Chapter 7

Good manufacturing practices for pharmaceutical products (GMP)

References
Good Practice and Quality Management: an Overview

- **Drug legislation**, **good practice concepts** and, lately, **quality system concepts** began to evolve as it was realized that the **setting of requirements** was not enough to guarantee **quality medicinal products**.

- The concept of GMP was established when it was realized that **quality is determined by the manufacturing process rather than by subsequent quality control**.

- **GMP regulations** aim to ensure the **pharmaceutical quality of medicinal products** and, therefore, regulate:
  - manufacturing personnel, facilities and equipment, documentation, manufacture, quality control, contract manufacture, product complaints, recall procedures, and self-inspections.

- The development of GMP was influenced mainly by the **FDA**, the **WHO**, the **Pharmaceutical Inspection Convention (PIC)**, and the **European Economic Community (EEC)**.
Historical background

• The term *Good Manufacturing Practice was first used in 1962* in the Kefauver-Harris amendment to the Food and Drug Act in the United States; the FDA has set the pace for the global development of GMP.

• In the 1970s and 1980s, GMP became the subject of regulations in most countries.

• In 1969, the WHO published GMP guidelines.

• The *Pharmaceutical Inspection Co-operation Scheme, PIC/S*, established in 1970 by the *European Free Trade Association* EFTA. issued a GMP guide based on the WHO document.

• In Japan, GMP was established in 1974 and enforced in 1975.

Historical background

• In 1985, the Association of Southeast Asian Nations (ASEAN)—Brunei, Indonesia, Malaysia, the Philippines, Singapore, and Thailand—published the **ASEAN GMP Guide**.

• The present WHO GMP guidelines are based on the EEC and the ASEAN guidelines and are strongly influenced by the ISO 9000 series issued by the International Organization for Standardization (ISO).
GMP/GLP/cGMP: Background

- Good Manufacturing Practice (GMP) regulates manufacturing and its associated quality control (in contrast to GLP which covers more drug development activities).
- GMP predates GLP. Industries were already familiar with GMP and thus GLP follows similar lines.
- The most significant difference is in archiving requirements for test samples and data.
- Good Manufacturing Practice regulations have been developed to ensure that medicinal (pharmaceutical) products are consistently produced and controlled to the quality standards appropriate to their intended use.
- They have been developed and introduced in 1963 in response to the US public’s concern about the safety, efficiency and overall quality of drugs.
- In the United States the regulations are called current Good Manufacturing Practices (cGMP) to take into account that the regulations are not static but rather dynamic.
Subparts of 21 CFR 211, 21 CFR 600 and 21 CFR 820

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cGMP requirements for medical devices, incorporating them into a quality system regulation (QSR). The regulations are codified in 21 CFR 820.
Complete list of GMP regulations for 21 CFR 211 requirements

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Statements of the regulations for drugs, biologics, and devices state that:

• Facilities used to manufacture the product should be clean and well controlled.
• Personnel should have the appropriate experience and training to perform their required tasks.
• Equipment should be qualified for use in the particular process.
• The receipt and release of all raw materials should be documented per procedure, that containers and closures are controlled.
• The method of production should be validated and in a controlled, reproducible state with in-process controls.
• Analytical methods should be validated.
• Materials should be traceable.
• Procedures should be covered by controlled standard operating procedures, SOPs, and activities documented at the time of performance. ("If it is not documented, it was not done.")
• There are procedures in place for making changes (change control), investigating deviations, product complaints, and adverse events.
• Records are retained for at least the minimum required time period.

In addition to the controls described above, devices are subject to design controls to ensure that performance requirements for the device are established before production, the specified design is verified and validated, and the design requirements are met.
FDA Enforcement Actions

• The FDA has two types of enforcement powers available to deal with noncompliance of cGMP regulations:
  – Administrative action
  – Judicial Action

• Administrative actions include inspections, Form FDA 483 Inspectional Observations, Warning Letters, and delay suspension, or withdrawal of product approvals.
  – The FDA initiates and proceeds on these actions without other government agency assistance.

• Judicial actions, performed by the U.S. Department of Justice, who serves as trial counsel to the FDA, filing injunctions, and moving on civil seizures and criminal prosecution.
Administrative Actions

• FDA enforcement actions begin with an inspection in which investigators look for evidence of noncompliance to GMPs.
• Essentially, the Agency is building a case against the product manufacturer.
• There are various types of inspections such as GMP (biennial-every two years).

