Blood and Human Tissue

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Blood and Blood Components Objectives

- Blood Regulations (CFR)
- Compliance Program
- Systems Based Approach (Level 1 & 2)
- Types of Establishments Covered
- Frequency of Inspections
- Attachments and Contacts (CP)
- FDA-483 and Regulatory Actions
Blood Regs. (Code of Federal Regulations)

- 21 CFR 600's
  - 601 – Licensing
  - 606 – cGMP’s
  - 607 – Registration and product listing
  - 610 – General Biologic Product standards
  - 630 – General Requirements (Donor Notification)
  - 640 – Additional Standards (section specific to type of blood products)
  - 660 – Additional standards for diagnostic substance for laboratory tests

- 21 CFR 211 (drug regs)
  - GMP's
Compliance Program (CP)

- Inspection of Licensed and Unlicensed Blood Banks, Brokers, Reference Laboratories, and Contractors – CP 7342.001
  - The CFR and CP can be found at www.fda.gov

Objective of this program is to ensure that blood and blood components for human use are safe, pure, effective, and are appropriately labeled.

The inspection of a blood establishment is to ensure that manufactures are making products that meet the standards described in the applicable regulations (21 CFR 600’s & 211), including those intended to protect the donor. Also to meet any additional conditions of licensure incorporated in the establishments approved Biologic License Application (BLA)
Systems Based Approach

- Quality Assurance System - various planned activities that provide confidence that all procedures/processes that influence product manufacture and overall quality are monitored to ensure they are working as expected.
- Donor (Suitability) Eligibility System - the system that protects donor safety, determines a donor's suitability for blood collection (including donor deferral from either history screening and/or testing), notifies donors of unsuitability for donation and donor re-entry.
- Product Testing System - the system(s) that tests for communicable diseases, blood grouping and typing, and cross matching blood for transfusion by direct testing or electronically.
- Quarantine/Inventory Management System - the system(s) pertaining to product storage, distribution and retrieval, quarantine and distribution (release for use or destruction).
- Production and Processing System - process controls in the manufacture of specific blood and blood components, and equipment quality control, calibration, and maintenance.
Level 1 and Level 2 Inspections

• Level 1 – Comprehensive evaluation of the establishment’s compliance (all systems)
• Level 2 – Streamline evaluation of an establishment compliance, when the facility has met a defined standard of performance during past FDA inspections.
  o 3 of the systems will be inspected (facility must have at least 4 or 5 systems employed to qualify
  o Level 1 and 2 inspections do not apply for conducting pre-licensing and pre-approval (CBER). Do not apply to “for cause” inspections and inspections conducted in follow-up to a report of fatality
Level 1

- Initial inspection of firms
- Firm’s that have history of fluctuating in and out of compliance
- Compliance F/U inspections
- Establishment that perform communicable disease agent testing
- After conducting 2 previous inspections under a level 2 option

**Just a few examples of when a Level 1 would be conducted**
Level 2

• Must include QA and the Donor (suitability) Eligibility System and one other system

• If a 4 system firm does not employ Donor (Suitability) Eligibility system, then inspection should include QA and 2 other systems (systems determined by evaluating files, history and other available information)

• Must meet certain criteria’s to be eligible
  o Satisfactory history of compliance (3 successive NAI and VAI)
  o 1 of 2 previous routine inspection was a level 1
  o No trends or problems found during preparation (ex. BPD’s)
Establishment Types

- Blood Banks
- Blood and/or Plasma Brokers
- Component Preparation Facilities
- Contractors
- Distribution Centers
- Donor Collection Centers
- Hospital Transfusion Centers
- Indian Health Service Hospitals
- Testing Laboratories
- VA Medical Ctr. and Military Facilities
Frequency of CGMP Inspections

- Generally conducted on a biennial schedule or as close as possible
- Exceptions to this may include firm’s under consent decree, newly registered firm and/or follow-up inspections.
Attachments/Contacts

• CP contains attachments that provide instructions for the coverage of critical areas of the 5 systems and other important issues.
• CP also contains contacts of personnel that may be contacted on various issues; such as fatalities, registration and blood related concerns.
• If you ever have a question, feel free to contact the investigators within your district (business cards).
FDA-483 Inspectional Observations

- Regulatory Actions that may take place after a 483 is issued depends on the severity of the problems
  - Voluntary corrections
  - Warning Letter
  - License Revocation
  - License Suspension
  - Seizure
  - Injunction
  - Prosecution

***THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.
Human Cells, Tissues and Cellular and Tissue-Based Products (HCT/Ps)
Human Tissue Objectives

- Regulatory Framework
- 351 vs. 361 Tissue
- Human Tissue Regulations
- Difference between 21CFR 1270 and 21CFR 1271
- Guidance Documents
Regulatory Framework

- **Statutes (Laws):** Passed by Congress and signed by the President
  - Food, Drug & Cosmetic Act (FD&C Act)
  - Public Health Service Act (PHS Act)

