Development of Gene and Cell Therapies

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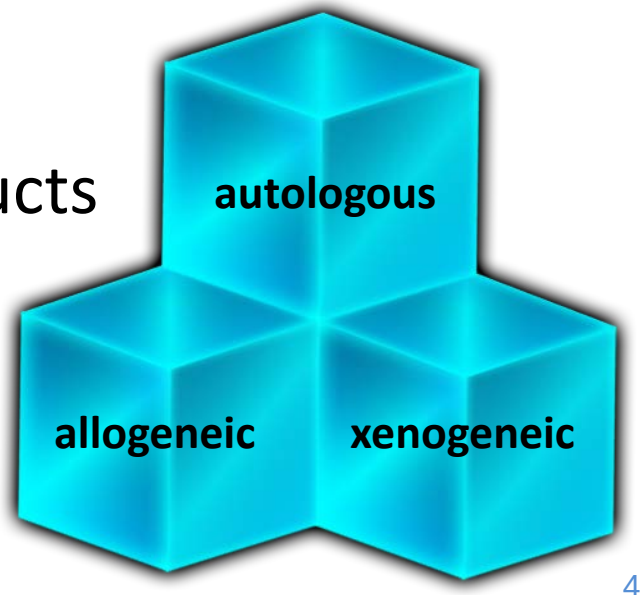
- I do not have any conflicts of interest

Regulatory Approach to Product Development

- Sufficient pre-marketing development program through the Investigational New Drug Application mechanism
    - expedited development programs and other incentives are available for diseases with unmet needs
    - product quality and consistency in manufacturing
- Substantial evidence of effectiveness
- Acceptable safety for the population with the disease or condition
- The available data demonstrate that the product's benefits outweigh its risks
    - at the time of approval, and
    - throughout the product's lifecycle

Examples of Cell Therapy Products

- Stem cell-derived products (adult, perinatal, fetal, embryonic, induced pluripotent)
- Somatic (functionally differentiated) cell-derived products
- Immune cell-derived products
- Genetically-modified cellular products



Examples of Gene Therapy Products

- Viral vector-based products
    - Replication-deficient
    - Replication-competent oncolytic
- Bacterial vector-based products
- Plasmid DNA products
- Genome-editing products

Considerations for Product Development

- Prolonged biological activity and the need for long-term follow-up
- Challenges with assessing the precise mechanism of action, evaluating product potency, and dosing
- Preclinical data may not always inform of all salient product's effects
- Cellular kinetics depends on the in situ microenvironment, disease state, concomitant medications, and intrinsic target cell distribution
- Immunogenicity
- Invasive procedures for product delivery; product-device biocompatibility
- Off target effects:
  - Unpredictable differentiation and proliferation (ectopic tissue and tumor formation)
  - Host responses to product administration (local and systemic)
- Vulnerable populations
  - Pediatric, rare diseases, the end of disease severity spectrum

Considerations for Product Development: Gene Therapies

- Vector persistence and biodistribution
- Expressed transgene persistence
- Viral replication, shedding, and excretion
- Insertional mutagenesis
- Genomic integration; germline transmission
- Immune responses to the vector or the expressed product

Risk-Based Approach to Product Quality

- Product characterization
  - Critical Quality Attributes
  - Safety of the source cellular material (donor screening and testing); Master Cell Banks; safety of the final product and intermediates
  - Product specifications and specific assays for sterility, identity, purity, and potency
  - Defining and limiting cellular phenotypes in manufacturing; evaluating potency for all active ingredients
  - Safety and product compatibility with the delivery system

- Process development, validation, and reassessment
  - Critical Process Parameters
  - Current Good Manufacturing Practices
  - Qualification program for all ancillary materials and reagents
  - Container closure systems
  - Refinement and scale-up during the product's lifecycle

Risk-Based Approach to Product Quality, Cont.

- Product characterization for gene therapy products
  - Derivation of the vector along with intermediate vector constructs (if any)
  - Analysis of the vector's annotated genetic sequence with relevant restriction sites and regulatory elements
  - Maintenance of Master Banks and Working Banks for cells and vectors

- Process characterization
  - Process qualifications with engineering manufacturing runs
  - In-process acceptance criteria and action limits
  - Terminal sterilization vs. qualified, validated aseptic manufacturing process
  - Lot release specifications

Considerations for Development of Patient-Specific Autologous or Allogeneic Cell Therapy Products

- High lot-to-lot variability reflective of patient-to-patient variability in cell behavior and quality
- Potential impact of disease state on cell function
- Timing for cell collection and “window” for treatment
- Challenges with demonstration of manufacturing consistency and product comparability with manufacturing changes
- It is important to distinguish the variability of the source material from the variability introduced by the manufacturing process to ensure consistent product output

Preclinical Evaluation: Scientific Basis and Safety for Conducting Clinical Investigations

- Objectives: Establish biological plausibility and feasibility of administration, identify safe and pharmacologically active doses, assess safety profile, and recommend potential parameters for clinical monitoring

- Preclinical evaluation may include animal testing, in-vitro testing, and in-silico testing, depending on product's characteristics
    - The 3Rs principle: the FDA fosters development of test methods and protocols that Reduce, Refine, and Replace animal use

Preclinical Evaluation: Considerations for Successful Product Development

- **Models of animals:** healthy and disease-related
  - Scientific justification for model selection
  - Comparative physiology and target tissue type and size helps with extrapolation to clinical dose levels
- **Product's kinetic profile:** vector biodistribution and cell fate
- **Route of administration:** as close as possible to the clinical scenario
  - Timing and rate of delivery, anatomical location, activity of the product in local micro-environment, cell viability
- **Standard toxicology assessments:** mortality, observations on treatment, body weights, gross and histopathology, and other endpoints, as recommended in the current guidances
- **Informative design:** randomized group assignments, appropriate controls, masked assessments, adequate study duration, and the assumption of product's persistence

