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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

2 Basic pharmaceutical terms



2.A What is a medicinal product? What are medical devices, combination products or therapies?

Whether a product is a *medicinal product* and therefore subject to GMP requirements is not decided by manufacturers or their marketing departments.

In the EU, **medicinal products** are defined as products that

- ✚ have the *purpose* of treating or curing disease – even when they prove to be ineffective (**medicinal product by presentation**) or
- ✚ exert a pharmacological, immunological or metabolic action in the human or animal organism – even when they are not used for medicinal purposes, but to build muscle in athletes, for example (**medicinal product by function**).

Not every illness can be diagnosed immediately. Sometimes the symptoms are non-specific: headaches or abdominal pain, for example, can have many different causes. It is difficult to select an effective therapy without first finding the cause. **Diagnostic products** are then used. These are aids that simplify or facilitate a diagnosis, e.g. dipsticks or special measuring instruments. These diagnostic products must also meet high quality standards because an incorrect measuring result can lead to the wrong therapy and negatively affect the patient's health.

This is why there are strict regulations for the manufacture of diagnostic products, e.g. **German Medical Devices Act (MPG)**. This law also affects medical aids such as prosthetic devices, dressing materials, medical devices and wheelchairs, implants, pacemakers, artificial tears and flushing solutions.

Although the Medical Devices Act contains requirements that are in some cases similar to those in the GMP for medicinal products, there are major differences. Whether a company produces medical devices or medicinal products is important: sometimes, a lawyer is needed when deciding if the manufacture of a particular product falls under GMP or the Medical Devices Act.

In the USA, there are special GMP requirements for products that combine medical devices and medicinal products (**combination products, 21 CFR4**).

Therapies include other medically supportive measures such as spa treatment, massage, ergotherapy and physiotherapy.

2.B How do medicinal products differ from food products, food supplements and cosmetics?

There are a number of other product groups that can be difficult to distinguish from medicinal products at first sight. In addition, the definition of food products, food supplements or medicinal products differs from country to country. As a result, some products that are regarded as medicinal products in Germany are defined as **food products** in others.

Differentiation is important, however, because medicinal products are governed by a different law (Medicinal Products Act) than food products, cosmetics and medical devices (product differentiation). In Germany, for example, marketing authorisation is required for a finished medicinal product (see chapter 3.B *Which medicinal products may be placed on the market?*). Health-related advertising of food products in Germany is not permitted (**Healthcare Advertising Act (HWG)**). The term **GMP** is not widely used in European food legislation; instead the concept of *safe* and/or *unsafe* food is used as set out in the **EU "food hygiene package"**. The situation in the US is different: the term **GMP** is also used in food manufacturing.

Food supplements (FSs), such as multivitamin preparations and fibre tablets, are classified somewhere between medicinal products and food products. They supply the body with additional nutrients or other substances that have nutritional or physiological effects. Under European law, food supplements are classified as food products, and in Germany fall under the **Foods, Consumer Goods and Feedstuffs Code (LFGB)**. The manufacturer/distributor is responsible for their safety and quality.

The situation with regard to **cosmetics** is similar. GMP requirements do *not* apply. Cosmetics are subject to the **LFGB** regulations. There is also a special **Cosmetics Directive** that specifies, for example, which preservatives and artificial colours may be used in cosmetics.



*Whether the manufacture of a product falls under GMP or some other law applies often has to be decided by legal experts.
The definition of medicinal products, food products, cosmetics and medical devices differs from country to country.*



Different forms of medicinal products require different manufacturing conditions, special testing and properly trained personnel.

2.F What are the most widely used dosage forms?



Ampoule: A sterile solution or suspension containing an API for injection or infusion in a hermetically sealed glass vial.

Capsule: A capsule is made of gelatine or other substances and contains the API in granulate (hard gelatine capsule) or in liquid/oily form (soft gelatine capsule).

Scrunch capsule: These capsules should not be swallowed, but scrunched so that the liquid content is released into the oral cavity. The effect is immediate because the API is absorbed through the oral mucous membrane without taking the long way around through the stomach and intestine.

Dragee: A core containing the API is covered in a smooth outer shell so that the dragee is easier to swallow than a tablet. In addition to giving the dragee a better taste and appearance, the shell protects the inner core, e.g. against gastric acid.

Emulsion: A viscous mixture of two or more liquids that are normally immiscible or only partly miscible (mostly oil and water).

Extract: An extract is a liquid, solid or highly viscous concentrated preparation made from dried plants or animal materials.

Gel: A semi-solid preparation made by mixing a liquid and a thickener. The APIs are dissolved in the liquid. Due to their cooling effect, gels are used for treating sunburn and mosquito bites.

Granule: A granule consists of powder particles that are stuck together. Granules are generally used to make tablets, but granular powders are also available as drinks or for oral application.

Metered-dose inhaler: An API solution or suspension with a propellant in a metal or glass canister. By pressing a metering valve, a metered quantity of API can be dispensed and inhaled.

Ointment: A spreadable semi-solid preparation for topical application on skin and mucous membrane. Other semi-solid forms include creams, gels, pastes and emulsions.

Solution: A clear liquid dosage form that contains the API in soluble form. Solutions are available as syrups, elixirs, and eye, ear and nasal drops or sprays.

Sublingual spray: These emergency medicines contain dissolved APIs in a small spray bottle. When the medicine is sprayed under the tongue, the effect is immediate because the API is absorbed through the oral mucous membrane.

Suppository: An oblong dosage form for insertion into the rectum or, in the case of gynaecological illness, into the vagina (**vaginal ovules**). Suppositories are solid at room temperature and melt or dissolve at body temperature.

Suspension: These medicines contain solid particles in a liquid. They have to be shaken before use because of their tendency to settle. Antibiotic syrups are a good example.

Tablet: Powder or granules containing one or more APIs are pressed into round or oblong shapes, sometimes with score lines. Tablets should generally be swallowed whole without chewing. However, there are exceptions:

-  **Chewable tablet/dissolving tablet:** These tablets are chewed or allowed to dissolve on the tongue. The API is immediately released and the effect occurs very quickly.
-  **Effervescent tablet:** These tablets also take effect quickly because the API is released when the tablet dissolves in water.
-  **Film or coated tablet:** These tablets are covered in a thin film coating. This makes them easier to swallow and neutralises their taste.
-  **Lozenge:** The addition of special ingredients means that lozenges dissolve slowly in the oral cavity and thus have a local effect over an extended period of time, e.g. for sore throats.
-  **Prolonged-release tablet:** The API is embedded in excipients in these special tablets so that it is slowly released over an extended period of time. The effect can continue for up to 24 hours.

Tincture: A liquid preparation for oral application or application on the skin or mucous membrane. Tinctures are manufactured from dried plant or animal materials.

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 **opaque 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 re-loading 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, com-

pleted 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