Early Phase Cell Therapy Product Development: Materials Specifications

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September 26, 2017

OBJECTIVE

1. Purpose and importance of material specifications in early phase product development.
2. Describe the process for determining material specifications requirements sufficient for translational research and as a foundation for later stage product development.
3. Define how to qualify raw materials and Supplier to prepare for use in later stage product development.

AGENDA

1. Raw Material (RM)
   - Define
   - Key Considerations in selection
2. Setting Specifications and Controls
   - Risk Assessment
3. Supplier and RM Qualification
   - 4 Step Strategy for Qualification
4. Conclusion

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DEFINITION

What is a Raw Material?

ICH Q7 definition
A general term used to denote starting materials, reagents, and solvents intended for use in the production of intermediates or APIs.

Modified definition
"Any element or component used in the manufacture of a biotechnology product that comes in contact with the API or the API starting material. A raw material may be reactive or non-reactive with the API"

(FDA reviewer, Office of Biotechnology Products)
http://c.ymcdn.com/sites/www.casss.org/resource/resmgr/imported/WCBPCMC09CordobaRodriguezSlides.pdf

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WHY IS RM SELECTION IMPORTANT?

1. Prevent delays in later phase product development
2. Key to ensure safety, quality and efficacy of clinical product
3. Ensures product is well-defined, consistent, and suitable for its intended use
4. Prevent delays in product / application approval

REGULATIONS / GUIDANCES FOR RM

- FDA: Guidance for Industry. Characterization and Qualification of Cell Substrates and other Biological Materials Used in the Production of Viral Vaccines for Infectious Disease Indications.
- FDA: Points to Consider in the Characterization of Cell Lines used to Produce Biologicals
- FDA: Current good manufacturing practices in manufacturing, processing, packaging, or holding of drugs. Code of Federal Regulations, Title 21, Part 210
- FDA: Current good manufacturing practices for finished pharmaceuticals. Code of Federal Regulations, Title 21, Part 211
- EMEA: Medicinal products for human and veterinary use. GMP Guide (Volume 4)
- EMEA: Sampling of starting and packaging materials. GMP Guide (Volume 4)
- EMEA: Manufacture of investigational medicinal products. GMP Guide (Volume 4)
- ICH: Good manufacturing practice for active pharmaceutical ingredients Q7.
- FDA: Guidance for Industry. Manufacturing, Processing, or Holding Active Pharmaceutical Ingredients

RM SELECTION: KEY CONSIDERATIONS

- GMPs require RM and Suppliers to be qualified
  - Robust and sustainable Supplier and RM qualification program required
  - Testing RM can be a challenge
    - Qualification of RM can occur in parallel with its use
  - Set specifications and procedures to control RMs
  - Keep good documentation to show data integrity
  - RMs considered critical should have a higher degree of testing

Example:
Use of cell lines in “pre-GMP” phase
- requires traceability of RMs used in development
- maintain good records of RMs so safety risk can be assessed
- use parental cell lines from trusted source
- if possible use GMP-qualified raw materials

RM SELECTION: KEY CONSIDERATIONS

- Quality Risk
  - Lot to lot consistency? Fully tested?
  - Supplier manufacturing process changes?
  - Require additional testing not conducted by Supplier?

- Origin risk (safety)
  - mitigate risk of adventitious agent contamination
  - Are there animal products used in its manufacture?
    - Fetal calf serum, bovine serum albumin, human serum albumin
- Appropriate for the intended application
  - Does the RM make product contact?
  - What quality is available (Research? GLP? GMP)
  - Sterility tested? Bioburden? Sterile filtered?
    - Can it be sterilized in-house?
    - Use irradiated serum to inactivate viruses (reduce risk of adventitious agents)

RM SELECTION: KEY CONSIDERATIONS

- Ensure continuous supply
  - Availability? Back-up options?
  - Manufacturer willing to support product long term?
- Storage (special storage needs)
  - Stability / expiration
  - Consider time it will take to qualify a new lot of material & build into manufacturing schedule
- Cost (Scale-up)
  - RM available in quantities needed for scale-up?
  - Changes in containers / closures may affect RM quality

