Dr Christine Oechslein

GMP Fundamentals

A Step-by-Step Guide
from Beginner to Advanced Level and Beyond

Maas & Peither
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Overview

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Preface

Dear readers,

Are you about to start exploring the complex world of GMP? Or have you been involved in GMP for some time and feel the need to fill the gaps in your knowledge of the subject?

Dr Christine Oechslein, one of our most experienced authors, has written a book describing important aspects of GMP in a concise and coherent way. "GMP Fundamentals" provides an overview of Good Manufacturing Practice for readers without previous knowledge of GMP. It can also be used by persons with GMP experience to improve their understanding of GMP and discover new aspects of the subject. The author succeeds in presenting GMP in a clear and concise manner. As consultants in the industry, we are confident that this book will improve the readers' understanding of GMP requirements.

The examples used in the book are based on European GMP requirements. We felt that a description of the subtle differences between the international GMP rules was neither required nor useful in a textbook that focuses on the basic principles of GMP. And the experts out there will forgive us for occasional simplification in the interests of clarity. If you wish to further your GMP studies, we recommend our comprehensive GMP MANUAL. It is an extensive source of GMP specialist information and contains more than 7,000 pages.

As publishers, we wish Dr Oechslein's book great success, because the greater the number of people who understand the intricacies of Good Manufacturing Practice, the better the implementation of GMP in companies will be. This knowledge is essential at all levels of a pharmaceutical manufacturing company, from the top to the bottom: if the principles outlined in this book are observed by everybody, the inspectors and auditors will have a lot less to find fault with in the future.

We would like to thank the author for accepting the challenge and producing a book on GMP that is comprehensive and easy to understand.

Another word of thanks is due to the publishing team at Maas & Peither Publishing. The images and illustrations in this book were provided by the creative and highly motivated editorial and production team.

Schopfheim, June 2015

Barbara Peither, Thomas Peither

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1 The purpose of GMP

1.A Introduction

It can happen to anyone: in the workplace, at home or on the street. One moment you're a health-conscious individual who believes in regular exercise, the next moment you're a patient.

You are quite lucky if you wake up in a well-organised, clean A&E department. With a life-saving infusion solution provided to treat eventual shock, circulatory collapse, organ failure and alleviate pain. A human life hanging on an IV line.

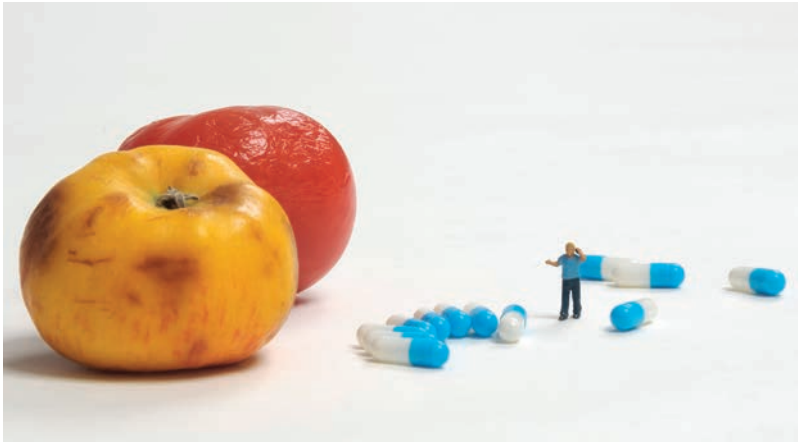
High-quality medicinal products save lives.

But what if the content of the infusion bag was not as it should be? And contaminants, bacteria or an incorrect active ingredient were fed directly into a vein in the patient's arm? Can we consumers be absolutely certain that medicinal products are of the highest quality?

Medicinal products are quite different from other products such as foodstuffs.

- The consumer has no way of determining the quality of a medicinal product, whereas fruit and vegetables can be judged fit for consumption based on their appearance, aroma and taste.
- You can eat large amounts of fruit, vegetable and other foodstuffs without a thought. Medicinal products, on the other hand, can have an enormous effect even when taken in tiny quantities, and often affect the entire body. Ex-

amples include antibiotics, hormones, anti-cancer drugs and medicinal products used to treat cardiovascular problems.



This means that medicinal products, if incorrectly manufactured and stored, can pose a particular risk for patients. Medicinal products are not always stored correctly, and an internationally recognised standard has not yet been agreed.

Fortunately, there are laws in the EU and in many other industrialised countries that regulate the manufacture and distribution of medicinal products in order to protect the consumer against substandard, and ineffective or dangerous medicinal products. The laws, regulations and standards describing the manufacturing process of a medicinal product from raw material to shipping are normally referred to as "Good Manufacturing Practice" or GMP rules, for short.

1.B What is GMP?

GMP stands for Good Manufacturing Practice. GMP rules apply to the manufacture, packaging and testing of medicinal products and must be strictly observed to ensure that only high-quality medicinal products come onto the market.

1.C Why do we need GMP?

