

# FDA Regulatory Oversight for Xenotransplantation Products

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# Learning Objectives

- Define a xenotransplantation product
- Identify the FDA Centers responsible for regulatory oversight of xenotransplantation products
- List the risks associated with xenotransplantation products
- List the stages of rejection of xenotransplantation products
- List measures that can be taken to reduce risks to recipients of xenotransplantation products

# Presentation Outline

- Definition of xenotransplantation
- History xenotransplantation activities
- Regulatory expectations for xenotransplantation products
- Recommendations for patient and animal sample collection

# Definition of Xenotransplantation



Xenotransplantation: any procedure that involves the transplantation, implantation, or infusion into a human recipient of either

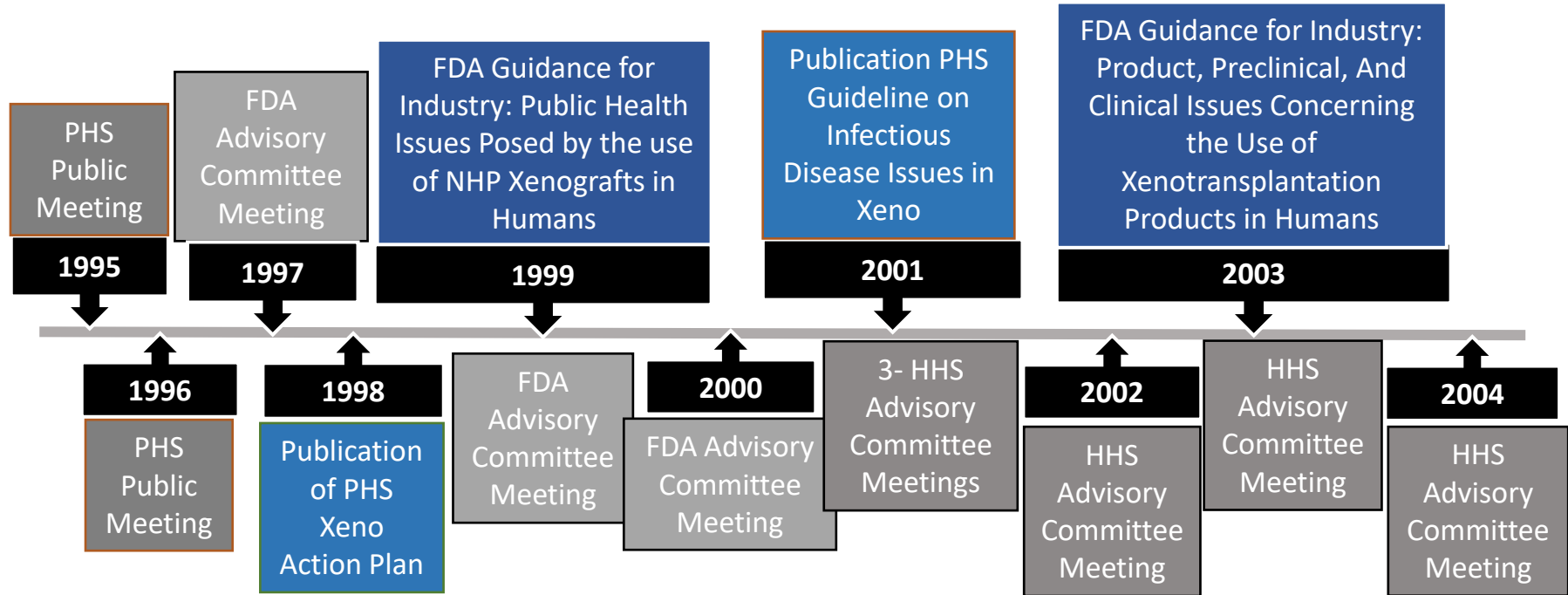
- live cells, tissues, or organs from a nonhuman animal source, or
- human body fluids, cells, tissues or organs that have had *ex vivo* contact with live nonhuman animal cells, tissues or organs.

