Frank Böttcher, Jürgen Eberlein, Annette Könemann,
Josef Künzle, Markus Limberger

GMP Series

Core Processes in the Pharmaceutical Laboratory

GMP-Conform Sampling and Handling of Substances

Excerpt from the GMP Compliance Adviser

Contents

1 Sampling

Frank Böttcher, PhD, Jürgen Eberlein, Annette Könemann, Josef Künzle, PhD

Here you will find answers to the following questions:
- Why is sampling classified as a critical process step?
- What regulatory requirements are to be upheld during sampling?
- What requirements are placed on the sample taker, the rooms and the environmental conditions?
- What equipment is necessary to ensure a representative sample?
- Which materials are to be sampled and what factors are to be considered?
- How can factors influencing the sampling process be determined as part of a risk assessment?
- How does one determine a representative sample size?
- What methods are there for drawing samples?
- What are the basic rules for ensuring that representative samples are taken?
- What requirements are placed on the documentation?
- What must be considered regarding the subsequent storage and shipment of the samples?
- How does a microbiological sample procedure differ from a sampling for chemico-physical characterization?

1.1 Introduction

What is the significance of sampling?

During sampling, a small amount of a batch is removed, analyzed and the result is used to evaluate the quality of the entire batch (see figure 1).

Thus sampling is the first link in the complete chain of quality control, and at the same time it is a critical process step. Mistakes made during sampling put the value of all subsequent steps in question and cannot be made up for by the most precise analytical methods after the fact! As a result it is necessary to plan and execute sampling procedures with great care.

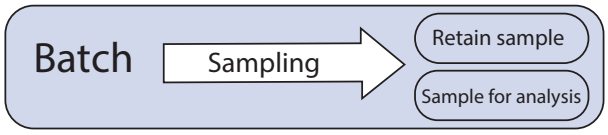

Figure 1 Sampling schematic

What prerequisites need to be fulfilled?

To ensure that the conclusions made based on the sample reflect upon the entire batch and thus its product quality, the following requirements must be fulfilled:
- the sample taking must be representative,
- the sample taking must be executed flawlessly,
- the sample taking must not be impaired by other influences.

The most important prerequisites to ensure that these needs are fulfilled are:
- risk-based determination of sample plans and methods considering all influential factors,
- specially qualified personnel which continually receive additional training,
- appropriate materials and environmental conditions.

Which materials are sampled?

Sampling is performed in every field of the chemicals and pharmaceuticals industries. It is applied for

- raw materials (excipients, APIs, packaging materials),
- utilities and secondary materials (water, gasses, etc.),
- intermediates,
- in-process control samples,
- finished products.

What regulatory requirements are to be upheld?

The requirements given in the GMP regulations which apply to sampling are described in detail in the following documents:

- EU GMP Guidelines Part I, Chapters 6.11 through 6.14
- EU GMP Guidelines, Annex 8 "*Sampling Starting and Packaging Materials*",
- EU GMP Guidelines Part II, Chapters 7.3, 8.3 and 11.7,
- 21 CFR 211, especially Subpart I

Additionally, there are further requirements in the pharmacopoeia to be upheld (e.g. Ph. Eur., 2.6.1 Sterility).

In the following chapters you will learn

- what requirements are placed on personnel, equipment, rooms so that the sample taking is not negatively impacted (chapter 1.2 *Factors influencing sample taking*),
- what special requirements are placed on sampling of various materials (chapter 1.3 *Materials to be sampled*),
- how to plan and perform sampling correctly (chapter 1.4 *Execution of sampling*),
- what requirements must be fulfilled for storage and shipping of samples (chapter 1.5 *Storage and shipping of samples*).

1.2 Factors influencing sample taking

1.2.1 Personnel

As part of a pharmaceutical quality system, high standards are placed on the personnel, which are described in detail in chapter 2 of the EU GMP Guidelines. In general an appropriate education and practical experience are required for a task. Furthermore, it is expected that continual training is continued to build upon the basic education and that the practical application of the learned skills is tested periodically.