Anyone who boards an aircraft must be confident that it was properly serviced, has been fuelled with a sufficient amount of the correct fuel, that the weather conditions along the flight path have been checked, and that the pilots and air traffic controllers are well-trained and concentrate when carrying out their jobs. The safe arrival of the passengers and crew at the destination airport cannot be left to chance. Everything must be carefully planned and checked and rechecked. The passengers have no way of confirming that everything has been carried out properly and cannot take corrective action.

3 Laws, licences and inspections

By now, the legislators in all of the important pharmaceutical markets (including the EU, USA and Japan) have introduced laws and directives which regulate how medicinal products are manufactured (see *chapter 11* and *chapter 3.E*).

Countries that do not yet have detailed statutory regulations in place should go by the recommendations of the World Health Organization (WHO) which has compiled detailed GMP Guidelines and GMP training materials.

All GMP requirements have the same objective: high-quality medicinal products without compromise to protect the patient.

3.A Who is allowed to manufacture medicinal products?

To prevent the manufacture of medicinal products under unhygienic conditions in an unsuitable location, authorisation must be sought from the authorities by any person who wishes to manufacture or test medicinal products. Before a **manufacturing authorisation** is issued, the responsible authority carries out an

inspection (see *chapter 3.G.1*) to ensure that all necessary requirements have been met. For example:

- Does the company have rooms that are suitable for the manufacture, testing and storage of medicinal products (see *chapter 7.A*)?
- Does the company have properly trained personnel in sufficient numbers (see *chapter 5.A*)?
- Does the company have proper machinery and equipment? Is the machinery and equipment regularly serviced and cleaned (see *chapter 7.B* et seq.)?
- Has the company defined and documented who is responsible for the various functions (organigrams and job descriptions, see *chapter 5.D*)?
- Has the company described all of the work and decision-making processes that affect quality in a quality management system (see *chapter 4.B.4* and *chapter 4.C*)?
- Has the company described every activity in written work instructions, and is each task recorded in a precise manner (see *chapter 6*)?
- Is the company GMP-compliant (**compliance**, see *chapter 3.F*)?

During regular follow-up inspections (see *chapter 3.G.1*), the authorities verify that the requirements for the manufacture and testing of medicinal products are still being fulfilled. If this is not the case, but serious contraventions are discovered, the manufacturing authorisation can be revoked.

A manufacturing authorisation is not only required for *typical manufacturing steps* such as stirring ointment or making tablets. Companies that only carry out **packaging** also require a manufacturing authorisation if they, for example, seal tablets into blister foils (push-through foils), package finished blisters into folding cartons or perform country-specific product labelling. Even **control laboratories** that carry out **analyses** for market release of (see *chapter 9.F.3*) medicinal products generally require an **operating licence**.

The requirements to be met are specified by each country individually. Manufacturers of medicinal products have to fulfil these national requirements – even if they wish to sell their medicinal products abroad, e.g. in the USA.

Only GMP-compliant companies are allowed to manufacture, package or test medicinal products.

3.B Which medicinal products may be placed on the market?

A company that possesses a manufacturing authorisation is not allowed to flood the market with all kinds of products that are currently selling well. On the contrary. A **marketing authorisation** must be sought from the authorities for every single medicinal product that is to be placed on the market. This involves submitting large amounts of data. This **marketing authorisation dossier** contains

Every individual in a GMP environment has a role to play, nobody is "insignificant". High-quality medicinal products can only be produced if each person carries out their tasks reliably and in accordance with the specifications.

5.D Who carries responsibility?

Certain functions in a GMP-compliant company carry great responsibility. These responsibilities are clearly defined in **job descriptions** and **organigrams**. Experienced **deputies** who can take over the tasks of an absent person are also needed.

These **key functions** carry a lot of responsibility, but *not the sole* responsibility. They can **delegate** some of their many tasks and responsibilities to other persons.

Every written work instruction, SOP or process instruction that an employee receives is a "delegated task". Each individual who completes a task and signs the record or log book confirms that he has carried out the task properly and takes responsibility for it.

The key functions must check on a regular basis that their instructions have been correctly understood and followed, e.g. during internal audits (see *chapter 3.G.3*).

Depending on whether a company manufactures medicinal products or APIs, holds marketing authorisations (see *chapter 3.B*) or trades in medicinal products, a number of different key functions must be filled. Their responsibilities are defined by law.

5.D.1 Head of Production

The **Head of Production** must approve manufacturing instructions and ensure they are strictly followed, ensure that storage is properly managed and that qualifications, validations, training and the maintenance of facilities and equipment in their department are carried out properly.

5.D.2 Head of Quality Control

The **Head of Quality Control** decides on the release of starting materials, packaging materials and intermediate products, and approves specifications as well as sampling and testing instructions. He or she must also ensure that all of the required tests are carried out and that qualifications, validations, training and maintenance of facilities and equipment in their department are carried out.

5.D.3 Qualified Person(QP)

The **Qualified Person** is responsible for releasing batches of medicinal product onto the markets of the EEA. Beforehand, he/she must check that the batch quality and manufacturing process comply with the marketing authorisation, that all tests and checks as well as additional tests required in the case of deviations have been carried out, that the documentation is complete and has been approved, and that the GMP rules were followed by all persons involved. Every company that applies for a **manufacturing authorisation** in the EEA (see *chapter 3.C*) must appoint a Qualified Person.

