Preclinical Assessment of Cell and Gene Therapy Products to Support an IND: A CBER/FDA Perspective

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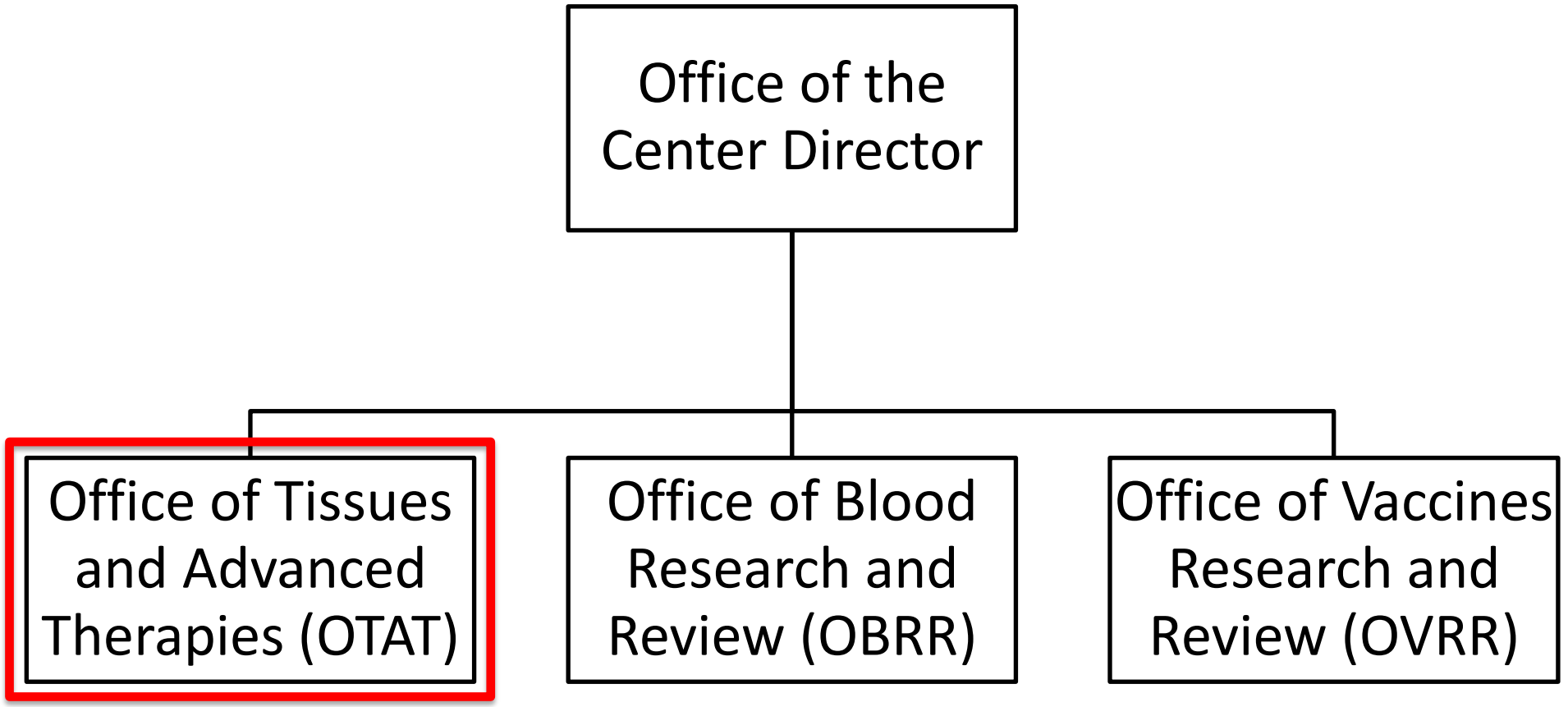
Society for Immunotherapy of Cancer

Presentation Outline

- Organizational structure of CBER/OTAT and regulated products
- Cell and Gene Therapy (CGT) Products
- Regulatory Review Principles
- Preclinical considerations for assessing the safety and activity of CGT products
- Potential Pitfalls/Regulatory Issues
- 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

