Preclinical Considerations for Gene Therapy Products: CBER Perspective

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Overview

- Regulatory Review Principles
- Questions to Ask
- Preclinical Study Design
  - Animal Species/Models
  - Pharmacology/Proof-of-Concept (POC)
  - Toxicology Study Design Considerations
- Transitioning to Clinical Trials
- Working with FDA/CBER
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Critical Path Development of Biotherapeutic Agents

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

IND Submission

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

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

Clinical Trials

Biologics License Application

Product License Granted

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)]
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)]
[Some] Questions that Should be Asked

- If the GT product is directly administered
  - What gene therapy (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 in vivo following delivery?

- If the GT product is ex vivo transduced cells
  - What cell type(s) will be used?
  - What is the source of the cell(s)?
  - How many cells are needed?
  - What happens to the cells in vivo following delivery?
[Some] More Questions…

- What is/are the biologically relevant animal species for your GT product?
- Are there potentially relevant animal models of disease/injury that can be used?
- What is the optimal method/route 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)

- Pharmacology/POC studies in relevant animal model(s) of disease/injury
- Toxicology (T) studies in healthy animals
- Hybrid pharmacology-toxicology study design
  - POC + T – incorporate activity & toxicity endpoints in an animal model of disease/injury
  - Local microenvironment & pathophysiology condition may impact the safety of the product
Selection of Appropriate Animal Species/Model

- **Direct gene transfer** - species should be sensitive to the GT product, permissive to vector transduction, the expressed transgene, & exhibit a biological response similar to humans
  - Species specificity issues similar to human recombinant proteins & mAbs
  - Use of analogous transgene is potentially feasible (IFN, EPO, FIX)
- **Ex vivo transduction** - immune tolerance to transduced cell product
  - Use of analogous cells
  - Use of immunosuppressed animals
  - Use of immunodeficient animals
Selection of Appropriate Animal Species/Model

- Comparative physiology of animal to human – improves predictability of human risks
- Route of administration
  - Systemic vs. targeted delivery
  - Delivery system/delivery procedure
  - Comparable to clinical
Selection of Appropriate Animal Species/Model

- **Traditional**
  - Normal animals; rodent & non-rodent

- **Non-traditional**
  - Spontaneous disease
    - Hemophilia A/B dogs
  - “Non-spontaneous” disease (induced, challenge)
    - Myocardial infarct models
  - Genetically modified/‘humanized’ animals
    - Fanca-/- / Fancc-/- mice
    - βIVS-2-654-thalassemia mice
Selection of ‘Non-Traditional’ Models

- Challenges
  - Inherent variability of the model
  - Paucity of background pathology/baseline data
  - Potential for increased sensitivity – may/may not be relevant
  - Validation of the model

- Understand the limitations of the species/model
  - Availability, size, gender/age, housing needs, cost, ACUC concerns, technical feasibility, historical/baseline data, statistical limitations
Selection of Appropriate Animal Species

- 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

......BUT......

Scientific justification must be provided for the selection of the animal species
Pharmacology/POC

- **In vitro / ex vivo** activity/mechanism of action
  - i.e., angiogenic activity (endothelial cells) – induction of vascular structures

- **In vivo** animal disease/injury model(s)
  - Feasibility/establishment of rationale
  - Optimize vector construct/dose/formulation
  - Optimize transduced cell dose/formulation
  - Optimize ROA/administration procedure
  - Optimize timing of product administration/dosing regimen
  - Identification of a minimal effective dose and any dose-response relationship
  - Identification of non-terminal biomarkers/activity endpoints
POC Study Design: Endpoints

- **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, formulation/concentration, ROA, delivery system, timing of delivery, dosing regimen, etc.
  - Use of immunosuppressive agents
  - Anatomical location/extent of the diseased/injured area
POC Study Design: Endpoints

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

- Morphological evaluation – target/nontarget tissues
  - Scheduled and unscheduled deaths
  - Pathologist blinded to treatment
  - Use of ‘standard’ stains, IHC, ISH, etc.
    - Injury size/location
    - Inflammatory/immune response, scar formation, necrotic cells, etc...
  - Transgene expression
  - Transduced cell fate
- Use of Q-PCR, RT-PCR
  - Vector biodistribution/transgene expression
- Imaging modalities – terminal/non-terminal
Toxicology Study Design: Specifics

- Consider the POC + T model when applicable
- Same design concepts for POC apply to toxicology studies
- Reasonable group sizes to provide adequate interpretation of the data
- The number of animals will vary depending on the species, disease model, delivery system, surgical procedures, etc.
Toxicology Study Design: Specifics

