Preparing For Unannounced Inspections: FDA, FACT, AABB

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Columbus, Ohio

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BMT Program

AABB, CAP, FACT, TJC Accredited

“We are committed to providing excellent care in a safe environment”
FDA FY07 Inspections

• Cord blood, peripheral blood stem cells
  – 18 (total 426 4%)
  – Mean inspection 26 hours
• NAI 15, VAI 3, OAI 0
• Deficiencies
  – Donor screening and testing
  – CAPA
  – Donor eligibility
• Observations
  – Equipment cleaning and maintenance
  – Records
  – SOPs
  – Facility cleaning
  – Quality Program

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Code Of Federal Regulations

• Code Of Federal Regulations
  – Contains 50 titles
  – Title 21 regulations pertinent to food and drugs
  – Chapter I – FDA cGMPs
  – Subchapters
    • F – biologics for human use (600 series)
    • C – drugs (200 series)
    • H – medical devices (800 series)
  – Parts/Subparts
  – Sections
  – Paragraphs

“We are committed to providing excellent care in a safe environment”
HCT/P General Provisions (A) Establishment Registration And Product Listing (B)

- Proposed 1998
- Final rule 2001
- Effective 2001/2004
  - 21 CFR 1271
  - Subparts A and B
Donor Eligibility (C)
Current Good Tissue Practices (D)
Inspection (E)
Enforcement (F)

• Published 11/24/2004
  – 69 FR 68612
• Effective May 25, 2005
  – 21 CFR 1271
  – Subparts C, D, E and F
Exceptions

• Solely for non-clinical scientific or educational purposes.
• Remove and implant from same individual during the same surgical procedure.
• Carrier who accepts, receives, carries or delivers as a carrier.
• Do not recover, screen, test, process, label, package or distribute, but only receives or stores solely for implantation, transplantation, infusion or transfer within your facility.
• Only recovers reproductive cells or tissues and immediately transfers them into a sexually intimate partner of the cell or tissue donor.
Current Good Tissue Practices (cGTP)

• Recover, process, store, label, package and distribute (HCT/P) and screen donors, to prevent introduction, transmission and spread of communicable disease.
• Ensure that HCT/P does not contain communicable disease agents, are not contaminated and does not become contaminated during manufacturing.
• Communicable disease agents include viruses, bacteria, fungi, parasites and TSE.

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CGTP Requirements
Subpart D

- Exemptions and alternatives (1271.155)
- Quality program (1271.160)
- Personnel (1271.170)
- Procedures (1271.180)
- Facilities (1271.190)
- Environmental control and monitoring (1271.195)
- Equipment (1271.200)
- Supplies/Reagents (1271.210)
- Recovery (1271.215)

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CGTP Requirements
Subpart D

• Processing and process control (1271.220)
• Process changes (1271.225)
• Process validation (1271.230)
• Labeling controls (1271.250)
• Storage (1271.260)
• Receipt, pre-distribution shipment, distribution (1271.265)
• Records (1271.270)
• Tracking (1271.290)
• Complaint file (1271.320)

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Adverse Reaction (1271.350)  
Subpart E

• Involve a communicable disease related to HCT/P made available for distribution.
• Noxious or unintended response to any HCT/P were there is reasonable possibility that the HCT/P caused the response.
• Medwatch:
  – 15 days if fatal, life-threatening, results in permanent impairment of a body function or permanent damage to a body structure or necessitates medical or surgical intervention, including hospitalization.

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HCT/P Deviation (1271.350) Subpart E

• Prevention of communicable disease transmission or HCT/P contamination.
  – Issued from your facility
  – Involve communicable disease transmission

• Related to cGTP if they occur in your facility or facility under contract with you within 45 days.

• Includes corrective and preventative action.
Inspection (1271.400) Subpart F

- No statutory requirement for FDA to conduct biannual inspections.
- District base inspections on resources available.
- Risk based priorities:
  - Firms last inspection was classified “Official Action Indicated (OAI)"
  - FDA received information that there is a potential violation of 21 CFR 1271
  - HCT/P deviations

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Enforcement (1271.440)
Subpart F

• Untitled letter (483)
  – Do not meet level of regulatory significance and can be addressed through other means.
• Warning letter
• Order of retention, recall, destruction
• Order of cessation of manufacturing
• Prosecution
  – Imprisonment – 1 year
  – Fines - $100,000 to $250,000

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Food And Drug Administration (FDA) Committee

• Formed to establish guidelines, policies and processes for continuous state of FDA inspection readiness
• Promotes, educates and monitors compliance with cGTP
  – Annual cGTP education
• Keeps abreast of FDA guidance and recommendations for compliance to cGTP
• Meets every two months and conducts tracers on off months
• Reports quarterly to hospital’s Accreditation Committee
Committee Representation

- Clinical Engineering – Director
- Facilities Services – Director
- Environmental Services – Manager
- Clinical Laboratories – Director
- Risk Management – Attorney
- Collection Facility – Manager
- Quality and Accreditation – Director
- BMT Program – Director and Manager
- Cell Therapy Laboratory - Director
Service Understandings

