U.S. FOOD & DRUG ADMINISTRATION

Clinical Readiness for IND Submissions

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Disclosures

- No conflicts of interest
- Nothing to disclose

Learning Objectives

- Understand **regulations and guidances** available to aid in clinical development plans and IND submissions.
- Describe **early interactions** with the FDA and patient communities to assist in clinical development and IND submission readiness.
- Describe considerations for **clinical development plans** for cell and gene therapies for rare diseases.
- Discuss considerations for **early phase, first-in-human trials** for cell and gene therapies.

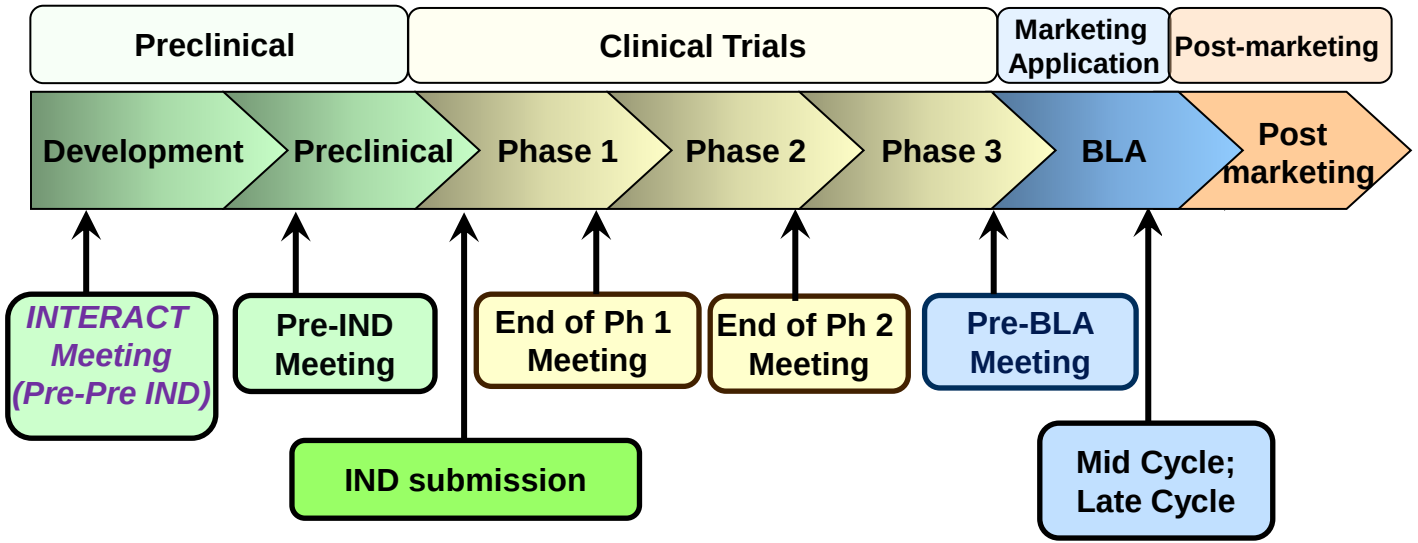
IND Regulations and Guidances

- Requirements for IND submission: **21 CFR 312.23**

- Guidance for Industry: Content and Format of Investigational New Drug Applications (INDs) for Phase 1 Studies of Drugs, Including Well-Characterized, Therapeutic, Biotechnology-derived Products (November 1995)

- Other cell and gene therapy guidance documents: https://www.fda.gov/vaccines-blood-biologics/biologics-guidances/cellular-gene-therapy-guidances

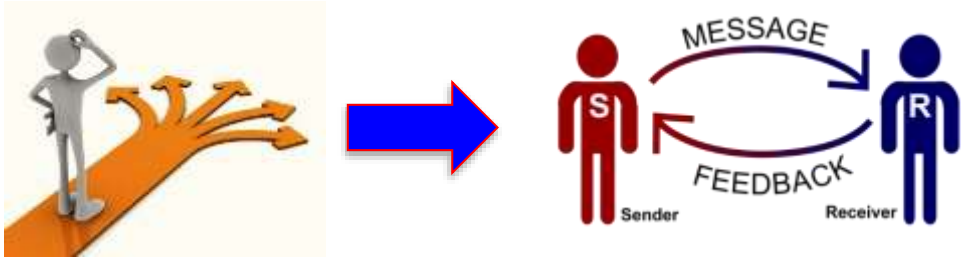
Opportunities for Interaction During Product Development



Opportunities for Early Engagement

Early communication with CBER/OTP

- INTERACT meeting
- Pre-IND meeting



Pre-IND Meeting

- **Product (CMC)**
  - Description of the product manufacturing process and testing conducted (in-process/final product) to demonstrate product identity, quality, and safety
  - Description of product formulation and storage conditions
- **Pharmacology/Toxicology**
  - **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 and BD studies** (animal species/models, dose levels, dosing regimen and procedure, study endpoints, sacrifice intervals, etc.)
- **Clinical trial synopsis/protocol**
  - Trial design
  - Objectives
  - Intended patient population
  - Dosing regimen
  - Delivery procedure, including device
  - Monitoring plan
  - Outcome measures

Considerations for Rare Disorders

- **Many rare disorders:**
  - are serious, with no approved treatments (unmet medical need).
  - are heterogeneous, with varied disease severity and time of onset.
  - present with clinical manifestations early in life.