- **Regulations (Implementation of the Statutes):** Written by FDA and approved by the Executive Branch
  - 21 CFR (Code of Federal Regulations)

- **Guidance (FDA’s interpretation of the Regulations):** Written and approved by FDA
  - Non-binding advice
The Difference Between Tissue Regulated Under 351 vs. 361 of the Public Health Act
Regulation is Based on Potential Risk to Public Health

351 HCT/Ps – Higher Risk
  • Sections 351 & 361 of PHS Act, FD&C Act
  • Premarket review and approval required
  • Product regulated under 21 CFR Parts 1271, 600, 200, 312, 812 among others

361 HCT/Ps – Lower Risk
  • Section 361 of PHS Act Only
  • Premarket review and approval NOT required
  • Product regulated solely under 21 CFR 1271
Regulation Solely Under Section 361 of PHS Act

21 CFR 1271.10

1. Minimally manipulated
2. Intended for homologous use only
3. Not combined with another article
   • Exception: water, crystalloids, or a sterilizing, preserving, or storage agent
4. Does not have a systemic effect and is not dependent upon the metabolic activity of living cells
   • Exception: autologous use, use in first or second degree blood relative, reproductive use
Examples of 361 Tissue

- Bone, ligaments, tendons
- Skin
- Arteries and veins
- Pericardium, heart valve allografts
- Dura mater
- Eye/Ocular tissue (ie: corneas, sclera)
- Reproductive tissue: semen, oocytes, embryos
- Hematopoietic progenitor/stem cells (cord or peripheral blood)
  - Autologous or family-related
Examples of 351 Tissue

- Cultured cartilage cells
- Cultured nerve cells
- Allogeneic pancreatic islet cells
- Gene therapy products
- Human cells used in therapy involving the transfer of genetic material (ie: cell or oocyte nuclei, mitochondrial genetic material)
- Unrelated allogeneic hematopoietic stem cells
- Unrelated donor lymphocytes for infusion
Human Tissue Regulations

21 CFR 1270
Applies to HCT/Ps recovered before May 25, 2005

21 CFR 1271
Applies to HCT/Ps recovered on or after May 25, 2005

Both focus on the prevention of communicable disease transmission
Regulated HCT/Ps

Examples of HCT/Ps recovered before 5/25/05 (regulated under 21 CFR 1270)
- Bone
- Tendon
- Ligament
- Fascia
- Cartilage
- Cornea
- Sclera
- Skin

Examples of HCT/Ps recovered on/after 5/25/05 (regulated under 21 CFR 1271)
- Bone and ligament
- Tendon and cartilage
- Fascia
- Skin
- Cornea and Sclera
- Dura mater
- Heart valve
- HPCs derived from peripheral and cord blood
- Semen, oocytes, embryos
21 CFR 1271

• **Subpart A**
  • General Provisions (purpose, scope, definitions & exceptions)

• **Subpart B**
  • Procedures for Registration and Listing

• **Subpart C**
  • Donor Eligibility

• **Subpart D**
  • Current Good Tissue Practice
  • Includes core CGTPs
21 CFR 1271 cont’d

• Subpart E
  • Additional Requirements for Establishments
  • Reporting requirements for Adverse Reactions and HCT/P Deviations
  • Contains labeling requirements

• Subpart F
  • Inspections and Enforcement
  • HCT/Ps offered for import
  • Orders of retention, recall, destruction, and cessation of manufacturing
Subpart C: Donor Eligibility (DE)

- **Purpose (1271.45):** Set out requirements for determining DE including donor screening & testing
  - Donor eligibility determination **required** for all donors (except as provided in 1271.90)
- Procedures
- DE determination requirements
- Records (accompanying, SOR, & retention)
- Quarantine & Storage
- Donor screening
- Donor testing
- Exceptions
Subpart D: Current Good Tissue Practice (CGTP)

- **Purpose (1271.145):**
  - Prevent the introduction, transmission or spread of communicable diseases

- **Governs the methods, facilities, & controls used in:**
  - Manufacture of HCT/Ps
  - Recordkeeping
  - Establishment of a quality program
Guidance Documents Applicable to HCT/Ps

• Guidance for Industry: CGTP and Additional Requirements for Manufacturers of HCT/Ps: Effective date – 12/2011

• Guidance for Industry: Certain HCT/Ps Recovered from Donors Who Were Tested for Communicable Diseases Using Pooled Specimens or Diagnostic Tests: Effective date – 4/16/2008

• Guidance for Industry: Regulation of HCT/Ps - Small Entity Compliance Guide: Effective date – 8/24/2007

• Guidance for Industry: Eligibility Determination for Donors of HCT/Ps: Effective date - 8/27/2007

Guidance Documents Applicable to HCT/Ps (cont’d)


- Guidance for Industry: MedWatch Form FDA 3500A: Mandatory Reporting of Adverse Reactions Related to HCT/Ps: Effective date – 11/30/2005


Location of Tissue Guidance Documents

- Available on the Internet: