# Production Assistance for Cellular Therapies

**Educational Web Seminar**

*Early Phase Cell Therapy Product Development*
*-Quality in the Lab-*

**Tuesday, September 26, 2017**

**12:00 noon – 1:00 PM ET**

## Description

PACT will be conducting a short web seminar series covering topics critical to early phase of cell therapy product development.

Materials specifications and laboratory quality management are the topics that will be discussed during this web seminar. Raw material and reagent specifications are the quality standards that are established to confirm the quality of these products used in the production of a cell product. All materials, reagents and processes should be subject to quality control systems and standard operating procedures to ensure their quality and consistency of protocols used in manufacturing a cell product.


Today's web seminar presentation slides are available publicly at www.pactgroup.net

## Objectives


**Laboratory Quality Management**

a. Recognize the importance of establishing a quality program early in product development

b. Identify quality management concerns for pre-clinical studies that have implications in later stage regulatory filings

c. Identify quality issues specific to pre-clinical studies and discuss effective management and troubleshooting of these challenges

**Material Specifications**

a. Recognize the purpose and importance of material specifications in early phase product development

b. Describe the process for determining material specifications requirements sufficient for translational research and as a foundation for later stage product development

# Speakers


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# Faculty Disclosure

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***Unless otherwise noted, individuals did not indicate any relevant affiliations or financial interests***

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# CE Credit

**Accreditation Statement**

In support of improving patient care, this activity has been planned and implemented by University of Minnesota, Interprofessional Continuing Education and The Emmes Corporation. The University of Minnesota, Interprofessional Continuing Education is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

**Credit Designation Statement**

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The University of Minnesota, Interprofessional Continuing Education designates this live activity for a maximum of 1.0 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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*1.0 hour of P.A.C.E. credit* (CEU) through the University of Minnesota Medical Laboratory Sciences Program will be offered for this session.

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# CE Credit

**CE credit is only offered to participants who have attended this live web seminar**

Each attendee must:

- Sign and email the attendee roster to pactupdates@emmes.com
- Complete the online survey w/in 48 hrs of the web seminar:
  1. Survey will display when you exit the web seminar
  2. Survey link provided in your email reminder sent Sept 25, 2017 https://www.surveymonkey.com/r/Pactwebinarsep2017
  3. PACT website Education>PACT web seminars>Sept 26 Web Seminar

**Note:** After the web seminar, rosters and surveys have been processed, a Statement of Participation will be issued via email to each participant listed on the attendee rosters requesting CE.

## Quality Management


CDER SBIA

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## Quality Assurance (QA)

- Inspect each non clinical laboratory study at regular intervals.
  - Assure the integrity of the study and maintain written documentation.
  - Written records are in place and in sufficient detail so the study can be reconstructed.
  - Review Training documentation of personnel.
  - Inspect equipments to ensure they are properly maintained and calibrated.
  - Review reagents and materials used for testing.

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## Quality Assurance (QA)

- Review Study Plan.
- Changes to protocols.
- Report any inspection results to management.

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## Quality Assurance

- Review study final study report.
  - Results accurately reflect the raw data.
- Statement whether study was conducted in compliance to GLP provided in the final study.


## Conclusion

- Pre clinical studies for cell therapy are significantly different from traditional small molecule studies or medical devices.
- All pre-clinical studies must be performed under GLP compliance.
- Quality system must be in place to ensure the study is conducted as per the regulations and the study can be reconstructed.

# Early Phase Cell Therapy Product Development: Materials Specifications

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Director, Office of Quality Systems
City of Hope National Medical Center
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

## 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

## 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)<br>On-site audit (high risk)<br>Consider QA/Supplier Agreement | Identity testing<br>Method Development & Qualification |
| Phase III / Validation | On-site audits<br>Monitoring of approved Raw Materials QA / Supplier Agreement | Full testing (CoA & in-house tests)<br>Stability studies<br>Method validation |
| Market (Phase IV) | Frequency of on-site audits based on experience | Check suitability of specifications for product intended use |

## 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


## Early Phase Cell Therapy Product Development
## -Quality in the Lab-

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