Characterization of Cell Therapy Products

Well Characterized Biological Products

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Overview

- Product characterization
  - 21 CFR 610 Biological Product Standards
- Unique challenges for cell therapy products
  - Identity
  - Purity
  - Potency
- Use of matrix of assays

Regulatory Requirements for Product Characterization

- All cellular products regulated as Biologics under Section 351 of PHSA must meet the General Biological Product Standards in 21 CFR 610 for licensure

Part 610 Test	Test Method	Test Timing	Specification
Sterility	Specified	Final Product	Negative
Mycoplasma	Specified	Final Product**	Negative
Purity (pyrogenicity)	Specified	Final Product	Pass
Identity	Not Specified*	Final Product	Product Specific*
Potency	Not specified*	Final Product	Product Specific*
Others as needed (ex: viability, cell dose, phenotypes)	Not Specified*	Final Product	Product Specific*

*To be developed by product manufacturer

** Recommend testing at cell harvest. Refer to 1993 PTC.

Good News & Not-so-good News for Purity, Identity, Potency

- Good News
  - Regs allow flexibility to develop product-specific assays and release criteria
- Not-so-good News
  - It’s not easy to develop product-specific assays and release criteria
  - Limited “success stories” to use as examples or to develop regulatory policy and guidance

Challenges in Developing Assays for Cellular Products

- Limited material to test
  - Lots are often patient-specific, limited doses
- Limited time to test
  - Many products administered within hours of harvest
- Limited stability of product
  - Storage/holding may effect viability, potency, etc.
- Limited availability of reference standards
- Product variability due to inherent variability in starting cells or tissue

Purity- 21 CFR

- 600.3 (r): Purity means relative freedom from extraneous matter in the finished product, whether or not harmful to the recipient or deleterious to the product. Purity includes but is not limited to relative freedom from residual moisture or other volatile substances and pyrogenic substances.

- 610.13: Products shall be free from extraneous material except that which is unavoidable in the manufacturing process…

Purity

- Endotoxin and pyrogens
- Residual solvents, antibiotics, animal products, growth factors, etc.
  - Validate removal, or
  - Develop & validate appropriate detection methods
- “Contaminating” cell populations
  - May have positive or negative effect on product quality and efficacy
  - Quantitative assessment of each cell type present

Identity- 21 CFR 610.14

- The contents of the final container of each filling of each lot shall be tested for identity after all labeling operations have been completed
- The identity test shall be specific for each product in a manner that will adequately identify it as the product designated on final container and package labels and circulars and distinguish it from any other product being processed in the same laboratory

Identity- 21 CFR 610.14 continued

Identity may be established either through:

- Physical or chemical characteristics
- Inspection by macroscopic or microscopic methods
- Specific cultural testing
- In vitro or in vivo immunological tests

Identity

- If product is comprised of multiple components (e.g. cell lines) then identity test method should identify all

- Autologous or patient-specific allogeneic products
  - Should identity testing be HLA or other genotyping to match to subject?

Discussion point for Workshop

Potency- 21 CFR

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…

Potency Assay Requirements

- Results should be available before the product is released
- Results should show the ability to effect a given result

Potency Assay Wish List

- Results are quantitative
- Results are stability indicating
- Results measure a biological activity that correlates with clinical function
- Results ensure lot-to-lot consistency
- Results are not highly variable

Potency Assay Development

- During preclinical and early clinical development, justify the critical biological activity of the product and develop an approach to potency determination
- No later than start of Phase III, potency assay should be in place
- Full validation in license application

Matrix of Assays for Potency

- For many cellular products the most appropriate potency measurement may be a matrix of several correlative assays
  - e.g. using a qualitative assay in addition to quantitative assay
- Why?
  - If assay that best measures biological activity is not quantitative
  - If quantitative assay does not correlate with biological function

Examples of Different Potency Approaches

- Functional assays
  - Cytotoxicity, cytokine release, antigen presentation, in-vivo immune response
- Analytical assay correlated to function
  - Phenotype correlated with cytotoxicity
  - Protein or RNA expression correlated with in vivo activity
- Matrix of assays correlated with function
  - Viability and phenotype correlated with cytokine release
  - Tumor antigen levels and binding correlated with antigen presentation

Cross-Over Between Product Characterization Parameters

- Assays intended to measure one parameter may be relevant to another parameter

Example:

Flow cytometric assessment of cell phenotype for purity may link to identity and/or potency

Status of Cell Product Characterization

- Many cellular therapy manufacturers are performing minimal characterization assays
  - Reason: Assay development is difficult, time-consuming, and expensive
  - Problem: Limits knowledge of your product and may hamper development in the long-term
  - Solution: find a better balance
    - Determine product parameters that:
      - Affect clinical efficacy
      - Demonstrate product integrity and stability
      - Can be used in comparability studies

Summary

- Importance of product characterization
  - Meet CFR Requirements
  - Gain valuable knowledge of your product
- Challenges
  - Developing product-specific assays
- Solutions
  - Matrix approach for single parameter or across parameters

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