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Annex 4

Supplementary guidelines on good manufacturing practices: validation

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1. Introduction

Validation is an essential part of good manufacturing practices (GMP). It is, therefore, an element of the quality assurance programme associated with a particular product or process. The basic principles of quality assurance have as their goal the production of products that are fit for their intended use. These principles are as follows:

- Quality, safety and efficacy must be designed and built into the product.
- Quality cannot be inspected or tested into the product.
- Each critical step of the manufacturing process must be validated. Other steps in the process must be under control to maximize the probability that the finished product consistently and predictably meets all quality and design specifications.

Validation of processes and systems is fundamental to achieving these goals. It is by design and validation that a manufacturer can establish confidence that the manufactured products will consistently meet their product specifications.

Documentation associated with validation includes:

— standard operating procedures (SOPs)
— specifications
— validation master plan (VMP)
— qualification protocols and reports
— validation protocols and reports.

The implementation of validation work requires considerable resources such as:

- *Time:* generally validation work is subject to rigorous time schedules.
- *Financial:* validation often requires the time of specialized personnel and expensive technology.
- *Human:* validation requires the collaboration of experts from various disciplines (e.g. a multidisciplinary team, comprising quality assurance, engineering, manufacturing and other disciplines, depending on the product and process to be validated).

These guidelines aim to give guidance to inspectors of pharmaceutical manufacturing facilities and manufacturers of pharmaceutical products on the requirements for validation. The main part covers the general principles of validation and qualification. In addition to the main part, appendices on validation and qualification (e.g. cleaning, computer and computerized systems, equipment, utilities and systems, and analytical methods) are included.

2. Scope

2.1 These guidelines focus mainly on the overall concept of validation and are intended as a basic guide for use by GMP inspectors and manufac-

turers. It is not the intention to be prescriptive in specific validation requirements. This document serves as general guidance only, and the principles may be considered useful in its application in the manufacture and control of active pharmaceutical ingredients (APIs) and finished pharmaceutical products. Validation of specific processes and products, for example in sterile product manufacture, requires much more consideration and a detailed approach that is beyond the scope of this document.

2.2 There are many factors affecting the different types of validation and it is, therefore, not intended to define and address all aspects related to one particular type of validation here.

2.3 Manufacturers should plan validation in a manner that will ensure regulatory compliance and ensuring that product quality, safety and consistency are not compromised.

2.4 The general text in the main part of these guidelines may be applicable to validation and qualification of premises, equipment, utilities and systems, and processes and procedures. More specific principles of qualification and validation are addressed in the appendices. Semi-automatic or fully automatic clean-in-place (CIP) systems and other special cases should be treated separately.

3. Glossary

The definitions given below apply to the terms used in these guidelines. They may have different meanings in other contexts.

calibration

The set of operations that establish, under specified conditions, the relationship between values indicated by an instrument or system for measuring (for example, weight, temperature and pH), recording, and controlling, or the values represented by a material measure, and the corresponding known values of a reference standard. Limits for acceptance of the results of measuring should be established.

computer validation

Documented evidence which provides a high degree of assurance that a computerized system analyses, controls and records data correctly and that data processing complies with predetermined specifications.

commissioning

The setting up, adjustment and testing of equipment or a system to ensure that it meets all the requirements, as specified in the user requirement specification, and capacities as specified by the designer or developer. Commissioning is carried out before qualification and validation.

concurrent validation

Validation carried out during routine production of products intended for sale.

cleaning validation

Documented evidence to establish that cleaning procedures are removing residues to predetermined levels of acceptability, taking into consideration factors such as batch size, dosing, toxicology and equipment size.

design qualification (DQ)

Documented evidence that the premises, supporting systems, utilities, equipment and processes have been designed in accordance with the requirements of GMP.

good engineering practices (GEP)

Established engineering methods and standards that are applied throughout the project life-cycle to deliver appropriate, cost-effective solutions.

installation qualification (IQ)

The performance of tests to ensure that the installations (such as machines, measuring devices, utilities and manufacturing areas) used in a manufacturing process are appropriately selected and correctly installed and operate in accordance with established specifications.

operational qualification (OQ)

Documented verification that the system or subsystem performs as intended over all anticipated operating ranges.

performance qualification (PQ)

Documented verification that the equipment or system operates consistently and gives reproducibility within defined specifications and parameters for prolonged periods. (In the context of systems, the term "process validation" may also be used.)

process validation

Documented evidence which provides a high degree of assurance that a specific process will consistently result in a product that meets its predetermined specifications and quality characteristics.

prospective validation

Validation carried out during the development stage on the basis of a risk analysis of the production process, which is broken down into individual steps; these are then evaluated on the basis of past experience to determine whether they may lead to critical situations.