Inspectional documentation includes:

• Form FDA 482: Notice of Inspection (officially notifies manufacturer that FDA inspection has begun
• Form FDA 483 — Inspectional Observations (list of items that may be deemed as noncompliant with cGMPs presented to the Manufacturer upon completion of the inspection.
• Form FDA 484 — Receipt of Samples (allows the FDA to take samples as evidence of noncompliance — adulterated product)
• Establishment Inspection Report (EIR) (official document written by the FDA investigator team that clearly describes issues identified on 483 with supporting evidence)

Actions taken by FDA:
• Delay approval of a new drug, biologic, or device. Delays could occur until either the objectionable conditions are corrected or the firm commits to completion of a corrective action plan.
• Suspension of product approval for human drugs may be accomplished if the FDA has evidence that there is an imminent hazard to the public.
• Withdrawal of product approval.
Regulatory requirements for withdrawal of product approval include:

The product is no longer safe and effective.

• The application contains untrue statements.
• Manufacturing changes implemented without submitting a supplement.
• Repeat or deliberate record-keeping problems.
• Refusal to permit FDA access to records.
• Inadequate methods/controls for manufacturing and packaging.
• False and misleading labeling not corrected within a reasonable time.
Judicial Actions

• An injunction is initiated to stop or prevent violation of the law either
  – by stopping adulterated products from reaching the public
  – or by requiring noncompliant conditions to be corrected.

• Defendants in an injunction proceeding may consent to a Decree of Permanent Injunction (Consent Decree) either after a hearing or as a result of a negotiated settlement between the firm and FDA.

• The settlement describes the measures that will be taken to bring the company into compliance, with a schedule for that process.

• If the schedule is not met, the firm incurs penalty charges.
• Recent consent decrees are listed in the Table below
• Seizure is a very effective enforcement tool; it is a civil court action used to confiscate foods, drugs, devices, or cosmetics and to remove them from the market.

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<tr>
<th>Company</th>
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<td>Schering-Plough Corporation</td>
<td>5/17/02</td>
<td>Four New Jersey and Puerto Rico sites $500M payment to U.S. Treasury immediately Additional payments of up to $175M $471,500 to cover inspection costs Company agreed to suspend manufacturing of 73 products Expert consultants — yearly inspections for 3 years</td>
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<tr>
<td>Elan Pharmaceuticals</td>
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<td>Gainesville, GA plant Independent expert — yearly inspection for 3 years</td>
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<td>Wyeth-Ayerst Laboratories (AHP)</td>
<td>10/3/00</td>
<td>Marietta, PA and Pearl River, NY Expert consultants Pay FDA $15,000/day for failure to meet schedule ($5M cap) Pay U.S. Treasury $30M within 15 day of decree</td>
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<tr>
<td>Abbott Laboratories</td>
<td>11/9/99</td>
<td>Diagnostic devices — Abbott Park, IL and North Chicago, IL Pay FDA $15,000/day for failure to meet schedule ($10M cap) Pay U.S. Treasury $100M within 10 days of decree Must be in compliance in 1 year or company must pay 16% of gross proceeds by sales of medically necessary products Independent auditors</td>
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Responding to FDA Enforcement Actions

• The company is required to inform the FDA of changes that affect the manufacture of the product. These include changes to the facility, equipment, process, formulation, labeling, and controls.

• Following the biennial inspection, the FDA has a variety of approaches that it can apply to ensure a company comes into compliance with cGMP.

• If objectionable conditions are observed during an inspection, the investigator will issue to the company an FDA-483 form that lists the observations.

• The company has the opportunity to discuss the observations during the closeout meeting.
• If the company feels that an observation is incorrect, evidence supporting that should be presented.
• If the information provided satisfies the investigator, he/she probably will annotate the observation on FDA-Form 483.
GMP/GLP/cGMP: Background

• In **1996** the FDA proposed a significant revision of the regulation.

• Any **drug marketed in the US must first receive FDA approval**, and must be manufactured in **accordance with the US cGMP regulations**.

• Because of this, FDA regulations have set an international regulation benchmark for pharmaceutical manufacturing.
GMP/GLP/cGMP: Background

- In Europe local Good Manufacturing Practice regulations exist in many countries.
- They are based on the European Union (EU) directive: Good Manufacturing Practice for Medicinal Products in the European Community.
- This EU GMP is necessary to permit free trade in medicinal products between the member countries.
- Regulations in the EU allow for the marketing of a new drug in the twelve member countries with a single marketing approval.
- The EU GMP is intended to establish a minimum manufacturing standard for all member states.
- The EU directive has been widely harmonized with the Guide to Good Manufacturing Practice for Pharmaceutical Products as developed by the Pharmaceutical Inspection Convention (PIC).
National and international GLP regulations

• Shortly after the US FDA introduced GLP regulations, the Organization for Economic Cooperation and Development (OECD) published a compilation of Good Laboratory Practices.

• OECD member countries have since incorporated GLP into their own legislations.

• In Europe, the Commission of the European Economic Community (EEC) has made efforts to harmonize the European laws.

• Guidelines on quality assurance for measuring equipment and for calibration laboratories have also been published by technical committees of the International Organization for Standardization (ISO) and others, for example in ISO/IEC 17025.
Memoranda of Understanding (MOU) and bilateral agreements

• To overcome trade differences and enable GLPs to be recognized abroad, bilateral memoranda of understanding (MOU) have been signed between many chemical trading nations.

• For example, bilateral agreements have been signed between all countries within the European Economic Community.

• After signing such agreements, data generated and approved by national GLP authorities within one country will be accepted by the national GLP authority of the other country.
Who has to comply with GLP/cGMP regulations?

- Originally, GLP regulations were intended for toxicity testing only.
- It was reserved for labs undertaking animal studies for pre clinical work.
- Their general nature, applicable to any analytical instrument and method, enables implementation in all scientific disciplines and particularly in those which perform analytical measurements.
- Some laboratories follow GLP’s whenever the studies are to be used to support applications for research or marketing studies to be submitted to the FDA,
- for example when doing biocompatibility testing of a new material.
• Non-clinical laboratory studies

• GLP regulates all non-clinical safety studies that support or are intended to support applications for research or marketing permits for products regulated by the FDA or other similar national legislation (see table 1).

• This includes medicinal and veterinary drugs, aroma and color additives in food, nutrition supplements for livestock, and biological products.

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Analysis under GMP and cGMP

- Quality control of drugs typically is regulated under Current Good Manufacturing regulations.
- But GMP is not limited to quality control laboratories in manufacturing.
- If, for example, a small volume ingredient is prepared in a research and development department, then the work should also be performed under GMP.
- Similarly, any production of material made for clinical trials also falls under GMP.

Availability of regulations and guidance documents

- Some organizations publish their documents on the Internet. For example the US FDA cGMP regulations are available on FDA’s Website http://www.fda.gov
- EU Directives can be downloaded from: http://dg3.eudra.org
• The English text of 27 national and international (current) Good Manufacturing Practice can be found in the book “International Drug GMP’s”

• International GMPs include the most recent versions from the World Health Organization (WHO), Asia, Pharmaceutical Inspection Convention (PIC) and the European Union (EU).

• Good guidance documents for laboratories are ISO/IEC guides and standards especially ISO/IEC 17025: “General requirements for the competence and testing of calibration and testing laboratories”.

• This standard is the internationally recognized basic document for accreditation of laboratories.

• The attainment of accreditation is mandatory for some regulatory work areas and frequently is the basis of contracts for analytical work.
Good Laboratory Practice

• GLP originated in the mid-1970s in the United States, when a variety of deficiencies were revealed in contract laboratories during an FDA inspection.
• These deficiencies included, among others,
  – the conduct of studies,
  – record keeping,
  – archiving,
  – animal husbandry.
• The scandal widened when inspections of other laboratories revealed similar discrepancies.
• As a response, the chemical industry suggested the implementation of a quality management system, which was later named GLP.
• The FDA adopted GLP regulations in 1979.
• The Organization for Economic Cooperation and Development (OECD) issued GLP guidelines in 1981 for chemicals.
• There is Community-wide legislation on GLP in the EU.
• In Japan, GLP was established in 1982 and enforced in 1983.
Good Clinical Practice (GCP)

