U.S. FOOD & DRUG ADMINISTRATION

Preclinical Assessment of Cell and Gene Therapy Products to Support an IND

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Society for Immunotherapy of Cancer (SITC)
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Learning Objectives

- Introduction to CBER / OTAT – regulated products including immunotherapies and preclinical regulatory review principles
- Gain familiarity with regulations governing preclinical testing
- Understand the preclinical expectations for early phase trials
- Identify safety concerns for cell and gene therapy products
- Preclinical considerations for CAR T cell therapies
- Identify potential pitfalls / regulatory issues
- Decide when to have early interactions with the FDA
- Bookmark FDA Guidance documents and other online resources

CENTER FOR BIOLOGICS EVALUATION & RESEARCH (CBER)

OFFICE OF TISSUES & ADVANCED THERAPIES (OTAT)

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 (Tregs)
- “Mesenchymal Stem Cells” (MSCs, ASCs, etc.)
- Cell-based Therapeutic Vaccines (e.g., dendritic cells, irradiated tumor cells, etc.)

PRECLINICAL TESTING (PHARMACOLOGY-TOXICOLOGY)

REGULATIONS

LIFE CYCLE OF DRUG DEVELOPMENT

INVESTIGATIONAL NEW DRUG (IND) APPLICATION

CBER REVIEW PROCESS

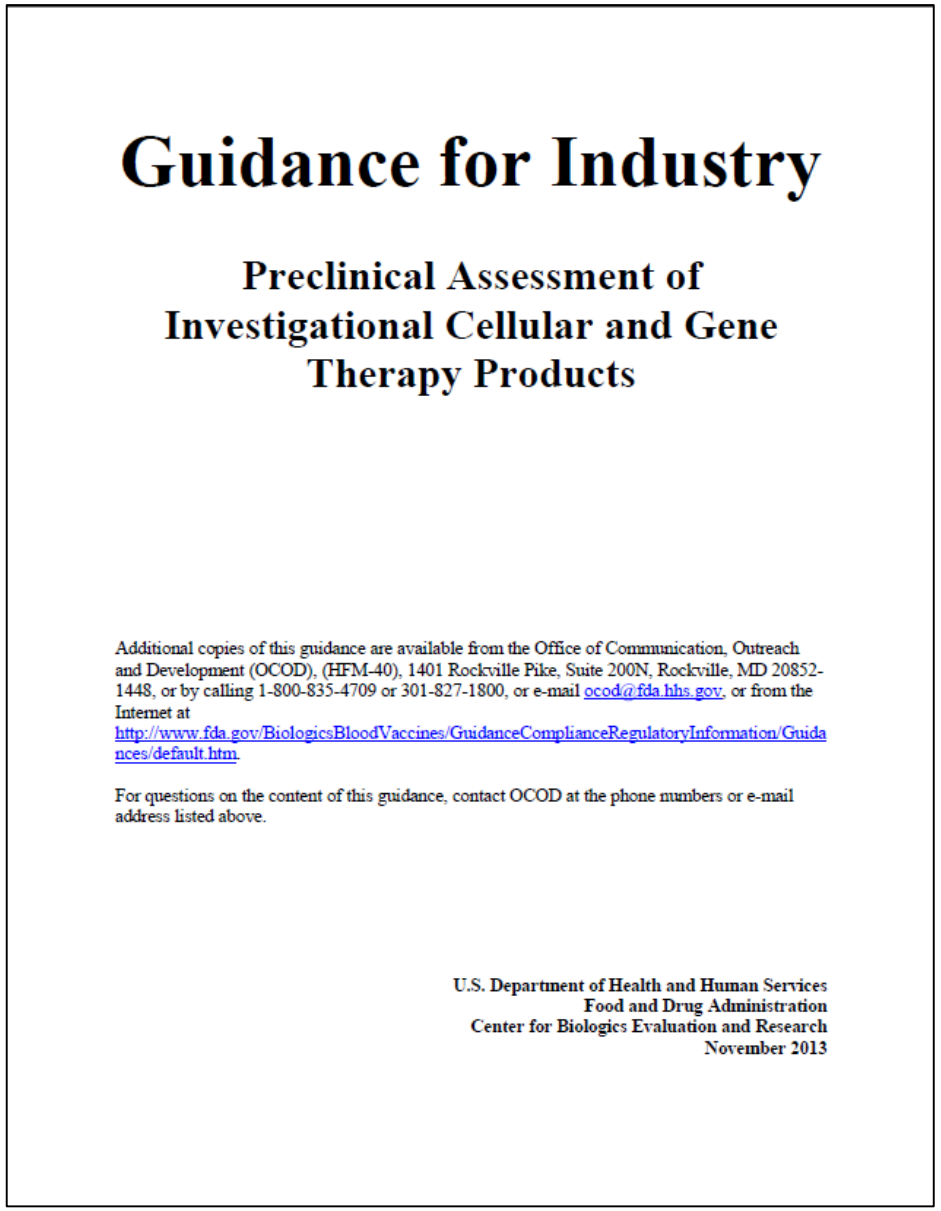
What Regulations Govern Preclinical Testing?

