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Preclinical Considerations for Cell-Based Immunotherapies

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American College of Toxicology Educational Webinar - May 30, 2018

Overview

- CBER/OTAT Organization and Products
- Scope – Preclinical Regulatory Review Principles
- Cell Therapy Safety Concerns
- Preclinical Evaluation
  - Animal Model Considerations
  - Study Design Considerations
- Potential Pitfalls / Regulatory Issues
- Working with OTAT
- Resources

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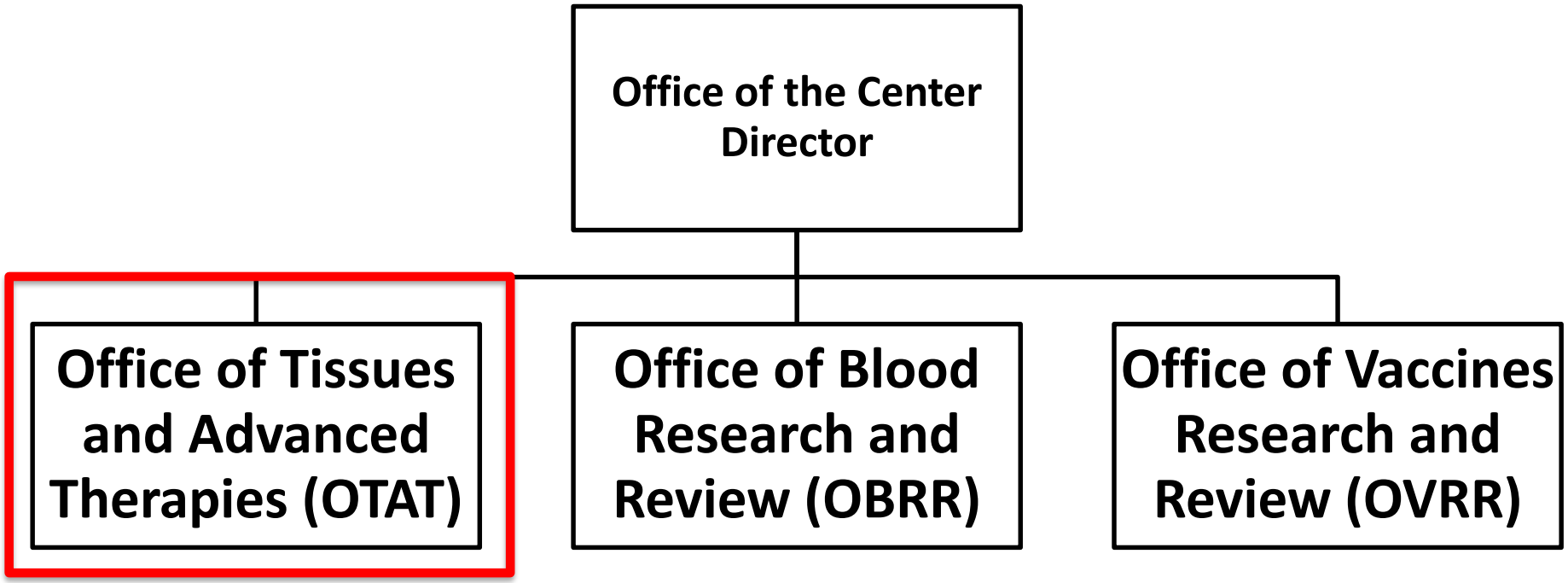
CBER Product Review Offices



Diversity of 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)
- **Products for xenotransplantation**
- **Functionally mature/differentiated cells** (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)
- **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
- **Combination products**
  - Engineered tissues/organs
- **Devices**
- **Tissues**

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, etc.)

