



U.S. Food and Drug Administration

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# Preparing an IND Application: Preclinical Considerations for Cell and Gene Therapy Products

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**Food and Drug Administration**





# Overview

- Regulatory Review Principles
- CBER/OCTGT-Regulated Products: Safety Concerns
- Preclinical Evaluation
  - Study Design Considerations
- IND Content
- Potential Pitfalls/Regulatory Issues
- Working with FDA/CBER/OCTGT



# ■ ■ ■ 21 CFR 312.20 Subpart B: IND Application

<input type="checkbox"/>	Form FDA 1571	21 CFR 312.23(a)(1)
<input type="checkbox"/>	Table of Contents	21 CFR 312.23(a)(2)
<input type="checkbox"/>	Introductory statement and general investigational plan	21 CFR 312.23(a)(3)
<input type="checkbox"/>	Investigator's brochure	21 CFR 312.23(a)(5)
<input type="checkbox"/>	Protocols	21 CFR 312.23(a)(6)
<input type="checkbox"/>	Chemistry, manufacturing, and control data	21 CFR 312.23(a)(7)
<input checked="" type="checkbox"/>	<b>Pharmacology and toxicology data</b>	<b>21 CFR 312.23(a)(8)</b>
<input type="checkbox"/>	Previous human experience	21 CFR 312.23(a)(9)
<input type="checkbox"/>	Additional information	21 CFR 312.23(a)(10)

# ■ ■ ■ What Regulations Govern Preclinical Testing?

## Pharmacologic & Toxicologic 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]*

# ■ ■ ■ Safety is Always Primary...

“FDA’s primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects, and, in Phase 2 and 3, to help assure that the quality of the scientific evaluation of drugs is adequate to permit an evaluation of the drug’s effectiveness and safety...”

*IND Regulations [21 CFR 312.22 (a) - General Principles of the IND Submission ]*

# ■ ■ ■ Potential Safety Concerns for Therapeutic Vaccines/Adjuvants

- Systemic toxicity
  - Immune mediated toxicity - autoimmune response, induction of pro-inflammatory response/cytokine release, organ toxicity
  - Hypersensitivity/anaphylaxis
  - Potential “off-target” toxicity
  - Adjuvant related toxicity
- Local toxicity
  - Injection site reaction

# ■ ■ ■ Potential Safety Concerns for Cell-Based Products

- Risks of the delivery procedure
- *Ex vivo* manipulation (e.g., expansion, genetic modification, encapsulation, scaffold seeding)
- Potential inflammatory/immune response to the administered cellular product
- Inappropriate cell proliferation (i.e., tumor formation)
- Inappropriate cell differentiation (i.e., ectopic tissue formation)
- Cell migration to non-target areas/tissues
- Interactions with concomitant therapies



# Potential Safety Concerns for Gene Therapy Products

- Risks of the delivery procedure
- Type of vector/virus
- Vector/virus biodistribution to non-target tissues
- Level of viral replication and persistence in non-target tissues
- Inappropriate immune activation
- Potential for insertional mutagenesis and/or oncogenicity
- Transgene related concerns
- Genetically modified cells – see cell therapy concerns

## ■ ■ ■ Expectations from Preclinical Data

- To support a **rationale** for the first-in-human clinical trial
  - For cell and gene therapy product the trial is conducted in the disease population, not in healthy volunteers
- To make **recommendations** regarding clinical trial design
  - Initial safe starting dose, dose-escalation scheme, dosing schedule, organ toxicity, eligibility criteria, clinical monitoring
- To meet **regulatory requirements**
  - 21 CFR 312.23 (a)(8)
  - 21 CFR 58 (GLP compliance)

# ■ ■ ■ Preclinical Expectations for Early Phase Clinical Trials

- Proof-of-concept [POC] – *in vitro* / *in vivo*
  - Potential mechanism of action [e.g., neuroprotective, neoangiogenesis, tolerance induction]
  - Establish pharmacologically effective dose(s)
  - Optimize route of administration (ROA)/dosing regimen
  - Rationale for species/model selection for further testing
- Safety of conducting clinical trial – risk/benefit
  - Dosing scheme
  - Potential target tissue(s) of toxicity/activity
  - Parameters to monitor clinically
  - Eligible patient population