As part of the selection process for sampling personnel the additional aspects given in figure 2 should also be fulfilled.

Requirements on personnel for sampling
• Dependability of the person with regard to "quality assessment of initial visual impression " (e.g. condition of the container to be sampled) • Command of aseptic working skills • Good observational skills • Ability to perform corresponding documentation

Figure 2 Requirements for sampling personnel

Considering these aspects the personnel should first be trained in the basic working methods so that the samples taken are representative of the unit being inspected.

The employee should be familiar with the associated risks and follow the proscribed protective measures. This applies both to risks to the employee (e.g. health risks from the product) as well as risks to the product (e.g. cross-contamination).

Furthermore, the sampling technician is to be made familiar with sampling plans and procedures and to be qualified further in both technical and personal regard via intensive **training** (see figure 3).

Training Plan for Sample Takers
Sample plans: Sample instructions
Sampling procedures including preparation of samples: **Individual samples, composite samples, division of samples**
Sampling methods and equipment: Tools and sample containers
Risks and precautionary measures during sampling: Protecting the product from contamination, Personal protective equipment
Importance of proper observation: The first impression principle
Protocolling unusual events: Example: soiled or damaged containers
Cleaning Sampling equipment and sampling rooms

Figure 3 Syllabus for sampling personnel

The correct behavior of personnel during sampling must be trained to match the purpose of the sample being taken.

- When sampling products for physico-chemical analysis the product quality of the goods in the container being sampled and protection of personnel from hazards are prioritized. As a rule of thumb, equivalent personal protection measures must be taken as for production conditions. This holds especially true for highly potent, carcinogenic, reproductive toxic and mutagenic substances.
- The situation is different, however for taking samples for microbiological testing. The appropriate hygienic behavior of the technician, a low-level germ environment and careful handling of materials and equipment are basic requirements for a representative sample.

Protective clothing

The most important step in preparing for sampling is to put on appropriate protective clothing, since the work is to be performed on open product. On the one hand this serves to protect the product, since humans represent a significant source of contamination due to the natural colonization of our exterior with germs. On the other hand the proper protective clothing also protects the employee from potentially hazardous materials during sampling.

In production areas with defined clean room requirements sampling personnel do not necessarily need specially defined clothing, as clothing requirements for access to production are already defined. The sampling personnel must also adhere to clothing and behavioral procedures when using personnel locks to enter production. Furthermore, individual safety measures may apply such as the use of disposable gloves, the wearing of mouth guards or a respiratory mask when handling hazardous materials.

Type of sample	Sample taken from	Sampling Devices
Liquid	containers, drums, piping networks, mixing vessels, tank trucks	Single or multi-use siphon, liquid zone sampler, single use syringe, beaker with handle or stem
Dry bulk goods e.g. granules, powders	sacks, drums, silos, containers, production lines, big bags	Single and multi-zone samplers, silo drills, spears, lances, spoons, scoops
Viscous, pasty goods e.g. pastes, creams	Containers, drums, piping networks, mixing vessels, tank trucks	Scoops, folding lances, liquid collectors, beakers, syringes, spatulas
Solids e.g. tablets, capsules	Production equipment, bulk containers, sacks, packaging lines	Scoops, beakers, spoons, sampling spatulas
Dosage units from production batches e.g. tubes, vials, blisters	Filling and packaging lines, warehouses	Manual sample taking

Figure 6 Overview of types of sample taking and sampling locations

Figure 7 Pharma Scoop
Sample scoop for powder goods, granulate, etc. for sampling from mixing vessels, sacks, containers, big bags. (Source: Bürkle)

Figure 8 Sampling spatula/ lance SteriPlast
For sampling powders, granulates and pastes. It can be stabbed directly into containers such as paper or plastic sacks. (Source: Bürkle)

For separate analyses of samples from different zones (e.g. top, middle, bottom) a so-called *multi sample thief*, can be used, which collects material in different zones. Various forms are available for solids or liquid goods. Examples are shown in figure 11 and figure 12.

