Production Assistance for Cellular Therapies

Welcome to the PACT Educational Web Seminar

October 11, 2007
12:00 Noon - 1:00 PM ET

About PACT

- An NHLBI-funded initiative committed to the advancement of effective cell therapies
- PACT supports the development of novel somatic cell therapy products by providing production assistance to the cell therapy community, as well as educational training via web seminars and at meetings
- PACT manufactures quality cell therapy products on behalf of investigators with funded clinical trials requiring support in product development and approval.
- PACT’s educational training focuses on three general areas: translational development/scale-up and manufacture of cell therapy products; and quality assurance and regulatory issues.

PACT Members

The PACT Group provides education, leadership and production assistance to the cell therapy community through federally-funded contract manufacturing of therapeutic cell products.
Web Seminar Objectives

- Learn the steps to follow when preparing for a facility inspection
- Learn what and what not to do during inspections
- Learn and understand what inspectors focus during inspections

Presentation Slides

The presentation slides for this web seminar are available publicly on the main page at: www.pactgroup.net

For prior web seminars choose “Educational Material → Web Seminars”

Today’s Education Web Seminar

Adrian Gee, MIBiol, PhD
Baylor College of Medicine
Center for Cell and Gene Therapy

Nancy Collins, PhD
University of Toledo Medical Center

Q & A Session
Web Seminar Description

Presenters will outline their approaches to the area of Good Manufacturing Practice specifically for facilities involved with products for cellular therapies. This web seminar will focus on preparing for an FDA inspection.

Faculty Disclosure Information

The Accreditation Council for Continuing Medical Education (ACCME) is the governing body that accredits AABB to provide continuing medical education credits for physicians. In accordance with the ACCME Standards for Commercial Support, all faculty for this event have signed a conflict of interest form in which they have disclosed any significant financial interests or other relationships with the industry relative to the topics they will discuss during this program. Such disclosure allows you to better evaluate the objectivity of the information presented in the lectures. Please report any undisclosed conflict of interest you may perceive on the evaluation form.

Thank You.

<table>
<thead>
<tr>
<th>Faculty Name</th>
<th>Nature of Relationship</th>
<th>Manufacturer/Provider</th>
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</thead>
<tbody>
<tr>
<td>Adrian Gee</td>
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<td>Nancy Collins</td>
<td>None</td>
<td>non-PACT member</td>
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<td>Debbie Wood</td>
<td>None</td>
<td>PACT member</td>
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PACT Updates

AABB Annual Meeting and TXPO 2007
October 20-23, 2007
Anaheim, California
PACT will be conducting a PACT session on
Tuesday, October 23 from 2:00pm-5:00pm
“Cell Therapy Challenges: Product Characterization,
Regulatory Compliance and Lessons Learned”
Visit www.aabb.org
for further details

PACT is supported with Federal funds from:

National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services

Administrative Center-The EMMES Corporation Contract Number: N01-HB-7166
Baylor College of Medicine Contract Number: N01-HB-37163
The University of Minnesota Contract Number: N01-HB-37164
The University of Pittsburgh Contract Number: N01-HB-37165
How to Survive Audits & Inspections

Adrian Gee
Center for Cell & Gene Therapy
Baylor College of Medicine
Houston, Texas

Types of Inspections
FDA Inspections
- What happens
- Areas of emphasis & advice for compliance
- Regulatory Body
- Inspection advice
- Do’s and Don’ts

Types of Inspection
- Internal – part of Quality Plan
- Institutional – part of Quality Program
- External
  - Contractor
  - Regulatory Body
  - State
  - Federal – FDA
External Inspections

Accreditation Agencies
- Voluntary programs
- Based on Standards
- Do not have the power of law
- Visits may or may not be scheduled in advance
- Occur on fixed schedule e.g. every 2 years

Regulatory Agencies
- Have the power of law
- May be scheduled or random
- Compliance is not optional
- Methods for compliance can vary
- Inspectors vary in experience
- Be prepared to explain products, processes and protocols

Upon arrival
- Will issue form FDA 482 “Notice of Inspection”
- Pre-designate a Facility contact
- Available throughout inspection
- Quality experience
- Inform Institution?
External Inspections

- Provide meeting space
- FDA will set agenda
  - Purpose of visit
- Usually will request tour
- Then start to request documentation/records
  - Initially will work in private