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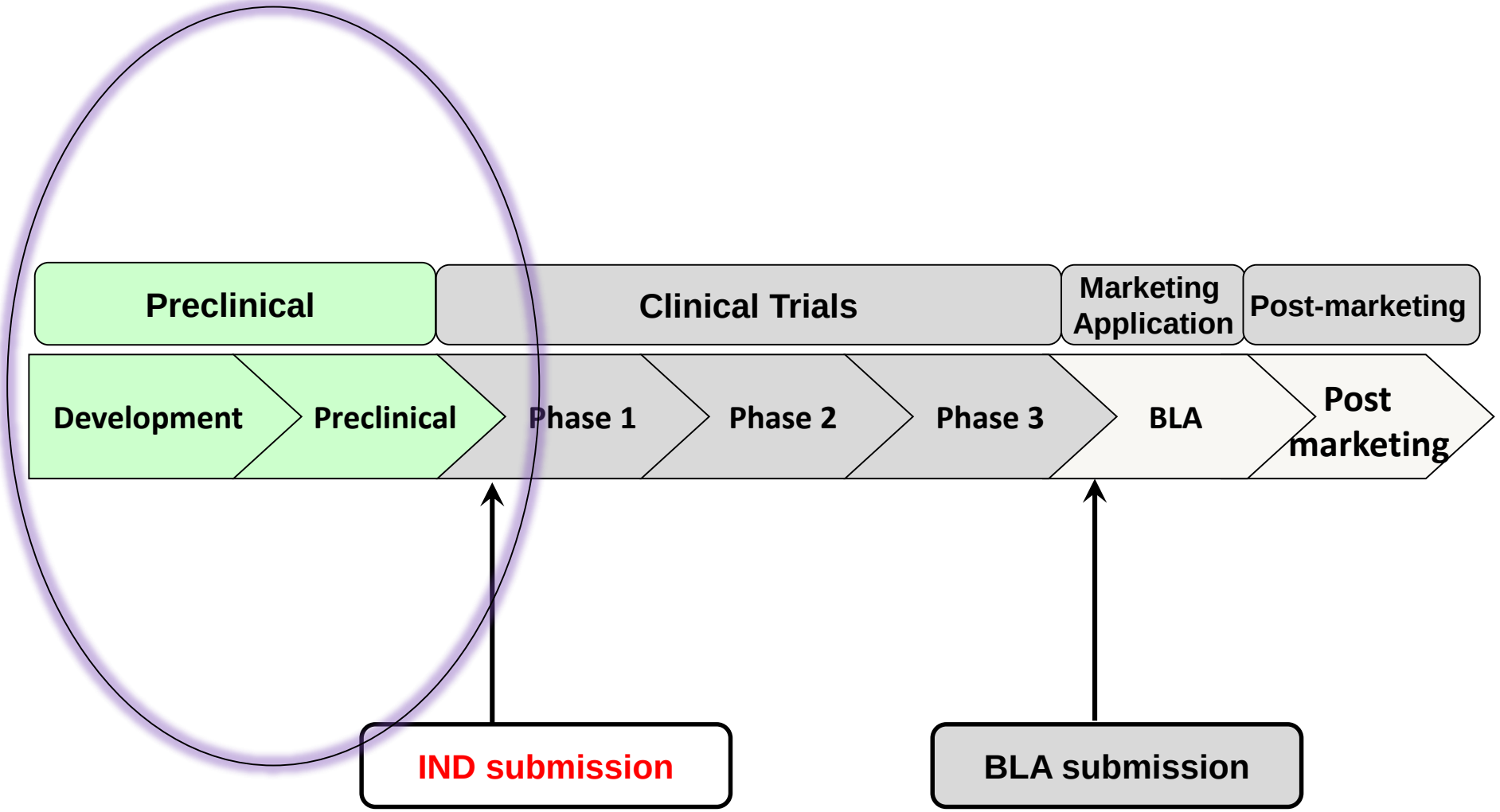