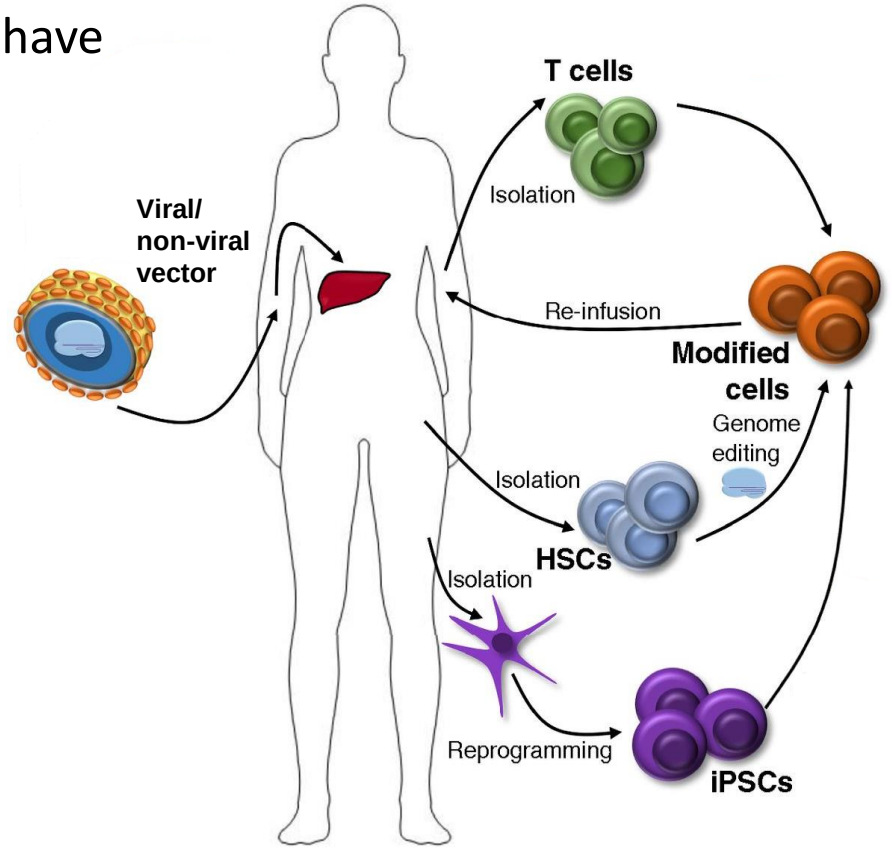


Diversity of CBER/OTAT-Regulated Products

- **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 products**
  - 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

CGT Products: Definition and Therapeutic Use in Human Diseases

- Cell therapy—autologous, allogeneic, or xenogeneic living cells that may or may not have been processed *ex vivo*



- Gene therapy—products that mediate their effects by transcription and/or translation of transferred genetic material, or by specifically altering host (human) genetic sequences
  - Vector based—viral/non-viral
  - *Ex vivo* genetically modified cells
  - Products incorporating genome editing

**Modified from https://stemcells.nih.gov/info/Regenerative_Medicine/2006Chapter4.htm*

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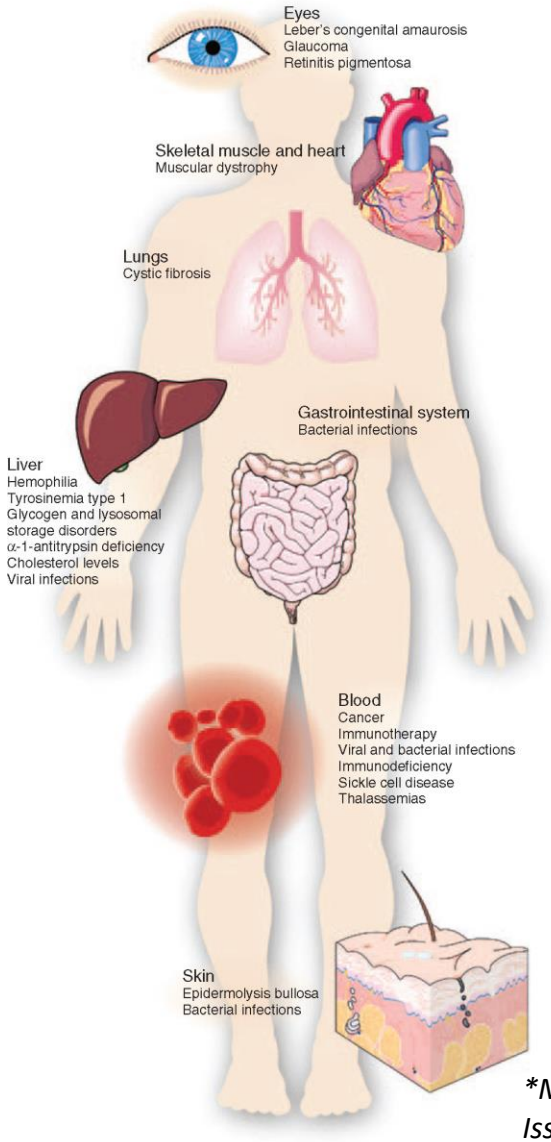

Examples

- Cell therapies: mesenchymal stem sells (MSCs), tumor-infiltrating lymphocytes (TILs), natural killer (NK) cells

