Product Manufacturing
What are cGMPs?

- cGMPs provide for systems that assure proper design, monitoring and control of manufacturing processes and facilities to ensure the identity, strength, quality and purity of drug products.

- BASIC PARADIGM:
  - Quality control (product meets specifications)
  - Quality Assurance (systems ensure control and consistency, validation)
  - Documentation (if it's not documented, it didn't happen)
What are cGMPs?

- Basic Elements:
  - Quality system and independent quality group to oversee the quality system;
  - System for monitoring process performance and product quality to ensure that a state of control is maintained;
  - Documentation of process performance and product quality through written records;
  - Change management system to assure that all changes are properly evaluated and documented;
  - Corrective action and preventative action systems to address items that may affect process performance and product quality.
Current cGMP Trends

- Risk-based assessment
- Up-to-date science-driven policy and standards (21 CFR 211)
- Integrated Systems Approach (quality, facilities & equipment, Materials, Product, Packaging & Labeling/Laboratory Controls, Record Keeping)
- International Standardization
  - International Conference on Harmonization (ICH) Q8 Pharmaceutical Development”
  - ICH “Q9 Quality Risk Management”
  - ICH “Q10 Pharmaceutical Quality System”
Current cGMP Trends

- FDA and ICH regulatory publications trending toward single set of regulations for all medical products throughout ICH community;
- Medical device concepts in QSR (21 CFR 820), as well as international quality standards (e.g., ISO) are being integrated into drug cGMPs;
  - “Pharmaceutical cGMPs for the 21st Century” (FDA, August 2002)
    - Guidance: “Quality Systems Approach to Pharmaceutical cGMP Regulations”
Current cGMP Trends

- Outsourcing to Specialized cGMP Manufacturing Companies/Facilities
  - Quality agreements becoming more important because Sponsor responsible.
Legal Basis

- §501(a)(2)(B) of the FD&C Act:
  - “[a] drug shall be deemed *adulterated* if…the *methods* used in, or the *facilities* or controls used for its *manufacture*, *processing*, *packing* or *holding* do not conform to or are not operated or administered in conformity with current good manufacturing practice…” (emphasis added)
  - “to *assure* that such drug meets the requirements of this *Act* as to *safety* and has the *identity* and *strength*, and meets the *quality* and *purity* characteristics, which it *purports* or is *represented to possess*.” (emphasis added)
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cGMP Legal Principles

- Product quality cannot be tested in; quality must be built into the product.
  - Must take care in created medical product

- Without cGMP compliance
  - Products are considered adulterated and pose a public health threat;
  - Firm and its management is responsible.
cGMP Legal Principles

- Failure to comply with cGMPs lead to the following public health risks:
  - Super-potency / sub-potency
  - Contamination of the product;
  - Misbranding
  - Bioavailability issues
  - Safety and efficacy limitations.
cGMP Legal Principles

- **Scope (i.e., what is covered?)**
  - Ingredients (bulk API and excipients)
  - Finished dosage forms administered to humans and animals:
    - OTC and Rx Drugs
    - Biologics
    - Veterinary drugs
    - Drugs undergoing study (IND)
  - Manufacturers, test laboratories, packagers (including pharmacies)
    - Does not include compounding (see CDER Compliance Policy Guide [withdrawn] and Guidance)
cGMP Legal Principles

“Current”
- dynamic standards evolving over time

“Good”
- These are minimal standards, though many firms are implanting comprehensive systems with modern technologies to comply
- Not “Best practices”; generally establishes a floor, not ceiling
- Doesn’t have to be the predominant approach
- Hallmark of cGMPs is flexibility
The cGMP Regulation

- cGMP for Finished Pharmaceuticals is located at Title 21 CFR §§210, 211
  - First issued June 1963, Current Version is September 1978
  - Substantive regulation carrying the force and effect of law
  - Establishes “what to do” not “how to do it”
    - Minimal standards
    - Flexibility; technology neutral
    - Specific where needed (e.g., penicillin contamination)
    - Scalable
cGMP Implementation Tools

- cGMP Guidance Documents
  - Offers routes to efficiency in meeting cGMP requirements, evaluation of compliance
  - Examples:
    - General Principles of Process Validation
    - Sterile Drug Products Produced by Aseptic Processing
    - Guideline on Preparation of Investigational New Drug Products
    - Investigating Out of Specification Test Results for Pharmaceutical Production
    - Manufacturing, Processing or Holding of Active Pharmaceutical Ingredients

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cGMP Compliance Programs

- These are instructions given to FDA inspectors.

- Generally, two programs:
  - Drug Manufacturing Inspections Programs
    - Systems based assessment of the site
  - Preapproval Inspection Program
    - Articulates points to inspect, reviews regulatory approaches and laboratory support
  - Guides help field investigators
    - Uncover need for cGMP changes and
    - Identify compliance with specific issues (e.g., cleaning validation)
cGMPs: Raw Materials

- FDASIA increased FDA’s authority by requiring that Manufacturers verify their suppliers meet cGMP requirements. (FD&C Act, §501)
- Active Ingredients
- Excipients
- Audit Suppliers on a Regular Basis
  - Review regulatory history of potential partner before contracting
  - Monitor regulatory compliance
  - Require notice of violations
- Test incoming Raw Materials
cGMPs: Buildings and Facilities

- 21 CFR §211.42-58
  - Separate or define areas as necessary to prevent contamination or mix-ups
    - Non penicillin on penicillin production line
  - Air filtration systems in production areas (HVAC)
  - Sanitation critical
cGMPs: Production and Process Controls

- 21 CFR §211.100 requires written SOPs:
  - “[w]ritten product 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.”
  - Note: different standards for early stage development products (Phase 1) – level of control required increases after investigational stage.
cGMP: In Process Testing

- 21 CFR §211.110
  - 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.
cGMPs: Expiration Dating

- 21 CFR §211.137(a)
  - “To ensure that a drug product meets applicable standards of identity, strength, quality and purity at the time of sale, it shall bear an expiration date determined by appropriate stability testing described in 21 CFR 211.166.

