1 Drug Formulations as Application System—Science and Legal Provisions

1.1 General Principles

The main objective to formulate a drug is to deliver it in a reproducible, reliable, safe, and optimally effective manner, thus allowing it to exert its proper therapeutic effect under quality-controlled conditions. Only in rare cases will it be possible to administer a drug without any formulation, such as a single, measured dose (e.g., a single-dose powder only containing the active ingredient itself). In most cases, however, the active agent(s) will have to be transformed into a medication (i.e., a drug formulation) by means of appropriate pharmaceutical techniques employing one or more preferably inert substances, while taking into consideration therapeutical and biopharmaceutical requirements, as well as machinability, stability, and appearance.

Thus, a drug product consists of active and inactive substances, as shown in Fig. 1-1.

The definition of the term *pharmaceutics* varies with the legislature of individual countries. Often, it includes active substances as well as drug products. But it may also refer to individual prescriptions, bulk formulations, or large-scale supplies of ready-to-use products. Pharmaceuticals are distinguished from medical devices (*for an elaborate definition, see chapter* 5.1) by their principal mechanism of action (metabolic, immunological, or pharmacological for the former, and physical or physicochemical for the latter, even if they serve therapeutic or diagnostic purposes).

The inactive substances, known as *excipients*, play an important role in the formulation of drugs (see chapter 5). Not only are they responsible for the characteristic appearance of a formulation, but most of all they ensure the drug's biological availability and therapeutic action as well as its controlled and economically accountable production.

It is only after an active agent has been transferred into a suitable formulation that a certain kind of application becomes possible. For example, for peroral administration, drugs are most often formulated as tablets or capsules, but liquid preparations such as solutions, suspensions, or emulsions may also serve as vehicles. For the treatment of skin conditions, ointments, pastes, and liniments are often applied (chapter 15). Suppositories or rectal capsules are suitable for rectal applications, while for application into the blood stream therapeutic agents are formulated as solutions or suspensions for injection or infusion (chapter 21).

Aerosols are most suitable for the treatment of bronchial or pulmonary epithelia (chapter 23). Particle dimensions of novel drug formulations tend to reach the micro- or nanometer range—for example, microparticles or nanoparticles such as liposomes (chapter 20.2). The turbulent development of molecular and gene technology requires multifunctional, "intelligent," and conductible (i.e., site-directed) formulations to allow effective delivery of medicines with limited water solubility, low-membrane permeability, or insufficient stability, such as peptides, proteins, DNA, RNA, or strongly lipophilic substances.

Voigt's Pharmaceutical Technology, First Edition. Alfred Fahr.

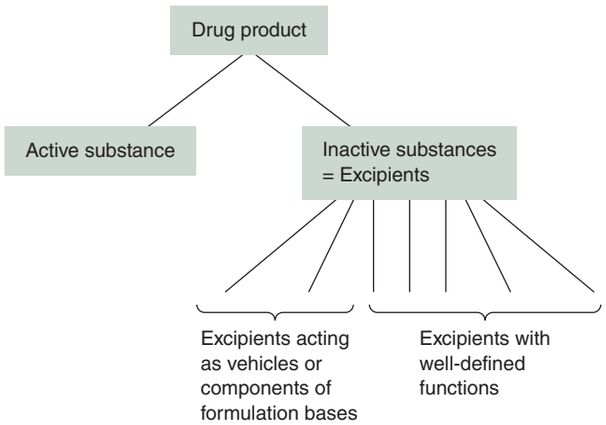


Fig. 1-1 Components of a drug product.

Definition of Active Pharmaceutical Ingredient (API) (or Drug Substance or Active substance) by the FDA (U.S.A.): "Any substance or mixture of substances intended to be used in the manufacture of a drug (medicinal) product and that, when used in the production of a drug, becomes an active ingredient of the drug product. Such substances are intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease or to affect the structure and function of the body." Also the expression AI (active ingredient) or pharmacon is used.

In contrast, the active ingredient in plant material is called *active constituent*.

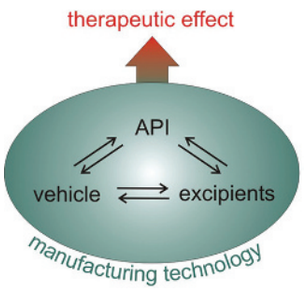


Fig. 1-2 The drug formulation as a system.

