

Preclinical Considerations for Cell and Gene Therapy Products: CBER Perspective

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Disclosure

- No financial relationships to disclose.

Overview

- Regulatory Review Principles
- GT and CT Product Overview and Associated Safety Concerns
- Questions to Ask...
- Preclinical Study Design(s)
 - Animal Species/Model Considerations
 - Pharmacology/Proof-of-Concept (POC)
 - Preclinical Study Design Considerations – Specifics
- Transitioning to Clinical Trials
- Working with FDA/CBER/OCTGT

Development Path for Biotherapeutics

- FDA Regulatory & Scientific Input
- ICH documents
- FDA guidances/21 CFR



Clinical Trials



Biologics License Application



**Product License
Granted**

IND Submission



- Basic Research
- POC Studies
- Toxicology/Safety
- Biodistribution/Cell fate



- Pre-PreIND discussions with FDA/CBER
- PreIND discussion with FDA/CBER

Discovery Phase/Safety Assessment

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]

How are Preclinical Studies Integrated into the Proposed Clinical Plan?

Pharmacologic & Toxicologic Studies

“...adequate information about the pharmacological & 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, & scope of animal and other tests required varies with the duration & nature of the proposed clinical investigations.**”

IND Regulations [21 CFR 312.23 (a)(8) - Pharmacology and Toxicology]

Translation from Preclinical to Early Phase Clinical Trials

- Proof-of-concept [POC] – *in vitro/in vivo*
 - Potential mechanism of action
 - Establish pharmacologically effective dose(s)
 - Optimize 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

Examples of Cell Therapies (CT)

- Stem cell-derived
 - Adult (hematopoietic, mesenchymal, cardiac, neuronal, adipose)
 - Perinatal (placental, umbilical cord blood)
 - Fetal, (amniotic fluid, neuronal)
 - Embryonic
 - iPS cells?
- Functionally mature/differentiated human/xenogeneic cells (i.e. chondrocytes, islet cells, hepatocytes, neuronal cells, various immune cells, etc..)

[Some] Potential Safety Concerns for CT Products

- Risks of the delivery procedure
- Ex vivo manipulation (i.e. expansion, genetic modification, encapsulation, scaffold seeding, etc..)
- Potential inflammatory/immune response to the administered CT (i.e. allogeneic, xenogeneic)
- Inappropriate cell proliferation (i.e. tumor formation)
- Inappropriate cell differentiation (i.e. ectopic tissue formation)
- Cell migration to non-target sites/tissues
- Interactions with concomitant therapies (i.e. immunosuppressive agents)

Examples of Immunotherapies (IT)

- Tumor vaccines
 - Gene-based non-viral and viral vectors expressing immunogenic molecules
 - *Ex vivo* modified immunologic cells (i.e. APCs, T & B cells, inactivated tumor cells, etc...)
- Vaccines for treatment of non-oncology diseases (i.e. Alzheimer's disease)

Examples of Gene Therapies (GT)

- Replication deficient viral vectors (i.e. retrovirus, adenovirus, AAV, vaccinia/fowlpox virus, HSV, lentivirus, viral particles) expressing various transgenes
- Replication-competent oncolytic vectors (e.g., retrovirus, measles, reovirus, adenovirus, vesicular stomatitis virus, vaccinia) – may express transgenes
- Non-viral vectors expressing various transgenes
- Genetically engineered microorganisms (*Listeria*, *Salmonella*, *Clostridium*, *Bacteriophage*, etc...) expressing various transgenes
- *Ex vivo* genetically modified cells
- iPS cells?

[Some] Potential Safety Concerns for GT 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 CT concerns

Some Questions to Ask

- If the GT product is directly administered
 - What GT product will be used clinically?
(vector type, promoter, transgene, etc...)
 - Is long-term or short-term transgene expression desired?
 - What happens to the vector following *in vivo* administration?
 - Will the GT product induce an immune response?

Some More Questions...

