A Life Cycle Approach to Raw Material Qualification for Cell and Gene Therapy Products

Angela Whatley, Ph.D.
Office of Tissues and Advanced Therapies
CBER/FDA

CMC Strategy Forum on Cell & Gene Therapies
July 18, 2017
Outline

- Definition of Raw Materials
- Regulatory Foundation
- Raw Material Qualification
- Requirements for Early vs Late Phase Development
- Case Studies
- Conclusions
Terms Used to Denote Raw Materials

- Components
- Ancillary materials
- Reagents
- Solvents
- Buffers
- Tissue culture media
- Ingredients
- Plasticware
- Final containers
What is a Raw Material?

- Not specifically defined in regulations
- For the purpose of this presentation:
  - A raw material may refer to any element or component used in the manufacture of a cell or gene therapy product or active ingredient
    - Including any material that comes in contact with an active ingredient or intermediate, but not the active ingredients themselves.
    - Raw materials may be inert or reactive with the active ingredient.
Regulations Relevant to Raw Materials

- 21 CFR 312.23(a)(7)
  - **All components** used in manufacturing shall be listed in the IND

- 21 CFR 210.3(b)(3) and 21 CFR 211.80
  - **Component** means any ingredient intended for use in the manufacture of a drug product, including those that may not appear in such drug product
  - **Components** and drug product containers and closures shall be controlled

- 21 CFR 211.110
  - **In-Process materials** shall be tested for identity, strength, quality, purity as appropriate, and approved or rejected by the control unit.

- 21 CFR 610.15
  - **Constituents** shall meet generally accepted standards of purity and quality.
Relevant Guidance Documents

**IND specific Guidance**

**BLA specific guidance**
- Content and Format of Chemistry, Manufacturing and Controls Information and Establishment Description Information for a Vaccine or Related Product (1999)
Why is Raw Material Qualification Important?

- Safety and quality of the drug product are affected by the quality of raw materials
- Sourced globally
- One source of contaminated or unsafe raw material can affect large number of product lots
- Potential for viral contaminants could affect not only the drug product but ultimately patient safety

www.fda.gov
Risks to Product Quality Due to Raw Materials

- Raw Materials which are not properly qualified can lead to issues with:
  - Quality/Safety/Efficacy
  - Lot-to-Lot consistency
  - Specification failures
  - Comparability
  - Adventitious agents
  - Chemical contaminants
  - Immunogenicity
Risk Based Approach to Qualification

- Risk assessment should be completed taking into account:
  - Inherent toxicity
  - Immunogenicity
  - Role and timing in manufacturing process
  - Severity of the disease the product is intended to treat
  - Number of patients to be treated by the product
Risk Assessment of Raw Materials

- Risk assessment aims to identify materials with the highest potential risk
- Focus on mitigating the risk of these materials
- A risk assessment should:
  - Be comprehensive in scope
  - Have appropriate prioritization
  - Use a comprehensive and appropriate analysis tool
  - Integrate all appropriate personnel levels
Control of Raw Materials

- Manufacturers should use highest quality reagents available
  - FDA-approved or cleared, USP or clinical grade reagents
    - FDA does not approve or clear reagents specifically for cell and gene therapy product manufacturing
    - CGMP grade sticker-may be misleading
      - FDA does not verify the grade of reagents
  - Provide valid CoAs and/or qualification data

Manufacturers are responsible for the quality, safety and suitability of all reagents used for product manufacturing
Animal Derived Raw Materials

- Avoid the use of animal-derived raw materials, when feasible
- Assure safety and quality (e.g., purity, potency, identity)
  - Use controlled animal source
  - Test for viruses
  - Perform viral clearance steps
  - Include robust steps to reduce adventitious agents and microbial contamination
  - Assure animal derived materials are compliant with requirement described in 9 CFR 113.53
  - Submit additional information depending on species

www.fda.gov
Bovine Derived Materials

- Example of commonly used material—Bovine Serum Albumin
- Mitigation of risk
  - Traceability of herd
    - From a country shown to be free of transmissible spongiform encephalopathy/bovine spongiform encephalopathy
  - γ-irradiation and heat inactivation
  - Examples of testing requirements (9 CFR 113.53):
    - Bovine viral diarrhea virus
    - Bovine adenovirus type
    - Bovine parvovirus
    - Bovine respiratory syncytial virus
  - Other Bovine and human specific adventitious agents
Porcine Derived Materials

- Example of commonly used material - Trypsin
- Examples of testing requirements:
  - Porcine Parvovirus
  - Porcine Adenovirus
  - Porcine Circavirus 1 and 2
  - Other Porcine and human specific adventitious agents
Murine Derived Materials

- Example of commonly used material—antibody affinity columns
- Examples of testing requirements:
  - Mouse retroviruses
  - Antibody production test (MAP/HAP/RAP)
    - Mouse, Hamster, Rat
  - Other murine and human specific adventitious agents
    - Minute Virus of Mice, Lymphocytic Choriomeningitis virus, Sendai Virus, Hantaan virus
Human Derived Materials

- Provide CoA or information on donor and/or reagent testing, use licensed material (i.e., insulin, albumin, etc.), if available

- Human AB Serum: processed from blood or plasma collected at FDA licensed facilities.

