

# Clinical Review Considerations for Xenotransplantation

**Patricia Beaston, M.D., PhD.**

Clinical

Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT)

Office of Tissues and Advance Therapies (OTAT)

Center for Biologics Evaluation and Research (CBER)

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# Learning Objectives

- Describe how Chemistry and Manufacturing Controls (CMC) and Pharmacology and Toxicology (PT) data are considered when reviewing a clinical study/protocol
- Describe the considerations for benefit risk assessment
- Describe the regulatory pathways to the clinic



# Presentation Outline

- Transplantation
- Xenotransplantation Products
- Pre-clinical Data Considerations
- Clinical Considerations

# Transplantation

- Surgical techniques for organ transplantation (heart, lung, intestines, liver and kidney) are well established
- Immunosuppression regimens for allogeneic transplants are well established
- Good clinical outcomes
- The number of human organ donations is not sufficient to meet the need.

# Xenotransplantation



The goal of xenotransplantation is to provide replacement of function for organs, tissues or cells that are no longer able to support life or treat serious and life-threatening conditions in patients

# Xenotransplantation Products

- Whole non-human organ transplanted into humans
- Implantation of non-human cells or tissues into humans
- Extracorporeal perfusion of human blood over/through non-human cells or organ(s)
- Administration of human cells previously cultured *ex vivo* with non-human cells into a human recipient

# Support for Clinical Studies



- Chemistry and Manufacturing Controls (CMC)
- Pharmacology and Toxicology (PT)

# Considerations for Non-Clinical Animal Models

- Route of administration should mimic the planned clinical transplant procedure
- Study endpoints – safety and function
- Study duration – durability of effect, safety



# Investigational New Drug (IND) Applications



- Preclinical studies to support an IND
  - Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2013)
    - <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/preclinical-assessment-investigational-cellular-and-gene-therapy-products>
- Early-phase clinical trial design
  - Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015)
    - <https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances>
- Xenotransplantation
  - Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans
    - <https://www.fda.gov/media/102126/download>

# Clinical Benefit Risk Assessment



- Benefit
- Risks
  - Route of administration
  - Physiologic mismatch
  - Immunologic
  - Infectious
  - Other

# Physiologic Risks

Xeno Kidney



- Fluid (Blood Pressure) and Electrolyte Balance
- Vitamin D-PTH Axis
- Erythropoietin
- Exogenous Drugs
- Coagulation

# Immunologic Risks

- Cell and antibody-mediated rejection
- Xeno-immune mediated glomerulonephritis
- Porcine proteins produced by the kidney
  - Potential for immune responses to porcine renin and erythropoietin that may neutralize the analogous human proteins

# Infectious Risk

- Bacteria, mycoplasma, fungi, viruses
  - Agents pathogenic in immunocompromised human
  - Agents pathogenic in source animals

# Zoonotic Infectious Risk

- Infection transmission to human cells
- Infection in the xenograft
- Pathogen transmission to close contacts (sexual partners, fetus), caregivers, family, or the general population

# Protocol Considerations

- Provide a rationale for the proposed therapy
- Identify “at risk” population
- Recommend safe starting dose levels and dose escalation schemes for the patient population
- Preliminary benefit / risk assessment
- Identify parameters for clinical monitoring



# Criteria for Subject/Patient Selection

- Patients with serious or life-threatening diseases with no other therapeutic options
- Patients who have the potential for significant benefit
- Bridge vs Destination therapy
- Availability of rescue therapy
- Patients able to comply with public health measures stated in the protocol, including long term follow-up
- Risks and benefits to patients and public health

