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The GxP Dictionary

1st edition

Definitions relating to GxP and Quality Assurance

Note:
Some of the information contained in this GxP Dictionary does not apply equally to all countries. Depending on the respective local legislation, other definitions may apply to certain terms and topics. The sections affected are not separately identified.

Foreword

Efficacy, identity and purity are quality attributes, which are required of products from the GMP-regulated environment. The term “Good Manufacturing Practice” sums up the quality assurance requirements from national and international regulations and laws. Other GxP forms have now been developed, whose scope also expands to adjacent sectors such as medical devices and life sciences.

The complex requirements of the “GMP-compliance” generate a variety of specific concepts and abbreviations.

This GxP-Dictionary explains the majority of terms relating to GxP, qualification, validation and quality assurance. It is intended as a compact reference guide and aid for all those involved in GxP, and does not purport to be complete.

Testo SE & Co. KGaA

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Terms and Definitions

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21 CFR 210/211

CFR: Code of Federal Regulations – Federal Regulations of the USA Title 21: Food and Drugs – contains the regulatory provisions for the food and drugs sector.

Part 210: current Good Manufacturing Practice (cGMP) in manufacturing, processing, packing, or holding of drugs; general

Part 211: current Good Manufacturing Practice (cGMP) for finished pharmaceuticals

The 21 CFR 210/211 contains very detailed GMP guidelines for the USA. **Part 210** refers to the manufacturing and packaging process of drugs and food, while Part 211 primarily includes the rules for finished pharmaceuticals.

483

The problem report is referred to as 483, and it is issued by FDA inspectors (FDA) and documents the complaints that arise during an inspection. The name is derived from Form No. 483, which is used to prepare the summary report. A 483 is normally published, but without naming the company or product names concerned. Depending on the relevance of the documented defects, a warning letter is created on the basis of the 483.

A

Active Pharmaceutical Ingredient (API)
The medically (pharmacologically) active ingredient in a drug.

Accompanying Validation
The validation takes place while the products intended for subsequent sale are being manufactured. Commencement of routine production prior to the completion of the validation process must be justified, documented and approved by authorized personnel. The validation batch is only released for trading following successful validation.

Action Limits
A limit value stipulated by laws, directives or internal company provisions. If this value is exceeded, then corrective actions must be initiated without delay, accompanied by analysis of the failure and removal of the cause.

ADI (Acceptable Daily Intake)
The ADI specifies the amount of a certain substance, e.g. of an active pharmaceutical ingredient, that does not present any health risk, on the assumption that a person is exposed to it on a daily basis over a lifetime.

Airlock Concept
Airlock Concepts consist of several rooms, arranged one behind the other, which allow the transition of persons and material from a cleanroom area to a cleanroom area with a higher or lower level of purity, without contaminating one of the areas.

Annex
Annexes are various appendices to the EU GMP Guidelines. Currently there's Annex 1 to Annex 19, there is no longer an Annex 18. Annex 18 was published in 2005 as EU GMP Guidelines Part II.

Annual Product Review (APR)
A retrospective review of the history of a drug, required by the FDA for products manufactured in or imported into the USA, undertaken on an annual basis.

API
See Active Pharmaceutical Ingredient

APR
See Annual Product Review

Audit

Inspection or survey of a site (e.g. a company, a production site) for the purpose of verifying compliance with the requirements it is supposed to fulfil (here: compliance with the GMP regulations and their specifications). An audit can be carried out by various bodies (e.g. representatives of contracting authorities or representatives of authorities other than the competent supervisory authority such as the FDA) and, in terms of how it is defined, is separate from an inspection, which may be carried out exclusively by the competent supervisory authority, i.e. inspectors of the state authorities.

Audit Trail

This is used to ensure the complete traceability of all activities, actions and system states by recording “traces”, which indicate when, by whom and/or what, a process was influenced. It usually consists of records of computer and software systems and is required by 21 CFR Part 11 as well as Annex 11 (EU GMP).

Authorization

Authorization refers to the marketing authorization for a medicinal product. In this regard, the product must always conform to the GMP.

B

Batch Record Review

Batch Record Review is a system that collates all the information about the batch certification. For example, these include batch production and test reports, as well as all records of deviations and OOS reports. This information is used by the QP (Qualified Person) as the basis for making decisions regarding the release of a batch (batch release).

Batch

A homogeneous and defined quantity of starting material, medicinal products or packaging material produced in a single operation or in a series of operations

Batch Documentation
The Batch Documentation includes instructions and protocols on manufacturing and packaging procedures, as well as the test report. This enables the entire history of a batch to be traced without any gaps. The Batch Documentation serves as a basis for the batch release and is particularly important when, at a later stage, quality defects are identified which were not detectable at the time of release.

Bulk Ware
= Any product which has passed through all processing stages except for final packaging.

Biological Safety Cabinet (BSC)
This is often used in microbiological or analytical laboratories and is a “room within a room” concept to protect employees and the environment, along with the product, when carrying out critical processes. **Class I:** BSC with work access opening; prevents airborne suspended contamination via inward flow of air and filtration of the exhaust air. **Class II:** BSC with work access opening; reduces the risk of cross-/product contamination via filtered circulating air and filtration of the exhaust air. **Class III:** BSC (e.g. isolator) with completely closed-off working area (physical barrier). Intervention in the working area is possible, e.g. using gloves.

C

CAPA
See Corrective Action/Preventive Action

Calibration
Calibration is the comparison of a reading or a material measure with the correct value under stipulated conditions, documentation of the deviation, calculation of the measurement uncertainty and creation of the certificate or calibration certificate. One of the most important criteria for professional calibration is complete metrological traceability to national and international standards.

Capacity Test
The Capacity Test is a long-term stress test to show whether an (IT) system remains functional even under full load over the long term. Possible capacity limits are therefore visible. For instance, a document management system should launch the correct workflow following a document becoming valid, even if, for example, hundreds of documents become valid at the same time.

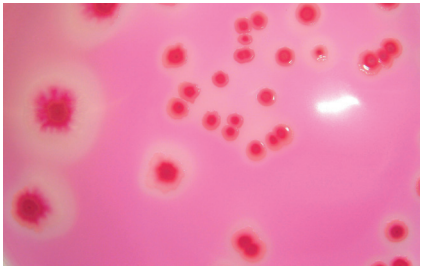
CEP (certificate of suitability of monographs of the European pharmacopoeia)
The certificate confirming that a drug has been produced in line with the monographs of the European Pharmacopoeia.

CFR

= Code of Federal Regulations: Federal regulations of the USA. Example: 21 CFR 210 and 211

CFU (Colony-Forming Unit)

Used for the qualification of micro-organisms/germs in microbiology. In a wipe test, for example, nutrient medium is applied to a surface for a certain time (e.g. 10 seconds). Following incubation of the nutrient medium, the micro-organism multiplies and becomes visible as a colony (= CFU).



