Characterization of Cell/Scaffold Products

Workshop on *In Vitro* Analysis of Cell/Scaffold Products
December 6, 2007

Kimberly Benton, PhD
Deputy Director
Division of Cellular & Gene Therapies
Office of Cellular, Tissue, & Gene Therapies

Addressing scientific questions
and
meeting regulatory requirements
are not separate goals!

They are overlapping elements
of successful product development.

Successful Product Development

- Demonstrate product to be safe, pure, potent, effective and stable
- Full product characterization
- Demonstration of manufacturing and product consistency
  - Control of manufacturing process
  - Ensure continued production of quality products

Regulatory Requirements for Testing of Biological Products

- Safety
- Sterility
- Purity
- Identity
- Potency

} Focus of presentation

Must be performed on each lot prior to release for administration

Regulatory Requirements for Testing of Cellular Devices

- Safety
- Sterility
- Purity
- Identity
- Performance

Focus of presentation

Must be performed on each lot prior to release for administration

Common Goal:
Characterization of cell/scaffold products at physical, structural, chemical, and functional levels

Cell/Scaffold Products are complex, dynamic and heterogeneous

- Products consist of multiple components with testing challenges
  - Living cells/viable tissues
  - Scaffold component
  - Dynamic combination of cells and scaffold
- How to perform in vitro analysis of interactive product parameters?

Cell/Scaffold Products are complex, dynamic and heterogeneous

- Some products have a lot size of 1
  - will require non-destructive tests
  - or production of a surrogate for testing
- Product Remodeling occurs after implantation
- Patients will differ in their capability for tissue remodeling
  - to what extent can this be assessed, controlled?

Gaining Control of a Complex, Dynamic, Heterogeneous Product

- Achieved by design of manufacturing process
  - starting materials, reagents, procedures, controls
- Assessed by development of in-process and final product testing and acceptance criteria
- Important when assessing product stability and comparability
- Important to interpretation of clinical data

Testing and Characterization of Cell/Scaffold Products

- Component testing and characterization
  - Scaffold components
  - Cellular components
- In-process testing
- Final product testing

Cell/Scaffold Component Testing and Controls- Scaffold

- Scaffold Components
  - Material & component description
    - Composition, purity, MW, density,
  - Mechanical properties characterization
    - Biomechanics, durability
  - Materials characterization
    - Surface characterization, dissolution, degradation, stability, adhesion testing for cells
  - Preclinical safety characterization
    - Biocompatibility

Cell/Scaffold Component Testing and Controls- Cells

- Cellular components
  - Cell/tissue source may introduce high degree of variability into starting material
    - What can you control about starting cells/tissue?
    - What test methods can you use to assess control?

In-Process Testing of Cells

- Test cells during different points in manufacturing
  - Cell Banks (where applicable)
  - During expansion/differentiation of cells
  - At time of seeding cells onto scaffold
- Microbiological testing- sterility, mycoplasma

In-Process Testing of Cells

- Characterization
  - Morphology
  - Phenotype
  - Cell number
  - Viability
  - Purity
  - Potency/Biological Activity

Final Product Testing

- Final cell/scaffold product -prior to implantation
  - Microbiological testing
    - sterility & endotoxin- construct container media, shipping media
  - Characterization -examples
    - Physical dimensions, volume, weight, appearance
    - Consistency of cell/tissue growth & scaffold coating
    - Potency/Biological Activity

Product Identity
Biologics: 21 CFR 610.14

- Test specific for a designated product
- Distinguish from any other product processed in facility
- Physical or chemical characteristics, macroscopic or microscopic assay,
  - morphology, cell surface markers of cells

Product Purity
Biologics: 21 CFR 610.13

- Pyrogenicity/Endotoxin
- Phenotypic Analysis of Cell types
  - Quantitative assessment of each cell type present
- Cell Viability
- Residuals from manufacturing
  - Media Components
  - Activating Agents
  - Chemical Agents

Product Potency
Biologics: 21 CFR 610.10

- 21 CFR 600.3 (s):
- The word potency is interpreted to mean the specific ability or capacity of the product…to effect a given result.