FDA Xeno Guidance <https://www.fda.gov/media/102126/download>  
PHS Guideline on Xeno <https://www.fda.gov/media/73803/download>

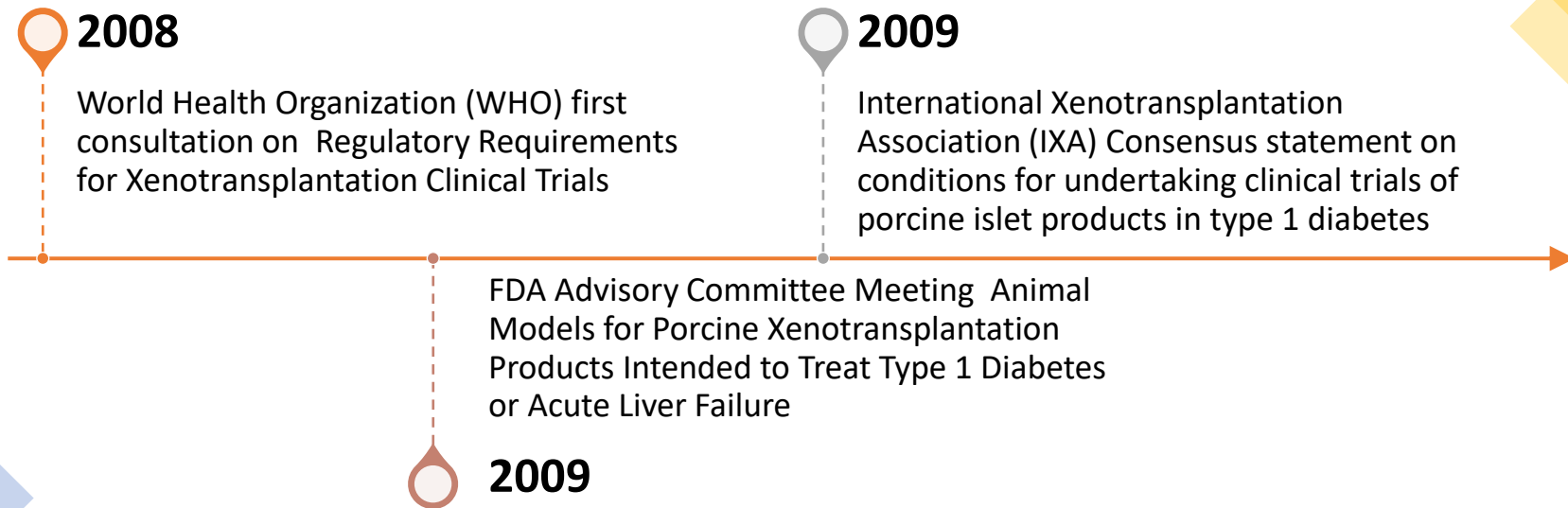
# Examples of Xenotransplantation Products

- Xenotransplantation includes:
  - Whole nonhuman organ transplanted into humans
  - Implantation of non-human cells or tissues into humans
  - Extracorporeal perfusion of human blood over/through nonhuman cells or organ(s)
  - Administration of human cells previously cultured *ex vivo* with nonhuman cells into a human recipient
- Xenotransplantation does not include:
  - Biological products, drugs or medical devices sourced from nonliving cells, tissues or organs, including but not limited to, porcine insulin and porcine heart valves

# Policy Development History for Xeno Products



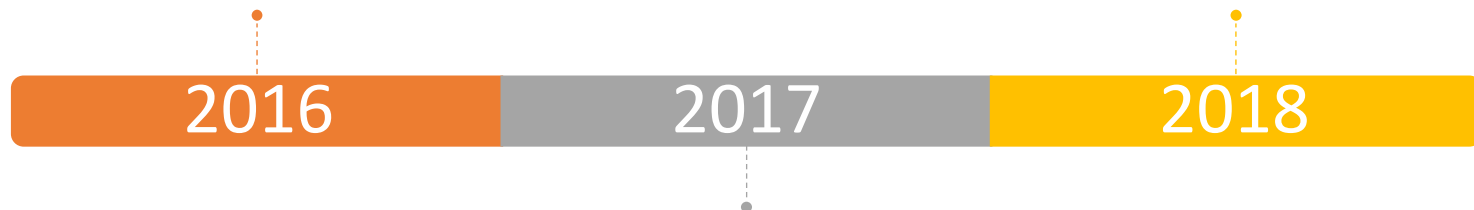
# Xenotransplantation Activities



# Xenotransplantation Activities 2016 - 2018

Guidance for Industry: Product,  
Preclinical, and Clinical Issues Concerning  
the Use of Xenotransplantation Products  
in Humans