- If the product is a CT or *ex vivo* transduced cells
 - What cell type(s) will be used?
 - What is their differentiation state/potential?
 - If mixed cell types – what is the composition of the final product?
 - What is the source of the cell(s)?
 - How many cells are needed to achieve a minimum/optimal biological effect?
 - What happens to the cells *in vivo* following delivery?

[Even] Some More Questions...

- If the product is a CT or *ex vivo* transduced cells
 - What is their intended mechanism of action?
 - Is cell survival/engraftment necessary to achieve the desired outcome?... For how long?
 - Are the cells intended to prevent further damage or to compensate for what has been damaged?
 - Do the administered cells replace lost/damaged cells?...do they stimulate endogenous mechanisms of repair?
 - Do the cells secrete growth factors/cytokines?
 - Are the cells delivered alone?...with a scaffold... encapsulated?

[And] Some More Questions...

- What is/are the biologically relevant animal species for your product ?
- Are there potentially relevant animal models of disease/injury that can be used?
- What is the optimal method/route/anatomical site to deliver the product?
- What is the optimal timing for product administration relative to the onset of disease/injury?
- Will repeat administration be needed?
- What is the risk/benefit ratio for the intended 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 & safety** endpoints in an animal model of disease/injury
 - Local microenvironment & 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

Selection of Animal Species

– Direct gene transfer

- Permissive to vector transduction
- Reactive to the expressed transgene
- Species specificity issues similar to human recombinant proteins & mAbs - Use of analogous transgene is potentially feasible (IFN, EPO, FIX)

– CT products or *ex vivo* transduced cells - immune tolerance to the cells

- Use of immunosuppressed animals
- Use of immunodeficient animals
- ‘Immune privileged’ administration site
- ‘Immune privileged’ cells
- Use of analogous cells

Animal Species/Models

- Use of a large, non-rodent species
 - Comparative physiology/biomechanics
 - Ability to access the anatomic site for product administration using the intended clinical delivery device
 - Organ/tissue size comparable to human to allow for administration of absolute human dose levels and extrapolation for targeted delivery
- Use of a rodent species
 - Ability to use robust numbers of animals
 - Transgenic or knockout models available
 - Genetically immune deficient rodents available for evaluation of human cells

Use of Existing Disease/Injury Animal Models to Assess Safety and Activity

- Advantages
 - Evaluate the safety/activity of the product in local microenvironment niche & pathophysiological condition
 - Provide insight regarding dose/activity and dose/toxicity relationships
 - Better define the risk:benefit ratio of novel, first-in-human products
 - Invasive delivery routes
 - Assumed 'permanent' nature of the product
 - Identify effectiveness/risk biomarkers that may be applicable for use in the clinical trials

Use of Existing Disease/Injury Animal Models to Assess Safety and Activity

- Limitations
 - Availability/statistical limitations
 - Inherent variability
 - Paucity of robust historical/baseline data
 - Technical limitations with the physiological and anatomical constraints
 - Validation of the model
 - Potential for increased sensitivity – may/may not be clinically relevant
 - Animal care issues/cost
 - Ethical issues

Appropriate Animal Species/Model

- There is no 'default' to the use of NHPs
- 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

Pharmacology/POC

- *In vitro* / *ex vivo* activity/mechanism of action
- *In vivo* animal disease/injury model(s)
 - Feasibility/establishment of rationale
 - Optimize vector construct/dose/formulation
 - Optimize transduced/nontransduced cell dose/formulation
 - Optimize ROA/administration procedure
 - Optimize timing of product administration/dosing regimen
 - Optimize the immunosuppression regimen, if needed
 - Identification of a minimal effective dose and any dose-response relationship
 - Identification of non-terminal biomarkers/activity endpoints

Preclinical Study Design: Specifics (1)

