Regulatory Considerations for Early-Stage Cell and Gene Therapies

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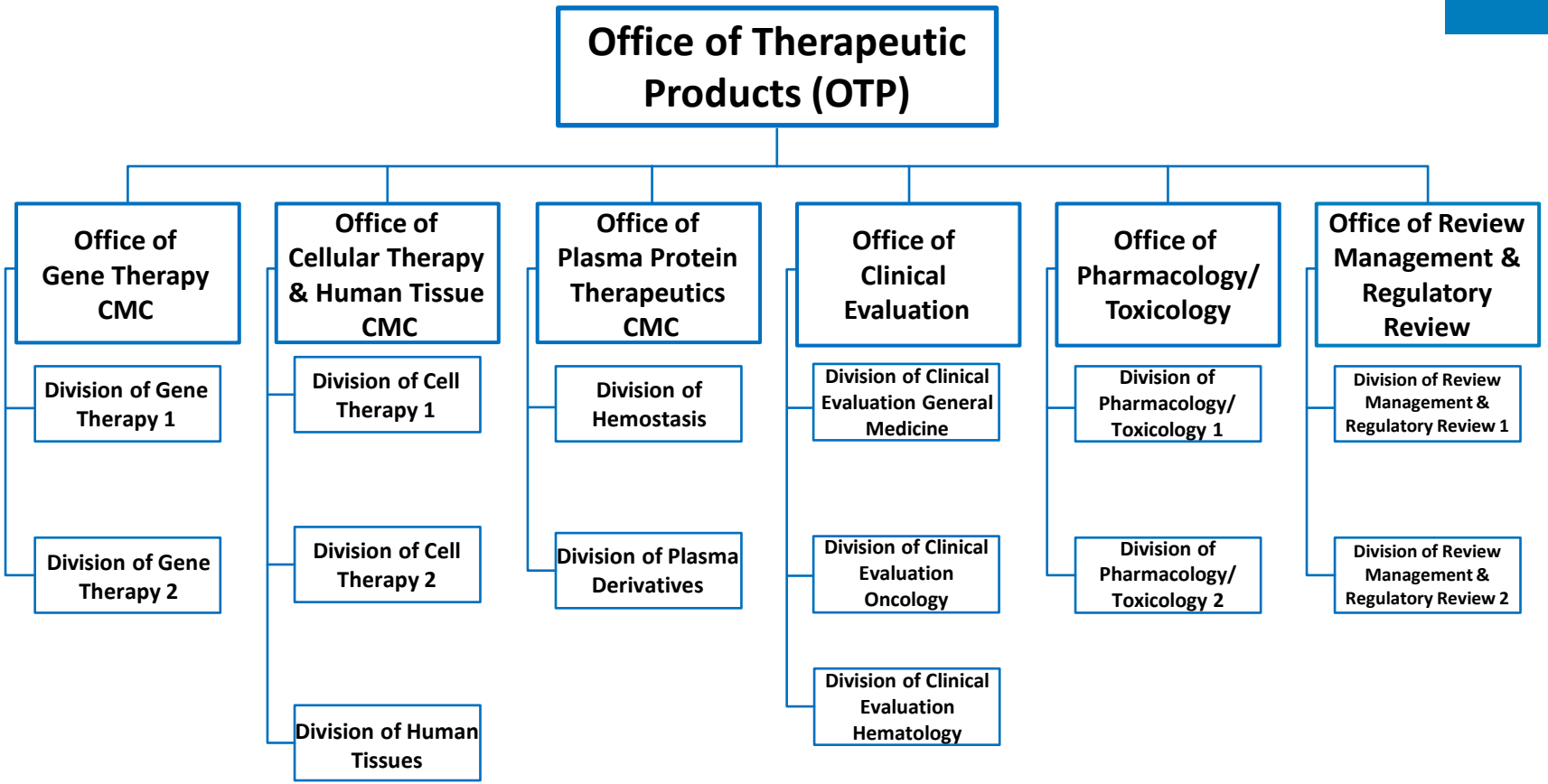
Office of Therapeutic Products (OTP)
Office of Gene Therapy CMC
Division of Gene Therapy 1
Division of Gene Therapy 2
Office of Cellular Therapy & Human Tissue CMC
Division of Cell Therapy 1
Division of Cell Therapy 2
Division of Human Tissues
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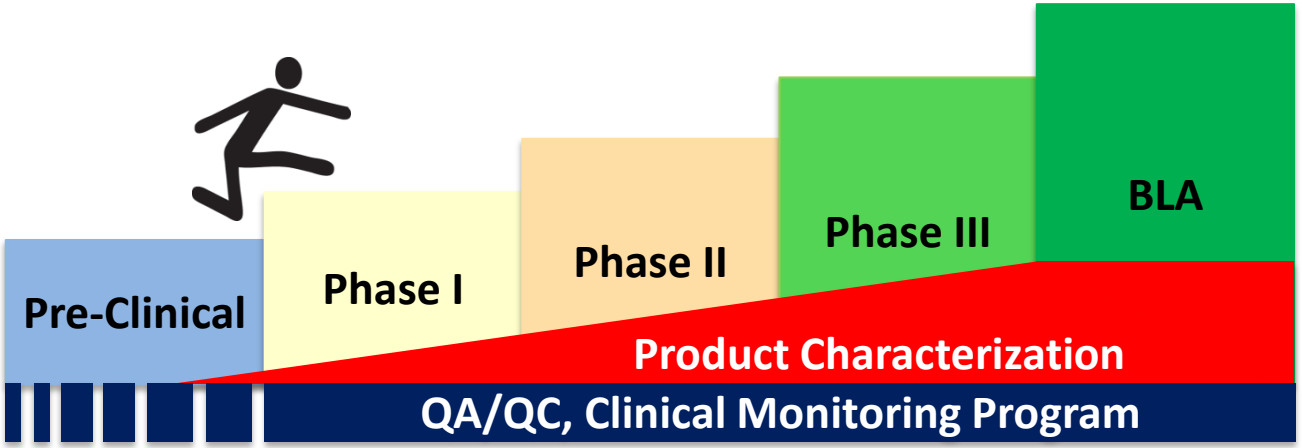
Human Gene Therapy Products (GTPs)