- 21 CFR 610.10:
- Tests for potency shall consist of either in vitro or in vivo tests, or both, which have been specifically designed for each product so as to indicate its potency…

Goal of Potency/Biological Activity

- Demonstrate that each product “lot” manufactured has the same biological activity
- Demonstrate product consistency
  - Lot to lot, Patient to patient
- Demonstrate product stability
- Interpretation of clinical data

Potency Assay Attributes

- Indicate biological activity(s) specific/relevant to the product
- Provide quantitative readout
- Results available for release of product
- Predefined acceptance and/or rejection criteria
- Include appropriate reference material/controls
- Validated for licensure
- Indicate product stability

Approaches for Potency Measurements

- Biological activity directly measured, or
- Surrogate characteristic measured
  - Demonstrated to correlate with biological activity
  - Sufficient, statistically sound data
    - preclinical/proof of concept data
    - In vivo animal or clinical data
    - in vitro cellular or biochemical data
- Multiple Assay (Assay Matrix)
  - combined results constitute potency measurement

Matrix Approach for Potency Measurements of Cell/Scaffold Products

- Characterization of cells when seeding onto scaffold
- Final cell/scaffold product
  - Viable cell density on scaffold
  - Protein synthesis by cells (extracellular matrix, growth factors)
  - Metabolites
  - Physical properties of cell/scaffold construct
- Correlated to intended biological activity through in vitro, pre-clinical, and/or clinical data

What Cell Characteristics to Measure for Potency?

- Simple cell identity markers may not change under conditions that affect cell function
- Need to identify functional biomarkers
  - Correlate with cell survival
  - Correlate with in vitro differentiation
  - Detect unacceptable behavior of cultured cells
  - Detect functional cells in complex mixture

- Develop genomic or proteomic techniques to identify functional biomarkers?

Stability

- Maintain product safety, identity, purity, and potency for expected period of use
- Establish dating period
- Establish storage and shipping conditions
- Evaluate holding points in manufacturing

Need appropriate tests with capacity to detect product degradation

Comparability

- Manufacturing changes may affect product safety, purity, potency, clinical effectiveness
- The need to make changes may be unexpected
  - starting materials: reagents, cell bank
  - manufacturing site
- If your preclinical studies use analogous animal cells, what test methods can you use to show comparability of animal and human product?

Need appropriate tests with capacity to assess effects of changes

Reconciling Regulatory Requirements with “Real World” Needs

- Each “lot” must be tested prior to release
- Limitations:
  - Samples available for testing
  - Time: Final results of testing often not available for product release
  - Complex nature of cell/scaffold product

Reconciling Regulatory Requirements with “Real World” Needs

- Approaches:
  - Component and In-process testing
  - Testing samples from surrogates or construct media
  - Development of rapid test methods and new technologies
  - Matrix approach
    - Complementary assays to meet goals of identity, purity, potency
    - Assays not used for release testing that can be used for stability, comparability, making correlation for other assays

Link between Assay Development and Product Development

- Assay development should at a minimum keep pace with product development
- Generate data to inform manufacturing process
- Generate data to inform pre-clinical testing
- Generate data to design clinical studies

References

- Advisory Committee Meeting: Potency Measurements for Cell and Gene Therapy Products

  http://www.fda.gov/ohrms/dockets/ac/cber06.html#CellularTissueGeneTherapies
- FDA Draft Guidance for Reviewers: Instructions and Template for Chemistry, Manufacturing, and Control (CMC) Reviewers of Human Somatic Cell Therapy Investigational New Drug Applications (INDs) (2003) at http://www.fda.gov/cber/gdlns/cmcsomcell.pdf
- Guidance for Human Somatic Cell Therapy and Gene Therapy- 3/30/1998 http://www.fda.gov/cber/gdlns/somgene.pdf