Supplies and Reagents

PACT Workshop: Design & Operation of GMP Cell Therapy Facilities

April 10th-11th, 2007

Molecular&Cellular Therapeutics
University of Minnesota

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NHLBI-sponsored PACT Group

Guidance for Industry INDs – Approaches to Complying with CGMP During Phase I

- SOP for handling, review, acceptance and control of components
- Components to be controlled (segregated, labeled) until examined (and tested) and released for production
- Keep record with relevant information

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Guidance for Industry

- Relevant Information:
  - Receipt date
  - Quantity in shipment
  - Supplier name
  - Lot #
  - IND batch #
  - Storage conditions
  - Expiration date

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Guidance for Industry

- Establish acceptance criteria for specified attributes if possible; attributes and acceptance criteria reviewed in IND application
- Certificate of Analysis and/or other documentation on each lot reviewed to ensure it meets acceptance criteria for specified attributes

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21 CFR Part 1271.210 Supplies and Reagents

- Verification:
  - Verification by establishment that uses the supply or reagent OR
  - Verification by the vendor
- Reagents: must be sterile
- In-house reagents: validate or verify production process

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21 CFR 1271.210 Supplies and Reagents

- Records
  - Receipt: type, quantity, manufacturer, lot #, date of receipt, expiration date
  - Records of verification:
    - Include test results if appropriate
    - C of A (if vendor verification)
  - Record of lot # used in manufacture

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Careful scrutiny of the materials used in manufacturing is necessary to prevent the introduction of adventitious agents or toxic impurities, as well as to ensure the ultimate safety, effectiveness, and consistency of the final product.

– U.S.P. <1043> Ancillary Materials for Cell, Gene, and Tissue-Engineered Products

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General Requirements

- Sterile
- Non-pyrogenic
- When possible, items approved for human use, injectable/infusable, USP grade, manufactured under U.S. License

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When possible, it is preferable to use materials/reagents that are approved or licensed therapeutic products:

- well characterized
- have an established toxicological profile
- manufactured according to controlled and documented procedures

Choices may be driven by production protocol

- unique functional contributions or biological effects

  e.g. FBS, cell culture media, DMSO

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Specifications

- Complete Specification Form
- Each item identified by unique part #
  - CHxxxxxx Chemicals/reagents
  - MAxxxxxx Materials
- Currently approx. 820 specs
- Database/paper copy
- Treated as a controlled document

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Material and Chemical Specification Form

MOLECULAR AND CELLULAR THERAPEUTICS
UNIVERSITY OF MINNESOTA

PART NUMBER: CH138869

Revision: H

Effective Date: 24-Aug-06

SPECIFICATIONS:

Chemical/ Material Name: Albumin (Human), USP, 25% Solution, 50 mL		
Description / Appearance / Composition: Licensed, sterile human albumin; nonpyrogenic; contains 12.5 gm albumin in aqueous diluent; 50 mL glass vial		
Other Information: N/A		
Certificate of Analysis ☑	MSDS Required ☐	Drug Accountability ☐
Certificate of Analysis must include: Sterility - sterile; pyrogen testing(if results available) complies/passes; all infectious disease testing negative; Baxter only: LAL NMT 1.67 EU/mL		
Expiration: See Pkg	Storage Conditions 15°C to 30°C; Not to exceed 30°C	
Precautions: N/A		

SOURCE:

Manufacturer	Manufacturer Cat #	Ordering Measure
Baxter Biotech/Hyland	060033	10 / Case
Alpha Therapeutic Corp	521302	10 / Case
Bayer/Talecris	692-20	10 / Case
Grifols	NDC 61953-0002-1	Each
ZLB Bioplasma AG	NDC 0053-7680-32	Each

SAMPLING INFORMATION:

Sampling Plan: N/A
Sample Size: N/A

PROGRAM DESIGNATIONS:

☑ **Cell Therapy Program**

☑ **Islet Transplantation Program**

QA Verification: MCO Date 29MAR07

Material and Chemical Specification Form

MOLECULAR AND CELLULAR THERAPEUTICS
UNIVERSITY OF MINNESOTA

PART NUMBER: MA500307

Revision: **New**

Effective Date: 16-Mar-05

SPECIFICATIONS:

Chemical/ Material Name: Tag, Warning, Not Evaluated for Infectious Substances		
Description / Appearance / Composition: White tie tag with red print; permanent ink; size 4 ¾ inches x 2 ⅜ inches; reinforced hole		
Other Information: See attached example		
Certificate of Analysis ☐	MSDS Required ☐	Drug Accountability ☐
Certificate of Analysis must include: N/A		
Expiration: N/A	Storage Conditions 15°C to 30°C	
Precautions: N/A		

SOURCE:

Manufacturer	Manufacturer Cat #	Ordering Measure
U Printing		Each

SAMPLING INFORMATION:

Sampling Plan: Labels,
Sample Size: 10% random

PROGRAM DESIGNATIONS:

☑ **Cell Therapy Program**

Finalized by MARIA O on 3/16/2005

QA Verification: MCO Date 29MAR07

Vendors

Acceptable Vendor(s)/Suppliers

- Specific vendor
- Multiple vendors
- Vendor history

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Vendor Qualification

- Possible
- Practical
- Cost effective

MCT Facility: approx. 300 vendors

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Vendor Qualification

- How?

  Audits/site visits – limited/specific

  - Local vendors
  - Provide critical service (Master Cell Bank qualification testing)
  - Provide critical ingredient (AB serum)

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Vendor Qualification

- How?
  - Audits/site visits (limited/specific)
  - Survey (phone, mail) – target specific vendors
  - Prior history with manufacturer: complaints, C of A
  - Determined by other, e.g. hospital contract, pharmacy
  - Use of licensed products whenever possible

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Materials Requirements Planning Matrix (MRP)

- Planning document used during product development; completed and approved prior to clinical production
- Means to identify critical supplies and reagents used in production
- Provides means to review how items are used, identify qualification requirements
- Materials and inventory planning document

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Appendix I: Example FF-114 Materials Requirement Planning Matrix

Master Cell Bank – SK23+ CD80

Item	Part Number	Description	C of A Requirement	Integral to Product	Approved for Human Use	MD Review Required	Approved Spec.	Justification	Tier	Number/ Run
X-Vivo 15	CH169012	Sterile Filtered; human source material	Sterility, endotoxin	Yes	No	Yes	Yes	Approved for use under IND	3	30
Human AB serum	CH100111	HS1022 Sterile Non-pyrogenic, heat inactivated, tested for HBsAg, HIV-1, HIV-2, HCV, HIV-1Ag or HIV-1 NAT, ALT and syphilis	Sterile, endotoxin, Mycoplasma, Infectious Disease Markers	Yes	No	Yes	Yes	Approved for use under IND	2	30
T-75 Flask	MA500065	Sterile, nonpyrogenic; tissue culture treated	N/A	No	No	Yes	Yes	Approved for use under IND	2	15
DPBS	CH100022	Sterile, nonpyrogenic	Sterility, endotoxin	No	No	Yes	Yes	Approved for use under IND	3	25
Trypsin-EDTA	CH100830	Sterile, porcine parovirus and mycoplasma tested	Sterility, mycoplasma, porcine parovirus	Yes	No	Yes	Yes	Approved for use under IND	3	25
Pall Filter	MA004583	Sterile, non-pyrogenic fluid path, single use only	N/A	No	Yes	No	Yes	N/A	1	15
Plasma-Lyte A	CH185485	Sterile, non-pyrognic isotonic solution	Sterility, endotoxin	Yes	Yes	No	Yes	N/A	1	6
DMSO	CH142790	Sterile, non-pyrognic	Sterility, endotoxin, specific gravity	Yes	No	Yes	Yes	Approved for use by MD	3	2
Human serum albumin 25%	CH138869	Sterile, non-pyrognic, U.S. Licensed	Sterility, pyrogen and/or endotoxin; infectious disease marker testing	Yes	Yes	No	Yes	N/A	1	10
Septum Caps	MA500111	Must be sterilized before use with clinical products	N/A	No	Yes	No	Yes	N/A	1	30
Cell Factory, CellSTACK, 10 tray	MA500822	Gamma irradiated, non-pyrogenic	N/A	No	No	Yes	Yes	N/A	2	10-30

APPROVALS	Signature	Date
Author		
Program Coordinator		
Materials Management		
Medical Director		
Quality Assurance		

