Indiana University Health

Transfusion Service cGMP

IUH BB Management Team

Presentation Summary

- Discuss the history of GMP and the Food & Drugs and Biologics industries and its impact on current FDA blood banking regulations
- Discuss terms and agencies important to the blood banking industry
- Discuss Quality in Transfusion Service Laboratory and cGMP application
- Discuss importance and responsibility for quality management

History of GMP

cGMP (Current Good Manufacturing Practices)

History (Food & Drug)

- Early 1900's – pressure to pass legislation governing food industry
  (Blood not considered a "drug")
- 1906 – Pres. Roosevelt read Upton Sinclair's *The Jungle* – pressured Congress
- 1906 – ***Pure Food and Drug Act*** – prohibited interstate commerce of adulterated/misbranded food/drugs
- 1931- Food, Drug and Insecticide Admin – renamed FDA – responsible to enforce 1906 Act
- 1938 – ***Food, Drug and Cosmetic (FD&C) Act*** – required new products prove safety prior to marketing
- 1962 – First Court decision ruling blood products were drugs
- 1963 – FDA established Good Manufacturing Practices (GMPs) within the Code of Federal Regulations (CFR) Part 211 –minimum requirements for drug manufacture that were legally binding.

History (Biologics)

(Blood "generally" considered "biologic")

- 1902 –*Virus, Serum and Antitoxin (PHS) Act* (*Biologic Control Act*, *Virus Toxin Law*) required licensure, labeling control & inspection by Hygienic Laboratory of Public Health Services
- 1903 –*PHS (Public Health Services) Act amended* – license required for interstate shipment, annual unannounced inspections (basis of annual license renew.)
- 1937 – First Blood Bank established – Cook County Hosp., Chicago
- 1944 – *PHS Act amended* – license issued after demonstrating safety
- 1946 – First BB licensed - Philadelphia
- 1970 – *PHS Act amended* –blood/blood products and derivatives defined as biologics

History (Biologics & Drugs)

- 1972 – *PHS Act* (define blood as biologic) and *FD&C Act* (define blood as drug) were merged - Biologics regulated by Bureau of Biologics of FDA
- 1975– FDA published Part 606 (cGMP) specific for blood
- 1978 – FDA major revision to Part 211 (cGMP)
- 1980 – FDA delegated regulation of Txn Service to HCFA (Health Care Financing Administration) and HCFA delegates inspections to CAP, AABB and State Health
- 1988 – **CBER** (Center for Biologics Evaluation & Research) & **CDER** (Center for Drug Evaluation & Research) formed by a split of the Center for Drugs and Biologics. Regulated by CBER, blood is still to be considered both a **biologic and drug**
- 1990s –CLIA '88 finalized. FDA treating blood establishments as manufacturers and strict compliance to CFR 200 (Drugs), 600 (Biologics) and 800 (Medical Devices).

Regulatory & Accreditation Agencies for Laboratory and Transfusion Services

Terms

- **Accreditation** – AABB, CAP, TJC
  - Membership in peer group
  - cannot bring legal action (loose accreditation)
- **Regulation** – FDA, OSHA, State
  - Law/rule/regulation for industry
  - Can bring legal action
- **Registered** – FDA
  - All blood establishments involved in production/handling of blood must be registered
  - Registered (but "unlicensed")
    - No interstate commerce, ship only within state
- **Licensed** – FDA (State)
  - Required for interstate commerce
  - Can only ship licensed product over state line
  - Exception for: "medical necessity" (infrequent, documented)

Regulatory & Accreditation Agencies

- **FDA** – Food & Drug Administration – CFR Title **21**

- **CMS –** Centers for Medicare/Medicaid

  CLIA – Clinical Laboratory Improvement Act 1967

  CLIA – Clinical Laboratory Improvement Amendment 1988

- **CAP** – College of American Pathologists
- **AABB** – previously American Association of Blood Banks

- **TJC** – The Joint Commission *(previously **JCAHO** – Joint Commission of Accreditation of Healthcare Organizations)*

- **OSHA** – Occupational Safety and Health Admin. - CFR Title **29**
- **ISDH –** Indiana State Dept. of Health

FDA Documents

- **Code of Federal Regulations** (CFR)
  - Legally binding, laws/rules posted via Federal Registry – (a daily publishing of federal agency actions)
  - Title 21 updated annually April 1st

50 Titles
⇓
Title 21 – Food and Drugs
⇓
Chapter I – GMPs
⇓
Subchapters
F - Biologics (600 series)
C – Drugs (200 series)
H - Medical Devices (800 series)
⇓
Parts 1-1300 +
(GMPs and standards for specific industries)

