Raw Materials Sourcing and Qualification

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Raw Materials Sourcing and Qualification
Workshop Topics

- Definition of materials
- Regulatory considerations
- Sourcing
- Selection
- Supplier qualification
- QA agreements
Raw Materials Sourcing and Qualification Workshop Topics (cont.)

- Raw material specifications
- Change control
- Qualification testing
- Materials management
- Qualification and control across multiple manufacturing sites
Raw Materials and Supplier Qualification

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This session will cover the following topics...

- Definitions
- Regulatory considerations
- Reagent selection
- Supplier qualification
- Quality agreements
- Materials management
Why is rigorous qualification necessary??

- Qualification matters because the materials used in manufacturing affect the safety and quality of the final cell therapy product.

- Companies manufacturing materials for use in cell therapy products are sourcing globally, therefore the need to control the supply chain is crucial. National regulations, standards and approaches to quality can vary greatly.

- As the manufacturer and distributor of a cell therapy product you are ultimately responsible for the quality and control of all raw materials.
Raw Materials

- Cells, tissues
- Reagents
- Critical components

Qualification should be in place for all!
Reagents

■ Ancillary materials
  ● Used in the manufacturing, but not intended to remain in final product (e.g. cytokines, serum, buffers, enzymes)
  ● May affect safety, purity, potency of final product
  ● Removed from final product; need to consider qualifying removal

■ Excipients
  ● Intentionally present in final product (e.g. cryopreservation solutions, HSA, infusion media)
Critical Components

■ Devices
  ● Biomaterials (animal-derived, synthetic)
  ● Scaffolds
  ● Delivery systems

■ Materials used in manufacturing process
  ● Culture containers, systems
  ● Cryopreservation bags
  ● Direct product contact
Regulations and Standards

- **21 CFR 1271.210**
  - Design reagent specifications to minimize risk of “introduction, transmission, or spread of communicable disease”
  - Reagents must be sterile

- **21 CFR 211.80 - 211.89**
  - More rigorous inventory control described: quarantine, release, FIFO
  - Re-testing program: identity, sterility
  - Typically tighter control for later phase and commercial products

- **21 CFR 820**
  - Purchasing controls
  - Evaluation of suppliers, contractors and consultants
Regulations and Standards

- **USP General Chapter <1043>**
  - Ancillary Materials for Cell, Gene, and Tissue-Engineered Products, Pharmacopeial Forum 30 (2) 2004
  - Guidance for reagent qualification program
  - Risk classification scheme

- **FACT**
  - Controlled materials management system
  - Reagents must be sterile and of the appropriate grade for intended use

- **AABB**
  - Evaluation of suppliers
  - Define extent of control of suppliers. Depends upon the type of material or service, the impact of the material or service on the quality of the cellular therapy product or final service, and the previous performance of the supplier.
Raw Material Selection

- Sterile, pure and potent

- Must work in your manufacturing process – tech transfer, process development, and clinical scale-up

- High quality
  - FDA approved or clinical grade
  - GMP manufactured
  - USP components used in manufacturing
Raw Material Selection (cont.)

- If material is animal-derived,
  - TSE concerns, documentation of country of origin important
  - Rigorous qualification and testing program should be in place

- Human derived blood products – HSA, serum
  - From qualified blood centers; adventitious testing, sterility
  - Ensure adequate donor pool
  - No recalled lots
Supplier Selection

- Companies with good performance history
  - Research vendors/manufacturers
  - Review literature and data to ensure supplier has established record in the industry
  - Talk to your peers. Have they used the material and would they recommend it? Have they had issues with a particular supplier?

- Need reliable suppliers and consistent supply
  - Is this a sole supplier, do you need back-up supplier(s)?

- Cost is a factor but need to balance with material quality

- Determine composition of material, or cross reference FDA master file
Supplier Qualification

Why?

- Ultimate responsibility for material quality is the manufacturer of the final cell therapy product; you need to understand how manufacturers control the quality of their materials.

When?