WHO-IXA Changsha Communique  
International Consensus on Clinical Trials  
for Xenotransplantation



FDA-IXA Joint Workshop on Advances in  
Xenotransplantation



# Porcine Organ Transplantations

Genetically altered pig kidney transplantation into human decedent

**2021**

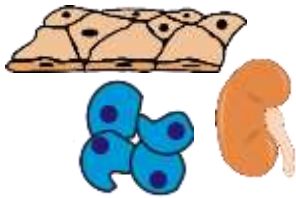
First Clinical-grade porcine kidney xenotransplant using a human decedent model Porrett , P. et al. (2022) *AJT* DOI: 10.1111/ajt.16930

First pig-to-human heart. *Nat Biotechnol* **40**, 145 (2022).  
<https://doi.org/10.1038/s41587>

**2022**

Genetically altered pig heart transplantation into a human recipient

# FDA Centers with Regulatory Oversight for Xenotransplantation Products



## Regulated Articles



### Center for Biologics Evaluation and Research (CBER)

- Animal organ, cell or tissue to be transplanted
- Follow-up on patient post-transplant
  - Function of the transplant
  - Monitoring for infectious disease transmission

### Center for Veterinary Medicine (CVM)

- Animals with Intentional Genomic Alterations (IGAs)
- Follow-up on the stability of the genetic alteration in the herd

SMG 4102 “Inter-Center Coordination of Regulatory Activities for Genetically Engineered Animals and their Expression Products” [\\*https://www.fda.gov/media/92780/download](https://www.fda.gov/media/92780/download)

# Components of CBER's Evaluation for Xenotransplantation Products

## Source Herd

- Appropriate breeding, maintenance of animal health, maintenance of animal facility

## Source Animal

- Procedures to minimize infectious disease risk, screening, harvest and handling of tissues, cells, organs

## Product Processing and Testing

- Process control (cGMP), product characterization, safety testing, lot release

## Preclinical Assessments

- Extrapolation of cross-species infections, immune reactions between source animal and recipient, function of xenotransplantation product, etc.

## Clinical Issues

- Protocol review, informed consent, patient selection, follow-up screening, etc.

Components of  
CVM New Animal  
Drug Applications  
(NADA) for  
Animals with  
Intentional  
Genomic  
Alterations

Product Description

Molecular Characterization of Construct

Molecular Characterization of IGA

Phenotypic Characterization of IGA

Claim Validation

Environmental/Food/Feed Safety

Genotypic & Phenotypic Durability Plan

## Risks Associated with the Use of Xenotransplantation Products

Transmission of known and unknown pathogens

Zoonotic infection to patient, personal contacts,  
health care professionals and general population

Adverse inflammatory and immunological responses  
by host to donor cells or secreted molecules