CFU on agar plate

cGMP

= current Good Manufacturing Practice: Since the US GMP guidelines are continuously being revised, the correct name is cGMP. Whereas in Europe the guidelines are only updated as required, so the c (current) is not necessary. So its title here is just GMP.

Challenge Test

Challenge Test refers to a qualification or validation test under worst-case conditions. This method is often supplemented by the deliberate inducement of faults in order to prove that these can be detected and remedied or prevented by the actions taken.

Change Control

Formal system for maintaining the defined status, e.g. the validation status. A systematic, risk-based assessment is carried out, to find out what measures are required due to an intended or actual change, in order to maintain GMP conformity and, for example, the specification. These measures are assessed by qualified representatives of the relevant department.

Clean Corridor Principle

The Clean Corridor is a protection concept for preventing cross-contamination. Here, a spatial arrangement is provided, in which the corridor, which leads to various processing areas, is the space with the highest pressure. Thus, the overflow is directed towards the production rooms, which prevents a product from being discharged into another area.

Cleanroom Principle

The Cleanroom Principle is a protection concept that works via a shell

Cleaning Validation

The Cleaning Validation is documented proof that a cleaning procedure can be used to achieve a plant status that is suitable for the production of medicinal products. The effectiveness and reproducibility of the entire cleaning procedure is verified to this end. The four decisive parameters that influence the success of the cleaning are portrayed in the Sinner's circle: Chemistry, mechanics, temperature and time (see Sinner's circle). Another prerequisite for successful cleaning is GMP-compliant plant design.

Cleanroom

A cleanroom is a room designed so as not to exceed a defined particulate and microbiological contamination. In accordance with the purity specifications that this type of room fulfils on a permanent basis, a purity classification is attributed to it. Moreover, a cleanroom is equipped with airlocks and access protection.

Cleanroom Classes

In DIN EN ISO 14644-1, the different cleanroom classes (ISO 1-9) are classified according to the maximum permissible particle concentration (in particles per cubic metre of air). ISO class 1 is the cleanroom class with the lowest permissible particle concentration. In the EU GMP guidelines, the letters A to D are assigned to the cleanroom classes, and a distinction is also made between production and idle state.model with overpressure to adjacent areas of low air purity. The overflow therefore moves away from the cleanroom, preventing any impure air from getting into the cleanroom (pressure cascades).

Classification limits in Annex 1

EC Guidelines to Good Manufacturing Practice, Revision to Annex 1, as of 2014

Room class	Maximum permissible number of particles per m3, equal to or greater than the tabulated size			
	Idle state		Production	
	0.5 µm	5.0 µm	0.5 µm	5.0 µm
A	3,520 ISO 5	20 ISO 4.8	3,520 ISO 5	20 ISO 4.8
B	3,520 ISO 5	29	352,000 ISO 7	2,900
C	352,000 ISO 7	2,900	3,520,000 ISO 8	29,000
D	3,520,000 ISO 8	29,000	Not defined	

Compliance
Conformity of conditions with standards and specifications.
GMP compliance is therefore compliance with the GMP Regulations, i.e. the relevant laws, directives and guidelines (e.g. EU GMP Guidelines).

Computer System/Software Validation (CSV)
See Computer Validation

Computer Validation
= Validation of computerized systems: According to the EU GMP Guidelines, a computer consists of “a combination of hardware components and associated software, designed and put together in order to carry out a specific function or group of functions”. During computer validation, the suitability of this hardware/software concept for achieving the required functions is checked and the results documented.

Conformity
See Compliance

Concurrent Validation
See Accompanying Validation

Containment
Containment of a biological agent or other substance within a defined space. **Primary containment:** Prevents leakage into the immediate work environment (e.g. via closed containers). **Secondary containment:** Prevents leakage to the outside or into other work environments (e.g. via rooms with special ventilation systems/airlocks).

Contamination
The unwanted introduction of foreign substances or impurities, chemical or microbiological, into or onto a starting material or intermediate or finished product during manufacture, sampling, packaging, storage or transport.

Continued Process Verification (CPV)
See Continuous Validation

Continuous Validation
Validation is no longer seen as a temporary, one-off activity, but as a permanent verification that accompanies the process over the entire period, from the design phase through to the market withdrawal of the product. The new process validation approach therefore consistently follows the life-cycle model. In a broader sense, therefore, each batch produced is a validation batch.

Continuous Validation/Verification
See Continuous Validation

Corrective Action/Preventive Action (CAPA)
Systematic approach that includes both corrective and preventive actions. **Corrective Action:** Action taken to eliminate the cause of a fault in an identified, undesirable situation and to have a strong chance of preventing recurrence in other areas too or in another procedure. Preventive Action: Action taken to actively prevent the cause of a potential failure. This is often done with the aid of risk analyses.

Corrective and Preventive Actions
See Corrective Action/Preventive Action

CPV
= Continued Process Verification. See Continuous Validation

Culture Media Filling
See Media Fill Test

CSV
= Computer System Validation/Computer and Software Validation (See Computer Validation)

D

Data Review

A Data Review can replace a practical revalidation, assuming that no critical changes have been made to the process since the validation. In that case, evaluating the process and product data for the last period is sufficient; there is no need to check the validated status for specific batches.

Disaster Recovery

= Recovery following an IT blackout; This includes the recovery of important data as well as the repair or replacement of destroyed hardware components.

Design Qualification (DQ)

Documented proof that the design of facilities, plants and equipment is suitable for its intended purpose. The DQ, which is carried out prior to purchasing the equipment, covers documentation of the planning phase and incorporates the decision-making with regard to purchasing a plant. The requirements for the planned installation should be defined and specified.
The elements of the DQ are usually:

- The design qualification plan
- The user requirement specification
- The requirement specification (= the client's requirements with regard to the scope of supply and services)
- The functional specification (the contractor's design for implementing the plant or the project) and
- The design qualification report.

The DQ is the documentation of the comparison between the requirement specification and the functional specification, as well as the underlying laws, regulations and standards.

Deviation
In general, a deviation may be described as a result or a situation within a process which does not comply with the plan or expectations or even a specific related provision. Examples of these are deviations involved in quality control, monitoring or product specifications.

Deviation Management
Deviation Management is the standardized, controlled handling of a deviation. This includes the detection, analysis or monitoring and also remedying of a deviation. Both the causes of a deviation and the related implications must be recorded and classified. This procedure ensures that failures and their consequences are corrected efficiently, and enables early detection of critical situations as well as the implementation of appropriate countermeasures in future.

DMS
See Document Management System

Document Management System (DMS)
Electronic document management system (therefore also often called eDMS) in the form of an IT solution.

