The Scilife Success Guide

Introduction to Good Manufacturing Practices (GMP)

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Introduction

Quality control is essential to not only pharmaceutical firms' success, but to patient well-being. This is precisely where GMP, or Good Manufacturing Practices, comes in.

Companies must be certified according to GMP guidelines to produce and sell their pharmaceutical products to the market. Adhering to these guidelines confirms the quality of the products to the governing authorities, confirming that the manufacturers' practices play an active role in ensuring safety.

With that, consider this guide your all-in-one GMP resource! The advice herein will outline everything you need to know about GMP, including the exact practices Life Sciences must follow to protect patient safety and promote product effectiveness.

In this guide, you will find a recap of all the relevant information shared during the training "Introduction to Good Manufacturing Practices (GMP)," along with extra references to deepen your knowledge on the topic.

GMP for patient safety

GMP consists of establishing consistent quality management systems, obtaining the appropriate quality of raw materials, implementing robust management and manufacturing process procedures, detecting and investigating product deviations, and maintaining reliable testing laboratories. It's a formal control system that, when put into practice, helps to prevent contamination, mix-ups, deviations, failures, and errors. In this way, the implemented system ensures drug products meet the relevant quality standards. **Patient safety is the most important part of GMP. The second most important pillar is drug effectiveness.**

01

What is GMP?

GMP, or Good Manufacturing Practices, are rules and procedures that pharmaceutical and biotech firms must follow to ensure their products are produced and consistently meet specific requirements for identity, strength, quality, and purity.

The fundamental standard for ensuring the quality of human pharmaceuticals is the cGMP regulation, according to FDA guidelines. cGMP stands for current Good Manufacturing Practices. It consists of several practices that focus on different phases of manufacturing, as well as quality.

It is worth noting that the cGMP regulation represents the minimum requirements that companies have already implemented in their quality and risk management systems.

01. A. FDA

In 1978, the U.S. Food & Drug Administration finalized the cGMP for drugs (21 CFR Parts 210 and 211).

Go further

Life Sciences companies can learn more about **Part 210 here**:. This part contains the cGMP for methods to be used in (and the facilities and controls to be used for) the manufacturing, processing, packaging, or holding of a drug or product to ensure safety, and to meet the quality and purity characteristics purported by the manufacturer.

cGMP **Part 211** is described in detail **here**. The regulations in this part contain the minimum requirements for the preparation of drug products (with the exception of positron emission tomography drugs).

01. B. EU

In 1991, the European Union published its own GMP guidelines. EudraLex Volume 4 describes GMP for human and veterinary medicinal products, as shown **here**.

The guidelines are set forth in in the EU Commission Directives 91/356/EEC, as amended by Directive 2003/94/ED and 91/412/EEC, respectively.

01. C. Building Blocks of GMP

GMP covers ALL aspects of production, from the starting materials, processes, and equipment, to personnel training and hygiene. There are five main building blocks of GMP:

> Machines
>
> Methods
>
> Materials
>
> Men (personnel)
>
> Milieu (environment)

02

Pharmaceutical quality system

Quality management, GMP, and quality risk management are interrelated. Based on ISO 9000 standards, a pharmaceutical quality system incorporates both GMP and quality risk management.

02. A. Objectives of the pharmaceutical quality system

> Realize the product with quality in mind.
>
> Create and maintain a state of control.
>
> Promote continuous improvement.
>
> Ensure knowledge transfer and management leveraging GMP, quality management, and quality risk management.

02. B. Quality management

A quality management system (QMS) is a set of policies, processes, and procedures required for planning and execution in the core business area of a Life Sciences organization. Quality management is achieved via a pharmaceutical quality system.

The goal of a QMS is to document processes, procedures, and responsibilities for achieving quality. It provides the structure for various functions within an organization to work in alignment and deliver the best quality products and services to the customer.

02. C. Quality risk management

According to the ICH guideline Q9, quality risk management is a systematic process for assessing, controlling, communicating, and reviewing the risks surrounding the quality of the pharmaceutical across the product lifecycle.

> Identify all risks.
>
> Analyze and evaluate those risks.
>
> Perform risk control (either reducing or accepting your risk).

Depending on the controls or actions that you take, you will have your output and your results. This creates a general flow of risk management.

03

Documentation

Documentation is essential to GMP compliance. Done adequately and consistently, it allows auditors to assess the quality of the manufacturer's operations and final product.

03. A. Good documentation practices

Here's a quote you'll want to remember:

> *"If it's not written down, it did not happen."*

Documentation maintains the traceability of all development, testing, and manufacturing activities.

