Society for Immunotherapy of Cancer

Preclinical Assessment of Cell and Gene Therapy Products to Support an Investigational New Drug (IND) Application: A FDA/CBER Perspective

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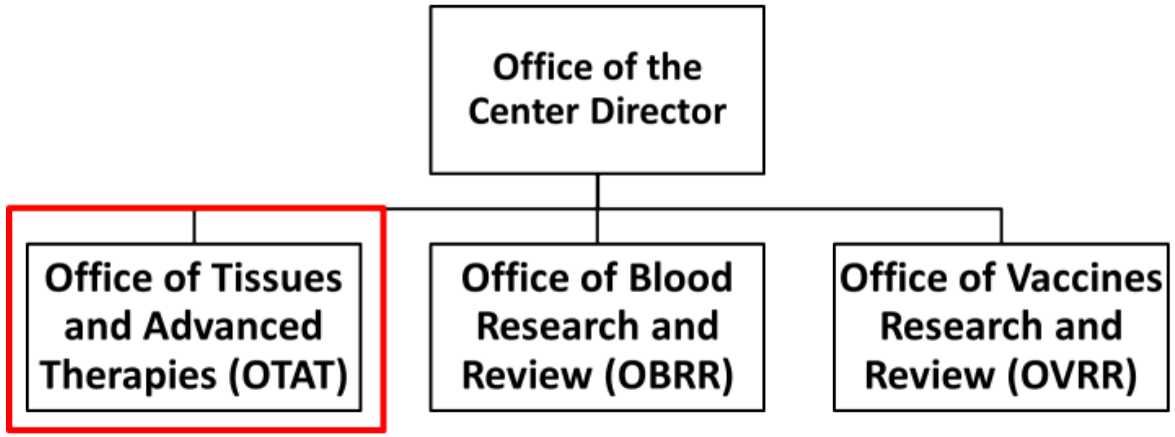
Team Lead

Office of Tissues and Advanced Therapies (OTAT)
Center for Biologics Evaluation and Research (CBER)
US Food and Drug Administration (FDA)

Overview

- ❑ CBER/OTAT Organization and Products
- ❑ Cell and Gene Therapy (CGT) Products
- ❑ Regulatory Review Principles
- ❑ CGT Safety Concerns
- ❑ Preclinical Testing Program- CGT immunotherapies
- ❑ Potential Pitfalls/Regulatory Issues
- ❑ Early Interaction with CBER/OTAT



*Created using www.wordclouds.com

Diversity of OTAT-Regulated Products

- **Gene therapies**
  - *Ex vivo* genetically modified cells
  - Nonviral 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**
  - Embryonic
  - Fetal (e.g., neural)
  - Perinatal (e.g., placental, umbilical cord blood)
  - Adult (e.g., hematopoietic, neural, cardiac, adipose, mesenchymal)
  - 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**
  - Peptide vaccines
  - Cellular immunotherapy (e.g., natural killer cells)

- **Blood- and plasma-derived products**
  - Coagulation factors
  - Fibrin sealants, Fibrinogen, Thrombin, Plasminogen
  - Immune globulins
  - Antitoxins, snake venom antisera