DQ
See Design Qualification

E

EDMF

= European Drug Master File: A Drug Master File documents the pharmaceutical production & quality assurance of drugs. This document is used for submission to the competent authority for medicinal products for the authorization of a drug. An EDMF is usually used when the manufacturer of the drug and the manufacturer of the finished dosage form are not identical. The pharmaceutical manufacturer can therefore safeguard its product secret by describing the synthetic routes and process development of the preparation only in the confidential section of the Drug Master File. This section is accessible to the competent authority, but not to the pharmaceutical manufacturer.

eDMS

See Document Management System

EC Directive

= Legislation of the European Community: Member States have a certain amount of flexibility when it comes to their transposition into national law (transposition into law or regulation).

EC Regulation

= Legislative act of the European Community: this has general application, is binding in its entirety and is valid in all Member States – i.e. it does not have to be transposed into national law, which also means that no modifications are possible.

EMA/EMEA

= European Medicines Agency: The EMA is a decentralized EU agency based in London. Since 1995, it has been responsible for the scientific evaluation of medicinal products developed by pharmaceutical companies for use within the European Union. The EMA plays a central role in drug registration within the EU and the EEA States, since the European Commission issues authorizations on the basis of its assessments.

EMA Guideline

Guideline issued by the European Medicines Agency, e.g. on human and veterinary drugs, health protection and GDP (Good Distribution Practice).

EP

= European Pharmacopoeia: Published by the European Directorate for the Quality of Medicines & Health Care (EDQM); this contains the official standards and methods applicable to medical devices and pharmaceutical substances within the EU.

ETA

See Event Tree Analysis

EU GMP Guidelines

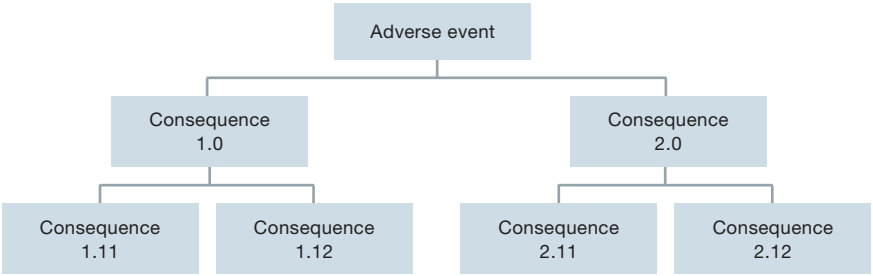
= Good Manufacturing Practice guidelines: The first version of these guidelines, in which the European directives are implemented in detail, was published in 1989. It now consists of 3 parts in addition to Annexes 1-19.
Part I: GMP principles for the manufacture of medicinal products.
Part II: Good Manufacturing Practice for active substances Part III: GMP-related documents (including quality risk management)

European Pharmacopoeia

See EP

Event Tree Analysis

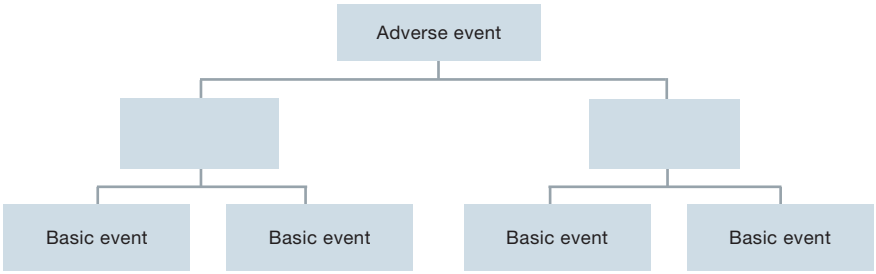
The “Event Tree Analysis” is a method for determining the possible consequences that are triggered by a failure. From an initial failure, a tree diagram is developed via various paths, which represent the possible reactions of the individual system components, culminating in all possible failure consequences and implications.



F

Factory Acceptance Test (FAT)
Acceptance/control of ordered devices and plants on site at the supplier's premises. The Site Acceptance Test (SAT) is usually carried out after delivery and installation.

Fault Tree Analysis
In Fault Tree Analysis, the tree diagram, in contrast to the event analysis (see Event Tree Analysis), progresses from the failure to the cause. In other words, this explores the most likely cause or combination of causes of a fault.



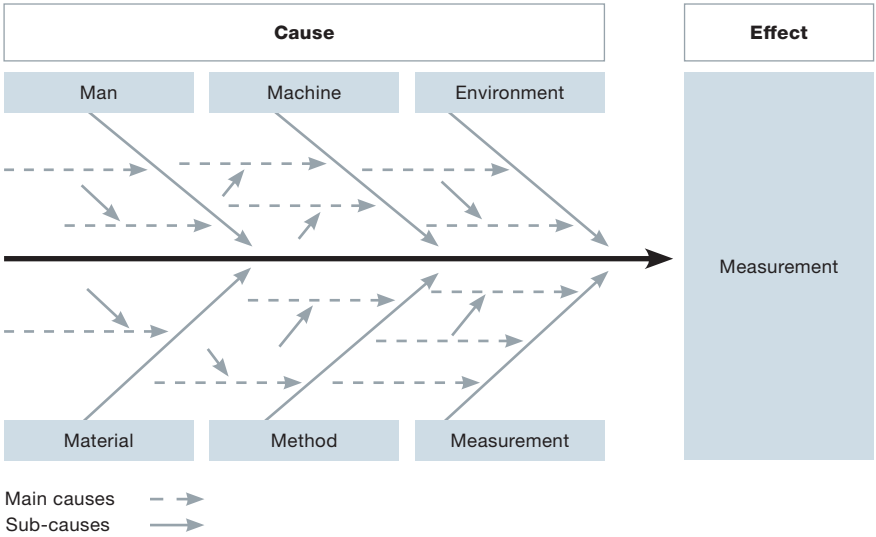
FDA
= U. S. Food and Drug Administration; the FDA is the highest health authority in the USA and is responsible for drug licensing. In order to ensure compliance with the standards also with regard to the many medicinal products imported into the USA, the FDA operates internationally and carries out audits among exporting producers outside the USA.

FDA Guidance for Industry – Process Validation
Contains non-binding recommendations for implementing the process validation, which are based on the current perspective of the US FDA agency. It is important to note that it is possible to also focus on other guidelines, provided that compliance with all GMP regulations is ensured.

FFDCA
See Federal Food, Drug and Cosmetic Act

Fishbone Diagram/Method

The Fishbone method (also Ishikawa diagram) is a graphical method for displaying failures/causes and resultant effects (consequence of failures). Its name is derived from the visual similarity to a fishbone. The method is often also named after the person who developed it, Kaoru Ishikawa. Thanks to the form of presentation, this method imparts a good understanding of the process, which leads to a clear objective.



