Ancillary Materials for Cell & Tissue Therapies

Definitions, US Regulatory Approach, and USP’s Risk-Tiered Approach

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Definitions

**USP chapter <1043>**

Ancillary materials are materials that

- Come into contact with the cell or tissue product during manufacturing, but
- Are not intended to be part of the final product formulation

Although not formally defined by FDA, ancillary materials

- Are a subset of “components” as defined in cGMPs
- Also include materials in containers/closures that come into contact with the product during processing
### Distinction of Ancillary Materials from Other Components

<table>
<thead>
<tr>
<th>Cell/tissue source</th>
<th>Ancillary Material</th>
<th>Excipient</th>
<th>Device (or Other) Component of Combination Product</th>
</tr>
</thead>
</table>
| • Source of cells that are processed to become the active ingredient in the final product | • Material that comes into contact with product during manufacturing, but is NOT intended to be in the final product | • Inactive ingredient that IS intended to be in the final product | • Material normally classified as device (or drug) that IS intended to be part of final product  
  • *e.g.*, *structural component or delivery device* |
Common Ancillary Materials

**Reagents**
- Anticoagulants
- Buffered solutions & culture media
- Cryoprotectants
- Cytokines
- Antibiotics
- Antibodies and peptides
- Paramagnetic beads
- Enzymes
- Human or bovine serum
- Cell lines for Ag presentation, etc

**Containers & Closures**
- Bags & transfer tubing
- Culture flasks
- Plastic disposable sets for processing
Importance of Ancillary Materials

- **Impact on product potency, quality, purity**
  - What are intended effects?
  - Are there unintended effects of material and impurities (adventitious agents, endotoxin, etc.)?
  - What is effect of supplier-to-supplier and lot-to-lot variability?

- **Availability**
  - Are they commercially available or do you need to custom manufacture?

- **Residual removal & testing in final product**
  - Failure to remove residuals may affect product safety and efficacy
  - But extensive measures to reduce residuals may impact product
  - Residual testing in final product may not be possible in rapid release products
How does the US FDA regulate ancillary materials?

361 HCT/Ps

- cGTP regs & guidance
- Supplies & reagents
- No prospective reviews, but subject to cGTP facility inspections

351 HCT/Ps

- cGMP regs & guidances
- Control of components, containers and closures
- “Sliding scale” approach to cGMP compliance ph 1-4
- Somatic cell therapy CMC guidance
- Prospective review of IND, BLA (and related inspections)
FDA requirements for ancillary materials 361 vs 351 HCT/Ps

<table>
<thead>
<tr>
<th>Requirement</th>
<th>361 HCT/Ps</th>
<th>351 HCT/Ps</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specifications (establish specifications and verify that material meets criteria)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Records (receipt, testing &amp; acceptance storage, use in manufacturing)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Qualification program (more detailed)</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Identity testing</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Specific requirements for human and animal-sourced reagents (donor screening and/or testing and/or sourcing information)</td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Residual reagent (qualification of removal method or testing each final product lot)</td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
US Pharmacopeia

- Independent, science-based, nonprofit public health organization
- Founded 1820 - Oldest pharmacopeia in the world
- Establishes written (compendial) and physical (reference) standards for medicines
- Standards for medicinal products are enforceable by FDA, but USP does not enforce
USP Approach to Ancillary Materials

General Information Chapter (Guidance)

Requirements for Specific Ancillary Materials

Ancillary Material Reference Standards

<1043> Ancillary Materials for Cell, Gene, and Tissue Engineered Products

Specific AM Chapters
<1024> Bovine Serum
<90> FBS Quality Attributes
<92> Cytokines and Growth Factors Quality Attributes
<123> Protein A Quality Attributes

Reference Standards
FBS
Interleukin-4
Protein A
USP Risk-Based Classification of Ancillary Materials

**Tier 1** – Low-Risk, Highly Qualified Materials with Intended Use as Therapeutic Drug or Biologic, Medical Device, or Implantable Material

**Tier 2** – Low-Risk, Well Characterized Materials with Intended Use as AMs, Produced in Compliance with GMPs

**Tier 3** – Moderate-Risk Materials Not Intended for Use as AMs (frequently produced for in vitro diagnostic use or reagent grade materials)

**Tier 4** – High-Risk Materials, Materials Not Produced in Compliance with cGMPs, and Materials Not Intended to be Used in Cell Manufacturing
Ancillary Material Qualification & Risk Reduction Activities by Risk Tier

<table>
<thead>
<tr>
<th>Activity</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>DMF cross reference (when possible)</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Certificate of analysis</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Assess lot-to-lot effect on process performance</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Assess removal from final product</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Assess stability as stored for use in manufacturing</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Confirm COA test results when critical to product</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Vendor audit</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Upgrade manufacturing process to GMP</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Develop stringent internal specifications</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Determine if lot-to-lot comparability testing is needed</td>
<td></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Verify traceability to country of origin</td>
<td></td>
<td></td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Assure country of origin is safe for animal diseases (e.g. TSE)</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
<tr>
<td>Adventitious agent testing for relevant animal viruses</td>
<td></td>
<td></td>
<td></td>
<td>✓</td>
</tr>
</tbody>
</table>
Example
FT1050 as a critical ancillary reagent in the manufacture of ProHema™-CB
FT1050

- Small molecule: synthetic analog of prostaglandin E2
- Potent regulator of hematopoiesis in all vertebrate species (Zon lab, Harvard)
- *Ex vivo* incubation of HSCs with FT1050 enhances their homing, engraftment & proliferation in rodent and non-human primate models
- Used as the key ancillary reagent for manufacture of ProHema™-CB (*ex vivo* CXCR4-upregulated CD34+ hematopoietic stem cells from cord blood), in phase 1-2 clinical trials
Incubation of HSCs with FT1050 enhances their homing, engraftment, and proliferation and is associated with upregulation of CXCR4.
Use of FT1050 in Manufacture of ProHema™-CB

- CBU Thaw
- CBU Post Thaw
- Wash #1
- CBU Post Wash
  - Incubate w FT1050
- CBU FT1050 Mod
  - Wash #2
- ProHema -CB
  - Filter & Rapid Release
Approach to FT1050 as critical ancillary reagent

- Manufacturer: CMO on behalf of Fate Therapeutics
- cGMP manufacture, according to sterile pharmaceutical standards
- Although a well-characterized small molecule, manufacturing & qualification require a high level of expertise
FT1050 Specifications (COA)
Progressively developed from phase 1 to 3 to ensure consistency and performance of manufacturing process

- Appearance of reagent and package
- pH
- Particulates
- Identity (HPLC)
- Purity (HPLC)
- Individual & total related substances (HPLC)
- Manufacturing variation
- Endotoxin
- Sterility
- Container-closure integrity
FT1050 Development Activities from Phase 1 to 3

• Prepare reference standard (identity and lot-to-lot comparability)
• Refine specifications for related substances
• Assess stability
  – In recommended and accelerated storage conditions, and in-use conditions at key processing steps
  – Protocol design according to FDA & ICH guidance for sterile parenteral products
• Assess FT1050 residuals in final cell product
• Assess lot-to-lot effect on process performance
  – Relationship between reagent (at specified concentration) and product potency
  – Robustness of FT1050 effect across range of starting cell sources (normal donor CBUs)
FT1050 Additional Development Activities

- Optimize formulation (excipient, concentration, dose form) for use in cell product manufacturing
- Optimize container/closure for use in cell product manufacturing (closed system)
- Identify & engage backup manufacturer
- Establish labeling and instructions/training for use in cell product manufacturing
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