Release Testing of Cell Therapy Products

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What is Release Testing?

For products regulated as biological products under section 351 of PHS Act

- 21 CFR 211.165 Testing and release for distribution

  (a) For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient, prior to release.

- 21 CFR 610 - General Biological Product Standards

Tabulation of Relevant Product Release Tests

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.

Purity

- The final product endotoxin and pyrogen levels must be below acceptable limits.
- Residual solvents, antibiotics, animal products, should be minimized
  - Validate removal or test for residuals using appropriate detection methods
- Quantitative assessment of all cell types including non-therapeutic populations

Identity

- Develop appropriate identity assay specific for the product
- If the product is comprised of multiple components (e.g. cell lines), then test method should identify each component
- Distinguish the final product from other products produced in the same facility

Potency

- **21 CFR 600.3(s)**

  "…potency is interpreted to mean the specific ability or capacity of the product, as indicated by appropriate laboratory tests or by adequately controlled clinical data obtained through the administration of the product in the manner intended, to effect a given result."

Potency

- **21 CFR 610.10**
  - "…shall consist of either *in vitro* or *in vivo* tests, or both, ..specifically designed for each product so as…. to satisfy the interpretation of potency given by the definition in 600.3(s) of this chapter."

Potency Assay

- Ideally, a quantitative bioassay that measures biological function associated with the *in vivo* mechanism of action
- If biological function can not be quantified, rationale must be provided for other approaches to ensure product potency
- By Phase III, a product specific potency assay should be in place

Potency - Examples

- Biological assay which reflects relevant function of product
  - Cytotoxicity assays (activity of a cell type)
  - Cytokine release assays
  - Expression of transgene/protein
- Correlate assay to function
  - Cytotoxicity correlated with phenotype
  - Activation correlated with expression of protein
  - Function correlated with viability and phenotype

Additional Product Characterization

- Stability of final product
- Cell morphology
- Gene/protein expression
- Cell viability
- Biological Activity-
  - other than that measured for potency

Release Testing Issues for Cell-Based Products

- Each “lot” of a biological product is required to be tested prior to release
- Product potency for living cell products may be compromised by extensive assay times
- Test sample volume may adversely affect therapeutic dose

Release Testing Solutions for Cell-Based Products

- Rapid, sensitive, and reliable test methods
- Some flexibility in how/when testing is done and availability of results

Alternatives to Standard Test Methods

- Biological product regulations allow use of “equivalent methods and processes” (21 CFR 610.9) if they are equal to or greater than the assurances provided by the specified method
- Validate to show equivalency by end of Phase III
- Potential approach: perform “old” test concurrent with “new” rapid test to obtain data during product development

Potential Types of Alternative Tests

- Rapid Analytical Methods - Examples
  - Sterility tests
    - Colorimetric, biochemical, NAT, etc..
  - Viability
    - O_2 consumption, ATP-bioluminescence, ELISA
  - Purity/Identity
    - Imaging, FACS, Gene expression profile, etc..
  - Mycoplasma – PCR increasingly used
  - Pyrogenicity – endotoxin by LAL widely used

Summary

- Lot release testing for cell-based products often presents challenges
- Development of rapid and reliable alternative test methods is encouraged
- Before using alternative test methods, consult with the Agency and refer to appropriate guidance documents and 21 CFR 610.9

CBER Contact Information

Reference documents and contact information for the Office of Cellular, Tissue and Gene Therapies (OCTGT) can be found at:
http://www.fda.gov/cber/genadmin/octgtprocess.htm

Additional CBER regulatory and guidance documents are available at:
http://www.fda.gov/cber/guidelines.htm