FDA Views on Xenotransplantation

Cellular, Tissue, and Gene Therapy Advisory Committee Meeting (CTGTAC)
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Judith Arcidiacono M.S.

U.S. Food and Drug Administration

Center for Biologics Evaluation and Research

Office of Tissues and Advanced Therapies

Definition of Xenotransplantation

Any procedure that involves the transplantation, implantation, or infusion into a human recipient of either

(a) cells, tissues, or organs from a nonhuman animal source, or

(b) human body fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman animal cells, tissues or organs.

2001 PHS Guideline on Infectious Disease Issues in Xenotransplantation https://www.fda.gov/media/73803/download

2016 FDA Guidance on Xenotransplantation https://www.fda.gov/media/102126/download

Purpose of this CTGTAC Meeting

Provide the Food and Drug Administration (FDA), xenotransplantation product developers, and stakeholders with insights and perspectives regarding requirements to ensure the efficacy and safety of xenotransplantation products

Overview of Discussion

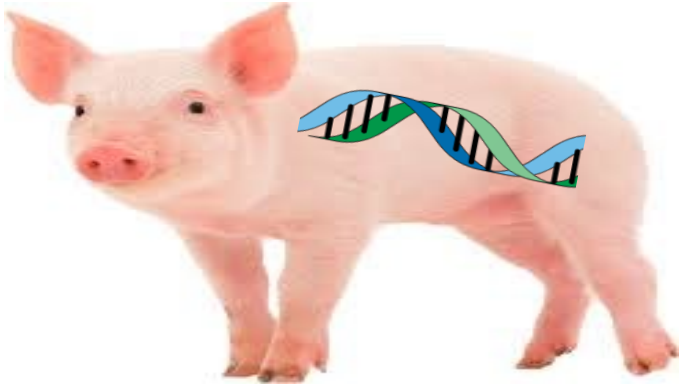
- Infectious disease risks associated with xenotransplantation products and porcine donor animals, and how to assess these risks.
- Infectious disease testing for xenotransplantation products that have *ex vivo* contact with animal cells.
- Strategies for meeting regulatory requirements for measuring identity, purity and potency of xenotransplantation products.
- Current strategies to control xenotransplant rejection by gene modification of donor animals and by systemic immune suppression of the human recipients.
- Characterization studies to ensure the function of the pig organs before and after transplantation.

Centers with Regulatory Oversight for Xenotransplantation Products

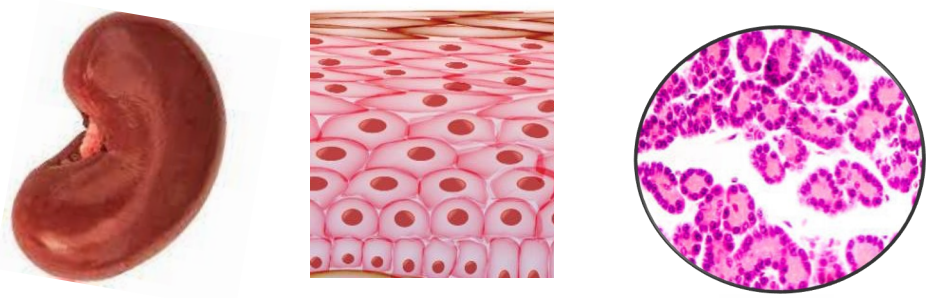
Center for Veterinary Medicine (CVM)

Center for Biologics Evaluation and Research (CBER)

REGULATED ARTICLES



Genetic Alterations in the Animal



ORGANS TISSUES CELLS

Review Teams for Xenotransplantation Products

Office of Tissues & Advanced Therapies	Other Offices at CBER	Other FDA Centers	Outside Consultants
• Project Manager • Chemistry, Manufacturing & Controls • Pharmacology /Toxicology • Clinical • Virology	• Compliance • Veterinary Sciences • Statistics • Epidemiology • cGMP Manufacturing CBER: Center for Biologics Evaluation and Research	• IGA animal expert (CVM) • Device Expert (CDRH)* • Drug Expert (CDER)** • Policy Experts *CDER: Center for Drug Evaluation and Research **CDRH: Center for Devices and Radiological Health	• Scientific Expert • Medical Expert • Patient Advocate • Ethicist
BASIC REVIEW TEAM	**EXTENDED REVIEW TEAM**	**POTENTIAL COLLABORATORS/CONSULTANTS**	

