Good Manufacturing Practice ("GMP") Compliance: GMPs EXPLAINED

Presented by

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Good Manufacturing Practice Regulations

- **Establishes minimum GMP for methods to be used, and the facilities or controls to be used for, the manufacture, processing, packing or holding of a drug to assure that the drug is:**
  - **Safe**
  - **Has the appropriate identity and strength**
  - **Meets quality and purity characteristics**

21 C.F.R. 210 and 211

cGMP Violations -- Severe Consequences

- **Product is “adulterated”**
- **Shutdown of manufacturing facility**
- **Seizure of product**
- **Recall product**
- **Front page press coverage**
- **Competitive disadvantage**

Severe Consequences *(cont.)*

- **GMP Hold on product applications**
  - **International sites**
- **Injunction / Consent decree**
  - **Schering Plough ($500 Million)**
  - **Abbott Laboratories ($100 Million)**
  - **Wyeth–Ayerst Laboratories ($30 Million)**
  - **Individual Defendants**
- **Criminal Investigations and Indictments**
- **Lawsuits**
  - **United States ex rel. King**

cGMP: Current Trends

- **21st Century: Risk-Based Approach**
  - **Risk-based assessment**
  - **Up-to-date Science-based policies and standards**
    - **Part 11**
  - **Integrated Systems approach**
    - **Quality / Facilities and Equipment / Materials / Production / Packaging and Labeling / Laboratory Control**
  - **International cooperation**
    - **ICH: International Conference on Harmonisation**
- **Proposed amendments regarding validation and cross-contamination**

cGMP: The Basics

- **Quality Control**
  - **Product meets specifications**
- **Quality Assurance**
  - **Systems ensure control and consistency**
  - **Validation, validation, validation**
- **Documentation**
  - **If it is not documented, it did not happen**

cGMP: Raw Materials

- Active ingredients
- Excipients
- Audit suppliers on regular basis
  - Before entering into contract, review regulatory history
  - Monitor regulatory compliance
- Test incoming raw material

cGMP: Buildings and Facilities

- **Separate or defined areas as are necessary to prevent contamination or mixups**
- **Air filtration systems (HVAC) in production areas**
- **Sanitation**

21 C.F.R. 211.42-58

cGMP: Production and Process Controls *("SOPs")*

Written production and process control procedures shall be followed in manufacturing and shall be documented at the time of performance. Any deviation from these procedures shall be recorded and explained or justified.

21 C.F.R. 211.100

cGMP: In Process Testing

- **Must have written procedures and testing of product while being manufactured to assure batch uniformity and integrity**
- **Control procedures shall be established to monitor output and to validate manufacturing processes that could cause variability**

21 C.F.R. 211.110

cGMP: Expiration Dating

- To assure that a drug product meets applicable standards of identity, strength, quality and purity at the time of use, it shall bear an expiration date determined by appropriate stability testing described in Section 211.166.

21 C.F.R. 211.137 (a)

- Expiration dates shall be related to any storage conditions stated on the labeling, as determined by stability studies described in Section 211.166.

21 C.F.R. 211.137 (b)

cGMP: Packaging and Labeling Operations

- **Company must have written procedures designed to assure that correct labels, labeling and packaging materials are used for drug products; such written procedures shall be followed.**
- **Label mix ups have been a major reason for drug product recalls.**

21 C.F.R. 211.130

cGMP: Laboratory Controls

- **Testing and release for distribution**
  - **For each batch of drug product, there shall be laboratory determination of satisfactory conformance to final specifications for the drug product, including the identity and strength of each active ingredient prior to release.**
  - **There shall be appropriate laboratory testing, as necessary, of each batch required to be free of objectionable microorganisms.**

21 C.F.R. 211.165 (a) & (b)

cGMP: Stability Testing

A written testing program designed to assess stability characteristics is required. Stability testing results must be used in determining storage conditions and expiration dates.

21 C.F.R. 211.166

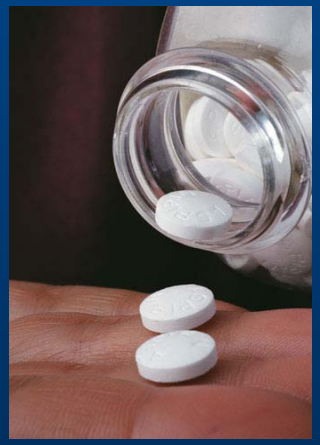
cGMP: Production Record Review

- **Production and control records shall be reviewed and approved by the quality control unit to determine compliance with all established, approved written procedures before a batch is released or distributed.**
  - **Product Impact Assessment**
  - **Trend Analysis**
  - **Distributed Product**

21 C.F.R. 211.192

cGMP: Deviation Investigations

- **Any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications must be investigated whether or not the batch has already been distributed.**
  - **Investigate other batches of same drug product**
  - **Investigate other drug products that may have been associated with the specific failure or discrepancy**
  - **Written record of investigation**



cGMP: Deviation Investigations (cont.)

- **Documenting the Investigation is Critical**
  - **Hypotheses should be scientifically based**
  - **Subject matter experts should be consulted throughout the investigation, including the initial identification of hypotheses**
  - **Once a hypothesis is identified, it must be investigated**
  - **All hypotheses should be validated or invalidated**

cGMP: Deviation Investigations (cont.)

- **Corrective and Preventative Action Program**
  - **As part of deviation investigations...**
  - **Root cause identification and definitive corrective actions**
    - **Company Program / System should audit:**
      - **Timeliness of corrective / preventative actions**
      - **Effectiveness of actions**
      - **Documentation**
    - **Example:**
      - **Environmental monitoring/Cleaning**

cGMP: Deviation Investigations (cont.)

- **Corrective and Preventative Action Program (cont.)**
  - **After an FDA inspection...**
  - **Establish scientifically sound corrective and preventative actions**
    - **Realistic timeframes**
  - **Ensure compliance with commitments to FDA**
    - **Systems**
    - **Specific Issues**
      - **E.g., Change Control / Training**

cGMP: Responsibility and Authority of Quality Control

- **Quality control unit "shall have the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products, and the authority to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated. The quality control unit shall be responsible for approving or rejecting drug products manufactured, processed, packed, or held under contract by another company."**

21 CFR 211.22(a)

cGMP: Complaints

- Written procedures describing the handling of all written and oral complaints
- Review by Quality Control unit
  - Possible failure to meet any specification
  - Determine need for deviation investigation
  - Adverse Drug Experience report assessment
- Documentation of complaint and investigation or reason for not investigating

21 C.F.R. 211.198

cGMP: Records and Reports

Contemporaneous documentation critical

- **Laboratory and production records**
- **Trending analysis**

Data Integrity

Internal review: OOS results, complaints, R&D

External review: FDA inspections, business deals (due diligence), and products liability cases

cGMP: Reports (cont.)

- **Field Alert Reports § 314.81(b)(1)**
  - Labeling
  - Failure to meet specifications — STABILITY FAILURES
  - Within 3 working days of receipt
  - Warner Lambert criminal case
- **Adverse Drug Experience Reports § 314.80**
  - ASAP but no later than 15 calendar days of initial receipt
  - Foreign and domestic
- **Recall Procedures and Preparation**

cGMP: Auditing

- **Independent Audit Group**
  - **Resources**
  - **Authority**
- **Global Approach - Harmonization of Quality Standards**
- **Audit priority systems / specific issues**
- **Follow-up audits**

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