IND-Enabling Studies: Preclinical Perspective

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Presentation Overview

- Introduction to CBER/OCTGT
- IND Basics
- Products Regulated by OCTGT
- Potential Safety Concerns for GT Products
- Questions to Ask…
- Animal Species/Model(s)
- Preclinical Study Design
- Submission of Preclinical Data in the IND
- Transitioning to Clinical Trials
- Working with CBER/OCTGT

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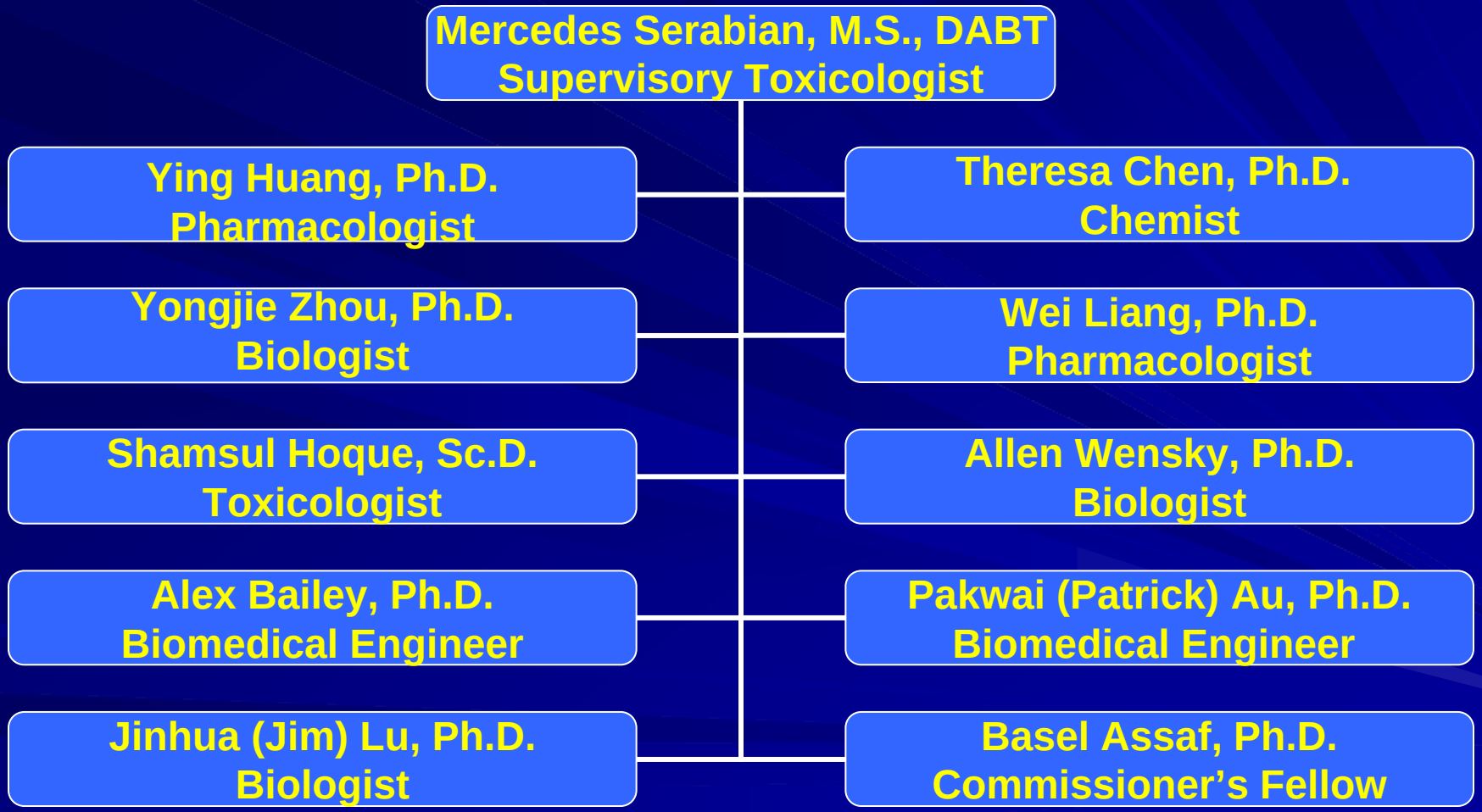


Investigational New Drug (IND)

- An IND is required to conduct a clinical trial of an unapproved drug or an approved product for a new indication or in a new patient population
- Regulations governing INDs are found in

  21 CFR 312
  - Use of the investigational drug
  - Submission of the application to FDA
  - Review by FDA
- The FDA has 30 days to review an original IND submission to determine whether the safety and rights of study subjects are adequately protected

Who can Apply for an IND?