FMEA (Failure Mode and Effects Analysis)

FMEA is a risk analysis method, which is used to analyze individual failures as well as failure effects and causes. It is widely used in industries where there are high standards with respect to product and process reliability. The FMEA is currently the most frequently used method for systematic risk analysis in the pharmaceutical industry and can also depict extremely complex considerations. Depending on the type of FMEA, the interaction of components in a complex system (system FMEA), the design of products or components (design FMEA) or the steps of a production or service process (process FMEA) are considered. In the FMEA, a Risk Priority Number is determined for each individual sub-step in a process. If this exceeds a pre-defined limit value, risk-reduction measures need to be taken.

FMECA (Failure Mode, Effects and Criticality Analysis)

FMECA is an extension of the FMEA to include the “criticality” factor or the “magnitude of the consequences of a failure”. See also FMEA.

Formulation
The formulation of a medicinal product includes its preparation with the appropriate ingredients as well as its form (dosage form). Once the formulation process of a product is completed, it is referred to as bulk ware.

FTA
See Fault Tree Analysis

Functional Specification
The Functional Specification contains the contractor's comments on the implementation and processing of a project (e.g. construction of a facility). It is the supplier's detailed description for the implementation strategy of the Requirement Specification, and should therefore contain all the obligatory requirements referred to therein. Often no separate Functional Specification is created. Instead it is replaced by the contractor's corresponding offer, provided that this has been adequately detailed.

G

GAMP
= Good Automated Manufacturing Practice; Refers to the validation of computerized systems.

GCP
= Good Clinical Practice; valid for clinical trials: Quality requirements for planning and conducting clinical trials.

GDP
= Good Distribution Practice: Controlled, safe drug distribution channel, from leaving the manufacturer through to the end consumer.

GEP
= Good Engineering Practice; relevant to engineering: Good and effective planning of plants.

GLP
= Good Laboratory Practice; relevant to laboratories: Validation of non-clinical safety tests and procedures.

GMP
= Good Manufacturing Practice; Good manufacturing practice for medicinal products: Sum total of national and international rules relating to medicinal product manufacture and quality assurance, which are intended to protect public health and to protect consumers from dubious products.

GMP-Compliant Plant Design
Plant planning and construction, which is based on the GMP regulations and aims to optimize subsequent GMP-compliant operation, for example easily accessible and cleanable machine components. (see Hygiene Design)

GSP
= Good Storage Practice; relevant to storage: Storage under controlled, constant conditions (temperature, humidity, light).

GxP
= Good x Practice; Umbrella term for specific GMP-regulated sub-areas, for example: GAMP, GCP, GEP, GLP, GDP, GSP.

H

Head of Production

The Head of Production is responsible for ensuring that production is implemented properly, that the production process is validated and that the production personnel are trained. The Head of Production must have a sufficient professional qualification. Appropriate proof of qualification and reliability (certificate of good conduct) must be submitted to the supervisory authority. The Head of Production must always be independent of the Head of Quality Control.

Head of Quality Control

The Head of Quality Control's responsibilities include the testing of starting materials, intermediate and final products, the approval of specifications, the validation of test procedures and the training of personnel in his division. Statutory requirements with respect to the Head of Quality Control are the reliability required to carry out his tasks and activities, as well as familiarity with the products and procedures.

I

ICH

= International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use; the ICH aims to harmonize the criteria for the authorization of a medicinal product in Europe, the USA and Japan. The European Commission, the FDA, and also the Japanese Ministry of Health Labour and Welfare (MHLW) are members.

Information Officer

The legal requirements with respect to the Information Officer are comparable to those imposed on a Qualified Person. The Information Officer is responsible for releasing scientific information about the medicinal product and, in this respect, is responsible for compliance with the principle of not misleading. He must ensure that the labelling, package insert, technical information and advertising are consistent with the content of the authorization and registration. His work therefore forms part of the preventive consumer protection. The Information Officer may, at the same time, hold the position of Qualified Person and Qualified Person for Pharmacovigilance.

In-Process Control

Tests carried out during ongoing production are referred to as in-process controls. The aim is to monitor and, where necessary, adapt the process to the given specifications. In a broader sense, inspection of the environment and equipment may also be considered part of the in-process controls.

Installation Qualification (IQ)

The installation qualification documents the correct implementation of previously defined requirements with respect to the installation and modification of the plant. The IQ is primarily based on the specifications written in the DQ. The relevant documents are checked to make sure they are complete and correct, and updated and supplemented where necessary. Furthermore, the IQ documents prove that all equipment components were delivered, assembled and installed professionally and in accordance with the law. Classic IQ tests include monitoring the acceptance procedure, testing the electrical installation and measuring and control points, and testing the inputs and outputs (I/O test).

IPC
See In-Process Controls

IQ
See Installation Qualification

Ishikawa Diagram/Method
See Fishbone Diagram/Method

ISO 13485
ISO 13485 defines the content and structure of the quality management system for medical devices, which can be applied to the design and development, production, installation and also maintenance of medical devices. It is derived from ISO 9001, and adds to this the specific requirements for the field of medical devices.

ISO 14644

ISO 14644 deals with cleanrooms and contamination control. The products and processes that benefit from controlled airborne contamination include those used in the aerospace, microelectronics, pharmaceutical and food industries as well as in medical technology and healthcare. In addition to the particle purity of the air, lots of additional aspects need to be taken into consideration in the planning, specification, operation and monitoring of cleanrooms and other related areas. The standard is therefore subdivided into different parts (as of: 11/2014):

- 14644-1*: Classification of air cleanliness by particle concentration
- 14644-2*: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration
- 14644-3: Test methods
- 14644-4: Design, construction and start-up
- 14644-5: Operations
- 14644-6: Vocabulary
- 14644-7: Separate devices (clean-air hoods, glove boxes, isolators and mini-environments)
- 14644-8: Classification of air cleanliness by chemical concentration (ACC)
- 14644-9: Classification of surface cleanliness by particle concentration
- 14644-10: Classification of surface cleanliness by chemical concentration
- 14644-12*: Specifications for monitoring air cleanliness by nanoscale particle concentration
- 14644-14*: Assessment of suitability for use of equipment by airborne particle concentration

ISPE

= International Society for Pharmaceutical Engineering; ISPE is an international non-profit organization which currently has 20,000 members in more than 90 countries all over the world, and is engaged in training and sharing information among employees in the pharmaceutical industry. Members are involved in preparing the FDA and EMA guidelines and they publish their own ISPE Guides. These ISPE Guides are extremely detailed and are state-of-the-art for the pharmaceutical industry.

L

Life-Cycle Model
See Life-Cycle Approach

Life-Cycle Approach
Quality assurance approach, to ensure that all QA measures (risk management, qualification, validation, etc.) depict the complete life cycle of a plant or process. The entire concept must be designed for the life-cycle of a process or the product.

Logbook
A logbook is used for continuous documentation of critical items of equipment. These generally include machinery, plants and devices, and in particular ventilation systems, water systems and rooms. The logbook records all validations, calibrations, maintenance work and repairs, cleaning and sterilization as well as all 55 modifications, conversion work and, where necessary, further operations.

