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Preclinical Considerations for Cell-Based Immunotherapies

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ACDRS-NIH Workshop: Cell-Based Immunotherapy:
From Bench to Bedside and Beyond
Masur Auditorium, NIH, Bethesda, MD
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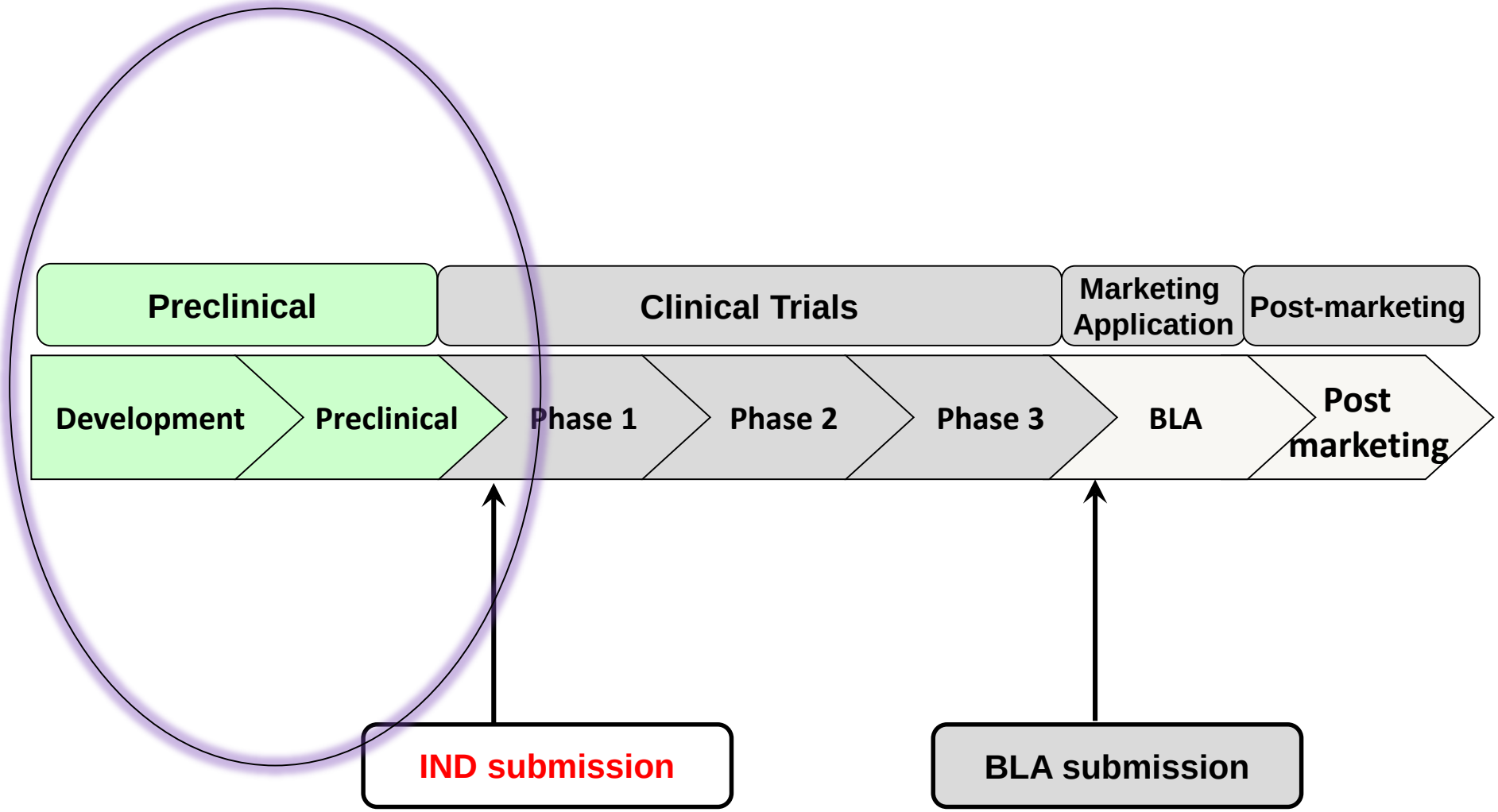
Overview