  Alzheimer's, graft versus host disease, solid tumors

**Molecular Therapy, Volume 24, Issue 3, March 2016, Pages 430-446*

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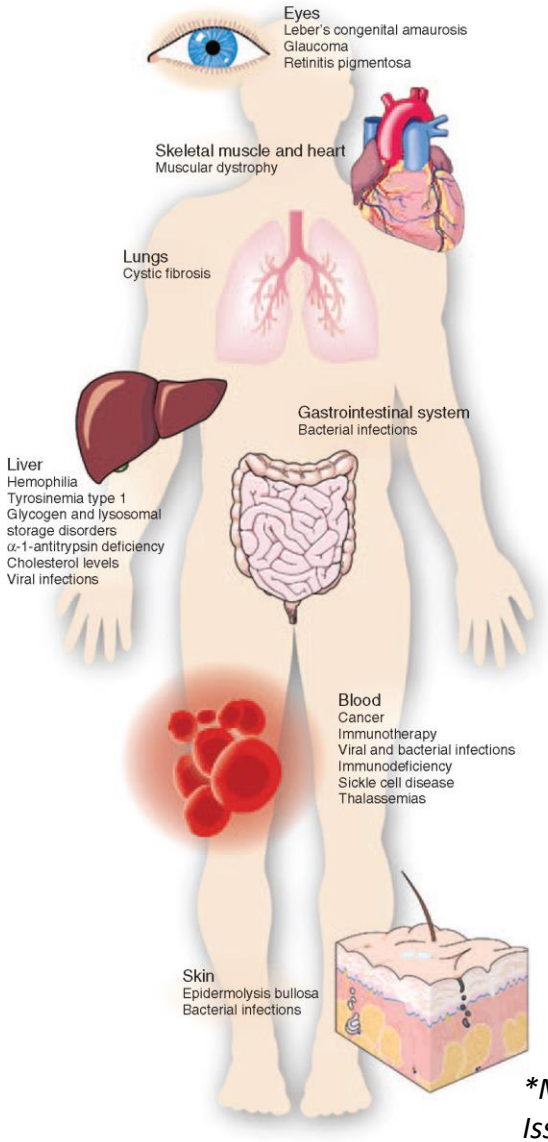

Examples

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- Genetically engineered cell therapies: CD34+, T cell receptor (TCR)-T, chimeric antigen receptor (CAR) T cell
  Blood disorders, hematologic malignancies, solid tumors

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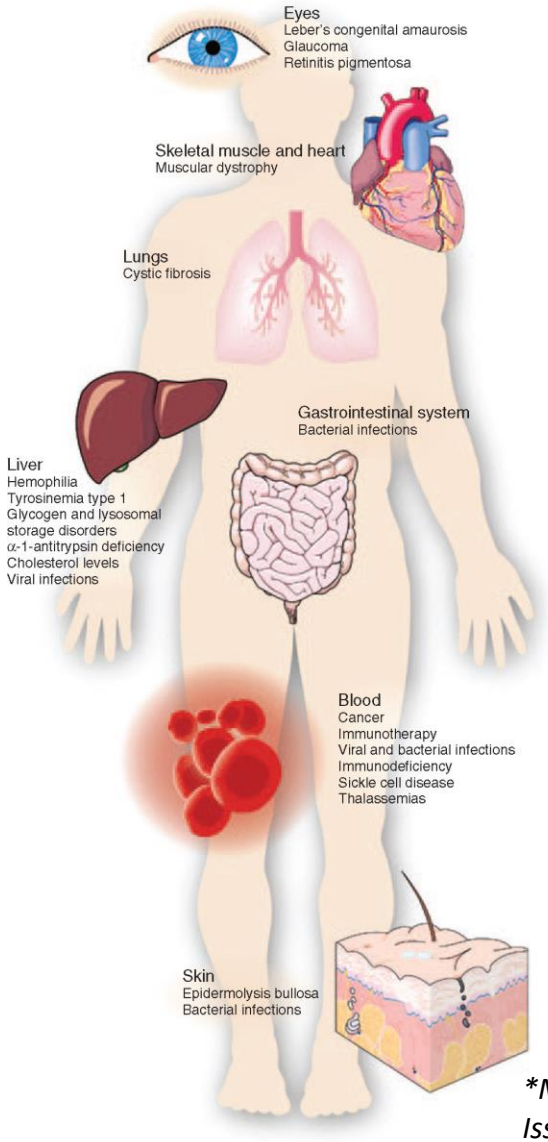
CGT Products: Definition and Therapeutic Use in Human Diseases



Examples

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  Alzheimer's, graft versus host disease, solid tumors
- Genetically engineered cell therapies: CD34+, T cell receptor (TCR)-T, chimeric antigen receptor (CAR) T cell
  Blood disorders, hematologic malignancies, solid tumor
- Vector-based gene therapies: viruses, plasmids
  Monogenic diseases, cancers

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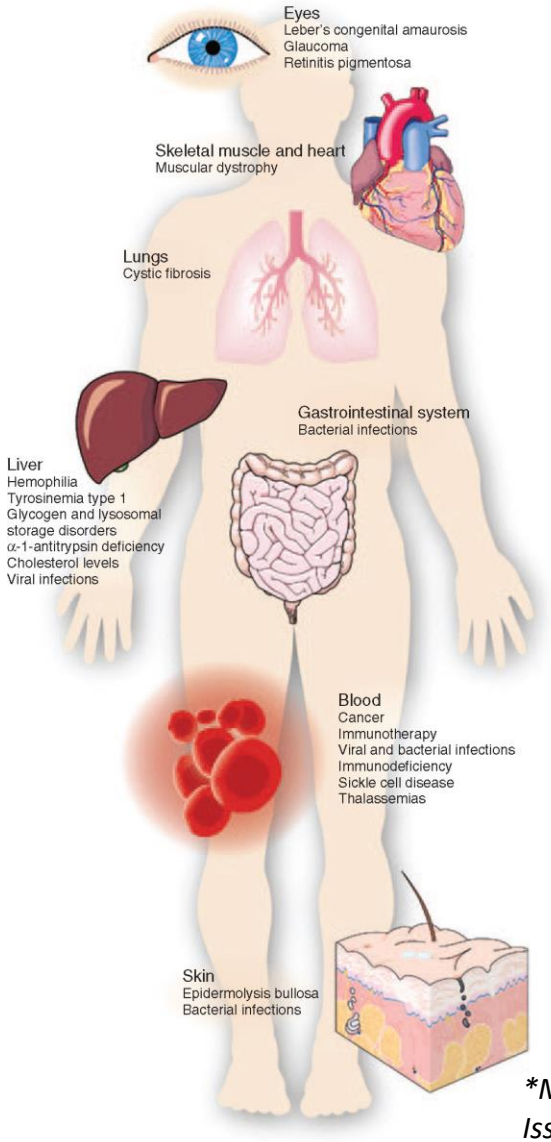
Examples of CGT-based Immunotherapy Products Regulated in OTAT