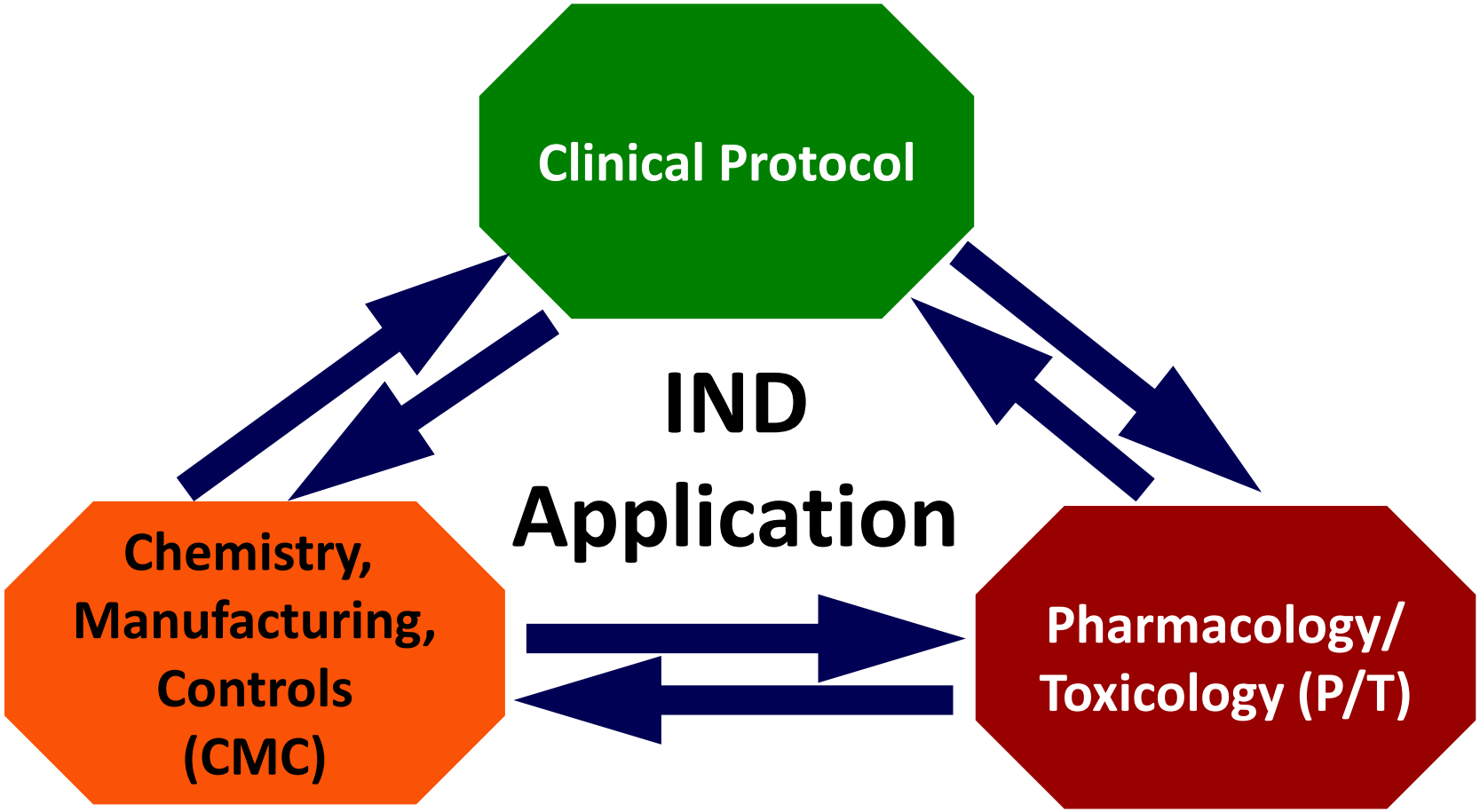
Product Lifecycle for Biologics: Focus on the Preclinical Phase