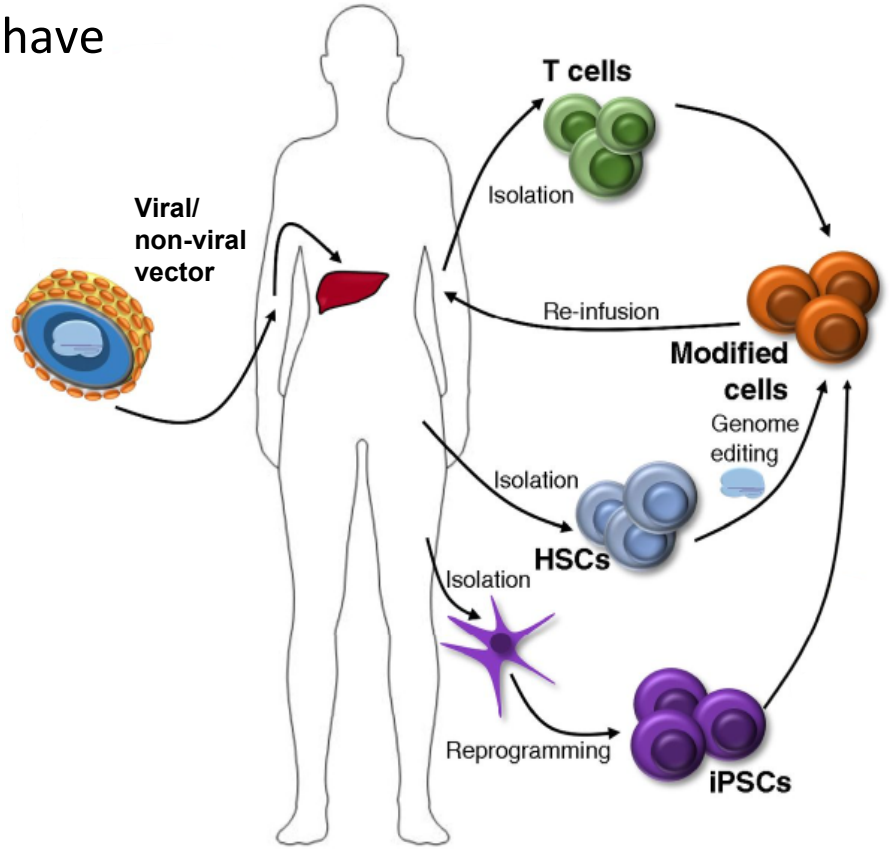
- **Tissues**

- **Devices**

- **Combination products**
  - Engineered tissues/organs

CGT Products: Definition and Therapeutic Use in Human Diseases

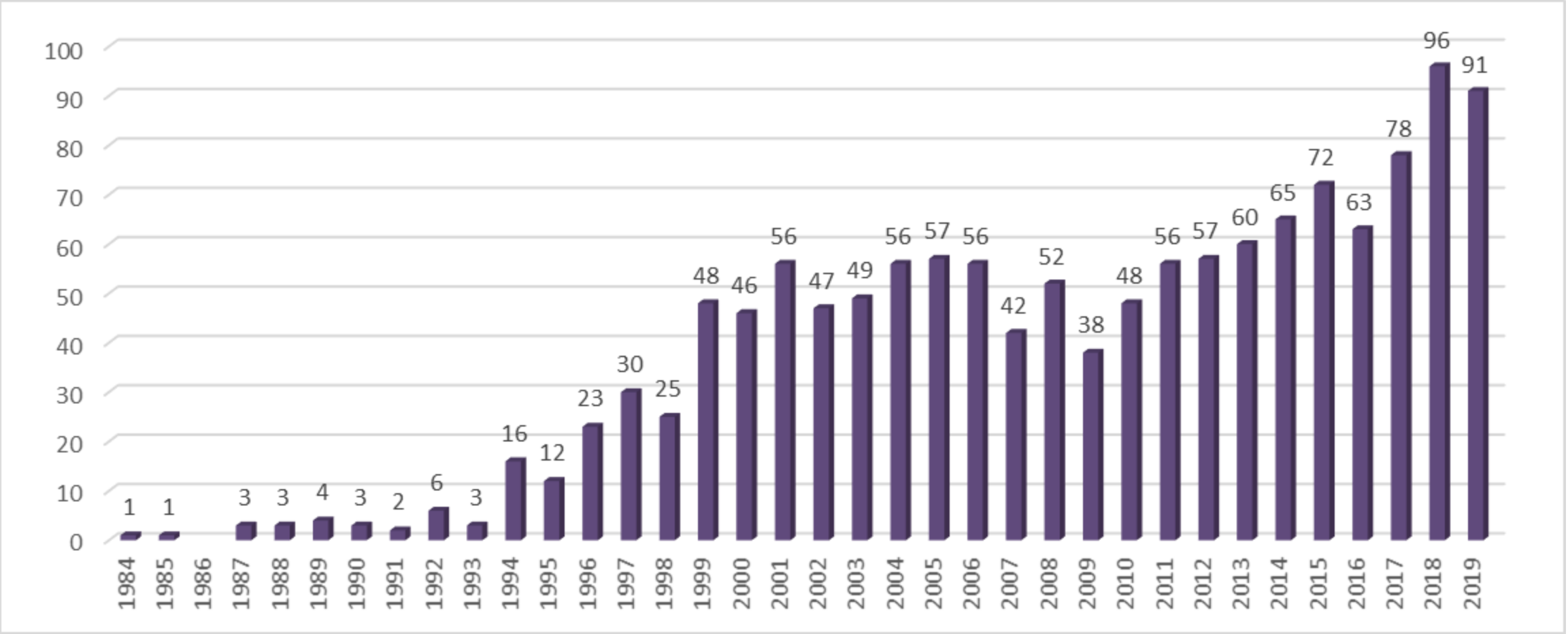
- Cell therapy—autologous, allogeneic, or xenogeneic living cells that may or may not have been processed *ex vivo*



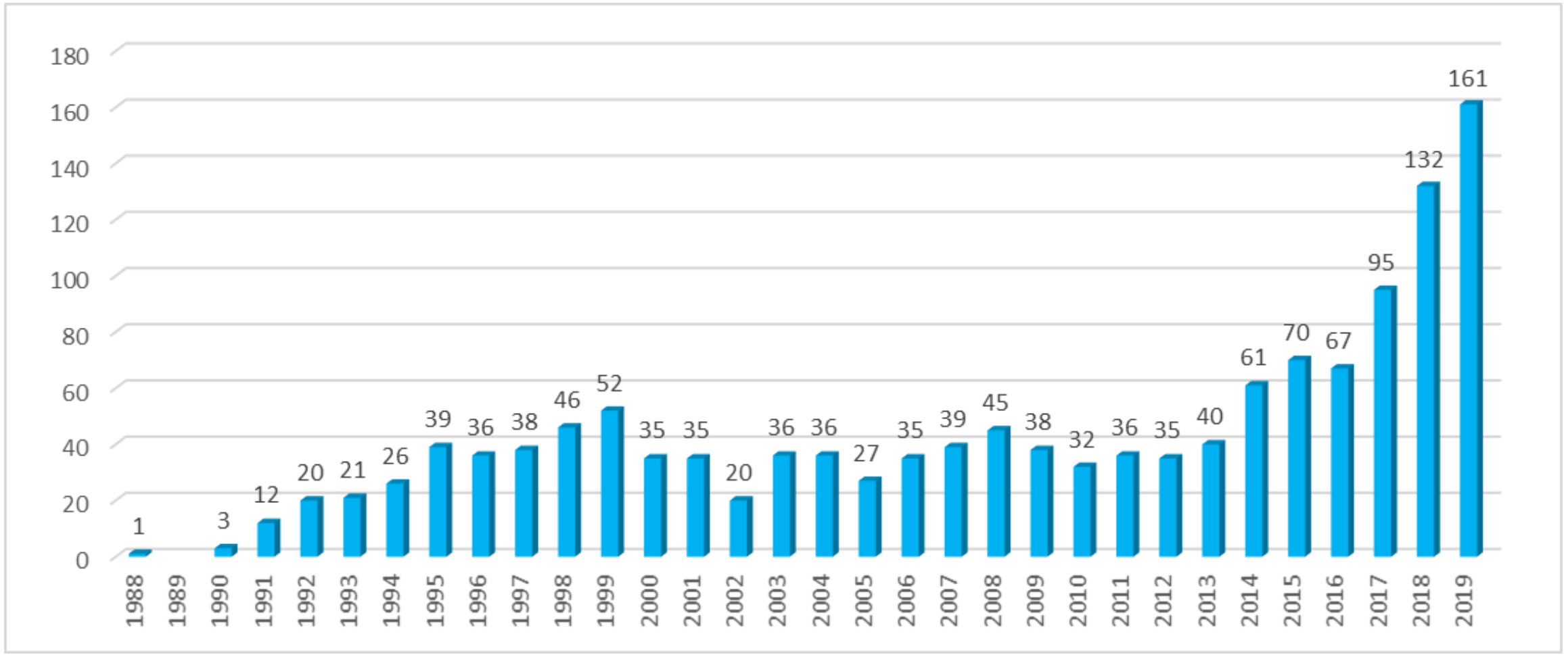
- Gene therapy—products that mediate their effects by transcription and/or translation of transferred genetic material, or by specifically altering host (human) genetic sequences
  - Vector based—viral/non-viral
  - *Ex vivo* genetically modified cells
  - Products incorporating genome editing