M

Major Change

Major Changes refer to changes to the process/to a plant that require monitoring, and which influence the product quality and/or process safety. Examples of this are changes in manufacturing/production, a move in the sense of a change of location or changes in the composition/process parameters.

Material Flow

Material Flow is the coordinated sequence of individual production and storage steps, from the raw materials through to the finished product. The purpose of the Material Flow is to eliminate the inadvertent omission of a quality-defining manufacturing or control step. Moreover, this prevents mix-ups and ensures compatibility with other manufacturing processes.

Matrixing

Matrixing is a cleaning validation method with the objective of reducing the scope of validation overall. The approach is equipment-based implementation.

Method Validation (analytical)

Proof that an analytical method, as specified in the test instructions, provides correct and reliable results. The text and methodology are harmonized in the ICH Q2 for the EU, Japan and the USA.

Metrological Traceability

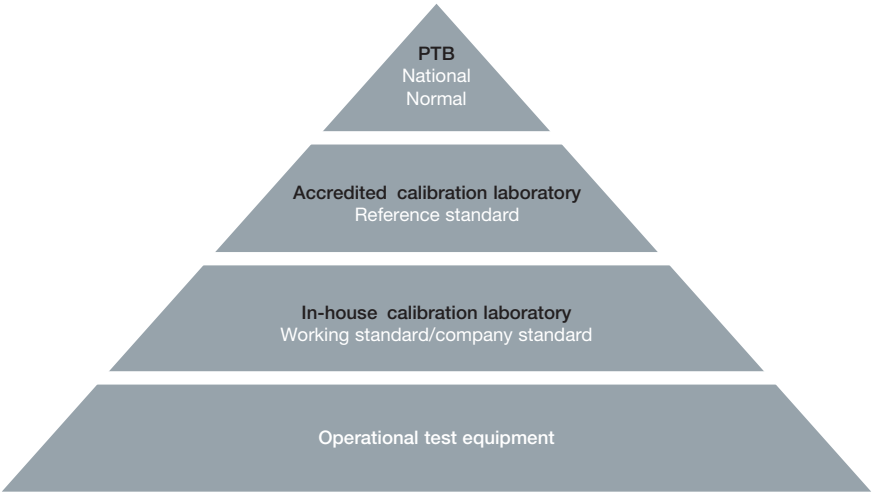
The property of a measurement result or the value of a standard whereby it can be related to stated references, usually international or national standards, through an unbroken chain of comparative measurements with stated measurement uncertainties; metrological traceability is thus ensured by referencing measurement results to international or national standards via an unbroken chain of calibrations.

Minor Change

Minor Change refers to a change that requires monitoring, and which has an influence on a unit that requires monitoring. This includes, for example, replacing a component, changing a detergent or changing the laundry for work clothes.

Monitoring

Monitoring compliance with specified parameters, e.g. monitoring the air cleanliness or monitoring the room climate in cleanrooms.



Calibration hierarchy Germany

N

NOAEL

= no observed adverse effect level: Maximum dose of a substance with no negative observable effect.

NOEL

= no observed effect level: Maximum dose of a substance with no observable effect or critical effect.

O

Official Calibration
Official Calibration is the official check for compliance with the calibration failure limits. An Official Calibration is carried out exclusively by the Landeseichamt. Only those measuring instruments and material measures with a type approval can be officially calibrated. In contrast to Calibration, during Official Calibration no deviation from the test specimen to a reference is determined. Instruments used to protect consumers and to protect the legal status (e.g. water meters, counter scales, traffic radar gauges) are primarily subject to Official Calibration.

OOS
See Out-of-Specification

OOT
See Out-of-Trend

Operational Qualification (OQ)
See Operational Qualification

Out-of-Specification (OOS)
A result that does not meet the specification.

Out-of-Trend (OOT)
A result which is still within the specifications, but owing to the fact that it does not correspond to the observed trend over an extended period, exhibits a certain abnormality.

P

Parenterals

Parenteral means “bypassing the digestive tract”. Accordingly, the European Pharmacopoeia defines Parenterals as “sterile preparations which are intended for injection, infusion or implantation into a human or animal body”. Enteral resorption and therefore the non-specific immune system (saliva, gastrointestinal tract) are bypassed. Therefore, impurities in parenterals are associated with high health risks.

Particle Monitoring

Particle Monitoring is used to monitor particulate air cleanliness. Excessive particle loading can result in excessive contamination of the relevant product with particles, but also with microbiological organisms.

Personnel Flow

A well thought-out, coordinated flow of personnel is a prerequisite for GMP-compliant production. It forms part of the implementation of the hygienic zone concept and prevents cross-contamination. It is also used for product and personal protection. The term “Personnel Flow” encompasses requirements to allow access to pharmaceutical areas only via airlocks and changing areas, to only employ appropriately trained personnel, and to constantly determine the number of people required for operating, monitoring and maintaining the facilities.

Performance Qualification (PQ)
Proof of the long-term specification conformity of a plant during operation. Here, the interplay or compilation of all plant components is checked and the performance limits are tested.
As a result, differentiation between Performance Qualification and Process Validation is not always clear. The Performance Qualification can be differentiated to the extent that product-specific proof of the effectiveness and reproducibility of the device/plant is to be provided.

Pharmacology
Pharmacology is the study of the interactions between drugs and living organisms.

Pharmaceutical Excipient
Pharmaceutical Excipients are substances which form part of a medicinal product, but are not active ingredients themselves. They are added in order to influence the form of the medicinal product or its release in the organism.

PIC/S
= Pharmaceutical Inspection Cooperation Scheme; merger consisting of lots of member states from all over the world, which has set itself the goal of working together to further develop GMP and harmonizing the resulting regulations. In addition, in order to prevent multiple inspections, the mutual recognition of inspections is to be improved and the movement of medicines simplified by dismantling trade barriers. The PIC/S issues PIC/S Guides and PIC/S Recommendations.

Postal Audit

A Postal Audit is carried out without an actual visit to the company being audited. Instead, a comprehensive questionnaire is sent by the auditor to the supplier, who independently fills this in with the appropriate information and relevant references. This information may be verified at a later date during an on-site appointment.

PPQ

See Process Performance Qualification

PQ

See Performance Qualification

PQR

See Product Quality Review

Primary Packaging

The Primary Packaging is the part of a package that immediately surrounds the product, i.e. is in direct contact with it. Thus, primary packages are often made of aluminium, glass or plastic, since these materials are inert or hardly cause any abrasion.