Natural History Studies

- **Natural history studies can potentially provide critical information to guide clinical development:**
  - Product selection
  - Comparator for treatment group
  - Inform study population and endpoint selection
  - If insufficient historical natural history data, additional data may be needed from a prospective natural history study

Patient Engagement

- **Impact of the disease and its treatment**

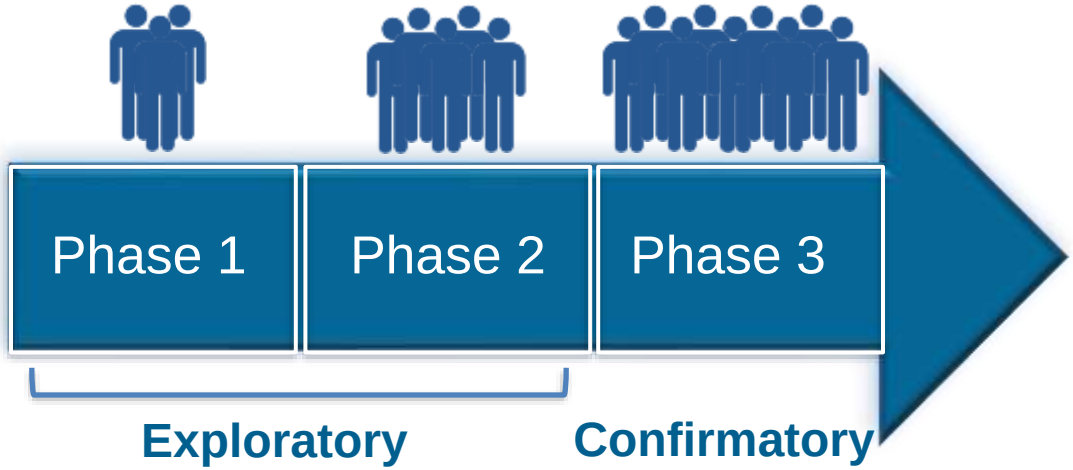
- **Perspectives about current and potential treatments**
  - Expectations of benefits
  - Tolerance for harms or risks

- **Clinical trial considerations**
  - Burden of participating in clinical studies
  - Willingness to participate in placebo-controlled trials

OTP Patient Engagement Activities

- **Patient-Focused Drug Development Meetings**
- **NORD Patient Listening Sessions**
- Meetings held by **patient advocacy organizations**

Conventional Clinical Development



Regulatory Requirements for BLA Approval

- Approval of drugs and biologics must be based on **substantial evidence of effectiveness** and evidence of safety.

- Evidence of effectiveness should be obtained from **adequate and well-controlled studies**.

- Certain aspects of product development that are feasible for common diseases may not be feasible for rare diseases. FDA regulations provide **flexibility** in applying regulatory standards (21 CFR 314.105).

Early-Phase Trials

- **Objectives**
  - **Primary: safety**
  - ***Secondary: bioactivity and efficacy***
- Study Population
- Study Design
- Dose Selection
- Treatment Plan
- Monitoring and Follow-Up

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015)

Early Phase Trial Objectives

- **Dose exploration**
- **Feasibility assessments**
- **Activity assessments**

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015)

Early-Phase Trials

- Objectives
- **Study Population**
  - **Patients with more severe vs less severe condition**
  - **Adults vs children**
- Study Design
- Dose Selection
- Treatment Plan
- Monitoring and Follow-Up

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015)

Study Population Considerations

- **Severity of disease:**
  - Risk and potential benefit, interpretability of study results
  - Subjects with severe or advanced disease:
    - May be more willing to accept potential risks
    - Potential for confounding adverse effects of disease
    - Tolerability of study procedures
- **Healthy volunteers typically not appropriate**

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015)

Study Population Considerations

- **Lack of other treatment options:**
  - Early-phase studies of CGT products often have significant risks and uncertain potential for benefit.
  - Consider subjects with poor response to available therapies or with no acceptable treatment options.

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015)

Study Population Considerations

- **Pediatric subjects:**
  - **21 CFR Part 50, Subpart D**: additional safeguards for children in clinical investigations
  - Not involving greater than minimal risk (21 CFR 50.51)
  - Greater than minimal risk but presenting prospect of direct benefit to individual subjects (21 CFR 50.52)

Study Population Considerations

- **Specific considerations:**
  - Genetic testing
  - Pre-existing antibodies to vector or transgene
  - Could the ability to safely and effectively receive future standard of care therapy be impacted by exposure to the investigational agent?

