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GMP Series

Qualification and Validation: Agency Expectations

GMP-Conform Implementation of Annex 15 EU GMP Guide

Excerpt from the GMP Compliance Adviser

Contents

Qualification: Official requirements and agency expectations

Here you will find answers to the following questions:
- What is the purpose of qualification?
- How is a qualification to be documented?
- Who is responsible for the qualification?
- How is qualification by third parties to be handled?
- How are the stages of qualification differentiated, what are the contents of each stage?
- What rules apply for a requalification?

1 Principles of qualification

A qualification serves to prove that equipment is fit for purpose. In this context "fit for purpose" means that it can be demonstrated that the equipment meets the proscribed requirements. "Fit for purpose" also means that the equipment meets the requirements in a reproducible manner – that is with a high level of statistical probability. Qualification activities are always associated with statistical investigations.

Qualification is oriented along the lifecycle of the equipment. Every phase from design up until decommissioning of the equipment is to be assessed in a risk-based manner.

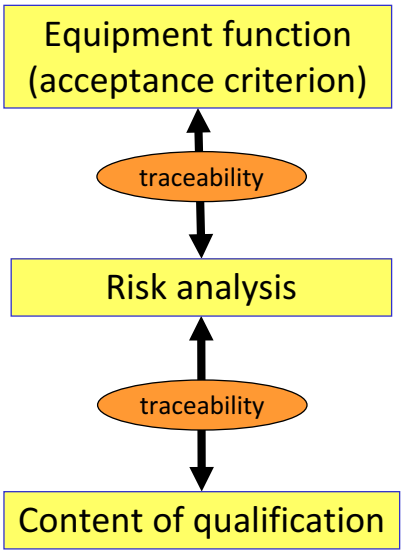
A fundamental requirement for a successful equipment qualification is the good design of the equipment. Good design ensures the desired functionality, effective controls as well as effective cleaning and maintenance of the equipment. The responsibility for the equipment design lies generally with the equipment supplier. Good Engineering Practice (GEP) as defined by the ISPE (International Society for Pharmaceutical Engineering) is *"Established engineering methods and standards that are applied throughout a project's life cycle to deliver appropriate, cost-effective solutions."* GEP Standards are established in norms such as ISO/DIN, the Society of German Engineers (VDI) and in the baselines of the ISPE.

Core elements of all qualification work are the **acceptance criteria**, such as limit values or specifications. Thus, it is necessary to set the acceptance criteria before performing the qualification. When determining the acceptance criteria requirements references can be made to the drug product manufacturing instructions, registration documents, industry norms or risk analyses.

The breadth and intensity of the required qualification work should be identified via **risk analysis**. This should reflect the complexity of the equipment design and the variability associated with it. The greater the complexity and variability of the equipment the higher the requirements will be on the control functions which can document the proper functioning of the equipment.

Critical equipment functions dictate the establishment of the risk analysis, and the risk analysis dictates the breadth of the qualification work. These relationships should be made clear in the documentation. Figure 1 provides a schematic of the relationship between these elements.

The robustness of the equipment functionality influences the reproducibility of manufacturing processes and thus the critical quality attributes. To recognize and assess these interdependencies it is necessary to have knowledge and experience in the operation of the equipment as well as relevant processes. This knowledge base is not always present at the manufacturing site. The greater the separation of labor is (catchword: outsourcing), the more necessary it is to maintain a functioning **Information and Communication Management System** among the involved parties. This includes the internal equipment installation and the customer in the pharma-production company as well as the equipment supplier and operator. A properly functioning exchange of information is an essential prerequisite for successful risk management and qualification.



Sub-function No. 2 „drying“ 2.1 Parameter		
Acceptance criterion No.	Risk analysis No.	Qualification test No.
2.1.1 Temperature	R 2.1.1	Q 2.1.1
2.1.2 Inlet air	R 2.1.2	Q. 2.1.2
2.1.3 Exhaust air	R 2.1.3	–
2.1.4 Duration	R 2.1.4	Q 2.1.4

Figure 1 Traceability of qualification exercises

It is a matter of course that experience in operations with similar or the same equipment should be reflected in the risk analysis and qualification. A compilation of multiple equipment units together to a group of which a single unit is taken as representative of the whole group and is qualified, however, is not acceptable. In contrast to process and cleaning validations, the **bracketing approach** is not possible for equipment qualifications. Most notably the installation and operation qualifications cannot be transferred from one equipment unit to another of the same type. A qualification evaluates and tests a specific piece of equipment individually.