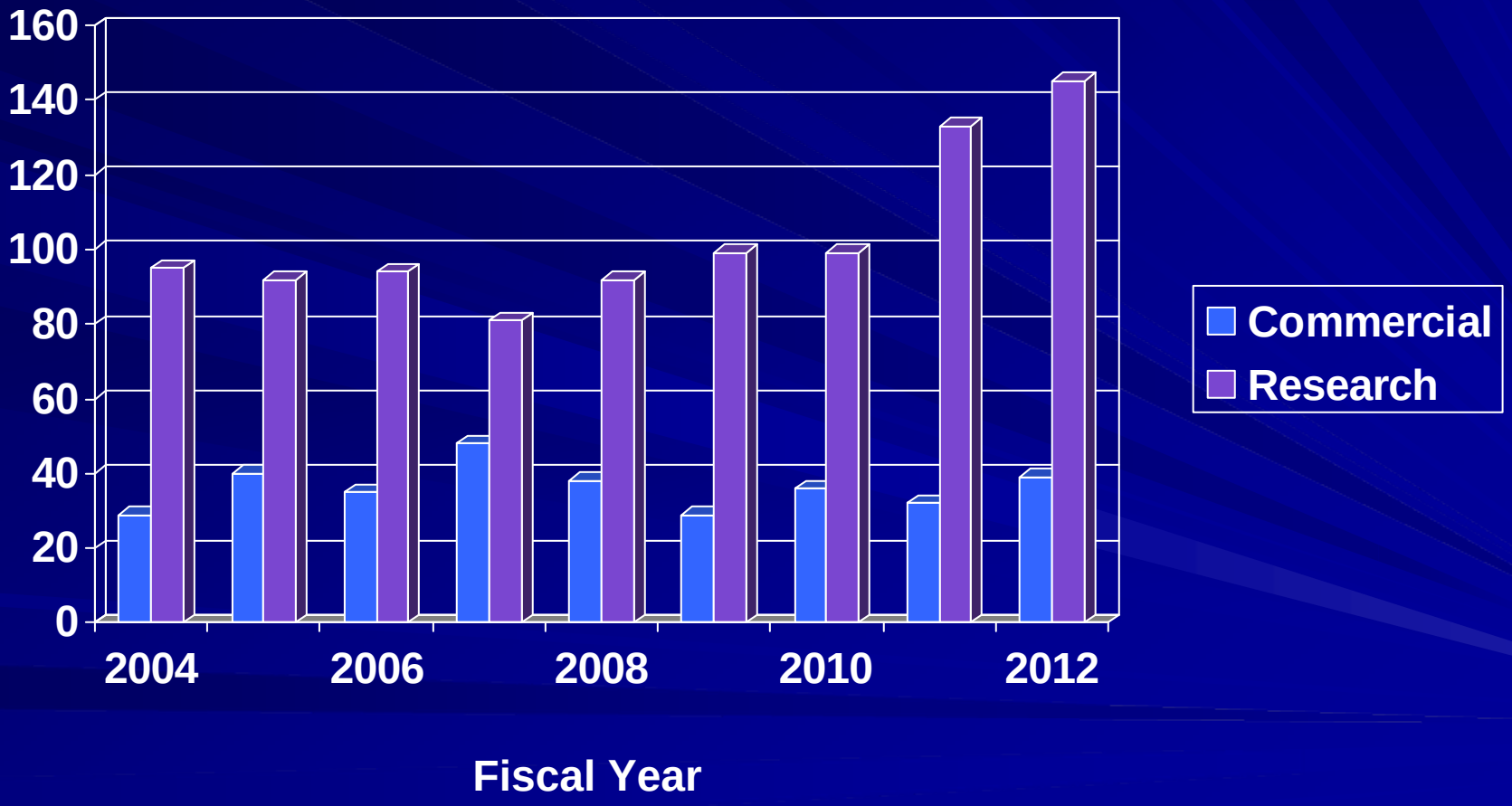
- An IND applicant is called a “sponsor”
  - Person who takes responsibility for, and initiates a clinical investigation
- An IND sponsor may be a company, institution, or an individual
- An IND sponsor-investigator is an individual who both initiates and conducts the clinical trial