Primary packaging of medicinal products

Process Performance Qualification (PPQ)
The PPQ is part of the new Life-Cycle Approach, and replaces or includes DQ, IQ, OQ and PQ for the existing validation approach. The stability of the process must be demonstrated in the PPQ. (See Life-Cycle Approach)

Product Quality Review (PQR)
Periodic Product Quality Review; regular quality reviews of medicinal products, with the aim of confirming the consistency of the current process and the adequacy of the current specifications for both the starting materials and for the finished product, in order to highlight trends and identify product and process improvements. The PQR should be carried out annually, taking into account previous review results.

Product Specification
A Product Specification should include all the information necessary for preparing the precise written instructions for processing, packaging, quality control, batch release and shipment of a product.

Prospective Qualification
Qualification of a new plant before the start of production.

Prospective Validation
Validation before the start of production/ marketing of a pharmaceutical product.

Process
Any defined organizational sequence or step in a process chain related to the procurement, handling, manufacture and distribution of medicinal products. Processes are clearly defined and clearly differentiated with regard to responsibilities.

Process Capability
Process Capability means that a process is manageable, stable and conforms to the specifications. This is the case if the critical parameters are only subject to purely random variation (normal distribution) and the corresponding values are within the upper and lower control limits/tolerance limits.

Process Capability Study
Statistical method for comparing the process information with the permissible tolerances, to draw conclusions about the process capability.

Process Validation (PV)
Process Validation is documented evidence that the process, within certain parameters, produces a medicinal product that fulfils predefined specifications and quality attributes, in a manner that is effective and reproducible. Here, it must be demonstrated that even difficult-to-control critical process steps follow a predefined sequence and the overall process is completely reproducible - with consistent quality and in compliance with the specifications. The scope of the PV is determined by risk management.

PV (Process Validation)
See Process Validation

Q

QA

See Quality Assurance

QbD

See Quality by Design

Qualification

Qualification is documented proof that a device/plant is suitable for the intended purpose, to fulfil the specified functions or to produce products, and that these meet the regulations and standards on a permanent basis (= are GMP-compliant).

Qualification Report

The Qualification Report always represents the conclusion of a qualification. All results are summarized here. Changes to the test plans and any deviations must be documented accordingly. It should be noted that at this point, all critical deviations must be remedied, only non-critical deviations can be accepted with appropriate justification. The report must also include the maintenance programs, recalibration data, operating instructions, SOPs and the qualification status of the installation. The Qualification Report is a prerequisite for clearance to use the plant or for validation.

Qualification Master Plan

The Qualification Master Plan is a superior document which depicts the qualification strategy and organizational structure in general. The individual qualification objects are defined and the necessary qualification steps are described, with the type and scope of qualification activities. It therefore serves as an overview of equipment and plants with regard to scheduling, and defines the appropriate responsibilities for completing the qualification activities.

Qualification Plan

The Qualification Plan contains the goal, subject and scope of the qualification, the designation of persons and responsibilities within the qualification team and the description of the qualification strategy. Key components are the detailed designation of individual tests, the descriptions relating to their implementation, and the corresponding acceptance criteria (also referred to as test plans, which may also be separate from the qualification plan). Furthermore, the plan should describe the qualification object and, if necessary, the process, should indicate the critical plant parameters and contain a list of documents. The document must finally be released.

Qualified Person (QP)

The Qualified Person must have proof of the necessary expertise (authorized pharmacist or medical/scientific degree with additional qualification). Additional requirements are the reliability required to carry out the tasks and activities as well as sufficient familiarity with the products and procedures. The Qualified Person is responsible for compliance with the relevant regulations governing the manufacture, testing and release of medicinal products prior to placing a drug on the market. His tasks therefore include:

- placing the batch release on the market
- securing Reserve Samples
- checking whether a company's QM system is being maintained
- being responsible for complete documentation, to demonstrate compliance with all regulations.

Quality Management Manual

The Quality Management Manual is a superior, binding document which depicts a company's quality policy and guidelines. As an essential element for long-term implementation of the quality management system, it includes a description of the operational and organizational structure and refers to the relevant procedures, standards and regulations.

Quality Risk Management (QRM)
(Quality) Risk Management is a systematic process for the assessment, control, communication and monitoring of risks to the quality of medicinal products over the entire life-cycle of the product. According to ICH Q9, the assessment of quality risks should be based on scientific knowledge and should always be viewed in the context of patient protection. This requires extensive knowledge of the process as well as clearly defined framework conditions. Quality Risk Management includes risk assessment, risk control, risk monitoring and risk communication. (See Risk Assessment, Risk Monitoring, Risk Communication, Risk Control)

Quality Assurance (QA)
Quality Assurance is a far-reaching concept which covers all the areas that individually or collectively control the quality of a product. It constitutes all the planned measures, undertaken to ensure that medicinal products are of the quality that is required for their intended use.

Quality by Design (QbD)
Quality by Design is a holistic, risk-based approach to the development and manufacture of medicinal products, which aims to develop a process that identifies critical, quality-relevant steps, measures their impact, and determines this within a specified “design space”.

Qualified Person for Pharmacovigilance

The tasks of the Qualified Person for Pharmacovigilance include:

- collecting reports on drug risks, assessing them and coordinating necessary actions
- monitoring clinical trials with regard to drug risks
- identifying serious side effects, interactions or misuse
- notifying supervisory authorities in the event of an abnormal restriction on supply (stopping deliveries, recall).

The Qualified Person for Pharmacovigilance must have appropriate expertise in the form of a completed university degree plus at least two years of professional experience. In principle, he should work independently of sales and distribution units; however, it is possible for him to act as a Qualified Person at the same time (§ 63a AMG).

R

RABS

See Restricted Access Barrier System

Reproducibility

Reproducibility is understood to be consistent product quality and invariable production processes. A process is GMP-compliant only if its result is reproducible. This is the only way to ensure that, for example, when testing a batch by random sampling, the findings obtained from this can also be transferred to all the individual products in this batch.

Restricted Access Barrier System (RABS)

RABS is a concept for isolating a machine, often used in aseptic production or as personal protection in the case of highly active substances. As a mixture of conventional cleanroom technology and isolator technology, active intervention is only possible using gloves; the process itself remains separated from the operator.

RABS (Image: Franz Ziel GmbH)

Reserve Sample
A Reserve Sample is a sample, for example, from a fully packaged unit from a finished product batch, which is stored for identification purposes.

Returns
The return of a medicinal product to the manufacturer or distributor, regardless of whether or not there is a quality defect.

Retrospective Qualification
A Retrospective Qualification is a qualification for already established systems or a qualification based on historical data. Retrospective Qualification can only be carried out if sufficient data is available for subsequent assessment and review of the critical parameters. From a GMP perspective, a Retrospective Qualification is no longer accepted.

Responsibility Delimitation Agreement
This completely and unambiguously sets out the interfaces, tasks and responsibilities between those involved in the manufacture, handling and distribution of a medicinal product. It provides the basis for legally secure cooperation, which, for example, ensures that all requirements for ensuring the quality of a medicinal product are fulfilled.

