

Validation and qualification

in the regulated environment



Validation and
qualification

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Introduction

The use of qualified equipment in a regulated industry is an essential part of the quality assurance process; it is also a legal obligation. This Whitepaper provides an overview of validation and qualification in a GMP¹ environment and describes the general qualification procedure using the following key steps: DQ², IQ³, OQ⁴, and PQ⁵. The focus is on device qualification, but the validation of computerized systems is also discussed.

This Whitepaper is aimed at individuals who have not come across these topics before.

¹ Good Manufacturing Practice, ² Design Qualification, ³ Installation Qualification, ⁴ Operational Qualification, ⁵ Performance Qualification

History

In order to guarantee consumer safety, every medicinal product is subject to strict administrative supervision throughout its entire life cycle. In order to fulfill the regulatory requirement that medicinal products are produced at a consistently high quality, quality assurance systems were introduced to the pharmaceutical industry as far back as the 1960s. These quality assurance systems are better known as good practices.

Good Manufacturing Practice (GMP)

For each phase in the life cycle of a drug there are good practices to follow: from development and trials to manufacturing and distribution.

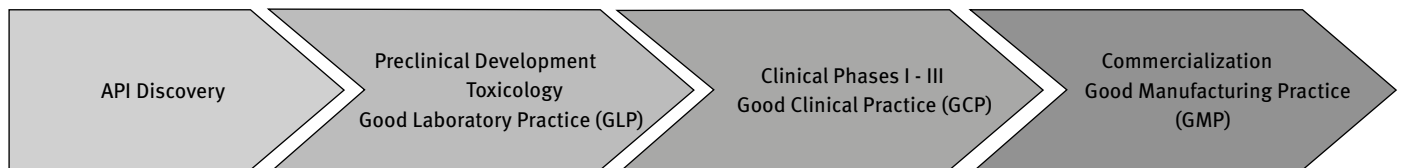


Fig. 1: Life cycle of a medicinal product

The term Good Manufacturing Practice (GMP) was introduced by the Food and Drug Administration (FDA). GMP is a globally recognized term and is a collection of rules and supplementary guidelines.

The first GMP rules were published by the World Health Organization (WHO) in 1968. Over the years, more good practices were introduced such as good laboratory practice and good clinical practice.

Although good manufacturing practices were originally designed with medicinal products in mind, today they are also used in the food and cosmetics industries.

GMP publications from different organizations

GMP guidelines have been published by regulatory authorities responsible for approving and monitoring medicinal products at both a national and international level. At the national level, these authorities include the FDA (USA) and the EMA (European Union); at the international level, these include the Pharmaceutical Inspection Co-operation Scheme (PIC/S) and the International Council for Harmonisation (ICH). The PIC/S is an international organization that campaigns for the mutual recognition of inspections carried out by each authority.

The ICH is an organization which endeavors to create consistent, universally accepted guidelines for the USA, Japan and the European Union.

An overview of useful documents about GMP and GLP are listed in the table below (list not exhaustive).

Organization	Guideline	Title	Content / comment
EMA	GMP	EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use Part I – Basic Requirements for Medicinal Products Part II – Basic Requirements for Active Substances used as Starting Materials	GMP requirement for drugs and active pharmaceutical ingredients (API): validated processes, continuous stability testing, risk management
	Annex 11	Computerized Systems	
	Annex 15	Qualification and Validation	
	Annex 20	Quality Risk Management	
FDA	Title 21 CFR Part 210 Title 21 CFR Part 211	CURRENT GOOD MANUFACTURING PRACTICE FOR FINISHED PHARMACEUTICALS	GMP requirements for drugs and active pharmaceutical substances
	Guidance for Industry	Process Validation: General Principles and Practices Final Guidance for Industry and FDA Staff	
WHO	WHO, Annex 2	Annex 2: WHO good manufacturing practices for pharmaceutical products: main principles	Minimum requirements for GMP worldwide
ICH	ICH, Q1A	Stability Testing of New Drug Substances and Products	Harmonized guidelines for the USA, Japan and the EU
	ICH, Q7A	Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients	
	ICH, Q8A	Pharmaceutical Development	
	ICH, Q9A	Quality Risk Management	
PIC/S	PI 006-3	RECOMMENDATIONS ON VALIDATION MASTER PLAN INSTALLATION AND OPERATIONAL QUALIFICATION NON-STERILE PROCESS VALIDATION CLEANING VALIDATION	Guidance
	PS/INF 11/2015	GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS ANNEX 15	Identical to Annex 15 of the European GMP

The USA's cGMP (Current Good Manufacturing Practice) is incorporated into the Code of Federal Regulations 21 CFR Part 210 (medicinal products) and 21 CFR Part 211 (active substances) and is legally binding for manufacturers and importers. The cGMP guidelines are subject to annual revisions.

In Europe, there are also two (EC) GMP guidelines: Part 1 is aimed at medicinal product manufacturers and Part 2 is aimed at manufacturers of active pharmaceutical substances.

Part 1 of the European GMP guidelines is made up of nine chapters, which set out basic quality assurance requirements for the development and manufacturing process, staff, facilities, and equipment, as well as for quality controls. An essential requirement for both GMP guidelines is that stability testing is continuously carried out on active pharmaceutical substances and the finished medicinal product. These stability tests can be conducted in BINDER's Constant climate chambers.

“(j) All manufacturing processes are clearly defined, systematically reviewed in the light of experience and shown to be capable of consistently manufacturing medicinal products of the required quality and complying with their specifications;
 (ii) Critical steps of manufacturing processes and significant changes to the process are validated;” European GMP Guideline Part 1

Validation

Validation is a method of quality assurance and an important part of the GMP. The European GMP guideline defines validation as follows:

“Action of proving, in accordance with the principles of Good Manufacturing Practice, that any procedure, process, equipment, material, or activity actually leads to the expected results (see also qualification).”
 European GMP Guideline Part 1

The FDA’s current definition requires manufacturers to have a clear understanding of the manufacturing process:

“Process validation:

The collection and evaluation of data, from the process design stage through to commercial production, which establishes scientific evidence that a process is capable of consistently delivering quality products.”

Guidance for Industry: Process Validation: General Principles and Practices, FDA

Both definitions aim to ensure that manufacturers of pharmaceutical products are accountable for and control all quality relevant processes, are aware of the risks involved and strive to maintain this validated status. Validation is required by GMP guidelines; however, they do not go into detail about what should be validated and how this can be achieved.

Annex 15 of the EU GMP guideline provides assistance for validation. It contains definitions and basic explanations for the terms validation and qualification as well as definitions for types of validation and the validation process. A risk assessment is also required to determine the breadth and scope of the validation. Annex 20 (Quality Risk Management) provides further information on risk assessments which has the same content as the ICH Q9 guideline: Quality risk management.

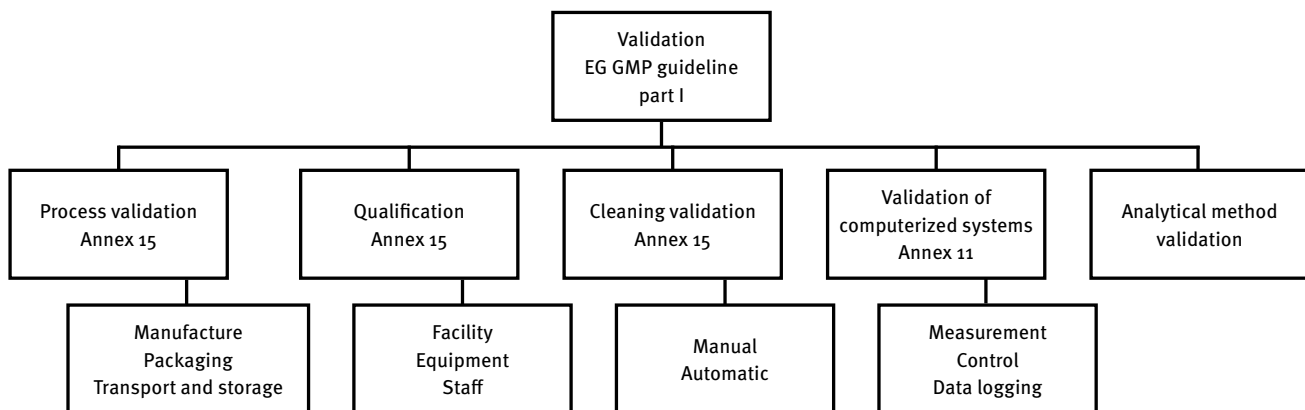


Fig.2: Overview of validation activities

The overview of the validation activities shows that validation is used as an umbrella term, but also describes stand-alone activities like process validation or computer validation. The term qualification is used exclusively for facilities, equipment, and staff. There is no official unified terminology in the EU GMP. However, over the years, qualification has come to mean anything tangible, whereas validation has come to refer to methods, procedures, and processes. The approach is the same for both validation and qualification.

A Validation Master Plan (VMP) must be in place before starting any validation activity. This overriding document contains information about the company, describes the validation project, and names the responsible persons. Furthermore, it contains the validation policy and describes the general validation approach.

The Validation Master Plan includes all relevant validation protocols and validation reports in line with GMP. The timescale is also included in the validation plan. Existing documents, as well as norms and standards, may be referenced.

Validation types

If possible, a prospective validation should always be carried out, i.e., prior to process implementation. Retrospective validations are used for existing systems and processes, and are based on the physical and analytical process data from the batches already produced. Concurrent validation is used when full validation can only be completed once the production process has begun.

Qualification

The definition of qualification is an analogous to validation:

“Action of proving and documenting that equipment or ancillary systems are properly, installed, work correctly, and actually lead to the expected results. Qualification is part of validation, but the individual qualification steps alone do not constitute process validation.”
 EU GMP guidelines Part 2: Basic Requirements for Active Substances used as Starting Materials

The qualification process has four steps:

- **Design Qualification (DQ)**
 The documented verification that the proposed design of the facilities, systems, and equipment is suitable for the intended purpose.
- **Installation Qualification (IQ)**
 The documented verification that the facilities, systems, and equipment, as installed or modified, comply with the approved design and the manufacturer’s recommendations.
- **Operational Qualification (OQ)**
 The documented verification that the facilities, systems, and equipment, as installed or modified, performs as intended in the specified operating ranges.
- **Performance Qualification (PQ)**
 The documented verification that facilities, systems, and equipment, as they are connected with each other, can perform effectively with reproducible results based on the approved process method and product specification.



› [Constant climate chamber KBF 1020](#)

The diagram below illustrates the qualification process and shows how the individual elements of the process interact with each other:

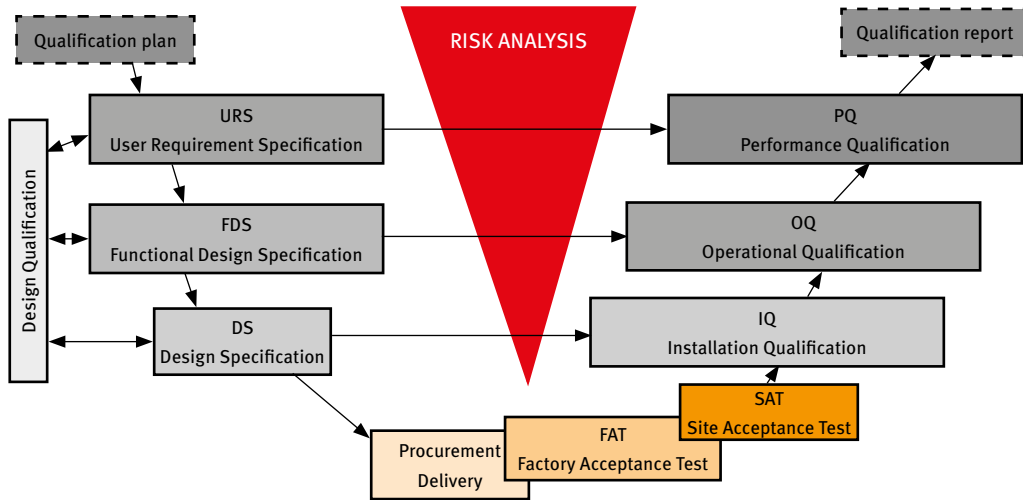
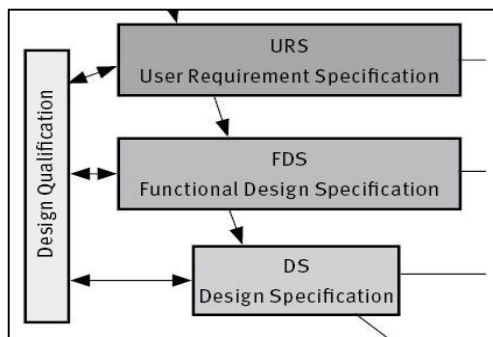


Fig. 3: Qualification diagram

A qualification plan must be in place before starting any qualification activity. In contrast to the validation plan, it describes all the measures to be executed during the qualification process in detail. It defines the people responsible as well as all tests to be carried out. In addition, it contains the risk assessment and acceptance criteria, i.e., the parameters to be verified, the key quality characteristics, and the different operating scenarios. The authorities and the GMP regulations do not provide any specifications regarding the scope of the qualification process. Each qualification phase must be approved prior to commencement and each phase must be concluded with a written summary of the qualification results in the relevant qualification report. In general, the qualification plan and the qualification report are combined in a single document.

The four qualification phases

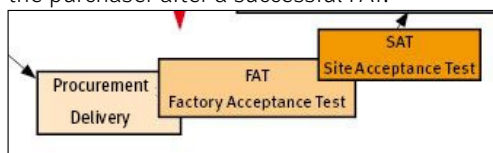
During the Design Qualification phase, a set of specification documents is created: the User Requirement Specification (URS), the Functional Design Specification (FDS), and the Design Specification (DS).



DQ in detail: The URS describes the requirements to be fulfilled by the piece of equipment or system. The URS is produced by the customer and also takes into account the GMP requirements. The URS serves as the basis for the Performance Qualification. The FDS is created in the next step using the URS as a basis. The FDS describes the technical functions of the equipment and explains how these fulfill the user's requirements. The FDS is verified by the Operational Qualification. The FDS serves as a basis for supplier selection. The next step is the DS, which is based on the FDS. The DS contains detailed information about the equipment or system, including accessories, modifications, and the necessary documentation. Proof that the DS is fulfilled is demonstrated and documented by the Installation Specification. For less complex devices such as incubators or climate chambers

for stability testing, it is possible to create just one specification document. The Design Qualification is the most important element in the qualification process, as the qualification plans, protocols, and the reports for IQ, OQ, and PQ are created alongside the specifications. The DQ is completed with the system/equipment order.

The Factory Acceptance Test (FAT) is performed at the manufacturer's site. The FAT provides the documented proof that the equipment or system was created according to the specification and that the equipment or system functions. The delivery is approved by the purchaser after a successful FAT.



The Site Acceptance Test (SAT) is usually performed at the purchaser's site to demonstrate that the equipment functions according to the specification. A FAT and SAT are only recommended for complex devices.

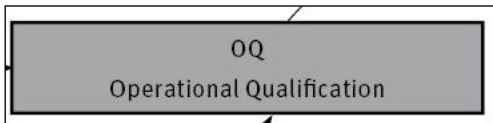
Standard equipment like **climate chambers** or **incubators** do not need to undergo an FAT. The SAT can be combined with the Installation Qualification.



The Installation Qualification (IQ) provides the documented proof that the equipment or system was delivered complete, intact, and according to the specification. After a successful visual examination, the equipment or system is installed according to the manufacturer's instructions. The users will receive training on the

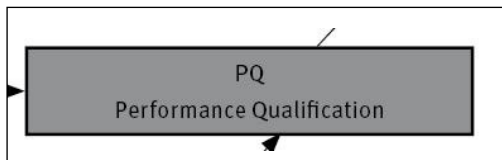
operation of the equipment. The sensors are calibrated and adjusted as part of the Installation Qualification if this has not already been carried out as part of the SAT.

All performed activities will be documented in a report. The approval of this report is required for the subsequent Operational Qualification.



The Operational Qualification (OQ) provides the documented evidence that the equipment or system works properly according to the specification. For example, for a climate chamber, this means that specified set points for temperature and relative humidity are entered and the actual values are documented. In addition, the temperature distribution, the recovery time after a door is opened, and the functionality of the temperature alarm can be verified if this is specified in the qualification plan. The chamber usually remains empty for the purposes of the Operational Qualification.

During this qualification step, the Standard Operating Procedures (SOP) for the users, maintenance plans, and the logbook must be available. Furthermore, the intervals for and the changes in circumstances requiring re-qualification of the system must be provided. The O Q is completed if the qualification report is approved by the responsible person. The OQ is usually carried out directly after the IQ.



The final qualification activity is **the Performance Qualification (PQ)**. This step provides the documented proof that the equipment produces the required results in a reproducible way under manufacturing conditions. The temperature distribution with different loading conditions is particularly relevant to climate chambers. In addition, "worst case" conditions can form part of the P Q if these are considered

to be relevant to the quality. These operating conditions which differ from the ideal conditions can show the extent to which the product quality is affected.

Written documentation is once again required. The equipment or system qualification is completed once the final qualification report is approved by the responsible person.

In general, a qualification should be performed according to the principle "as much as needed and as little as possible." in order to remain economical. To reduce expenses, existing documents can be used.

Particularly in the case of standard equipment like Constant climate chambers, standardized qualification documents created by the manufacturer can be integrated into in-house documentation. BINDER offers qualification documents for performing IQ, OQ, and PQ which can be adapted to the customer's specific requirements. These qualification documents describe the methodology and contain checklists and summaries.

CO₂ incubators

Constant climate chambers

Validation of computerized systems

Computerized systems for measuring, control, and data logging are well established in pharmaceutical industry. Annex 11 of the EU GMP guideline explicitly states that the software should be validated and the IT infrastructure should be qualified, provided that the information processing is considered to be relevant to the quality.

In the USA, this is also a legal requirement, as per 21 CFR Part 820. In addition, Part 11 also regulates the use of electronic signatures. There is also FDA guidance for industry and FDA staff which describes the implementation of 21 CFR Part 820.

BINDER climate chambers are used for stability studies and can be connected to corresponding software for control and data logging.

The process for validating/qualifying an IT system is the same as that for validating/qualifying equipment or systems.

Validated system

The successful qualification and computer validation, as well as the validation of the cleaning and analytical methods, forms the basis for the validation of the entire manufacturing process in which the system or equipment is involved. Validation and qualification are not one-time events: The validated state must be maintained.

Trends

A new approach in the GMP guidelines in Europe and the USA is the requirement for an Ongoing Process Verification to replace regular re-validation in order to guarantee that the validated state is continuously maintained. This new approach transfers the life-cycle approach from the manufacturing process to the process validation, considering all phases from planning right through to decommissioning.

The authorities increasingly prefer pharmaceutical manufacturers to apply scientific principles instead of insisting on adhering to prescribed forms. For device qualification, this means that transparent operational and performance qualification tests should be planned and carried out regularly to maintain the validated state of the equipment or system.

BINDER CO₂ incubators

[Request more info >](#)

Concluding remark

The user in the regulated environment has no choice but to validate processes which are relevant to quality. Depending on the complexity of the equipment or system to be validated, a certain amount of effort is required in order to achieve a validated system. A validation can be very cost intensive and also can tie up other company resources.

However, planning, , analyzing, and continuously verifying processes certainly has its advantages: Precise and detailed planning combined with a risk analysis can also save costs, as “surprises” are unlikely to occur later down the line during operation. Maintaining the specified product quality prevents expensive product recalls and helps boost customer satisfaction.

Literature

WHO, Annex 2 WHO good manufacturing practices for pharmaceutical products: main principles

EudraLex - Volume 4 Good manufacturing practice (GMP) guidelines

Part I – Basic Requirements for Medicinal Products

Part II – Basic Requirements for Active Substances used as Starting Materials

Annex 11 Computerized Systems (revision January 2011)

Annex 15 Qualification and validation

ICH, Q1A, Stability Testing of New Drug Substances and Products

ICH, Q7A Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients

ICH, Q8A Pharmaceutical Development

ICH, Q9A Quality Risk Management

ICH, Q10A Pharmaceutical Quality System

FDA, Guidance for Industry: Process Validation: General Principles and Practices

General Principles of Software Validation; Final Guidance for Industry and FDA Staff

FDA, General Principles of Software Validation; Final Guidance for Industry and FDA Staff

PIC/S: GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINAL PRODUCTS ANNEX 15 *

PIC/S, PI 006-3:RECOMMENDATIONS ON VALIDATION MASTER PLAN INSTALLATION AND OPERATIONAL QUALIFICATION NON-STERILE PROCESS VALIDATION CLEANING VALIDATION

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Company profile:

About BINDER:

BINDER is the world's largest specialist in simulation chambers for the scientific and industrial laboratory. With its technical solutions, the company contributes significantly to improving the health and safety of people. Our range of products is well-suited for routine applications, highly specialized work in research and development, production, and quality assurance. With approx. 400 employees worldwide and an export quota of 80%, BINDER sales in 2015 came to over 60 million euros.

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