5.D.4 Responsible Person (only in companies underlying GDP-requirements)

In companies that only trade in medicinal products and do not require a manufacturing authorisation, there is no *Qualified Person* (QP). The management must appoint a **Responsible Person (RP)** who is responsible for introducing and establishing a QMS and for GDP compliance. Other responsibilities must be defined in job descriptions and SOPs. If there are several storage or distribution locations, a Responsible Person must be appointed at each site.

9 Quality Control and market release

9.A What does Quality Control check?

Quality Control ensures that the active ingredients, excipients, packaging materials, and final products comply with the specified quality requirements (**specifications**, see *chapter 6.B.2*). Other tasks include stability tests, tests for residues after cleaning (**cleaning validation**, see *chapter 7.B.1*), microbiological analysis of the room air and surfaces (**microbiological monitoring**, see *chapter 7.A.4*) and the development of new methods of analysis.

There are usually several control laboratories in Quality Control that carry out very different tasks and, for this reason, are located in separate areas.

9.A.1 Chemical and physical tests

During these tests, the **identity** of active ingredients, the **purity** of excipients, the **active ingredient content** of medicinal products and the **degradation products** after storage are analysed. The **content uniformity (CU)** of mixtures, the dissolving time of tablets, and the water content of granules are also analysed.

9.A.2 Microbiological laboratory

Many excipients are obtained from natural sources and may therefore be contaminated with bacteria and fungi. The bioburden in the water supply system

and in the ambient air in the production rooms must also be checked on a regular basis. If a company manufactures sterile products (e.g. eye drops, ampoules, infusion solutions), the bioburden of the starting materials, intermediates and final products must be checked. These tests are carried out in microbiological laboratories and are often complex and time-consuming, but they are indispensable.

9.A.3 Control of packaging materials

Laboratories also test the quality of aluminium or plastic foils used for blisters. The **leaktightness** of ampoules, vials (small glass bottles with rubber stoppers), screw tops or tubes are important for the stability of the medicinal products. **Printed data** on folding cartons, tubes, labels and patient information leaflets must be checked thoroughly, because even small printing errors can have severe consequences for the patient.

9.B How must a control laboratory be organised and equipped?

9.B.1 Personnel and responsibilities

The Quality Control department must be able to make decisions independent of the Production department. For this reason, QC has its own **Head of Quality Control** (see *chapter 5.D.2*). This person is responsible for ensuring that laboratory personnel are qualified and receive training on a regular basis, and that they only work in suitable rooms using qualified laboratory equipment. The Head of Quality Control in many companies is also responsible for approving specifications, sampling and test instructions and for releasing raw materials. However,

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Since 1997 Christine Oechslein, PhD, is a free-lance GMP instructor and leads internal GMP training activities for a diverse set of pharmaceutical companies, manufacturers of active ingredients, and suppliers. After graduating in pharmaceutical sciences from the University of Erlangen, Germany, she worked as a project leader in galenical development at 3M Medica/Kettelhack-Riker before joining Sandoz Pharma AG in Basel (Switzerland). There Christine Oechslein worked in pharmaceutical development while in parallel completing her PhD thesis. After completing her PhD at the University of Marburg she moved to the technical R&D – Quality Assurance Unit, compiled a quality manual for pharmaceutical development and oversaw the SOP system. When Novartis Pharma AG was formed Christine Oechslein continued until 2010 as a free-lance contributor in the area of quality systems.

As a speaker and coach in training seminars Christine Oechslein focuses her work on the topics of process validation, GMP in development, train the trainer, efficient coaching methods, and metrics for success. Furthermore attending classes at the College of Education at the University of Freiburg she has broadened her skill set in the area of adult education.

Christine Oechslein is an author and co-author of the following GMP-publications and educational material which has been published by Maas & Peither AG – GMP Publishing:

- GMP MANUAL: Chapter on Process Validation as well as Research and Development
- GMP Audit Checklist for Pharmaceutical and API Manufacturers
- GMP-Questionnaire: Contract manufacturing / Contract analysis
- Quality Agreement
- Technical Agreement and Delimitation of Pharmaceutical Responsibilities
- Documenting Process Validation
- Preparing for the EU GMP Inspection

This hand book is a practical and easy to read guideline, giving you a quick and comprehensive overview of the complex world of **G**ood **M**anufacturing **P**ractice (GMP) without the need of previous acquired knowledge.

Some topics are:

- GMP: Purpose and basic pharmaceutical terms
- Laws, licenses and inspections
- Personnel: Responsibility and hygiene
- Standard Operating Procedures (SOP) and documentation
- Design of rooms and facilities
- Processing and packaging
- Quality control and market release
- Suppliers, storage and logistics (**G**ood **D**istribution **P**ractice = GDP)
- Alphabetical index and abbreviations

Using practical examples and comparisons to every-day life help to easily understand GMP regulations.

GMP Fundamentals is a helpful guide which facilitates the entry into the GMP world and teaches the necessary basics.

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