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

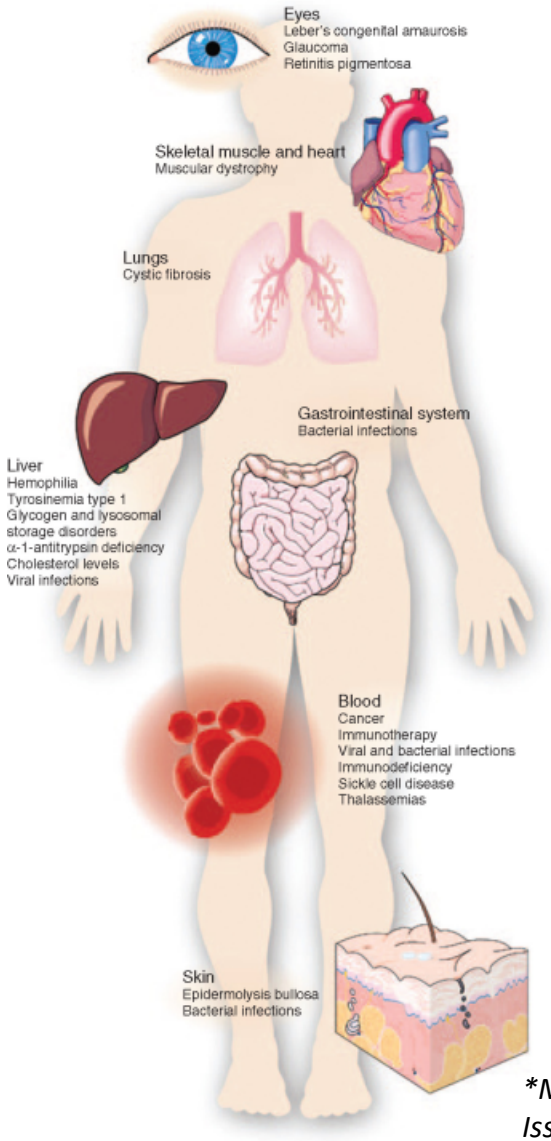
All IND Submissions with Cell Therapy Products, CY 1963–2019



All IND Submissions with Gene Therapy Products, CY 1963–2019



CGT Products: Definition and Therapeutic Use in Human Diseases



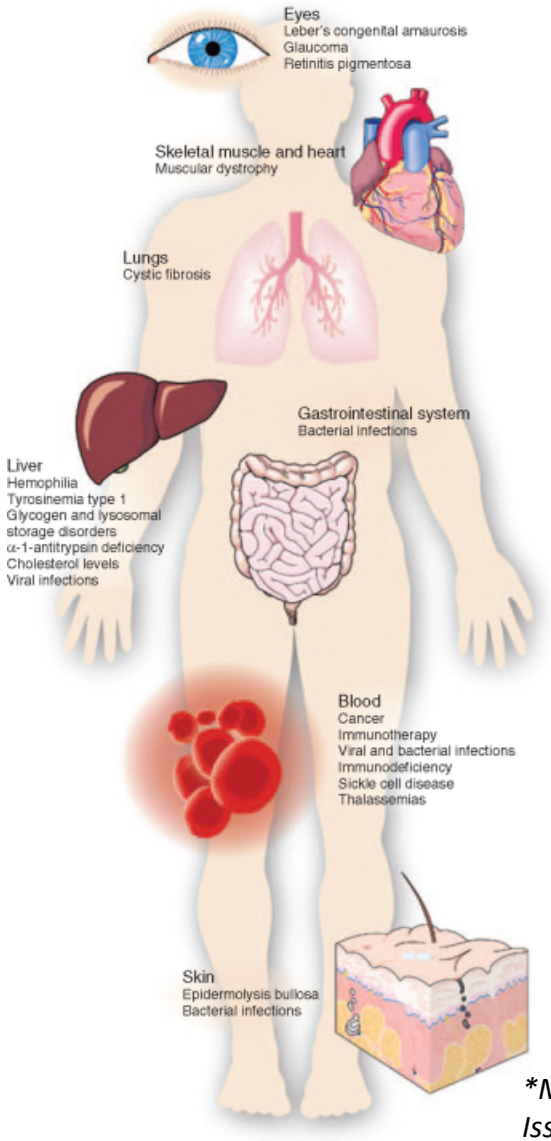
Examples

- ❑ 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*

CGT Products: Definition and Therapeutic Use in Human Diseases



Examples

- ❑ Cell therapies: mesenchymal stem sells (MSCs), tumor-infiltrating lymphocytes (TILs), natural killer (NK) cells
  Alzheimer's, graft versus host disease, solid tumors
  - ❑ Genetically engineered cell therapies: CD34+, T cell receptor (TCR)-T, chimeric antigen receptor (CAR) T cells
    Blood disorders, hematologic malignancies, solid tumors