All qualification tests should be performed under *near-operational conditions*. This includes, for example, environmental conditions, equipment parameters and their upper and lower limits, the run time per shift as well as equipment stops and interventions.

Qualification teams should be made up of representatives of multiple disciplines. This may include representatives from Engineering, Production, Quality Assurance and Quality Control.

Personnel which are involved in the qualification should be adequately qualified for the conferred task. Only approved procedures should be employed. All tasks and documents should be monitored. The QS system should define who the qualification personnel reports to.

An exceptional procedure for **existing equipment** is no longer intended. In the past it was possible to perform retrospective qualifications based on reviews of past experience. It is now expected that existing equipment be qualified according to Annex 15, which went in effect in 2001 for the first time. All the special exceptions were removed with the revision of Annex 15 in 2015. Qualified equipment is imperative for manufacturing and it is not permitted to operate existing equipment with the intention of performing a retrospective qualification at a later time.

2 Legal framework and responsibilities

The requirement for qualification is established in the EU GMP Guidelines. "Manufacturing equipment should be designed, located and maintained to suit its intended purpose." (EU GMP Guidelines, Chapter 3.34). Annex 15 “Qualification and Validation” to the EU GMP Guidelines controls how these requirements are to be met.

The EU GMP Guidelines and their annexes themselves are not enforceable by law. It does however represent the interpretation of the principles laid out in Commission Directive 2003/94/EC. According to Article 4 Section 1 of this directive the manufacturer is responsible to ensure that all manufacturing steps uphold the rules of Good Manufacturing Practice. According to Article 8, Section 3 of the directive, premises and equipment to be used are subject to appropriate qualification and validation.

The member states have established this guideline in their national laws; in Germany this is included in the German Drug law (AMG) and in the Ordinance on the Application of Good Manufacturing Practice for the Manufacture of Medicinal Products and Active Pharmaceutical Ingredients and on the Application of Good Expertise Practice for the Production of Products of Human Origin (Medicinal Product and Active Pharmaceutical Ingredient Ordinance – AMWHV.)

The requirements of the EU GMP Guidelines represent the current state of the art. Most notably the granting of a manufacturing permit is dependent upon the suitability of the rooms and facilities of the premises as well as the assurance that production and inspection is performed according to scientific and technological state of the art. If the manufacturer is not able to prove that availability of suitable facilities and equipment this can lead to the revocation of the manufacturing permit or that it be revoked retroactively.

Prior to the revision of Annex 15, the PIC/S Document PI 006 "*Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation"* could be referenced regarding the interpretation and implementation of the requirements in Annex 15. This document, however, originates from 1996 and should be interpreted in this historical context.

Who is responsible for qualification?

- *Senior management* bears responsibility for providing adequate resources (EU GMP Guidelines, chapter 2.4). Other internal departments may be involved in the execution (e.g. Engineering) or external service providers (e.g. consultants).
- The head of the Production Department and the head of Quality Control are responsible to ensure the qualification and maintenance of their respective department, premises and equipment (EU GMP-Guidelines, chapter 2.7.(iv) and 2.8.(v).

2.1 Qualification by Third Party

When the execution of a qualification exercise is commissioned to a third party the responsibilities must be clearly defined. A written contract must be established between customer and client for all *commissioned work*. This requirement is derived from Article 12 Section 1 und 2 of the 2003/94/EC and 91/412/EEC directives.

The contract should clearly define the responsibilities of each party, especially for the upholding of Good Manufacturing Practice. The Head of Production should be confident that all the qualification steps are performed according to the scientific and technical state of the art. By commissioning the work, the responsibilities according to medicinal product regulations are not transferred to the third party. This remains with the Head of Production.

There are numerous reasons why companies often commission third parties to perform their qualifications. Most often it is a lack of internal resources with adequate knowledge and experience to perform a qualification according to the state of the art or personnel resources are limited in general. This is a typical field of work for consultancies. The spectrum of their work ranges from individual consultations to complete execution of the qualification including documentation.

The acquisition of external expertise is permitted and in many cases it is logical. Companies are often unaware that the work can be delegated to third parties but not the responsibility. The PIC/S Document PI 006 provides clear reference in Chapter 2.5.11 that the client retains responsibility for the proper execution of the validation work: "*In such cases, the responsibility lies with the contract giver to ensure that the required standards of the quality of the work which is carried out, for programme control and for documentation are met.*"

In the end the manufacturer is responsible for the data integrity which third parties (e.g. external service providers) provide. In the Section "General" of Annex 15 it states: *"Data supporting qualification and/or validation studies which were obtained from sources outside of the manufacturers own programmes may be used provided that this approach has been justified and that there is adequate assurance that controls were in place throughout the acquisition of such data."*

5 Design qualification (DQ)

The qualification of equipment and machinery is performed throughout its **lifecycle** (see figure 2).