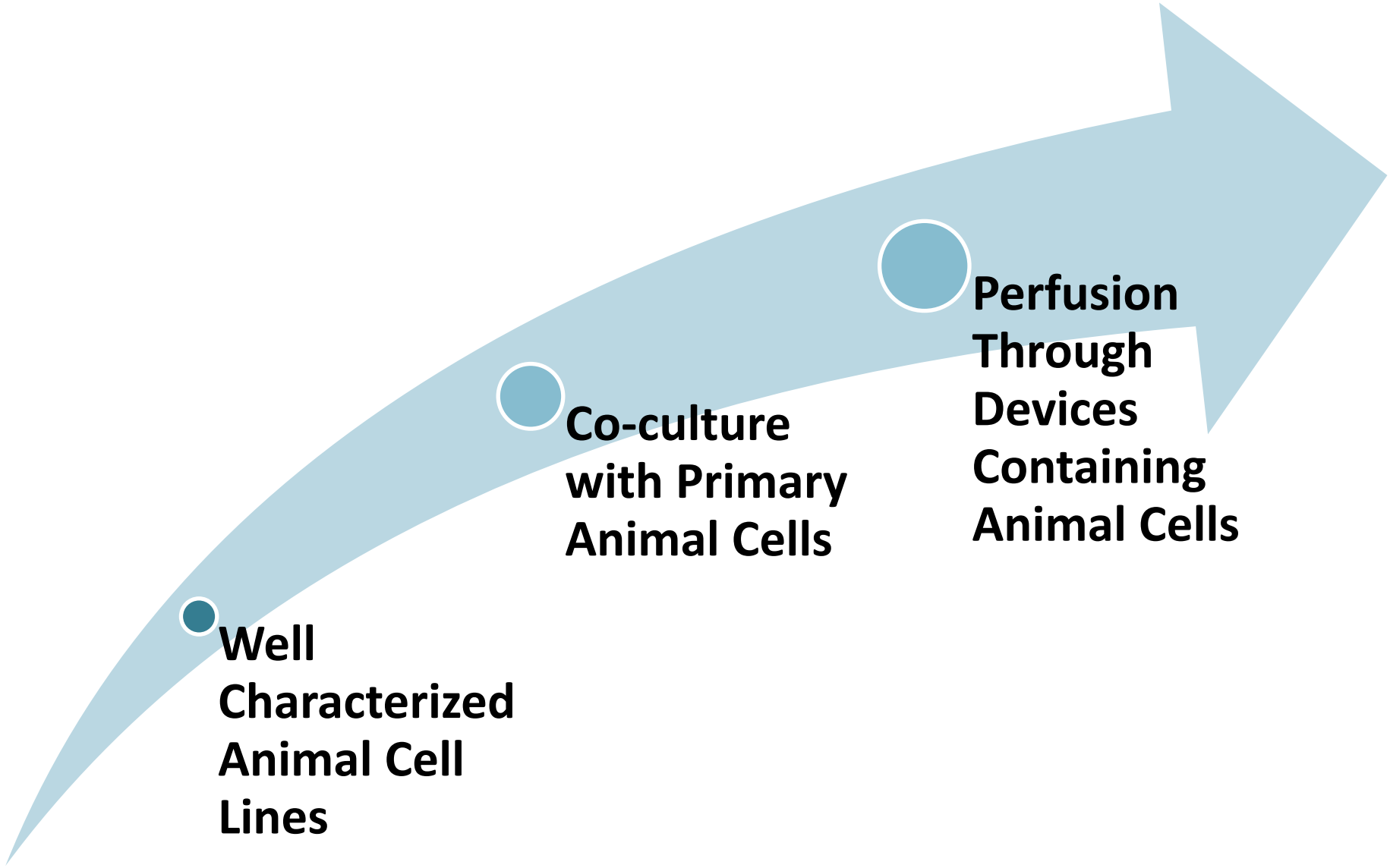
Risks Associated with the Use of Xenotransplantation Products