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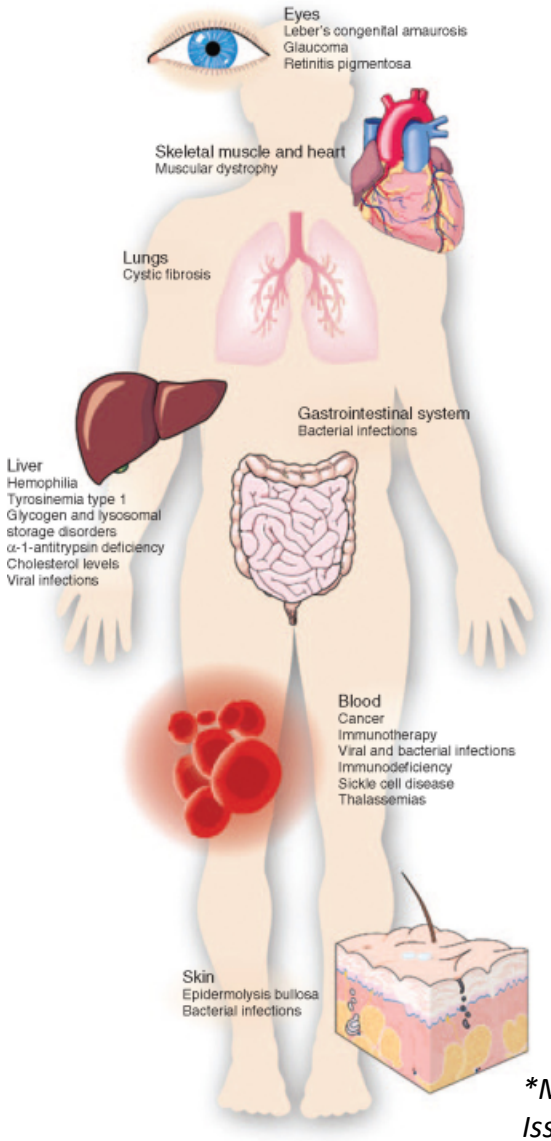
CGT Products: Definition and Therapeutic Use in Human Diseases



Examples

- Cell therapies: mesenchymal stem sells (MSCs), tumor-infiltrating lymphocytes (TILs), natural killer (NK) cells
  Alzheimer's, graft versus host disease, solid tumors
  - Genetically engineered cell therapies: CD34+, T cell receptor (TCR)-T, chimeric antigen receptor (CAR) T cells
    Blood disorders, hematologic malignancies, solid tumors
    - Vectors-based gene therapies: viruses, plasmids, lipid nanoparticles carrying mRNA
      Monogenic diseases, cancers

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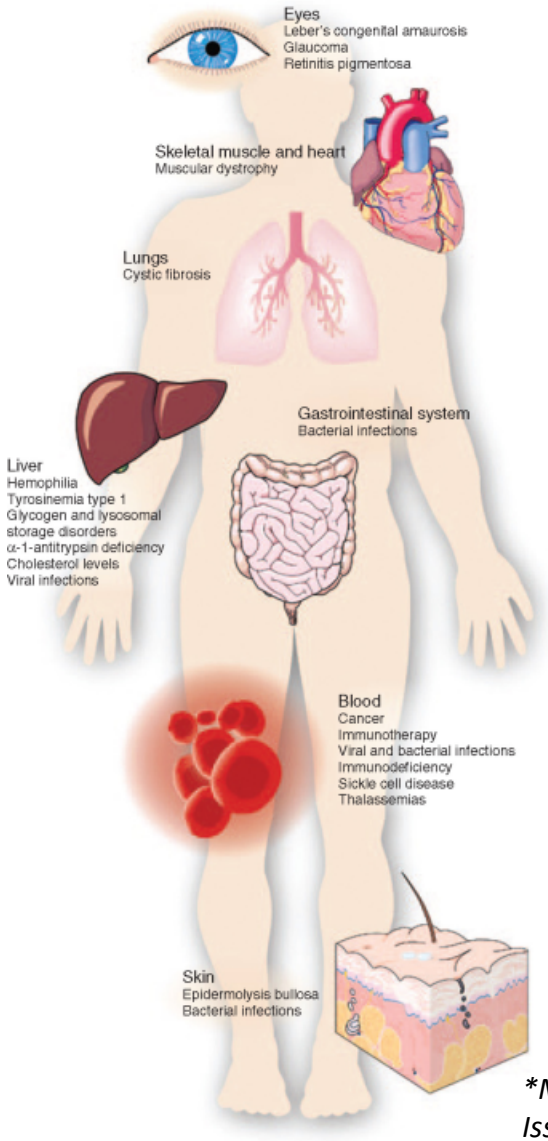
Examples of CGT-based Immunotherapy Products Regulated in OTAT



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, etc.)

