Preclinical Development Considerations for Cellular Therapies: A CBER/FDA Perspective

Danielle Brooks, Ph.D.
Center for Biologics Evaluation and Research (CBER)
Office of Tissues and Advanced Therapies (OTAT)
Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT)
Pharmacology/Toxicology Branch 2 (PTB2)
danielle.brooks@fda.hhs.gov

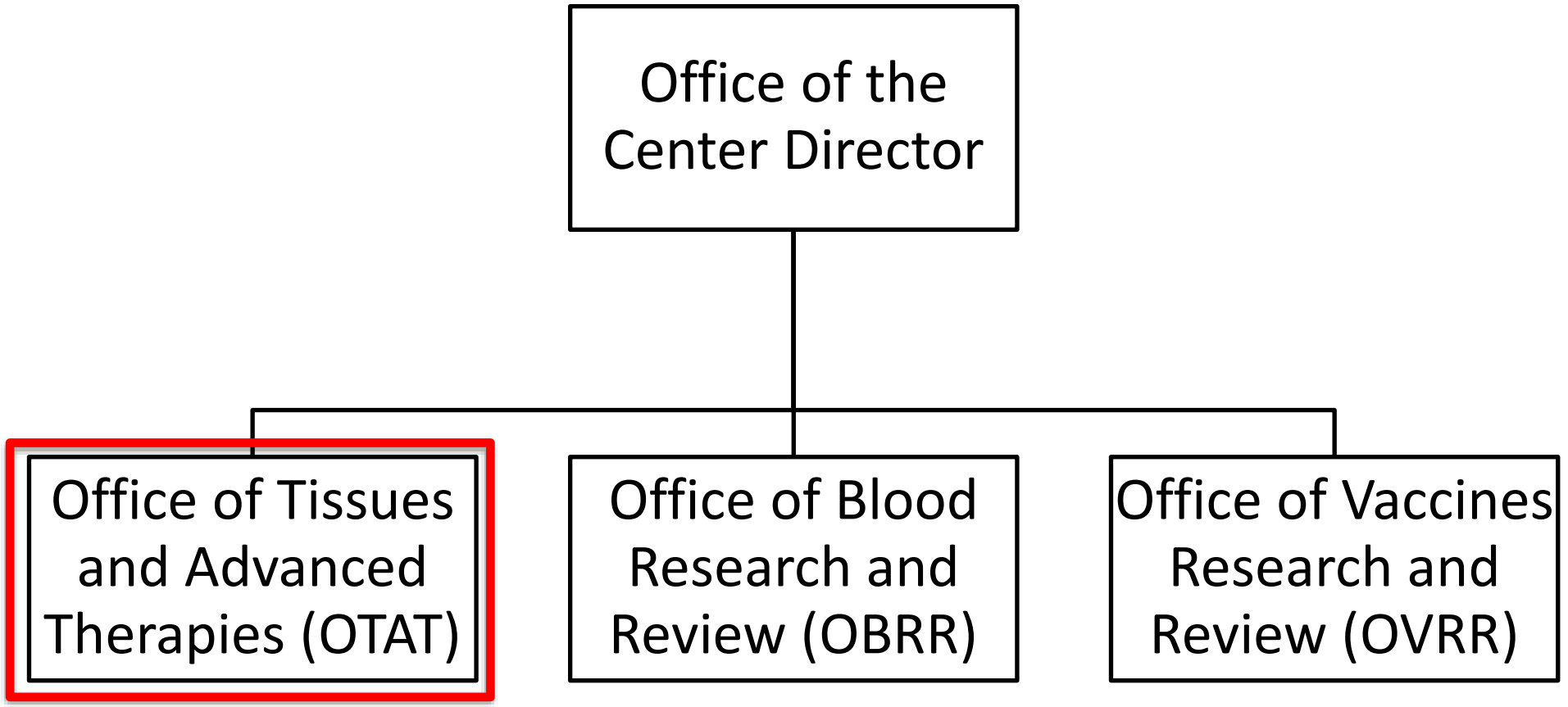
FDA Small Business Regulatory Education for Industry (REdI)
July 22, 2021

