

Preclinical Studies to Support Clinical Applications of Gene Therapy Products

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CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

Presentation Overview

- Regulatory Review
- GT Associated Safety Concerns
- Questions to Ask...
- Considerations for Animal Species/Models and Preclinical Study Design
- Transitioning to Clinical Trials
- Working with FDA/CBER/OCTGT

Translational Development of Biotherapeutic Agents

- FDA Regulatory & Scientific Input
- ICH documents
- FDA guidances/21 CFR
- Standards (ISO, USP, ASTM, ANSI)

IND Submission

- Pre-preIND discussion with FDA/CBER
- PreIND meeting with FDA/CBER

- Basic Research/Discovery
- POC Studies
- Toxicology/Safety
- Biodistribution

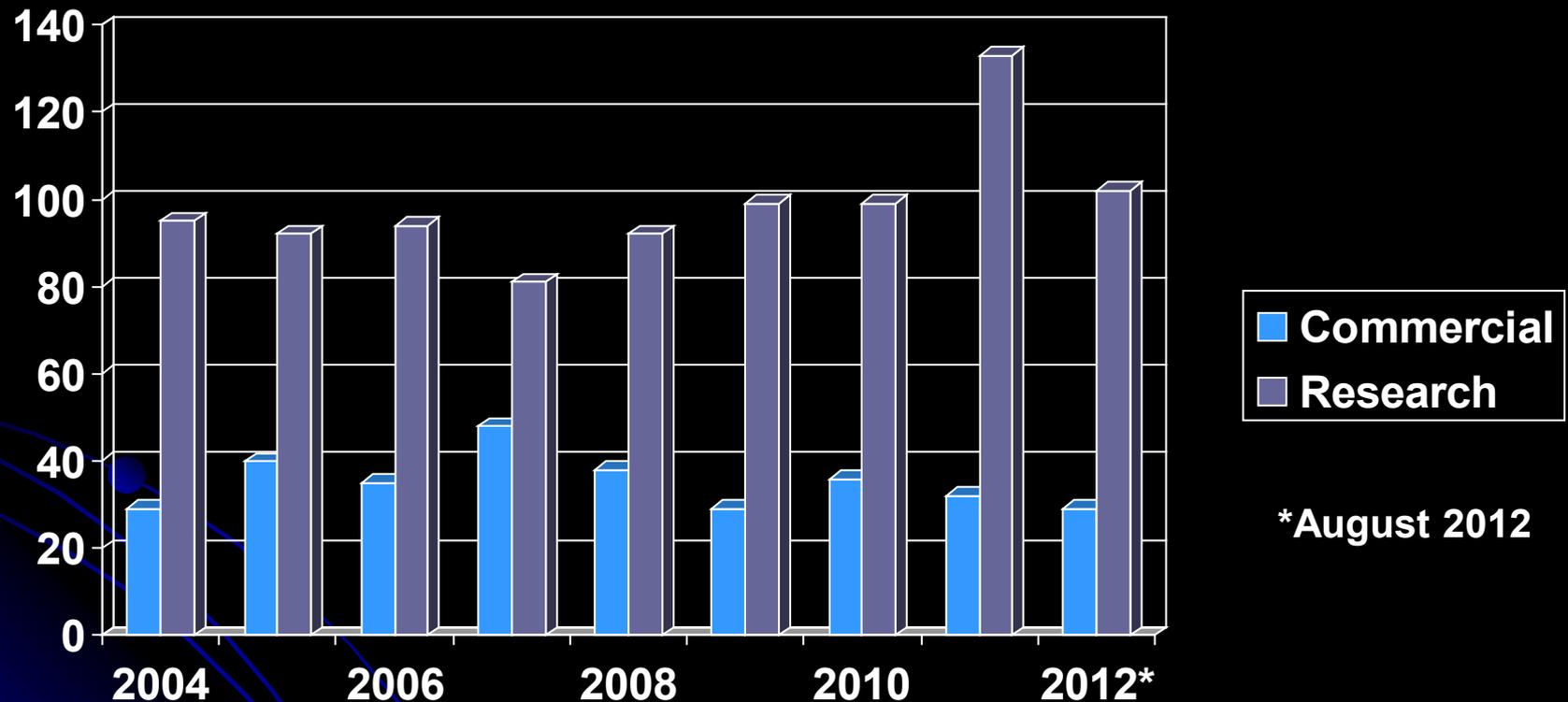
Clinical Trials

Biologics License Application

**Product License
Granted**

Discovery Phase/Safety Assessment

Regulatory Files Submitted to OCTGT: Commercial or Research Sponsors



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Pediatric/Adult Rare Diseases and Orphan Drug Indications in OCTGT

- Neurodegenerative diseases
- Lysosomal storage disorders
- Metabolic disorders
- Immunodeficiencies
- Retinal disorders
- Cardiovascular disease
- Hemoglobinopathies
- Pulmonary disease
- Cancer