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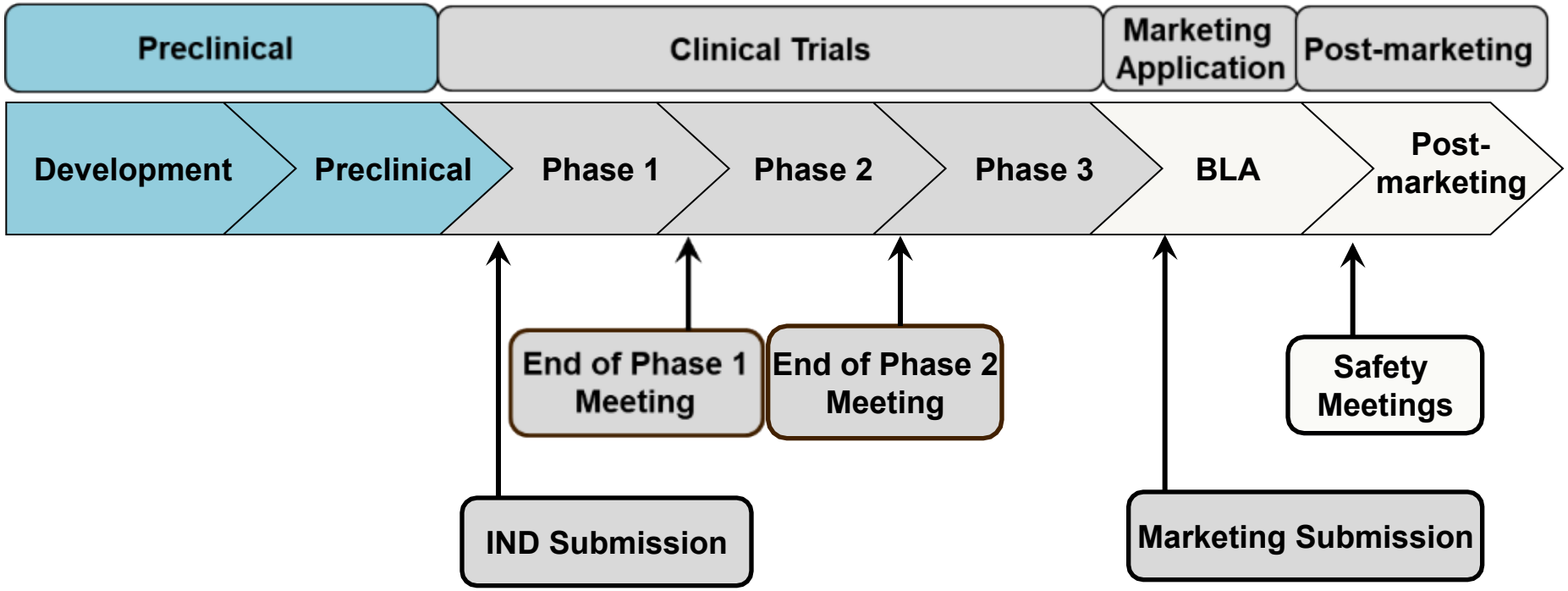
Product Lifecycle for CGT: Focus on the Preclinical Phase



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 US FDA review clock
  - Governing regulations: 21 Code of Federal Regulation (CFR) 312

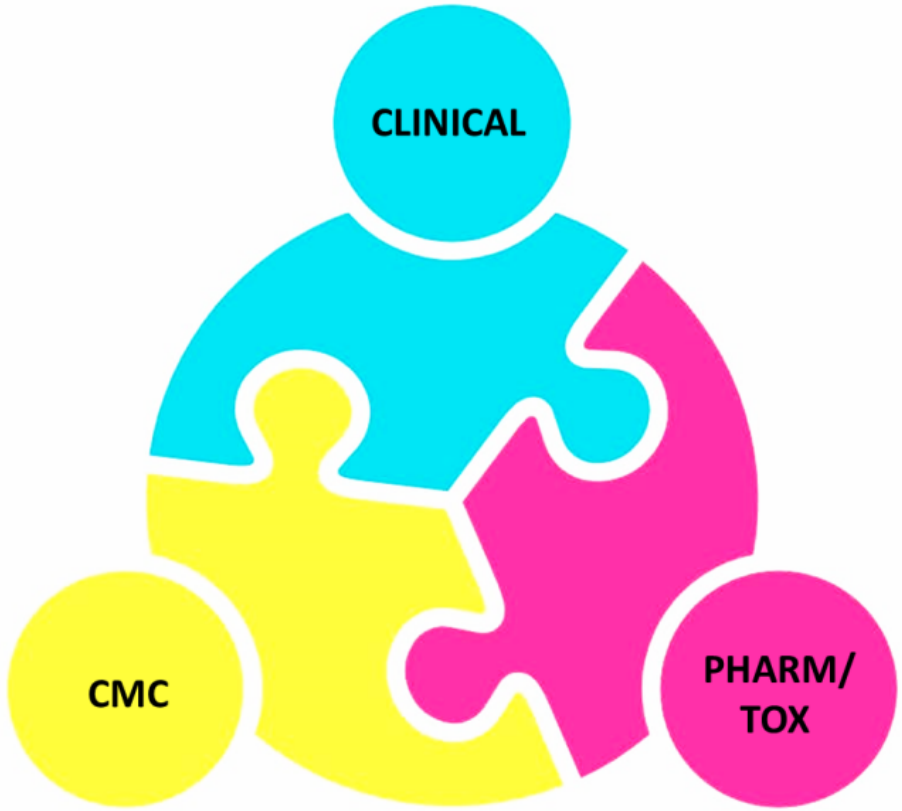
- IND review team:
  - Is interdisciplinary
    - Regulatory Project Manager (RPM)
    - Chemistry, Manufacturing, and Controls (CMC) reviewer
    - **Pharmacology/Toxicology (P/T) reviewer**
    - Clinical reviewer
    - Statistical reviewer
    - Consult reviewer(s) (as needed)
  - Reviews information 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—eligibility criteria, endpoints, monitoring during the trial, and long-term follow-up



