The Office of Cellular, Tissue, and Gene Therapies
Web Seminar Series
presents:

Preclinical Considerations for Products Regulated in OCTGT

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Presentation Outline

- Regulatory review principles
- OCTGT regulated products
- Potential safety concerns
- Preclinical evaluation
  - Animal species/models
  - Pharm/Tox study designs
- Communication with the FDA

Critical Path Development of Biotherapeutic Agents

- Investigational products regulated by OCTGT originate from basic research projects
- OCTGT provides regulatory and scientific input on the pre-clinical program for these investigational products through pre-preIND and preIND phases
- Guidance documents generated by FDA and ICH available which can be used to support the IND

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 Animal Studies Integrated into the Proposed Clinical Plan?

- **21 CFR, part 312.23(a)(8)**
  - 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."**

Examples of CBER/OCTGT-Regulated Products

- **Cell and Gene Therapies**
  - **Cancer vaccines**
  - **Therapeutic vaccines**
  - **Xenotransplantation Products**
  - **Tissue engineered Products**
  - **Devices**
  - **Combination Products**

Examples of Cell Therapies (CT)

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

Potential Safety Concerns for CT Products

- Cell migration/trafficking to non-target site(s)
- Cell differentiation to undesired cell types
- Ex vivo manipulation (i.e. expansion, genetic modification)
- Potential inflammatory/immune response to allogeneic/ xenogeneic cells
- Inappropriate cell proliferation (i.e. tumor formation)
- Inappropriate cell differentiation (i.e. ectopic tissue formation)
- Interactions with concomitant therapies (i.e. immunosuppressive agents)

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, VSV, vaccinia) – may express transgenes**

Examples of Gene Therapies (GT) cont.

- **Non-viral vectors expressing various transgenes**
- **Genetically engineered microorganisms (*Listeria, Salmonella, Clostridium, Bacteriophage*, etc…) expressing various transgenes**
- ***Ex vivo* genetically modified cells**

Potential Safety Concerns for GT Products

- 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

Examples of Cancer/Therapeutic Vaccines

- **Conventional antigen-based vaccines**
  - **Synthetic peptides, protein antigens, tumor lysates, conjugated vaccines, etc…)**
- **Cell-based vaccines**
  - **Irradiated tumor cells**
  - **Dendritic cell (DC) vaccines**
  - **Tumor infiltrating lymphocytes (TILs)**
- **Genetically engineered vaccines**
  - **Viral, non-viral, or yeast-derived vectors expressing immunogenic molecules**
  - **Ex vivo modified immunologic cells (i.e. DCs, T & B cells, inactivated tumor cells)**

Potential Safety Concerns for Therapeutic Vaccine/Adjuvant Products

- **Systemic toxicity**
  - **Immune mediated toxicity - autoimmune response, induction of pro-inflammatory response/cytokine release, organ toxicity**
  - **Hypersensitivity/anaphylaxis**
  - **Potential “off-target” toxicity**
  - **Adjuvant related toxicity**
- **Local toxicity**
  - **Injection site reaction**

Preclinical Expectations for Early Phase Clinical Trials

- **Scientific basis for conducting clinical trial**
  - **Feasibility/establishment of rationale**
  - **"Proof-of-concept" (POC)**
    - **Establish pharmacologically effective dose(s)**
    - **Optimize ROA/dosing regimen**
    - **Provide rationale for species/model selection for further testing**

Preclinical Expectations (cont'd)

- **Safety of conducting clinical trial – risk/benefit**
  - **Recommend initial safe dose & dose escalation scheme in humans**
  - **Potential target tissue(s) of toxicity/ activity**
  - **Parameters to monitor clinically**
  - **Eligible patient population**

Preclinical Study Design(s) (1)

- 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

Preclinical Study Design(s) (2)

- **Consider clinical indication, patient population, product characteristics and delivery method**
- **Often studies have to be “individualized” to address specific safety concerns**
- **Apply the 3 R’s – Reduce, Refine, Replace**

Selection of Animal Species/Model (1)

- Comparative anatomy, physiology, age, etc… to humans
- Microenvironmental niche
- Route of administration - comparable to clinical
- [for GT] Permissive to vector transduction
- [for GT] Reactive to the expressed transgene
- [for CT or *ex vivo* transduced cells] Immune tolerance to the cells

Selection of Animal Species/Model (2)

- 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

Selection of Animal Species/Model (3)

- **The use of NHPs is NOT a default**
- **The use of multiple species (e.g. a rodent and a non-rodent) is NOT a default**
- **But scientific justification must be provided for the selection of the animal species/models used**

Use of Disease/Injury Animal Models to Assess Safety/Activity (1)

- **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 Disease/Injury Animal Models to Assess Safety/Activity (2)

