

Nonclinical Assessment of Cell and Gene Therapy (CGT) Products to Support an IND

Devaveena Dey, PhD

Center for Biologics Evaluation and Research (CBER)

Office of Therapeutic Products (OTP)

Office of Pharmacology and Toxicology (OPT)

Division of Pharmacology/Toxicology 2-Branch 4 (DPT2-PTB4)

Devaveena.Dey@fda.hhs.gov



Learning Objectives

- Gain familiarity with regulations governing nonclinical testing
- Nonclinical considerations for early phase trials
- Decide when to have early interactions with the FDA (The 'INTERACT' and Pre-IND)
- Bookmark FDA Guidance documents



What Regulations Govern Nonclinical Testing?



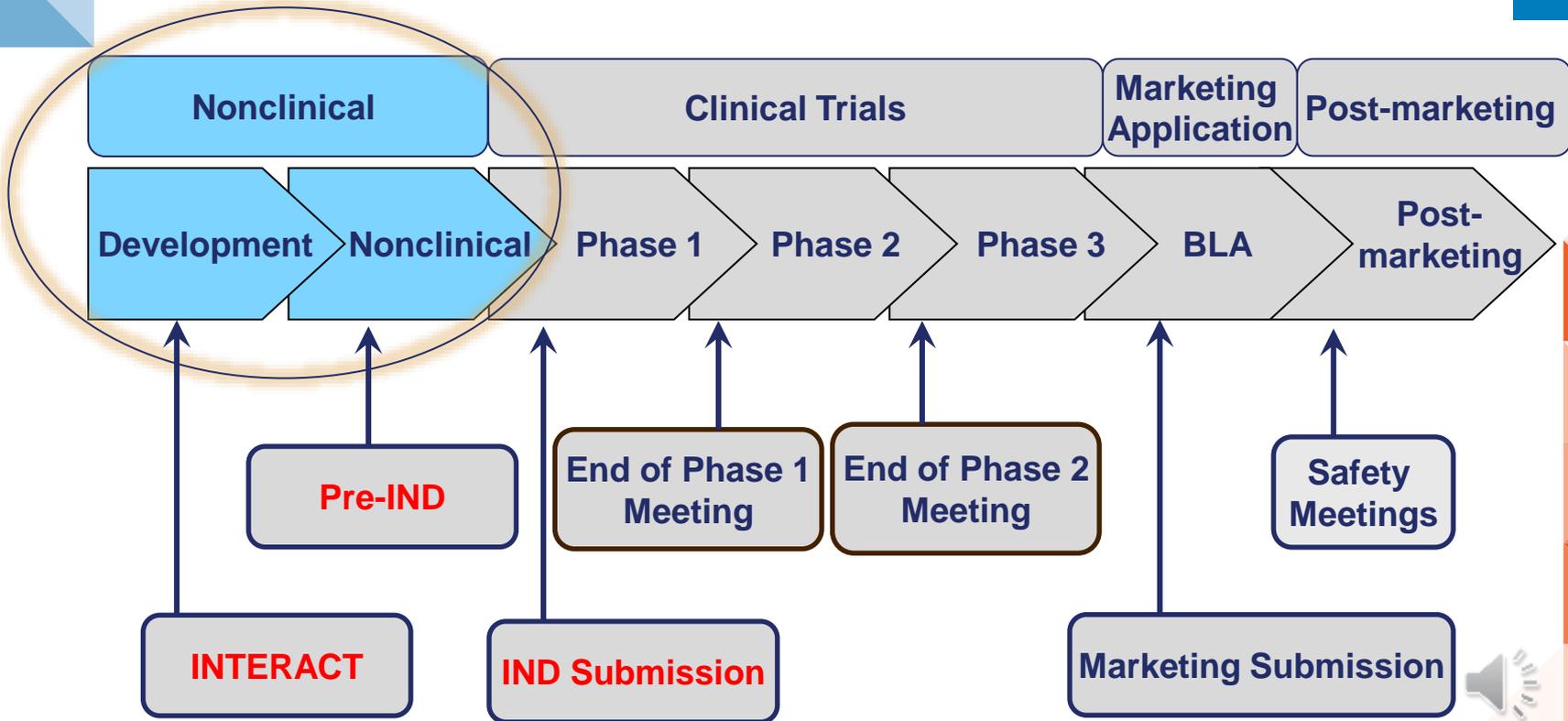
Pharmacology & Toxicology Studies

“...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]*



Lifecycle of Drug Development



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

Sources of Data to Support an IND



- Good Laboratory Practice (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



General Expectations for a Nonclinical Testing Program for CGT Products



☐ Toxicology

- Provide comprehensive safety assessment of the CGT product in a **relevant animal species**, if available, to support clinical trials
- Determine a No-Observed-Adverse-Effect-Level (NOAEL)
- Cell/vector/transgene presence is important in the interpretation of any findings



General Expectations for a Nonclinical Testing Program for CGT Products



☐ Toxicology continued:

- Characterize adverse findings following product administration:
 - ✓ Identify target tissue(s) of toxicity
 - ✓ Local or systemic effects
 - ✓ Acute, delayed, or prolonged findings
 - ✓ Cell/vector/transgene-related immune responses
 - ✓ Tumorigenicity risk
 - ✓ Dosing procedure or device-related toxicities