External Inspections

- Will then meet with facility contact
  - Q and A, Clarification
  - Additional information
    - Processing records
    - Variances
    - Training records
    - Equipment records
    - Environmental records
    - Additional documents

External Inspections

- Exit interview
  - Outstanding issues
  - Formal notification of problems – Form 483
  - Time frame for compliance?
  - Closure of Facility if extensive non-compliance
Areas of Emphasis

Documentation

- Standard Operating Procedures
- Manufacturing records
- Equipment records
- Training records
- Quality plans – meetings, audits etc.
- Variances – provide a history of problems

Advice on Standard Operating Procedures

- Allow for biological variability
- Every deviation must generate a Variance
- Match closely to worksheets/batch records
- Avoid too many cross-references
- Couple to Training Program

Standard Operating Procedures

- Make sure you have SOPs for Core GTP Requirements (21CFR 1271.150)
  - Facilities
  - Environmental control
  - Equipment
  - Supplies and Reagents
  - Recovery
  - Processing & Process Controls
  - Labeling Controls
  - Storage
  - Receipt, Pre-distribution, shipment & distribution of HCT/Ps
  - Donor eligibility, screening and testing
Areas of Emphasis
Documentation
- Standard Operating Procedures
- Manufacturing records
- Equipment records
- Training records
- Quality plans – meetings, audits etc.
- Variances – provide a history of problems

Documentation
Manufacturing Records
- Detail all steps in manufacturing per SOP
- Identify person performing steps
- Verification of critical steps & calculations
- Appropriate correction procedure
- Inclusion of all supporting documentation
- Timely review

Documentation
Training Records
- Training SOPs
- Documentation of ALL training
  - Initial, annual and any retraining
  - Competency assessments
- Educational activities
  - Continuing education
  - OSHA
  - Blood Borne Pathogens
  - Safety
Areas of Emphasis

**Variances/Deviations**
- Available for all deviations from SOPs
- Generated and reviewed promptly
- Include potential impact on product & patient
- Include corrective actions
  - For current variance
  - To prevent future occurrences
- Follow-up on corrective actions

**Areas of Emphasis**

**Contamination**
- Donor screening
  - Health history
  - Infectious disease testing
- Aseptic Technique & Facility Cleaning
- Changeover procedures between products
  - Removal of product, paperwork & reagents
  - Cleaning of equipment - documented
- Handling of multiple products
  - Segregation by room, incubator, shelf, time

**Environmental monitoring**
- Types of contaminants
- Ability to detect contaminants
- Rationale for pressure relationships
- Rationale for type and frequency of monitoring
- Alert and Alarm levels and actions
- Records and response to Alerts & Alarms
Areas of Emphasis

Product Tracking
- Donor to recipient & vice versa
- Notification of non-conformity
  - Positive culture on product after infusion
  - Non-conforming donors
  - Recalls of products/reagents
- Complaints file – actions & follow-up

Areas of Emphasis

Labeling
- New GTP regulations
- Required language present
- Required warnings present
- Complies with IND application
  - Product name
  - Specific requirements under IND

Tips during Inspections
- Listen to the inspector!
  - Respond carefully to what was asked
- Do not argue or become frustrated
- Explain rationale for methods used
- Admit deficiencies – do not try to hide
- Seek advice from inspector
- Correct on-site if possible
- Learn from the experience!
- Keep copies of requested information
Advice for Inspections

Prepare
- SOP?, pre-designate contact person, determine who will be informed of inspection
- Participate in accreditation programs, mock inspections, audit programs
- Review documentation – primary focus, audit
- Make documents easy to review - organized

Good Luck!
FDA INSPECTION:
PREPARATION, INSPECTION & FOLLOW UP
Nancy H. Collins, PhD.
Memorial Sloan-Kettering Cancer Center
University of Toledo Medical Center

MSKCC CYTOTHERAPY LABORATORY
- Facility: Unclassified space, 500 ft² lab, 4 BSC, clerical & laboratory space
- 600 ft² freezer space (>6000 products, 13 LN₂, 3 mechanical)
- Isolex, ClinMACS

MSKCC CYTOTHERAPY LABORATORY
- 30 years servicing 432-bed hospital, Allo lab merge with Auto lab 2001
- FDA & New York State registered
- FACT, AABB, & JCAHO accredited
- CAP & in-house proficiency studies
- NMDP collection and transplant center
- Personnel: 1 supervisor, 4 technologists, 1 data manager, Laboratory Director, Medical Director
MSKCC CYTOTHERAPY LABORATORY