Pencils, erasers, fluids, post-its, and markers are not allowed in GMP documentation. Only writing utensils that are legible and permanent—like a high-quality pen—are acceptable.

If you need to make a correction to your documentation, the original record must be preserved. To make a correction, strike a single line through the error or discrepancy (so that it is still legible), and then write the correction next to it. Be sure to sign and date the correction.

03. A. I ALCOA principles

A well-known GMP documentation abbreviation is ALCOA.

A stands for **Attribute**.

All actions must be signed and dated.

L stands for **Legible**.

Legibility, traceability, readability, and recoverability are key.

C stands for **Contemporaneous**.

Documentation must be recorded at the time of action.

O stands for **Original**.

The original record needs to be archived and stored.

A stands for **Accurate**.

The written record must be correct and reflect what truly happened.

04

Premises and equipment

A key part of GMP compliance is evaluating your premises and equipment to minimize the risk of errors, avoid cross-contamination, and prevent the build-up of dirt and dust. This is all in an effort to avoid adverse effects on product quality.

04. A. How to minimize the risk of contamination and cross-contamination

Pest control: Keep insects and other animals off the premises.

Access control: Ensure only authorized people can enter certain rooms—for example, via badge or card reader).

Cross-contamination prevention via quality risk management: Use dedicated facilities when needed. Say products A and B are produced in the same factory. Product A is a toxic chemotherapy pharmaceutical, and Product B is a simple cosmetic. You'll want to produce the two products in different facilities to eliminate the risk of cross-contamination.

04. A. I Cleaning and maintenance

Effective cleaning and maintenance:

> Avoid difficult-to-clean materials.
>
> Avoid standing water (which is an ideal breeding ground for bacteria).
>
> Avoid open channels/drains (to prevent microbiological contamination).

04. A. II Controlled conditions: air, humidity, and temperature

Controlled conditions reduce contamination in a sterile production environment:

> **Air**
>
> Controlling air pressure helps to manage the pressure cascade. Meanwhile, the use of HEPA (high-efficiency particulate air) filters helps to manage particles. Both actions reduce contamination.
>
> **Humidity**
>
> **Temperature**

04. A. III Controlled conditions: air, humidity, and temperature

Monitoring is essential. Air, humidity, and temperature should be monitored and documented at every step. A reminder that per the GMP standard, if it's not written down, it did not happen.

04. A. IV Closed vs. open systems

Closed systems cannot exchange matter with their surroundings. This makes them more high-tech. However, they also have fewer quality requirements. This is because the environment has a greater influence on product quality in an open system.

It is important to evaluate your risk and then decide between a closed vs. an open system. Closed systems are an investment—one that might be overkill for a simple cosmetic product, but not for a toxic chemotherapeutic, for instance.

05

Personnel

All pharmaceutical and biotech personnel receive comprehensive GMP training and training specific to their role. This section will describe the importance of both training and personnel hygiene.

05 A. Training

Training is required for all personnel (including temporary personnel):

> Basic GMP training
>
> Training based on the job description or specific operations. For example, lab training and manufacturing training will be different.
>
> Ongoing (re)training
>
> Periodic assessment of practical effectiveness: a risk-based approach involving training, evaluation, and certification
>
> Proper storage of training records

05 B. Personnel hygiene

Personnel hygiene protects employees and consumers. The next section will list several do's and don'ts, along with a number of dress procedures designed to keep personnel hygiene in check.

05. B. I Do's and don'ts

> DO take special precautions for personnel with infectious diseases or open wounds.
>
> DON'T allow personnel to eat, drink, chew gum, or smoke in production or storage areas.
>
> DO store food, drinks, smoking materials, and personal medication outside of production and storage areas.

05. B. II Dress procedures

Dress procedures are meant to:

> Avoid direct product contact
>
> Prevent the contamination of product (e.g., sterile products) and of personnel (e.g., chemotherapeutics)

The higher the risk of contamination, the more severe the precautions (and the more personnel will need to cover up). Gowns are generally required for sterile production; conversely, they aren't necessary for the production of most tablets or simple cosmetics.

06 Production

Pharmaceuticals should be consistently produced to GMP standards. The following sections will describe best practices for achieving this.

06 A. Validation and revalidation

> Demonstrate suitability for the production process (as well as for materials and equipment).
>
> Validate significant changes.
>
> Complete periodic revaluations.

Regulations change, machines deteriorate, and it's important to revisit these things as needed.