Rejection of source animal cells, tissues or organs

Physiologic and metabolic incompatibility

Deleterious effects from the use of high-dose  
immunosuppressive agents

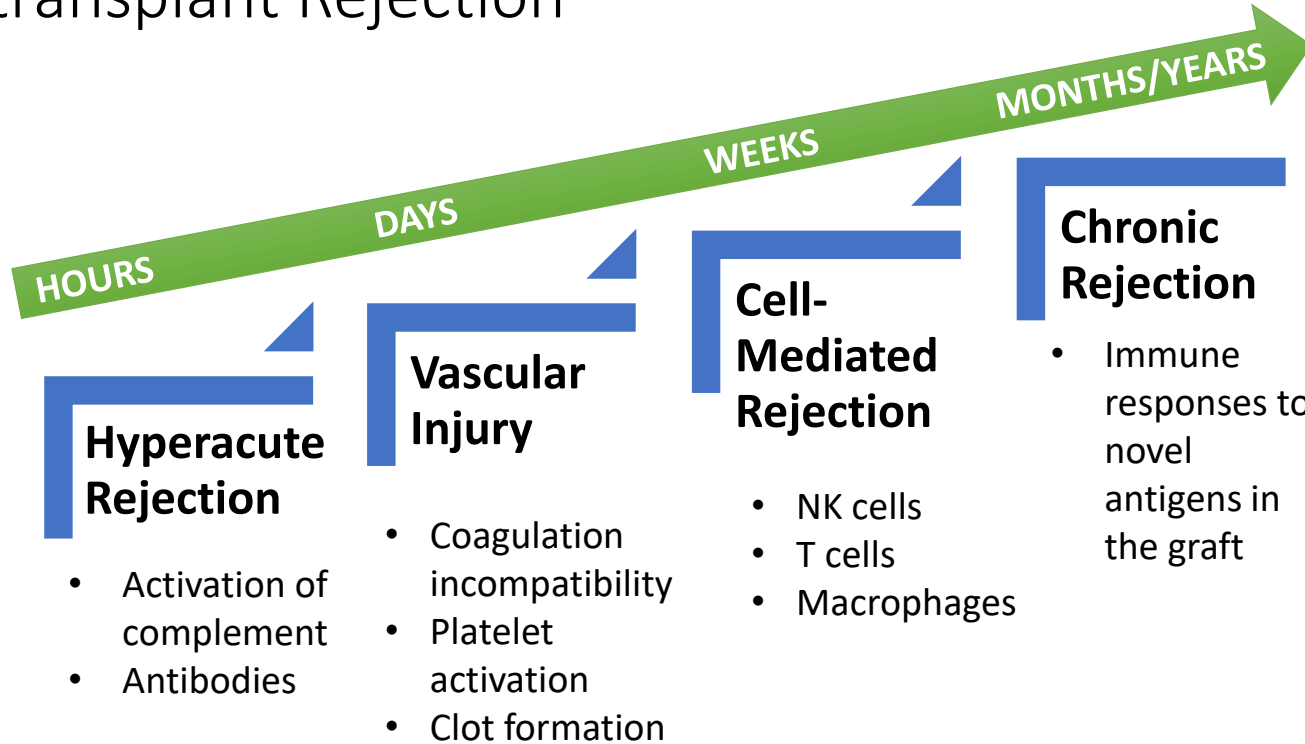
# Pigs as Source Animals for Xenotransplantation Products

# Why are Pigs Used as Donor Animals for Xenotransplantation Products?

- Similarities with humans regarding size and function of tissues, organs, and cells.
- Humans have been exposed to domesticated pigs for centuries
- Pigs can be genetically modified to make them compatible with humans



# Challenges for Use of Pigs As Source Animals: Xenotransplant Rejection





# Porcine Genetic Modifications Described in the Literature (1)



Gene Modification	Function
GGTA1 knockout	Deletion of Gal xenoantigen
CMAH knockout	Deletion of Neu5Gc xenoantigen
Beta4GALNT2 knockout	Deletion of SDa xenoantigen
Human CD55 gene expression	Complement regulation
Human CD46 gene expression	Complement regulation
Human TBM gene expression	Coagulation regulation
Human EPCR gene expression	Coagulation regulation
Human TFPI gene expression	Coagulation regulation
Human CD39 gene expression	Coagulation regulation
Human HO-1 gene expression	anti-inflammatory/antiapoptotic
Human A20 gene expression	anti-inflammatory/antiapoptotic

# Porcine Genetic Modifications Described in the Literature (2)



Gene Modification	Function
HLA-E expression	Regulation of NK-cell-mediated responses
ULBP1 knock-out	Regulation of NK-cell-mediated responses
human CD47 gene expression	Regulation of macrophage-mediated responses
human CTLA4-Ig expression	Regulation of T cell-mediated responses
SLA class I knock-out	Regulation of T cell-mediated responses
PERV inactivation	Prevention of xenozoonoses
Pig Growth Hormone Receptor knock-out	Prevention of pig organ growth after transplantation