- CBER/OTAT Immunotherapy Products
- Scope – Preclinical Regulatory Review Principles
- Cell Therapy Safety Concerns
- Example: CAR T cells
- Potential Pitfalls / Regulatory Issues
- Working with OTAT
- Resources

Examples of Cell-based Immunotherapy Products Regulated in OTAT

- Chimeric Antigen Receptor (CAR) T cells
- TCR transgenic (Tg) T cells
- Non-T cell CARs (B cell, NK cell, etc.)
- Regulatory T cells (Treg)
- “Mesenchymal Stem Cells” (MSCs, ASCs, etc.)
- Cell-based Therapeutic Vaccines (e.g., dendritic cells, irradiated tumor cells, etc.)

Product Lifecycle for Biologics: Focus on the Preclinical Phase



What Regulations Govern Preclinical Testing?

Pharmacology & Toxicology Studies

"…adequate information about the pharmacological and toxicological studies…on the basis of which the sponsor has concluded that it is reasonably safe to conduct the proposed clinical investigations. The kind, duration, and scope of animal and other tests required varies with the duration and nature of the proposed clinical investigations."

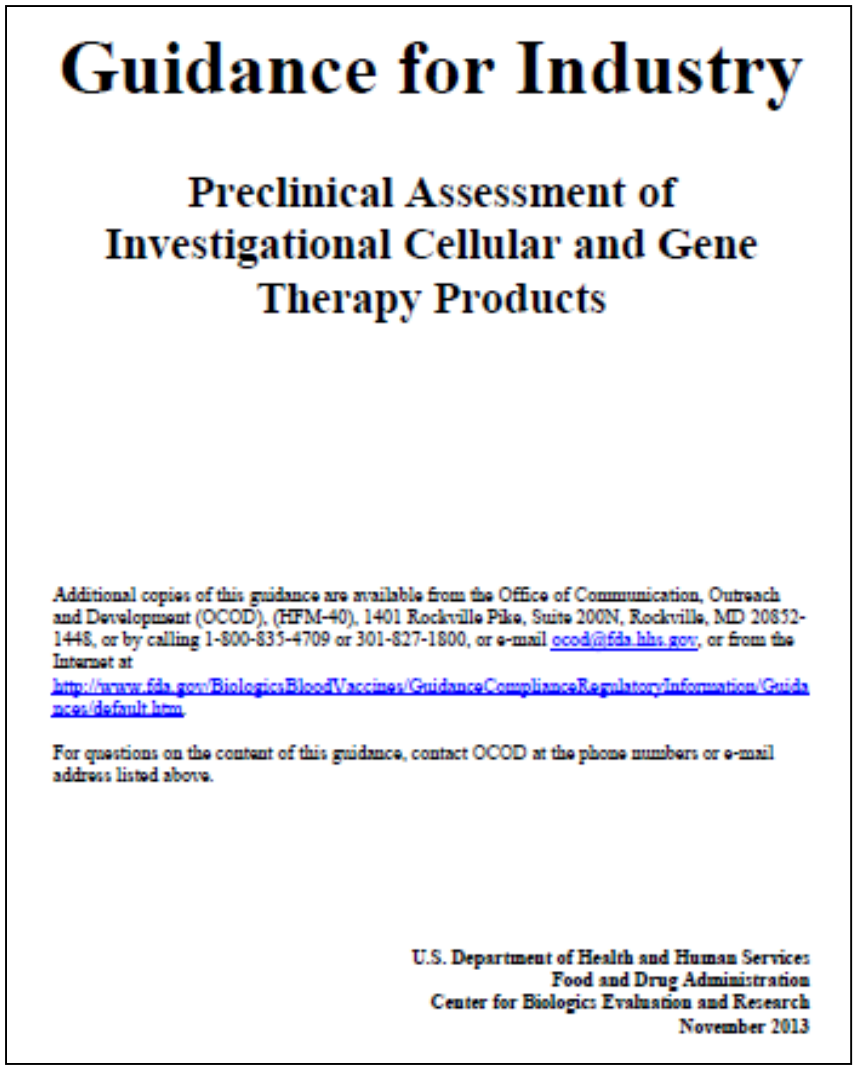
IND Regulations [21 CFR 312.23 (a)(8) - Pharmacology and Toxicology]