These are only a few examples, but they clearly illustrate the many available possibilities to design appropriate formulations to administer pharmaceutically active agents in or on the human and animal body. The choice of formulation will depend on the site to be treated and the site of action, the type of disease, the patient population (i.e. adults or children), and the desired effect. Nowadays, such formulations are often referred to as *drug delivery systems*, meant to allow tailored deployment of a pharmaceutical agent for a defined and exclusive therapeutic goal (targeted delivery). So-called therapeutic systems release the active drug at the site of action in a controlled way with a well-defined premeditated constant release rate for a fixed time period. Examples of such systems are the Transdermal Therapeutic Systems (TTS) (see chapter 16) or the Oral Osmotic Systems (OROS) (see chapter 12.6.3).

It is important to note that the formulation has, by no means, only a carrier function. The basic ingredients and excipients, as well as the manufacturing technology, strongly influence the ultimate effect of the drug. The onset, duration, and intensity of the drug action depend on the way it is formulated. Therefore, the formulation plays a substantial role in the ultimate efficacy of the drug. It represents a complex system whose individual components (active substance(s) and excipients (see Fig. 1-1)) should not just be regarded as isolated entities, but rather, in combination with the numerous possible interactions of the individual components. It is important to stay aware that the manufacturing technology may act on each of them in many different ways (see Fig. 1-2).

Accurate dosing of the drug formulation is important for the patient not to experience harmful side effects as a result of dose deviations. This implies that weight and drug content of single-dose medication, e.g. individual tablet, is controlled in a narrow range.

A further requirement of the formulation concerns sufficient stability of the active ingredient, but also all excipients. Often, the proper choice of packaging may already diminish or prevent stability loss.

Drug formulations should as well have an appealing appearance. Most pharmacopeias, therefore, allow the use of pigments (water-soluble, fat-soluble, or insoluble coloring substances; see section 5.4.1). For the sake of making the product more appealing, for better recognition (to prevent mixing up different medicines) or psychological aspects. This is, in particular, used for (coated) tablets, capsules, and suppositories. Coloring of medicines does not always come without problems. Under certain conditions, dyes may be oncogenic, embryotoxic, or teratogenic. Therefore, only formally approved dyes have to be used. Initiatives are underway to establish their safety by scientific data as a prerequisite for permanent listing. Depending on the physicochemical properties of the dyes, undesirable changes in the drug system, including interactions or incompatibilities between active ingredient and excipients, cannot be rigorously excluded. Apart from that, the sustainability of a medicine also applies to the stability of the applied pigments (check by means of color charts or colorimetry).

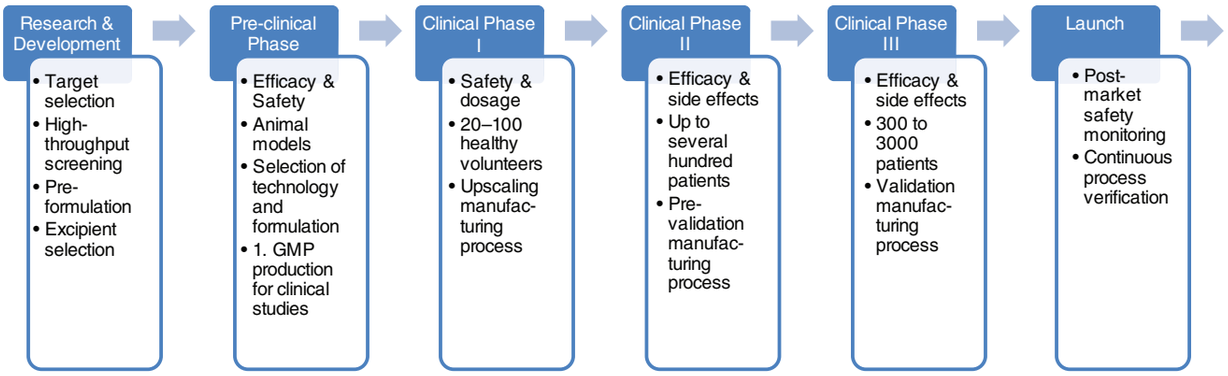


Fig. 1-3 Drug development process.

Furthermore, in the case of orally administered medicines, it is advisable to conceal bad flavor or odor with suitable excipients.