Examples

- ❑ 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)
- ❑ Therapeutic Vaccines (e.g., dendritic cells, irradiated tumor cells, peptide vaccines, lipid nanoparticles carrying mRNA , etc.)

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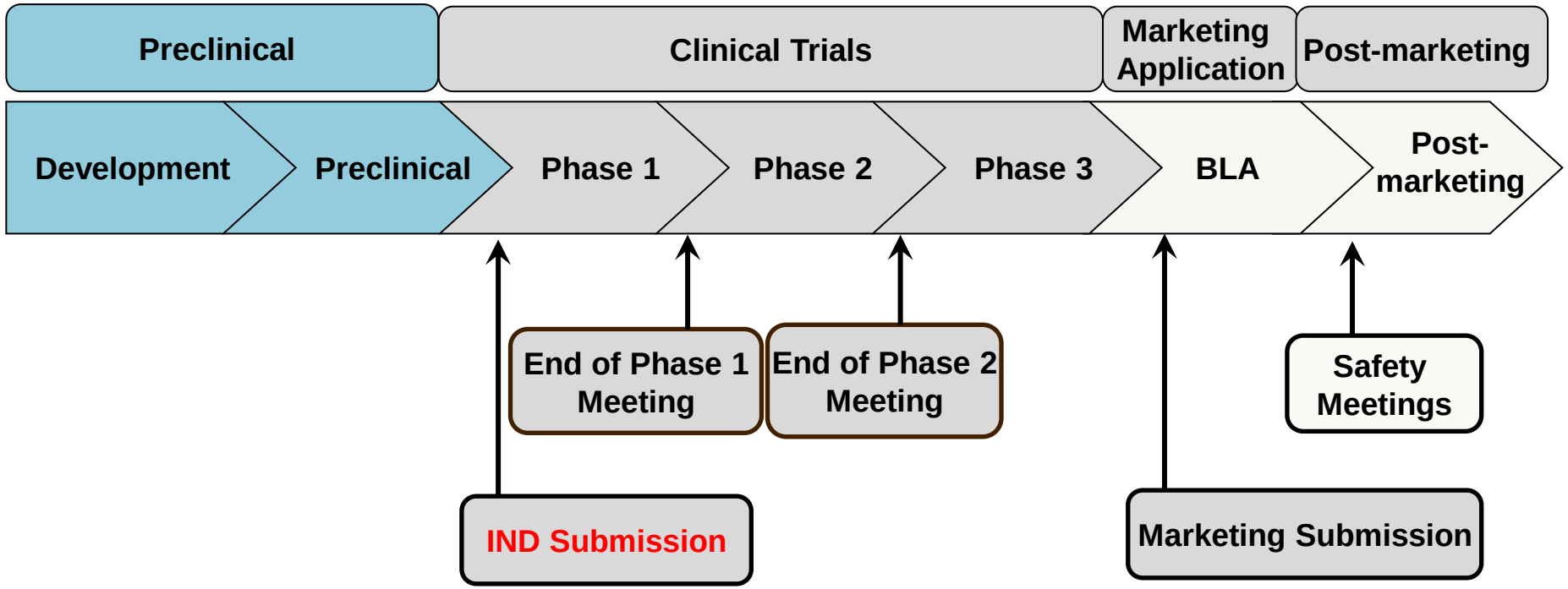
Lifecycle for Investigational Products



Evaluating Safety and Activity of CGT Products to Support an IND

- IND Application: required to conduct a clinical trial in the US
  - Using an investigational product in a first-in-human (FIH) trial
  - Using an approved/investigational product for a new clinical indication/route of administration (ROA)/formulation
  - Has a 30-day FDA review clock
  - Governing regulations: 21 Code of Federal Regulation (CFR) 312