Learning Objectives

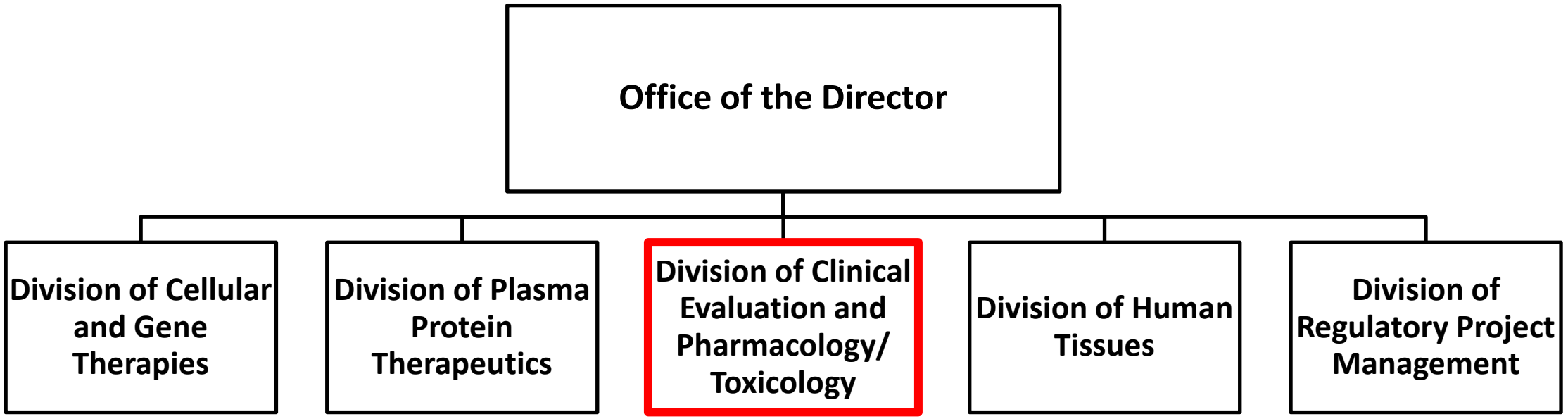
- Describe the organizational structure of CBER/OTAT/DCEPT and regulated products
- Understand preclinical considerations for assessing the safety of cell-based products
- Understand the principles for selecting appropriate animal species/models for preclinical studies
- Be familiar with opportunities for early interaction with CBER/OTAT

CBER Organizational Structure and Products Regulated by OTAT

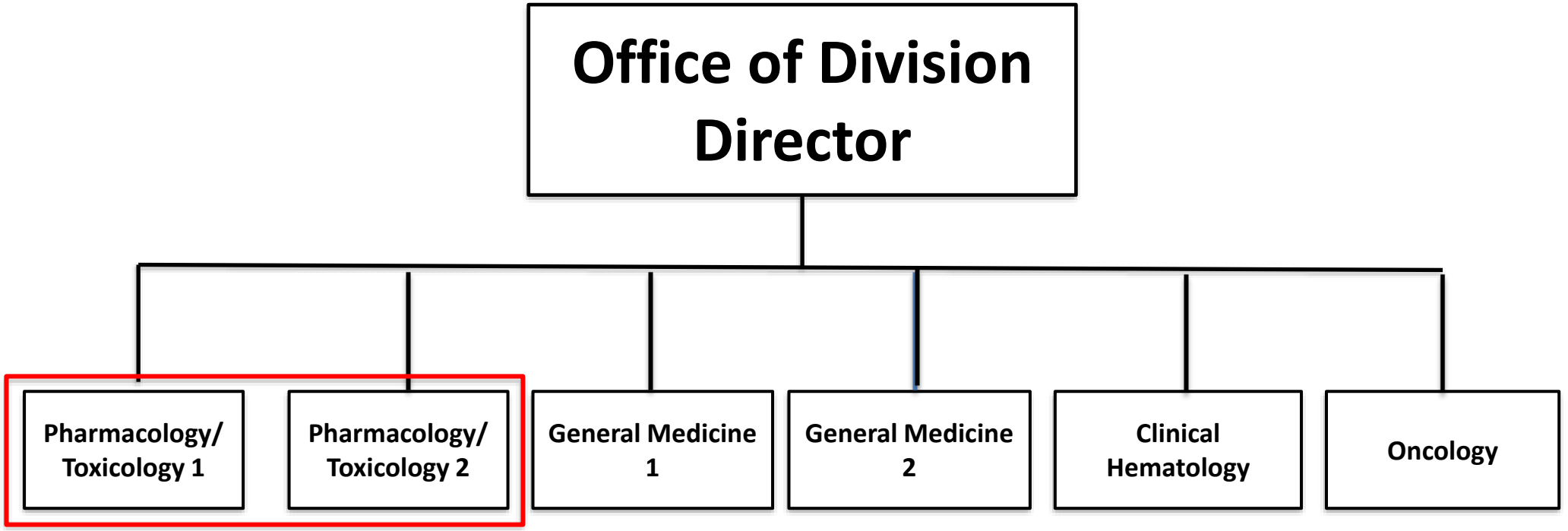
Center for Biologics Evaluation and Research (CBER) - Product Review Offices