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]

Final Guidance



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.

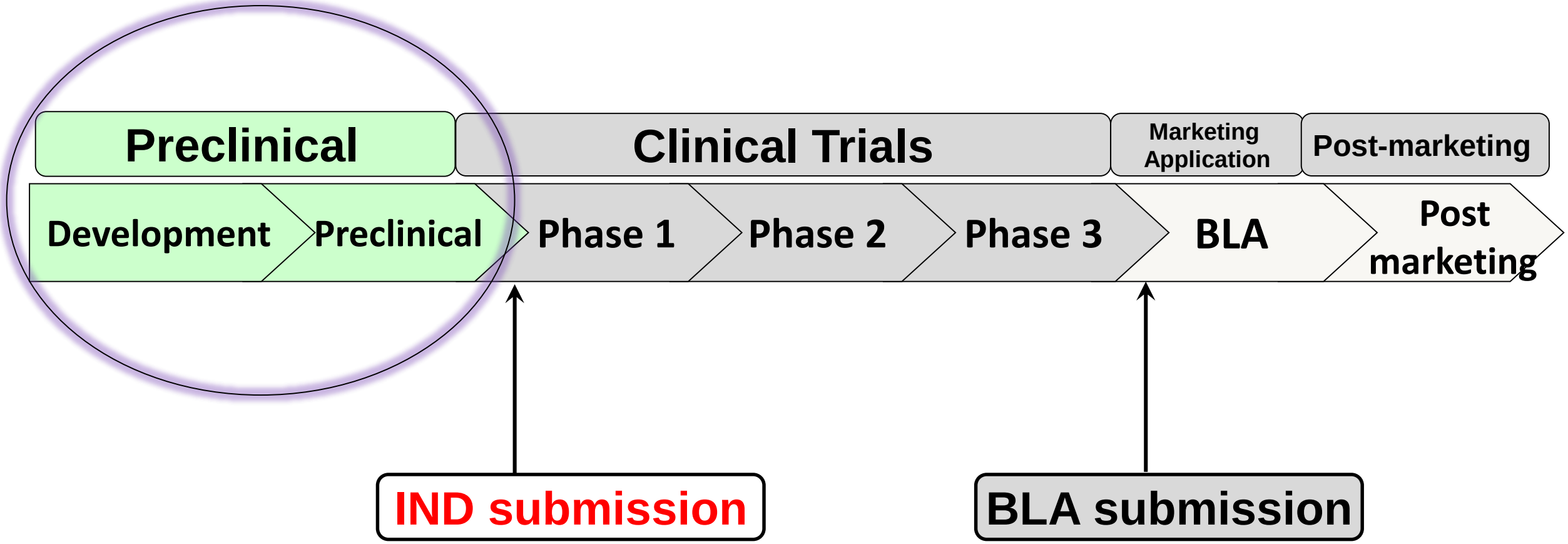
For questions on the content of this guidance, contact OCOD at the phone numbers or e-mail address listed above.