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 ‘Good Laboratory Practice’ (GLP), or an explanation should be provided
- Oversight of the conduct of all non-GLP toxicology studies and the resulting final study report by an independent ‘quality assurance’ (QA) unit/person is strongly recommended (21 CFR 58.35)



General Expectations for a Nonclinical Testing Program for CGT Products



□ Pharmacology

- Provide **rationale** or **proof-of-concept** (POC) for cell and gene therapy (CGT) product administration in a specific clinical population
- Understand mechanism of action and biological activity in a **relevant** animal species/disease or injury model or alternative test system
- Select **optimal dose levels, and dosing regimen**
- Assess **vector biodistribution/cell fate *in vivo*** to support activity following clinically relevant route of administration (ROA)



Potential Safety Concerns for CGT Immunotherapies



□ Product-related

- Manufacturing (e.g., expansion, genetic modifications etc.)
- Inappropriate cell proliferation (i.e., tumor formation)
- Inappropriate cell differentiation (i.e., ectopic tissue formation)
- Toxicities due to cell/vector distribution to non-target sites
- Immune response to the administered product
- Toxicity to host tissues/organs (e.g., graft-versus-host disease (GVHD))
- Toxicities due to cross-reactivity, on-target/off-tumor, off-target activity
- Interaction with concomitant therapies

□ Procedure and/or device-related



CGT Product Administered in Nonclinical Studies



- ❑ **Product should be as similar as possible to the intended clinical product**
 - Tissue/sample source, harvesting procedure, expansion, culturing, formulation, seeding, storage, etc.
 - Vector production, construct, transgene expression, final titer etc.
- ❑ **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 and human product
 - Translation of data to humans: Human-equivalent dose (HED) calculations

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 OR rodents OR both.
- 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 subject 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



Nonclinical Study Design Considerations



- ❑ **Nonbiased-** Consider randomization
- ❑ **Mimic the planned clinical scenario as closely as possible**
- ❑ **Administration of appropriate control(s) 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 nonclinical programs**
 - ✓ **Reduce**
 - ✓ **Refine**
 - ✓ **Replace**



Nonclinical Study Design Considerations

continued



- Sufficient study duration** to assess both acute and long-term outcomes
- Multiple time points** for evaluations
- Multiple specific in-life/terminal assessments**



Study Assessments and Endpoints



- ❑ **Multiple in-life and post-mortem time points for safety and activity**
 - Biochemical, functional outcomes (e.g., neurological, cardiac, ophthalmic) which are disease dependent
 - Biodistribution, persistence and clearance of CGT product
 - Tumorigenicity
 - Transgene activity
 - Immunogenicity

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



Early meetings (The 'INTERACT')



- ❑ **Timing:** When the sponsor has generated preliminary nonclinical data (POC and safety) but is not yet ready to conduct definitive nonclinical safety studies.

- ❑ **Pharmacology/Toxicology (P/T) advice:**
 - Design of POC or other pilot safety/distribution studies
 - Adequacy of the selected animal species/disease models
 - Acceptability of innovative nonclinical testing strategies, products and/or delivery modalities
 - Study designs: Endpoints, dose levels, route of administration, dosing regimen
 - Advice on modification of a nonclinical program or study design, as applicable, to ensure judicious use of animals



Early meetings (The 'pre-IND')

- ❑ **Goal:** To achieve a successful IND submission

- ❑ **Timing:**
 - POC and preliminary safety studies completed
 - Ready to conduct definitive studies

- ❑ **Nonclinical data expectations:**
 - A comprehensive summary of all completed in vitro and in vivo nonclinical studies.
 - Complete protocols for the proposed definitive nonclinical safety/toxicology and biodistribution studies

*** The advice from the INTERACT meeting should be considered when preparing your pre-IND meeting package.**



Summary



- ❑ The nonclinical program for any CGT product is determined on a case-by-case basis
- ❑ Nonclinical 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 early feedback from the FDA on nonclinical development plans prior to IND submission
- ❑ Novel therapies mean novel testing paradigms. Hence, **pre-submission interactions with FDA is encouraged.**



FDA Guidances for Human CGT Products



- ❑ 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: S12 Nonclinical Biodistribution Considerations for Gene Therapy Products (May 2023): <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/s12-nonclinical-biodistribution-considerations-gene-therapy-products>
- ❑ Guidance for Industry: Human Gene Therapy Products Incorporating Human Genome Editing (Jan 2024) <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-products-incorporating-human-genome-editing>
- ❑ Considerations for the Development of Chimeric Antigen Receptor (CAR) T Cell Products (Jan 2024) <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-development-chimeric-antigen-receptor-car-t-cell-products>
- ❑ Guidance for Industry: Human Gene Therapy for Rare Diseases (Jan 2020) <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/human-gene-therapy-rare-diseases>



Contact Information

FDA

Devaveena Dey: Devaveena.Dey@fda.hhs.gov

Regulatory Questions:

OTP Main Line: 240-402-8190

Email: OTPRPMS@fda.hhs.gov

Interactions with Office of Therapeutic Products website:

[Interactions with Office of Therapeutic Products | FDA](#)

OTP Learn Webinar Series: [OTP Learn](#)

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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