CMC Challenges during Accelerated Development of Human Cell & Gene Therapy Products

A CBER Perspective

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CASSS Cell and Gene Therapy Products: Manufacturing, Quality and Regulatory Considerations
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Diversity of Cell & Gene Therapy (CGT) Products

**Gene Therapy Products (GTPs)**
- Ex vivo modified genetically engineered cells: stem cells, immune cells (CAR-Ts, NKT)
- Genome-edited T cells or stem cells
- Microbial Vectors; e.g., Listeria
- Viral Vectors; e.g., AAV, Ad
- Oncolytic viruses
- Tumor vaccines: peptides (tumor derived or synthetic), Plasmids, mRNA

**Cell Therapy Products (CTPs)**
- Stem cells: HSCs, MSCs, cord blood-derived etc.
- Cell products derived from pluripotent stem cells (iPSCs, ESCs)
- Pancreatic Islets
- Chondrocytes
- Keratinocytes
- Hepatocytes
- Xenotransplantation products
CGT products encompass a wide spectrum of products, each with its own concerns

**Common concerns**
- Mechanism of action, material qualification, challenges establishing specifications, manufacturing facility, product shipping/handling, major manufacturing changes

**Specific concerns**
- Product tracking and segregation
- High product variability
- Limited material or time for testing
- Short shelf life
- Manufacturing logistics
- Scale-out

- Donor eligibility
- Qualification of cell banks
- Reproducibility of replacement bank
- Stability of cell banks and intermediates
- Scale up
Lifecycle Approach to Product Development

Assurance of product quality increases with clinical development

- Implementation of complete cGMPs
- Process and assay qualification and validation
- Establishment of appropriate release criteria
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Challenges for accelerated development of CGT Products

• When a clinical program advances rapidly the timelines from early to late product development may be compressed

• Planning for product commercialization, including when comparability studies may be needed, should be conducted early

• Expedited development does not change regulatory requirements
CMC challenges for accelerated development of CGT Products

• Limited manufacturing experience:
  – Not many lots produced
  – Multiple rounds of process changes

• Limited in-process testing:
  – Process variables and critical process parameters (CPP) not known

• Limited product characterization:
  – Critical Quality Attributes (CQAs) not known
  – Limited knowledge of product- and process-related impurities

• Limited assay development (potency, purity)
• Limited product stability data collected
CGT Product Manufacturing is Complex

- There is often a need for significant in-process characterization.

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Manufacturing changes are inevitable

- React to a manufacturing problem or contamination
- Reagent or material is no longer available or in short supply
- Cell bank has expired or been exhausted
- Improve product quality based on new scientific or clinical information
- Switch to a more modern, more efficient or streamlined process
- Reduce costs
- Change can occur at any point in the product lifecycle, but you need to ensure that the change does not negatively impact product quality
Possible Changes During CGT Product Development

- Reagents, starting materials, components, manufacturing equipment
- Manufacturing processes
  - Change to suspension cultures
  - Change to stimulation method
  - Change to purification procedures
- Scale of manufacturing
- Manufacturing site
- Formulation
  - Buffer (cryopreservation, lyophilization)
  - Concentration
- Change in analytical testing procedures
Product Comparability

When changes are made to the manufacturing process, the sponsor generally evaluates the relevant quality attributes of the product to demonstrate that modifications did not occur that would adversely impact the safety and efficacy of the drug product.

Determinations of product comparability can be based solely on quality considerations if the manufacturer can provide assurance of comparability through analytical studies. Additional evidence from nonclinical or clinical studies is considered appropriate when quality data are insufficient to establish comparability.
Analytical Comparability Study Considerations

• Perform a risk assessment evaluating the impact of the change

• Assess attributes relevant to product quality and safety and most likely to be affected by the change

• Predefine acceptance criteria for comparability for each attribute being evaluated using appropriate, robust statistical methods

• Recommend making changes prior to initiating clinical studies intended to support efficacy for a marketing application (BLA)
  – If changes are introduced in late stages of development, the expected level of comparability demonstration will be significantly higher.
  – If analytical comparability study data are not sufficient to establish comparability, additional pre-clinical and/or clinical studies may be required to demonstrate comparable safety and efficacy.
Challenges for Establishing CGT Product Comparability

- Limited manufacturing experience:
  - Not many lots produced
  - Not enough retention or test samples available

- Limited in-process testing: process variables and CPPs not known

- Limited product characterization: CQAs not known, product and process related impurities not well characterized

