
# FDA Regulations for Apheresis Centers

Ann Kemp, Regulatory Compliance Manager
Kathy Graham, Sr. Regulatory Compliance Associate

Financial Disclosures – None



# Learning Objectives

At the end of this session, you'll be able to:

- Apply the regulations to the work at your AC
- Examine audit findings and learn from them
- Understand what the future under licensure may look like

# AC Audits

## What do we audit against?

- 21 CFR 1271 – Tissue Regulations – GTPs
- 21 CFR 210 & 211 – Drug Regulations - GMP




# 361 vs 351

- Refers to section of the Public Health Services Act

- "361" Products are regulated as tissue only (1271 only)
  - Unmanipulated allogeneic stem cells from first /second degree relative
  - Autologous stem cells
- "351" Products are regulated as tissue and drug (1271 & 210/211)
  - NMDP's allogeneic stem cells for transplantation
    - HPC, Cord Blood
    - HPC, Apheresis
    - TC, Whole Blood
    - TC, Apheresis

# 361 vs 351

- For most ACs majority of products are tissue only – 1271
- NMDP products add a new layer of regulations – drug regulations – 210 & 211




# Summary of AC Audits

- 40 ACs audited July 2011 – Aug 2013
  - 48% of domestic ACs
  - 63% of domestic PBSC collections
- Breakdown
  - 21 Hospital
  - 14 Blood Center
  - 4 Blood Center in hospital
  - 1 Independent Center

# Hospital vs. Blood Center



# Hospital vs. Blood Center

- Hospital based ACs
  - Part of BMT program
  - FACT accredited
  - Quality Plan - medically focused
- Blood Center based ACs
  - Blood product manufacturer
  - AABB accredited
  - Quality Plan - manufacturing focused

# Summary of Findings

- 114 total findings were cited
  - Average 2.85 findings per AC
- Top issues
  - Supply Management – 24 findings
  - Training/Comp Assessment – 17 findings
  - Records – 13 findings
  - SOPs – 12 findings
  - Facilities – 11 findings



# GTPs & GMPs

# GTP/GMP Topics

- Quality Program
- Contracts/ agreements
- Personnel (org chart, job description, qualification)
- **Training/ competency**
- **Procedures and forms (versions & use)**
- **Records – paper & electronic (completion, review, retention)**
- Complaint / deviation investigations & corrections
- Adverse events
- **Facilities (clean, secure, light/vent, trash, bugs)**
- Environmental controls (for aseptic processing)
- Equipment (calibration, maintenance, validation)
- **Supplies/reagents (receipt, qualification, use)**
- Recovery (Collection)
- Processing & Process Controls
- Process Changes and validation
- Labeling controls (inventory, no mix-ups)
- Storage / quarantine/release
- Receipt/ transfer and distribution
- Traceability of unique ID
- Computers - validation and use



# Supply Management

- Vendors qualified
- Defined list of critical supplies
- Defined process to receive, check in supplies
  - Verify order
  - Record lot #, expiration date
  - Check for defects, damage, contamination
  - Certificate of Analysis, Sterility Certificate
  - Check package insert (PI) for version, check for changes, change SOPs as necessary
  - Qualify, as necessary
  - Quarantine until all checks complete

# Supply Management

- Store in appropriate temp per PI (Documented temp monitoring)
- First In – First Out (FIFO)
- Documentation of lot # in use
- Separate quarantine area (Clear what is available for use and what is not)
- Process to quarantine and return/destroy defective or recalled supplies



# What do we look for?

- SOP on Vendor Qualification
- Logging in supplies when received
  - Lot number & expiration date
  - Acceptability criteria
  - Check of C of A and PI
- Temperature monitoring
- Quarantine area/process
- FIFO
- Documentation of lot # in use
- Storage up, off of floor
- Appropriate storage of filgrastim

# Common Findings

- No C of A and/or PI on file
- No quarantine area
- No defined quarantine process
- No temp monitoring



# Training & Competency

- Defined process for training
- Maintain records of training
- Define release of staff to perform task independently
- Define trainer qualifications
- Training linked to job description and to SOPs
- Training on SOP revisions
- Safety Training
- GMP Training
- Documented periodic competency assessments
- Defined process to handle failed competency assessment