• Cases of violations of human rights and scientific misconduct or fraud (cheat) in connection with clinical trials in the United States in the 1960s and 1970s led the FDA to issue regulations and to control compliance.
• The European approach was characterized by a greater emphasis on guidelines and quality assurance rather than on quality control.
• The development of GCP in the EU was influenced by various initiatives, for example, by proposals of individual pharmaceutical companies, but also by FDA regulations, which in case of noncompliance would function as a trade barrier.
• A CPMP note for guidance on GCP was issued in 1990 and came into force in July 1991.
• The legal status was that of recommendations. Real legal power was given to GCP by Directive 91/507 /EEC.
Good Clinical Practice (GCP)

- Another contribution to the development of GCP came in the form of the Nordic Good Clinical Trial Practice (GCTP) guideline of 1989.
- Between 1985 and 1990, several national GCP documents were published from various countries, including Germany, France, Italy, and Spain. Japan introduced GCP in 1989 (enforced in 1990).
- The early 1990s saw the rise of two global GCP initiatives driven by the WHO and by the ICH.
- The ICH has recently issued a Step 4 document that has been approved by the CPMP and will be mandatory for studies in the EU commencing after January 1997 (31).
- Yet another important influencing factor for GCP is the Declaration of Helsinki and the development of the Ethics Committee system.
Good manufacturing practice

• Good manufacturing practice is that part of quality assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization.

• GMPs are aimed primarily at diminishing the risks inherent in any pharmaceutical production. Such risks are essentially of two types:
  – Cross contamination (in particular of unexpected contaminants)
  – and mix-ups (confusion) caused by, for example, false labels being put on containers.
GMP Requirements for manufacturers of pharmaceutical products

Under GMP:
(a) all manufacturing processes are clearly defined, systematically reviewed in the light of experience, and shown to be capable of consistently manufacturing pharmaceutical products of the required quality that comply with their specifications;
(b) qualification and validation are performed;
(c) all necessary resources are provided, including:
   (i) appropriately qualified and trained personnel
   (ii) adequate premises and space
   (iii) suitable equipment and services
   (iv) appropriate materials, containers and labels
   (v) approved procedures and instructions
   (vi) suitable storage and transport
   (vii) adequate personnel, laboratories and equipment for in-process controls
GMP Requirements for manufacturers of pharmaceutical products

(d) instructions and procedures are written in clear and unambiguous language, specifically applicable to the facilities provided
(e) operators are trained to carry out procedures correctly;
(f) records are made (manually and/or by recording instruments) during manufacture to show that all the steps required by the defined procedures and instructions have in fact been taken and that the quantity and quality of the product are as expected; any significant deviations are fully recorded and investigated
(g) records covering manufacture and distribution, which enable the complete history of a batch to be traced, are retained in a comprehensible and accessible form;
(h) the proper storage and distribution of the products minimizes any risk to their quality;
(i) a system is available to recall any batch of product from sale or supply;
(j) complaints about marketed products are examined, the causes of quality defects investigated, and appropriate measures taken in respect of the defective products to prevent recurrence.
Good Manufacturing Practices (GMPs) and Enforcement Actions

- Legislation for Good Manufacturing Practices (GMP) was developed to ensure that producers of drugs, biologics and medical devices maintain a level of quality, safety, and consistency during manufacturing.
- The laws are upheld and enforced by the Food and Drug Administration (FDA).
- Enforcement is primarily by various types of facility inspections for drugs or devices marketed in the U.S.
- Failure of a producer to comply with any GMP regulation shall be subject to regulatory enforcement action.
- The cGMPs apply to any product intended for interstate commerce in the U.S.
• All food and drug related laws are contained in Title 21 of the CFR.

• Each title of the CFR is updated annually. Title 21 is updated as of April 1 of each year.

• A regulation is a law. In the United States, all federal laws have been arranged or codified in a manner that makes it easier to find a specific law.