FDA Inspections

- **FDA Inspections**
  - unannounced
  - Every 2 years
  - Form 482 – Notice of Inspection
  - Form 483 – Inspectional Observations
    - Opportunity for voluntary correction
    - Regulatory/Administrative sanctions – jeopardize licensure
      - **Warning letter** – continued pattern of noncompliance
      - **License/Registration suspension** – prevent interstate commerce
      - **License/Registration revocation** – lengthy process
    - Legal/Judicial sanctions
      - **Seizure** – condemn product, take physical possession
      - **Consent degree** – mutual agreement between facility and court
      - **Injunction** – court ordered prohibiting operations
      - **Prosecution** – criminal action against firm/individuals

AABB Documents

- *Technical Manual* – blood banking principles and procedures
- *Standards* – minimum requirements for accreditation
  - Blood Banks & Transfusion Services
  - Relationship Testing Laboratories
  - Immunohematology Reference Laboratories
  - Perioperative Autologous Blood Collection and Administration
  - Cellular Therapy Services
  - Molecular Testing for Red Cell, Platelet and Neutrophil Antigens
  - Patient Blood Management Program
  - Out-of-Hospital Transfusion Administration Services
- Others:
  - *AABB Bulletins*
  - *Transfusion* – monthly hardcopy
  - *AABB News* – monthly hardcopy
  - *Weekly Report* – weekly email
  - *SmartBriefs* – daily email

AABB Quality Essentials

- Developed by AABB in 1997
- Response to FDA 1993 Draft *Guidelines for Quality Assurance in Blood Establishments* (Final Guidance 1995, now 21 CFR 211 & 606)
- Consistent with ISO 9000 Standards
- First appeared in
  - Tech Manual (1999 13th Ed)
  - AABB Standards (1997 18th Ed.)

AABB Quality Essentials

- Organization
- Resources
- Equipment (Calibration and Maintenance)
- Supplier and Customer Issues
- Process Control (Final Inspection and Handling)
- Documents and Records
- Deviations, Nonconformances, and Adverse Events
- Assessments: Internal and External
- Process Improvement Through Corrective and Preventive Action
- Facilities and Safety

AABB & CAP Inspections

- **AABB Inspections**
  - Unannounced
  - Every 2 years

- **CAP Inspections**
  - Unannounced
  - Every 2 years
  - Can be Coordinated with AABB Inspection for Transfusion Services

What is Quality in Transfusion Service?

Application of cGMPs

Definition of Quality

- “The degree of excellence.”
- The primary goal of transfusion services in all aspects of care and services.
- Is everyone’s job - all the time.

Quality Assurance

- The sum of ALL activities planned and performed to provide confidence that all systems and their elements that influence the quality of the product are functioning as expected and relied upon.

Quality cGMP Requirements

- **Recordkeeping:**

Documentation is extremely important in what we do and is an area of GMP compliance which the FDA investigates closely.

- Detailed and consistent recordkeeping is essential for quality manufacturing.
- Through the GMPs, the FDA requires manufacturers to keep detailed data on production parameters, processes and test specifications.

Manufacture

- CFR 600.3: Manufacture means all steps in propagation or manufacture and preparation of products and includes but is not limited to, filling, testing, labeling, packaging, and storage by the manufacturer.

- Documents (i.e. Forms) become a record once completed
- Must be reviewed by supervisory personnel
- Record retention time periods are specified by AABB, FDA and the CFR

Quality cGMP Requirements

- **Effective Documentation**

  Note: this includes legible documentation

  WRITE OVER is not acceptable error correction. Original result must remain legible. Single line through with initials and rewrite correct result is the appropriate way to document a clerical correction

- Effective documentation should provide:
  - Trackability: Does the documentation provide an audit trail whereby the complete process can be followed sequentially?
  - Traceability: Must be able to trace any unit of blood or component from its source to its final destination
    - Important in investigating adverse events and look-backs
    - a) Can we tell what was done, who did it, when it was done, which components were used, what equipment was used, etc.?
    - b) Can we develop a complete history of components used in this process?

- **REMEMBER: If it is not documented, it did not happen !**

Quality cGMP Requirements

- **Facility and Equipment Requirements**

Facilities should be of suitable size and design to assure cleaning, maintenance and proper flow of operations in designated areas. Areas must be clearly separated and designated for particular purposes. For example, quarantined blood can be stored in the same refrigerator as blood for transfusion, provided it is physically separated in some way and labeled accordingly.