- Transmission of known and unknown pathogens
- Spread of Infectious disease from the patient to the public
- Adverse inflammatory and immunological responses by the recipient to donor cells or secreted molecules
- Associated adverse effects due to rejection of donor animal cells, tissues or organs
- Physiologic and metabolic incompatibility
- Deleterious effects from the use of immunosuppressive agents

Xenotransplantation Products that have Ex Vivo Contact with Animal Cells

1. Human cells co-cultured with irradiated/inactivated, well characterized animal cell lines
2. Human cells co-cultured with irradiated/inactivated primary (freshly isolated) animal cells
3. Human cells that are perfused through a device containing live animal cells

Perceived Risks for Ex vivo Products



Xenotransplantation Products with *ex vivo* Exposure to Living Animal Cells

- Use of well characterized mouse cell lines as feeder cells
  - Derivation history or animal husbandry well known
  - Applies to some approved products: Epicel, Stratagraft
- Are current analytical technologies sufficiently sensitive to allow flexibility or less stringent archival and donor deferral recommendations?
- Other modes of *ex vivo* contact
  - Discussion of factors that may permit application of regulatory flexibility

Multiple Layers of Safety for Donor Animals

- Animals bred from closed herds of known origin
- Maintenance of animal health
- Maintenance of appropriate animal facilities
- Procedures in place to minimize infectious disease risk
- Screening for infectious agents prior to transplantation
- Quarantine of donor animals prior to harvest
- Documented harvest and handling of donor animal cells, tissues, and organs
- Archiving of samples prior to harvest and post-harvest

Animal and Human Samples

COLLECTION, HARVESTING AND STORAGE

Recommendations from PHS Guideline on Xenotransplantation and FDA Guidance on Xenotransplantation

Samples to be Collected and Archived

Donor/Source Animals

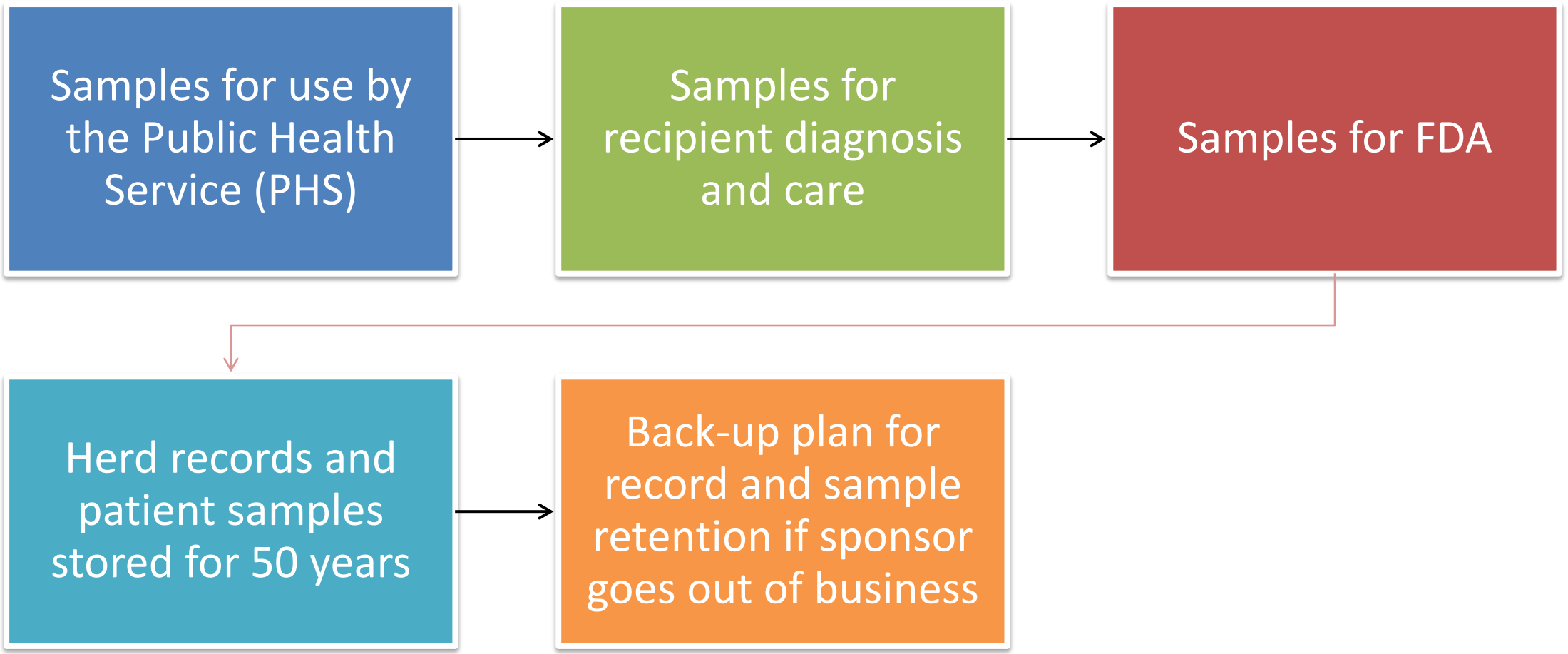
- Portions of the harvested material (cell, tissue or organ)
- Tissues samples from major organ systems at necropsy
- Plasma and leukocytes from the source animal
- Collection times: at pre-determined intervals prior to harvest, at time of harvest, and post-mortem