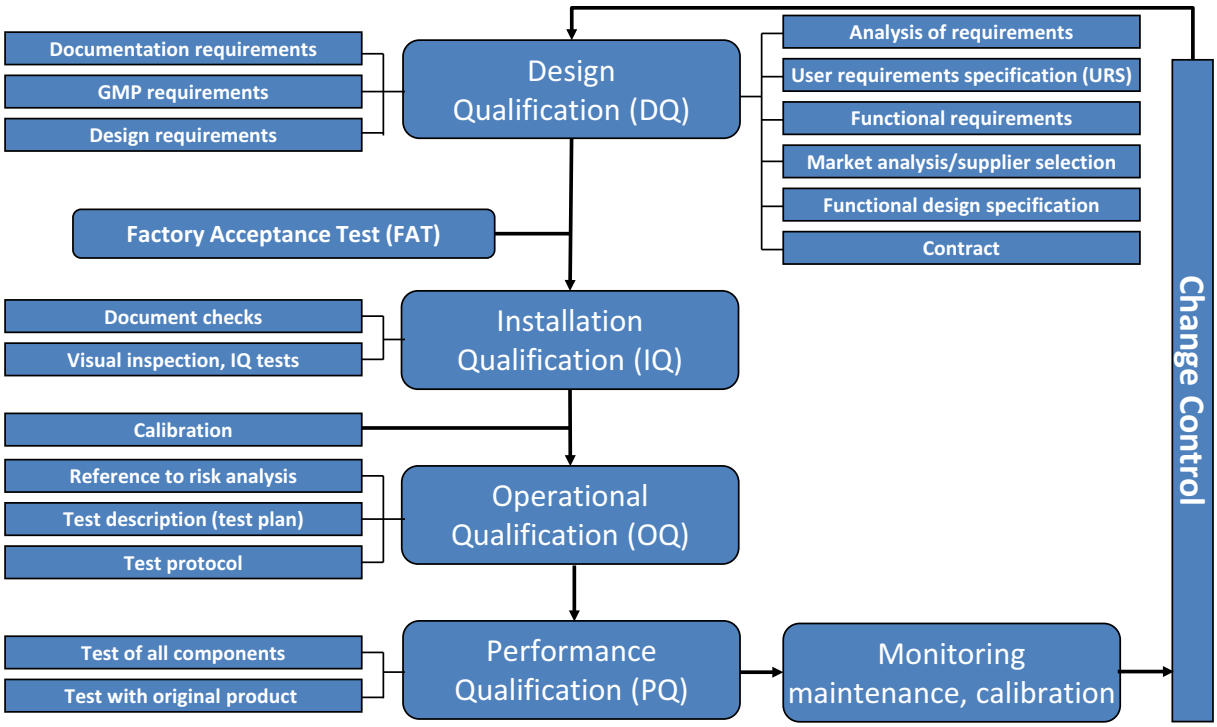


Figure 2 The qualification lifecycle

The first step in a qualification is the design qualification (DQ). According to Annex 15 it is to be demonstrated and documented that the design matches the GMP requirements for the equipment.

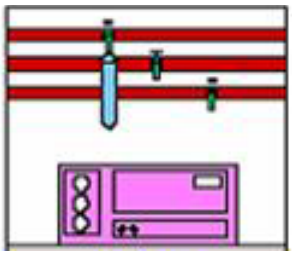
The design qualification includes the documentation of the planning phase including the decision making process for the equipment. The DQ should define and verify the requirements for the entire unit.

The design qualification documents (see figure 3) include the requirements of the user regarding the equipment and services to be delivered (*user requirement specification*) as well as the agreement with the supplier regarding the realization and execution of the project (*functional design specification*).

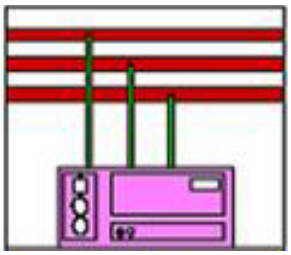
Before acquisition of new equipment the drug manufacturer should identify the requirements (processes, products, performance). Various areas in the site are typically involved in the definition of the requirements which yields an informal *profile of requirements* for the new equipment. This profile of requirements is translated into a user requirement specification (URS). The **URS** should contain the requirements from the perspective of the equipment operator as well as all boundary conditions. These should be able to be qualified and tested. The URS represents the economic, technical and organisational expectations of the client placed on the equipment. The goals and purpose of the equipment are defined in the URS.