Office of Tissues and Advanced Therapies (OTAT) - Divisions



Division of Clinical Evaluation and Pharmacology/Toxicology (DCEPT) - Branches



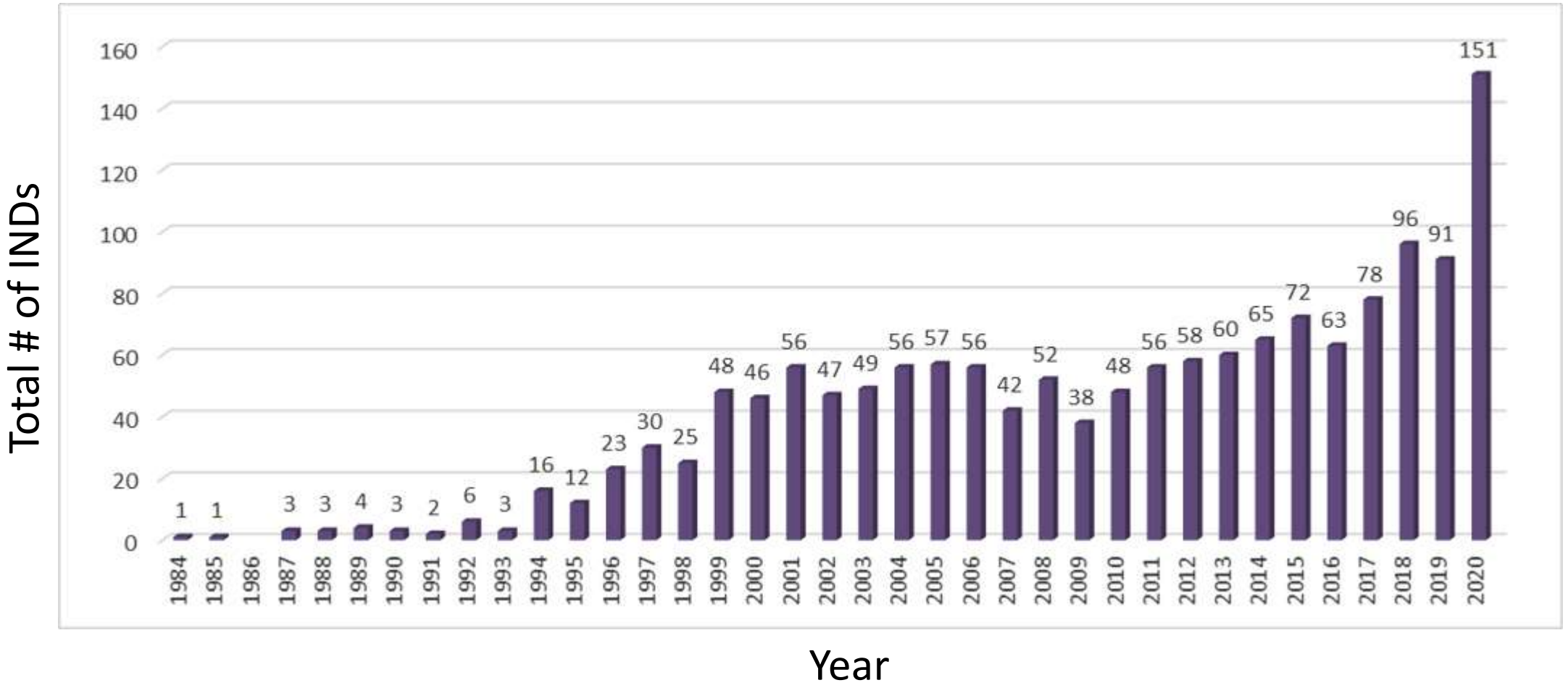
Diversity of CBER/OTAT-Regulated Products