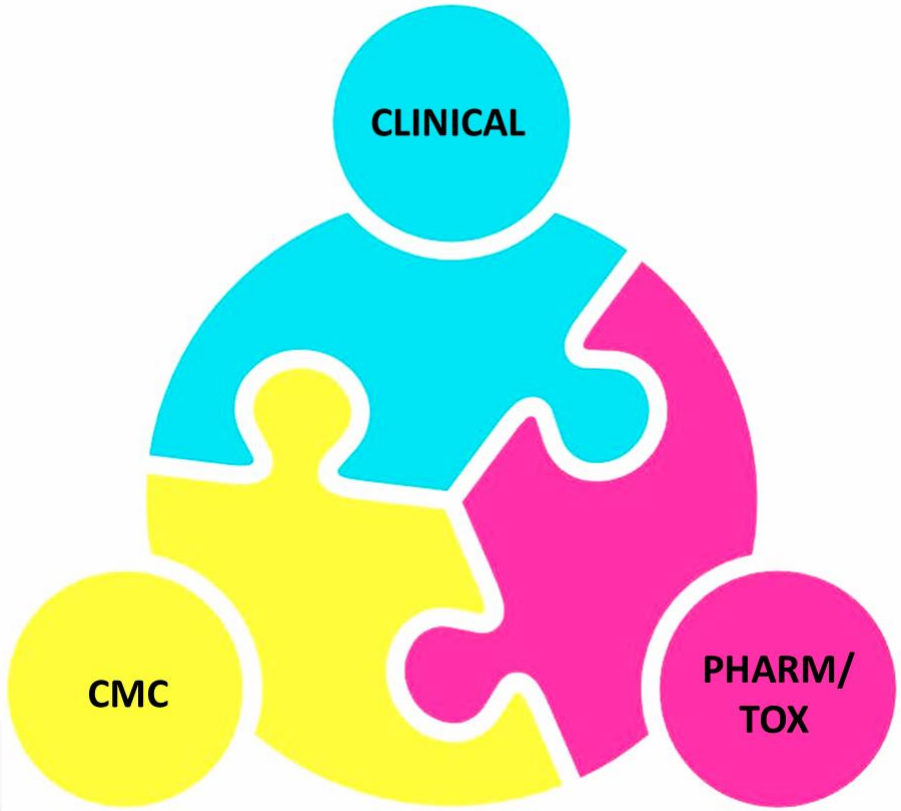
- IND review team:
  - Is interdisciplinary
    - Regulatory Project Manager (RPM)
    - Chemistry, Manufacturing, and Controls (CMC) reviewer
    - **Pharmacology/Toxicology (P/T) reviewer**
    - Clinical reviewer
    - Statistical reviewer
    - Consult reviewer(s) (as needed)
  - Reviews information supporting rationale and safety of the trial
  - Interacts with the sponsor, as needed, to resolve issues or concerns
  - Makes a “go” or “hold” decision by the 30-day date

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 in Regulatory Review of CGT Products

- Science-based approach to regulation
- Product manufacturing (CMC)
- Pharmacology/Toxicology (P/T)
- Clinical trial design



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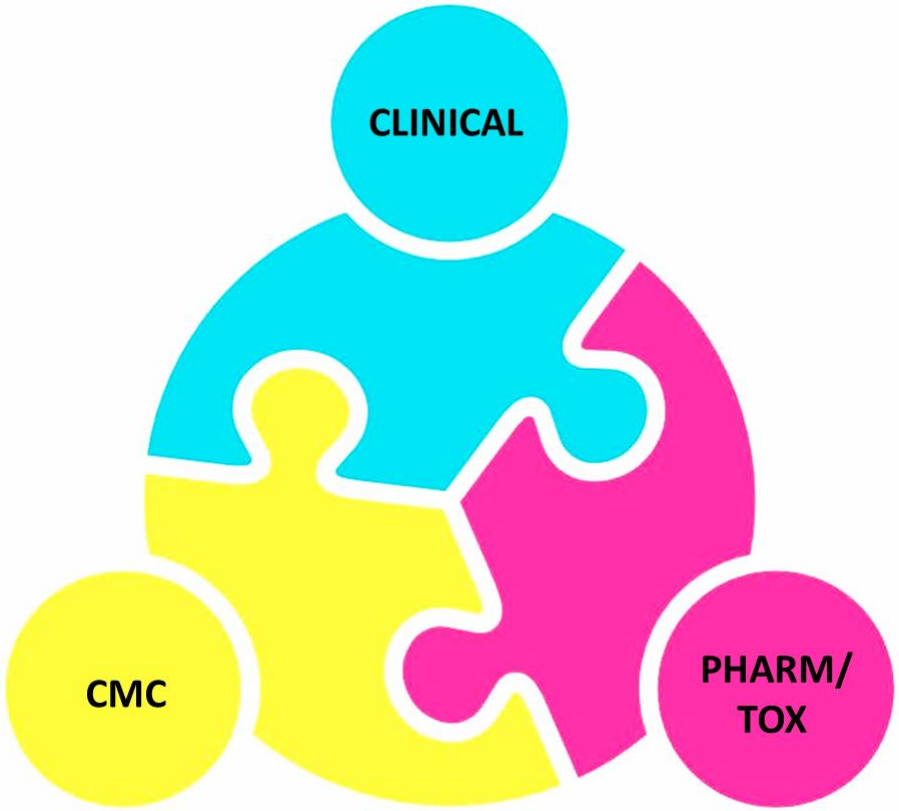