Areas Addressed by GMP Equipment and Facility Requirements

- Orderliness
- Flow design
- SOPs
- Equipment maintenance
- Calibration/Validation
- Cleanliness
- Space
- Physical separation of supplies/blood components
- Labeling of specified space

Quality cGMP Requirements

- **Facility Management**
  - Organized to promote effective quality management system
  - Organizational structure must clearly define responsibilities for the provision of blood, blood components, products, and services
  - Clearly identifies responsibilities of key personnel
  - Personnel must have appropriate education, training, and experience to ensure competent performance of assigned duties - job descriptions
- Training program
- Competency program
- Quality Plan

Quality cGMP Requirements

- **Calibration:** the comparison of a measurement standard or instrument of known accuracy with another standard or instrument of unknown accuracy to confirm, delete, correlate, report or eliminate by adjustment any variation in the accuracy of the item being compared.
  - important in all phases of blood establishment manufacturing, but especially in laboratory testing and for equipment which supports lab processes. There is little or no room for error in these measurements, as such errors could be detrimental to someone's health.
- **What needs to be calibrated?** Automatic, mechanical, and electronic equipment, including computers, that are used in the manufacture, processing, packing, and holding of a drug product must be routinely calibrated, inspected, or checked according to a written program designed to assure proper performance. (21 CFR 211.68)

Quality cGMP Requirements

- **Validation:** a process which establishes documented evidence providing a high degree of assurance that a specific process will consistently produce a product that meets its pre-established quality and performance specifications.

Areas Where Validation is Needed (3 Ps)

Procedures

Processes

Personnel

- Steps in Validation
  - Determine what you expect the end result to be
  - Determine the critical process parameters
  - Perform functional testing to determine that all specifications are met (all functions)
  - Perform functions in "worst case scenario"
  - Determine if results acceptable
  - Write summary report
  - Responsible person review/sign-off on summary

Quality cGMP Requirements

- **Standard Operating Procedures**
  - CFR 211.100 There shall be written procedures for production and process control designed to assure that products have the identity, strength, quality, and purity they purport or are represented to possess.
  - CFR 606.100 Written standard operating procedures shall be maintained and include all steps to be followed in the collection, processing, compatibility testing, storage and distribution of blood and blood components….procedures shall be available to the personnel for use in the areas where the procedures are performed.

- A Standard Operating Procedure is one form of control in the transfusion service. SOPs related to each individual's responsibilities are to be followed when performing those duties.
  - Deviation from SOPs may at times be necessary. Any such occasions should be documented according to a written protocol. **Deviation** is the occurrence of any variation from approved manufacturing methods, materials or test procedures contained in established SOPs or records. These variations may or may not impact the finished product quality.
  - All Transfusion Service personnel should have documentation of continued competency of procedures

Quality cGMP Requirements

- **Labeling**

- The purpose in applying a label to a product is to give information
  - that information must be correct.
- Just placing a label on a product is not sufficient
  - it must be the CORRECT label for that product or the product is misbranded.
- There must be intensive control in the area of labeling.
- Label validation requires a final comparison between the labeled unit and the record for that unit to ensure that the proper labels have been applied to that unit.
- Although a transfusion service may not collect or process whole blood donations, the need for labeling occurs with component modifications:
  - CMV status, Irradiation, and other special indications (washing, aliquotting, etc.)
  - These labels must be used appropriately and accurately.

Quality cGMP Requirements

- **Audits**
  - a systematic investigation to confirm or negate that established, approved policies and SOPs are being properly implemented. An **internal audit** is conducted by individuals within the organization, whereas an **external audit** is conducted by outside agencies
  - Each audit should have a checklist of the details to be reviewed.
  - Communication should be an important aspect of audit process.

- Internal
  - purpose is to identify opportunities for improvement of processes.
  - should be planned and periodic.
  - Monitor the effectiveness of quality system continuously.

- External
  - AABB Inspection
  - CAP Inspection
  - FDA Inspection

Quality cGMP Requirements

- **Handling, Storage, Distribution, and Transport**
  - Process must ensure proper handling, packaging, and transport of blood and blood components.
    - Critical storage temperatures
    - Transport containers
    - Records detailing complete history (QC records, Forms, computer system)
    - Final Inspection and Testing
      - Ensures the finished blood component is acceptable prior to distribution or issue.
        - » Acceptable units are those which have had all testing performed, have been properly stored during all phases of manufacture, and all cGMP requirements have been met for producing a product that is safe, potent, and pure.