- **Gene therapies (GT)**
  - Ex vivo genetically modified cells
  - Non-viral vectors (e.g., plasmids)
  - Replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus, lentivirus)
  - Replication-competent viral vectors (e.g., measles, adenovirus, vaccinia)
  - Microbial vectors (e.g., Listeria, Salmonella)
- **Stem cells/stem cell-derived**
  - Adult (e.g., hematopoietic, neural, cardiac, adipose, mesenchymal)
  - Perinatal (e.g., placental, umbilical cord blood)
  - Fetal (e.g., neural)
  - Embryonic
  - Induced pluripotent stem cells (iPSCs)
- **Functionally mature/differentiated cells** (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)
- **Products for xenotransplantation**
- **Therapeutic vaccines and other antigen-specific active immunotherapies**
- **Blood- and Plasma-derived products**
  - Coagulation factors
  - Fibrin sealants, Fibrinogen, Thrombin, Plasminogen
  - Immune globulins
  - Anti-toxins
  - Snake venom antisera
- **Tissues**
- **Devices**
- **Combination products**
  - Engineered tissues/organs

Examples of Cell-Based Products Regulated by OTAT

- Mesenchymal stromal/stem cells (MSCs, ASCs, etc.)
- Cell-based therapeutic vaccines (e.g., dendritic cells, irradiated tumor cells, etc.)
- Exosomes/Extracellular vesicles
- iPSC and ESC based products
- Immune cells (e.g., NK cells, tumor infiltrating lymphocytes, virus specific T cells, regulatory T cells, etc.)

INDs with cell therapy development programs



Considerations for Preclinical Programs for Cell Therapy Products

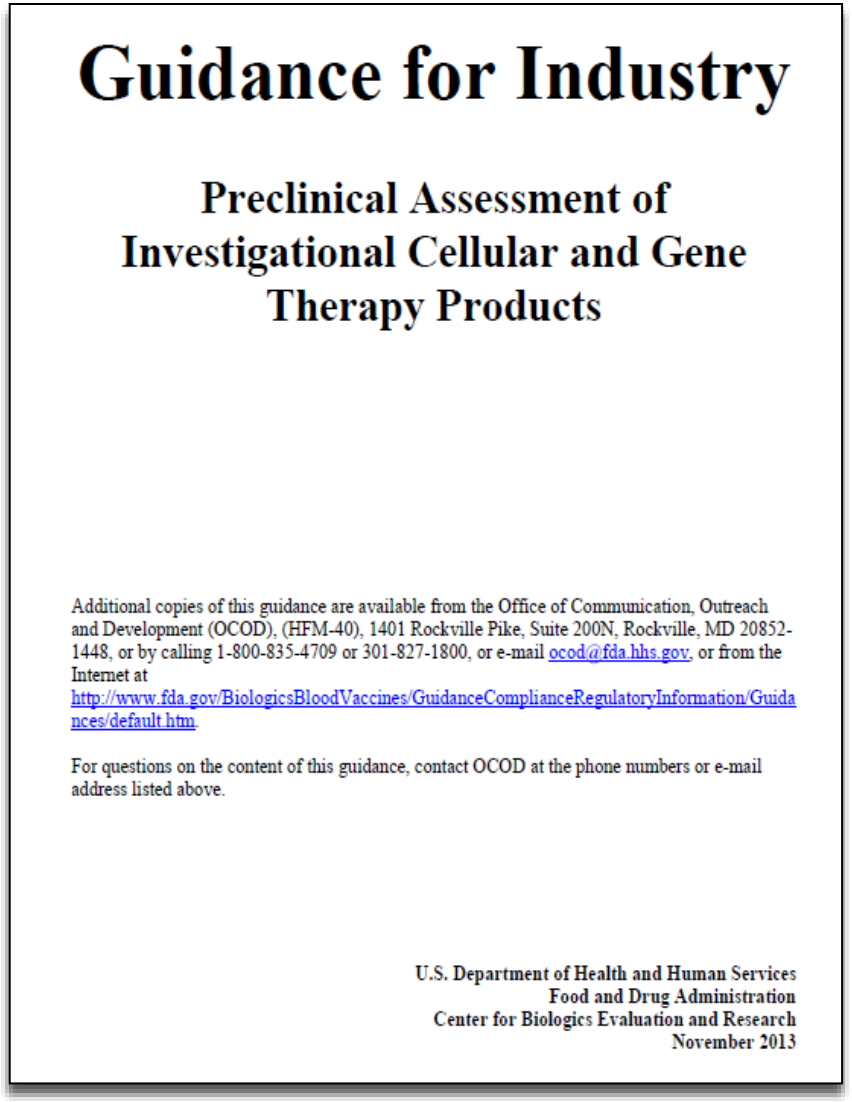
How Does Preclinical Data Contribute to the Proposed Clinical Plan?