• Created with departments providing services covered under cGTP
• Outline of applicable regulatory requirements and standards
• General responsibilities of each party
• Process for quality review, including audits
• Service Understanding reviewed every two years or upon changes
• Information suggesting department non-compliance, a meeting is scheduled to assist with compliance
FDA Registration And Inspection SOP

• Registration
• Inspection plan
  – Inspection aids
  – Call tree
  – Web-based paging system
  – Overhead announcement
  – Flowchart for inspection
FDA Tracers

- Tracer developed based on core cGTP
- Initially started as paper tracers, then moved to “real-time.”
  - Performed by committee members
  - On-site inspection
  - Documentation of compliance
  - Corrective action for non-compliance
  - Results reported to hospital’s Accreditation Committee
<table>
<thead>
<tr>
<th>Tracer</th>
<th>Description</th>
<th>Yes</th>
<th>No</th>
<th>Notes</th>
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<td><strong>OSUMC Clinical Laboratories</strong></td>
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<td>Current FDA Registration</td>
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<td>Current CLIA Certificate</td>
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<td><strong>Indiana Blood Center Testing Control</strong></td>
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<td>Notation in contract and follow cGMPs, cGTPs</td>
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<td>FDA Registration</td>
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<td>CLIA Certificate</td>
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<td>Using FDA approved donor screening test kits</td>
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<td>SOP for notification of testing problems</td>
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<td>SOP for acceptable samples and shipping samples to Central Indiana Blood Center</td>
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<td><strong>Review HBsAg Package Insert</strong></td>
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<td>Confirm using appropriate sample (e.g., anticoagulant, age, storage temperature)</td>
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<td>Compare SOP for testing to package insert (note discrepancies)</td>
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<td>Results interpreted according to manufacturer's instructions</td>
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<td><strong>HBsAg Reagent</strong></td>
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<td>Confirm FDA approved donor screening test kit</td>
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<td>Confirm appropriate reagent storage temperature</td>
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<td>Review reagent and supply receipt</td>
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<td>Verify not mixing different lots</td>
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<td><strong>Technologist</strong></td>
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<td>Documented training in cGTP/cGMP</td>
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<td>Review annual competency evaluation</td>
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<td>Review initial training HBsAg</td>
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<td>Review proficiency testing for HBsAg</td>
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<td>Have technologist simulate testing process</td>
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<td>Proper instrument settings</td>
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<td>Proper incubation time</td>
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<td>Proper incubation temperature (e.g., room temp)</td>
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<td>Documentation of reagent and control lots</td>
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<td>Proper interpretation of test and control results</td>
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<td>Explain transmission of test results</td>
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<td>Identification of technologist performing work (e.g., initials and dated)</td>
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<td><strong>Equipment</strong></td>
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<td>Review equipment manual (e.g., manufacturer's recommendations)</td>
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<td>Review equipment quality control, calibration and preventative maintenance SOPs</td>
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<td>Review quality control, calibration and preventative maintenance records</td>
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<td>Review validation of instrument for HBsAg testing</td>
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<td>Records maintained and well organized (e.g., electronic back-up)</td>
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<td><strong>Event</strong></td>
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<td>Review an event in regards to HBsAg testing for CAPA</td>
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<td>Review SOP for notification of BMT Program when testing problems encountered</td>
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Quality Improvements

- Surgical suite level cleaning of collection and processing facilities
- Better control and measurement of air quality, air exchanges and positive pressure
- Increased inspection of HVAC
- More timely equipment PM and calibration
- Increased frequency of infectious disease testing
- Availability of documentation
- Record retention
- Review of SOPs
FDA Committee Summary

• Organizational understanding of cGTP
• Dedication of resources to assure compliance
• Mechanism to monitor, audit, discuss and report quality issues related to cGTP
FDA Inspection Recommendations

• Escort the FDA inspector
• Copies of records involve Risk Management (legal counsel)
  – Data from quality audits, meeting minutes or investigations
  – Photocopies of documents or patient records
  – Photographs
  – Signatures on affidavits or agreements
  – Financial Information
• Maintain a list and copy of records given to the FDA
  – “Copy”
  – “Confidential”
FDA Inspection Recommendations

• Reserve a private room
• Request and verify FDA inspector’s credentials
  – Purpose for inspection (for cause notify accreditation organizations; CAP)
  – Length of inspection
• Assign “scribe”
• Direct questions by FDA inspector to most knowledgeable staff member
FDA Inspection Recommendations

• Listen to questions carefully
  – Answer truthfully, accurately and concisely
  – If answer unknown, inform the FDA inspector the answer is unknown
  – Do not rely on memory, refer to resources

• Observation
  – Take your time and focus
  – Error is made briefly explain
FDA Inspection Recommendations

• FDA will be documenting in a notebook
• Request an exit interview if only inspected for “information only.”
• FDA 483
  – Promptly prepare a written response
  – CAPA
Contact Information

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