When assembling the requirements for the URS, a differentiation should be made between essential (obligatory) and desired (optional) requirements. Not all of the requests placed by the future operators can be realized in practical operation. It depends on the market situation whether equipment suppliers can be found for a specific piece of equipment and if these are able to supply the necessary quality. The services available are determined as part of a carefully executed *market analysis*. The result of the market analysis can make it necessary to update the previously approved URS, since new aspects may come up which impact the equipment design, which were not originally reflected.

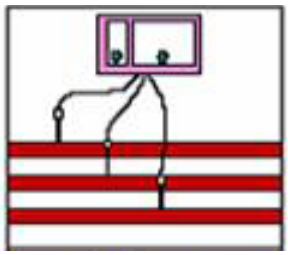
If *external service providers* are involved in the validation, it must be ensured that their data is reliable. To do this, adequate checks must be in place when the data is being collected. Correct and precise *analytical procedures* are the basis for reliable data. An essential prerequisite is knowing the analytic approach to take, the methods to use and when and where the analysis should be carried out. The use of process analytical technology (PAT), including in-line, on-line and at-line process controls is recommended (see figure 2).



At-line:
An analytical method where the sample is isolated from the process and analysed in the process environment



On-line:
An analytical method where the sample is isolated from the process, analysed and, if appropriate, returned to the process



In-line:
An analytical method where the sample is analysed during the ongoing process

Figure 2 Process analytical measurement techniques

1.4 Personnel qualification

To carry out the validation, the personnelmust be adequately qualified. The persons involved generally work together in a multidisciplinary **team**. Who takes part (Production, Technology, QA, QC, Microbiology, external service providers) depends on the question being asked.

1.5 Acceptance criteria

The key element in every validation are the acceptance criteria. Acceptance criteria can be defined as process-related parameters or as product-related specifications. At the heart of the process validation are the **critical process parameters (CPPs)** and **critical quality attributes (CQAs)**, see figure 3. A parameter that is controlled and monitored within a specific range is not automatically a non-critical parameter. What matters is the potential risk to quality.

Critical process parameter (CPP)
A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.
Critical quality attribute (CQA)
A physical, chemical, biological or microbiological property or characteristic that should be within an approved limit, range or distribution to ensure the desired product quality.

Figure 3 Critical acceptance criteria in accordance with Annex 15, EU GMP Guidelines

Acceptance criteria must be established before the validation is carried out. They are the key element in every validation protocol. When acceptance criteria are being drafted, the requirements in manufacturing instructions, authorisation documentation or risk analyses, for example, can be consulted.