Requalification
Qualification following changes or periodic, cyclical inspection of critical parameters to ensure that the plant/device is still in a qualified state.

Requirement Specification

Forming part of the qualification, the requirement specification documents the requirements of the client regarding the scope of delivery and services. These technical or regulatory requirements are defined by the relevant departments (Engineering and QA) in collaboration with the operator. Contents of the requirement specification may be:

- Purpose of the device/plant
- Key technical data, such as sizing
- Details of the design (materials, surfaces in contact with the product)
- The nature of the control system
- Warranty services/service requirements for the suppliers
- Requirements with respect to materials and surfaces
- Information on customer service (availability, response time, etc.)
- Requirements for GMP compliance

Revalidation

A periodic, cyclical inspection or repetition of a validation to ensure that changes to the process or equipment made in accordance with certain change control procedures do not impair the process characteristics or the product quality.

Risk Analysis (RA)

The Risk Analysis forms part of the Risk Assessment. In the Risk Analysis, the assessment or weighting of the risk/possible failure previously identified during the Risk Assessment is carried out. In GMP-regulated areas, the Risk Analysis is often carried out using the FMEA method (see FMEA).

Risk-Based Qualification Systems
The goal of the Risk-Based Qualification System is to ensure GMP compliance throughout the entire life-cycle of a plant/device. To this end, the Risk Analysis, i.e. determining the influencing factors which have a negative impact on product quality, is used as the basis for the qualification measures and for determining their scope. The effort put into the qualification and documentation of it are tailored to the seriousness and significance of the risks.

Risk Assessment
The goal of the Risk Analysis is to identify hazards as well as to analyze and assess the risks arising from these hazards. To this end, the problems and issues posed by the risk must first be clearly defined as part of the Risk Assessment. Firstly, potential hazards are identified (risk identification), as a result of which the Risk Analysis takes place (what is the probability of occurrence and of detecting the fault?). Finally, the Risk Assessment (what are the consequences?/what is the extent of this?) is carried out.

Risk Communication
The findings obtained from the Risk Analysis process should be communicated throughout the quality risk management process; however, all decision-makers and participants really need to be informed about the conclusions, because identifying a risk can only contribute to the quality assurance if all process participants are informed about it and it can be purposefully avoided.

Risk Management
See Quality Risk Management (QRM)

Risk Priority Number (RPN)
The formula for determining the Risk Priority Number (RPN) is:
RPN = P x S x D. Where the individual parameters are defined as follows:
P = Probability of occurrence
S = Severity of the failure
D = Detection probability

Risk Reduction
Risk Reduction forms an integral part of Risk Control, and includes measures to reduce the extent and probability of a failure, or to improve or increase the detectability of a failure. The Risk Assessment should be re-evaluated once the appropriate measures have been implemented and the potential change assessed.

Risk Control
The goal of Risk Control is to reduce risks to an acceptable level. Appropriate measures are established to reduce a risk (Risk Reduction) or an acceptable risk is classified as non-critical (Risk Acceptance).
(See Risk Reduction)

Risk Monitoring
Since the Risk Assessments made as part of the quality risk management only ever represent a snapshot, they must be checked at regular intervals. This ensures the timeliness and suitability of the Risk Assessment throughout an entire life-cycle, and takes account of changes or new sources of failure and integrates these into the Risk Management.

Robustness
Robustness describes the capacity of a system/process not to respond to external changes.

S

Secondary Contamination
Secondary Contamination refers to contamination of the product after manufacture, e.g. due to improper sampling, packaging or storage.

Secondary Packaging
The Secondary Packaging encloses the Primary Packaging and, unlike this, is not in direct contact with the product.

Self-Inspection
Self-Inspection is a critical evaluation and review of in-house processes. The Head of Production and the Head of Quality Control play a fundamental role in carrying this out. This internal quality audit is mandatory in the EU GMP Guidelines.

Site Acceptance Test (SAT)
SAT refers to the acceptance of a device/plant after delivery. All the requirements specified in the Requirement Specification and the Functional Specification are checked as part of this process. The Site Acceptance Test is used to determine the as-built state. Subsequent changes must therefore be taken into consideration in the manufacturer's technical documentation.

Site Master File (SMF)
= Company description; The Site Master File (SMF) is an internally-generated company description for external authorities and customers. This should include general information about the company, the QM system, products, self-inspection and relevant plants. Requirements for the SMF are explained in the GMP Guidelines Part III.

SOP (Standard Operating Procedure)
SOPs are documents that provide organizational, administrative, and technical information and instructions for carrying out regularly recurring work processes. They are aimed primarily at a company's employees and are intended to ensure that quality-relevant work is carried out correctly by every employee right from the start.

Specification
The Specification covers the entire scope of testing, including the test instructions, which are established for each specific product and which are, in principle, based on the latest developments in science and technology (e.g. pharmacopoeial monograph, guideline on drug testing). This includes the establishment of acceptance criteria as well as specific requirements for storage.

Sterility
Sterility refers to the complete absence of living micro-organisms, including their resting stages (such as spores).

Sterilization
During Sterilization, all micro-organisms are killed or viruses inactivated during reproduction and dormancy. Sterilization in GMP areas is carried out physically by means of thermal processes (heat treatment) or chemical processes (e.g. via ethylene oxide). Sterilization via high-energy radiation is also frequently used (e.g. gamma radiation).

Stress Test
A Stress Test is used to check the stability of a product or process under extreme conditions (high temperatures, humidity, etc.). In the case of medicinal products, this includes the light stability test, for example.

Supplier Audit
Auditing of a company/organization (supplier) by a customer. See Audit

T

TAMC
Total Aerobic Microbial Count

Test Plan
A Test Plan is a document that describes the objective(s), design, methodology, statistical considerations as well as the organization of a test prospectively.

Third-Party Audits
Audit by a third party not directly involved in the manufacture of a product (not manufacturer or supplier). For example, according to GMP regulations, a pharmaceutical manufacturer is required to audit its active ingredient suppliers to ensure that the active ingredients were produced in accordance with Good Manufacturing Practice. However, the pharmaceutical manufacturer can also use an appropriately qualified, impartial third party to have these mandatory audits carried out at the supplier.

Traceability Matrix

The Traceability Matrix is used to display the relationships between user requirements, technical requirements, specifications and test cases. It provides proof that the user requirements, via the technical requirements, have been fully converted into technical specifications, which the project manager is obligated to adhere to. It is also possible to link the Requirement Specification and Risk Analysis requirements with the qualification tests.

Track & Trace

Track & Trace refers to the individual labelling of each product, as well as the recording of every movement and every transportation step that a product goes through, from manufacture to end consumer. In the pharmaceutical industry, this method can be used to combat product counterfeiting, because the sale of each pharmaceutical product can be retraced in order to determine where the product comes from and whether it is an original or a copy.