Considerations for Preclinical Programs for CGT Products

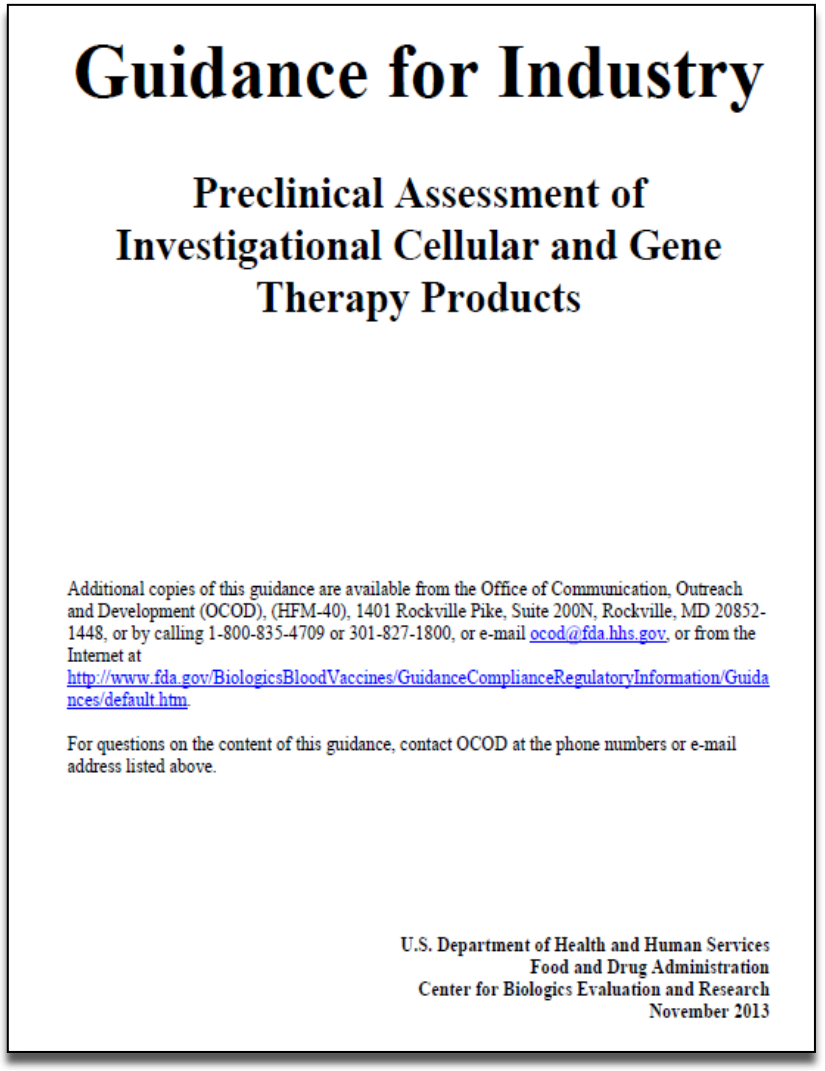
How Do Preclinical Data Contribute to the Proposed Clinical Plan?

- Provide **rationale** or **proof of concept (POC)** for the first-in-human (FIH) clinical trial in subjects with the target disease
- Make recommendations to inform clinical trial design
  - Eligibility criteria
  - Route of administration (ROA), initial safe starting dose level, dose escalation scheme, dosing regimen
  - Potential toxicities, clinical monitoring, risk mitigation
- Provide comprehensive **safety assessment** in a relevant animal species/model
  - Identifying any acute and chronic, local and systemic toxicities
  - Risks of the proposed ROA, delivery procedure

General Considerations for Preclinical Testing Programs

How does CBER/OTAT evaluate preclinical safety and activity?

…and what sponsors should consider 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 CGT 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

Sources of Preclinical Data to Support an IND

- Appropriately designed, well-executed POC studies
- Good Laboratory Practice (GLP)-compliant toxicology studies
- Published data in peer-reviewed journals
- Authorized cross-reference to similar products in previous US FDA submissions

General Expectations for a Preclinical Testing Program for CGT Products

- Pharmacology
  - Provide **rationale** or **POC** for CGT product administration in a specific clinical population
  - Understand mechanism of action and biological activity in a relevant animal species/disease or injury model
  - Select optimal dose levels, and dosing regimen
  - Assess vector biodistribution/cell fate *in vivo* to support activity following clinically relevant ROA
- Prospect of Direct Benefit (PDB) is required for clinical studies in children *(per 21 CFR 50.52 Subpart D)—if the trial represents more than minimal risk*

General Expectations for a Preclinical Testing Program for CGT Products

❑ Toxicology

- Provide comprehensive **safety assessment** of the CGT product in a relevant animal species to support clinical trials
- Determine a No-Observed-Adverse-Effect-Level (NOAEL)
- Characterize adverse findings following product administration:
  - ✓ Identify target tissue(s) of toxicity
  - ✓ Local or systemic effects
  - ✓ Acute, delayed, or prolonged findings
  - ✓ Cells/vector/transgene-related immune responses
  - ✓ Tumorigenicity risk
  - ✓ Dosing procedure or device-related toxicities

- Cell/vector/transgene presence is important in the interpretation of any findings

Potential Safety Concerns for CGT Immunotherapies

- Product-related
  - Manufacturing (e.g., expansion, genetic modification, encapsulation, scaffold seeding)
  - Inappropriate cell proliferation (i.e., tumor formation)
  - Inappropriate cell differentiation (i.e., ectopic tissue formation)
  - Cell/vector distribution to non-target sites and potential toxicities
  - Inflammatory/immune response to the administered product
  - Toxicity to host tissues/organs (e.g., GVHD for allogeneic T cell products)
  - Toxicities due to cross-reactivity- on-target/off-tumor, off-target activity
  - Toxicities due to pharmacological action of CGT- cytokine release, tumor lysis, etc.
- Procedure and/or device-related