Investigational New Drug (IND) Application

- An IND submission is required to conduct a clinical trial
  - Using a novel investigational product
  - Using an approved product for a new indication, new route of administration, new formulation
- Regulations governing INDs are found in 21 Code of Federal Regulation (CFR) 312
- 30-day FDA review clock to determine whether the safety and rights of study subjects are adequately protected

Key Elements of the IND Submission



IND Review Team

- CMC reviewer
- P/T reviewer
  - Preclinical testing including in silico, in vitro, and in vivo data
- Clinical reviewer
- Statistical reviewer
- Consult reviewer (as needed)
- Regulatory Project Manager (RPM)

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

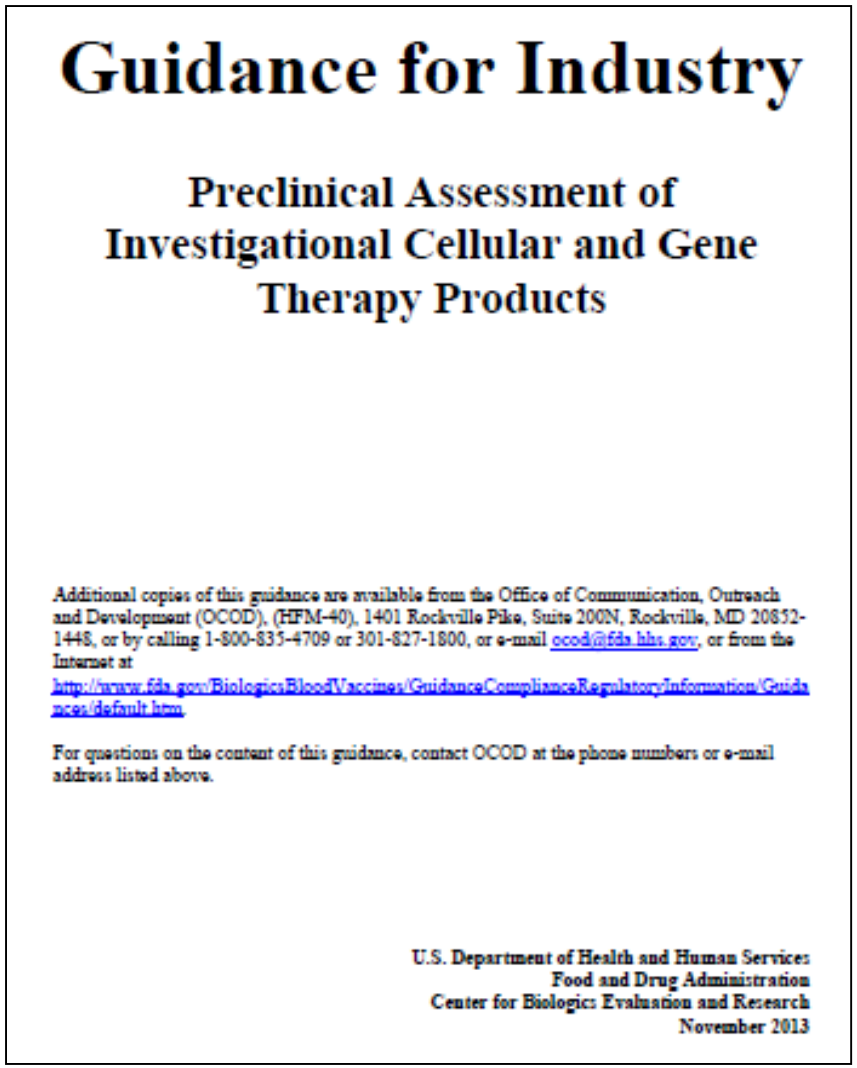
- To support a rationale for the first-in-human clinical trial
  - For cell and gene therapy products, the trial is usually conducted in the disease population, not in healthy volunteers
- To make recommendations regarding the proposed clinical trial
  - Initial safe starting dose, dose-escalation scheme, 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)

CBER Review: Product-Based

- No “one size fits all” regulatory approach
- Data necessary to support development depends on the characteristics of the product
- Preclinical studies are designed to support use of a specific product for a specific clinical indication.
- Review approach is based on balancing risk and benefit.