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

https://www.fda.gov/media/87564/download

- 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

Product Lifecycle for Biologics: Focus on the Preclinical Phase

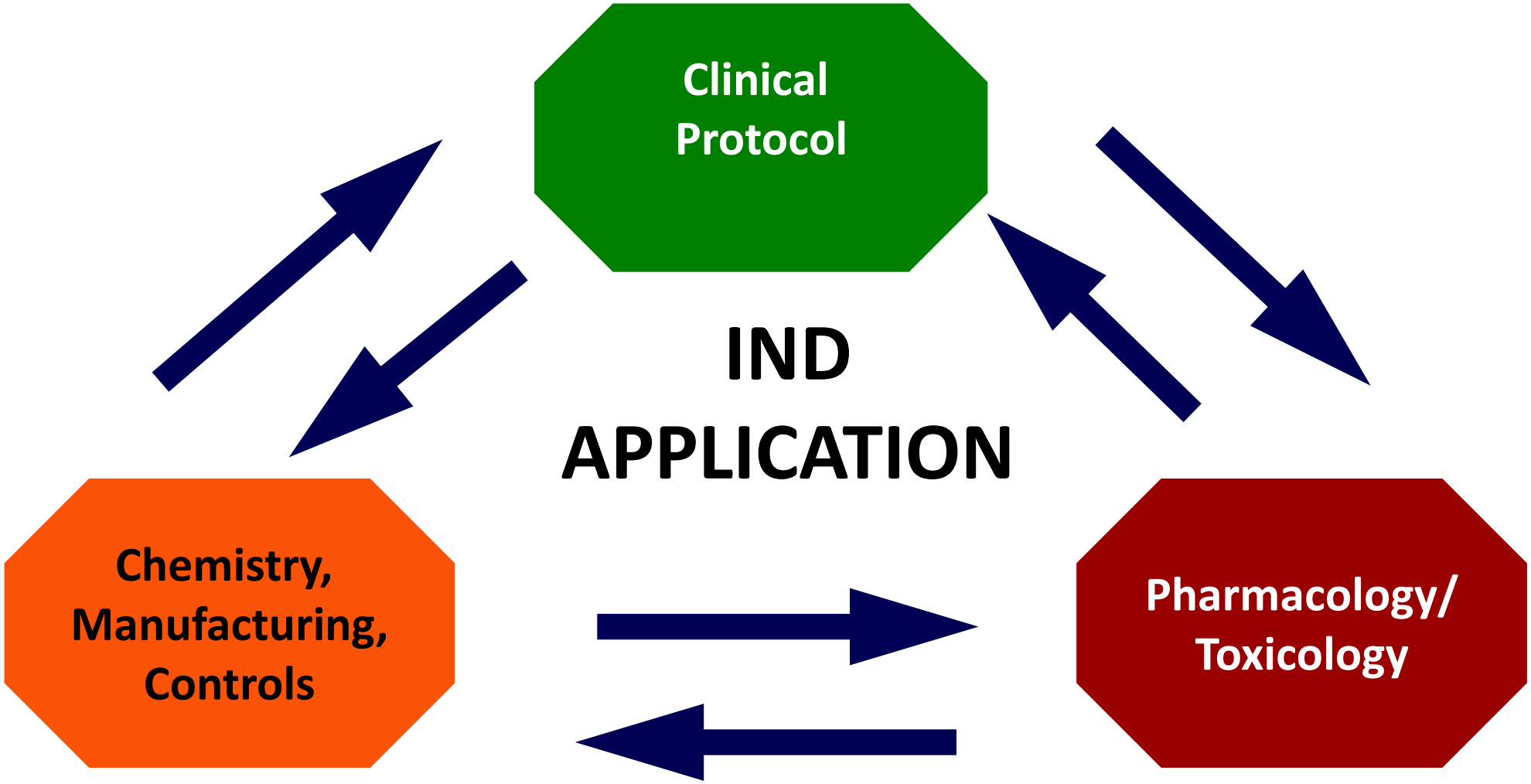


https://www.fda.gov/patients/learn-about-drug-and-device-approvals/drug-development-process