# ■■■ Preclinical Study Design(s)

- Assess pharmacology/**POC**/**vector distribution/cell fate** in relevant animal model(s) of disease/injury, as feasible
- Assess safety/toxicology (**T**)/**vector distribution/cell fate** in healthy animals
- Hybrid pharmacology-toxicology study design
  - **POC + T + product fate** – incorporate **activity** and **safety** endpoints in an animal model of disease/injury
  - Local microenvironment and pathophysiology status of the model may impact the safety/bioactivity of the product
- Apply the 3 R's – **Reduce, Refine, Replace** – in preclinical study designs



# Comparability of the Cells Administered to the Intended Clinical Product

- Manufacturing process of the cellular product used in the preclinical studies should be as similar to the intended clinical product as possible
  - Tissue/sample harvest, cell isolation, expansion, culturing, formulation/scaffold seeding, encapsulation procedure, storage conditions, etc.
- Adequate product characterization
  - Cellular morphology and phenotype
  - Molecular/biochemical markers

# ■ ■ ■ Preclinical Study Design: Specifics

- Nonbiased design
  - Randomized assignment to groups
  - Appropriate controls (e.g., sham, vehicle)
  - In-life and postmortem assessments conducted in a blinded manner
- Mimic clinical scenario as closely as possible
  - Use cells intended for clinical use...or analogous cells
  - Cell viability, concentration/formulation, volume, rate of delivery, implant site, number of implants/ injections, etc
  - OA, delivery system, timing of cell delivery, dosing regimen, etc
  - Anatomical location/extent of the diseased/injured area

## ■ ■ ■ Preclinical Study Design: Specifics (cont'd)

- Adequate numbers of animals/group to ensure statistically and biologically robust interpretation
- Sufficient study duration and multiple time points - depending on the biology of the product - to allow for adequate assessment of:
  - Functional, laboratory, and morphological outcomes
  - Cell fate
  - Onset and persistence profile of significant findings in target/non-target tissues

## ■ ■ ■ Preclinical Study Design: Specifics (cont'd)

- Standard Toxicology Endpoints
  - Mortality
  - Clinical observations, body weights, appetite, etc
  - Clinical pathology - hematology, coagulation, serum chemistry, urinalysis
  - Pathology – target and non-target
    - Scheduled and unscheduled deaths
    - Comprehensive gross pathology
    - Microscopic pathology – blinded assessment
- Terminal/non-terminal assessment
  - Various imaging modalities
  - PCR, IHC, ISH

## ■ ■ ■ Preclinical Study Design: Specifics (cont'd)

- Product-dependent endpoints
  - Depends on the vector/transgene
    - Potential for insertional mutagenesis
    - Potential for carcinogenicity/tumorigenicity
    - Host immune response to vector and/or transgene
  - Depends on the transduced/nontransduced cell type
    - Host immune response to transduced cell
    - Potential for unregulated growth/tumorigenicity
  - Depends on the disease/injury of focus (cardiac, neurological, status/function of hematopoietic cells, etc)

## ■ ■ ■ Preclinical Study Design: Specifics (cont'd)

- Product-dependent endpoints [tumorigenicity, immunogenicity, etc]
- Disease-dependent endpoints [cardiac, neurological, etc]
- Cell fate following administration
  - Survival/engraftment
  - Integration (anatomical/functional)
  - Differentiation/phenotype expression
  - Transdifferentiation/de-differentiation
  - Migration/trafficking
  - Proliferation

## ■ ■ ■ GT Biodistribution (BD) Profile

- Determine potential for vector BD in germline, target, and non-target tissues
  - Distribution profile
  - Persistence and clearance profile
- Determine the transgene expression profile in ‘vector positive’ tissues
  - Distribution profile
  - Persistence and clearance profile
- For details regarding sample collection and the PCR assay refer to: *Guidance for Industry: Gene Therapy Clinical Trials - Observing Subjects for Delayed Adverse Events (11/06)*
- BD data may impact study design (e.g., duration, dosing regimen, etc)



# Considerations for Appropriate Animal Species/Model

- Comparative physiology of animal to human
  - Model of disease/injury
  - Local microenvironment may impact the safety of the product
- Route of administration – comparability to clinical
  - Systemic vs. targeted delivery
  - Delivery system/delivery procedure
- Species specificity of the product
- Species specificity of the innate immune response



# Appropriate Animal Species/Model

- There is no 'default' to the use of nonhuman primates
- There is no 'default' to the use of both a rodent and a non-rodent species
- There is no 'default' to the use of multiple species
- Understand the limitations of the species/model(s) used
- Scientific justification should be provided for the animal species/model(s) used