- Transplants: 200 Auto & 120 Allo Tx
- Collections: >700 PBPC collections, 30 BM harvests
- Auto, Allo, GU transplants:
  - Minimally manipulated (MM) & more than MM
  - Protocol (including CTN & multi-center), & off-protocol (standard of care) patients
- Closed & open systems
- IDE & IND trials prior May 2005 & in development (none on-going at time of inspection)
- Cellular therapy (DLI, vaccines, NK & support for research studies

MSKCC CYTOTHERAPY LABORATORY

QA STRUCTURE

- Hospital QA system
- Departmental QA program
- Multi-departmental Transplant Service QA Committee
- Transfusion Committee, quarterly report
- Operate within Blood Bank Quality Plan
- Majority QA activity done by lab personnel
- No independent Quality Specialist who covers all aspects of program
- BB Quality specialist signs off occurrence reports
- Some institutional support (QA for research labs)
- Yearly audit
- Development of institutional SOPs

INITIAL PREPARATION

- Obtain information from ISCT, FACT, ASBMT, AABB, & other laboratories
- Follow development of federal regulations
  - Establish which regulations apply
  - Tissue type, source & extent manipulation
- Registered & reregistered with FDA
- Follow development of New York State regulations
  - Registered & inspected
  - Yearly activity report
PRACTICAL PREPARATION (1)

- Goal: operational systems & QA to meet most rigorous regulation/standard
- Support from Department of Clinical Laboratories & MSKCC in biosafety, IT, personnel training, intra-laboratory proficiencies, HIPAA issues
  - Established separate QA Committee for lab, network with other cellular therapy programs
  - Participate in CAP stem cell survey

PRACTICAL PREPARATION (2)

- FACT preparation (with mock inspection) established program wide QA, better documentation within transplant program
- AABB surveys (with mock inspection) resulted in clarification of process and design issues
- JCAHO inspection highlighted review & QA problem areas
- Meetings with administrative committee & staff to outline cGTP requirements (e.g., EM in unclassified space)

PRACTICAL PREPARATION (3)

- Establish which systems are the most important to the regulatory approach, concentrate on those
- Core GTPs: Processing, recovery, donor issues (eligibility, screening, testing), receipt, distribution, cleaning
  - Contamination, cross-contamination
  - Quality systems
  - SOPs
  - Record keeping, review, worksheet design
PRACTICAL PREPARATION (4)

- Central list of critical procedures, supplies, reagents with validation or qualification
- Standard format of worksheets, with review and conclusions clearly indicated and easy to present to inspector

USING REGULATIONS AS A GUIDE

- Read regulations and compliance document
- Outline regulations
  - List evidence of local compliance (laboratory organization and/or operations, relevant SOPs)
  - List example and its location
- Alert personnel from outside laboratory for help

CORE GTPs: THE PLACE TO START

- Facilities
- Environmental control
- Equipment
- Supplies & reagents
- Recovery of HCT/Ps
- Processing & processing controls
- Labeling
- Storage
- Receipt, pre-distribution shipment, distribution
- Donor eligibility
EVIDENCE OF COMPLIANCE

<table>
<thead>
<tr>
<th>Regulation</th>
<th>Requirement</th>
<th>Evidence of Compliance &amp; Notes</th>
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<tbody>
<tr>
<td>1271.160 quality program.</td>
<td>SOP 1.2 “Quality Program” SOP 1.1 “Management of SOP Manual” SOP 1.2 “Quality System” SOP 1.8 “Organizational Table and Job Descriptions” Transfusion Committee QA reports Minutes Cyto Lab QA Committee</td>
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FDA INSPECTION:
- Unannounced, 2 day August 2005, coupled with BB and Donor Room inspection (3 day)
- Inspection followed GTP’s & compliance document, exactly and in order
- Standard review of documentation & charts
- Assistance from coordinated clinical team assembled for FACT accreditation
- Special interest in donor eligibility product release & review event/complaint reporting

PROBLEMATIC ISSUES
- Complexity of operations (allo vs. auto)
- Laboratory chart format
- Levels of review: immediate 2nd tech check of worksheets, product release, final chart review & sign-off
- Division of responsibility: e.g., Donor eligibility documents in clinical charts
- Making copies of documents and charts
NOTE: Do not question...
MSKCC INSPECTION OUTCOME