CGT Product Administered in Preclinical Studies

- **Product should be as similar as possible to the intended clinical product**
  - Tissue/sample source, harvesting procedure, expansion, culturing, formulation, encapsulation/scaffold seeding, storage, etc.
  - Vector production/vector construct/transgene expression/final formulation/titer

- **Adequate product characterization**
  - Cellular morphology, phenotype
  - Molecular, biochemical markers
  - Vector sequence, genomes, empty capsids

- **Animal-derived analogous product**
  - Characterize the level of analogy between the animal product and the intended human product
  - Translation of data to humans

Considerations for Appropriate Animal Species/Model(s)

- Scientific justification should be provided for each animal species/model(s) used
  - 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, distribution, and bioactivity using appropriate animal species/model(s)
- Understand the limitations of each species/model(s) 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

Preclinical Study Design Considerations

- Nonbiased
- Mimic the planned clinical scenario as closely as possible
- Administration of appropriate control product and multiple dose levels of the investigational product
- Adequate numbers of animals/group to enable robust study interpretation
  - Incorporate the three R's of animal testing into preclinical programs
    - ✓ **R**educe
    - ✓ **R**efine
    - ✓ **R**eplace

Preclinical Study Design Considerations

- Sufficient study duration to assess both acute and long-term outcomes
- Multiple time points for evaluations
- Comprehensive bioactivity, distribution, and safety assessments
- Other specific in-life/terminal assessments

Mirror the Clinical Scenario (as Feasible)

- Mimic clinical scenario as closely as possible
  - Test clinical product and formulation
  - Mimic clinical injection procedure, anatomical location, delivery system / device**, timing of product delivery, dosing regimen

**Conduct bench testing of the delivery device with the CGT product to determine product-device compatibility and verify the dose level administered

Study Assessments and Endpoints

- **Multiple in-life and post-mortem time points for activity and safety**
  - Biochemical, functional outcomes (e.g., neurological, cardiac, ophthalmic) which are disease dependent
  - Bio Distribution—cells, vector
  - Tumorigenicity—cells, vector, transgene
  - Transgene—expression, activity
  - Immunogenicity—cells/vector/transgene
- **Standard toxicology parameters**
  - Mortality, in-life—body weights, food consumption, etc.
  - Clinical observations
  - Clinical pathology
  - Gross pathology and histopathology—target and non-target tissues (use of standard IHC, ISH etc., microscopic pathology)
  - Nature/timing/severity/frequency of adverse findings

Vector Biodistribution /cell fate

❑ Biodistribution profile in biofluids and tissues

Target and nontarget tissues: Distribution, Persistence, and Clearance

- For GT products

✓ Vector presence and clearance profile in target, non-target, and germline tissues

✓ Transgene expression (level and duration) in vector positive tissues

- For CT products

✓ Cell survival, engraftment, integration, proliferation, differentiation, and migration

❑ Important to evaluate the POC and Safety results with vector biodistribution /cell fate data

❑ Guidance for GT-based BD assessment:

- Guidance for Industry: Long Term Follow-up After Administration of Human Gene Therapy Products (Jan. 2020)
- Expectations for Biodistribution (BD) Assessments for Gene Therapy (GT) Products, International Pharmaceutical Regulators Programme (IPRP) Reflection Paper (April 2018)
- S12 Nonclinical Biodistribution Considerations for Gene Therapy Products; International Council for Harmonization; Draft Guidance for Industry (2021)