Products that mediate their effects by transcription or translation of transferred genetic material, or by specifically altering host genetic sequences

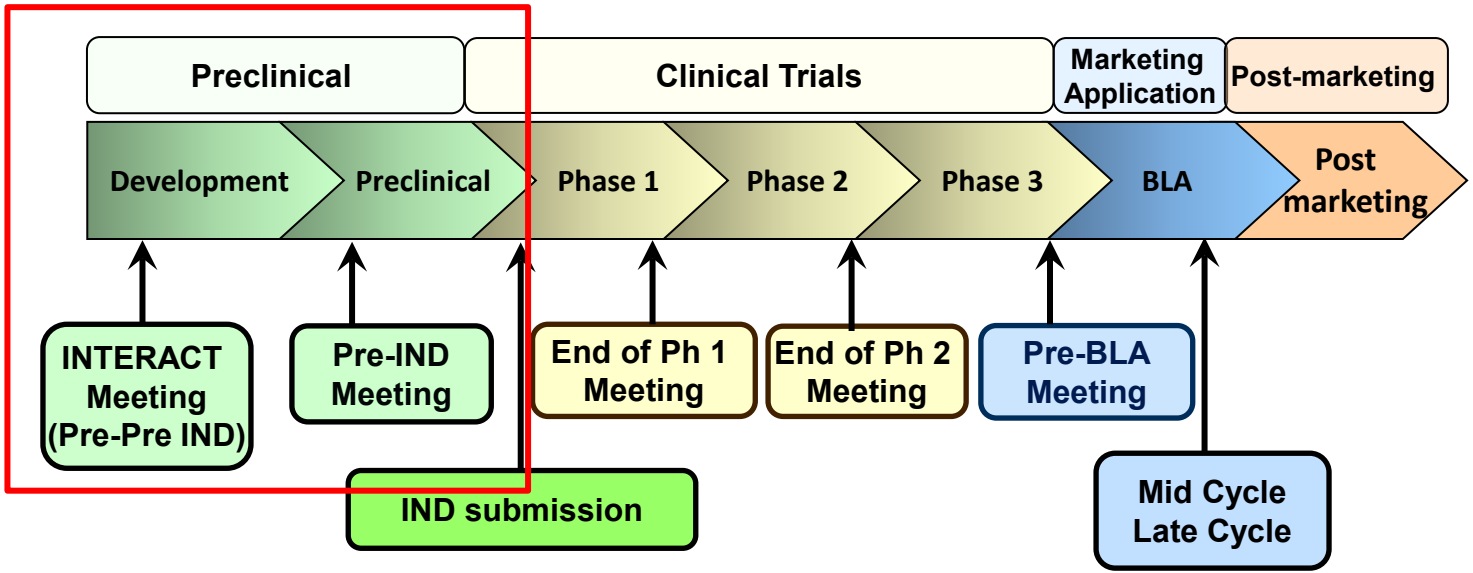
- Variety of products
  - Viral vectors
  - Bacterial vectors
  - Nucleic acids (DNA, mRNA)
  - Human genome editing products (e.g., gRNA, RNP, endonucleases)
  - Ex vivo genetically modified cells (e.g., CAR T)

