

2.1 Introduction to pharmaceutical validation

Validation is documented evidence that a process, equipment, system or method does what it is designed to do, consistently and reproducibly. In the words of the regulatory definition used worldwide, process validation is documented evidence that a process, operated within established parameters, can perform effectively and reproducibly to produce a product meeting its predetermined specifications and quality attributes. Validation is not testing a few finished batches and hoping they pass; it is building proof, in advance and in writing, that the process is in control.

Validation sits inside the quality system between qualification of facilities and equipment (section 2.8) and routine quality control. Qualification shows the equipment is installed and works correctly; validation shows the whole process, using that equipment and those materials, repeatedly makes a product of the required quality.

2.2 Scope and merits of validation

The scope of validation covers every part of manufacture that can affect product quality:

- **Process validation:** the manufacturing process itself, for each product.
- **Cleaning validation:** proof that cleaning procedures remove residues of product, cleaning agents and microbes to below accepted limits, so there is no cross contamination.
- **Analytical method validation:** proof that a test method is accurate, precise, specific and reliable for its purpose.
- **Equipment and utility validation (qualification):** presses, autoclaves, ovens, purified water and HVAC systems.
- **Computerised system validation:** software and automated systems that control or record production.

The merits of validation are practical as well as regulatory: it is required by GMP law and by every regulator; it reduces batch failures, rework and rejections; it gives a deep, documented understanding of the process, so deviations can be judged on evidence; it lowers the cost of quality because testing of finished product alone cannot detect every failure; and it makes technology transfer and scale up safer, because the critical parameters are already known.

2.3 Validation master plan and calibration master plan

The validation master plan (VMP) is the company level document that describes the whole validation programme: the philosophy and policy, the facilities, systems, equipment and processes to be validated, the responsibilities of each department, the order and priority of work, the documents to be produced (protocols and reports), and how changes and revalidation are handled. Every validation activity in the plant traces back to the VMP, and auditors ask for it early.

Calibration is the comparison of a measurement against a known standard, with adjustment or correction where needed, so that instruments read truly. The calibration master plan lists every instrument that needs calibration (balances, pressure and temperature gauges, pH meters, autoclave sensors, dissolution baths), the standard used, the frequency, the acceptance limits and the action when an instrument is found out of

calibration. An uncalibrated instrument silently invalidates every result it touches, which is why calibration is planned and documented with the same discipline as validation.

2.4 ICH and WHO guidelines for calibration and validation of equipment

The ICH guidelines give the internationally harmonised framework. ICH Q7 (GMP for active pharmaceutical ingredients) and the general GMP guides require qualification and calibration programmes; ICH Q8, Q9 and Q10 add the modern lifecycle thinking: pharmaceutical development, quality risk management and the pharmaceutical quality system. ICH Q2 covers validation of analytical procedures. The WHO GMP guidelines and their supplementary guidelines on validation (including the WHO guideline on process validation and on heating, ventilation and air conditioning systems) give detailed expectations used widely by regulators in India and other countries: written protocols, predefined acceptance criteria, calibration at defined intervals with traceable standards, and documented evidence for every claim.

In practice, for equipment this means: each instrument and system is identified and listed; critical parameters are defined; calibration is done against standards traceable to national or international references; labels show calibration status and due date; and validation or qualification is performed before the equipment is used for GMP production, and repeated after major repair or relocation.

2.5 Types of validation

Process validation is classified by when it is done relative to routine production:

- **Prospective validation:** carried out before a new product or process is released for routine sale, on the basis of development and pilot or initial commercial batches. This is the standard and preferred type.
- **Concurrent validation:** carried out during routine production, in exceptional circumstances, for example where a product has a long history of good results and a justified reason exists; data are collected on actual production batches.
- **Retrospective validation:** based on review of historical production and testing data for a product already on the market. It is acceptable only where processes are well established and rich data exist, and its use is now limited.
- **Revalidation:** repetition of validation after a significant change (equipment, material source, process parameter, site) or periodically, to confirm the process remains in the validated state.