Samples to be Collected and Archived

Human Recipient/Patient

- Blood, plasma, saliva, leukocytes
- Collection times: pre-transplant, post-transplant at pre-determined intervals, and post-mortem

PHS Guidelines for Sample Archiving



Storage Conditions of Samples

- Samples should be labeled and catalogued in a manner allowing for the linkage between patient samples and donor animal samples.
- Samples should be stored in media appropriate for RNA, DNA, cell viability, and antibody preservation.

Porcine Viruses of Concern in Xenotransplantation

- Porcine Endogenous Retrovirus (PERV)
- Porcine Circovirus (PCV)
- Porcine Cytomegalovirus (PCMV)
- Porcine Roseolovirus (PRV)
- Porcine Lymphotropic Herpes Virus (PLHV)

Porcine Endogenous Retrovirus (PERV)

- Type C gamma retrovirus
- Subtypes
  - PERV A - infects human and pig cells
  - PERV B - infects human and pig cells
  - PERV C- infects pigs only
  - PERV A/C recombinants- infect human cells, 500-fold more infective than PERV A alone

Porcine Circovirus (PCV)

- Three species:
  - PCV 1 - does not cause disease in pigs
  - PCV 2- causes of post-weaning multi-systemic wasting syndrome (PMWS)
  - PCV 3 - causes porcine dermatitis and nephropathy syndrome (PDNS), reproductive failure, cardiac and multisystemic inflammation
- PCV 3 transmission has been observed some in pig-to-baboon orthotopic heart transplantation

Porcine Cytomegalovirus (PCMV)/Porcine Roseolovirus (PRV)

- PCMV is closely related to human herpesvirus 6 and 7.
- Human Cytomegalovirus (HCMV) causes fatal infections in human organ transplant recipients.
- PCMV transmission observed in pig orthotopic heart transplantation in baboons, and associated with a reduced survival time of recipient baboons

Porcine Lymphotropic Herpes Virus (PLHV)

- Gamma herpesvirus that is widespread in pigs
- Closely related to the Epstein-Barr virus (EBV) and Kaposi sarcoma virus, which cause serious disease in humans
- PHLV 1 associated with post-transplantation lymphoproliferative disease (PTLD) in experimental transplantation in mini-pigs
- PTLD is a complication of human allotransplantation and is linked to EBV

Examples of Methods Used to Detect Infectious Disease

- Non-specific in vitro adventitious virus tests with indicator cell lines
- Polymerase Chair Reaction (PCR)
- Next Generation Sequencing (NGS)
- Infectivity assays
- Western Blot
- ELISA and others

Chemistry, Manufacturing and Controls

Product Characterization

- Identity
- Purity
- Potency
- Sterility

Chemistry Manufacturing Controls

Process control (CGMPs)

- Procedures, reagents, and test methods
- Controls for tracking, labeling, and cross-contamination
- Conditions for processing, storage, and shipping