21 CFR 312.20 Subpart B: IND Application

☐	Form FDA 1571	*21 CFR 312.23(a)(1)*
☐	Table of Contents	*21 CFR 312.23(a)(2)*
☐	Introductory statement and general investigational plan	*21 CFR 312.23(a)(3)*
☐	Investigator's brochure	*21 CFR 312.23(a)(5)*
☐	Protocols	*21 CFR 312.23(a)(6)*
☐	Chemistry, manufacturing, and control data (including environmental assessment	*21 CFR 312.23(a)(7)*
☑	**Pharmacology and toxicology data**	*21 CFR 312.23(a)(8)*
☐	Previous human experience	*21 CFR 312.23(a)(9)*
☐	Additional information	*21 CFR 312.23(a)(10)*
☐	Biosimilar User Fee Cover Sheet	*Form FDA 3792*
☐	Clinical Trials Certification of Compliance	*Form FDA 3674*

Key Elements of the IND Submission



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.

PRECLINICAL TESTING (PHARMACOLOGY-TOXICOLOGY)

CONSIDERATIONS & EXPECTATIONS

SOURCES OF DATA TO SUPPORT IND

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, 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 previous submissions to FDA
- Detailed clinical study reports from clinical trials

Preclinical Expectations for Early Phase Clinical Trials

- Gain understanding of potential mechanism of action (e.g., targeted killing, anti-tumor activity, tolerance induction)
- Establish pharmacologically effective dose(s)
- Optimize route of administration (ROA)
- Establish rationale for species / model selection

Preclinical Expectations for Early Phase Clinical Trials

- Establish a dosing scheme / dosing regimen
- Potential target tissue(s) of toxicity / activity
- Parameters to monitor clinically

Preclinical Study Designs

- Assess pharmacology / proof-of-concept (POC) / vector distribution / cell fate in relevant animal model(s) of disease / injury, as feasible
- Assess safety / toxicology (T) / vector distribution / cell fate in healthy animals
- Hybrid pharmacology-toxicology study design
  - POC + T + product fate – 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

Considerations for Appropriate Animal Species / Model

- There is no ‘default’ to the use of:
  - nonhuman primates
  - both a rodent and a non-rodent species
  - multiple species
- Understand the limitations of the species / model(s) used
- Scientific justification should be provided for the animal species / model(s) used

PRECLINICAL TESTING (PHARMACOLOGY-TOXICOLOGY)

SAFETY CONSIDERATIONS

ENGINEERED IMMUNE CELL PRODUCTS / CAR T CELL

Potential Safety Concerns for Engineered Immune Cell 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)
- Product-mediated cytotoxicity against host tissues/organs (e.g., GVHD for allogeneic T cell products)

Potential Safety Concerns for Engineered Immune Cell Products (Cont'd)

- Cell migration to non-target areas / tissues
- Interactions with concomitant therapies
- For vector transduced cells
  - Vector insertion/integration/transformation (e.g., gene disruptions)
  - Unintended immune responses to vector or transgene
  - Transgene effects

Example 1: 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 1: Safety Concerns for Genetically-Engineered T-cell Products (cont'd)

- Addition of novel drugs, devices, and/or biologics – safety of individual components and combination

- Effects of other genetic modifications:
  - multiple chimeric antigen receptors (CARs)
  - Lentivirus, AAV, or other gene transfer vectors
  - RNA interference (RNAi)
  - CRISPR-Cas9, and other gene editing technologies

Example 2: 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 on- and 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 2: Data Used to Support a CAR T Cell Product Using a Single-Chain Variable Fragment (scFv)

- Antitumor response in immunocompromised xenograft 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.)