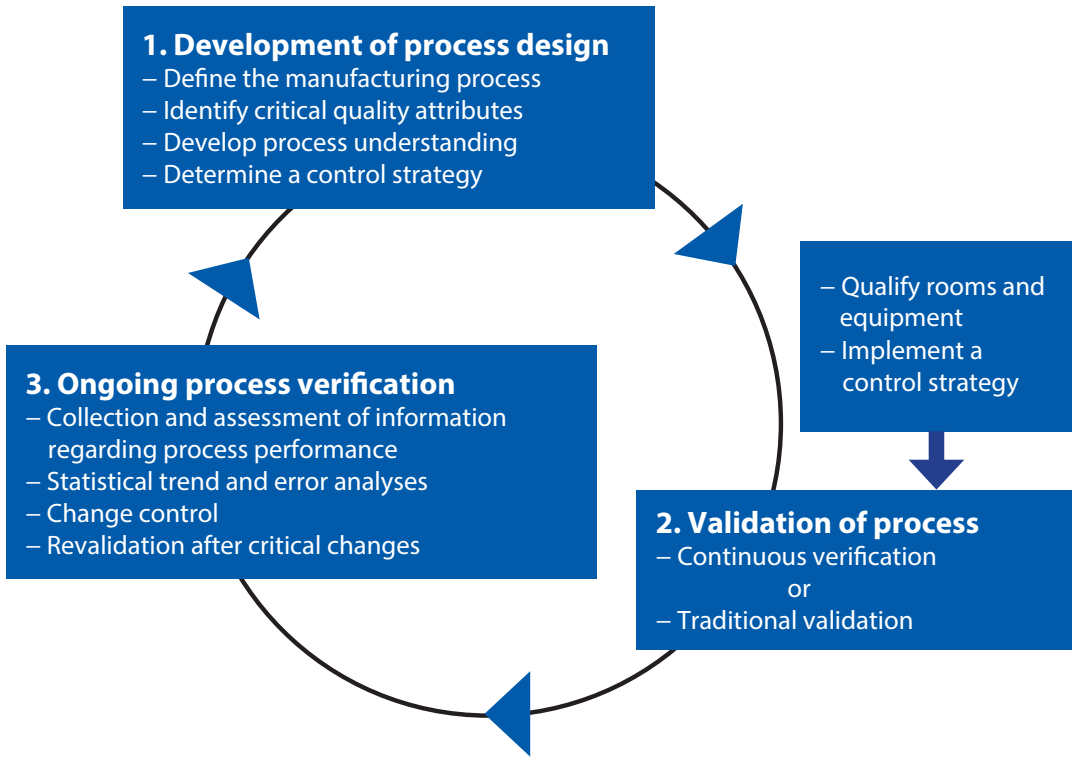


Figure 10 Life cycle of processes

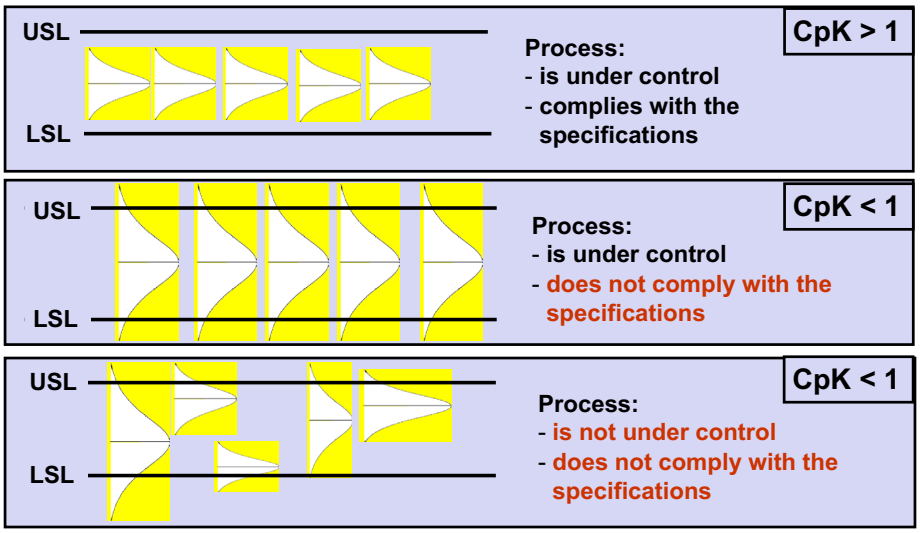
4.1 Development and optimisation phase

The foundation for a reproducible quality of medicinal product is laid during the *development and optimisation phase* of the manufacturing process ("Development of a process design"; see figure 10).

During this phase, the applicant must submit a detailed process description during the **authorisation procedure** (CTD, Module 3). This description contains critical process steps and intermediate products and facilitates a link between the proposed control strategy and the process validation. During the process development phase, critical process attributes should be identified and the causes for their fluctuation and/or variation determined. An initial check of the suitability of the procedure and its in-process controls should be carried out by manufacturing *laboratory scale batches* (one hundredth to one thousandth of the subsequent commercial size). If during the process optimisation phase, *pilot batches* are manufactured for purposes of validation, their batch size should be at least 10% of the subsequent commercial batches. The transition from laboratory scale via pilot batch size to commercial batch size (**scale-up**) should prove that an increase in the batch size has no negative impact on the quality of the product.

When the *formula* for a new marketing authorisation is submitted, the applicant must provide documented evidence for the smallest and largest *batch sizes*. If batches are divided into sub-batches which are subsequently processed separately, the division must be limited and justified clearly. In the case of continuous production processes where fixed batch sizes are not expected, the batch size can be defined using the campaign duration, for example. When production times are potentially critical for the quality of the product (e.g. filling processes in the case of aseptic medicinal products), the duration and every interruption of the manufacturing process must be justified.

