



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

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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"/>	Pharmacology and toxicology data	21 CFR 312.23(a)(8)
<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]



CBER Review: Product-Based

- No “one size fits all” regulatory approach
- Data necessary to support development depends on the characteristics of the product
- Preclinical studies are designed to support use of a specific product for a specific clinical indication
- Review approach is based on balancing risk and benefit



Preclinical Regulatory Testing Strategy

- A 'standard set' of preclinical tests and testing parameters uniformly applicable to all products does not exist
- The diversity and inherent biological properties of cell and gene therapy products necessitate a case-by-case testing strategy
- An overarching set of general considerations to guide preclinical testing





Guidance for Industry

Preclinical Assessment of Investigational Cellular and Gene Therapy Products

DRAFT GUIDANCE

This guidance document is for comment purposes only.

Submit one set of either electronic or written comments on this draft guidance by the date provided in the *Federal Register* notice announcing the availability of the draft guidance. Submit electronic comments to <http://www.regulations.gov>. Submit written comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. You should identify all comments with the docket number listed in the notice of availability that publishes in the *Federal Register*.

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), (HFM-40), 1401 Rockville Pike, Suite 200N, Rockville, MD 20852-1448, or by calling 1-800-835-4709 or 301-827-1800, or e-mail ocod@fda.hhs.gov, or from the Internet at <http://www.regulations.gov> and <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
November 2012



■ ■ ■ 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

■ ■ ■ 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

■ ■ ■ 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

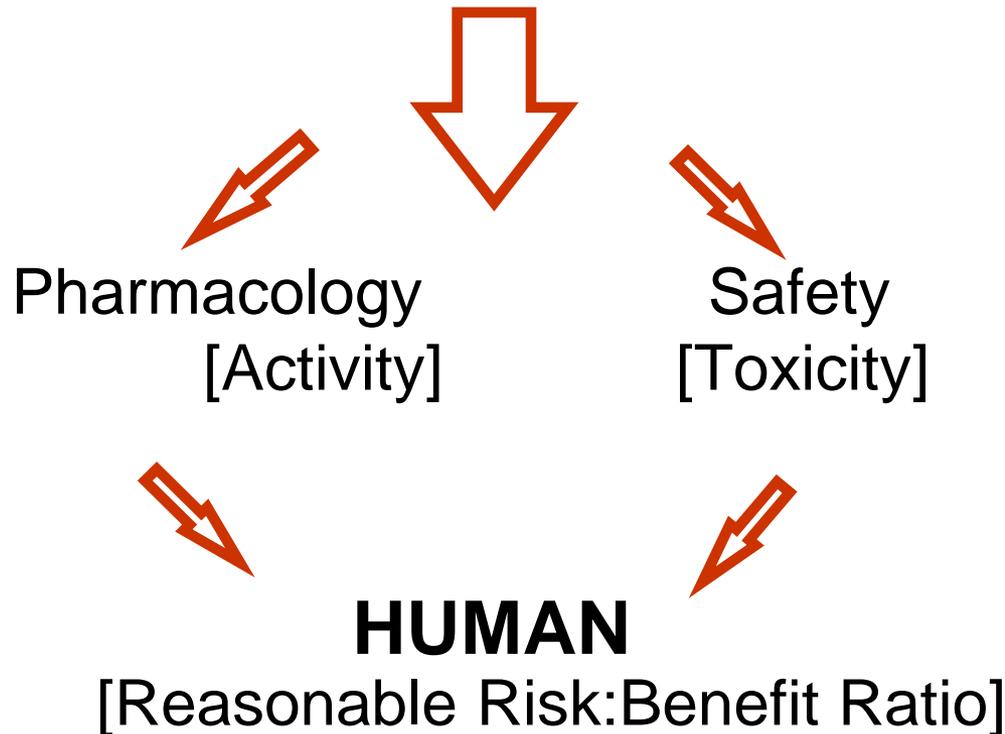
■ ■ ■ Sources of Data to Support an IND

- 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

Relevant Animal Species/Model(s)





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 (e.g., extrapolation to clinical dose) and duration
 - Route of administration/anatomic site of delivery



■■■ 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

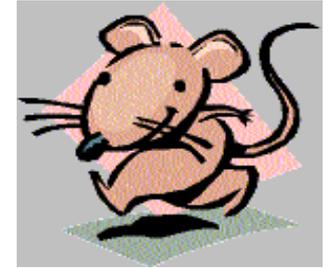
■ ■ ■ Early Communication with OCTGT

- 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
- 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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Regulatory Questions: Contact the Regulatory Management Staff in OCTGT at
CBEROCTGTRMS@fda.hhs.gov or
Lori.Tull@fda.hhs.gov
or by calling (301) 827-6536

OCTGT Learn Webinar Series:
<http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm>



Public Access to CBER

CBER website:

<http://www.fda.gov/BiologicsBloodVaccines/default.htm>

Phone: 1-800-835-4709 or 301-827-1800

Consumer Affairs Branch (CAB)

Email: ocod@fda.hhs.gov

Phone: 301-827-3821

Manufacturers Assistance and Technical Training Branch
(MATTB)

Email: industry.biologics@fda.gov

Phone: 301-827-4081

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Resource Information...

- CBER/FDA Cellular, Tissue, and Gene Therapies Advisory Committee Mtg:
<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccineandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/default.htm>
 - Cardiac repair products
 - Cartilage repair products
 - Human embryonic stem cell derived products
 - Xenotransplantation products
 - Cell and gene therapy products for treatment of retinal disorders
- Fink, Jr DW , Bauer SR, Au P, Haudenschild CC, Lee MH, McCright BK, “Regulatory considerations of stem/progenitor cell-based products: US Food and Drug Administration” In: A. Atala, editor. Progenitor and stem cell technologies and therapies. Woodhead Publishing, Cambridge, UK (2012)
- Au P, Hursh DA, Lim A, Moos MC Jr, Oh SS, Schneider BS, Witten CM. FDA oversight of cell therapy clinical trials. *Sci Transl Med*. 2012 Aug 29;4(149):149fs31.
- 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

- Draft Guidance of Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products (November 2012)
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM329861.pdf>
- Guidance for Industry: Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage (December 2011)
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/UCM288011.pdf>
- Guidance for Industry: Cellular Therapy for Cardiac Disease (December 2010)
<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
- Guidance for Industry: Clinical Considerations for Therapeutic Cancer Vaccines (October 2011)
<http://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Vaccines/UCM278673.pdf>
- Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events (November 2006)
www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/ucm072957.htm



Selected Guidances

- ICH S6 document: Preclinical Safety Evaluation of Biotechnology Derived Pharmaceuticals (July 1997)
www.fda.gov/RegulatoryInformation/Guidances/ucm122049.htm
- 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>
- ICH – Gene Therapy Discussion Group (GTDG) documents: *ICH Considerations: General Principles to Address Virus and Vector Shedding* (June 2009)
<http://www.ich.org/products/consideration-documents.html>
- ICH – Gene Therapy Discussion Group (GTDG) documents: *ICH Considerations: Oncolytic Viruses* (September 2009)
<http://www.ich.org/products/consideration-documents.html>