- **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**

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 administrations, 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 abnormal findings
  - Correlate with vector biodistribution profile
  - Correlate with fate of the transduced/nontransduced cell

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, and histopathology**
    - **Pathologist blinded to treatment**

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

Preclinical Study Design: Functional Outcome

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

GT Biodistribution Profile

- **Determine potential for vector BD in germline, target, and non-target tissues**
  - **Distribution and persistence profile**
- **Determine the transgene expression profile in 'vector positive' tissues**
  - **Distribution and persistence 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

- **Survival/engraftment**
- **Integration (anatomical/functional)**
- **Differentiation/phenotype expression**
- **Transdifferentiation/de-differentiation**
- **Migration/trafficking (potential for ectopic tissue formation)**
- **Proliferation**

Influenced by local microenvironment…

Dose Extrapolation

- **Use the preclinical study data to recommend a starting clinical dose level and dose escalation scheme that are safe and biologically plausible**
  - **POC data – minimally active dose level**
  - **Safety data – NOAEL**
- **Calculate clinical dose levels based on**
  - **Fixed dose level (e.g., absolute dose)**
  - **Body weight**
  - **Organ mass (volume/weight)**

Preclinical Safety Evaluation Involving the Use of a Device

- **Is this device approved/cleared for the intended use?**
- **If not - has a Master File been submitted to CDRH?**
  - **Yes - Need to include a letter of cross reference in your IND**
  - **No - Need to consult with CDRH as to what data are required for submission**
- **Perform preclinical safety evaluation studies using the intended clinical device**

Findings Resulting in Possible Modification to Clinical Trial(s)

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

Preclinical Summary

- **Pharm/Tox studies should be:**
  - **Rational, problem-solving in study design**
  - **Assessed based on the best available technology, methods to date**
  - **Scientifically designed & judicious use of animals**
  - **Conclusions are data-driven**

Submit Complete Study Reports (1)

- Not just summarized statements
- Detailed description of the study performed
  - Test system (i.e. animal species/model)
  - Test articles/ROA/delivery system
  - Study methodology - dose levels, dosing schedule, dose procedure, test parameters, etc…

Submit Complete Study Reports (2)

- **Complete data sets for all parameters evaluated**
  - **Submit individual animal data for all parameters evaluated**
  - **Submit summarized and tabulated results**
  - **Submit your analysis/interpretation based on the resulting data**

Sources of Preclinical/Clinical Data to Support an IND

- GLP-compliant toxicology studies conducted by a certified testing facility
- Well-controlled studies conducted in house
- Published data in peer-reviewed journals
- Cross-reference to similar products in previously submitted MFs/INDs
- Detailed study reports from completed clinical trials conducted in the US or foreign countries

Early Communications

- **Pre-pre-IND interactions**
  - **Non-binding, informal scientific discussions between CBER/OCTGT nonclinical review disciplines (Pharm/Tox & CMC)**
- **Pre-IND meetings**
  - **Meeting emphasis - summary data and sound scientific principles to support use of a specific product in a specific patient population**

What About After the Clinical Trial has Started?

- **Sponsor can request pharmacology/ toxicology advice during product development**
  - **Formally via submission of amendments and/or informal discussions; for example:**
    - **Changes in manufacturing and formulation of the product**
    - **Changes in the clinical protocol (e.g. dose levels, ROA, dosing regimen)**

Contact Information

Presenter

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OCTGT Regulatory Questions

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Selected Guidances

- Guidance for Industry: Guidance for Human Somatic Cell Therapy and Gene Therapy (March 1998)
- Guidance for Industry: Gene Therapy Clinical Trials – Observing Subjects for Delayed Adverse Events (November 2006)
- Guidance for Industry (draft): Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage (July 2007)
- Guidance for Industry: Considerations for Plasmid DNA Vaccines for Infectious Disease Indications (November 2007)
- Guidance for Industry (draft): Somatic Cell Therapy for Cardiac Disease (March 2009)
- Guidance for Industry: Considerations for Allogeneic Pancreatic Islet Cell Products (September 2009)
- ICH S6: Preclinical Safety Evaluation of Biotechnology Derived Pharmaceuticals (July 1997)

http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/default.htm

Selected Advisory Committee Meetings

- **Cellular Products for Joint Surface Repair (March 3-4, 2005)**
- **Cellular Therapies Derived from Human Embryonic Stem Cells Scientific Considerations for Pre-Clinical Safety Testing (April 10-11, 2008)**
- **Animal Models for Porcine Xenotransplantation Products Intended to Treat Type 1 Diabetes or Acute Liver Failure (May 14, 2009)**

http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/CellularTissueandGeneTherapiesAdvisoryCommittee/default.htm