# Risks Associated with Genetically Altered Source Animals for Xenotransplantation



## **Genetic alterations must be justified**

Unknown minimal number/types/combination of genetic modifications needed for effective control of host responses to xeno products



## **Off-target effects can lead to**

Altered organ function  
Metabolic changes in organs or organ systems



## **Long-term effects**

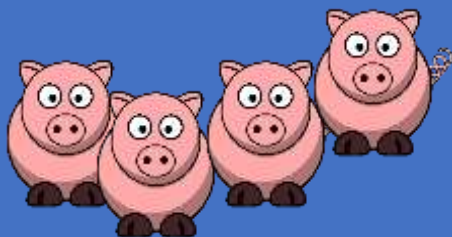
Unknown Impact on performance of the organ over time

# FDA Goals for Source Animals Used for Xenotransplantation



- Balanced risk assessment
- Layers of safety
- Use of best practices and validated technologies

# Source Herd Requirements



## Animals bred from closed herds of known origin

- Documented origin and infectious disease status
- 2+ generations in \*SPF conditions before clinical use
- Control of all animals including gamete donors

## Maintenance of animal health

- Screening/sentinel animal testing (agents, methods, frequency all must be justified)
- Appropriate feed (free of rendered animal materials and natural, non-sterile materials)
- Appropriate health care

## Maintenance of appropriate animal facility

- Well-controlled and monitored pathogen free facility
- Appropriately trained staff with limited access
- Subject to inspection

\*SPF-Specific Pathogen Free

# Requirements for Donor Animals



- Procedures in place to minimize infectious disease risk
  - Quarantine prior to use (generally >3 weeks)
  - Bio-secure transportation (animal facility to clinic)
  - Well controlled surgical environment for harvesting cells, tissues and organs
- Screening
  - Biopsy of to-be-used tissue is preferred
  - Infectious disease as well as histopathology
  - Full necropsy of source animal is recommended
- Documented harvest and handling of cells, tissues and organs
- Archiving of samples

Animal and Human Samples

# COLLECTION, HARVESTING AND STORAGE

*Recommendations from PHS Guideline on  
Xenotransplantation*

# Goals for Establishing Sample Archives

- Ensure health and safety of the patient/recipient and their close contacts
- Provide a source of materials for “look-back” in the case patient health or public health issues arise





# Samples to be Collected and Archived

## Donor/Source Animals

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

## Human Recipient/Patient

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

# Use of Archived Samples



Sample for use by the Public Health Service (PHS)



Sample for recipient diagnosis and care



Samples for use by the sponsor



Samples for use by FDA

## Expectations for Archived 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.
- Back-up plan for record and sample retention if sponsor goes out of business
- Herd records and patient samples stored for 50 years

# Challenge Question #1

**Which of the following are **NOT** examples of xenotransplantation products?**

- A. Pig kidney transplant into human recipients
- B. Pig heart valve implantation
- C. Human stem cells cultured on mouse feeder layers
- D. Pig epidermis to treat burns in humans

# Challenge Question #2

**Which of the following measures can be taken to reduce risks to recipients of xenotransplantation products?**

- A. Source pigs from closed herds
- B. Genetically modify pigs
- C. Source pigs from slaughterhouses
- D. Screen pigs for infectious diseases
- E. A, B, and C
- F. A, B, and D

## Summary

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The use of appropriate source animals with multiple levels of safety can reduce the risk of zoonotic infections in humans.

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Genetic alterations in pigs may prevent rejection and reduce the transmission of infectious diseases.

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Collecting and archiving cells and tissues from source animals and can protect the health and safety of the patient and the public.

# Resources

- Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans  
<https://www.fda.gov/media/102126/download>
- PHS Guideline on Infectious Disease Issues in Xenotransplantation  
<https://www.fda.gov/media/73803/download>
- CVM GFI #187 Regulation of Intentionally Altered Genomic DNA in Animals <https://www.fda.gov/media/74614/download>
- Coordination of Regulatory Activities for Genetically Engineered Animals and their Expression Products  
<https://www.fda.gov/media/92780/download>

# Questions?

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**<https://www.fda.gov/vaccines-blood-biologics>**