Objective of FDA Review (21 CFR 312.22)

- Lifecycle approach to product development
- In all phases of the investigation, to assure the safety and rights of subjects
- In phase 2 and 3 studies, to assure that the quality of the scientific evaluation of drug product is adequate to permit an assessment of the drug's effectiveness and safety



Opportunities for Interactions with FDA During Product Development



INTERACT Meetings

INitial Targeted Engagement for Regulatory Advice on CBER/CDER producT

- **Goal:** To obtain early feedback on a product development program for a novel investigational agent
- **Timing:** When you have generated preliminary preclinical data (POC and some safety), but are not yet ready to conduct definitive preclinical safety studies
- **Format/Process**
  - Provide a concise briefing package with key issues for consideration clearly identified
  - OTP will review the package and determine if appropriate for an INTERACT meeting, based on the allowed scope
  - OTP grants one INTERACT meeting

Pre-IND Meetings

A non-binding, formal scientific discussion between all CBER/OTP review disciplines (CMC, Pharm/Tox, and Clinical) and the sponsor

- **Timing:** Should be requested prior to the conduct of the definitive preclinical safety studies
- **Format/Process**
  - Meeting request: to cberdcc_emailsub@fda.hhs.gov, cc line: OTPRPMS@fda.hhs.gov
  - The meeting package needs to be submitted no later than 30 days prior to the scheduled meeting date
  - The meeting package should comprehensively communicate the product/clinical development plan
    - Product characterization issues
    - Preclinical testing program
    - The scope and design of the planned clinical trial

Type D Meetings

- **Purpose**
  - To discuss narrow set of issues limited to no more than 2 focused topics and 3 disciplines
  - To address a follow-up question that raises a new issue after a formal meeting (more than a clarifying question)
  - A general question about an innovative development approach that does not require extensive, detailed advice

- **Process**
  - Must submit package **with** the meeting request
  - Not more than 3-5 questions including sub-questions
  - Agenda and prioritized list of questions discussed at meeting is due at least 2 days before the scheduled meeting

Other Meetings under PDUFA VII

- **Type A Meeting** – a meeting which is necessary for an otherwise stalled drug development program to proceed (a "critical path" meeting) or to address an important safety issue

- **Type B Meeting** – includes Pre-IND, Pre-BLA/NDA, and RMAT/BT designated product meetings, etc.

- **Type B (EOP) Meeting** – End-of-Phase (EOP) 1 and EOP2/Pre-Phase 3 meetings

- **Type C Meeting** – any meeting other than a Type A, Type B, Type B (EOP), INTERACT, or Type D meeting regarding the development and review of a product

Meeting Formats

- **Face-to-face** [Virtual with Cameras on or In Person (hybrid)]
  - Typically scheduled for Type A, EOP2, Pre-BLA meeting, as requested by the sponsor
- **Teleconference**
  - Typically scheduled for INTERACT, Pre-IND, Type B, Type C meetings, as appropriate
- **Written responses**
  - Can be requested in lieu of a face-to-face or telecon by the sponsor for any meeting type
- FDA may change a requested meeting format, pending review of the meeting request and/or package