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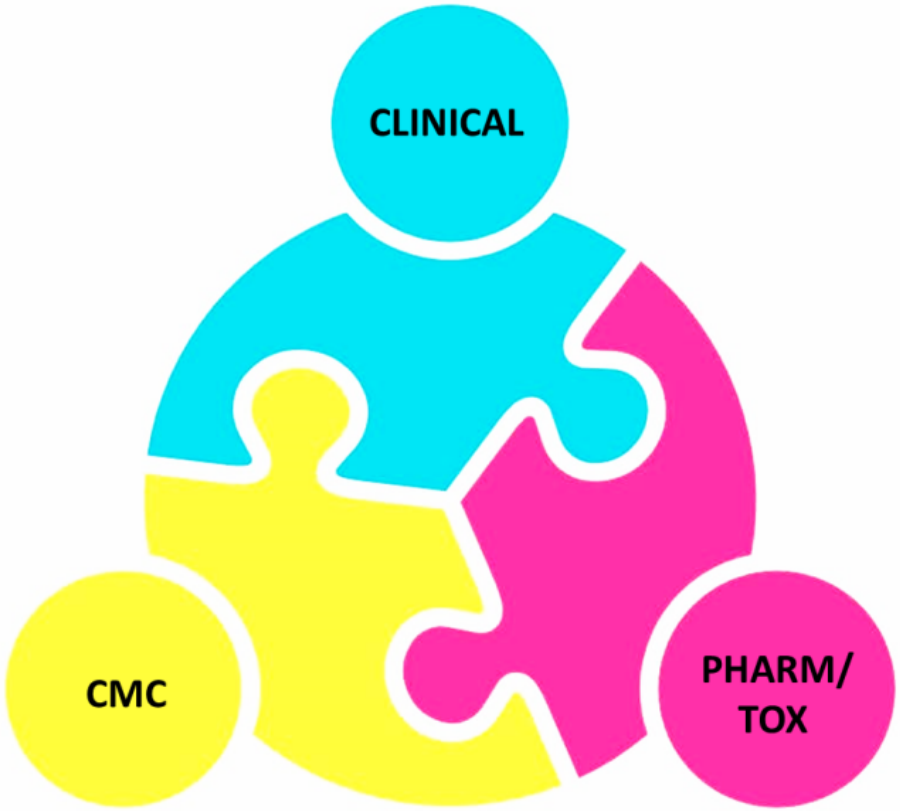

General Expectations for a Preclinical Testing Program for CGT Products

- Provide **rationale** or **proc**
  - Understanding biologi
  - *In vitro* and *in vivo* stu
- Provide comprehensive **s**
  - Identifying any acute a
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  - Potential toxicities, cli

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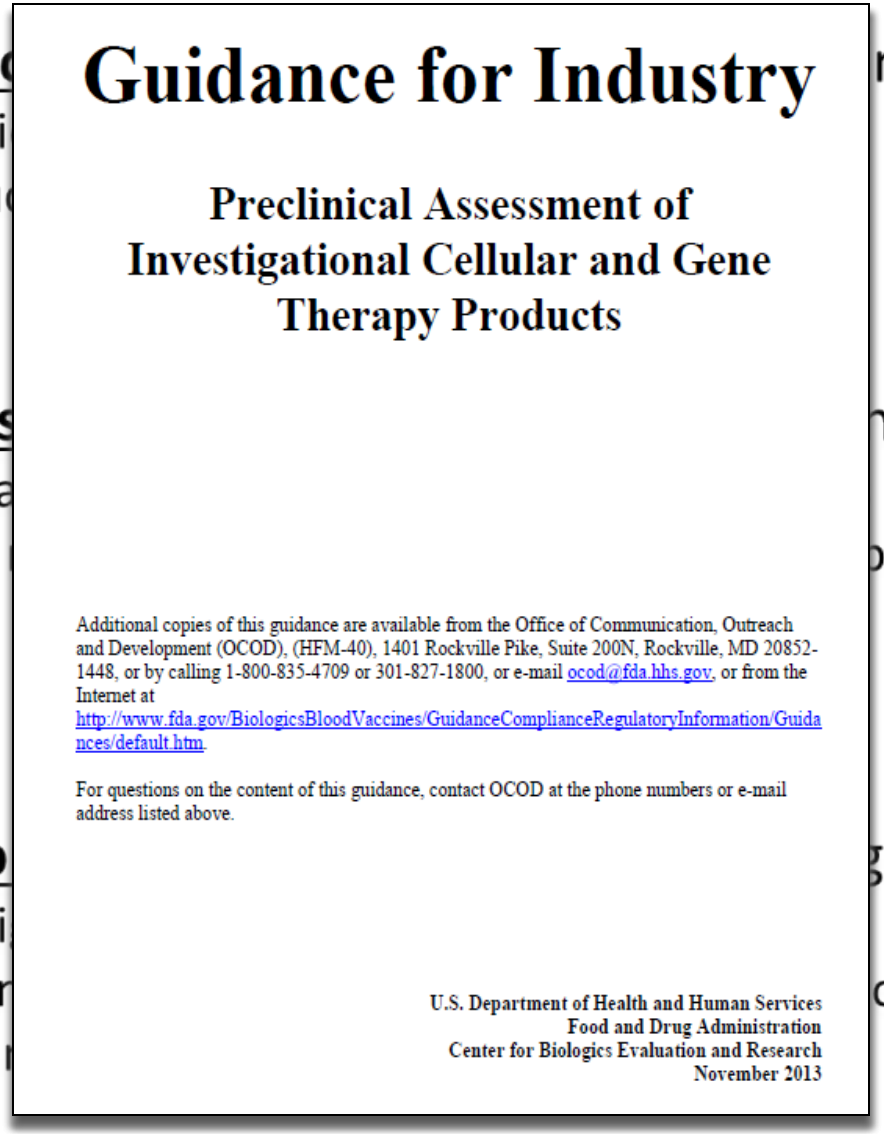


Guidance for Industry

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/

General Expectations for a Preclinical Testing Program for CGT Products

- Provide **rationale** or **proof of concept (POC)** for the FIH clinical trial
  - Understanding biological activity, mechanism of action
  - *In vitro* and *in vivo* studies in an animal model(s)

- Provide comprehensive **safety assessment** in a relevant animal species/model
  - Identifying any acute and chronic, local and systemic toxicities
  - Risks of the proposed route of administration (ROA), delivery procedure

- Provide **recommendations** to inform the clinical trial design
  - Patient population, eligibility criteria
  - ROA, initial safe starting dose level, dose escalation scheme, dosing regimen
  - Potential toxicities, clinical monitoring, risk mitigation

Distinction from Small Molecules and Traditional Biologics

- First-in-human clinical trials in patient population
- Animal models of disease (Pharmacology/POC)
- Biodistribution (BD)
- Toxicology assessment
- A case-by-case approach

