

NATIONAL MARROW DONOR PROGRAM

BE THE MATCH

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FDA Regulations for Apheresis Centers

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

Financial Disclosures – None

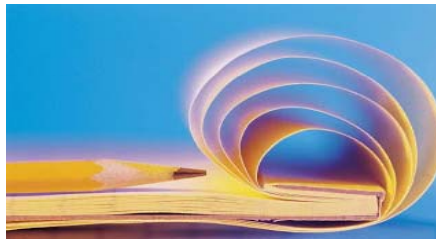
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Learning Objectives

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



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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



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Hospital vs. Blood Center



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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

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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

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GTPs & GMPs



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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



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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

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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



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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



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Common Findings

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



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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



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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



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Common Findings

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



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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



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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



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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



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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



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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



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Common Findings

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



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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)



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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



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Common Findings

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



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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

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Best Practices

- 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



Best Practices

- 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

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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

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The Future



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The Future

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



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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)



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



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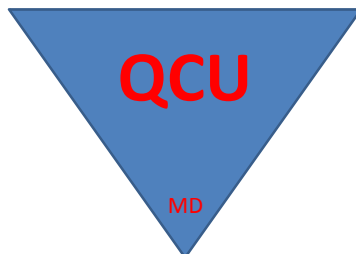


- Independent Quality Unit with Authority to:
 - Ensure controls implemented for mfg process
 - Ensure procedures developed/specifications followed
 - Approve/reject incoming materials and in-process materials
 - Review production records/ investigate discrepancies

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



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

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- **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

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

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- **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

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- **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

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- **Facilities/Environmental Control and Monitoring**

- HVAC
- Clean Rooms

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- **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

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- **Stability Studies (Expiration Date)**

- Product maintains critical characteristics under storage conditions for period of time as defined
 - Viability
 - CD34
 - Sterility

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- Validated Computer Systems (Part 11 Compliant)

- Controlled access
- Audit trail
- System validation
- Electronic signature

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- 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

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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

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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

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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

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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

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Issues to Consider



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

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In Conclusion



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



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akemp@nmdp.org

612-465-7839

kgraham@nmdp.org

612-884-8234

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