- Although raw materials derived from human origin are not considered HCT/P or blood components, we recommend that the human donor of raw materials meet DE according to 21 CFR 1271

- Guidance for Industry: Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps)
Raw Material Qualification Program

- The process of acquiring and evaluating data to establish the source, identity, purity, biological safety, and overall suitability of a specific raw material
Supplier Qualification

- Utilize a risk-based approach for qualification program
- Qualify suppliers early in product development
- Focus on high risk raw materials
- Ensure continuous supply for critical raw materials
- Develop a standard process to qualify potential manufacturers
Supplier Qualification 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
- Establish Quality Agreements
Quality Agreements

- Establish Quality Agreement with supplier for critical raw materials
- Quality Agreement should be approved by Quality Assurance unit, and senior management at the supplier and cell/gene therapy manufacturer
- Address the following areas:
  - Material specifications
  - QA/regulatory requirements
  - Supply chain
  - Shipping
  - Changes in manufacturing
  - Recalls, complaints
  - Audits, inspections
Receiving Raw Materials

- Develop SOPs which describe how raw materials are received, tested and handled at the manufacturing site
- Quarantine materials upon receipt
- Predetermine release criteria
- Test for identity, purity, strength
- Release only lots that pass release testing
In-house Testing of Raw Materials

- Conduct additional in-house testing to ensure safety and quality of raw materials and to verify CoA when needed:
  - Safety testing (sterility, endotoxin, mycoplasma, species-specific adventitious agents, as needed)
  - Purity testing (if not defined on COA)
  - Functional analysis
  - Other assays demonstrating absence of potentially harmful substances
Providing Quality Information to FDA

- Describe material and quality
- Provide CoA for Critical Raw Materials
  - Documenting raw material is safe and suitable for intended use
  - In some cases you may cross reference an existing IND for this information
    - Requires a Letter of Authorization from the individual who submitted the existing information
    - Letter should indicate the nature of the cross referenced information and where it can be located in the IND/MF
- Raw material manufacturers may submit a Master File (MF) for information which is proprietary and not provided on the CoA. Letter of Authorization from the MF holder should be provided.
Information to Provide in IND

- Tabulate all reagents used
  - Reagent name
  - Vendor/Supplier
  - Source (human, bovine, recombinant, etc.);
    If animal-derived, identify source organism and country of origin
  - Grade (licensed product, clinical grade, research grade, etc.)
  - Final concentration
  - Certificate of Analysis (CoA)
  - Cross-reference to regulatory file (include authorization letter)
Information to Provide in IND (Cont’d)

- Provide Information on
  - Qualification programs
  - Residuals amounts
  - Removal from final product
  - Patient notification and monitoring as appropriate
    - Hypersensitivity issues (antibiotics, animal components, etc.)
Life Cycle Approach for Controlling Raw Materials

- Quality should be built into product design
  - Utilize highest quality raw materials
- Expand control as product development matures
- Conduct stability assessments for reagents stored for a long period.
Considerations for Later Stages of Product Development

- Make major changes before the BLA supporting studies.
- Depending on the change, it may be necessary to assess the impact on product safety and quality. For example:
  - A change in media formulation may require a study to assess impact on product quality and stability.
    - May need to establish product comparability.
  - A change in antibody used in cell selection may require a study to demonstrate the final product continues to meet release specifications.
Supply Chain Vulnerabilities

Cytokines

Culture media and supplements

Test kits for lot release

Affinity column

Vials
Stoppers
Excipients

How will changes in raw materials affect the final product?
Case Study 1: Chromatography Resin

Observation
- Supplier for chromatography resin used in AAV purification goes out of business.

Investigation
- Prior to switch sponsor should qualify new resin as:
  - Free of microbial contamination
  - Of reasonable purity
  - Appropriate strength to perform its intended function (that the resin binds with a particular strength)
  - Test if resin leaches into the product
Case Study 2: Collagenase

Observation

- FDA learned that the microbial fermentation media used in manufacturing certain formulations of collagenase contained bovine brain-heart infusion (BHI) broth, which posed a potential TSE risk.

Impact

- FDA sent letters to all sponsors using these reagents asking them to inform all subjects of the risk and to take additional steps to address the concern.
Case Study 3: Human AB Serum

- Obtained from a variety of vendors
- Most are for research use only
- Extent of material qualification varies greatly between vendors

Points to consider:
- Donor screening & testing
- Testing of AB Serum
- Viral reduction methods (e.g., heat inactivation, filtration)
Summary: Control of Raw Materials

- Manufacturers should establish SOP for qualification of raw materials
- Manufacturers should use highest quality materials available when manufacturing drug products
- Manufacturers should provide FDA documentation that all raw materials used in drug product manufacture are appropriately control to assure safety of product
- Manufacturers are responsible for the quality, safety and suitability of all reagents used for product manufacturing
Contact Information

- Angela Whatley, PhD
  angela.whatley@fda.hhs.gov

- **Regulatory Questions:**
  OTAT Main Line – 240 402 8190
  Email: OTATRPMS@fda.hhs.gov and
  Lori.Tull@fda.hhs.gov

- **OTAT Learn Webinar Series:**

- **CBER website:** [www.fda.gov/BiologicsBloodVaccines/default.htm](http://www.fda.gov/BiologicsBloodVaccines/default.htm)

- **Phone:** 1-800-835-4709 or 240-402-8010

- **Consumer Affairs Branch:** ocod@fda.hhs.gov

- **Manufacturers Assistance and Technical Training Branch:** industry.biologics@fda.gov

- **Follow us on Twitter:** [https://www.twitter.com/fdacber](https://www.twitter.com/fdacber)

---

www.fda.gov