06 B. Prevention of mix-up and cross-contamination

> Physically and administratively quarantine materials prior to release.
>
> Identify and label all containers, materials, and equipment.
>
> Depending on the risk, take technical and organizational measures using single-use disposable technology, blow-fill-seal technology, or an isolator.

06 C. Supplier management

Pharmaceutical and biotech companies cannot do everything on their own. Often, packaging materials are outsourced. Suppliers should be carefully selected, qualified, and approved. Those selected must be audited on a regular basis to ensure GMP compliance

06 D. Starting materials

Starting materials are the active materials, or ingredients, used in production. Crucial to the manufacturing process, these materials should be consistently validated, revalidated, and documented.

06 E. Processing operations

Processing operations feature three types of controls: offline, in-line, and on-line.

06. E. I Types of controls: offline, in-line, and online

> **Offline controls**: These controls check the performance of any printing and embossing operation (for example, code numbers and expiration dates).
>
> **In-line controls**: These include in-line probes—for instance, the use of a pH probe.
>
> **On-line controls**: Is the package complete? Make sure to check the total weight of both the product and the packaging!

06 F. Packaging materials

Primary packaging materials are the most critical—yet secondary and tertiary materials are still important.

06. F. I Primary

This material comes into direct contact with the pharmaceutical. It is imperative that it be low-risk, high-quality, and audited to a high standard.

06. F. II Secondary

Secondary material comes into direct contact with the primary material, but not the product itself.

06. F. III Tertiary

Tertiary material comes into direct contact with the secondary material.

07

Quality control

Quality control is yet another important department in the GMP environment.

07 A. Sampling

Several types of samples should be taken from each product batch:

> Analytical samples
>
> Reference samples (for reanalysis in the event that something goes wrong.
>
> Retention sample (for identification)

07 B. Types of controls: in-process, environmental and release

> **In-process**: This type of control involves testing products during the manufacturing process.
>
> **Environmental control**: This type of control ensures production zone sterility and should encompass both product and environment. It is important to take samples from the walls, floors, and ceiling; incubate the samples; and check for microbial growth.
>
> **Release testing**: This type of control ensures compliance with a given specification. If you are testing a vial, for instance, you'll know that vials must be sterile—so sterility needs to be tested for release in order to comply with the product specifications.

07 C. Testing

Validated methods, calibrated and qualified equipment, and results documentation are crucial to GMP-compliant testing.

07. C. I Validated Methods

Only validated methods should be used during testing.

07. C. II Analytical method transfers

Analytical method transfers are defined, documented processes that qualify one company or entity to use an analytical method that originated from another.

07. C. III Documents and procedures

Document, document, document! This is yet another reminder that in the GMP world, if you don't write it down, it didn't happen.

07. C. IV Good documentation practices

Write in pen, keep everything legible, and sign and date any corrections or updates.

07. C. V Reagents and materials

All reagents and materials should be tested using validated methods to control quality.

07. C. VI Equipment qualification, maintenance, and calibration

Always use calibrated and qualified equipment. This will keep results accurate by comparing any variations to a defined standard.

07. C. VII Personnel qualifications

A designated, trained, well-qualified team of quality control professionals should oversee this aspect of GMP compliance.

07. C. VIII Retention and reference samples

> Reference samples are starting material samples stored for analysis during the shelf life of the pharmaceutical.
>
> Retention samples are fully-packaged samples stored for identification purposes.
>
> The reference and retention samples may be identical in some cases.

07. C. IV Stability program

A stability program is based on an approved protocol. It involves testing the product for deviations in strength, quality, purity, and safety.

08

Outsourced activities

A company cannot do everything itself. Any outsourced QMS/GMP activity (e.g., QC testing) should be defined, agreed upon, and controlled. It should also feature a written contract, or quality agreement, between the contract giver and the contract acceptor.

Responsibilities of the contract giver:

> Audit the contract acceptor.
>
> Provide all the necessary information to the contract acceptor.
>
> Review results, records, and other relevant materials belonging to the contract acceptor.
>
> The contract giver is ultimately responsible for the delivered product.

Responsibilities of the contract acceptor:

> Seek permission from the contract giver before implementing major changes.
>
> Remain GMP-compliant at all times.

08 A. Quality agreements and contracts

Quality agreements and contracts are a simple Word document with labeled sections describing who is responsible for what. The agreement must be signed in order to be valid.

09

Complaints, investigations, and recalls

These topics are essential for quality assurance personnel. The following sections will provide a detailed overview of complaints, investigations, recalls, and more.

09 A. What is a complaint?

Complaints are issues involving products that are **already on the market.**

If you receive a complaint, you must always distinguish between quality and **cosmetic defects**.