A *siphon* is typically used for sampling powdered bulk goods, liquids or viscous materials from open or sealed containers, drums, tanks and silos (see figure 13 and figure 14). It offers the advantage of being able to take a sample from the interior of the material in the container, while a scoop or spoon is typically only used to collect material from the upper layers.

For taking samples of liquid or viscous goods *folding lances*, or other equipment such as *pipettes* or *disposable syringes* as well as *beakers with handles or stems*can be used. Examples are provided in figure 15 and figure 16.

Figure 17 *Glass sample bottles*
Glass laboratory bottles are especially suited for sampling and then analyzing the samples on site. (Source: Bürkle)

Figure 18 *Wide mouth bottles*
Plastic bottles for storage and shipping of powders, granulate, etc. (Source: Bürkle)

Disposables are especially suited when the subsequent cleaning of a sample container is difficult due to the material properties, e.g. for highly viscous or adhesive materials. In general, single-use containers such as *plastic beakers, wide mouth bottles and jars* or *minigrip bags* which can easily be sealed are easy to handle. Examples are given in figure 19 and figure 20.

Figure 19 *Sample bags SteriBag StandUp*
Sterile sample bag with stable bottom for filling with liquids, powders, solids or paste samples. (Source: Bürkle)

Figure 20 *Aseptic sample jars*
Suited for filling with liquids, granules, solids or viscous sample materials. (Source: Bürkle)

To meet higher demands for product protection, sterilized disposables or autoclaved glass bottles can be used. If it is necessary to ensure samples are not tampered with by unauthorized persons, there are various systems on the market with anti-tamper seals.

Requirements for sampling devices and containers

All sampling devices and sample containers must be clean, dry and free of dust before use. The equipment used for sample taking and storage must have inert contact surfaces. Additionally, the containers must be protected from environmental effects and be tightly sealed so that secondary contamination can be avoided.

1.3 Materials to be sampled

Sampling processes can be categorized basically as samples for identity testing and quality aspect testing of raw and packaging materials, samples for in-process controls and samples for testing of finished products (see figure 25).

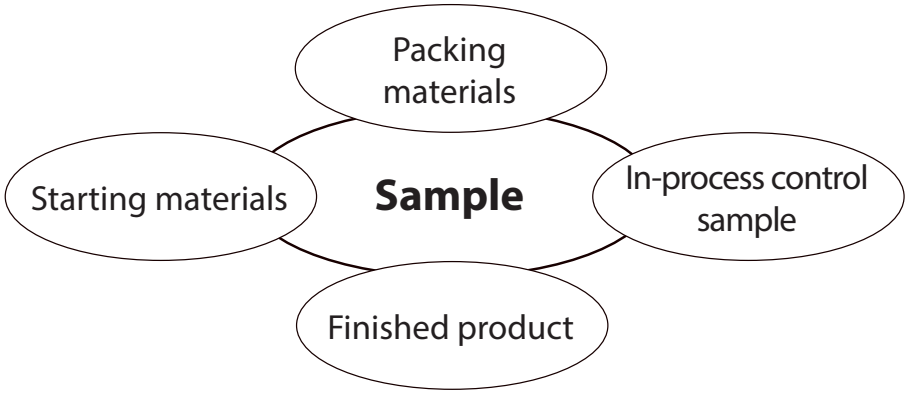

Figure 25 Materials to be sampled

Depending on the material different procedures for sampling are required which are described below.

Sampling performed as part of process and cleaning validations are covered in the specific validation protocols.

1.3.1 Starting materials

The term starting materials is used to encompass both active ingredients and excipients.