Alongside these, cleaning validation, analytical method validation and equipment qualification follow their own protocols but share the same logic: define, test against criteria, document.

2.6 Validation of specific dosage forms

The same framework is specialised for each dosage form, because the critical parameters differ:

- **Tablets:** validation of blending (blend uniformity), granulation end point, drying (moisture), compression (weight, hardness, friability across the run) and coating.
- **Capsules:** blend uniformity, fill weight control, moisture of shells.
- **Liquid orals and suspensions:** mixing time and order, homogeneity of sampling, preservative effectiveness and fill volume.
- **Sterile products:** sterilisation cycle validation (heat distribution and penetration, biological indicators), aseptic process simulation by media fill, container closure integrity and environmental monitoring.

In each case the protocol names the critical process parameters, the sampling plan, the tests and the acceptance criteria before a single batch is run; the report compares the results with the criteria and

concludes whether the process is validated.

2.7 Government regulation and the manufacturing process model

Validation is a legal expectation, not a company preference. In India, the Drugs and Cosmetics Act and Rules, with Schedule M, require validated processes and equipment; the US FDA states the requirement in 21 CFR Parts 210 and 211 and in its process validation guidance, which organises validation as a lifecycle of process design, process qualification and continued process verification; the EU GMP Annex 15 does the same in Europe. Exporting companies must satisfy the strictest market they supply.

The manufacturing process model used in protocols shows the process as a chain: inputs (materials, equipment, utilities, trained people, environment) enter defined process steps with controlled parameters, and produce outputs (intermediate and finished product) that are measured against specifications. Validation studies the chain step by step: it identifies which parameters are critical to quality, sets their proven acceptable ranges, and shows by evidence that holding the parameters inside those ranges always gives an acceptable output.

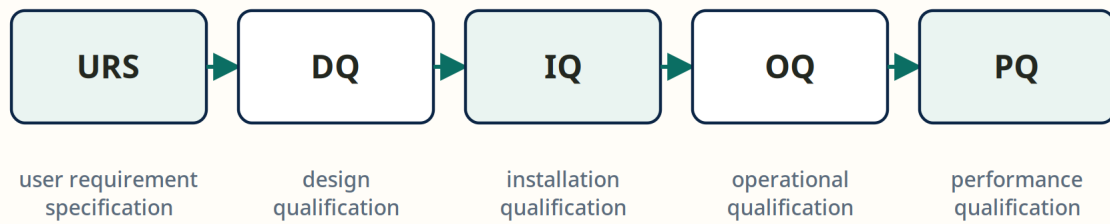
2.8 Qualification of facilities: URS, DQ, IQ, OQ, PQ

New facilities and equipment pass through a documented qualification sequence before validation of products begins:

- **User requirement specification (URS):** the user department writes what the equipment or facility must do: capacity, performance, materials of construction, utilities, regulatory and documentation requirements. The URS is the contract against which everything else is checked.
- **Design qualification (DQ):** documented verification that the proposed design meets the URS and GMP requirements, done before purchase or construction is finalised.
- **Installation qualification (IQ):** checking and recording that the delivered equipment is installed as designed and as the manufacturer specifies: identity, components, utilities connected, manuals and drawings received, calibration of instruments started.
- **Operational qualification (OQ):** testing that the equipment operates within its specified ranges across its working limits, for example an oven holding temperature uniformly at its set points, or a press running at its speed range.
- **Performance qualification (PQ):** showing the equipment, in the real process with real materials, consistently produces the required result, for example consecutive batches meeting all specifications.

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Qualification sequence for facilities and equipment
User requirement specification (URS)
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    v
Design qualification (DQ): design checked against URS and GMP
    |
    v
Installation qualification (IQ): installed as specified
    |
    v
Operational qualification (OQ): works across its operating ranges
    |
    v
Performance qualification (PQ): performs in the real process
    |
    v
Equipment released for process validation and routine use
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Qualification Sequence: URS to PQ



Each stage is documented and approved before the next begins

Figure: The qualification sequence for facilities and equipment: URS, DQ, IQ, OQ and PQ, each documented and approved before the next begins.