Tier System (USP)

- General Chapters: <1043> Ancillary Materials for Cell, Gene, and Tissue-Engineered Products (USP 29 NF 24 – official 4-1-06)
- 4 Tiers
- Definitions
- Examples
- Qualification or Risk Reduction Activities

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Tier 1

- Definition: low-risk, highly qualified materials that are well-suited for use in manufacturing and have a strong safety profile.
  - Licensed biologic, an approved drug, an approved or cleared medical device, or intended for use as an implantable biomaterial.
  - Obtained as a sterile packaging system or dosage form.
  - Items may be used according to the manufacturer's instructions or may be utilized "off label" in the manufacturing process.
- Examples: Human Albumin, Insulin, Pulmozyme, Saline, Dextran 40, Isolex reagents, etc.

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Tier 2

- Definition: low-risk, well-characterized materials that are well-suited for use in manufacturing.
  - Intended use is for drug, biologic, or medical device manufacture, including cell, gene, and tissue-engineered products as materials or reagents, and they are produced under relevant cGMPs.
  - Most animal-derived materials are excluded from this category.
- Examples: Human AB serum, items manufactured under IDE such as cell selection beads, etc.

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Tier 3

- Definition: moderate risk materials that will require a higher level of qualification than previous tier materials.
  - Frequently, these materials are produced for in vitro diagnostic use and are not intended for use in the production of cell, gene, or tissue-engineered clinical products
  - In some cases, upgrade of manufacturing processes may be necessary in order to employ the material in manufacturing of these products
- Examples: cell/tissue culture media such as AIM-V, Ex-vivo, MEM, HBSS, RPMI, etc.

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Tier 4

- Definition: the highest risk level for materials or reagents. Extensive qualification is necessary prior to use in manufacturing.
  - The material is generally not produced in compliance with cGMPs.
  - Tier 4 materials and reagents are not intended for use in the production of cell, gene, or tissue-engineered products.
  - This risk level includes highly toxic substances with known biological mechanisms of action, and also includes most complex, animal-derived fluid materials not subjected to adventitious viral removal or inactivation procedures.
  - In the early stages of development the necessity of these materials should be evaluated and alternative substances or sources explored.
- Examples: Fetal Bovine Serum, Animal or human cells used as feeder layers

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Qualification or Risk Reduction Activities – Tier 1

- DMF cross reference (when possible or practical)
- Certificate of Analysis
- Assess lot-to-lot effect on performance
- Assess removal from final product
- Stability assessment on materials as stored for use in manufacturing

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Qualification or Risk Reduction Activities – Tier 2

- Same as Tier 1 plus:
  - When relevant, confirm certificate of analysis test results critical to product (could include functional assay)
  - Vendor audit

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Qualification or Risk Reduction Activities – Tier 3

- Same as Tier 2 plus:
  - Work with manufacturer to upgrade manufacturing process for material to GMP
  - Develop stringent internal specifications
  - Determine if lot-to-lot biocompatibility, cytotoxicity, or adventitious agent testing are needed

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Qualification or Risk Reduction Activities – Tier 4

- Qualification or Risk Reduction Activities – same as Tier 3 plus:
  - Verify traceability to country of origin
  - Assure country of origin is qualified as safe with respect to source-relevant animal diseases, including TSE
  - Adventitious agent testing for animal source-relevant viruses

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Current Practice

- ☑ SOPs for handling materials and reagents
- ☑ Critical supplies/reagents listed in CMC
- ☑ Specifications
- ☑ Systems to record information
- ☑ Segregation/inspection/labeling prior to release
- ☑ QA Review of C of A at receipt
- ☑ In-house reagents: perform validation, verification

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Needs Improvement

Vendor audits – limited to a few vendors that perform manufacturing or testing

Additional Qualifications:

- Compare lot to lot variability (FBS)
- Reserve one lot for clinical trial
- Additional testing on a few items (cell lines, DMSO when vendor changed)

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Sources:

- Guidance for Industry INDs – Approaches to Complying with CGMP During Phase I; FDA January 2006
- 21 CFR Part 1271; FDA, 2005
- U.S.P. <1043> Ancillary Materials for Cell, Gene, and Tissue-Engineered Products; 29 NF 24 – official 4-1-06

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