Regulatory Expectations for Toxicology Studies

21 CFR 312.23 (a)(8) – Pharmacology and Toxicology

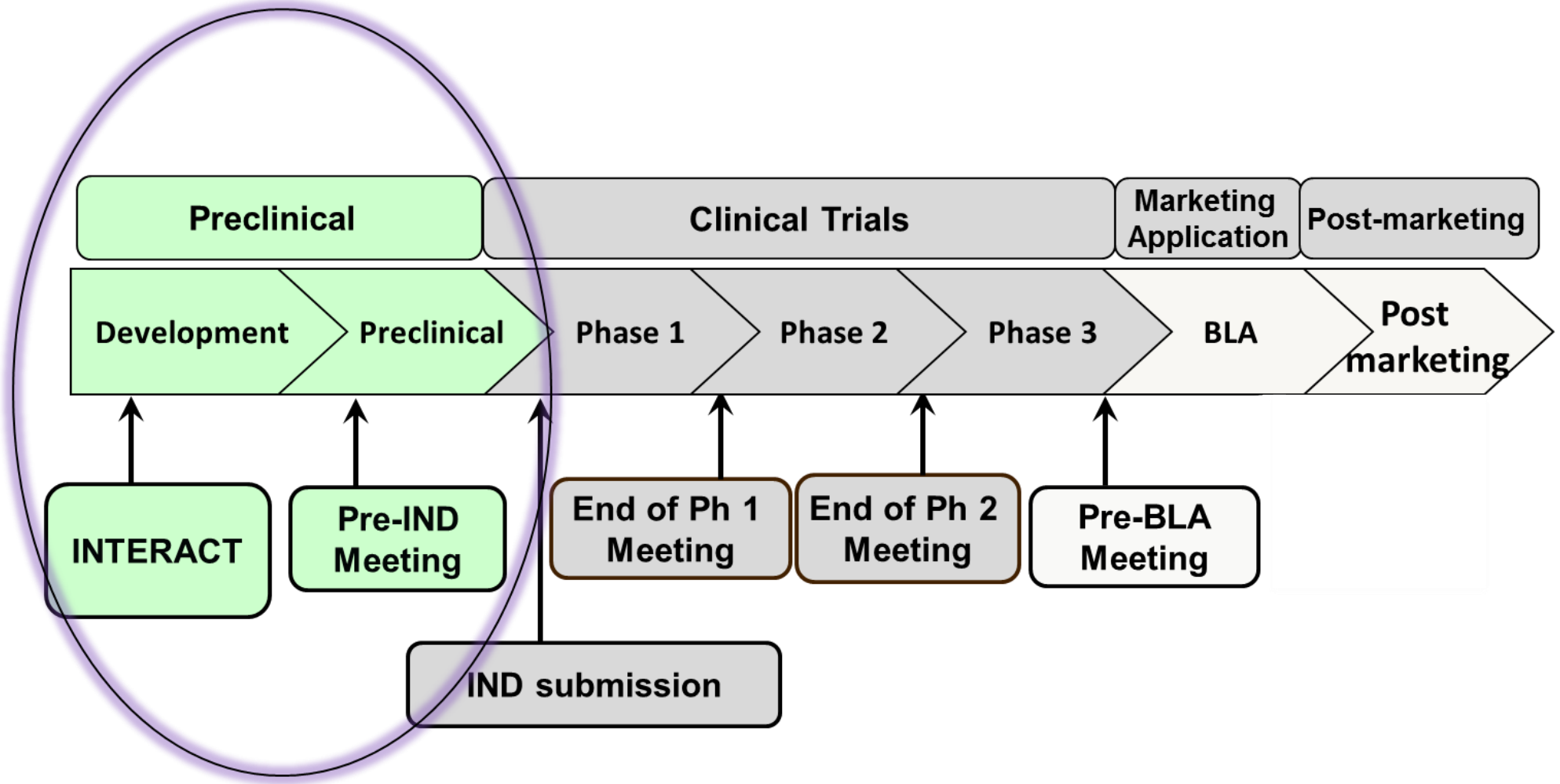
- For each toxicology study intended primarily to support safety, a full tabulation of data should be submitted
- Each toxicology study submitted should be performed per GLP (21 CFR Part 28), or an explanation provided
- Oversight of the conduct of all non-GLP toxicology studies and the resulting final study report by an independent QA unit/person is strongly recommended (21 CFR 58.35)

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 safety study reports
- Inadequate preclinical study design
  - ✓ Differences between preclinical and clinical products
  - ✓ Irrelevant animal species/model
  - ✓ Irrelevant ROA
  - ✓ Inadequate animal numbers/dose levels/study duration
  - ✓ Inadequate evaluations (safety/activity endpoints)

- Inadequate data to support PDB in a FIH study in children (21 CFR 50 Subpart D)

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'd)

- **Timing:** When you have generated preliminary preclinical data (POC and some safety), but are not yet ready to conduct definitive preclinical safety studies
- **Pharmacology/Toxicology (P/T) advice:**
  - Design of POC or other pilot safety/distribution 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 definitive safety studies

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, distribution studies
  - Animal species/models, dose levels, dosing regimen and procedure, study endpoints, sacrifice intervals, etc.

FDA Guidance for Human CGT Products

- Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2013)
  https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM376521.pdf

- Guidance for Industry: Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (June 2015)
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-early-phase-clinical-trials-cellular-and-gene-therapy-products

- Guidance for Industry: Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (IND) (Jan 2020)
  https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM610795.pdf

- Guidance for Industry: Long Term Follow-Up After Administration of Human Gene Therapy Products (Jan 2020)
  https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM610795.pdf

FDA Guidance for Human CGT Products (Cont'd)

- Guidance for Industry: Human Gene Therapy for Retinal Disorders (Jan 2020)
  https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM610803.pdf

- Guidance for Industry: Human Gene Therapy for Rare Diseases (Jan 2020)
  https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM610802.pdf

- Guidance for Industry: Human Gene Therapy for Hemophilia (Jan 2020)
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-hemophilia

- Draft Guidance for Industry: Human Gene Therapy for Neurodegenerative Diseases (July 2021)
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-neurodegenerative-diseases

- Draft Guidance for Industry: S12 Nonclinical Biodistribution Considerations for Gene Therapy Products (September 2021)
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s12-nonclinical-biodistribution-considerations-gene-therapy-products

Summary

- OTAT resides within CBER and regulates a wide array of products, including cell and gene-based therapies
- The preclinical program for any CGT product is determined on a case-by-case basis
- Preclinical data submitted in the IND should support the safety and biological activity of the CGT product in the proposed clinical indication
- There are multiple opportunities to obtain FDA feedback on preclinical development plans prior to IND submission
- Novel therapies mean novel testing paradigms, therefore, pre-submission interaction with FDA is encouraged

Acknowledgements

- Colleagues in OTAT/CBER

Contact Information

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- **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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Thank you!