# June 29-30, 2022 CTGTAC Discussion Questions

1. Pigs can harbor endogenous viruses that may impact the health of transplanted tissues or organs or impart infectious disease risk to the recipient and their close contacts. Porcine circovirus 3 (PCV 3), porcine endogenous retrovirus (PERV) and porcine cytomegalovirus (PCMV) have been identified as viruses that may impact organ function after transplantation or be transmitted to recipients of xenotransplantation products, their contacts, and the public. Please discuss the following:

    a. Describe sensitive detection systems available for the detection of infectious agents in pigs used for xenotransplantation, and which methods should be used orthogonally.

    b. PCV 3 transmission from donor pigs to baboons has been reported in preclinical studies. Please discuss the potential for PCV 3 xenozoonotic infections in humans.

    c. PCV 3-infected pigs have been reported to exhibit cardiac and multisystemic inflammation. Please discuss the impact of PCV 3 on transplanted organs.

    d. Three subtypes of PERV (A, B, C) and PERV A/C recombinants have been found in various breeds of pigs. Please discuss which subtypes present the greatest risk and how PERV risk can be mitigated or eliminated.

    e. Please discuss any other known or emerging viruses that should be considered in the context of human xenotransplantation.

2. Archiving of source animal, product, and patient samples for up to 50 years is the current FDA expectation outlined in FDA-issued guidance titled, *"Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans"* (December 2016). Archived samples can aid in investigation of adverse events, and the archiving recommendations apply to xenotransplantation products, including those that have had ex vivo contact with animal cells, but are not themselves of animal origin. Please discuss whether the expectations for archiving of patient samples should be modified in terms of length of storage and/or sample sizes.

    a. Please discuss technologies that could be used to analyze cell banks and final products and that might be sufficiently sensitive to allow for modification of archiving requirements.

    b. Please discuss conditions that would alter the expectations for patient follow-up.

    c. Please discuss conditions, if any, under which patient follow-up for disease transmission should not be required.

    d. Please discuss conditions under which recipients of xenotransplantation products should be allowed to donate blood or tissues/organs.

3. Pig cells or organs transplanted into humans are FDA-regulated articles and are subject to regulatory requirements such as identity, purity, and potency. Please discuss assays or testing strategies that might be appropriate to perform prior to transplantation to evaluate the safety and efficacy of these articles.

4. Transplantation of animal cells and organs into humans is associated with hyperacute rejection, vascular injury, cell-mediated rejection, and chronic rejection. Options for controlling rejection include genetic modification of donor pigs and modulation of the immune response in the recipient. Please

discuss the most promising strategies to prevent rejection of pig organs. In your discussion, please consider the balance between the potential benefits of the desired genetic modifications and/or immune response modulation and the potential for detrimental transplant outcomes.

5. Transplantation of pig cells and organs is intended to provide replacement for non-functioning/damaged human cells and organs. Therefore, it is important to understand the characteristics of these cells or organs in the pig to ensure they have the characteristics needed to provide replacement therapy for the human recipient before transplantation. And, it is important to monitor these cells and organs to demonstrate that they provide the expected functions after transplantation. Please discuss existing data to address the following issues related to pig cells and organs intended for transplantation into humans:

a. The ability of the target pig organ to support full organ function in humans.

b. The natural aging of the target organ in the pig relevant to expected organ function over time in humans.

6. Transplanted pig organs are likely to be exposed to a variety of drugs that were not routinely used in the donor animals. Such drugs could include products to treat the recipient's underlying medical condition(s) (e.g., diabetes, hypertension), as well as drugs (e.g., immunosuppressants) intended to ensure the success of the transplant. The transplanted organ may alter the pharmacodynamic and pharmacokinetic profiles of these drugs, with consequences for the medical management of the recipient. In addition, these drugs could be toxic to the transplanted organ. Please discuss the importance, limitations, and feasibility of studies of such drugs in the pig model prior to transplanting the pig organ into humans.