Quality cGMP Requirements

- **Vendor/Suppliers/Reagents**
  - Products and services of a transfusion service can only be as reliable as the raw materials or services we utilize.
  - Products used in the collection, testing, processing, holding and distribution of blood that have the potential to affect the quality of blood must be purchased from suppliers who meet requirements.
- Suppliers/Vendors
  - Supplier Qualification
  - Agreement Review
- Supplies and Reagents:
  - Prior to use, incoming supplies and critical materials must be inspected and tested to ensure they are satisfactory for their intended use.
  - must be used in a manner consistent with the manufacturer's directions.
  - Documentation of receipt allows us to trace supplies from the time we took control of it. Inspecting supplies allows us to determine if it meets our acceptance requirements and meets or exceeds FDA regulations.
    - Applies to reagents, supplies, equipment, blood and blood components.

Why is Quality Management important & who is Responsible?

Purpose of Quality Management

- *Prevent* rather than *correct* errors
- Evaluate processes through “root cause analysis” to uncover cause of errors
- Develop process improvements to decrease errors and implement effective manufacturing processes to ensure product safety and quality
  - cGMPs were published by FDA as requirements for process control to uphold quality and safety in manufacturing of products
- Early detection of trends makes it possible to develop corrective action before blood products or patient safety are adversely affected

Purpose of Quality Management

- **Deviation/Error Management**
  - Must have a process in place to capture and assess incidents, errors, and accidents (occurrences).
  - the key element of GMP compliance and continuous quality improvement strategies.
  - We know and the FDA knows: **because we are humans, we are going to make mistakes**
  - Documentation of BPDs (Blood Product Deviations) result in root cause analysis and improvement of processes, not in punitive measures for individuals responsible.
- **Types of Events Under Deviation Management**
  - Accidents
  - Incidents
  - Variances
  - Complaints
- **Goals of a Quality Assurance program**
  - decrease errors/accidents
  - ensure credibility of test results
  - implement effective process/system controls
  - emphasize error prevention
  - report BPDs appropriately

Purpose of Quality Management

- Report to responsible parties
  - Medical Director
  - As required, may include patient's physician, source facility, manufacturer, outside agencies
- Develop criteria
  - Establish thresholds for monitors
  - Identify negative trends

BPDs: Reportable or NOT?

- **Ask yourself these questions:**
  - Was the event associated with the manufacturing?
  - Was there a deviation or unexpected event that may affect safety, purity, or potency of the product?
  - Did you have control over the product when the deviation occurred?
  - Was the product distributed by your facility?
- Distribution is defined as having left the control of the transfusion service.
- **Non-reportable:**
  - Component Preparation— tech initials of person preparing unit was missing
  - Testing—documentation deviation if other information indicates testing was performed appropriately
  - Labeling—unit labeled with shortened expiration date
  - QC & Distribution—frozen product breaks during thawing and is discarded
- **Reportable:**
  - Component Preparation---specific procedures for irradiation not performed or performed inappropriately
  - Testing---incorrect incubation time/temperature
  - Labeling---unit labeled with incorrect information regarding **leukoreduction, irradiation, or washing**
  - QC & Distribution---**CMV neg, Irradiation, or Leukoreduction** required, but either not done or not labeled appropriately

Quality is Everyone's Responsibility

- **Remember:** **Error reporting is everyone's responsibility.**

The QA Unit is the designated group to oversee quality assurance activities, ***EVERY INDIVIDUAL*** within a blood establishment has a responsibility to ensure the quality of products produced.

Glossary of Terms:

- **Accident**—an unexpected occurrence during a manufacturing process, not attributable to a human
- **Center for Biologics Evaluation and Research (CBER)**---section of the FDA under which the regulation of blood establishments falls
- **Code of Federal Regulations (CFR)**---publication of the federal government consisting of 50 titles; contains the Good Manufacturing Practices. The 200 series addresses pharmaceuticals, the 600 series addresses biologics and contains specifics for blood establishment, and the 800 series addresses medical devices
- **Current Good Manufacturing Practices (cGMPs)**---minimal standards found within the Code of Federal Regulations for the manufacture of drugs and biologics. These are legal requirements and are designed to ensure that drug and biologic products are safe and have the identity and strength, quality and purity characteristics each purports to have.
- **Deviation**---any variation from accepted operating procedures whether or not product quality is affected
- **Document control**---a plan for the management of all documents within an organization which includes, but is not limited to, document design, issuance of documents, removal of obsolete documents, document revision, etc.
- **Error**---a mistake attributable to a human. **Reportable errors (deviations)** are those deemed by the FDA to represent failure to comply with good manufacturing practices
- **National Institute of Standards and Technology**---an organization which provides certified standards for measurement accuracy (NOTE: BB uses a NIST thermometer to calibrate BB thermometers)
- **Worst case scenario**---conditions which are not ideal for manufacturing, but which may occur during manufacturing