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

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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

Potential Safety Concerns for Cell-based Therapeutic Vaccines/Adjuvants

- Systemic toxicity
  - Immune-mediated toxicity - autoimmune response, induction of pro-inflammatory response/cytokine release, organ toxicity
  - Hypersensitivity / anaphylaxis
  - Potential “off-target” toxicity
  - Adjuvant-related toxicity
- Local toxicity
  - Injection-site reaction

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

- Vector concerns – Insertional mutagenesis, transformation
- "On-target, off-tumor" toxicity
  - Expression of target antigen in normal tissues
- "Off-target" toxicity
  - Recognition of off-target, unintended proteins
  - Autoimmunity
- Combination product concerns
  - Novel preparative regimens
  - Cancer drug/antibodies + CAR T cells
- Novel suicide genes – Effects of expressed gene + novel drug inducer
- Cytokine release, tumor lysis, macrophage activation syndromes

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Considerations for Appropriate Animal Species / Model

- 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
- There is no ‘default’ to the use of multiple species
- **Understand the limitations of the species/ model(s) used**
- **Scientific justification should be provided for the animal species / model(s) used**

Considerations for Appropriate Animal Species / Model (cont'd)

- Comparative physiology of animal to human
  - Model of disease / injury
  - Local microenvironment may impact the safety of the product
- Route of administration – comparability to clinical
  - Systemic vs. targeted delivery
  - Delivery system / delivery procedure
- Species specificity of the product
- Species specificity of the immune response

Considerations for Appropriate Testing System

- Apply the 3 Rs – Reduce, Refine, Replace – in preclinical study designs
  - We encourage you to explore opportunities for reducing, refining, and replacing animal use in your preclinical program.
  - Consider *in vitro* or *in silico* testing to complement or replace animal studies
  - We encourage the submission of proposals with justification for any potential alternative approaches

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Preclinical Study Design(s)

- Assess pharmacology / (POC) / cell fate in relevant animal model(s) of disease, as feasible
- Assess toxicology (T) / safety / cell fate in healthy animals
- Hybrid pharmacology-toxicology study design
  - POC + T – incorporate activity and safety endpoints in an animal model of disease / injury
  - Local microenvironment and pathophysiology status of the model may impact the safety / bioactivity of the product

Preclinical Study Design: Specifics (cont'd)

- Nonbiased design
  - Randomized assignment to groups
  - Appropriate controls (e.g., sham, vehicle)
  - In-life and postmortem assessments conducted in a blinded manner
- Mimic clinical scenario as closely as possible
  - Use cells intended for clinical use…or analogous cells
  - Cell viability, concentration / formulation, volume, rate of delivery, implant site, number of implants / injections, etc.
  - ROA, delivery system, timing of cell delivery, dosing regimen, etc.
  - Anatomical location / extent of the diseased / injured area

Preclinical Study Design: Specifics (cont'd)

- Adequate numbers of animals / group to ensure biologically robust interpretation
- Sufficient study duration and multiple time points - depending on the biology of the product - to allow for adequate assessment of:
  - Functional, laboratory, and morphological outcomes
  - Cell fate
  - Onset and persistence profile of significant findings in target / non-target tissues

Preclinical Study Design: Specifics (cont'd)

- Standard Toxicology Endpoints
  - Mortality
  - Clinical observations, body weights, appetite, etc.
  - Clinical pathology - hematology, coagulation, serum chemistry, urinalysis
  - Pathology – target and non-target
    - Scheduled and unscheduled deaths
    - Comprehensive gross pathology
    - Microscopic pathology – masked assessment
- Terminal / non-terminal assessment
  - Various imaging modalities
  - Immunohistochemistry, *in situ* hybridization, PCR

Example: Preclinical Data Used to Support a CAR T Cell Product Using a Novel 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 tumor target using other immunotherapies
- Vector insertional mutagenesis testing: insertion copy/site analysis by PCR/sequencing (case-by-case)
- Replication competent retrovirus/lentivirus (RCR/RCL) testing

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

- Expression profile of target (e.g., in silico analysis, RT-PCR, IHC, 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 (IFN-γ) release assays
  - Cytolysis of target cells
  - Antigen dependent T cell proliferation in vitro

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

- Anti-tumor response in xenogeneic immunocompromised animal models (e.g., NSG mice bearing tumor expressing target antigen)
- 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.)

