Considerations for the Characterization of Xenotransplantation Products as Biologics

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Xenotransplantation products include human cells or tissues which have had ex vivo contact with animal cells, cellular or tissue products derived from animals, and whole organs derived from animals.

Xenotransplantation products regulated as biologics must meet General Biological Product Standards as outlined in Part 610 of the Code of Federal regulations:

- potency (21 CFR 610.10)
- sterility (21 CFR 610.12)
- purity (21 CFR 610.13)
- identity (21 CFR 610.14)

Potency

- Tests for potency shall consist of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency in a manner adequate to satisfy the interpretation of potency given by the definition in 21 CFR 600.3 (s).

- 600.3 (s) The word potency is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result.

Sterility

Manufacturers of biological products must perform sterility testing of each lot of each biological product's final container material or other material, as appropriate and as approved in the biologics license application or supplement for that product.

Identity

The contents of a final container of each filling of each lot shall be tested for identity after all labeling operations shall have been completed. The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on final container and package labels and circulars, and distinguish it from any other product being processed in the same laboratory. Identity may be established either through the physical or chemical characteristics of the product, inspection by macroscopic or microscopic methods, specific cultural tests, or in vitro or in vivo immunological tests

Purity

Products shall be free of extraneous material except that which is unavoidable in the manufacturing process described in the approved biologics license application.

- (b) Test for pyrogenic substances. Each lot of final containers of any product intended for use by injection shall be tested for pyrogenic substances.

Cellular Xenotransplantation Product

- Potency - a test of cellular function such as insulin production for islet cells
- Identity - cellular phenotyping using flow cytometry or immunohistochemistry
- Sterility - by an established method
- Purity -
  - Tests for any residual reagents from manufacturing or transport
  - Endotoxin testing for pyrogens

Whole Human Organs

Human allogeneic organ transplantation is regulated by the Public Health Service through the Health Resources and Services Administration (HRSA) under CFR Title 42, Section 121

(a) Tests. An Organ Procurement Transplant Network (OPTN) member procuring an organ shall assure that laboratory tests and clinical examinations of potential organ donors are performed to determine any contraindications for donor acceptance, in accordance with policies established by the OPTN.

(b) Acceptance criteria. Transplant programs shall establish criteria for organ acceptance, and shall provide such criteria to the OPTN and the OPOs with which they are affiliated.

Established Human Organ Testing, Using Kidney As A Model

- Health status of donor
  - Cause of death
  - Pre-donation creatinine level < 1.5 mg/dL
- Macroscopic inspection of organ
  - Tumors, anatomical variation, thrombosis, scarring
- Biopsy of organ
  - No clear consensus as to how histology correlates to recipient risk or outcome

Methods Under Development

- Ex vivo perfusion measurements
  - Glomerular Filtration Rate (GFR), renal blood flow, intra-renal resistance
- Machine perfusion characteristics
  - Perfusate biomarkers: lactate dehydrogenase, Glutathione-S-transferase
- Omics approaches
  - Transcriptomic markers of kidney injury

Release Criteria For Xeno Organs

- **Safety**
  - Pathogen testing
    - Routine surveillance of herd
    - Whole animal
    - Organ and/or surrounding tissues
      - Retention samples
- **Identity**
  - Verification of intentional genetic alterations
    - Genotypic Stability through generations
  - Visual inspection
    - Size matching
- **Purity**
  - Endotoxin testing
  - Sterility
  - Residual transport fluids

- **Potency**
  - Assessment of organ viability
    - Visual inspection-anatomical variation, tumors scarring
  - Assessment of organ function
- **Multiple timepoints will be required, with justification**
  - Whole animal, before and after transport
  - After organ removal
  - After transport to clinical site

Question 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.