# ■ ■ ■ 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 GLP, or an explanation provided

# ■ ■ ■ Submit Complete Reports for Toxicology Studies

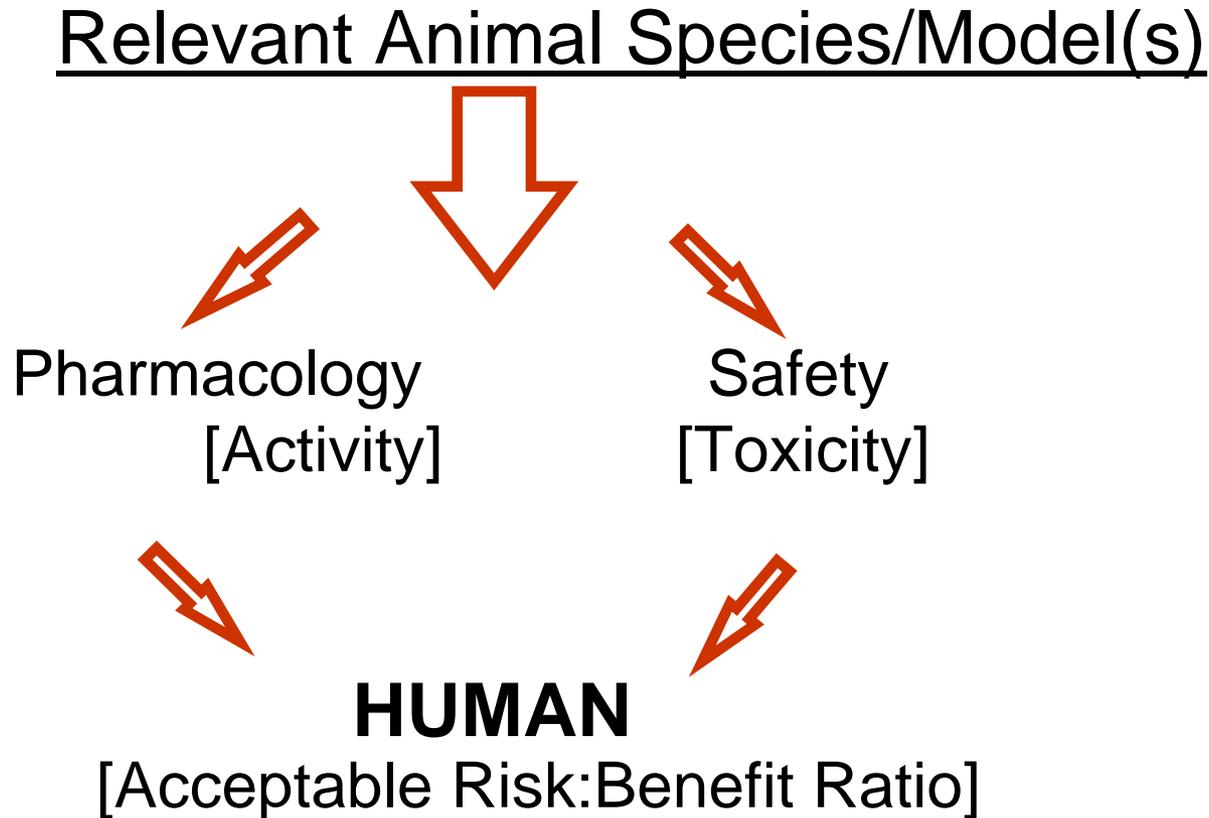
- Detailed description of the study performed:
  - Test articles (i.e., relevance to the clinical product)
  - Test system (i.e., animal species/model)
  - Delivery device information if applicable
  - Dose levels/dose regimen/study duration
  - Study groups (controls, test article groups, group size, etc)
  - Prospective study endpoints
- Results: for all parameters evaluated-
  - Submit **individual animal data** for all parameters evaluated
  - Submit summarized and tabulated results
- Interpretation of the data

# ■ ■ ■ Sources of Data to Support an IND

- 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 previously submitted Master Files (MFs)/INDs
- Detailed clinical study reports from clinical trials



# Assessment of Safety and Activity





# Potential Pitfalls When Submitting an IND

- Insufficient information to assess patient risk
  - Lack of preclinical safety data
  - Incomplete safety study reports
  - Insufficient product characterization
- Inadequate preclinical study design
  - Safety monitoring (safety/activity endpoints)
  - Animal number
  - Study dose and duration
  - Route of administration