Meeting Resources

- Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products – Draft Guidance for Industry, September 2023
  https://www.fda.gov/media/172311/download

- Best Practices for Communication Between IND Sponsors and FDA Staff During Drug Development. Guidance for Industry and Review Staff, December 2017
  https://www.fda.gov/media/94850/download

- Regulatory Meetings with Sponsors and Applicants for Drugs and Biological Products - CBER SOPP 8101.1
  https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/ProceduresSOPPs/UCM324381.pdf

OTP Town Halls and CBER Webinars

- Recent OTP Town Halls and CBER webinars:
  - Considerations for the Development of CAR T Cell Products, March 2024.
  - Human Gene Therapy Products Incorporating Human Genome Editing, February 2024.
  - Nonclinical Assessment of Cell and Gene Therapy Products, August 2023.
  - Gene Therapy Chemistry, Manufacturing, and Controls, April 2023.
- Town halls rotate between GT CMC, CT CMC, Clinical/Preclinical
- Answer pre-submitted and live questions
- Recordings available through FDA website: OTP Events, Meetings, and Workshops

FDA Guidance for GT Products

- **Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products, January 2024.**
- **Human Gene Therapy Products Incorporating Human Genome Editing, January 2024.**
- Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs), January 2020.
- Testing of Retroviral Vector-Based Human Gene Therapy Products for Replication Competent Retrovirus During Product Manufacture and Patient Follow-up, January 2020.
- Studying Multiple Versions of a Cellular or Gene Therapy Product in an Early-Phase Clinical Trial, November 2022.
- Potency Assurance for Cellular and Gene Therapy Products DRAFT, December 2023.
- Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products DRAFT, July 2023.

https://www.fda.gov/regulatory-information/search-fda-guidance-documents

GT CMC Guidance Clarifies What Information Should be Provided in IND

Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs)

Guidance for Industry

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
January 2020

www.fda.gov

Ensuring Product Quality and Safety

- Suitable qualification of starting materials & components
- Development of a well-defined process with controls
- Process qualification (e.g., engineering runs)
- CGMP manufacturing
  - Guidance for Industry: CGMP for Phase 1 Investigational Drugs (2008)
  - Later phase per full CGMP
- Informative product characterization & testing

Starting Materials and Reagents

- List all manufacturing reagents and provide quality documentation
  - Select the highest quality reagents (e.g., media, serum, growth factors, stimulation beads, stimulating antigen) available and establish vendor/reagent qualification program
  - Cross reference information if a Master File exists

    Draft Guidance for Industry: Drug Master Files (2019)
- Establish acceptance criteria for reagents, including those used for analytical purposes
  - Recommended cellular starting material qualification: minimum cell number, phenotype, viability, sterility, mycoplasma, adventitious viruses, etc.
- Ensure sufficient supplies of critical materials

Plasmids are Critical Starting Material

- Research-grade plasmids are not recommended
- Establish bacterial cell banks for plasmid production (tested for identity, contaminating organisms, cell count, etc.)
- Describe manufacturing process, raw materials, and manufacturing equipment
- Procedures put in place by plasmid manufacturer to prevent cross-contamination
- Data supporting cleaning effectiveness for non-single use equipment/materials
- Procedures/testing in place at vector manufacturing facility to qualify the incoming plasmids for manufacture of GMP lots

Parameter	Examples of Tests
Safety	Sterility/Bioburden, endotoxin
Identity	Sequence of vector plasmid, size and restriction enzyme digestion pattern, etc.
Purity	A260/A280 ratio, open circular/nicked plasmid DNA, residual *E.coli* DNA, RNA, protein, solvents, chemicals, RNase, etc.
Characterization	Concentration, appearance, pH, etc.