The names, amounts and specifications of all the starting materials must be defined for the *ingredients* of a batch (formula). This also applies to those substances that are added during the manufacturing process and then removed (e.g. granulating liquids, solvents and gases) or excipients that are not



USL = upper specification limit
LSL = lower specification limit

Figure 18 Process capability testing

The **Cp value** is defined as

$$Cp = \frac{USL - LSL}{6\sigma}$$

Because the mean value of a process parameter does not necessarily correspond to the centre of the specification range, determination of the **Cpk value** is more common. The process capability index *Cpk* is a measurement of the expected share of nonconforming units in the process. The larger the index, the smaller the share of nonconforming units. The Cpk is defined using the mean value μ, the corresponding standard deviation σ and the upper or lower specification limit range (USL, LSL):

$$Cpk = \frac{\min(\mu - USG; OSG - \mu)}{3\sigma}$$

The higher this value is, the more certain it is that all the units of the examined volume comply with the specification.

Whereas the Cp value only specifies the relationship between the process distribution and a defined tolerance, the Cpk value also includes the location of the mean value in relation to the specified centre of tolerance. The Cpk value is thus always identical to or smaller than the Cp value (*Cpk ≤Cp)*

If the Cpk = Cp, the mean value of the quality attribute (process mean) is at the exact centre of tolerance. The smaller Cpk is in relation to Cp, the further the process mean is from the centre of tolerance. Process capability can be assumed from a Cpk value >1.33 (see figure 19).

Process capability in accordance with DIN 55350	
Cpk <1.0	No process capability
1.0 < Cpk <1.33	Conditional process capability
Cpk >1.33	Process capability present

Figure 19 Process capability in accordance with DIN 55350

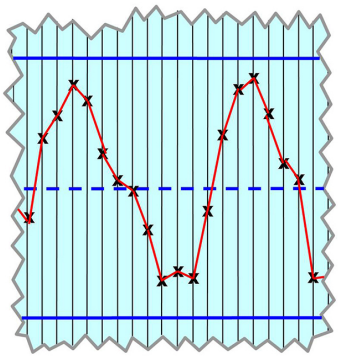


Figure 23 A "pattern" on a quality control chart

A **pattern** (see figure 23) is a curve progression that is not random, e.g. the periodic *oscillation* around the specified mean value. It may indicate temperature fluctuation, for example, which can affect the size of the manufactured parts.

If 7 measurement points are above or below the set mean value, a new real mean value has been created. This is referred to as a **run** (see figure 24). This can indicate, for example, that a stamp in a tablet press has been damaged and the manufactured pellets will be smaller or larger from now on.

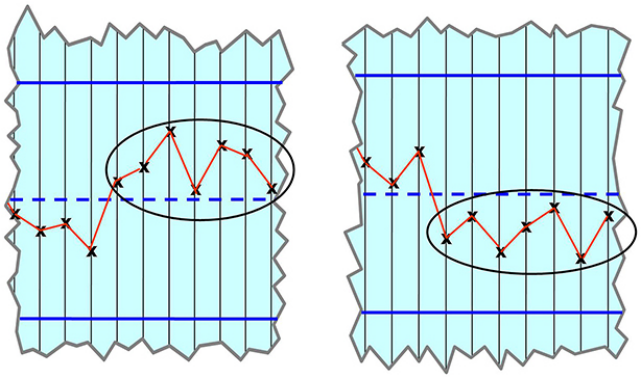


Figure 24 A "run" on a quality control chart

The PQR as part of ongoing verification

One of the objectives of the annual product quality review (PQR, see figure 25) is to verify the stability of the process. As explained above, this means providing proof of process control and process capability. The PQR must include statistical methods that facilitate this procedure.

Product quality reviews as part of ongoing verification
"Regular periodic or rolling quality reviews of all authorised medicinal products, including export only products, should be conducted with the objective of *verifying the consistency of the existing process*, the appropriateness of current specifications for both starting materials and finished product, to highlight any trends and to identify product and process improvements." (EU GMP Guidelines, Part I, Chapter 1.10)

Figure 25 Product quality review

When these requirements are met, the PQR can also be used as a tool for ongoing process verification.

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After graduating in Pharmacology and receiving a PhD, he worked as Laboratory Manager and GMP Inspector in the area of pharmacovigilance. He is currently responsible for supervising GMP inspections.

He was Head of the Qualification/Validation expert group for more than ten years and is co-author of the aide mémoire "Inspektion von Qualifizierung und Validierung in pharmazeutischer Herstellung und Qualitätskontrolle" (Inspection of qualification and validation in pharmaceutical manufacture and quality control). He is also involved in a number of international organisations, including the European Medicines Agency (EMA).

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