qualification

Action of proving and documenting that any premises, systems and equipment are properly installed, and/or work correctly and lead to the expected results. Qualification is often a part (the initial stage) of validation, but the individual qualification steps alone do not constitute process validation.

retrospective validation

Involves the evaluation of past experience of production on the condition that composition, procedures, and equipment remain unchanged.

revalidation

Repeated validation of an approved process (or a part thereof) to ensure continued compliance with established requirements.

standard operating procedure (SOP)

An authorized written procedure giving instructions for performing operations not necessarily specific to a given product or material but of a more general nature (e.g. equipment operation, maintenance and cleaning; validation; cleaning of premises and environmental control; sampling and inspection). Certain SOPs may be used to supplement product-specific master batch production documentation.

validation

Action of proving and documenting that any process, procedure or method actually and consistently leads to the expected results.

validation protocol (or plan) (VP)

A document describing the activities to be performed in a validation, including the acceptance criteria for the approval of a manufacturing process — or a part thereof — for routine use.

validation report (VR)

A document in which the records, results and evaluation of a completed validation programme are assembled and summarized. It may also contain proposals for the improvement of processes and/or equipment.

validation master plan (VMP)

The VMP is a high-level document that establishes an umbrella validation plan for the entire project and summarizes the manufacturer's overall philosophy and approach, to be used for establishing performance adequacy. It provides information on the manufacturer's validation work programme and defines details of and timescales for the validation work to be performed, including a statement of the responsibilities of those implementing the plan.

verification

The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with the GMP principles.

worst case

A condition or set of conditions encompassing the upper and lower processing limits for operating parameters and circumstances, within SOPs, which pose the greatest chance of product or process failure when compared to ideal conditions. Such conditions do not necessarily include product or process failure.

4. Relationship between validation and qualification

Validation and qualification are essentially components of the same concept. The term qualification is normally used for equipment, utilities and systems, and validation for processes. In this sense, qualification is part of validation.

5. Validation

5.1 Approaches to validation

5.1.1 There are two basic approaches to validation — one based on evidence obtained through testing (prospective and concurrent validation), and one based on the analysis of accumulated (historical) data (retrospective validation). Whenever possible, prospective validation is preferred. Retrospective validation is no longer encouraged and is, in any case, not applicable to the manufacturing of sterile products.

5.1.2 Both prospective and concurrent validation, may include:

- extensive product testing, which may involve extensive sample testing (with the estimation of confidence limits for individual results) and the demonstration of intra- and inter-batch homogeneity;
- simulation process trials;
- challenge/worst case tests, which determine the robustness of the process; and
- control of process parameters being monitored during normal production runs to obtain additional information on the reliability of the process.

5.2 Scope of validation

5.2.1 There should be an appropriate and sufficient system including organizational structure and documentation infrastructure, sufficient personnel and financial resources to perform validation tasks in a timely manner. Management and persons responsible for quality assurance should be involved.

5.2.2 Personnel with appropriate qualifications and experience should be responsible for performing validation. They should represent different departments depending on the validation work to be performed.

5.2.3 There should be proper preparation and planning before validation is performed. There should be a specific programme for validation activities.

5.2.4 Validation should be performed in a structured way according to the documented procedures and protocols.

5.2.5 Validation should be performed:

— for new premises, equipment, utilities and systems, and processes and procedures;
— at periodic intervals; and
— when major changes have been made.

(Periodic revalidation or periodic requalification may be substituted, where appropriate, with periodic evaluation of data and information to establish whether requalification or revalidation is required.)

5.2.6 Validation should be performed in accordance with written protocols. A written report on the outcome of the validation should be produced.

5.2.7 Validation should be done over a period of time, e.g. at least three consecutive batches (full production scale) should be validated, to demonstrate consistency. Worst case situations should be considered.

5.2.8 There should be a clear distinction between in-process controls and validation. In-process tests are performed during the manufacture of each batch according to specifications and methods devised during the development phase. Their objective is to monitor the process continuously.

5.2.9 When a new manufacturing formula or method is adopted, steps should be taken to demonstrate its suitability for routine processing. The defined process, using the materials and equipment specified, should be shown to result in the consistent yield of a product of the required quality.

5.2.10 Manufacturers should identify what validation work is needed to prove that critical aspects of their operations are appropriately controlled. Significant changes to the facilities or the equipment, and processes that may affect the quality of the product should be validated. A risk assessment approach should be used to determine the scope and extent of validation required.

6. Qualification

6.1 Qualification should be completed before process validation is performed. The process of qualification should be a logical, systematic process and should start from the design phase of the premises, equipment, utilities and equipment.