Identity testing

The EU GMP Guideline describes in chapter 5.30 and in Annex 8, that the identity of a starting or raw material lot is only ensured when a sample has been taken from each container and tested (**ID testing of individual containers**). Typically simple and rapid tests are performed such as NIR methods, which can be performed directly on the goods in the container without separate sample taking. RAMAN spectroscopy can even be performed on goods without opening the primary package depending on the type of packaging materials. It is recognized as valid, however, to take samples from a portion of the containers instead of performing complete individual testing (**reduced ID testing**) if a validated procedure is in place which ensures that incorrect labelling of even a single container can be ruled out. This can only be fulfilled pending a regular **supplier qualification** including an audit. When testing the validated procedure the items listed in figure 26 are to be reflected.

Requirements to be fulfilled to justify reduced ID testing
• Type and status of the manufacturer and supplier as well as their understanding of GMP requirements for the pharmaceuticals industry • QS Systems in place at manufacturer and supplier • Conditions under which the raw material is produced and tested • Type of raw material as well as the drug product for which it will be used • Mode of transport, delivery and storage • Risk analysis and assessment

Figure 26 Requirements for reduced ID testing

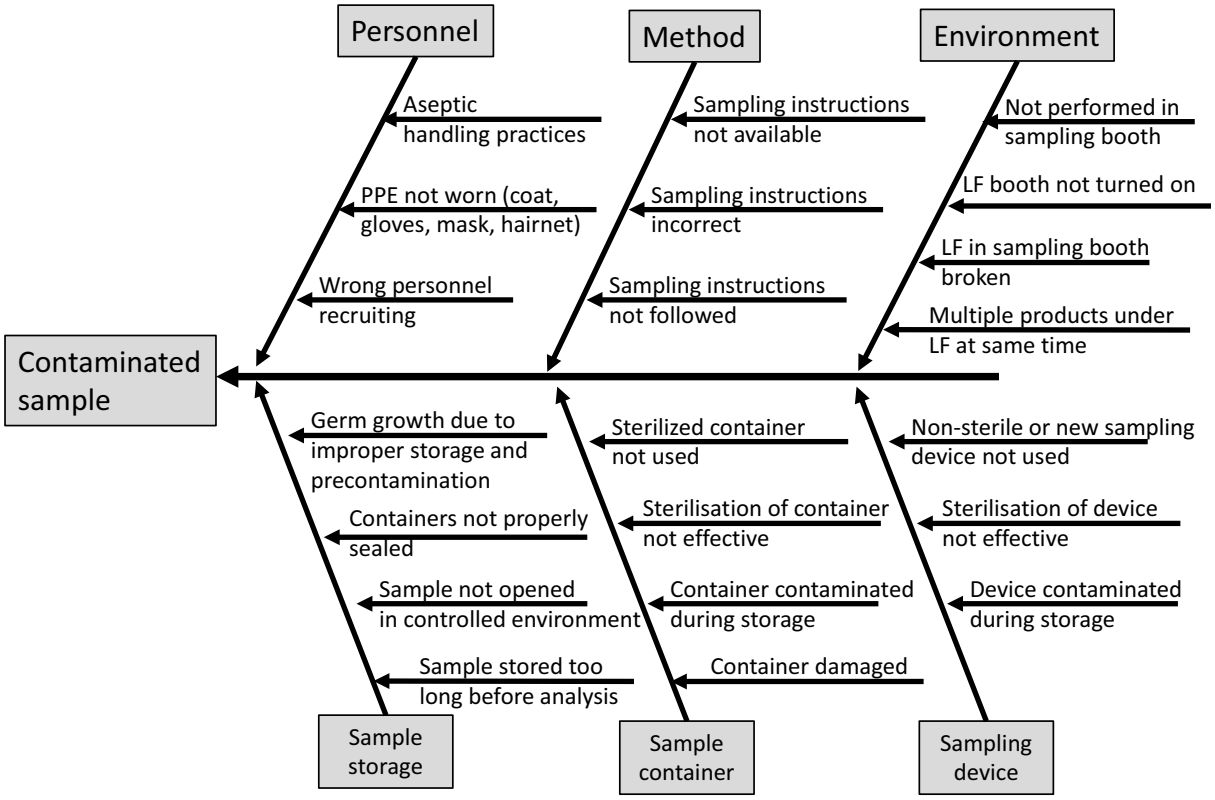

Figure 27 *Sources of potential microbiological contamination of analytical samples (source: Pharma Technologie Journal, Risk Management in the Pharma Industry, F. BÖTTCHER, Risk Assessment in Microbiological Labs/Focus on Microbiological Methods for Quality Control of Drugs, Editio Cantor Publishers, Aulendorf, Germany, 2007 (title translated))*

Requirements included in a sampling plan

- Location for sampling (production, sampling booth, etc.)
- Purpose of the sample (e.g. for microbiological analysis),
- Individual or composite sample (not allowed for identifying identity of individual containers or for testing content uniformity)
- Sample taking procedures
- Required equipment
- Sampling scheme or number of samples
- Sample amount (adequate for 2 analyses and retain sample)
- Sample point location (e.g. top, middle, bottom)
- Instructions for any division of samples as required
- Requirements for generating individual or composite samples
- Requirements for collecting retain samples
- Sample container to be used
- Labelling (containers sampled as well as containers holding the samples)
- Precautionary measures (personal and product protection, especially for sterile or harmful substances)
- Special instructions (e.g. storage conditions, cooling requirements, handing of narcotic substances, etc.)
- Requirements for cleaning and storage of sampling equipment

