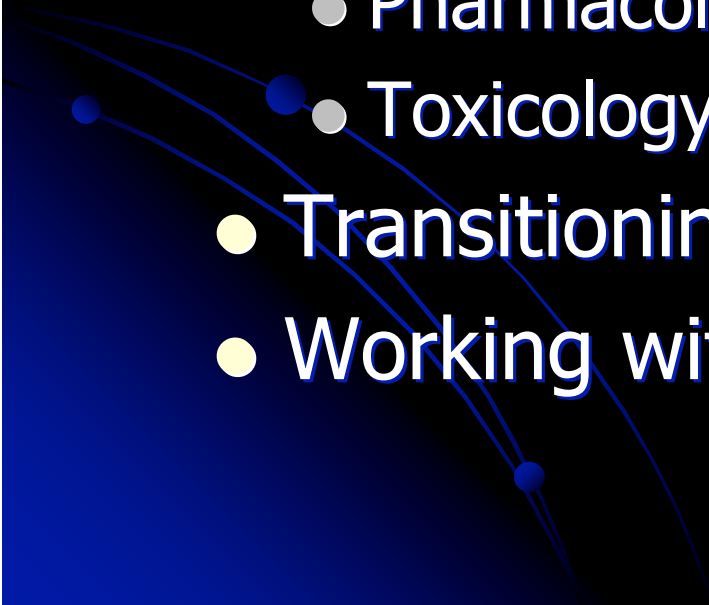


Preclinical Considerations for Gene Therapy Products: CBER Perspective

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Blood Diseases
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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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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 animals 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?

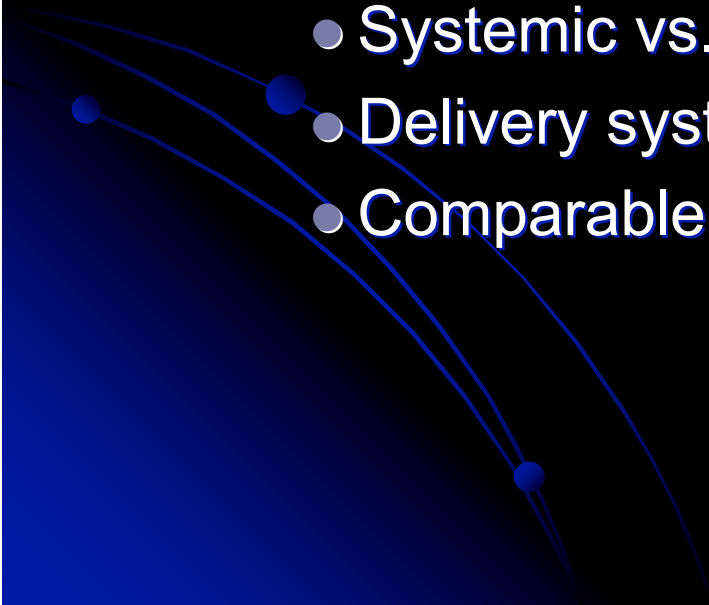
Preclinical Study Design(s)

- 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
 - $\beta^{\text{IVS-2-654}}$ -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

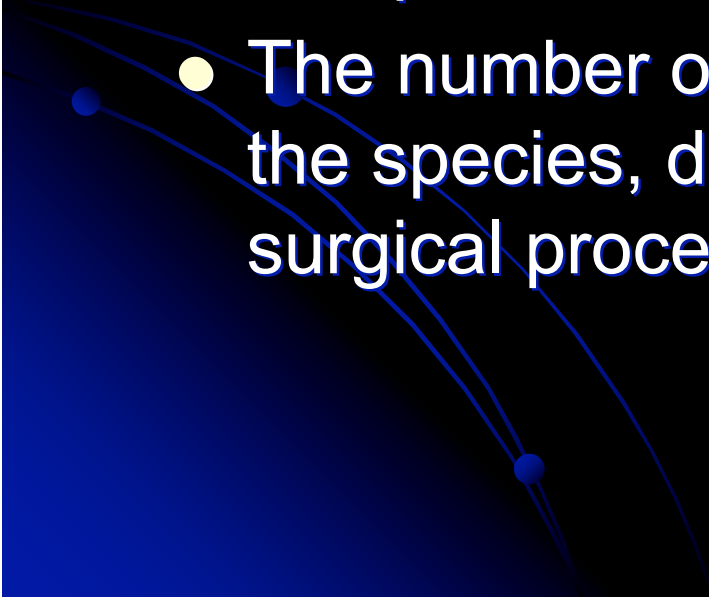
POC Study Design: Endpoints

- 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 ≤ 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

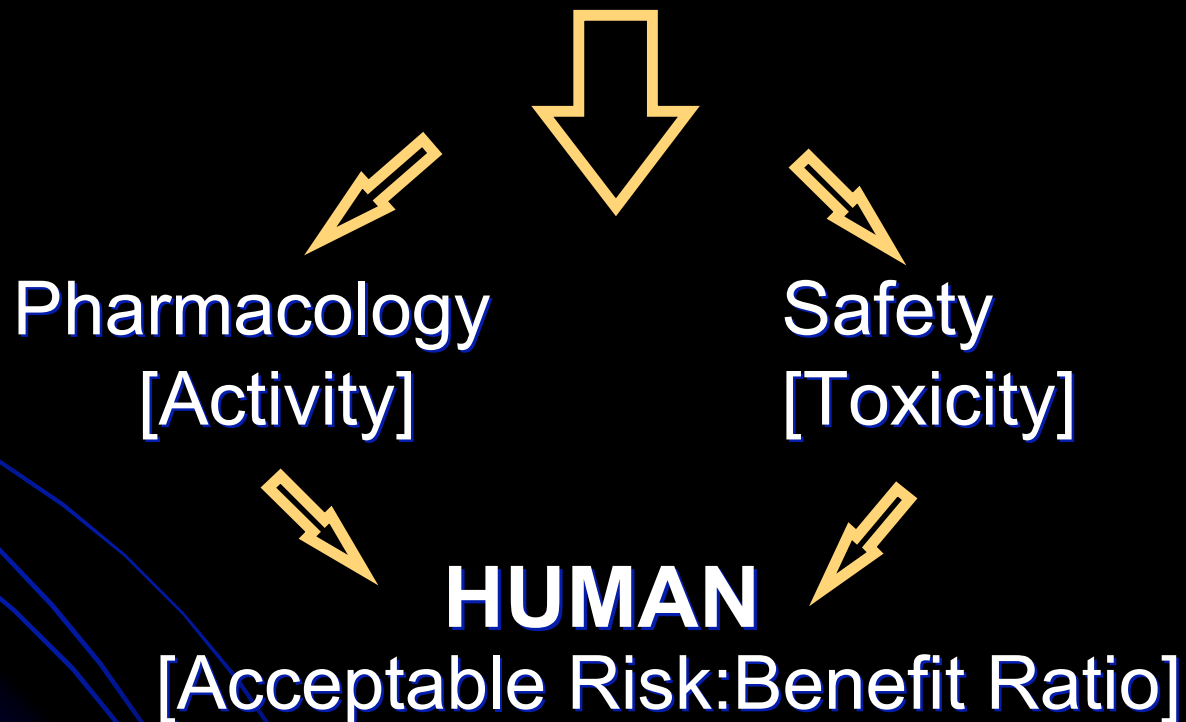
- **Not just summarized statements**
- Detailed description of the study performed:
 - Test system (i.e., animals)
 - Test articles/ROA
 - Dose levels/dose regimen/study duration
 - Study groups (controls, test article treatment groups, group size, etc...)
- Results: for all parameters evaluated -
 - 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)



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...

- Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy (1998) www.fda.gov/cber/gdlns/somgene.pdf
- ICH Documents
<http://www.fda.gov/cber/guidelines.htm>
- Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events [‘LTFU’ document]
www.fda.gov/cber/gdlns/gtclin.pdf

Contact Information

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General CBER Issues

Office of Communication, Training & Manufacturers
Assistance (OCTMA)

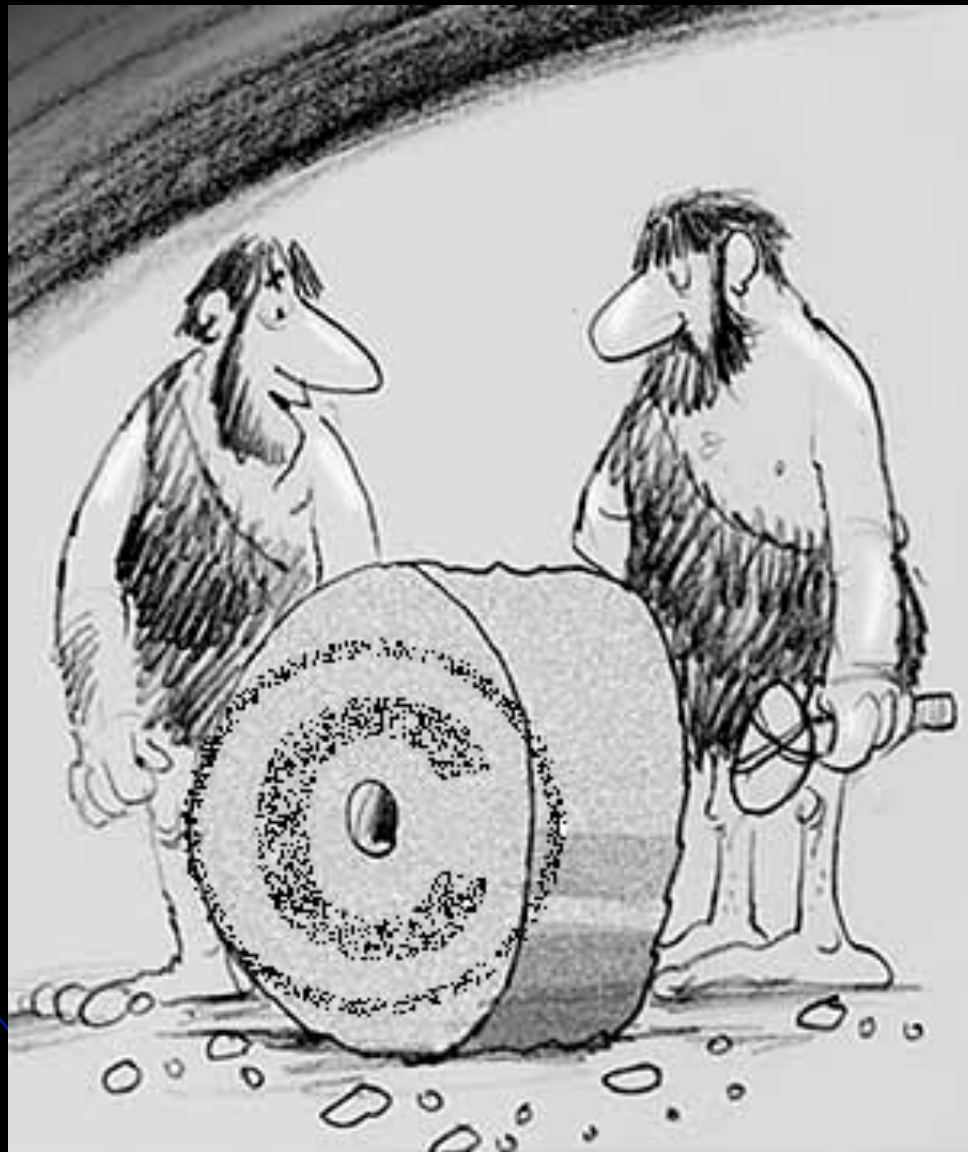
Manufacturers Assistance and Technical Training Branch

Telephone: 800-835-4709 or 301-827-1800

E-mail: matt@cber.fda.gov

Internet: <http://www.fda.gov/cber/manufacturer.htm>





*"Nope, not quite...what I had in mind was more
a sort of double belly."*