- Implement program early in clinical development before IND - qualification can take time, especially if manufacturers do not meet qualifications, and you need to find alternative suppliers.
- If GTP manufacturer, and a formal supplier qualification program is not in place, develop SOP, start with critical materials; focus on safety; need more than COA to determine supplier quality.

Who?

- Risk-based, tiered approach (e.g. USP model); qualify suppliers of high risk materials first.
Supplier Qualification (cont.)

- **How?**
  - Need resources to manage this activity; should be under the direction of QA
  - For GTP products in hospital/academic setting consider leveraging expertise in blood bank/transfusion service

- **Steps in the process:**
  - Initiate communication with supplier
  - Submit supplier questionnaire
    - Business overview
    - Facility details
    - Regulatory history
    - Regulatory/quality system requirements – develop a checklist
  - Perform audit, as needed
Supplier Audits

- Responsibility of QA unit
- Determine frequency
  - Initially, then every 2-3 years, or when deemed necessary
- Using a risk-based approach determine which suppliers require audits
- Determine audit scope, send letter to supplier requesting audit, schedule date
  - Include agenda for day of
Supplier Audits

Day of the audit
- Facility tour
- View manufacturing process (if possible)
- QA systems review
- SOP and document review
- Complete an audit checklist
- Close-out meeting
- Identify and communicate observations

Send out audit report, request response in 30 days

Request action plan for corrective actions

Determine if supplier qualified, qualified conditionally (need to define conditions), or not qualified
Quality Agreements

- Recommended for critical raw materials (e.g. cells, tissues, scaffolds, sole suppliers)
- Agreement between supplier and company
- Approved by QA and senior management
- Address the following areas:
  - Material specifications
  - QA/regulatory requirements
  - Supply chain
  - Shipping
  - Changes in manufacturing
  - Recalls, complaints
  - Audits, inspections
Raw Material Specifications

- Documented quality parameters for each critical raw material

- Elements of specification sheet:
  - Material identification
  - Manufacturer(s)
  - Specifications from manufacturer (certificate of analysis or product insert)
  - Required quality documentation
  - Shipping and storage conditions; expiration date
  - Testing and sampling requirements
  - Inspection requirements
  - QA, manufacturing approval

- If changes in material specification should go through change control process
Materials Management

- Purchasing controls
- Incoming receipt, quarantine, inspection, release prior to use in manufacturing
- Material tracking: minimum quantities, by lot and by shipment, identify lot used in manufacturing
- Procedures for handling recalls and materials not meeting specifications
- Appropriate storage conditions and segregation
- Tracking systems: manual or computerized (Part 11 compliant)
SOPs and Documentation

- Supplier qualification
- QA agreements
- Purchasing controls
- Raw material specifications
- Change control
- Receipt, acceptance, quarantine and release of Raw Materials
- Materials Storage
- Transfer of materials to the cell production facility
- Material recalls
- Raw material validation protocols/reports
Summary

- Select and qualify materials and suppliers early in clinical development
- Critical suppliers should be trustworthy and qualified
- Assure sufficient supply
- Materials should meet safety specifications
- Materials should produce consistent results in your manufacturing process
- When changing to a new manufacturer, need formalized change control
- Demonstrate comparability in your process
- Inventory control systems should be in place to assure controlled handling, storage and tracking
References

1. 21 CFR 210 and 211 Current Good Manufacturing Practices for Finished Pharmaceuticals
2. 21 CFR 1271 Human Cells, Tissues, and Cellular and Tissue-Based Products
3. Draft cGTP and Additional Requirements for Manufacturers of HCT/Ps January 2009
4. FACT-JACIE International Standards for Cellular Therapy Product Collection, Processing and Administration, 4th Edition
5. AABB, Standards for Cellular Processing Services, 3rd Edition
6. USP General Chapter <1043>, Ancillary Materials for Cell, Gene, and Tissue-Engineered Products, Pharmacopeial Forum 30 (2) 2004
Thank you for your attention!
Enjoy the Beach!