Figure 28 *Requirements included in sampling plans*

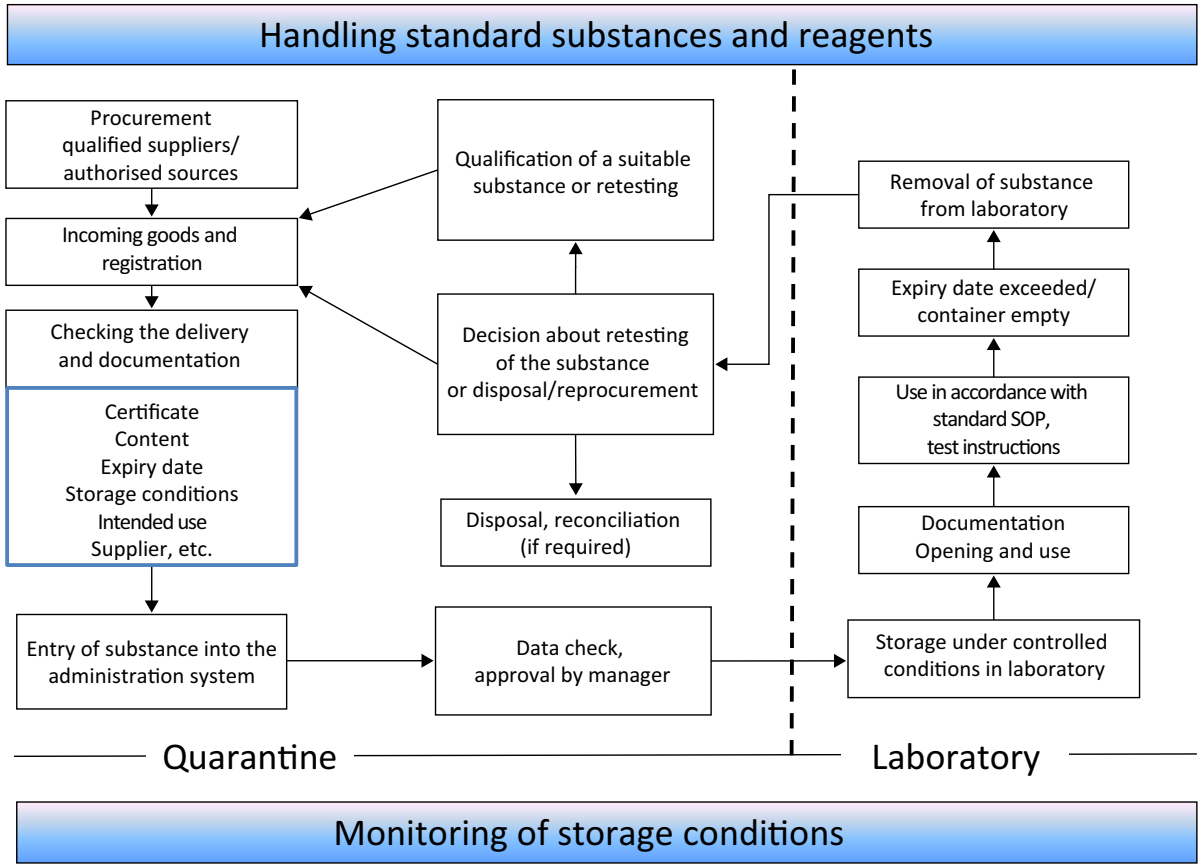

Figure 39 Workflow for standard substances and reagents

2.7.1 Incoming goods and registration

Reagents and standard substances should be delivered to a specially designated area. Operational areas should not have direct access to this area. Provisions should be in place for storage of quarantined goods under the specified storage conditions (e.g. chilled and frozen storage, uninterrupted cold chain). This also applies to the rooms themselves (controlled room temperature).

The first step is to check the accompanying documentation of the delivered substances for completeness (compare the delivery note with the goods delivered) and for the correctness and integrity of the delivery (visual inspection). If goods are delivered under controlled conditions, the respective data logger must be checked for alarm messages and evaluated. If the required evaluation software is not available, the logger can be returned to the sender for evaluation. Particular attention should be given to photosensitive substances (light protection) and hygroscopic substances (desiccants), because the storage requirements must also be met.

The substance data (cf. chapter 2.8 *Documentation*) is entered in a paper-based or electronic management system (LIMS) and checked (4-eyes principle). After approval by a manager and proper labelling, the substances can be moved out of quarantine to their storage location or user.

2.7.2 Use and disposal

When the substances are handled in the operational area, the analyst is responsible for their correct and proper use. Before use, the material safety data sheets must be read. The reagents and standard substances also undergo a visual inspection before use during which the intended use and expiry date are checked. If containers are opened, this information should be entered in the management system. The labelling of reagent or standard solutions prepared in the laboratory is carried out in such a way that traceability of the starting materials is guaranteed.