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Potential Preclinical Pitfalls When Submitting an IND

- Inadequate preclinical study design(s)
  - Safety monitoring (safety / activity endpoints)
  - Animal model issues
  - Study dose(s) and duration
  - Route of administration

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

Complete Reports for Toxicology Studies

- Detailed description of the study performed:
  - Test articles (i.e., relevance to the clinical product)
  - Test system (i.e., animal species / model)
  - Delivery device information if applicable
  - Dose levels / dose regimen / study duration
  - Study groups (e.g., controls, test article groups, group size, etc.)
  - Prospective study endpoints
- Results: for all parameters evaluated-
  - Submit individual animal data for all parameters evaluated
  - Submit summarized and tabulated results
- Interpretation of the data

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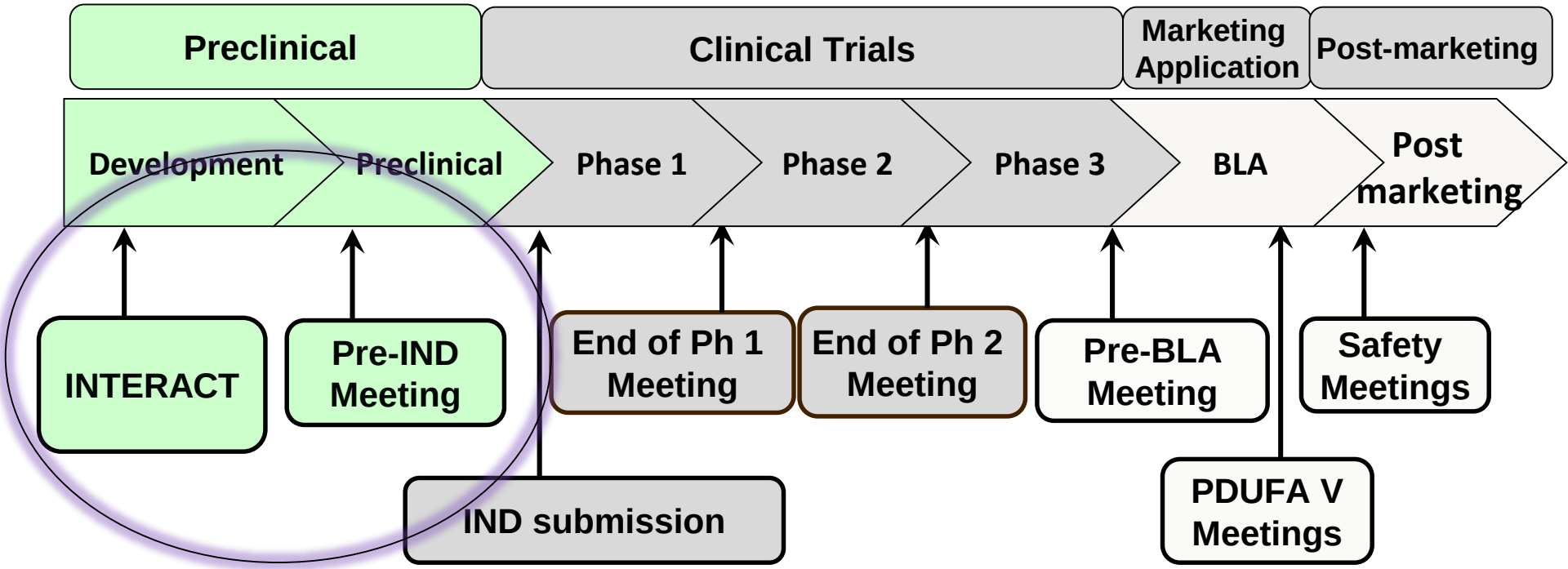
Opportunities for Interaction - -Preclinical Development



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: Mercedes Serabian mercedes.serabian@fda.hhs.gov

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

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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

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