Traceability

Traceability refers to the ability to trace all the steps and processes of a product, a batch or even a measure itself at a later date.

U

URS (User Requirement Specification)

In the URS, the requirements for the device/plant being manufactured with respect to the product to be produced are described from the user's perspective. The URS, together with the technical and regulatory GMP requirements for the plant, forms the Requirement Specification.

V

Validation

Provision of documented proof which provides a high degree of assurance that a specific process or a Standard Operating Procedure will produce a product that conforms to the pre-defined specifications and quality characteristics – in accordance with AMWHV § 2-16. The Validation therefore provides proof that methods, processes, plants, equipment, materials and systems bring about the expected results in accordance with the principles of Good Manufacturing Practice. Validation therefore ensures and documents the most important attributes of a process: Reproducibility and Robustness.

Validation Report

The Validation Report is used to document the validation. This contains the production protocol, which includes the results of the in-process controls, the results of the validation tests including any deviations detected, and also the evaluation and assessment of the validation and the related implications with regard to routine production, change control and, where necessary, revalidation.

Validation Master Plan (VMP)

The Validation Master Plan (VMP) specifies a company's validation strategy and philosophy and summarizes concepts, intentions, responsibilities and procedures with regard to validation. According to EU GMP Guidelines Annex 15, “all validation activities should be planned. The key elements of a validation program should be clearly defined and documented in a Validation Master Plan (VMP) or similar document”. The Qualification Master Plan may form part of the VMP.

Validation Matrix

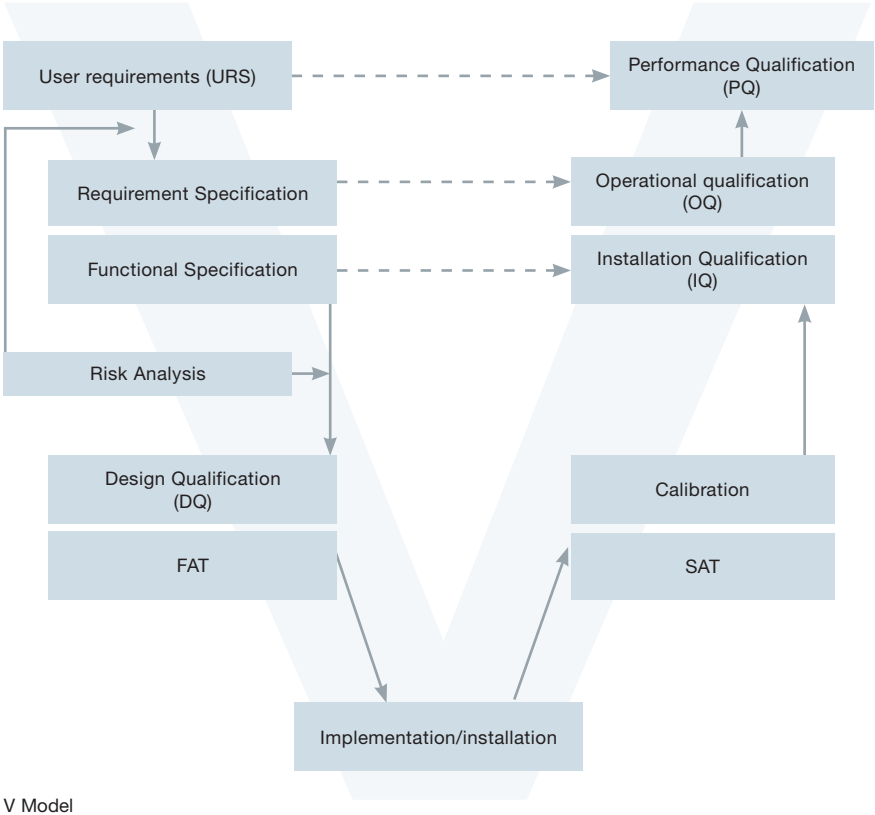
A Validation Matrix is used to depict the relational links between the individual validation components (products, processes, systems) and the assigned actions (validation/qualification tasks). In order to simplify the overview of complex validations, the appropriate responsibilities and priorities should also be noted.

Validation Plan

The Validation Plan is written before the validation is carried out, and it contains information about the product (specifications, analytical methods) and about the process (process description including flow chart, RA) as well as about rooms and facilities (allocation of rooms, hygienic status, calibration status) and about the process validation (tests, sampling, analytical methods, acceptance criteria, timetable, responsibilities).

V Model

In the so-called V Model, all activities and documents containing a qualification and validation are depicted in their logical sequence. Moreover, the direct links between the requirement documents (URS, Functional Specification, Requirement Specification) and the corresponding qualification documentation (PQ, OQ, IQ) are demonstrated.



V Model

W

Warning Limit

The Warning Limit is a defined limit value, which enables early warning of possible deviation from regular operating parameters. This does not necessarily involve corrective measures, but the cause does need to be investigated.

Warning Letter

A Warning Letter is issued by the FDA to a pharmaceutical company if critical deficiencies were identified and not remedied during a previous inspection (or audit). The team of inspectors lists the deficiencies on the 483 form. The company is granted a period within which the deficiencies must be dealt with, otherwise there is a risk that the authorization will be rejected or imports banned. A Warning Letter is published by the FDA on its website, in order to bring the shortcomings therein and the company concerned to the notice of the public.

WHO

= World Health Organization; the World Health Organization is the superior authority of the United Nations when it comes to international healthcare. It is currently made up of 194 member states. The WHO agenda contains six key points:

- two health objectives: promoting development and promoting health and safety;
- two strategic requirements: strengthening the health system and utilizing research results, data and findings;
- two operational approaches: expanding partnerships and improving performance.

Worst-Case Scenario

The Worst-Case Scenario describes the most critical state that could possibly occur. This means, for example, that process parameters reach their upper or lower limit values, making it significantly more likely that process or product failures will occur.

Work Directive

See SOP

Z

ZLG

= Central Authority of the Länder for Health Protection with regard to Medicinal Products and Medical Devices; as a coordinating body for the German federal states in the field of human and veterinary medicine, ZLG is responsible for maintaining and improving the quality and safety of medicinal products and medical devices. Thanks to standardization of the inspection standards within Germany, which ZLG initiates, in comparison to Europe, Germany is portrayed as one cohesive unit despite federal structures in the healthcare system.

GxP Regulations and Guidelines

Europe:

- EC Guidelines on Good Manufacturing Practice
  (EU GMP Guidelines Part I, II, III;
  Annexes 1-19), including supplementary guidelines
- Guidelines on Good Distribution Practice for medicinal products for human use (GDP guideline)

Other/standards:

- DIN EN ISO 14644 Cleanrooms and associated controlled environments
- DIN EN ISO/IEC 17025 Quality management and general requirements for the competence of testing and calibration laboratories

Notes

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