Expectations from Preclinical Data

- To support a rationale for the first-in-human clinical trial
  - For cell and gene therapy products, the trial is usually conducted in the disease population, not in healthy volunteers
- To make recommendations regarding the proposed clinical trial
  - Initial safe starting dose, dose-escalation scheme, dosing schedule, organ toxicity, eligibility criteria, clinical monitoring
- To meet regulatory requirements
  - 21 CFR 312.23 (a)(8)
  - 21 CFR 58 (Good Laboratory Practice (GLP) compliance)

Sources of Data to Support an IND

- GLP-compliant toxicology studies conducted by a certified testing facility
- Well-controlled studies conducted in house
- Published data in peer-reviewed journals
- Cross-reference to similar products in previously submitted files to FDA
- Detailed clinical study reports from clinical trials



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

- Final Guidance
  - Current thinking of the Agency on this topic
  - First comprehensive FDA guidance on preclinical assessment of cell and gene therapy (CGT) Products
  - Explicitly incorporates 3 R's: recommendations to reduce, refine, and replace animal use in a preclinical program

Potential Safety Concerns for Cell-Based Products

- Risks of the delivery procedure
- *Ex vivo* manipulation (e.g., expansion, genetic modification, encapsulation, scaffold seeding)
- Potential inflammatory / immune response to the administered cellular product
- Inappropriate cell proliferation (i.e., tumor formation)
- Inappropriate cell differentiation (i.e., ectopic tissue formation)

Potential Safety Concerns for Cell-Based Products (cont'd)

- Cell migration to non-target areas / tissues
- Interactions with concomitant therapies
- For vector transduced cells
  - Vector insertion/integration/transformation
  - Unintended immune responses to vector or transgene
  - Transgene effects – potentially permanent

Example: Safety Concerns for Genetically-Modified T-cell Products

- Vector concerns – Insertional mutagenesis, transformation
- “On-target, off-tumor” toxicity
- “Off-target” toxicity
- Novel suicide genes – Effects of expressed gene + novel drug inducer
- Cytokine release, tumor lysis, macrophage activation syndromes

Example: Preclinical Data Used to Support a CAR T Cell Product Using a Single-Chain Variable Fragment (scFv)

- Any previous clinical experience with similar CAR T cell products (same scFv)
- Any previous experience with investigational or approved monoclonal antibody with identical specificity
- Any published experience with same target
- Vector insertional mutagenesis testing (case-by-case)
- Replication competent retrovirus/lentivirus (RCR/RCL) testing

Example: Preclinical Data Used to Support a CAR T Cell Product Using a Single-Chain Variable Fragment (scFv)

- Expression profile of target (e.g., in silico analysis, RT-PCR, immunohistochemistry, flow cytometry, etc.)
- Product off-target testing against various cell lines, primary cells, iPSC-derived 3D cell cultures from various tissue sources
- On target activation/killing using final CAR T cell product
  - Cytokine release assays (e.g., IFN-γ)
  - Cytolysis of target cells
  - Antigen dependent T cell proliferation in vitro