Viral Vectors Used for Ex Vivo Genetic Modification

- Various viral vector types: retrovirus/lentivirus, AAV, etc.
- Information should be provided in a complete Drug Substance (DS) section
- Manufactured according to cGMP
- Master and working cell banks should be fully characterized and tested
- Release testing completed prior to manufacture of genetically modified cells and stability program established
- Using standard amount of vector (e.g., MOI) is a critical process control
- One-time sequence verification of the entire integrated vector region should be performed

Parameter	Examples of Tests
Safety	Sterility, Endotoxin, Mycoplasma, in vitro adventitious agents, Replication competent retrovirus/lentivirus if applicable (End of Production (EOP) cells and vector supernatant)
Identity	Presence of transgene sequence (PCR, Sequencing methods, etc.)
Purity	Process and product-related impurities (residual BSA, antibiotics, host cell DNA, etc.)
Strength	Vector titer (e.g., transducing units/ml)
Potency	Cytokine production, tumor cell killing, gene expression, phenotype, etc.

Establishing Lot Release Acceptance Criteria

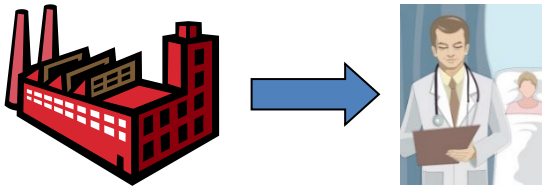
- When limited information is available at IND submission
  - Set broad initial acceptance criteria (AC)
  - Refine as knowledge of product increases
  - Determine Critical Quality Attributes (CQAs)
  - Use product characterization to support specification setting
- Setting limit-based AC may be appropriate
  - Lower limit for efficacy
  - Upper limit for safety
- Use appropriate statistical methods to set AC
  - (e.g., tolerance interval methods)

Lot Release Testing Example: CAR T Cells

Parameter	Tests
Safety	Mycoplasma, Sterility, Endotoxin, replication competent virus (if applicable) Viability (≥ 70%) Vector copy number per transduced cell (integrating vectors)
Identity	Presence of transgene (e.g., flow cytometry specific for CAR), cellular phenotype (e.g., CD3+ cells)
Purity	Absence of process & product-related impurities (e.g., BSA, beads, reagents etc.) T cell purity Transduction efficiency (% CAR^+ cells)
Dose	Number of viable CAR expressing T cells
Potency	Biologically relevant function (e.g., cytokine production, tumor cell killing, etc.)

Product Stability Testing

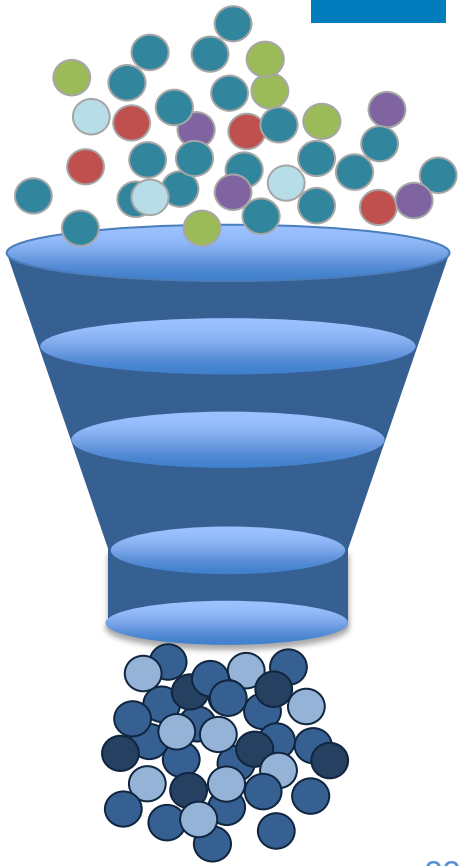
- The final product should be of suitable quality not just at the GMP facility, but also during shipping to and preparation at the clinical site



- Preliminary stability data is expected even at Phase 1
- Stability studies should get more robust as you work towards commercial process

Summary

- Understand your product attributes during preclinical studies and early phase clinical studies
- Have a comprehensive quality and control program to maximize product quality
- Utilize available resources for successful IND submissions:
  - OTP webinars and town halls
  - FDA Gene Therapy Guidances
  - FDA meetings: INTERACT and pre-IND



Contact Information

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- **Regulatory Questions:**
  OTP Main Line – 240 402 8190
  Email: OTPRPMS@fda.hhs.gov

- **OTAT (OTP) 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
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