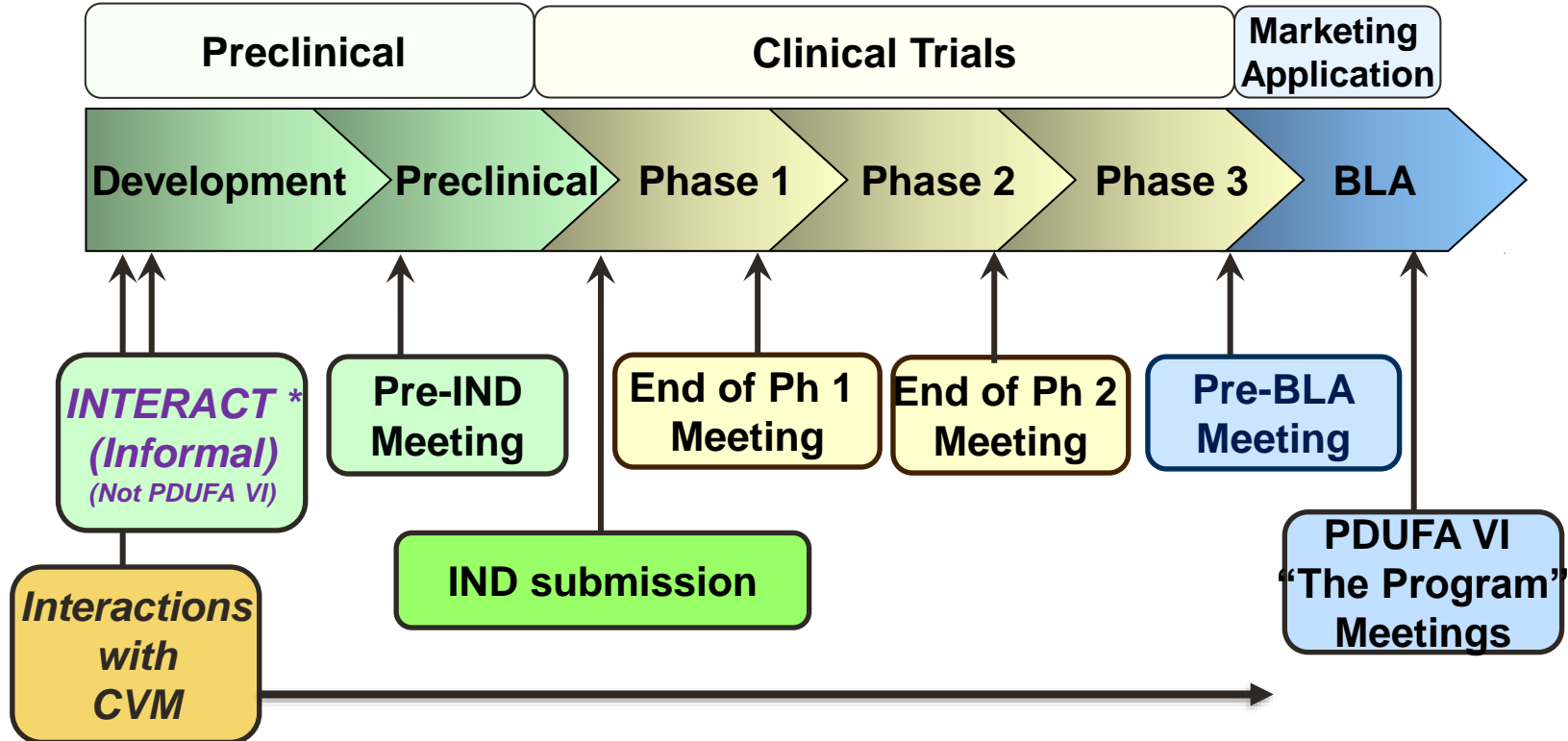


# Considerations for Risk Monitoring/Mitigation



- Staggering enrollment
- Stopping criteria
- Xenograft-specific issues
- Pathogen surveillance
- Recipient agreement not to donate organs or blood

# Meetings with the FDA





# How to Request a Meeting

- Requesting an information meeting with FDA (INTERACT)
  - [INTERACT-CBER@fda.hhs.gov](mailto:INTERACT-CBER@fda.hhs.gov)
  - \*<https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm>
  - SOPP 8214 at <https://www.fda.gov/media/124044/download>, which describes CBER's expectations for INTERACT meeting requests and meeting packages
- Requesting a formal meeting with FDA (e.g., a pre-IND meeting)
  - Draft Guidance for Industry: Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products (March, 2015)
  - <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/formal-meetings-between-fda-and-sponsors-or-applicants-pdufa-products-guidance-industry>



# Summary

- Decisions to permit first-in-human trials of porcine cellular products are based on established regulatory principles for early-phase studies of all cellular products.
- There is a need for demonstration of proof-of-concept in preclinical studies.
- Evaluation of potential benefits and risks is specific to each product and clinical indication.
- Sponsors/investigators are encouraged to discuss their programs with FDA early in development.



# Challenge Question #1

Which of the following are potential risks associated with xenotransplantation?

1. Physiological mismatch
2. Neutralizing antibodies to analogous human proteins
3. Increased risk of rejection
4. Zoonoses
5. All of the above

## Challenge Question #2

Well developed preclinical assessments CMC and PT are required to provide the data necessary to support first in human studies and risk mitigation strategies.

- True
- False

# Contact Information

FDA

- **Patricia Beaston**

patricia.beaston@fda.hhs.gov

- **Regulatory Questions:**

OTAT Main Line: 240-402-8190

Email: [OTATRPMS@fda.hhs.gov](mailto:OTATRPMS@fda.hhs.gov)

- **OTAT Learn Webinar Series:**

<http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>

- **CBER website:** [www.fda.gov/BiologicsBloodVaccines/default.htm](http://www.fda.gov/BiologicsBloodVaccines/default.htm)

- **Phone:** 1-800-835-4709 or 240-402-8010

- **Consumer Affairs Branch:** [ocod@fda.hhs.gov](mailto:ocod@fda.hhs.gov)

- **Manufacturers Assistance and Technical Training Branch:** [industry.biologics@fda.hhs.gov](mailto:industry.biologics@fda.hhs.gov)

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Thank you