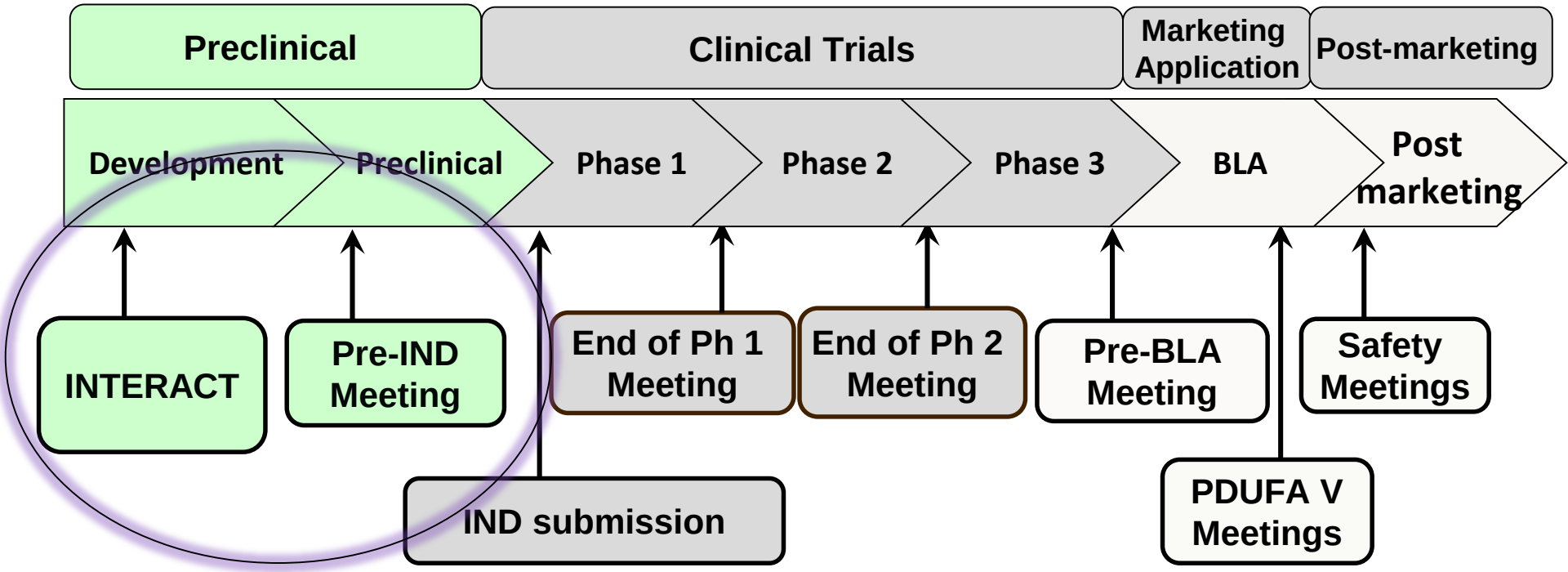
Example: Preclinical Data Used to Support a CAR T Cell Product Using a Single-Chain Variable Fragment (scFv)

- Anti-tumor response in xenogeneic immunocompromised animal models
- POC / Tox studies in appropriate animal models
- Studies using homologous CAR T cells in animal models
- Any additional product- and indication-specific testing (e.g., novel suicide gene, combined with drug, etc.)

Potential Preclinical Pitfalls When Submitting an IND

- Insufficient information to assess subject risk
  - Insufficient product characterization
  - Lack of preclinical safety data for intended product
  - Incomplete study reports

Opportunities for Interaction - -Preclinical Development



Early Communication with OTAT

- INTERACT - INitial Targeted Engagement for Regulatory Advice on CBER producTs
  (previously known as pre-pre-IND interactions)
  - Non-binding, informal scientific discussions between CBER/OTAT nonclinical review disciplines (P/T & CMC) and the sponsor
  - Initial targeted discussion of specific issues
  - Primary contact: INTERACT-CBER@fda.hhs.gov
  - Website: https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm

Early Communication with OTAT

- Pre-IND meetings
  - Non-binding, but formal meeting between FDA and sponsor (with minutes generated)
  - Meeting package should include summary data and sound scientific principles to support use of a specific product in a specific patient population

Summary

- It is important to keep FDA/CBER/OTAT involved at an early phase of the product development program
- The preclinical study designs should be supported by scientific rationale / data
- Novel therapies mean novel testing paradigms

Selected Guidances

- Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2013)
  http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM329861.pdf

- Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015)
  http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM359073.pdf

- Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines (October 2011)
  http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM278673.pdf

Public Access to CBER

CBER website

- http://www.fda.gov/BiologicsBloodVaccines/default.htm
- Phone: 1-800-835-4709 or 240-402-8010

Consumer Affairs Branch (CAB)

- Email: ocod@fda.hhs.gov
- Phone: 240-402-7800

Manufacturers Assistance and Technical Training Branch (MATTB)

- Email: industry.biologics@fda.gov
- Phone: 240-402-8020

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FDA Headquarters

- **OTAT Learn Webinar Series:**

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

- **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
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