# What do we look for?

- SOPs defining training and competency assessment
- Employee training records
  - Training on tasks they perform
  - Documentation that employee “released” to perform tasks independently
  - Evidence of training on SOP changes
- Trainer qualifications defined
- Periodic assessment of competency
- Retraining in specified situations
- GMP and Safety training




# Common Findings

- No GMP training (hospitals in particular)
  - Required by 211.25
- No clear release to task
- No competency assessment

# Paper Records

- Defined policy/procedure on record creation, correction, and retention
- Legible & indelible
- Appropriate error correction – no white out, no scribble over, no write over
- Concurrent documentation
- Date & initial all entries and added comments
- Timely review for completeness and accuracy
- Stored to maintain confidentiality and unauthorized access or tampering
- Retained indefinitely
- Microfilm/electronic copies verified
- Easily retrievable



# What do we look for?

- Forms filled out completely, legibly, indelibly with appropriate error correction
- Concurrent documentation – Record it as you do it.
- Date and initials on all added information
- Timely review
- Security from unauthorized access
- Clear record of what happened and in what order
- SOP defining good documentation practices

# Common Findings

- Poor documentation practices
  - Use of arrows down
- Multiple people filling areas on one form – no date and initials for each one
- Forms not completely filled out
- No SOP on defining documentation practices



# Document Management

(SOPs and Forms)

- Defined process for managing, writing, and updating documents (SOP on SOPs)
- Standard format
- Approval process–SME, manager, med staff, quality
- Version control
- Periodic review
- Master List of documents
- Readily available to staff in work area
- SOPs for critical tasks including GTP/GMP practices
- SOPs validated–clear and easy to follow, get expected outcome
- Staff follows SOPs and uses forms as intended
- SOP/form changes linked to training

# What do we look for?

- An SOP defining document control system
- A system of version control
- Current versions of forms and SOPs are in use
- SOPs readily available to staff
- Staff are familiar with SOPs
- SOPs are followed as written
- Documented training on revisions
- SOPs define critical tasks and GTP/GMP
- SOPs follow Manual of Operations




# Common Findings

- SOPs don't define specifics for NMDP collections
  - Labeling
- SOPs not followed as written
- Uncontrolled documents

## Facilities & Environmental Controls

- Adequate space,lighting,ventilation
- Defined space for specific tasks to prevent mix ups of product or records
- Privacy for donors
- Secure from unauthorized access (records, computers)

- Appropriate storage for supplies, records, equipment
- Appropriate temperature/humidity as required for equipment or supplies
- Documented cleaning (disinfection, garbage disposal)



## What do we look for?

- Donor privacy maintained
- Prevention of mix ups
- Limited access to manufacturing areas and to records
- Documented temp/humidity monitoring of collection area and lab
- Documented temp monitoring of storage areas
- SOP defining cleaning/pest control
  - Disinfection of work surfaces
- Biohazardous waste disposal
- Sufficient space

# Common Findings

- No humidity monitoring in collection area
  - COBE Spectra has humidity specs
- Cleaning that is done is not documented



# Other Findings

- Record Retention
  - Indefinite – specify in SOP or other doc
- Bloodborne Pathogen (OSHA)
  - No food or drink in collection areas
  - No product or samples in office areas
- Traceability
  - 2 sided forms – identifiers on both sides


- Documented hand-offs
  - Sign out from Apheresis
  - Sign in to CT Lab
  - Document condition


- Defined release criteria -1271.265(c)
  - Document criteria is met
  - Distinction between NMDP and other products
  - Failure to meet criteria
- Defined process for returned products




- Training/Competency documentation
  - Clear release to task
  - Competency assessment that measures problem solving skills
- Label control
- Defined Quality Indicators
  - Reporting to Management
- Traceability
  - Linkage of all assigned numbers

- Audits have been well received
- Issues discovered at ACs are fairly minor and easily corrected
- Overall good compliance




# What is Next?

# History


- 1990-1997 FDA begins to process to regulate all cells and tissues
- Codified under 21 CFR 1271- May 25, 2005
  - Prevent inadvertent use of infected tissue
  - Prevent improper handling/processing of tissues
  - Ensure clinical safety and efficacy of tissues



# History


- HPC, Cord
  - "Discretionary Enforcement"
    - FDA provided a grace period for manufacturers to comply
    - Didn't enforce inspection
    - Manufacturer didn't need to apply for a license, yet
    - IND was voluntary
- Final Cord Blood Guidance Issued 2009
- "Discretionary Enforcement" ended 2011