Example 2: Data Used to Support a CAR T Cell Product Using a Single-Chain Variable Fragment (scFv)

- Previous clinical experience with similar CAR T cell products (e.g., same scFv)
- Previous experience with investigational or approved monoclonal antibody with identical specificity
- Published experience with the same target
- Vector insertional mutagenesis testing (case-by-case)
- Replication-competent retrovirus/lentivirus (RCR/RCL) testing

Potential Preclinical Pitfalls When Submitting an IND

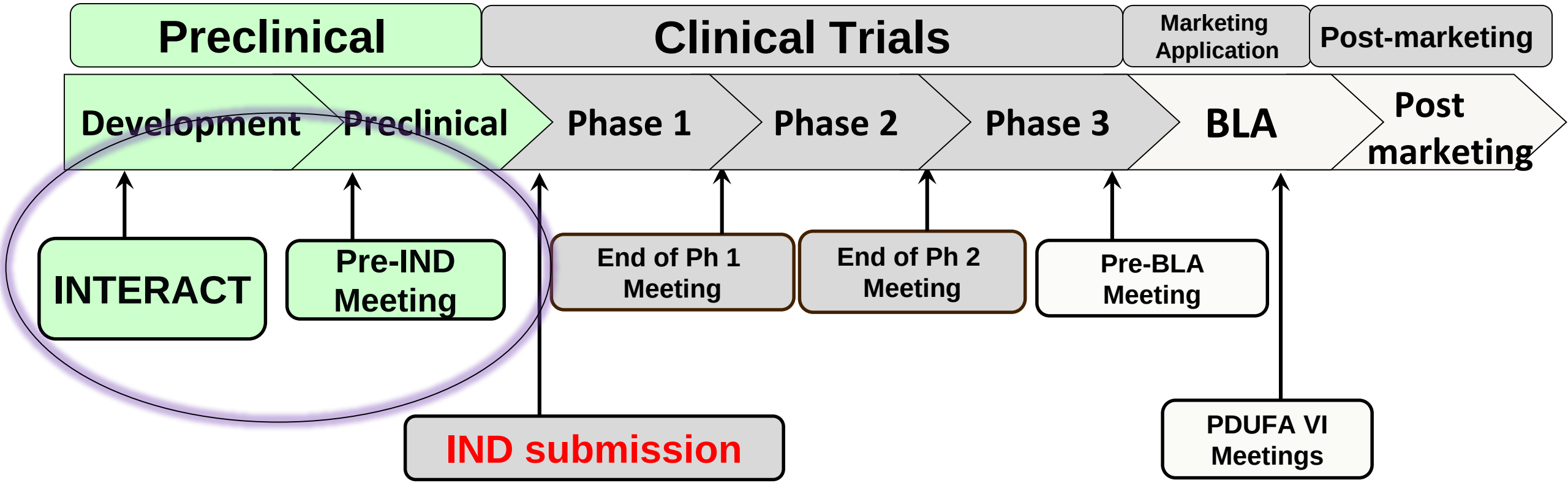
- Insufficient information to assess subject risk, including:
  - Insufficient characterization of product safety
  - Lack of preclinical safety data for intended product
  - Incomplete study reports

EARLY COMMUNICATIONS WITH FDA/CBER

INTERACT MEETING (PRE-PRE-IND)

PRE-IND MEETING

Opportunities for Interaction - Preclinical Development



Product development is an iterative process that may involve multiple FDA and sponsor interactions

INTERACT Meeting*

- **IN**itial **T**argeted **E**ngagement for **R**egulatory **A**dvice on **C**BER produc**T**s
  - *a specific investigational product or product-derivation strategy should be selected by time of INTERACT meeting request*

- CBER recognizes that the development of innovative investigational products has unique challenges
  - Complex manufacturing technologies and issues
  - Unknown safety profiles
  - Use of cutting-edge testing methodologies
  - Incorporation of new devices/delivery systems

- **Goal:** *To obtain early feedback on a product development program for a novel investigational agent*