- Limited assay development (e.g., purity, potency)
  - Assays not qualified or not stability indicating
  - Reference standards not established or adequately characterized
CQAs and CPPs are used together to help ensure quality and manufacturing consistency.
CGT Product CQAs

A Critical Quality Attribute (CQA) is a physical, chemical, biological, or microbiological property or characteristic that should be within an appropriate limit, range, or distribution to ensure the desired product quality. - ICH Q8 (R2)

• Explore many CQAs during early development
  • Report results early in development
  • Choose relevant tests for later phase studies

• Evaluate multiple measures of CQAs (especially potency)
  • Matrix of assays
  • Orthogonal methods
  • Stability indicating
Matrix Approach to CGT Product Testing

Biochemical
- Enzyme activity
- Protein expression

Immunological
- Immuno-typing (FACs)
- Cytokine expression (ELISA)

Cell-based
- Cell proliferation/killing
- Cell differentiation
- Cell viability

Animal-based

Biophysical
- Cell integrity
- Cell adhesion/morphology
- Viral capsid integrity and purity
- Protein structure
- Post-translational modifications
- Formation of aggregates

Nucleic acid-based
- qPCR
- Sequencing
- Transcriptional analysis RT-qPCR

In vivo: immune response

In vivo functionality: Expression/persistence/homing/targeting

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Assay Development Timeline

- **Preclinical**
  - Determine CQAs
  - Product characterization

- **Phase I**
  - Investigate Mode of Action

- **Phase II**

- **Phase III**

- **BLA**
Assay Development Timeline

- **Preclinical**
  - Investigate Mode of Action
  - Determine CQAs

- **Phase I**
  - Assay Development
    - Assay 1: X Reject
    - Assay 2: X Reject
    - Assay 3: X Reject
    - Assay 4: Validated

- **Phase II**
  - Development Qualification Validation

- **Phase III**
  - BLA

- **Product Characterization**
Assay Development Timeline

Preclinical
- Investigate Mode of Action
- Determine CQAs
- Concurrent & early assay development

Product characterization
- Assay development
  - Assay 1: X Reject
  - Assay 2: X Reject
  - Assay 3: X Reject
  - Assay 4: Validated

Phase I
- Investigate Mode of Action
- Determine CQAs

Phase II
- Investigate Mode of Action
- Determine CQAs

Phase III
- Investigate Mode of Action
- Determine CQAs

BLA
Common issues with CGT Product release specifications

• Specifications not capturing key product attributes (critical quality attributes)
• Criteria inconsistent with manufacturing experience
• Lack of supportive data or rationale
• Only measuring what you want and not what you don’t want
• Criteria set for a very wide range
  • Could add variability to clinical trial
  • May make it more difficult to qualify assays and processes
• Misinterpretation or over-interpretation of data
Impact of product variability

- There are advantages to targeting narrow versus wide tolerances for specifications
- Narrower tolerances make it easier to assess comparability

Goalpost

Narrow tolerances

Wide tolerances

Need to have a very good understanding of your process and product, with sufficient control points

Difficult to rely on just lot release specifications to show consistency and comparability
Potency Assay Challenges

• Mode of action may not be fully known
• Time constraints for release testing
• Limited material available to test
• Limited availability of reference standards and controls
• Cell-based assays can be highly variable
Changes to Analytical Testing

- Change in assay method
  - Assessment of how assays differ (output, sensitivity, reference material, etc.)
- Assay transfer or addition of testing sites
  - Demonstrate results are comparable between sites

- Side-by-side testing of the same material using both tests
- Establish comparability/correlation between the assay results
- May also impact stability studies
Stability Testing

- Carefully assess interference from components in the drug substance and drug product (residuals, excipients etc.)
- Include stability indicating assays
- Use new and sensitive technologies to characterize CGT Products stored under stress/accelerated conditions
- Device compatibility studies
  - Should include a measure of product strength/content and potency
  - Collect data using product doses, devices and conditions that will be used in the clinic
Summary

• The number of CGT Products being evaluated clinically has reached an all time high

• CGT Products are complex biologics requiring significant forethought regarding lifecycle management, particularly those in accelerated development

• Product and process characterization and assay development should be started early and continued throughout the product lifecycle
  – To develop a robust manufacturing process
  – To identify product CPPs and CQAs
  – To assist in the ability to establish product comparability

• Process and analytical testing changes are expected during the lifecycle of a CGT Product
  – Plan ahead, try to resolve potential CMC issues early in product development
  – When necessary, conduct thorough, well-designed comparability studies
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