The development of a drug formulation is a complex process that, grossly simplified, is characterized by the following stages (see Fig. 1-3):

- In the pre-formulation stage, the physicochemical properties of the active ingredient (e.g., solubility, stability, distribution coefficient, acid-base characteristics, particle size, salt selection, polymorphism, etc.) is intensively investigated. This is meant to serve as the basis for the selection of a suitable formulation, to predict the behavior of the new drug form and to facilitate planning of the developing process by identification of critical parameters at this stage.
- Furthermore, investigations are conducted with the aim to select suitable excipients for the formulation of a medicine—for instance, with respect to possible interactions with the active ingredient. While earlier these processes were predominantly depending on a trial-and-error approach, nowadays a more rational strategy, based on statistically supported research planning is prevailing.
- Based on the results of these investigations formulation development takes place under laboratory conditions. Using different excipients and technologies a suitable formulation for first human studies is developed and assessed for stability.
- The selected formulation is produced under GMP conditions in order to supply the first clinical study
- After successful completion of a series of first clinical studies (so-called phase I, conducted on healthy volunteers to determine patient tolerance, the distribution in the body, single ascending dose and multiple ascending dose) upscaling follows (verification in the pilot facility).
- If the clinical phase II study (activity and dose finding in several hundreds of patients) turns out to be successful as well, the project will finally be transferred to the production department of the pharmaceutical industry.
- This transfer to mass production, also described as upscaling, may cause problems in the adjustment of methodology, especially in case of complex novel drug formulations. Efforts spent in the developing process are decisive for the technical feasibility and, in connection to that, the economic feasibility of the project, precipitating in the production costs.

The leading principle is most certainly the implementation of the regulations concerning quality certification of the entire production process. Pioneering work in this connection was performed by the approval authorities of the United States, who brought together a number of already-existing guidelines, drawn up in 1962, under the concept of Good Manufacturing Practice (GMP). Several other countries also adopted these efforts. Global guidelines were worked out by the *International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use* (*ICH*) and should, at least for Europe, the United States, and Japan, form the

basis for approval. The WHO-GMP guidelines are, however, directional in more than 100 (predominantly developing) countries.

1.2 Good Manufacturing Practice (GMP)

Since the late 1960s, recurring incidents with medicines such as switching incidents (mix-ups of medications), cross contaminations, (bacterial) contaminations, and the discovery of serious shortcomings during test procedures have gradually led to the introduction of stringent measures *vis-à-vis* quality security of active ingredients, excipients, and drug product. Since then, solid proof of safety, efficacy and quality of the drug as well as drug products for the entire shelf life is requested.

Fulfillment of these essential requirements must be undisputable before approval will be obtained. They are laid down in drug laws that regulate the development, approval, and commercialization of medicines. The approval of medicines is granted at the national level, such as a request of approval in a given country is submitted to the qualified authorities in that country (e.g., USA: FDA; Germany: BfArM; Japan: MHLW). Within the European Union, centralized and decentralized procedures can be distinguished. In case of a centralized procedure, the request is filed at the European Medicines Agency for all EU countries alike. In case of decentralized procedures (DCP), there is an additional distinction as compared to the Mutual Recognition Procedures (MRP). For a MRP, an approval request is first submitted to only one country, and after obtaining approval a procedure is started to obtain mutual approval in other EU countries. In the DCP, approval requests are filed simultaneously in several countries and one of them is selected as a reference country. The other countries carry out an evaluation of the submission in a coordinated mutual approval process.

The World Health Organization (WHO) drafted in 1968 a document called "Draft Requirements for Good Manufacturing Practice in the Manufacture and Quality Control of Drugs and Pharmaceutical Specialties" as an instrument for the introduction of quality criteria, suggested for use in all member states, to accomplish a harmonized standard of production and quality control.

This document, which in its current version is called "WHO Good Manufacturing Practices: Main Principles for Pharmaceutical Products," has repeatedly been supplemented and revised over the years. Nowadays its key message is worldwide known as Good Manufacturing Practice (GMP).

As a further completion of the original *WHO-GMP Guidelines*, (mainly European) authorities in charge of its surveillance on their turn launched a frequently up-dated agreement on the mutual recognition of inspections of pharmaceutical industries (PIC—Pharmaceutical Inspection Convention) in 1970.

In this agreement, furthermore, the basic rules and regulations for GMP-compatible manufacturing of pharmaceutical products are laid down (PIC-GMP rules). The document stipulates in particular the guidelines for the manufacturing of sterile products, the handling of raw materials, and the packaging of pharmaceutical products.

In the early 1990s, the EU established its own GMP rules (EU-GMP-regulations) that were basically adopted from PIC. Today, the EU-GMP regulations consist of two parts, the mandatory guidelines and the nonmandatory but highly recommended manual.