- Nonbiased design
 - Randomized assignment to groups
 - Appropriate controls (sham, vehicle, etc..)
 - In-life and postmortem assessments conducted in a blinded manner
- Mimic clinical scenario as closely as possible
 - Product construct...human/analogous cells
 - Cell viability, product concentration/formulation, volume, rate of delivery, administration site, number of injections, etc...
 - ROA, delivery system/device, timing of product delivery, dosing regimen, etc...
 - Comparable conditioning/immunosuppression regimens
 - Anatomical location/extent of the diseased/injured area

Preclinical Study Design: Specifics (2)

- Adequate numbers of animals/group to ensure statistically & 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
 - Local/systemic effects in target/non-target tissues
 - Time of onset and persistence profile of significant findings
 - Correlate with vector biodistribution profile
 - Correlate with fate of the transduced/nontransduced cells

Preclinical Study Design: Specifics (3)

- ‘Standard’ toxicology endpoints
 - Mortality, clinical obs, body weights, appetite
 - Clin path - serum chemistry, hematology, coagulation, urinalysis
 - Pathology - target & non-target tissues
 - Scheduled & unscheduled deaths
 - Comprehensive gross pathology, organ weights

Preclinical Study Design: Specifics (4)

- Morphological evaluation – target & non-target tissues
 - Scheduled & unscheduled deaths
 - Pathologist blinded to treatment
 - Use of ‘standard’ stains, IHC, ISH, PCR, etc...
 - Fate of administered product
 - Vector biodistribution/transgene expression
 - Transduced/nontransduced cell fate
- Imaging modalities – terminal/non-terminal

Preclinical Study Design: Specifics (5)

- Functional outcome
 - Provide the rationale for each functional test used
 - Validated/standardized testing paradigms
 - Adequate concurrent controls (positive/negative)
 - Reproducible
 - Rationale for the testing time points post-product delivery
 - Blinded personnel conducting the tests
 - Blinded personnel interpreting test data
 - Adequate numbers of animals/group tested to ensure statistically & biologically robust interpretation

Preclinical Study Design: Specifics (6)

- 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 administered cell
 - Potential for unregulated growth/tumorigenicity
 - Depends on the disease/injury of focus (cardiac, neurological, status/function of hematopoietic cells, etc...)

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...)

Cell Fate Following *In Vivo* Delivery

- Influence of local microenvironment
 - Survival/engraftment
 - Integration (anatomical/functional)
 - Differentiation/phenotype expression
 - Transdifferentiation/de-differentiation, fusion
 - Migration/trafficking (potential for ectopic tissue formation)
 - Proliferation

Regulatory Expectations for Preclinical Studies

- Preclinical data should be adequate to support the proposed clinical trial
 - Range of doses, schedule and/or duration of treatment, route of administration should mimic those planned for the clinic
 - Sufficient safety data should be available to determine endpoints for monitoring in the clinic

IND Regulations [21 CFR 312.23 - IND Content and Format]

Regulatory Expectations for Toxicology Studies

- 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

IND Regulations [21 CFR 312.23 (a)(8) - Pharmacology and Toxicology]

Regulatory Issues for Clinical Trials

- Does the submission contain sufficient information to assess risks to the subjects in the proposed trial?
 - Are source materials, manufacturing process, and final product sufficiently characterized to provide adequate assurance of safety?
 - Were adequate preclinical studies performed?
 - Were data submitted in sufficient detail to conduct an independent review?
 - Does the design of the clinical trial contain adequate safeguards for subject safety?
 - Is the design of the clinical trial adequate to achieve stated aim?
- If sufficient data are present, are the risks to human subjects unreasonable?