- Provides justification for the first-in-human clinical trial in subjects with the target disease
- Supports the starting clinical dose level, dosing regimen, route of administration (ROA)
- Establishes feasibility and reasonable safety of the product administration procedure
- Supports patient eligibility criteria
- Identifies potential toxicities and physiologic parameters to help guide clinical monitoring

General Considerations for Preclinical Testing Programs

How does CBER/OTAT evaluate preclinical safety and activity?

…and what should I be thinking about when developing a new product?



Guidance for Industry

Preclinical Assessment of Investigational Cellular and Gene Therapy Products

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or e-mail ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or e-mail address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2013

Initial Considerations for a Preclinical Testing Program

- The diversity and biological properties of cell therapy products necessitate a flexible testing strategy - no “one size fits all”
  - Based on accumulated knowledge and experience
  - Based on available technology
  - Science-based
  - Data-driven

Initial Considerations for a Preclinical Testing Program

- The putative mechanism of action (MOA) and the intrinsic properties of the product
- The proposed clinical indication
- Appropriate animal species / model
- The quality and applicability of existing data (preclinical and clinical) for:
  - The clinical product or a similar product
  - The proposed patient population
  - The clinical route of administration

Potential Safety Concerns for Cell-Based Products

- Change in cell properties resulting from ex vivo manipulation
- Potential inflammatory / immune response
- Tumorigenicity
- Inappropriate cell differentiation
- Cell distribution to non-target sites or tissues
- Risks of the delivery procedure

Preclinical Testing Program for Cell-Based Products

- Proof-of-Concept (POC) studies
  - Demonstrate evidence of biological activity
- Cell fate assessment
  - Persistence, distribution, phenotype, proliferation
- Immunogenicity and host response
- Safety and tumorigenicity assessment

Preclinical Study Design Considerations

- Nonbiased
- Mimic the planned clinical scenario as closely as possible
- Administration of clinical vehicle formulation and multiple dose levels of the investigational product
- Adequate numbers of animals/group to enable robust study interpretation

Preclinical Study Design Considerations, cont.

- Sufficient study duration to assess both acute and long-term outcomes
- Multiple time points for evaluations
- Comprehensive bioactivity and safety assessments
- Other specific in-life/terminal assessments (e.g., imaging, PCR, immunohistochemistry, etc.)