The current, revised and expanded WHO-GMP set of rules encompasses and goes beyond all principles, standards, and procedures contained in the *PIC-GMP-guidelines*. For example, in the WHO documents, the requirements for in-process control procedures are more precise.

That means that as a rule, a WHO-conformed quality control will be in line with PIC requirements; reversely, however, PIC-conform quality control systems may not necessarily be fully in accordance with the WHO guidelines. That refers also to the EU-GMP guidelines, as this set of GMP rules, except for minor differences (e.g., in educational requirements), is identical to the PIC-GMP guidelines.

Earlier, the GMP rules were not covered by legal jurisdiction in the context of national legislature, but were to be interpreted as strong recommendations on how to achieve pursued quality goals and to fulfill basic quality requirements.

Today, the GMP set of rules forms, together with GLP (Good Laboratory Practice) and GCP (Good Clinical Practice), constitutes an integral part of a complex quality assurance system and requires comprehensive surveillance and quality control in each phase of the manufacturing process, adjusted to state of the art of science and technology. Compliance with the GMP rules is a strict precondition to obtain approval of the product.

Also, the requirements of the quality management system according to ISO 9000 series of standards (established in 1994 and revised in 2005, *describing fundamentals of quality management systems*) are fully covered by the extensive legislative provisions on medicines as well as the current framework of GMP rules.

The essential requirements of the WHO-GMP guidelines (extended form) are:

- Extreme care during all production phases by well-trained quality-aware and responsible personnel.
- Availability of appropriate spatial arrangements providing separate spaces for manufacturing, packaging, labeling, and testing of the medicines.
- Erroneous switching incidents and cross-contamination should be avoided by appropriate spatial separation of different production and packaging processes, as well as unambiguous labeling of the contents of all containers and pieces of equipment used in the different steps of production.
- To avoid contamination, production hygiene should be meticulous, ascertained by regular cleaning of all working spaces and equipment as well as by regular health checks of the personnel and environmental monitoring.
- In order to fulfill the requirements of microbial purity, hygienic measures are particularly mandatory in the production of medicines, which are not subjected to sterilization.
- Active ingredients with exceptionally high bioactivity must be processed in separate spaces provided with an adequate ventilation system in order to avoid cross contamination.
- High quality of all materials involved in the production of the medicine must be guaranteed; the guidelines were expanded with additional paragraphs concerning reagents, culture media, reference standards, and waste materials.
- Further recommendations concern the quality control system and the handling and documentation of complaints as well as reports of unwanted (side) effects.
- In-process controls: Quality should be produced and should be reproducible! The controls should support and confirm the GMP-conform production of a medicine as an auxiliary measure, and apply to all critical parameters during the production process
  - These control procedures make it possible to improve quality assurance as well as continuous monitoring/correction/optimization of the running production processes (e.g., control of tablet mass, disintegration time, homogeneity of mixtures, filling volume of ampoules).
- Control of raw materials as well as of final products including packaging material
- Registration of each individual production step that might affect the quality of the final product
- Control of stability of the medicine
- Control of the batch protocols
- Throughout the product lifecycle, all processes are monitored and evaluated. This additional knowledge is utilized for adjustment of processes as part of the continual improvement of the drug product.
- Guidelines for the manufacturing of sterile pharmaceutical products; for example, sterile filtration is considered to be a sterilization process.
- The requirements with respect to self-inspection and audit have to be expanded with aspects concerning the extent of self-inspection and the subsequent follow-up measures, as well as supplier control (audit). In the context of the audit, the contract provider is obliged to ascertain the competence of the supplier. The supplier is obliged to act according to GMP rules and must have the necessary equipment and personnel at his disposition.

One key aspect of the GMP idea is the "validation" principle that was introduced in the late 1970s, initially for the sterile production of parenterals and later for all other drug products. According to the EU-GMP guideline, validation is the systematic and documented proof that procedures, processes, equipment, materials, production cycles, or systems reliably, reproducibly and truly lead to the intended results, in line with the principles of good manufacturing practice. This regards the validation of processes, methods, cleaning, and installation of instruments, computers, and other equipment. In the latter cases, we speak, in a narrower sense, of qualification. All actions with respect to a validation or qualification must be planned and documented, and specified outcomes and acceptance criteria must be indicated.