Preclinical Support of Early-Phase Clinical Trials

- Adequate information to support the safety and the scientific basis for the administration of an investigational product in the target patient population
 - Recommend starting dose level; dose escalation scheme; dosing schedule
 - Support the planned route of administration (ROA)
 - Identify potential target tissue(s) of toxicity/activity
 - Determine parameters for monitoring in the clinical trial
 - Determine eligible patient population

Acceptable Risk:Benefit Profile

Potential Safety Concerns for Gene Therapy (GT) Products

- Toxicities due to the components of the final formulation
- Vector/virus biodistribution to non-target tissues
- Level of viral replication and persistence in non-target tissues
- Level and persistence of transgene expression in non-target tissues
- Unregulated transgene expression
- Undesirable immune response against vector, transgene, or cells
- Insertional mutagenesis and/or oncogenicity
- Germline transmission
- Viral shedding
- Risks of the ROA and the delivery procedure

Some Questions to Ask

- Direct administration of vector construct
 - 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?
- *Ex vivo* transduced cells
 - What target cell population will be transduced?
 - What is the transduction efficiency?
 - What is the differentiation potential of the cells?
 - What is the proliferation potential of the cells?
 - What is the expected *in vivo* persistence profile of the cells?

Some More Questions...

- What is/are the biologically relevant animal species for testing 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 study design(s) will provide the most useful information to assess long-term risks?
- Do *in vitro* methods that can supplement animal studies exist?

Preclinical Safety Assessment

- The preclinical testing approaches/ paradigms will depend on the product, the ROA, and the target clinical population
- Additional studies for specific safety considerations will be based on risk:benefit assessment of the product and the proposed indication

Preclinical Safety Assessment (con't)

- Assess **proof-of-concept (POC)/product fate** in relevant animal model(s) of disease/injury, as feasible
- Assess **safety/toxicology (T)/product fate** in healthy animals
- Hybrid pharmacology-toxicology study design
 - **POC + T + product fate** – incorporate **activity & safety** endpoints in an animal model of disease/injury
- Apply the 3 R's of animal use – **Reduce, Refine, Replace**

Considerations for Selecting Animal Species/Model

- Species specificity
 - Permissiveness/susceptibility to infection by, and replication of, viral or microbial vectors
 - Reactive to the expressed transgene
 - Immune tolerance to the administered cells
- Comparative physiology and anatomy of animal to human
 - Model of disease/injury
 - Local microenvironment and pathophysiology may impact the safety of the product and the 'predictability' of human risk

Considerations for Selecting Animal Species/Model (cont)

- Feasibility of using the planned clinical delivery system/procedure
- Route of administration – comparable to proposed clinical ROA
 - Systemic vs. targeted delivery
 - Delivery system/delivery procedure
- Understand the limitations of the species
 - Availability, size, gender/age, housing needs, cost, IACUC concerns, technical feasibility, historical/baseline data, statistical limitations

Preclinical Study Design(s)

- Biologically relevant animal species – healthy and/or model of disease/injury
- Appropriate controls and multiple dose levels of product
- Dosing regimen/procedure – mimic clinical
- Sufficient study duration
- Endpoints measured in surviving animals at multiple intervals
- Attempt to reduce bias as much as possible (randomization, blinded assessments)

Preclinical Study Design(s) (cont)

- 'Standard' endpoints
 - Mortality, clinical observations, body weights, appetite
 - Serum chemistry, hematology, coagulation, urinalysis
 - Pathology – target & non-target tissues
- Vector biodistribution/transgene expression
- Functional outcome
 - Disease-dependent [cardiac, neurological, ophthalmic, status/function of hematopoietic cells, etc...]
 - Provide the rationale for each functional test used
 - Standardized testing paradigms
 - Appropriate controls and numbers of animals
 - Blinded assessment

Preclinical Study Design(s) (cont)

- 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 cell type
 - Host immune response to transduced cell
 - Potential for unregulated growth/tumorigenicity
 - Depends on the disease/injury of focus

GT Product Biodistribution (BD)

- Prior to product administration in humans, BD analysis should be considered for:
 - Investigational GT products that belong to a new vector class
 - Established vectors with significant changes in the vector backbone
 - Established vectors with a significant formulation change
 - Established vectors with a significant change in the ROA
 - Established vectors with a significant change in the dosing schedule and/or the vector dose levels
 - Vectors expressing a new transgene(s) with an unknown potential to induce toxicity
 - Vectors expressing a transgene with a known or suspected potential to induce toxicity if aberrantly expressed in non-target tissues

GT Product BD (cont)

- Determine vector BD profile in target/non-target tissues (distribution, persistence, and clearance)
- Determine transgene expression profile in 'vector positive' tissues
- The results may impact the toxicology study design (e.g., dosing regimen, study duration)
- Sample collection and qPCR assay methodology; refer to: *Guidance for Industry: Gene Therapy Clinical Trials - Observing Subjects for Delayed Adverse Events (2006)*