Selecting appropriate animal species/models for preclinical studies

Considerations for Appropriate Animal Species / Model(s)

- There is no ‘default’ to the use of nonhuman primates
- There is no ‘default’ to the use of both a rodent and a non-rodent species
- Assess safety and bioactivity using an appropriate animal disease model
- Understand the limitations of the species / model used
- Scientific justification should be provided for the animal species / model used

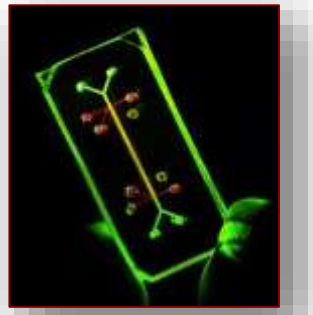
Selection of Animal Species/Model(s)

- Comparability to the target patient population
  - Phenotype, pathophysiology, clinical outcomes
- Permissiveness to cell product
  - Human derived, autologous, allogeneic
- Anatomic site of product delivery
  - Comparable to clinical, if feasible
- Feasibility of using the intended clinical delivery system/procedure

Selection of Animal Species/Model(s)-Other Considerations

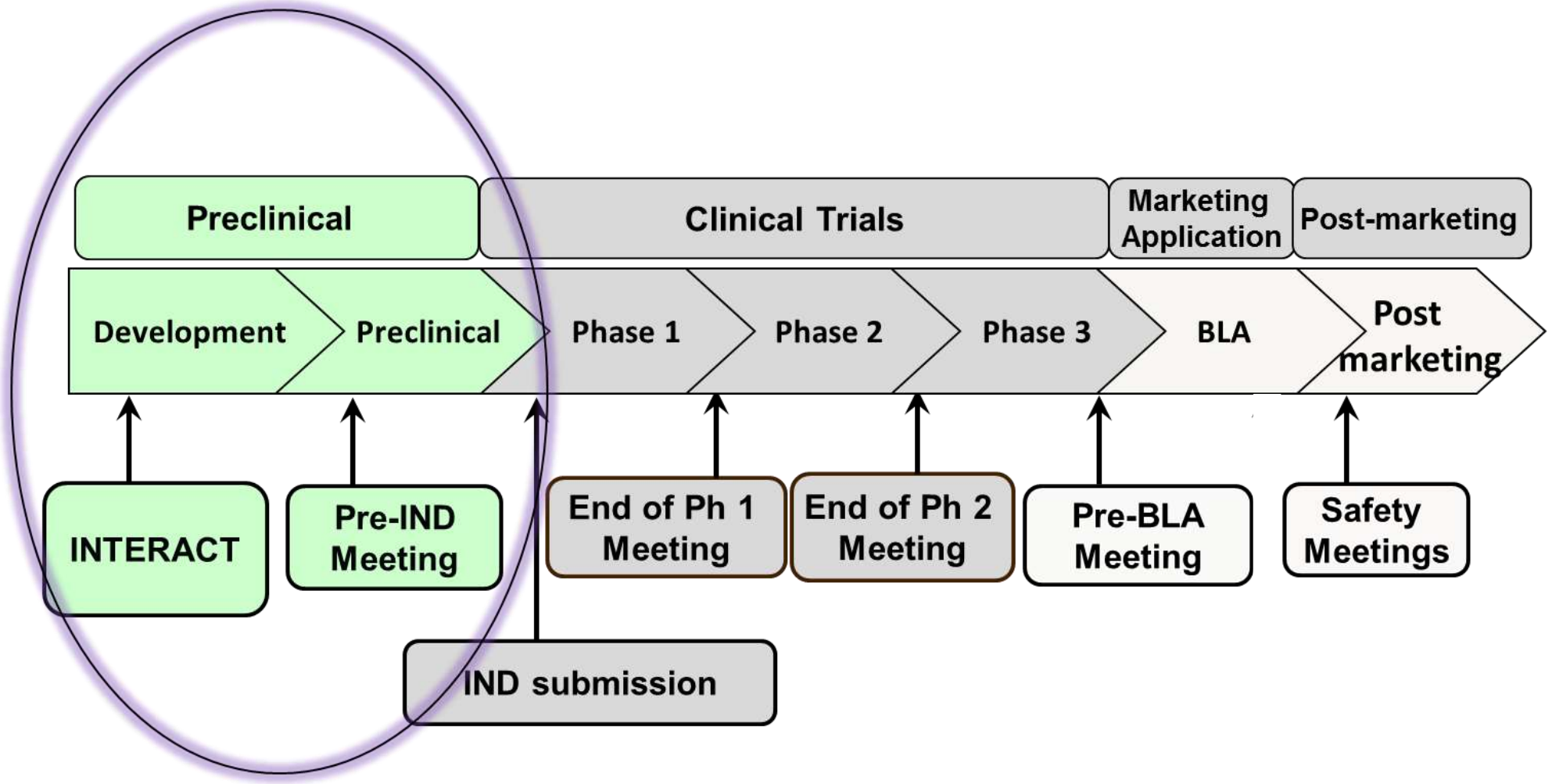
- Availability of animals and cost
- Size, sex, age, and housing needs
- Animal care concerns
- Technical feasibility,
- Historical/baseline data
- Statistical limitations

