseline plasma and frozen PBMCs and testing only if there is a direct high-risk exposure or if PERV is detected in the recipient's testing. Personnel involved in post-mortem examinations should don appropriate personal protective equipment and on-site embalming or cremation of the decedent is recommended after the post-mortem.

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[1] **Fishman JA. Infections in Solid Organ Transplantation. New Eng J Med. 2007,** 357:2601-14. Fishman JA. Infection in Organ Transplantation. Am J Transplant. 2017; 17:856-879. doi: 10.1111/ajt.14208 PMID: 28117944.

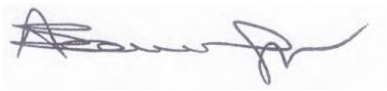
IV. Creation and Management of a Central Database, Sample Repository and Advisory Committee

In section 5 of the 2001 PHS guidelines on Infectious Disease Issues in Xenotransplantation, a number of public health needs are detailed that include development of: 1) A National Xenotransplant Database, 2) a Biologic Specimen Archive, and 3) a Secretary's Advisory Committee on Xenotransplantation (SACX). We strongly encourage the agency to begin active development of each of these initiatives as soon as possible. Specifically, we recommend that a record system be developed that allows for easy, accurate, and rapid linkage of information among the specimen archive, the recipient's medical records, and the records of the xenotransplant source animal for 20 years. The guideline for 50 years of data and specimen retention was based on the potential risk for cross-species transmission of pathogenic persistent virus. Although the development of such a record system is a one-time burden, the ongoing data and specimen collection, as well as the maintenance of this repository represents a significant burden on both sponsors and transplant programs with resultant significant cost and hardship that could deter xenotransplant progress.

A central repository for both data and specimen collection is essential for the successful clinical application and monitoring of xenotransplantation, albeit with institution of a more realistic retention of 20 years, rather than 50 years, for both data and specimen collection. Furthermore, the central repository should reside under the purview of the sponsor for early clinical trials in xenotransplantation - with transference mechanisms in place should the sponsor become unable to provide this function within the designated 20 year follow up period. Public health authorities would be provided access if required for epidemiological investigations resulting from infectious disease exposures. The biological specimen archive should ultimately be maintained centrally by the Agency to maximize safety and fidelity of the process. Loss of critical specimens due to the transitory nature of companies, could threaten the performance of epidemiologic investigations in the future. Once xenotransplantation achieves widespread utilization akin to standard of care, the onus of the central repository should fall wholly upon a centralized, national system run by, or under contract with, the federal government. The Secretary's Advisory Committee on Xenotransplantation (SACX) should oversee the process of transference to a centralize federally funded approach, to provide oversight and a public forum for discussion of related issues. We suggest that the structure and functions of the SACX now be actively developed, as proposed 20 years ago in the PHS Guideline on Infectious Disease Issues in Xenotransplantation.

If you have any questions regarding ASTS' position on these issues, please do not hesitate to contact Jennifer Nelson-Dowdy, ASTS Advocacy Manager at Jennifer.Nelson-Dowdy@asts.org or by calling (703) 414-7870.

Sincerely,



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