As a rule, validations are performed *prospectively* (i.e., before market authorization) or, alternatively and only when supported by solid argumentation, concurrent with market authorization on minimally three consecutive batches. Nowadays, retrospective activities of already established installations by exploitation of preexisting data material (approx. 10 to 30 production cycles) hardly stand a chance to become formally recognized. The basis for all validation work is knowledge of all critical parameters in which minor changes have a significant influence on the quality of the final product, which normally involves practical determinations by experiments covering all parameter influences (according to "Design of Experiments" methodology; DoE). The determination and characterization of these parameters and their importance are collectively referred to as risk analysis.

It is generally understood that qualification of instruments, installations, and equipment implies documented proof that such systems have been constructed according to predefined specifications and function in accordance with those. This documentation must be continuously available during the entire life cycle of the system.

A permanent, verifiable, and orderly documentation is a compelling condition for the surveillance and transparency of the overall process and thus of the reliability of pharmaceutical quality. According to EU-GMP guidelines, availability of the following documents is imperative:

- *Standard operation procedures* (SOP) are defined working instructions for a process with an unequivocally documented outcome. Such instructions have to be followed most accurately in order to ascertain comparability of results and reproducible quality of the final product.
- *Specifications* define the requirements of the raw materials, in-process products, and final product.
- *Manufacturing protocols* (*Master Batch Records*) and packaging instructions determine all outcomes and procedures with respect to processing and packaging.
- *Protocols* (Executed Master Batch Records) document the complete course of events of each individual batch produced.

According to EU-GMP guidelines, extreme care should be taken to avoid any unpredicted deviation from an adopted standard. Deviations may occur during the manufacturing as well as during the testing of medicines and can be characterized as either process-dependent (e.g., inadequate optimization or design of the process) or process-independent (e.g., failure of equipment or human errors). If deviations occur, the root cause(s), the effect on product quality, and measures to solve the problem must all be identified.

In contrast to deviations, changes are defined as planned and lasting modifications of an adopted standard. Changes are introduced in the course of processes and procedures preferentially based on progress in technical developments. In a change control procedure, all actions leading to the modification, as well as their effect on the validation status and approval, have to be defined and coordinated.

In its narrow sense, a qualified person is just responsible for the release of the batch, but this presupposes completion and testing of the batch.

The *qualified person* (*QP*) is responsible for the completion and testing of each individual batch, according to GMP protocols. This is anchored in the drug law.

In 2002, the FDA launched a new offensive by means of the GMP initiative "Pharmaceutical cGMPs for the Twenty-First Century—A Risk-Based Approach" with four objectives:

1. Encourage development and innovations in pharmaceutical development.
2. Exploit modern science and techniques in a more goal-oriented and efficient way.
3. Modernize pharmaceutical regulations.
4. Improve approval, surveillance, and safety procedures.

In this connection, process understanding and risk management deserve reinforced significance.

Formerly, the traditional approach in the production of medicines was characterized by exploiting empirical methods with a focus on final product testing. By contrast, nowadays a system is created by means of process analytical technology (PAT) for the design, analysis, and monitoring of the production process using real-time assessments of critical parameters of quality and performance of raw materials, in-process products, and processes, thus safeguarding the quality of the final product. The thorough understanding of the overall process and the application of novel technologies—in particular, real-time assessments and real-time release—should enhance safety, shorten production time, enlarge yields, and reduce costs.

As another follow-up of the FDA initiatives, the quality by design (QbD) concept was introduced as an extension of the systematic pharmaceutical development program with its own guideline (Quality Systems Approach Guideline). QbD can be seen as a systematically structured developmental effort, starting with predefined targets particularly emphasizing process understanding and control. The initiative rests on solid scientific grounds and intensive quality-risk management.

The concept includes the following principles:

- Prospective definition of the quality characteristics of a product as a *quality target product profile* (QTPP), which exerts an essential influence on factors such as activity, quality, and safety
- Recording of critical chemical, physical, and biological quality attributes of active ingredient as well as excipients (e.g., identity, purity, content etc.), which sums up to CQA (critical quality attribute of the drug product) and CMA (critical material attributes of excipients or API)
- Selection of an appropriate production process allowing the achievement of the chosen characteristics
- Defining of a control strategy and suitable control mechanisms to monitor process performance and process quality
- Demonstrate process capability and efficiency of the control strategy
- Surveillance and monitoring of the process capability during the entire life cycle of the project

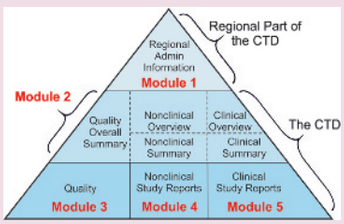
The principles for this concept are risk management, statistic calculations, and PAT.