Sources of Preclinical Data to Support an IND

- Appropriately designed, well-executed proof of concept studies
- GLP-compliant toxicology studies
- Published data in peer-reviewed journals
- Authorized cross-reference to similar products in previous US FDA submissions

*Detailed clinical study reports from clinical trials conducted in the US and in foreign countries (may/may not be under an IND)

General Expectations for a Preclinical Testing Program for CGT Products

- Pharmacology
  - Provide **rationale** or **POC** for CGT administration in a specific clinical population
  - Understanding mechanism of action and biological activity in a relevant animal species/disease or injury model
  - Assessing BD (fate/persistence/distribution) *in vivo* to support activity
  - Prospect of Direct Benefit (PDB) is required by law 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 to support human trials
  - Product-specific safety assessment following administration in a relevant animal species
    - Cells/vector/transgene-related immune responses
    - Tumorigenicity risk of CGT
    - Dosing procedure or device-related toxicities
  - Assessing BD as part of safety evaluation

General Expectations for a Preclinical Testing Program for CGT Products

- Provide recommendations to inform the clinical trial design
  - Patient population, eligibility/exclusion criteria
  - ROA, safe starting dose level, dose escalation scheme, dosing regimen
  - Potential toxicities, clinical monitoring, risk mitigation

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
  - Toxicities due to pharmacological action of CGT- cytokine release, tumor lysis, etc.
- Procedure and/or device-related
- Concomitant therapies

Preclinical Considerations for Pharmacology and Safety Aspects of CGT

- Product administered in preclinical studies
- Animal species and disease/injury model
- Study design—POC, BD, safety—assessments and endpoints
- Mirror the clinical scenario as closely as possible

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/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

Animal Species and Disease/Injury Model

- **Biological Relevance**
  - Disease pathophysiology (e.g., biochemical, histopathological, functional)
  - Timing of administration (e.g., stage and severity of disease)
  - Safety and activity of CGT

- **ROA**
  - Anatomical delivery site
  - Feasibility of using the intended delivery system/procedure

- **There is no "default" to the use of:**
  - Nonhuman primates
  - Both a rodent and a nonrodent species

*Considerations for alternative testing to support animal studies and application of the 3Rs (reduction, refinement, replacement) are encouraged

Study Design—POC, BD, Safety

- **Adequate numbers of animals/group to enable interpretation of resulting data**
- **Nonbiased design**
  - Random assignment to groups
  - Appropriate controls
  - Staggered dosing of animal across the groups
  - Masked analysis of key protocol–specified assessments
- **Inclusion of multiple dose levels that bracket the clinical dose level range**
- **Justification of the dosing schedule/regimen**
- **Multiple sacrifice intervals (as appropriate) and sufficient study duration**
- **Appropriate study endpoints**

Study Assessments and Endpoints

- **Multiple in-life and post-mortem time points for activity and safety**
  - Biochemical, functional outcomes
  - Distribution—cells, vector
  - Tumorigenicity—cells, vector
  - Transgene—expression, activity
  - Immunogenicity—cells/vector/transgene

- **Standard toxicology parameters**
  - Mortality, in-life—body weights, food consumption, etc.
  - Clinical observations
  - Clinical pathology
  - Gross and histopathology—target and non-target tissues
  - Nature/timing/severity/frequency of adverse findings

Vector Biodistribution

- **BD profile in biofluids and tissues**
  - Target and nontarget tissues
  - Distribution
  - Persistence
  - Clearance

- **Transgene expression levels**

- **Identify whether observed toxicities are due to the vector and/or the transgene**

- **Guidance for 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)

Mirror the Clinical Scenario (as Feasible)

- **Administration of the intended clinical product**
  - Product manufacturing/formulation
  - ROA, dose levels, dosing regimen
  - Delivery device and procedure

**Freepik.com*

P/T Data to Address Potential Safety Concerns for CGT Immunotherapies

- *In vitro* and *in vivo* studies that assess
  - Expression profile of target (e.g., in silico analysis, RT-PCR, immunohistochemistry, flow cytometry, etc.)
  - On- and off-target cross-reactivity/cytotoxicity to cells derived from various tissues
  - Tumorigenicity assessment
  - Distribution to target and non-target sites
  - Inflammatory/immune response to the administered product
  - Toxicity to host tissues/organs (e.g., GVHD for allogeneic T cell products)
  - Procedure, device, and/or combination therapies-related toxicities

