Regulatory Requirements for Safety Testing of Cell Therapy Products

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ISCT 2011
Rotterdam
Cell Therapy Product Development Pathway

- Stage of product development determines key aspects of regulatory review. **Safety is a consistent, critical focus throughout product development.**

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US FDA OCTGT
Safety Considerations for Cell-based Products

• Infection, infectious disease transmission
  – Microbial contamination of starting material, or in processing
  – Adventitious agents (donor origin or other raw materials)
• Tumorigenicity, cell transformation
• Immunogenicity, rejection
• De-differentiation, loss of function
• Ectopic distribution to non-target tissues

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EMA CAT
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Elements of Characterization Testing

• Based on requirements described in 21 CFR 610

• Safety
  – Sterility, endotoxin, mycoplasma, adventitious agents
  – Emphasis on microbiologic safety

• Purity, Identity
  – Cell viability, concentration, morphology, immunophenotype, gene expression, karyotype, other

• Potency
  – Relevant biological function

• Stability

• Tumorigenicity, karyotype

• Reagents/ancillary materials, excipients
Safety Testing I

• Sterility cultures
  – Minimally manipulated products - aerobic culture only
  – More-than-minimally manipulated - aerobic, anaerobic, and yeast/fungal cultures
  – Automated blood culture methods acceptable, validate against CFR 610 or USP sterility by Phase III

• Endotoxin
  – Multiple analytical methods - gel clot, endpoint chromogenic, kinetic chromogenic or turbidimetric, Endosafe PTS
  – Specification <5 EU/Kg/hr for i.v. administration

• Mycoplasma
  – Rapid PCR-based assay may be used, if validated against 28-day Points-to-Consider method
Safety Testing II - Adventitious Agents

- Testing for human-derived adventitious agents based on blood donor screening panel
  - HIV-1/2
  - HBV surface and core antigens
  - HCV
  - *T. pallidum*
  - HTLV-1/2 and CMV (if cells or tissues contain viable WBC)

- Tests must be FDA-licensed, approved, or cleared

21 CFR 1271
Safety Testing Strategy

• Cryopreserved products
  – Thaw and administer product when release testing complete
  – Release testing performed on pre-cryopreservation product
    • Validate cryopreservation and thaw
    • Product thawed and administered \textit{without further testing} (!)

• Limited-stability products (non-cryopreserved)
  – Culture 24-48 hr pre-harvest, repeat at harvest
  – Release based on negative 24-hr or 48-hr culture (final results pending), Gram stain and endotoxin at harvest
    • Gram stain has poor sensitivity, high false-positive rate in this setting
  – Policy and action plan for positive culture results, other QCT failures, obtained after product administration
Animal-derived Reagents May Increase Testing Requirements

• More extensive adventitious agent testing may be required if cells extensively expanded or exposed to animal-derived materials
• Species-specific viral testing if using certain animal-origin materials
• Growth on xenogeneic feeder cell layers creates potential for retroviral and zoonotic contamination
• Monoclonal antibodies used for cell isolation have potential to introduce adventitious agents - uncommon
• Animal-origin materials require additional qualification and documentation, particularly if bovine-derived
# Cell Bank Testing

<table>
<thead>
<tr>
<th></th>
<th>Master Cell Bank</th>
<th>Working Cell Bank</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Sterility</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>• Mycoplasma</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>• Human pathogen testing</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>• Adventitious agents, species-specific virus testing</td>
<td><em>In vitro and in vivo</em></td>
<td><em>In vitro</em></td>
</tr>
<tr>
<td>• Tumorigenicity (if required)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>• Retroviral testing (if required)</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td><strong>Purity/identity</strong></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>Stability</strong></td>
<td>✓</td>
<td></td>
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</tbody>
</table>
Adventitious Agent Testing

- **In vitro testing**
  - Culture in 3 cell lines capable of detecting potential viral agents, at least one human cell line and one of reagent/product species

- **In vivo testing**
  - Inoculate with cell lysate
  - Test in adult and suckling mice, guinea pigs, hen eggs

- **Species-specific virus testing**
  - Bovine, porcine, murine, etc.
  - Antibody production testing
    - i.e., MAP testing for cells in contact with murine tissues or products
Tumorigenicity Testing

• Required for cell therapy products with potential risk of tumorigenesis
  – Cell banks isolated from certain types of stem cells, from genetically modified cells, or from extensively expanded cells

• Tumorigenicity testing should be performed under conditions that resemble the intended use of the cells
Summary

• Safety is a major concern throughout cell therapy development. Safety testing encompasses cells, tissue, cell banks, and materials/reagents.

• Turnaround time and complexity of certain assays present additional challenges.

• Nature and extent of safety testing depends in part on the manufacturing process, clinical application, and cell properties.
Resources

- Good Manufacturing Practices: 21 CFR parts 210, 211, 225, & 226
- Biological Product Regulations: 21 CFR parts 600, 601, & 610
- Tissue Rules: 21 CFR 1271
- Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products
  - www.fda.gov/cber/gdlns/tissdonor.htm
- 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)
  - www.fda.gov/cber/gdlns/gtindcmc.htm
- Assay Validation International Conference on Harmonization; Validation of Analytical Procedures: Methodology; Q2B, 1996
  - www.fda.gov/cder/guidance/ichq2b.htm