Elements of an IND Application

☐	Form FDA 1571	**21 CFR 312.23(a)(1)**
☐	Table of Contents	**21 CFR 312.23(a)(2)**
☐	Introductory statement and general investigational plan	**21 CFR 312.23(a)(3)**
☐	Investigator's Brochure	**21 CFR 312.23(a)(5)**
☐	Protocols	**21 CFR 312.23(a)(6)**
☐	Chemistry, manufacturing, and control data	**21 CFR 312.23(a)(7)**
☑	Pharmacology and toxicology data	**21 CFR 312.23(a)(8)**
☐	Previous human experience	**21 CFR 312.23(a)(9)**
☐	Additional information	**21 CFR 312.23(a)(10)**

Regulatory Files Submitted to OCTGT:

Commercial or Research Sponsors



CBER Review: Product-Based

- NOT a ‘one size fits all’ regulatory approach
- Data necessary to support development depends on the characteristics of the product
- Preclinical studies are designed to support the administration of a specific product for a specific clinical indication
- Review approach is weight-of-evidence: balancing risk and benefit

The IND Review Process - Team Concept

- Regulatory project manager (RPM)
- Product reviewer (CMC)
- Preclinical reviewer (P/T)
- Clinical reviewer
- Biostatistics reviewer (when applicable)
- Consult Reviewer (when applicable)

OCTGT Regulated Products

- Cell-based products (CT)
  - Stem cell and stem cell-derived products
    - Adult (e.g., hematopoietic, neural, mesenchymal, cardiac, adipose, skin)
    - Perinatal (e.g., placental, umbilical cord blood)
    - Fetal (e.g., amniotic fluid, neural)
    - Embryonic
    - iPS [If reprogrammed using gene transfer, considered **GT**]
  - Functionally mature/differentiated cells (e.g., chondrocytes, pancreatic islet cells, hepatocytes, neuronal cells, various immune cells)
  - Xenotransplantation products
- CT products in combination with delivery devices (e.g., scaffolds, encapsulation, catheter delivery)
- Selected devices for the manufacture of cells

OCTGT Regulated Products (cont)

- Therapeutic vaccines (oncology and non-oncology)
- Gene Therapy products (GT)
  - Non-viral vectors (e.g., plasmids)
  - Replication-deficient viral vectors (e.g., adenovirus, adeno-associated virus (AAV), retrovirus, lentivirus, poxvirus, herpes simplex virus (HSV))
  - Replication-competent oncolytic viruses/vectors (e.g., measles, reovirus, adenovirus, vesicular stomatitis virus, vaccinia)
  - Genetically modified microorganisms (e.g., *Listeria, Salmonella, E. coli*, Bacteriophage)
  - *Ex vivo* genetically modified cells
  - Express transgenes, siRNAs, etc…
- GT products in combination with delivery devices

Clinical Applications for CT and GT Products: Examples

CT and GT Products,***

- Immunodeficiencies
- Hemoglobinopathies
- Cancer
- Coagulation disorders
- Neurodegenerative diseases
- Cardiovascular diseases
- Infectious diseases
- Pulmonary diseases
- Ophthalmic disorders
- Metabolic diseases

*CT Products***

- Bone marrow failure
- Emerging regenerative approaches in
  - Brain and spinal cord injuries
  - Neurologic diseases
  - Muscle & ligament regeneration
  - Knee cartilage repair/ replacement
  - Wound care/burns

** ASGCT NIH Gene Therapy Symposium, Sept. 26-27, 2011*

***www.clinicaltrials.gov*

Translational Development for Biotherapeutic Agents

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

Clinical Trials

IND Submission

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

- Basic Research/Discovery
- POC Studies
- Toxicology/Safety
- Cell Fate/Vector Biodistribution