No 483’s

INSPECTION OUTCOME (1)

- Verbal recommendations only
- Relationship with Blood Bank problematic
- Occurrence reports not detailed enough
- Separate lab operations from Blood Bank
- Separate tracking & trending occurrences from Blood Bank
- Complaint file format not reflect core GTPs
- Occurrences follow-up

INSPECTION OUTCOME (2)

- Verbal recommendations only
- Forms completion (cross-outs, areas of responsibility)
- Forms medical review (dates)
- Equipment files: organization, QC schedule, archiving
- Evaluation adverse reactions
- Clarification of responses to problems (ABO/Rh)
FDA INSPECTION FOLLOW UP

- Written report to Administrative Committee (who, what, where, when)
- Debriefing staff
- Notes on all verbal recommendations with action items
- Thanks to institutional staff

THINGS I WISHED I HAD DONE

- Rearranged equipment files
- IQ, OQ, PQ
- Eliminated chronological filing
- Aligned systems more closely with GTPs & used more similar language
- Reviewed after review of records
- Instituted stronger relationship with institutional QA system
- Mock FDA inspection

COMPLIANCE DOCUMENT INSTRUCTIONS

1. Review procedures for preparing the summary of records.
2. Determine if HCT/Ps that have completed the donor eligibility process are accompanied by a summary of records.
3. Are the records accurate, indelible, and legible?
Combined Top Observations
for all Inspections Done FY05 & FY06

- ... written procedures for prevention of infectious disease, cross-contamination during processing
- ... written procedures for all significant steps for obtaining, reviewing, assessing the relevant medical records of a donor
- ... records which are accurate, indelible, legible
- ... fail to identify the person performing the work, the date the work was performed and the particular tissue involved
- ... fail to include documentation of destruction or other disposition of human tissue

Combined Top Observations
for all Inspections Done FY05 & FY06

- ... written procedures for designating and identifying quarantined tissue
- ... not accompanied by a summary or copies of the donor’s relevant medical records
- ... all steps performed in the testing, screening, determining of donor eligibility... were not established, maintained, and followed
- ... documentation of receipt and/or distribution...
- ... test donor specimens for communicable viruses using FDA licensed donor screening tests
- SOP for the release of HCT/Ps from donors that test reactive for CMV
- Environmental conditions are not monitored...

Combined Top Observations
for all Inspections Done FY05 & FY06

- ...Procedures not established for processing, labeling control, storage/distribution, handling positive test results
- ...Procedures not followed for donor screening
- ...quality program not established, not ensure documentation of corrective actions, investigation and trending of deviations
- Supplies and reagents not verified, receipt not recorded
- Records not identify person performing work
- Donor testing not done with FDA approved/cleared tests, manufacture’s instructions not followed
ACKNOWLEDGEMENTS

Cytotherapy laboratory staff & Administrative Committee
MSKCC administration
Department of Clinical Laboratory administration and support staff
FACT preparation team
Clinical transplant teams (auto & allo)

RESOURCES

FDA website
Guidance documents
www.fda.gov/cber/genetherapy/gtpubs.htm
HTC/P compliance documents
www.fda.gov/cber/cp/cps.htm
ISCT, www.celltherapysociety.org
LRA, Member’s Lounge
AABB, www.aabb.org
PACT, www.pactgroup.net
NMDP, www.marrow.org
A little help from your friends
Speaker Contact E-mails

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Nancy H. Collins, PhD
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Presentation Slides

The web seminar presentation is available publicly at http://www.pactgroup.net
Select “Educational Material”

CME Accreditation Statement

AABB is an approved, accredited provider (Provider number 0000381) by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. AABB designates this education activity for a maximum of 1 category 1 credit toward the AMA Physicians Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.
CME Credit

If you are interested in obtaining CME credit for attending this web seminar, please note that each attendee must:

- Sign and fax roster to 240-306-2527
- Complete an online survey

http://www.surveymonkey.com/s.aspx?sm=wVTV_2966kajpqF2Mx_fWWQQ_3d_3d
(link above embedded in the reminder email sent Wednesday, October 10th)

Note: Please complete within 48 hrs of the program.

AABB Live Learning Center

After the rosters have been processed, you will receive an email from AABB with instructions on how to print your CME/CE certificates.

Thank you for attending!

To register for updates on upcoming web seminars, workshops, and PACT attended meetings visit us on the web at:
www.pactgroup.net