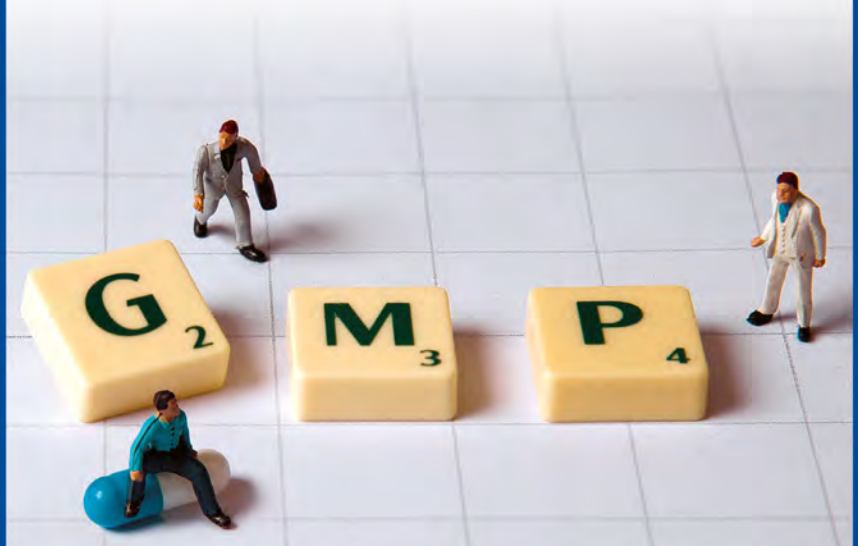
Christine Oechslein, PhD

GMP Fundamentals

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



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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 Compliance Adviser. 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. Examples 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

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 *Conclusion* and chapter 3.E *What are the most important GMP regulations?*).

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 *Inspections by the authorities*) 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 *Where is manufacture and storage permitted?*)?
- Does the company have properly trained personnel in sufficient numbers (see chapter 5.A *What does personnel qualification mean?*)?
- Does the company have proper machinery and equipment? Is the machinery and equipment regularly serviced and cleaned (see chapter 7.B *What requirements apply to facilities and equipment?* et seq.)?
- Has the company defined and documented who is responsible for the various functions (organigrams and job descriptions, see chapter 5.D *Who carries responsibility?*)?
- 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 *What does a QM system look like?* and chapter 4.C *What typical situations must be controlled by a quality management system?*)?
- Has the company described every activity in written work instructions, and is each task recorded in a precise manner (see chapter 6 *Work instructions, records and documentation*)?
- Is the company GMP-compliant (**compliance**, see chapter 3.F *What is compliance?*)?

During regular follow-up inspections (see chapter 3.G.1 *Inspections by the authorities*), 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.

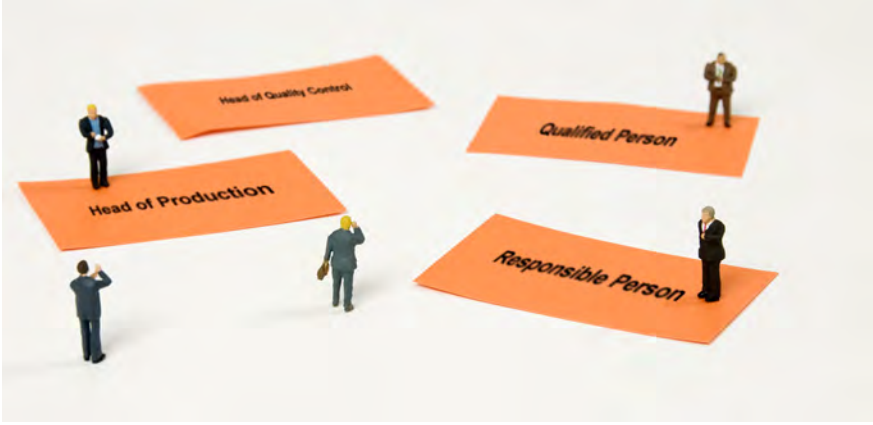
A manufacturing authorisation is not only required for *typical manufacturing steps* such as stirring ointment or making tablets. Companies that only carry out **packaging** also require a manufacturing authorisation if they, for example, seal tablets into blister foils (push-through foils), package 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 *Market release and batch certification*) 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.

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 *Self-inspection (internal audits)*).

Depending on whether a company manufactures medicinal products or APIs, holds marketing authorisations (see chapter 3.B *Which medicinal products may be placed on the market?*) 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.