Biologics License Application

Product License Granted

Discovery Phase/Safety Assessment

Preclinical Support of Early-Phase Clinical Trials

- Adequate preclinical 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 clinical route of administration (ROA) and anatomic location of product delivery
  - Identify potential target tissue(s) of toxicity/activity
  - Determine parameters for monitoring in the clinical trial
  - Determine eligible patient population
  - Determine ‘at risk’ patient population

Acceptable Risk:Benefit Profile

[Some] Potential Safety Concerns for GT Products

- Vector/virus biodistribution to non-target sites/ tissues
- Transduced cell distribution to non-target sites/ tissues
- Unregulated level of viral replication, viral persistence, and/or transgene expression in target/ non-target tissues
- Undesirable immune response against vector, transgene, or transduced cells
- Inappropriate cell proliferation (i.e., tumor formation)

Potential Safety Concerns (cont)

- Insertional mutagenesis and/or oncogenicity
- Germline transmission
- Viral shedding (3rd party exposure)
- Toxicities due to the components of the final formulation
- Interactions with concomitant therapies (i.e., immunosuppressive agents)
- Risks of the delivery procedure and the anatomic site of delivery

Some Questions to Ask

- Direct administration of the 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 happens to the cells *in vivo* following delivery?
  - What is the expected *in vivo* persistence profile of the cells?

[and] Some More Questions…

- What is the optimal method/route/anatomical site for product delivery?
- What is the optimal timing for product administration in humans relative to the onset of disease/injury?
- Will repeat administration be needed?
- Will immunosuppression be needed?
- What is/are the biologically relevant animal species for testing your product?
- Are there potentially relevant animals models of disease/ injury that can be used?
- What preclinical 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 Assessment

- 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 animal model(s) of disease/injury
  - Local microenvironment & pathophysiology status of the model may impact the safety/bioactivity of the product
- Apply the 3 R's of animal use – Reduce, Refine, Replace

Considerations for Selecting Animal Species/Model(s)

- Species specificity
  - Permissiveness/susceptibility to infection by, and replication of, viral or microbial vectors
  - Reactive to the expressed transgene
  - Immune tolerance of the species to the administered human cells
    - Use of immunosuppressed animals
    - Use of immunodeficient animals
    - ‘Immune privileged’ administration site
    - ‘Immune privileged’ cells
    - Use of analogous cells

Considerations for Selecting Animal Species/Model(s) (cont)

- Feasibility of using the planned clinical delivery system/procedure
  - ROA and anatomic site of product delivery – comparable to clinical
- Comparative physiology and anatomy of animal to human
- Understand the limitations of the species/ model
  - Availability, size, gender/age, housing needs, cost, IACUC concerns, technical feasibility, historical/baseline data, statistical limitations

Pharmacology/POC

- *In vitro*/*ex vivo* activity/mechanism of action
- *In vivo* animal model(s)
  - Feasibility/establishment of rationale for the clinical trial
  - Optimize vector construct/dose level/formulation
  - Optimize transduced cell dose level/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

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

Product Delivery Device

- Is the device cleared for use in the intended anatomical location in humans?
- Will need to conduct ‘bench testing’ using the clinical delivery device to determine the biocompatibility of the intended clinical product with the device
- Can your product be administered using cleared ‘off-the-shelf’ devices (i.e., catheters) or are you limited to a proprietary device from a single manufacturer?
- Use the intended clinical delivery device in animals

Preclinical Study Design (cont)

- Adequate numbers of animals/group to obtain statistically & biologically robust data 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 the persistence profile of significant findings
- Correlate findings with vector biodistribution profile
- Correlate findings with transduced cell fate

Preclinical Study Design (cont)

- 'Standard' toxicology endpoints
  - Mortality, clinical observations, body weights, appetite, etc…
  - Clinical pathology - serum chemistry, hematology, coagulation, urinalysis
  - Pathology - target & non-target tissues
    - Scheduled & unscheduled deaths
    - Comprehensive gross pathology, organ weights

Preclinical Study Design (cont)

- 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 cell fate
- Imaging modalities – terminal/non-terminal

GT Product Biodistribution (BD)