• The Code of Federal Regulations (CFR) is a compilation of all federal laws published in the Federal Register by the executive departments and agencies of the federal government. as of April 1 of each year.
GMP requirements for manufacturers of pharmaceutical dosage form

- **General Provisions**
- This section pertains to the manufacture of drug products for humans or animals.
- These requirements will not be enforced for over-the-counter (OTC) drug products if the products and all their ingredients are ordinarily marketed and considered as human foods and which products may also fall within the legal definition of drugs by virtue of their intended use.
Organization and Personnel

1. Responsibilities of quality control unit

2. Personnel qualifications

3. Personnel responsibilities

4. Consultants that advise on the manufacture, processing, packing or holding of drug products must have sufficient education, training, and experience to advise on the subject for which they are retained. The manufacturer must maintain records of name, address, and qualifications of any consultants and the type of service they provide.
Buildings and Facilities

1. Design and construction features
2. Adequate lighting should be provided in all areas.
3. Heating, ventilation, and air conditioning (HVAC)
4. Plumbing
5. Sewage, trash, and other refuse in and from the building and immediate premises must be disposed of in a safe and sanitary manner.
6. Adequate washing facilities should be provided. This is to include hot and cold water, soap or detergent, air driers or single - service towels, and clean toilet facilities easily accessible to all work areas.
7. Sanitation
8. All buildings used for GMP - related purposes must be maintained in a good state of repair.
Equipment

1. Equipment should be of appropriate design, adequate size, and suitably located to facilitate operations for its intended use and for cleaning and maintenance.

2. Equipment construction

3. Equipment cleaning and maintenance

4. Automatic, mechanical, and electronic equipment

5. Filters for liquid filtration used as a part of the manufacture, processing, or packing of injectable drug products intended for human use must not release fibers into such products.
Control of Components and Drug Product Containers and Closures

1. General requirements
2. Receipt and storage of untested components
3. Testing and approval or rejection of components
4. Use of approved components (including drug product containers and closures) must be rotated to assure that the oldest approved stock is used first.
5. Components must be retested and/or reexamined after storage for a long period of time or after exposure to the atmosphere, heat, or other condition that might adversely affect the component.
6. Rejected components should be identified and controlled under a quarantine system designed to prevent their use in manufacturing or processing.
7. Containers and closures
Production and Process Controls

1. Written procedures and procedure deviations

2. Charge - in of components — Written production and control procedures must include the following, which are designed to assure that the drug products produced meet all specifications and standards.

3. Actual yield and percentage of theoretical yield should be determined at the completion of each appropriate phase of manufacturing, processing, packaging, or holding.

4. Equipment identification

5. Sampling and testing of in-process materials and drug products

6. When appropriate, time limits should be established for the completion of each phase of production

7. Control of microbial contamination

8. Reprocessing
1. Materials examination and usage criteria
2. Issuance of labeling
3. There must be written procedures designed to assure that correct labels, labeling, and packaging materials are used.
4. Tamper - evident packaging requirements for OTC human drug products
5. Drug product inspection
6. Expiration dating
Holding and Distribution

1. Warehousing procedures
2. Distribution procedures

Laboratory Controls

1. General requirements: establishment of any specifications, standards, sampling plans, test processes, or other laboratory control mechanism required by this part of the regulation,
2. Testing and release for distribution
3. Stability testing
4. Special testing requirements
5. Reserve samples
6. Animals used in testing components,
7. the nonpenicillin drug product must be tested for the presence of penicillin.
Records and Reports

1. General Requirements

2. A written record of major equipment cleaning, maintenance (except routine maintenance), and use must be included in individual equipment logs that show the date, time, product, and lot number of each batch processed. The persons performing and double checking the cleaning and maintenance should date and sign or initial the log indicating that the work was performed. Entries in the log must be in chronological order.

3. Component, drug product container, closure, and labeling records

4. Master production and control records

5. All drug product production and control records, including those for packaging and labeling, must be reviewed and approved by the quality control unit

6. Laboratory records
7. Distribution records must contain the name and strength of the product and description of the dosage form, name and address of the consignee, date and quantity shipped, and lot or control number of drug product. For compressed medical gas products, distribution records are not required to contain lot or control numbers.

8. Complaint files
1. Returned drug products must be identified as such and held.

2. Drug product salvaging — Drug products that have been subjected to improper storage conditions, including extremes in temperature, humidity, smoke, fumes, pressure, age, or radiation due to natural disasters, fires, accidents, or equipment failures, must not be salvaged and returned to the marketplace.