*** https://www.fda.gov/vaccines-blood-biologics/industry-biologics/interact-meetings-initial-targeted-engagement-regulatory-advice-cber-products**

INTERACT Meeting

- **Features:**
  - Non-binding, informal scientific discussions with CBER/OTAT review disciplines
  - Initial targeted discussion of specific issues (e.g., early product characterization, early POC studies, new delivery devices, general early-phase trial design elements)
  - FDA will help identify critical issues or deficiencies early in development

  - *Primary contact: INTERACT-CBER@fda.hhs.gov*

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

INTERACT Meeting – Pharmacology-Toxicology (P/T)

- Overall P/T advice related to the *design of proof-of-concept* or other *pilot safety/biodistribution studies* necessary to support administration of an investigational product in a First-in-human (FIH) trial
  - Adequacy of the selected animal species and animal models of disease/injury
  - Study designs (e.g., endpoints, dose levels, route of administration, dosing regimen)
  - 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

INTERACT Meeting: Out of Scope

- The sponsor has not decided between multiple product options or the investigational clinical product has not been identified
- The sponsor has previously received formal regulatory advice about a similar product and indication
- Questions / discussion regarding the adequacy and design of definitive toxicology studies
- Review of final study reports for completed proof-of-concept or toxicology studies
- Questions on a preclinical testing plan where no preliminary data from pilot studies are provided

INTERACT Meeting (cont'd)

- To facilitate a future pre-IND meeting:
  - Include the FDA written INTERACT comments and your responses in your pre-IND meeting package
  - The advice from the INTERACT meeting should be considered when preparing your pre-IND meeting package and when preparing the protocols for the definitive preclinical studies

- Requests for INTERACT meetings:

  INTERACT-CBER@fda.hhs.gov

Pre-IND Meeting

- Non-binding, but formal meeting between FDA and sponsor (with meeting minutes generated)

- Meeting package should include summary data and sound scientific principles to support use of a specific product in a specific patient population

- Can be helpful in developing a strategy for drug development by obtaining feedback on studies that will support the initiation of clinical trials

Pre-IND Meeting: Preclinical

- What to include in the preclinical section?
  - A comprehensive summary of all completed preclinical studies:
    - *in vitro* and *in vivo* studies
    - animal species/models
    - study designs
    - product manufacturing and formulation
    - resulting data and interpretation
  - Discussion of the planned preclinical program

    (e.g., animal species/models, product manufacturing and formulation, study designs, etc.)

Do's for INTERACT and Pre-IND Meetings [Preclinical Perspective]

- Do read and understand FDA/ICH Guidances, regulations, etc. before meeting with FDA
- Do include the preclinical development plan
- Do specify similarities and differences between the preclinical and clinical products
- Do specify similarities and differences between the preclinical and clinical delivery devices/procedures
- Do include the design of your completed and proposed preclinical studies
- Do make the package reader-friendly

Don’ts for INTERACT and Pre-IND Meetings [Preclinical Perspective]

- Don’t conduct the definitive preclinical studies without seeking input from CBER/OTAT at the pre-IND meeting
- Don’t forget to discuss the limitations for each test system used
- Don’t forget to consider new *in vitro* and *in vivo* test models as the science and technology progress
- Don’t forget that the preclinical testing program may need to be adapted to the specific cell and gene therapy product and level of risk

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, therefore, pre-submission interaction with FDA is encouraged

Take-home message

What are the major objectives of a preclinical program for a CBER-regulated product?

- ✓Establish scientific rationale to support a planned trial
- ✓Provide recommendations for the conduct of the proposed clinical study
- ✓To meet regulatory requirements

Selected Guidance Documents

- 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

- Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2017)

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-early-phase-clinical-trials-cellular-and-gene-therapy-products

- Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (July 2018)

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/long-term-follow-after-administration-human-gene-therapy-products

- Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines (October 2011)

  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/clinical-considerations-therapeutic-cancer-vaccines

Contact Information

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  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
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