- Prior to direct GT 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, clearance)
- Determine transgene expression levels in ‘vector positive’ tissues
- The results may impact the design of the toxicology studies and the clinical trial (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 Study Design (cont)

- Functional outcomes
  - Provide the rationale for each functional/behavioral 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 obtain statistically & biologically robust data interpretation

Preclinical Study Design (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 the cells
    - Potential for unregulated growth/tumorigenicity
  - Depends on the disease of focus (cardiac, neurological, hematopoietic cell function, etc…)

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
- At a minimum, oversight of the conduct of the toxicology study and the resulting final study report by an independent QA unit/person is strongly recommended (21 CFR 58.35)

Submit Complete Reports for the Preclinical Studies

- Detailed description of the study performed:
  - Test article(s) (i.e., relevance to the clinical product)
  - Test system (i.e., animal species/model)
  - Study groups (controls, test article groups, group size, etc…)
  - Dose levels/dose regimen/study duration
  - Delivery device information, if applicable
  - Prospective study endpoints
- Results: for all parameters evaluated-
  - Submit individual animal data for all parameters evaluated
  - Submit summarized and tabulated results
- Analysis and interpretation of the data

Potential Preclinical Hold Issues

Based on a review of 100 hold letters that were issued by CBER/OCTGT between 2002 and 2005*:

Table 3. Common pre-clinical reasons for hold

Insufficient information to assess patient risk
Safety data
Safety study reports
Delivery device (primarily cardiac catheters)
Product characterization (cellular therapy products)
Non-therapeutic components (excipients, residuals, etc.)
Inadequate study design
Safety monitoring
Product administration (dose, route, etc.)
Animal models
Erroneous, misleading, or incomplete investigator brochure
Presentation of pre-clinical studies and findings

Many of these reasons remain prevalent today

Wonnacott et al., Cytotherapy. 10:312-6, 2008

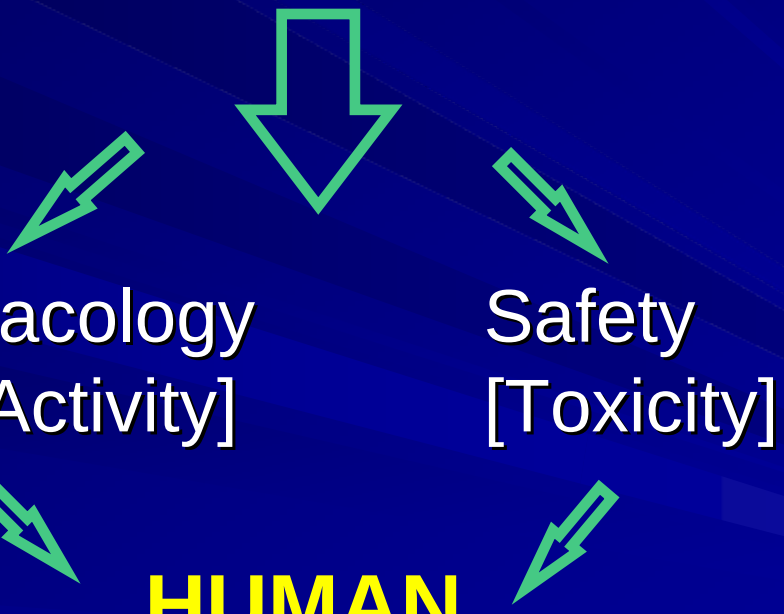
Regulatory Issues for Clinical Trials

- 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?

Preclinical Translation to Clinical

Relevant Preclinical Testing Paradigm

Weight-of-Evidence



Summary - Preclinical Study Goals

- Employ study designs that address safety and the scientific basis for conducting a clinical trial
  - Robust study designs based on the product and the perceived risks
  - Preclinical data should be adequate to support the proposed clinical trial
  - Does the IND submission contain sufficient information to assess the risks to the subjects in the proposed trial?

