

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

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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?



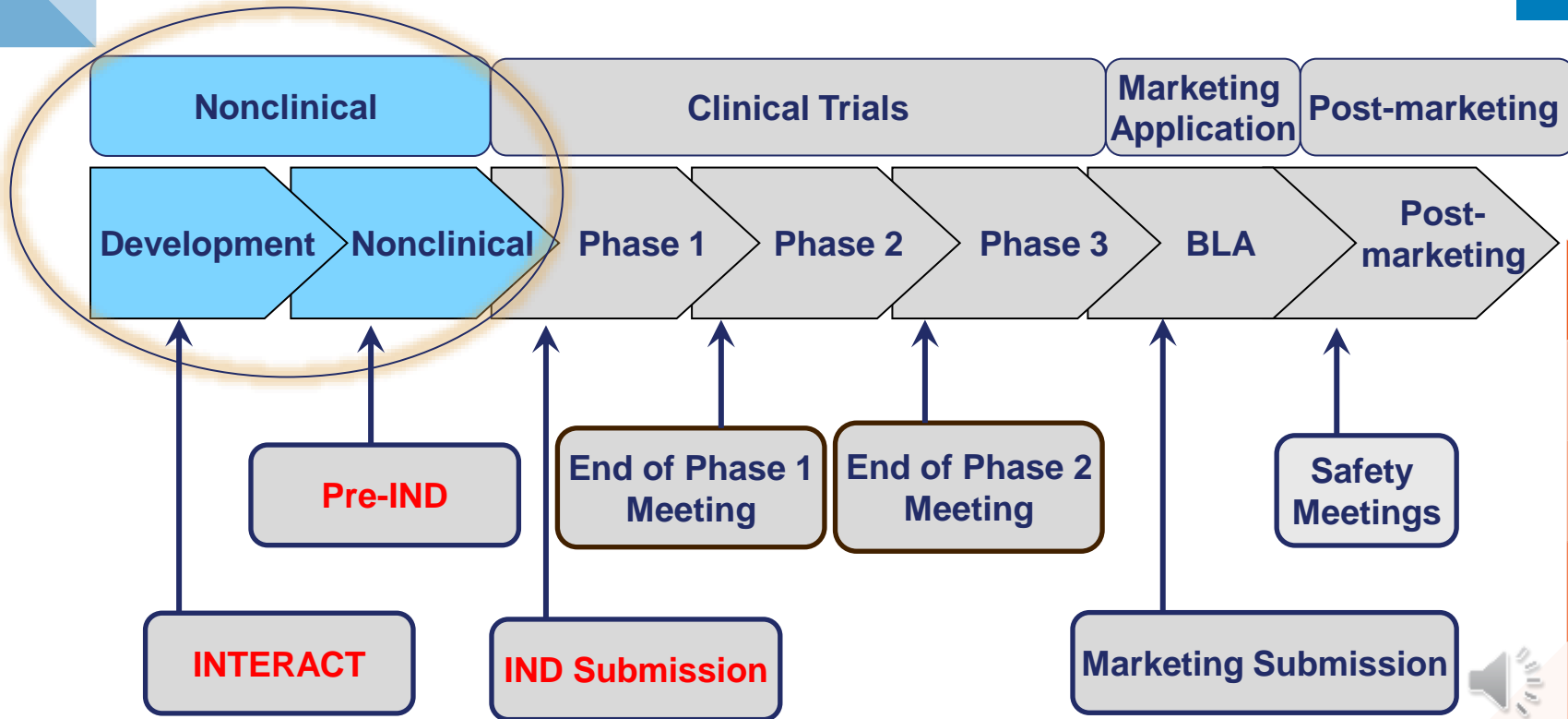
Pharmacology & Toxicology Studies

“...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>



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

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