EXAMPLE OF MATERIAL RISK ASSESSMENT

General Components of Mammalian Cell Culture

Criteria/Material	Origin / complexity	Product Contact	Impact on DS process	Risk
Inorganic salts/buffer components	No	Yes	Yes / No	Medium/High
Carbohydrate/energy source	No	Yes	No	Medium
Trace elements	No	Yes	No	Medium
Amino acids	No	Yes	No	Medium
Vitamins, Antioxidants	No	Yes	No	Medium
Nucleotides	No	Yes	No	Medium
Recombinant proteins	Yes	Yes	No	High
Serum or serum components	Yes	Yes	No	High
Hydrolysates/Peptones	Yes	Yes	Yes	High
Antifoam agent (cell protection)	No	Yes	Yes	High

Definition: 1 Yes = Medium Risk 2-3 Yes = High Risk and Criticality

* PDA, Jan 05, 2015, Strategies for Controlling Raw Materials in Biologics Manufacturing

DEFINING RISK ASSESMENT LEVELS

	Low	Medium	High
CoA Review *(qualify RM parallel with use)*	✓	✓	✓
Test Various Lots		✓	✓
RM & Supplier Qualification		✓	✓
On-Site Audits Risk Assessment for Cross-Contamination			✓
Quality Agreement / Contract			✓

STRATEGY FOR QUALIFICATION

Step 1: Collect RM Information

- Determine what grade of material is available (research, GLP, GMP, clinical)
- Is RM listed in compendium (US Pharmacopeia, EU Pharmacopeia)?
- Conduct risk assessment. Is the RM critical?
  - Sole Supplier

Step 2: Qualification of RM

- CoA review (all tests reported on CoA?)
  - (collect CoA of different lots to determine variability, trend release data)
  - Stability data / expiration date
- Verify each lot meets Suppliers specifications, are there any changes in specifications?
- Are animal derived materials used in its manufacture? (CoO)
- Is there a need to conduct additional tests?

STRATEGY FOR QUALIFICATION (Con't)

Step 3: Supplier Qualification

- Questionnaire, site visit for critical Suppliers
- Is there an independent quality unit?
- Adequate changeover procedures?
- MF on file with FDA?
  - Changes in manufacturing process, facilities or equipment
- Has material been used to manufacture a clinical product?
- Supplier been inspected by regulatory agencies, FDA
- Will the Supplier support the product long term?
- Manufactured on the same line as other products?
- Provide an ADM or BSE / TSE statement?

STRATEGY FOR QUALIFICATION (Con't)

Step 4: Maintain RM & Supplier Records

- Maintain a list of qualified RM & Suppliers
- Conduct periodic review of RM & Supplier (on-site audits, questionnaire, phone surveys)
- Established procedures for frequency of requalification
- Consider time it will take to qualify a new lot of material build that into your manufacturing schedule
- Collaborate with Supplier to improve RM quality
- Implement a quality agreement

Ensure you have adequate QA personnel

SUMMARY OF RM REQUIREMENTS AT VARIOUS DEVELOPMENT PHASES

PHASE	LEVEL OF QUALIFICATION	TESTING / RELEASE
Pre-GMP Phase (process development)	Documentation of source (CoA, CoO)	Testing parallel to use
Phase I/II	Supplier risk assessment (questionnaire) On-site audit (high risk) Consider QA/Supplier Agreement	Identity testing Method Development & Qualification
Phase III / Validation	On-site audits Monitoring of approved Raw Materials QA / Supplier Agreement	Full testing (CoA & in-house tests) Stability studies Method validation
Market (Phase IV)	Frequency of on-site audits based on experience	Check suitability of specifications for product intended use

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CONCLUSION

To ensure constant supply of materials and appropriate quality and safety of clinical product:

- establish an appropriate definition of a raw material
- select the appropriate RM early in process / product development to achieve GLP / GMP readiness of clinical product
- conduct risk assessment to identify critical & non-critical RM
- establish a strategy to qualify RMs & Suppliers and maintain records of qualified RMs & Suppliers
- involve QA personnel early in product development process

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