Considerations for Product Dosing (examples)

Dose response curves may be flat or non-linear

Determination of dosing is aided by batteries of assays

- **Cell therapies** are often mixtures of different cell types
  - The total number of cells delivered, cell viability
  - The total number of a specific cell type per all cells delivered

- For **gene therapies**, transfection/transduction efficiency is an important characteristic of the dose
  - Number of transduced cells
  - Mean number of copies of vector sequences integrated per cell

- **Clinical trials** should consider:
  - Pre-specified range of exposure; appropriate dose measurements
  - Characterization of safety profile of the feasible doses
  - Scientific rationale for justification of dose escalation or de-escalation

Tumorigenicity: Risk Reduction Through All Stages of Development

- **Product**
  - Minimizing residual or undifferentiated cell types in the final product
  - Ensuring genetic stability of the cell lines and in vitro assessment for cytogenetic abnormalities; pre-specified cell passage level limit
  - Quality control testing for the product and process and appropriate master bank testing for source material
- **Preclinical**
  - Assessment in studies of sufficient duration
  - Appropriate animal models susceptible to tumor formation
- **Clinical**
  - Recognition of background tumor formation in disease populations
  - Long-term follow-up (where feasible in pre-marketing), clinical studies and registries, ensure interpretability

Considerations for Clinical Program Design: Efficacy

- Feasibility of product manufacturing and clinical administration should be addressed early on
    - For patient-specific products, trial analyses should account for both treatment effects and manufacture failures
- Large clinical trials with diverse populations vs. smaller clinical trials with specific patient populations
    - Early studies in patients rather than healthy volunteers
- Disease state, timing of treatment, and the immune system functionality
- In addition to clinical outcome measures, trial endpoints may need to include biological and immunological endpoints to further evaluate product's persistence and biological activity
- A well-designed natural history study may be a good alternative to concurrent control group(s) in rapidly progressing, serious, and rare conditions

Considerations for Clinical Program Design: Safety

- Dose-limiting toxicity may not be readily observable early in development
    - Duration of follow-up to be tailored to individual products
- Monitoring for immediate reactions to cellular and vector delivery
- Careful product administration
    - Staggering regimen; stopping criteria
- Monitoring for occurrence of graft-versus-host disease, autoimmune phenomena, cytokine release syndrome, engraftment syndrome, and other immune reactions
- Evaluation of product persistence and long-term effects
    - Appropriate measurements in body fluids and tissues, where possible
    - Clinical monitoring and imaging studies for ectopic growth
    - Recommendations for conditions of safe use and additional information gathering (long-term follow-up up to 15 years for gene therapies and life-time follow-up for xenotransplants)

Additional Considerations for Program Design

- Pediatric patients
  - Where possible, clinical programs should obtain safety and tolerability data in adults first
  - 21 CFR 50 requires determination of the level of risk and the prospect of direct benefit for treatments presenting greater than minimal risk
- Disease severity spectrum
  - Remaining functional reserve and anticipated risks
- Rare diseases
  - A well-designed and informative study with interpretable data permits enrollment of fewer patients

Goals of Product Development

- Evidence of effectiveness
  - Two adequate and well-controlled trials
  - One informative and interpretable trial may be sufficient with supportive data
- Quality and consistency in manufacturing
- Effective and safe dosing range to ensure accurate recommendations in the labeling
- Well-described risks with clinical recommendations for their prevention, monitoring, and treatment
- Safe and effective delivery by appropriately trained healthcare personnel
- Any associated companion diagnostics, devices, etc. co-developed in time and become available with the product

Conclusions

- Optimized product development for a cell or gene therapy requires understanding of clinical issues at the product design stage and product design issues at the clinical investigation stage

- Anticipated product risks are expected to be defined during the pre-marketing development with remaining uncertainties to be addressed in each subsequent stage of investigation and, where appropriate, in the post-approval stage

- Favorable benefit/risk product profile is best supported by the demonstrated benefit and by the monitorable, preventable, and treatable risks that are acceptable to patients

Selected Guidance Documents

- Recommendations for Microbial Vectors Used for Gene Therapy, 09/2016
- Design and Analysis of Shedding Studies for Virus or Bacteria-Based Gene Therapy and Oncolytic Products, 8/2015
- Considerations for the Design of Early-Phase Clinical Trials of Cellular and Gene Therapy Products, 6/2015
- Target Product Profile, 3/2007
- Preclinical Assessment of Investigational Cellular and Gene Therapy Products, 11/2013
- Preparation of IDEs and INDs for Products Intended to Repair or Replace Knee Cartilage, 12/2011
- Potency Tests for Cellular and Gene Therapy Products, 1/2011
- Cellular Therapy for Cardiac Disease, 10/2010
- Considerations for Allogeneic Pancreatic Islet Cell Products, 9/2009
- Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Gene Therapy Investigational New Drug Applications (INDs), 4/2008
- Guidance for FDA Reviewers and Sponsors: Content and Review of Chemistry, Manufacturing, and Control (CMC) Information for Human Somatic Cell Therapy Investigational New Drug Applications (INDs), 4/2008
- Expedited Programs for Serious Conditions – Drugs and Biologics, 5/2014
- Guidance for Industry: Gene Therapy Clinical Trials - Observing Subjects for Delayed Adverse Events, 11/2006

https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/CellularandGeneTherapy/default.htm

Public Access to CBER

- **CBER website:**
  - http://www.fda.gov/BiologicsBloodVaccines/default.htm
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- Learn Webinar Series:
  http://www.fda.gov/BiologicsBloodVaccines/NewsEvents/ucm232821.htm


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