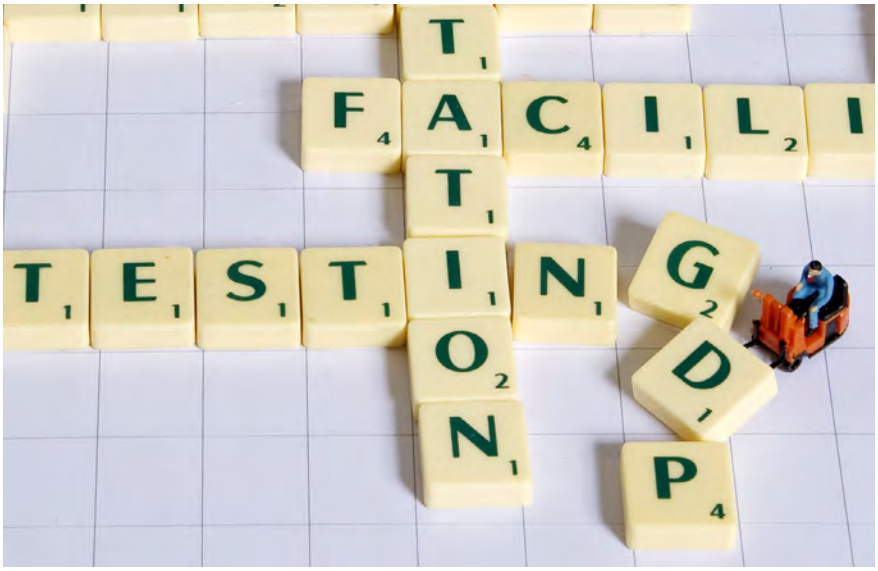
5.D.3 Qualified Person(QP)

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 *What licence or authorisation is needed?*) 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.

10 Suppliers, storage and logistics – GDP



10.A What is the purpose of GDP regulations?

20 years ago, **GDP** (Good Distribution Practice) was of no major importance. Active ingredients and medicinal products were manufactured domestically or in neighbouring countries. The **transport routes** were short and easy to manage. Overseas pharmaceutical manufacturers played a tiny role in supplying the European market. The opposite is now the case.

Cost pressure in health care has resulted in increasing **imports** of medicinal products from other countries. Most **active ingredients** are now produced in Asia and shipped on partly **intransparent distribution routes** to pharmaceutical manufacturers all over the world.

The preliminary and intermediate stages in the manufacture of medicinal products often take place **at different locations**. Repeated unloading and reloading can lead to confusion and **mix-ups with inferior materials**.

It is no longer enough just to focus on the careful manufacture and testing of medicinal products. Controls must be carried out much earlier during the **manufacture of active ingredients and excipients**. In addition Quality assurance efforts must continue after the product has been shipped by the pharmaceutical manufacturer, until the product arrives at the hospital or pharmacy.

The purpose of the **GDP guidelines** is to close the gaps. They are meant to ensure that

- active ingredients and excipients produced by reliable manufacturers are transported on safe transport routes to the pharmaceutical manufacturer without any loss in quality.
- medicinal products reach the patient in unaltered quality and their replacement with counterfeits can be ruled out.

At this stage, the GDP guidelines also apply to logistics, storage and transport companies that previously did not have to deal with the special requirements that have to be observed when handling medicinal products. The standard processes used in pharmaceutical quality assurance and the comprehensive documentation are often met with resistance. However, various service providers have recognised that meeting GDP requirements is a business opportunity and now specialise in the area of pharmaceutical logistics.

10.B What is a supply chain?

10.B.1 Supplier qualification, sourcing and traceability

The quality of medicinal products largely depends on the quality of the ingredients. For this reason, pharmaceutical starting materials (**active ingredients**, **excipients** and **packaging materials**) must be handled with great care. Furthermore, these materials must only be sourced from **qualified suppliers**, i.e. suppliers who have signed **quality agreements** and have been checked by Quality Assurance (**supplier qualification**, see chapter 4.C.2 *Outsourcing (contracting third parties)*).

The required quality of the input materials are defined by the pharmaceutical company in **specifications** (description of properties, see chapter 6.B.2 *Specifications*) that are submitted to the authorities as part of the **marketing authorisation documentation** (**dossier**, see chapter 3.B *Which medicinal products may be placed on the market?*). The supplier of the input materials is also identified in the marketing authorisation documentation. For this reason, a company has to carry out a thorough internal evaluation (**change control**, see chapter 4.C.5 *Change Control*) and submit a **change request** to the authorisation authorities before switching suppliers.

To ensure that the quality of the supplied input materials meets the specifications, samples are taken on receipt of the materials (sampling, see chapter 9.D.1 *Sampling*) and analysed by Quality Control (see chapter 9.A *What does Quality Control check?*).

If the suppliers are not the actual manufacturers of the active ingredient or excipient, they must provide the customer with the quality-relevant manufacturing information, e.g. the batch names used by the manufacturer, expiry

12 The author

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 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 Compliance Adviser: Chapter on Process Validation as well as Research and Development
- Questionnaire for preparing GMP-Inspections
- GMP-Questionnaire: Contract manufacturing /Contract analysis
- Quality Agreement
- Technical Agreement and Delimitation of Pharmaceutical Responsibilities
- Managing Process Validation