## ■■■ Regulatory Issues for Clinical Trials

- Common reasons for not allowing a clinical trial to proceed (clinical hold) are:
  - Clinical start dose: Insufficient safety data to support the intended human start dose
  - Dose escalation scheme: Too aggressive
  - Safety monitoring: Inadequate monitoring plan to observe potential toxicities
  - Patient population: Eligibility criteria inappropriate
  - The potential benefits do not outweigh potential risks

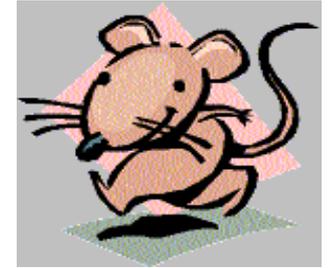
# ■ ■ ■ Early Communication with OCTGT

- Pre-preIND interactions
  - Non-binding, informal scientific discussions between CBER/OCTGT nonclinical review disciplines (P/T & CMC) and the sponsor
  - Initial targeted discussion of specific issues
  - Primary contact: Mercedes Serabian  
[mercedes.serabian@fda.hhs.gov](mailto:mercedes.serabian@fda.hhs.gov)
- PreIND meetings
  - Non-binding, but formal meeting between FDA and sponsor (with minutes generated)
  - Meeting package should include summary data and sound scientific principles to support use of a specific product in a specific patient population

## ■ ■ ■ Summary

- It is important to keep FDA/CBER/OCTGT involved at an early phase of the product development program, to enable identification of potential issues and the appropriate pathway to resolution
- The preclinical study designs should be supported by scientific rationale/data
- Novel therapies mean novel testing paradigms

# ■■■ Contact Information



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301-827-3880

Regulatory Questions: Contact the Regulatory Management Staff in OCTGT at

[CBEROCTGTRMS@fda.hhs.gov](mailto:CBEROCTGTRMS@fda.hhs.gov) or

[Patrick.Riggins@fda.hhs.gov](mailto:Patrick.Riggins@fda.hhs.gov)

or by calling (301) 827-6536

OCTGT Learn Webinar Series:

<http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>



# Resource Information...

- ICH Documents <http://www.fda.gov/cber/guidelines.htm>
- CBER/FDA Biological Response Modifiers Advisory Committee Mtg:  
<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/default.htm>
  - Cardiac repair products
  - Cartilage repair products
  - Human embryonic stem cell derived products
  - Xenotransplantation products
- DW Fink, Jr., and Bauer, SR. “Stem Cell-based Therapies: FDA Product and Preclinical Considerations.” In The Essentials of Stem Cell Biology (Second Edition). Ed. R Lanza, J Gearhart, B Hogan, D Melton, R Pedersen, J Thomson, E Thomas and I Wilmut; Elsevier Academic Press: Burlington, MA, pp. 619-630, 2009
- Serabian M and Huang Y. “Preclinical Safety Evaluation of Gene Therapy Products”. Chapter 32, In *Preclinical Safety Evaluation of Biopharmaceuticals – A Science-Based Approach to Facilitating Clinical Trials*. Ed. Cavagnaro JA. John Wiley & Sons, Inc., Hoboken, NJ, pp. 713-747, 2008



# Selected Guidances

- Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy (March 1998)  
[www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072987.htm](http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072987.htm)
- Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events (November 2006)  
[www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072957.htm](http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072957.htm)
- Guidance for Industry (draft): Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage (July 2007)  
[www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072952.htm](http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072952.htm)
- Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications (November 2007)  
[www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074770.htm](http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/ucm074770.htm)
- Guidance for Industry: Somatic Cell Therapy for Cardiac Disease (March 2009)  
[www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm164265.htm](http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm164265.htm)
- Guidance for Industry: Considerations for Allogeneic Pancreatic Islet Cell Products (September 2009)  
[www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm182440.htm](http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm182440.htm)
- ICH S6 document: Preclinical Safety Evaluation of Biotechnology Derived Pharmaceuticals (July 1997)  
[www.fda.gov/RegulatoryInformation/Guidances/ucm122049.htm](http://www.fda.gov/RegulatoryInformation/Guidances/ucm122049.htm)



# Selected Guidances

- Addendum to ICH S6 Document: *Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals* S6(R1) (Step 4; June 2011)  
<http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html>
- ICH – Gene Therapy Discussion Group (GTDG) documents: *ICH Consideration: General Principles to Address the Risk of Inadvertent Germline Integration of Gene Therapy Vectors* (October 2007)  
<http://www.ich.org/products/consideration-documents.html>