# The Future




# The Future

- Licensure of HPC, Apheresis
- Guidance from FDA
- Similar to HPC, Cord

# Lessons from CBU Licensure


- Quality Unit (Independent)
- Change control
- Process control
- Process validation
- Method Validation
- Line Clearance
- Facilities/Environmental Control and Monitoring
- Batch Records
- Lot Release
- Stability Studies (Expiration Date)
- Validated Computer Systems (Part 11 Compliant)

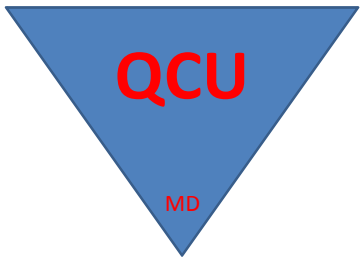


# What does all that mean and will it be the same for PBSC?


- Independent Quality Unit with Authority to:
  - Ensure controls implemented for mfg process
  - Ensure procedures developed/specifications followed
  - Approve/reject incoming materials and in-process materials
  - Review production records/ investigate discrepancies




Research and clinical/medical practice are inherently different than drug manufacturing




- Managing change to prevent unintended consequences
  - Any change affecting quality of products and/or processes, equipment, systems and methods




- Change Control Process:

  Process to ensure changes to materials, methods, equipment and software are properly documented, validated, approved and traceable
  - Includes:
    - Identification
    - Documentation
    - Review
    - Approval


- Procedures ensure changes implemented in a controlled manner
- Quality Unit has responsibility and authority for management/approval of changes




- Process Control/Validation
  - Product quality is consistent from batch to batch
  - Use in process controls
  - Monitor output
- Method Validation
  - Consistent test results from a particular method

- Line Clearance
  - Assuring components, labels, and documents from the previous work have been removed and accounted for before starting a new work
  - Control mix-ups
  - Prevent contamination



- Facilities/Environmental Control and Monitoring
  - HVAC
  - Clean Rooms

- Batch Records
  - Manufacturing records for product
  - Recreate manufacturing process from records
- Lot Release
  - Criteria must be met to allow product to be distributed and infused
    - Donor screening/testing
    - Product specifications (viability, TNC, sterility)

Note: Now a shared function; traceability/tracking



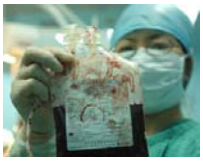

- Stability Studies (Expiration Date)
  - Product maintains critical characteristics under storage conditions for period of time as defined
    - Viability
    - CD34
    - Sterility

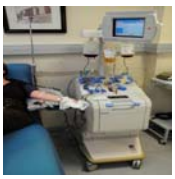
- Validated Computer Systems (Part 11 Compliant)
  - Controlled access
  - Audit trail
  - System validation
  - Electronic signature




- Continue under IND for several years
  - FDA issues Draft Guidance document (comment period to affect Final Guidance)
  - Grace period for licensure
  - Licensure required
- Continue under IND indefinitely

# Cord vs. PBSC





- PBSC is “real time” product
- No stored inventory that is many years old
  - Less leeway with testing requirements/mfg process
- Rapid timeframe for infusion
  - Sterility testing
- Special TC requests outside of licensure requirements need to be addressed
  - T cells



# Issues to Consider

- Lot number for the product for identity
- Specifications/minimum acceptance criteria for product release
- Potency assay/standardized methodology for testing/method validation
- Test method for product sterility
- Expiration date needed with data to support

# Issues to Consider

- Storage and shipping temperature ranges based on stability data
- Process for shipping or transporting quarantined units
- Process for corrective action when product not shipped appropriately



# Issues to Consider

International Products

- Importation of PBSCs is essential to meet need
- Framework needs to allow continued importation when GMP/GTP equivalency can't be met
- Not FDA's intent to limit the units available for US patients to only licensed units

# Issues to Consider

- Contracted Manufacturing process (AC/DC)
  - FDA Guidance on Contract Manufacturing
- Who holds the license
  - AC
  - Registry
  - Other



# In Conclusion


- Uncertain Future
- ACs on the right path
- Quality is good business practice




akemp@nmdp.org 612-465-7839
kgraham@nmdp.org 612-884-8234

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