- Use the product intended for clinical use if at all possible (identical vector backbone sequence, promoter, transgene, cell type, formulation, etc.).
- Use a clinically relevant route/method of administration
  - Clinically comparable device (infusion pump, catheter, etc...)
  - Clinically comparable administration conditions (rate of delivery, pressure, etc...)
- Target clinically relevant anatomical sites
- Mimic the number of injections per tract/site, etc...
- Comparable (bone marrow) conditioning regimen
Delivery System – Catheters/Injection Device

- Is the device cleared for use in the intended anatomical location in humans?
- Conduct ‘bench testing’ using the delivery device
  - Biocompatibility of the intended clinical product to the device
- Can your product be used in multiple catheters or delivery devices... or are you limited to a proprietary device from a single manufacturer?
- Use the intended clinical device in the animal studies
Toxicology Study Design: Specifics

- Selection of dose levels
  - Dose extrapolation from animal to human
    - Based on BW, surface area
    - Based on target organ volume, weight
  - Include multiple dose levels in order to determine No-Observed-Adverse-Effect-Level [NOAEL] and a dose-toxicity response relationship
Toxicology Study Design: Specifics

- ‘Standard’ toxicology endpoints
  - Mortality, clinical observations, body weights, appetite
  - Hematology and coagulation
  - Serum chemistry
  - Pathology – target & nontarget tissues
    - Comprehensive gross pathology, organ weights
    - Microscopic pathology – blinded assessment
    - Standard/other stains
Toxicology Study Design: Specifics

- **Other endpoints**
  - Depends on the vector/transgene
    - Potential for carcinogenicity/tumorigenicity
    - Host immune response to vector and/or transgene
  - Depends on the transduced cell type
    - Host immune response to transduced cell
    - Potential for unregulated growth/tumorigenicity
  - Depends on the disease/injury of focus
    - Cardiac enzymes, ECHOs, EKGs
    - Status/function of hematopoietic cells
Toxicology Study Design: Specifics

- Sufficient study duration, depending on the biology of the product, to allow for adequate assessment of:
  - Functional, laboratory, and morphological outcomes...
  - ...and the potential for resolution of findings

- Include several time points for measuring non-terminal/terminal parameters to evaluate early and late findings post-product administration
  - Correlate with vector biodistribution
  - Correlate with fate of the transduced cell
Biodistribution**...**

- Determine potential for vector biodistribution in the 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

**The results may impact the toxicology study design (e.g. duration, dosing regimen, etc...)**
Biodistribution Assay...

- Vector detection by Q-PCR assay
  - Real time analysis recommended
  - 3 samples/tissue, 0.25-1 ug genomic DNA each
  - 2 samples run unspiked, 1 sample/tissue run with spiked control to determine PCR efficiency
  - Sensitivity of \( \leq 50 \) copies of vector/ug genomic DNA

If the spike control fails to meet the PCR efficiency, the tissue DNA should be purified and PCR reanalyzed.
Sources of Preclinical Data

- Preclinical pharmacology and toxicology data in support of a clinical trial can come from:
  - GLP-compliant toxicology studies conducted by a contract laboratory
  - Well-controlled studies conducted in house
  - Published data in peer-reviewed journals
  - Cross-reference to similar products in previously submitted MFs/INDs
Regulatory Expectations for Toxicology Studies

21 CFR 312.23 – IND Content and Format

- 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
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

- Not just summarized statements
- Detailed description of the study performed:
  - Test system (i.e., animals)
  - Test articles/ROA
  - Dose levels/dose regimen/study duration
  - Study groups (controls, test article treatment groups, group size, etc...)
- Results: for all parameters evaluated -
  - Submit individual animal data for all parameters evaluated
  - Submit summarized and tabulated results
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?
Assessment of Safety/Activity

Relevant Animal Species/Model(s)

Pharmacology
[Activity]

HUMAN
[Acceptable Risk:Benefit Ratio]

Safety
[Toxicity]
Early Communication

- Pre-pre-IND interactions
  - Non-binding, informal scientific discussions between CBER/OCTGT nonclinical review disciplines (pharm/tox & CMC) and sponsor
  - Minimal pre-read materials submitted by sponsor
  - Targeted discussion of specific issue of interest
  - Allows for information exchange – a “two-way street”
Early Communication

- **Pre-IND meetings**
  - Non-binding, *but formal* meeting between FDA and sponsor
  - Pre-read materials must be submitted by sponsor *at least 30 days* prior to meeting
  - Formal minutes generated by FDA - sent to sponsor within 30 days after meeting
  - Meeting emphasis - summary *data* and sound scientific principles to support use of a specific product in a specific patient population
Resource Information...

- ICH Documents [http://www.fda.gov/cber/guidelines.htm](http://www.fda.gov/cber/guidelines.htm)
Contact Information

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General CBER Issues
Office of Communication, Training & Manufacturers Assistance (OCTMA)
Manufacturers Assistance and Technical Training Branch

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Internet: http://www.fda.gov/cber/manufacturer.htm
"Nope, not quite...what I had in mind was more a sort of double belt."