FDA Regulations for Apheresis Centers

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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 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
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

- 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