Preclinical Findings Resulting in Possible Modification to Clinical Trial

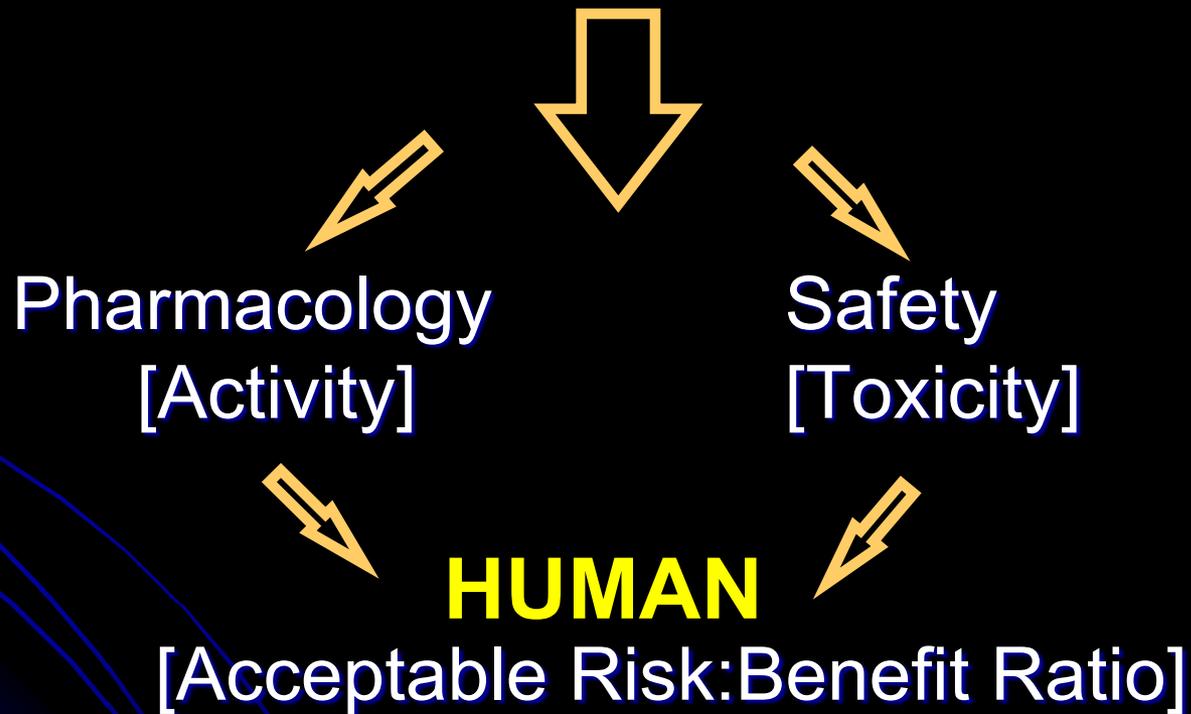
- Significant adverse findings
- Delayed effects
- Irreversible effects
- Additional findings in long-term studies
- Enhanced toxicity in an animal model of disease
- Similar adverse findings displayed in several animal species/models
- Malignancies/tumor formation

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 reasonable?

Preclinical Translation to Clinical

Relevant Preclinical Testing Paradigm



Early Communication with CBER/OCTGT

- Pre-preIND interactions, if applicable
 - Non-binding, informal scientific discussions between CBER/OCTGT nonclinical review disciplines (Pharm/Tox and CMC) and the sponsor
 - Initial targeted discussion of specific issues
- PreIND meetings
 - Non-binding, but formal scientific discussions with clinical and nonclinical review disciplines (minutes generated)
 - Sponsor should provide summary data and sound scientific principles to support use of a specific product in a specific patient population

Preclinical Study Goals

- Employ study designs that address safety and scientific basis for conducting a clinical trial
 - Robust study designs based on product and perceived risks
 - Preclinical data should be adequate to support the proposed clinical trial

Important to understand your product

- Work to minimize the number of studies and number of animals necessary to adequately address the safety and potential efficacy of the investigational GT product

FY2012 Program Priority - Draft Guidance for Industry: Preclinical Assessment of Investigational Cellular and Gene Therapy Products

Contact Information for CBER / OCTGT

- Regulatory Questions:
Contact the Regulatory Management Staff in OCTGT at CBEROCTGTRMS@fda.hhs.gov or [Lori Tull@fda.hhs.gov](mailto: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)

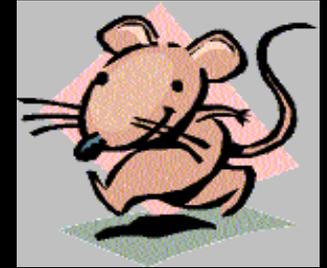
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Thank You



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