It is 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 your investigational product

To that End…

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

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

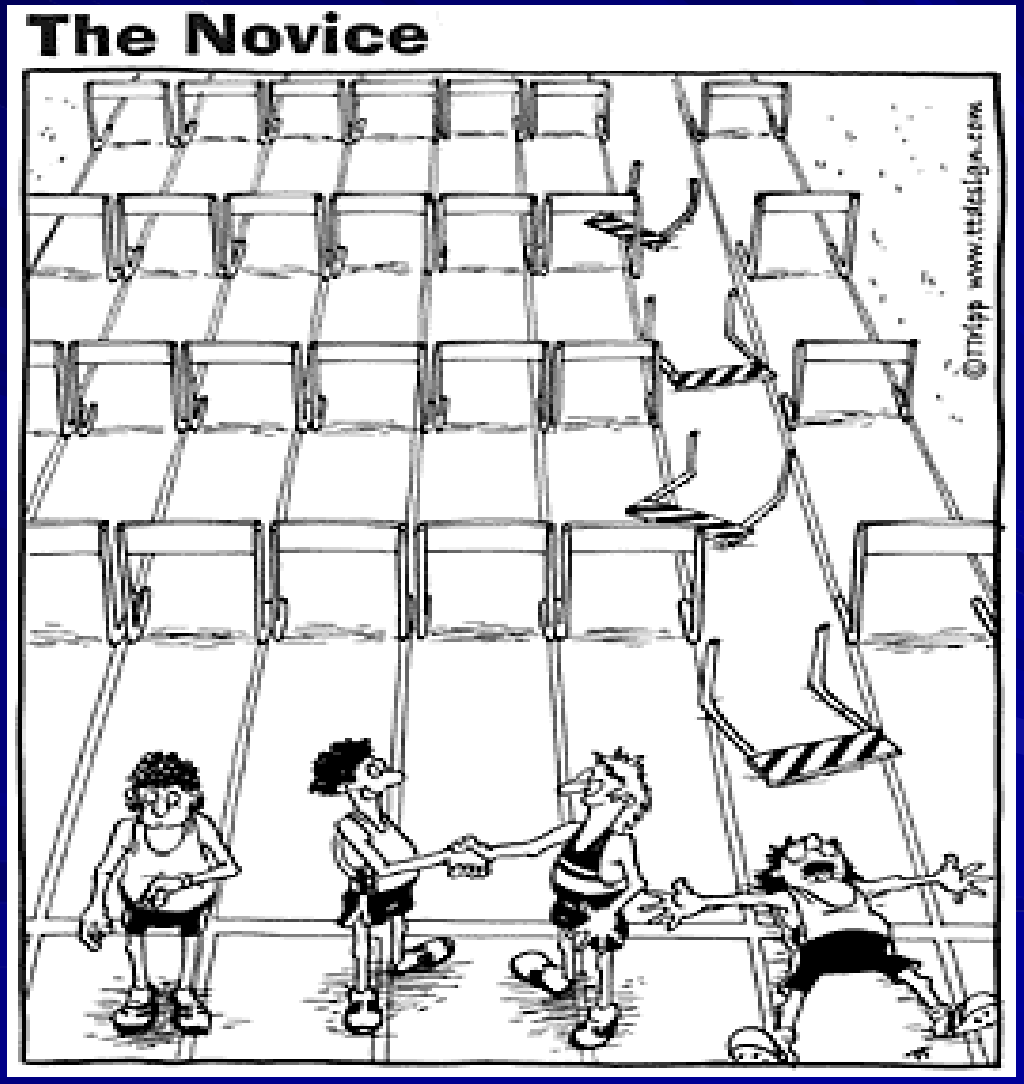
Of Interest to the Field…

The journal, *Human Gene Therapy Clinical Development* – anticipated in early 2013*

- "…to publish peer-reviewed papers describing pre-clinical animal and in vitro studies designed to assess the safety of gene and cell therapy products used to support clinical trials."
- "…an immediate benefit of peer-reviewed publication of these [pre-clinical] results will be more informed translational decisions and access to experimental designs."
- "…to publish clinical data even if the study was of insufficient impact to pass through peer review in our parent journal. Included in this category are phase I studies without definitive efficacy data (e.g., direct measures of gene transfer or quantitation of relevant biomarkers) and later stage clinical trials which fail to show efficacy. The bottom line is that all clinical data – positive or negative – are important."

**JM Wilson, Human Gene Therapy. 23:1029-30.2012.*

Teamwork is Key



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
  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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Thank You!

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