Considerations for alternative testing to support animal studies



Opportunities for Early Interaction with CBER/OTAT

Opportunities for Interaction During Preclinical Development



INTERACT Meetings

INitial Targeted Engagement for Regulatory Advice on CBER producTs

- **Goal:** To obtain early feedback on a product development program for a novel investigational agent
- **Purpose:**
  - A mechanism for early communication with OTAT
  - Non-binding, informal scientific discussions between CBER review disciplines and the sponsor
  - Initial targeted discussion of specific issues
- **Requests** for INTERACT meetings should be sent to INTERACT-CBER@fda.hhs.gov

https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm

INTERACT Meetings, cont.

- **Timing**: When you have generated preliminary preclinical data (POC and some safety), but are not yet ready to conduct definitive preclinical safety studies
- **P/T advice**:
  - Design of proof-of-concept or other pilot safety/biodistribution studies
  - Adequacy of the selected animal species/models
  - Acceptability of innovative preclinical testing strategies, products and/or delivery modalities
  - Advice on modification of a preclinical program or study design, as applicable, to ensure judicious use of animals

Pre-IND Meetings

- **Goal:** To achieve a successful IND submission
- **Purpose:**
  - Non-binding, formal scientific discussion between all review disciplines (CMC, P/T, and Clinical) and the sponsor
  - Comprehensively communicate the product/clinical development plan
  - Discuss the format of the IND submission
- **Timing:**
  - POC and preliminary safety studies completed
  - Ready to conduct pivotal safety study

Pre-IND Meetings – Preclinical Data

- A comprehensive summary of all completed preclinical studies
  - *In vitro* and *in vivo* studies, animal species/models, study designs, resulting data and interpretation
- Complete protocols for the proposed definitive preclinical safety/toxicology and BD studies
  - Animal species/models, dose levels, dosing regimen and procedure, study endpoints, sacrifice intervals, etc.

Knowledge Check #1

What types of products are regulated by CBER/OTAT?

A. Device/biologic combination products

B. Gene therapy products

C. Tissues

D. Cell therapy products

E. All of the above

Knowledge Check #2

Nonhuman primates must be used to evaluate the safety of cell therapy products.

1. True
2. False

Summary

- OTAT resides within CBER and regulates a wide array of products, including cell-based therapies.
- The preclinical program for any cell therapy product is determined on a case-by-case basis.
- Preclinical data submitted in the IND should support the safety and biological activity of the cell-based product in the proposed clinical indication.
- There are multiple opportunities to obtain FDA feedback on preclinical development plans prior to IND submission.

Contact Information

- **Danielle Brooks, PhD**

  Danielle.Brooks@fda.hhs.gov

- **Regulatory Questions:**

  OTAT Main Line – 240 402 8190

  Email: OTATRPMS@fda.hhs.gov and

  Lori.Tull@fda.hhs.gov

- **OTAT Learn Webinar Series:**

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

FDA Headquarters

- **CBER website:** www.fda.gov/BiologicsBloodVaccines/default.htm
- **Phone:** 1-800-835-4709 or 240-402-8010
- **Consumer Affairs Branch**: ocod@fda.hhs.gov

- **Manufacturers Assistance and Technical Training Branch**: industry.biologics@fda.hhs.gov
- **Follow us on Twitter:** https://www.twitter.com/fdacber

Thank you!