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015)

Early-Phase Trials

- Objectives
- Study Population
- **Study Design**
  - **Early randomized controlled trials, even in first-in-human studies**
  - **Concurrent control with blinding, whenever feasible**
- Dose Selection
- Treatment Plan
- Monitoring and Follow-Up

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015)

Early Phase Study Design

- The importance of concurrent controls and blinding in any specific trial depends on multiple factors:
  - study **objectives**
  - extent to which study procedures and outcome assessments are subject to **bias**

- **Objectives of early-phase trials usually focus on safety; efficacy assessments usually exploratory:**
  - Comparison to a concurrent control, blinding may not be necessary

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015)

Early Phase Study Design

- **A control group can be particularly useful to:**
  - interpret safety & efficacy data, particularly if pivotal study
  - understand course of diseases where NH is not well characterized
  - understand outcomes for subjects with wide range of disease severity

- **Standard-of-care and no-treatment controls:**
  - Allow evaluation of the risk of the investigational treatment
  - Blinding of the subject and investigator may not be feasible

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015)

Early-Phase Trials

- Objectives
- Study Population
- Study Design
- **Dose Selection**
  - **Consideration of preclinical and clinical data**
  - **Extended duration of effect; many single dose**
- Treatment Plan
- Monitoring and Follow-Up

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015)

Considerations for Product Dosing

- Adequate and complete investigation of the effective and safe dose range
- Cell therapies are often mixtures of different cell types
- Dose response curves may be flat and non-linear
  - Scientific rationale for dose escalation or de-escalation
  - Pre-specified range of exposure; appropriate dose measurements
- Characterization of safety profile of the feasible doses

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015)

Early-Phase Trials

- Objectives
- Study Population
- Study Design
- Dose Selection
- **Treatment Plan**
  - **Number of subjects, cohorts, staggering**
  - **Limited number of study sites**
  - **Operator training**
- Monitoring and Follow-Up

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015)

Considerations for Treatment Plan

- Number of subjects (total and in each cohort) to achieve study objectives
- Staggered treatment to limit the number of subjects who might be exposed to an unanticipated safety risk
- Operator training:
  - When individual skill in administering a product may affect safety or effectiveness
  - Specify minimum requirements for training, experience, level of proficiency

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015)

Early-Phase Trials

- Objectives
- Study Population
- Study Design
- Dose Selection
- Treatment Plan
- **Monitoring and Follow-Up**
  - **Assessments: safety and efficacy**
  - **Special monitoring for CGT products, duration of follow-up**
  - **Study stopping rules**

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015)

Safety

- Routine general safety evaluations, using standard clinical measurements
- Safety assessments to monitor for adverse events that can be anticipated with cellular or gene therapies
- Safety assessments informed by *a priori* safety concerns for the investigational product
- All adverse events are relevant to assessment of safety of the product

Additional Safety Considerations

- Dose-limiting toxicity may not be readily observable early in development
- Careful product administration: staggering, stopping criteria (subject and study)
- Monitoring for: graft-versus-host disease, autoimmune phenomena, cytokine release syndrome, other immune reactions
- Evaluation of product persistence and long-term effects
  - Measurements in appropriate body fluids and tissues, where possible
  - Clinical monitoring and imaging studies for ectopic growth
  - Duration of follow-up specific to product, condition (up to 15 years for gene therapies)

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015)
Draft Guidance for Industry: Long Term Follow-up After Administration of Human Gene Therapy Products (July 2018)

Efficacy

- Feasibility of manufacturing & administration should be addressed early

- Population:
  - Large trial, diverse populations vs. smaller trial, specific patient populations
  - Disease state, timing of treatment, and the immune system state

- Endpoints:
  - Clinical outcomes
  - Biological and/or immunological endpoints

- Inclusion of a concurrent control group in early stages, if feasible

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015)

Stopping Rules

- Specify conditions for temporary suspension of enrollment and dosing until a safety assessment can be completed.
- Stopping rules are not necessarily intended to lead to study termination.
- Limit the number of patients put at risk, if early experience uncovers important safety problems.
- Based on the outcomes of the safety assessment, protocol revision may be warranted.

Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products (2015)

Challenge Question #1

Which of the following is NOT a potential benefit of natural history studies?

A. Informing study eligibility criteria
B. Informing study endpoints
C. Provide healthy volunteers for a treatment study
D. Providing a comparator group for the treatment population

Challenge Question #2

Which of the following is ideal, if feasible, for first-in-human early phase clinical trials of cell and gene therapy products?

A. Randomized blinded controlled trial
B. Healthy volunteers as study population
C. A large number of study sites
D. Lack of staggering between study subjects

Summary

- There are unique challenges and opportunities in clinical development of cell and gene therapy products for rare diseases.
- Clinical development for cell and gene therapies must be individualized, particularly when developed for rare diseases.
- Early interactions with FDA are encouraged to ensure the study is designed to meet its objectives.
- Whether or not an early phase study is intended to be a pivotal study has important implications for trial design.

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