Thus, in the last decades, the notion of quality has developed from mere quality control, in which only at the end of the process is a test performed to ascertain that the final product meets all predetermined specifications, to comprehensive quality management involving the integrated action of people, technique, and organization processes. What began in the early twentieth century as a simple final quality control (QC) of a significant percentage of the produced items has evolved as a result of increasing production rates, via quality assurance (QA) based on random sampling into statistically secured test protocols. It was recognized that workers in their interaction with technique and organization are essential to QA. This initially led to the concept of quality management (QM) and later—upon integration of company exceeding factors such as environment, client demands, security, and economics—to the notion of total quality management (TQM). This company philosophy presumes the collaboration of all actively involved individuals to achieve the ultimate goal of the system: quality.

As can already be sensed from this introductory chapter, each newly developed drug is a true challenge for pharmaceutical technology, despite the vast body of knowledge that has been accumulated over many decades and in numerous places. That holds true for all stages on the way of development, from the initial formulation design to its optimization and then onto its mass production for the market. The ever-sharpening quality requirements for the protection of the patient are not merely tested but, rather, incorporated in the process. During the development stage, that applies particularly to newly introduced excipients for a given API but also to (new) combinations of known components. Even in the late stages (e.g., the scaling-up phase) the complexity of the interactions between all components may present unexpected problems. Profound knowledge of the individual process steps, including seemingly simple procedures like mixing or granulation, and the combination of knowledge on the individual steps is necessary to prevent the pharmaceutical scientist from getting lost

The Common Technical Document (CTD) is a set of specifications for application dossier for the registration of Medicines and designed to be used across Europe, Japan and the United States. It is an internationally agreed format for the preparation of applications regarding new drugs intended to be submitted to regional regulatory authorities in participating countries. It was developed by the European Medicines Agency (EMA, Europe), the Food and Drug Administration (FDA, US) and the Ministry of Health, Labour and Welfare (MHLW, Japan). The CTD is maintained by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH).

The CTD consists of five modules:



in a thicket of information. It is only then that we will be able to meet the ever-increasing demands concerning quality security of medicines, in a predictable yet scientific manner.

Despite all available protocols, rules and regulations, the development of a new formulation is still an exciting endeavor. And often even, this endeavor turns out to be an open-ended adventure, because numerous poorly understood factors engaged in ill-defined interactions with each other, may turn out to play an essential part in the process. George Wald described this sensation in his Nobel lecture (1967) with the words, "I have often had cause to feel that my hands are cleverer than my head." This notion is also quite commonly experienced by pharmaceutical scientists, who in many cases have to rely on the phenomenon of "serendipity" (keyword: "chance favors only the prepared mind"). It may be comforting to the reader that this book, even though not helpful in affecting chance, may do so by preparing the reader's mind.

A note to the Pharmacopeia Boxes

As written in the foreword, these boxes help

1. to show how scientific expertise find its way into legal context
2. to see how tests are performed
3. to identify the differences between three main pharmacopeias in this world

The boxes in the German version of this book were originally based on the Ph. Eur. rules. Three main pharmacopeial commissions (JP, Ph. Eur., USP) work together for harmonization of the pharmacopeias (cf. General part Ph. Eur. 5.8). Many other countries (e.g., China, India, Russian Confederation) are *observer countries* and work in harmonization groups (see, e.g., www.ich.org) on this behalf. Despite these efforts, there are still many differences between the main pharmacopeias. We compare in the pharmacopeia boxes and in the monography chapter the rules described in the three main pharmacopeias for a better understanding. If only one or two pharmacopeias are mentioned in a box, this normally means, that there is no information about the special items in those pharmacopeias. This might work as a guidance for the professional pharmacist.

USP–NF is a combination of two compendia, the United States Pharmacopeia (USP) and the National Formulary (NF). Monographs for drug substances, dosage forms, and compounded preparations are featured in the USP. Excipient monographs are in the NF.

JP is the Japanese Pharmacopeia. The basis for our comparative work is USP 38, NF 38, and JP 16. The German book was based on Ph. Eur. 7.8, which we took as reference. In this book we had adapted the relevant text from Ph. Eur. 9.1. These editions of the main pharmacopeias are also the basis of the appendix (Selected Pharmaceutical Preparations (Compared between Ph. Eur., USP, and JP). Each of the pharmacopeias contains at least one chapter on pharmaceutical dosage forms where definitions, sub-classifications and relevant tests can be found. The appendix describes the dosage forms which are listed there and compares the requirements specified in the three different pharmacopeias.