[Some] Limitations of Preclinical Studies

- Lack of information/understanding regarding fundamental biochemical and physiological mechanism of action
- Target site/receptor absent in test species
- Treatment does not lead to sufficiently sustained protein concentrations at target site
- Lack of available animal model(s) of disease
- Extrapolation to relevant physiological state

Findings Resulting in Possible Modification to Clinical Trial(s)

- Significant adverse findings
- Delayed effects
- Irreversible effects
- Additional findings in long-term studies
- Enhanced toxicity in an animal model of disease
- Similar adverse findings displayed in several models
- Tumor development

Early Communication with OCTGT

- Pre-preIND interactions
 - Non-binding, informal scientific discussions between CBER/OCTGT nonclinical review disciplines (pharm/tox & CMC) and the sponsor
 - Initial targeted discussion of specific issues - a “two-way street”
- PreIND meetings
 - Non-binding, but formal meeting between FDA and sponsor (with minutes generated)
 - Summary data and sound scientific principles to support use of a specific product in a specific patient population

We are all striving for
the same goal

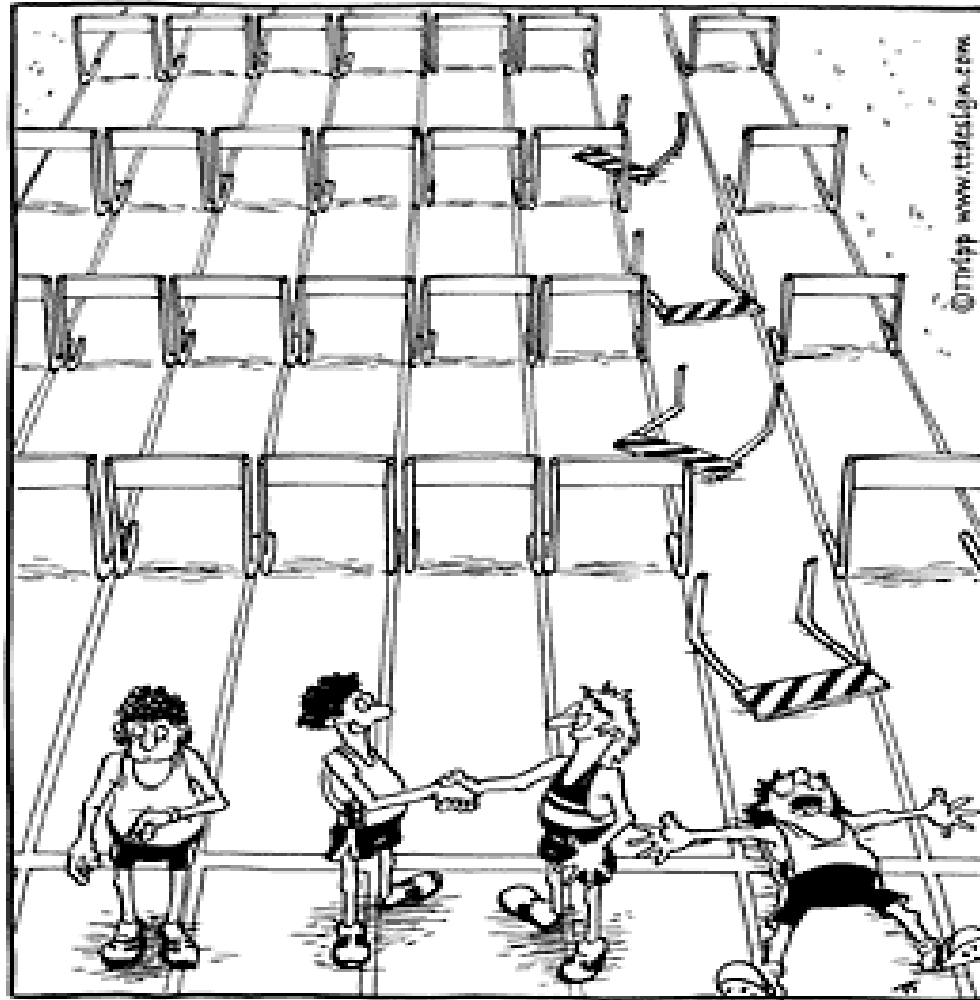


There is often more than one way to achieve the goal



Teamwork is Key

The Novice



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