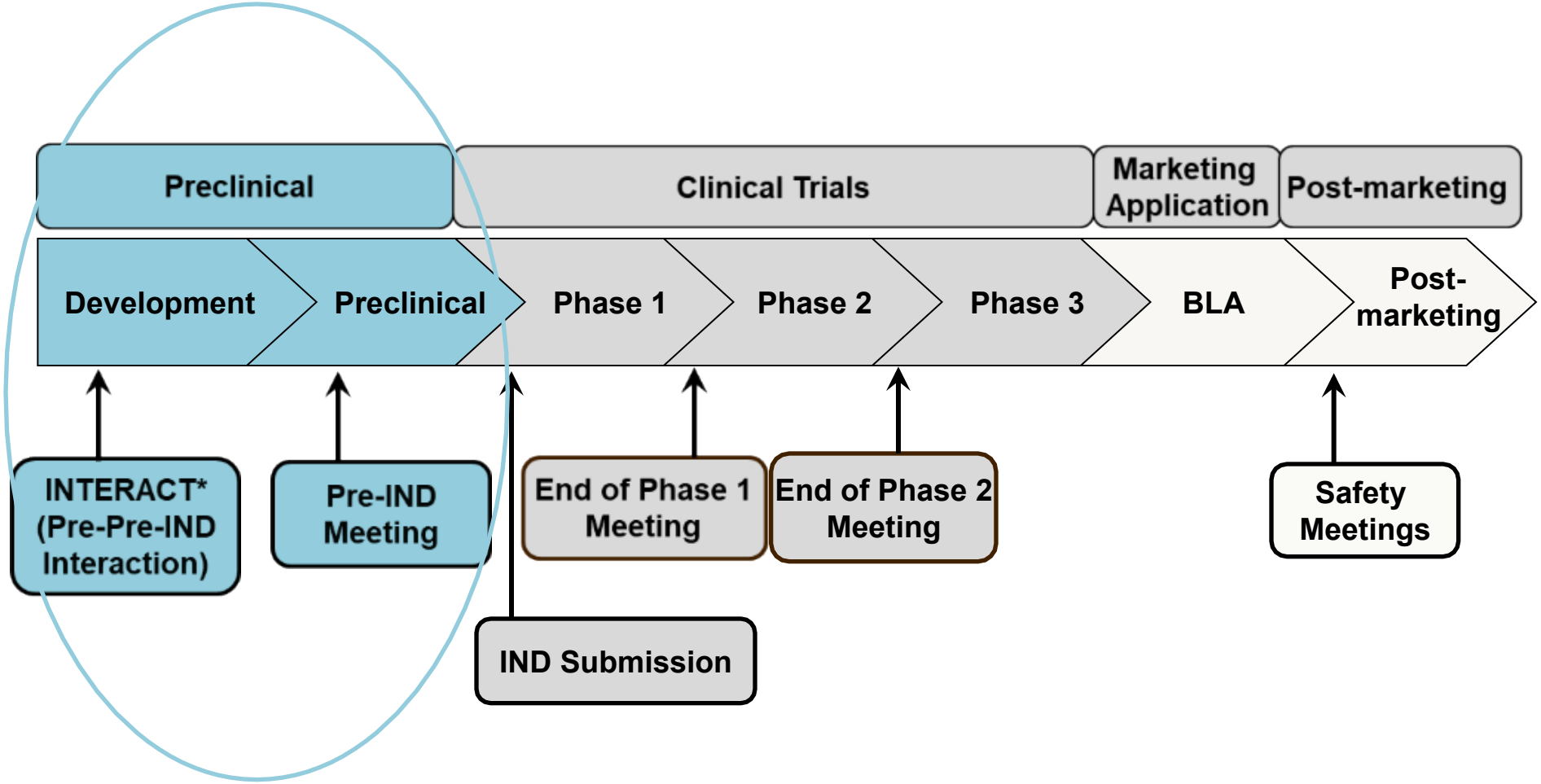
Potential Pitfalls

- Insufficient information to assess risk to subjects
  - Absence of preclinical safety data
  - Incomplete safety study reports
  - Insufficient product characterization
  - Inadequate clinical trial design

- 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

Opportunities for Early Interactions with CBER/OTAT



*INTERACT: INitial Targeted Engagement for Regulatory Advice on CBER producTs

Opportunities for Early Interactions with CBER/OTAT

- INTERACT Meetings
  - INitial Targeted Engagement for Regulatory Advice on CBER producTs
  - Non-binding, informal scientific discussion between CBER review disciplines and the sponsor
  - Initial targeted discussion of specific issues before conduct of definitive preclinical studies
  - Request with a briefing package to be submitted to INTERACT-CBER@fda.hhs.gov
  - SOPP 8214 (https://www.fda.gov/media/124044/download)

- Pre-IND Meetings
  - Non-binding, formal meeting between CBER review disciplines and the sponsor to discuss CMC, preclinical program, and planned trial design
  - Should be requested prior to the initiation of definitive preclinical safety studies
  - Briefing package should include summary data and sound scientific principles to support use of a specific product in a specific patient population
  - Request to be submitted to Lori.Tull@fda.hhs.gov and OTATRPMS@fda.hhs.gov

FDA Guidances for Human Cell and Gene Therapy 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 Guidances for Human Gene Therapy 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
  https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-neurodegenerative-diseases

Approved CG Cancer Immunotherapies *

- KYMRIAH: CD19-directed genetically modified (lentiviral vector) autologous T cells
  Patients (up to 25 years of age) with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse, adult patients with relapsed/refractory large B-cell lymphoma

- YESCARTA: CD-19-directed genetically modified (retroviral vector) autologous T cells
  Adult patients with relapsed/refractory large B-cell lymphoma

- TECARTUS: CD19-directed genetically modified (retroviral vector) autologous T cells
  Adult patients with relapsed or refractory mantle cell lymphoma

- BREYANZI: CD19-directed genetically modified (lentiviral vector) autologous T cells
  Adult patients with relapsed/refractory large B-cell lymphoma after two or more lines of systemic therapy

*https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

Summary

- Preclinical PK/PD and safety studies should establish activity and safety of a CGT product to support an IND

- The evaluation of benefit-risk associated with CGT products requires a rigorous and comprehensive approach

  - Manufacturing controls and product characterization
  - Preclinical safety and activity—ROA, dose levels, regimen, device, procedure
  - Clinical trial design—target population, monitoring, long-term follow-up
  - No “one size fits all”; so, a “case-by-case approach”

- Interactions with CBER/OTAT at early stages of product development may be beneficial

Acknowledgements

- Colleagues in OTAT/CBER
- SITC
- Everyone in the mission of protecting public health

Contact Information

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- Regulatory questions: Lori.Tull@fda.hhs.gov, OTATRPMS@fda.hhs.gov
- CBER phone: 240.402.8190 (OTAT Main Line), 1.800.835.4709, 240.402.8010
- OTAT Learn Webinars: http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm
- CBER website: www.fda.gov/BiologicsBloodVaccines/default.htm
- US FDA Consumer Affairs Branch: ocod@fda.hhs.gov
- Manufacturers Assistance and Technical Training Branch: industry.biologics@fda.hhs.gov
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https://www.fda.gov/

Society for Immunotherapy of Cancer

Questions?