A **quality defect** hinders the effectiveness or safety of a product. A cosmetic defect is simply aesthetic, though it must still be rectified.

Pay attention to falsification when looking into complaints—for example, a 2D barcode, a seal that's been tampered with, etc.

09 B. What is an investigation?

Investigations are issues involving products that have not yet been released onto the market.

09 C. Procedures for handling and investigating complaints

(including possible quality defects)

To investigate complaints:

> Record a detailed description.
>
> Understand the scope—is the issue limited to one or several products or batches?
>
> Evaluate the recurrence of the complaint.
>
> Assess the severity of the complaint (minor, major, or critical).
>
> Conduct root-cause analysis.
>
> Take corrective actions and complete effectiveness checks.

09 D. Root-cause analysis

Root-cause analysis is a process for identifying the underlying cause of a problem or event.

Only by finding the real root cause of the problem will your corrective actions be effective.

Consider an investigation surrounding a failed sterility test. Perhaps you identify that someone working in your lab had contaminated hands. Your action would be to retrain that person. Then, if you see the same issue a few months later—but that person is now retrained and washes their hands in an effective manner—you might dig deeper and discover that the soap that person was using is no longer effective. This changes the root cause of the problem. By conducting root-cause analysis in this way, you'll learn that introducing a better cleaning product is the real solution.

09 E. Corrective and Preventative Actions (CAPAs) and effectiveness checks

An effectiveness check determines whether your CAPAs have helped to solve the problem at hand (the complaint or investigation).

09 F. Product recalls

In the event of a product recall:

> Inform the Competent Authorities.
>
> Keep distribution records readily available.
>
> Clearly identify recalled goods and keep them separate in the storage area.
>
> Record the recall (tracking delivered vs. recovered products).

10

Self-inspection

Every pharmaceutical company is audited by the authorities. But that's not enough to stay GMP-compliant. Organizations must also complete frequent self-inspections.

Self-inspections consist of the self-monitoring of implementation and compliance with GMP guidelines.

They involve:

> A detailed record of the actual audit.
>
> A report composed of observations and proposed CAPAs.
>
> A record of all corrective actions taken as a result of the audit.

10 A. Internal vs. external

Self-inspections can be conducted internally or externally (the latter by independent, competent entities like in Quality by Design, or QbD).

11

Q&A

1. When is a supplier audit required during a qualification (per GMP guidelines)?

CFR Chapter 5 "Production" does not literally state that an audit is required during the initial qualification of a supplier. It is, however, implied—specifically for active substances/excipients.

Audits must be carried out on the suppliers of active substances to ensure GMP compliance for the appropriate duration and scope. Further audits should be conducted at intervals predetermined in the quality risk management (QRM) process. Finally, the manufacturer should perform internal or external audits at appropriate intervals based on the risk of the starting materials' testing and sampling sites.

Basically, the assessment depends on the overall risk management involved. This means that it depends on what the supplier ultimately provides. An audit may be required for empty syringes, for example, but not for shipper boxes.

2. Does GMP documentation expire? How long must companies keep the documentation?

CFR Chapter 5 "Documentation" (EudraLex Volume 4) outlines the unique requirements for protecting the integrity of GMP documentation.

There are specific requirements for batch documentation, which must be kept for one year following the batch expiration or at least five years after the completion or discontinuation of the last clinical trial that involved the batch. Other requirements may specify longer retention periods.

For non-batch documentation, retention requirements may vary.

3. Are GMP guidelines mandatory during the product development stage?

GMP Annex 13 covers the **"Manufacture of Investigational Medicinal Products",** including pharmaceuticals used in clinical trials.

4. If you select a supplier, you are outsourcing activities. Does this mean that suppliers fall under "outsourced activities"?

A quality agreement must be in place when working with a supplier of starting materials (active ingredients, excipients) or of packaging materials, as stated in CFR Chapter 5 "Production." This chapter documents specific requirements for these materials.

CFR Chapter 7 "Outsourced Activities" explains the structure of a formal quality agreement.

5. Are IQ, OQ, and PQ (not applicable in R&D) applicable for investigational devices?

Medical devices are not part of the GMP; GMP only covers pharmaceuticals. There are, however, specific regulations for medical devices. See **ISO 13485** for details.

6. We are a biopharmaceutical equipment manufacturer not subject to authority inspections. What measures shall be implemented for equipment used in biopharma applications?

We suggest you read **CFR Chapter 3 "Premises and Equipment"** (EudraLex Volume 4), as well as Annex 15 **"Qualification and Validation."**

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