The process used for returning empty containers or expired reagents and standards (into quarantine) should be clearly defined in the workflow and monitored on a daily basis by senior managers

Contributors

Frank Böttcher, PhD
frank.boettcher@labor-ls.de

Pharmacist
Labor LS SE & Co. KG, Bad Bocklet/Großenbrach

Frank Böttcher is a pharmacist who has specialised in pharmaceutical analysis. He has worked in the pharmaceutical industry for many years and has held positions in different companies. He became CEO of Labor LS SE & Co. KG in 2015 and is responsible for Operations, Quality, HR and Finance.

Frank Böttcher is an authorised expert in accordance with the German Drugs Act (AMG § 65.4) and is involved in a number of different working groups that focus on the testing of medicinal products and medical devices. His other areas of expertise include contract agreements in the area of contract manufacture and testing as well as the manufacture and testing of sterile products.

Frank Böttcher started his professional career in the pharmaceutical industry in 1994, his first position involving the analysis and approval of phytopharmaceuticals. He then held different positions in an international company and at a contract manufacturer where he was responsible for supplier management and the control and approval of packaging materials, starting materials and finished medicinal products. In 2003, he joined Labor LS SE & Co. KG where he was responsible for quality assurance, the testing of sterile products and chemical and physical analysis.

Frank Böttcher has a wealth of experience in the area of auditing and official inspections. In addition, he works as a speaker and author with a focus on quality assurance, risk management, validation, verification and transfer of analytical processes.