- 21 CFR §211.137(b)
  - Expiration dates shall be related to any storage conditions stated on the labeling, as determined by stability studies described in Section 211.166.
cGMPs: Packaging and Labeling

- 21 CFR §211.130
  - Company must have written procedures designed to assure that correct labels, labeling and packaging materials are use for drug products; such written procedures shall be followed.
  - Label mix ups are a primary reason for drug product recalls as well as a large percentage of Adverse Events.
cGMPs: Laboratory Controls

- 21 CFR §211.165(a)-(b)
  - 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.
cGMPs: Stability Testing

- 21 CFR §211.166
  - “A written stability testing program designed to assess stability characteristics is required. Stability testing results must be sued in determining storage conditions and expiration dates.”
cGMPs: Product Record Review

- 21 CFR §211.192
  - “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.”
- Considerations:
  - Product Impact Assessment
  - Trend Analysis
  - Distributed Product
cGMPs: Deviations

- 21 CFR §211.100
  - “Any unexplained discrepancy or the failure of a batch or any of its components to meet and of its specifications must be investigated whether or not the batch has already been distributed.”
  - Investigation must be broad enough to capture scope of problem:
    - Investigate other batches of same drug
    - Investigated other drugs associated with the specific failure or discrepancy
    - Make a written record of the investigation
cGMPs: Deviation Investigation

- Proper documentation of the investigation is critical:
  - SME-driven hypothesis developed and tested
  - Validate or invalidate it
cGMPs: CAPA

- Corrective and Preventative Action Program (CAPA):
  - As part of the investigation, identify root cause and definitive corrective actions
  - Should be followed by audit of correction effectiveness
  - Should be documented
  - If FDA inspection generated the cGMP violation:
    - Establish scientifically-sound CAPA
    - Articulate reasonable timeframes to FDA
    - Do not hide the ball, but don’t roll over on debatable, Guidance-driven observations
    - Ensure compliance w/ commitments to FDA
cGMPs: Quality Control

- 21 CFR §211.22(a)
  - 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 ensure 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 contact by another company.”
cGMPs: Complaints

- 21 CFR §211.198
  - Requires written procedures describing the handling of all written and oral complaints
  - Review by Quality Control unit for:
    - Possible failure to meet any specification
    - Determine need for deviation investigation
    - Adverse Drug Experience/Event (ADE) report assessment
  - Documentation of complaint and investigation or reason for not investigating.
cGMPs: Records and Reports

- Failures in data integrity reveal a systemic problem in FDA’s view.
- Accordingly, follow the following prudential principles:
  - Emphasis organizational data integrity
  - Ensure documentation is contemporaneous with events
  - Conduct internal reviews at specified intervals (could use independent audit group)
  - Learn from external (FDA, partner due diligence, product liability) reviews
cGMPs: Reports

- Field Alert Reports (21 CFR §314.81(b)(1))
  - Labeling
  - Failure to meet specifications (stability failures)
  - Must be reported w/in 3 days of receipt

- Adverse Drug Event Reports (21 CFR §314.80)
  - Must be reported ASAP but no later than 15 calendar days of initial receipt
  - Applies to both foreign and domestic
  - Should have written recall procedures prepared
cGMPs: Auditing

- Independent Audit Group
- Global Approach (ICH)
- Audit Priority Systems/Specific Issues
- Follow-up Audits.
cGMP Inspections

- Initiated by FDA Form 482 (Notice of Inspection)
- Inspection concluded with presentation of 483 (Inspectional Observations)
- From the 483, an Establishment Inspection Report (EIR) is created for FDA internal review and classification:
  - No action indicated (NAI)
  - Voluntary action indicated (VAI) [substantial issue but not regulatory action required]
  - Official Action indicated (OAI) [further administrative or judicial actions are required]
cGMP Violations

- Consequences may include:
  - Warning letter that states violation of law and notice that failure to correct could result in further action.
    - 15 days to respond; must be comprehensive
  - Application Action
    - May defer substantive action on application if potentially fraudulent submissions; may refer to OCI
  - Recall
    - 3 Types depending on severity
cGMP Violations

- Severe consequences can ensure if there is a violation:
  - Product is adulterated under the FD&C Act
  - Shutdown of manufacturing facility (impact on other lines)
  - Seizure of product
  - Recall
  - Unwanted press coverage
  - Competitive disadvantage
cGMP Violations

- Severe consequences can ensure if there is a violation (continued):
  - GMP hold of pending product applications
    - Domestic v. foreign
  - Injunction/Consent decree/Disgorgement
    - Schering Plough ($500 million)
    - Abbott Laboratories ($100 million)
    - Wyeth-Ayerst Labs ($30 million)
  - Criminal Investigations and Indictments
    - U.S. v. Park
  - Lawsuits (Tort, etc.)