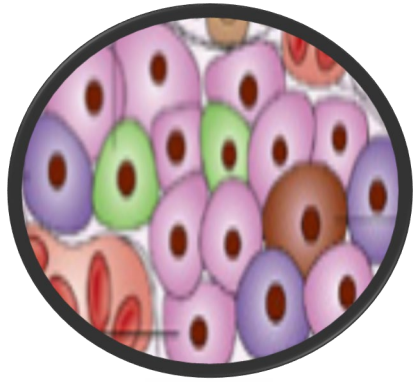
Product characterization

- Identity, purity, potency

Safety testing

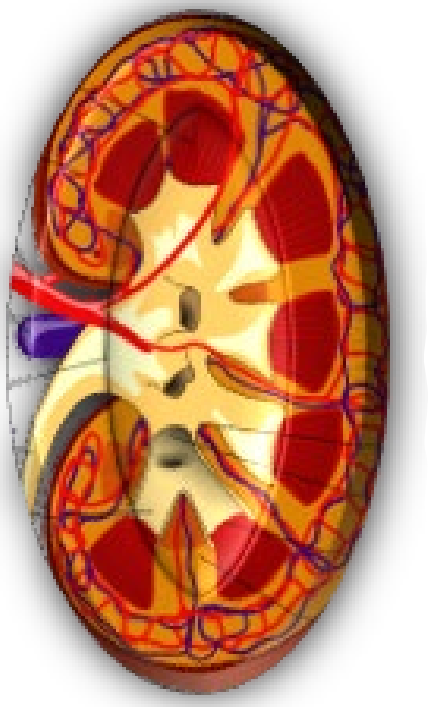
- Infectious disease testing
- Sterility
- Virus inactivation or removal, if possible

Testing of Cells and Tissues that are Processed and/or Stored



- Characterization
  - Identity of desired cells or tissue types
  - Purity – presence of desired cell types and contaminating cell types
  - Potency assays that measure and reflect the intended activity of the tissue or cell type
- Testing for infectious disease
- Qualify all cell culture procedures & reagents for microbial contamination and maintenance of sterility
- Develop a plan for in-process and final product testing

Whole Organ Testing



- Identity- scans of organ to be transplanted
- Purity (adventitious agents)- biopsy to determine cell/tissue types
- Potency- physiological function tests and laboratory measurement of organ function
- Sterility and viral testing- sampling site is important to ensure the ability to detect infectious agents
- Certain testing results may not be available before use
  - Testing of donor animal prior to organ harvest is recommended
- Consult FDA on the testing strategy

Strategies to Control Rejection

- Animals: Intentional Genomic Alterations in Source Pigs
  - Knockout of pig antigens that induce the production of human antibodies
  - Knock-in or expression of human genes that prevent vascular injury and cell-mediated rejection
- Administration of targeted immunomodulatory drugs in combination with genetic alterations
  - Blocking co-stimulatory pathways with monoclonal antibodies (e.g., CTLA4)
  - Calcineurin-inhibiting drugs (e.g., Tacrolimus)
  - T and B cell inhibitors (e.g., anti-thymocyte globulin (ATG) and rituximab)

Needed Information on the Prevention of Rejection

- What are the number and types of genetic alterations needed?
  - Are there organ-specific requirements?
- What is the correct balance between intentional genetic alterations and systemic immunosuppression of recipient?
- Effects of human immunosuppressive drugs on the animal organ.

Conclusion

- Advances in understanding xenotransplant rejection and technologies enabling the genetic modification of pigs for xenotransplantation have moved the field closer towards initiating clinical trials.

- Many questions remain with respect to infectious disease transmission, the effect of intentional genetic alterations on the donor cells, tissues, and organs of the pig, and the use of systemic immunosuppression of the patient/recipient of the xenotransplantation product.

Judith Arcidiacono, M.S.

International Regulatory Expert

Lead for Regenerative Medicine Therapies Standards Program

Xenotransplantation Policy Expert

US Food and Drug Administration
Center for Biologics Evaluation and Research
Office of Tissues and Advanced Therapies

Judith.Arcidiacono@FDA.HHS.GOV

For Regulatory Questions Specific to Office of Tissues and Advanced Therapies
Email: OTATRPMS@fda.hhs.gov
Phone: 240 402 8190