Jürgen Eberlein
juergen.eberlein@labor-ls.de

Pharmacist
Labor LS SE & Co. KG, Bad Bocklet

Jürgen Eberlein has been working as a Qualified Person and Control Sample Expert in accordance with the German Drugs Act (AMG § 65.4) in the QA department of Labor LS SE & Co. KG since 2014. He also carries out customer audits and official inspections.

After graduating in Pharmacology in Würzburg, Mr Eberlein worked in a number of different retail pharmacies. Between 2007 and 2012, he was Assistant Head of Production of Bulk Medicinal products at Abbott GmbH & Co KG. He then became Assistant Head of QC of starting materials, packaging materials and sampling at AbbVie GmbH & Co KG. In 2014, he was a member of the packaging material working group.

Annette Könemann
annette.koenemann@labor-ls.de

Food Technology Engineer
Labor LS SE & Co. KG, Bad Bocklet

Annette Könemann has been Head of Quality at Labor LS SE & Co. KG since 1994. She is responsible for the organisation of the integrated management system at Labor LS SE & Co. KG and for ensuring compliance with national and international regulations during the testing of medicinal products and medical devices.

Her tasks include the further development of existing quality standards such as GMP, cGMP, GLP and ISO 17025. Ms Könemann also carries out supplier and customer audits and prepares and supports official inspections. Her other tasks include in-house training and employee qualification at Labor LS SE & Co. KG. She also brings her expert knowledge to external training events and provides consultancy for GMP and hygiene requirements in the pharmaceutical industry.

Josef Künzle, PhD
josef.kuenzle@basilea.com

Chemist
Basilea Pharmaceutica International Ltd, Basel

Josef Künzle joined Basilea in 2007. In August 2015, he was appointed Head of Global Quality Management and is responsible for all GxP departments. He had previously worked in the pharmaceutical industry for 18 years in the areas of analytical R&D, quality control and quality management. He has taken part in official inspections and global supplier audits.

After graduating in Chemistry, receiving a PhD in Organic Chemistry from the University of Zurich and working as a post-doctoral scholar at Stanford University, he began his professional career in 1989 as Head of Laboratory in analytical R&D at Sandoz Pharma AG. Upon transfer to QC, he was responsible for the blockbuster Sandimmune, including a successful FDA inspection for Sandimmune Neoral. He was responsible for the Sandoz peptide products at Novartis Pharma AG.

In 1998, he joined the Carbogen group where he held a senior position and supported the development and strengthening of all aspects of quality.

From the end of 2003, he was Technical Manager and Head of QM for the Quality department of Permamed AG.

He works as a GMP trainer and shares his expert knowledge at GMP training events on a regular basis.

Markus Limberger, PhD
m.limberger@quasaar.de

CEO
Quasaar GmbH, Überherrn

Markus Limberger is co-founder of the QUASAAR GmbH which has been providing GMP consultancy in product development and product control to the pharmaceutical and life sciences industries since 2015. His areas of expertise include method transfer, OOX process, qualification of standard substances and reagents, auditing and increased efficiency in the laboratory.

Markus Limberger studied Chemistry at the University of the Saarland and received a PhD in Pharmaceutical and Medical Chemistry in 1999 (Hermann Schlosser fellowship, Phoenix Pharmaceutical Science Award 2000). After holding a number of different positions in the area of galenic development, characterisation of active ingredients and pharmaceutical analysis, he joined PHAST GmbH in 2002 where he was responsible for the development of Quality Control (FDA-approved) and GMP units.

Markus Limberger is an expert speaker and author. His scientific activities include the GMP-compliant development and implementation of innovative methods and techniques in the GMP environment. He is a member of the APV (Association for Pharmaceutical Technology, pharmaceutical expert in the expert group for quality assurance and analysis) and has been part of the team of authors of Maas & Peither AG – GMP Publishing since 2014.

Index