6.2 Depending on the function and operation of the equipment, utility or system, only installation qualification (IQ) and operational qualification (OQ) may be required, as the correct operation of the equipment, utility or system could be considered to be a sufficient indicator of its performance (refer to Section 11 for IQ, OQ and performance qualification (PQ)). (The equipment, utility and system should then be maintained, monitored and calibrated according to a regular schedule.)

6.3 Major equipment and critical utilities and systems, however, require IQ, OQ and PQ.

7. Calibration and verification

7.1 Calibration and verification of equipment, instruments and other devices, as applicable, used in production and quality control, should be performed at regular intervals.

7.2 Personnel who carry out calibration and preventive maintenance should have appropriate qualifications and training.

7.3 A calibration programme should be available and should provide information such as calibration standards and limits, responsible persons, calibration intervals, records and actions to be taken when problems are identified.

7.4 There should be traceability to standards (e.g. national, regional or international standards) used in the calibration.

7.5 Calibrated equipment, instruments and other devices should be labelled, coded or otherwise identified to indicate the status of calibration and the date on which recalibration is due.

7.6 When the equipment, instruments and other devices have not been used for a certain period of time, their function and calibration status should be verified and shown to be satisfactory before use.

8. Validation master plan

The validation master plan (VMP) should reflect the key elements of the validation programme. It should be concise and clear and contain at least the following:

— a validation policy
— organizational structure of validation activities
— summary of facilities, systems, equipment and processes validated and to be validated
— documentation format (e.g. protocol and report format)
— planning and scheduling

— change control
— references to existing documents.

9. Qualification and validation protocols

9.1 There should be qualification and validation protocols describing the qualification and validation study to be performed.

9.2 As a minimum the protocols should include the following significant background information:

— the objectives of the study
— the site of the study
— the responsible personnel
— description of SOPs to be followed
— equipment to be used; standards and criteria for the relevant products and processes
— the type of validation
— the processes and/or parameters
— sampling, testing and monitoring requirements
— predetermined acceptance criteria for drawing conclusions.

9.3 There should be a description of the way in which the results will be analysed.

9.4 The protocol should be approved prior to use. Any changes to a protocol should be approved prior to implementation of the change.

10. Qualification and validation reports

10.1 There should be written reports on the qualification and validation performed.

10.2 Reports should reflect the protocols followed and include at least the title and objective of the study; reference to the protocol; details of material, equipment, programmes and cycles used; procedures and test methods.

10.3 The results should be evaluated, analysed and compared against the pre-determined acceptance criteria. The results should meet the acceptance criteria; deviations and out-of-limit results should be investigated. If these deviations are accepted, this should be justified. Where necessary further studies should be performed.

10.4 The departments responsible for the qualification and validation work should approve the completed report.

10.5 The conclusion of the report should state whether or not the outcome of the qualification and/or validation was considered successful.

10.6 The quality assurance department should approve the report after the final review. The criteria for approval should be in accordance with the company's quality assurance system.

10.7 Any deviations found during the validation process should be acted upon and documented as such. Corrective actions may be required.

11. Qualification stages

11.1 There are four stages of qualification:

— design qualification (DQ);
— installation qualification (IQ);
— operational qualification (OQ); and
— performance qualification (PQ).

11.2 All SOPs for operation, maintenance and calibration should be prepared during qualification.

11.3. Training should be provided to operators and training records should be maintained.

Design qualification

11.4 Design qualification should provide documented evidence that the design specifications were met.

Installation qualification

11.5 Installation qualification should provide documented evidence that the installation was complete and satisfactory.

11.6 The purchase specifications, drawings, manuals, spare parts lists and vendor details should be verified during installation qualification.

11.7 Control and measuring devices should be calibrated.

Operational qualification

11.8 Operational qualification should provide documented evidence that utilities, systems or equipment and all its components operate in accordance with operational specifications.

11.9 Tests should be designed to demonstrate satisfactory operation over the normal operating range as well as at the limits of its operating conditions (including worst case conditions).

11.10 Operation controls, alarms, switches, displays and other operational components should be tested.

11.11 Measurements made in accordance with a statistical approach should be fully described.

Performance qualification

11.12 Performance qualification should provide documented evidence that utilities, systems or equipment and all its components can consistently perform in accordance with the specifications under routine use.

11.13 Test results should be collected over a suitable period of time to prove consistency.

Requalification

11.14 Requalification should be done in accordance with a defined schedule. The frequency of requalification may be determined on the basis of factors such as the analysis of results relating to calibration, verification and maintenance.

11.15 There should be periodic requalification, as well as requalification after changes (such as changes to utilities, systems, equipment; maintenance work; and movement). (See also point 5.2.5 above and section 12 below.)

11.16 Requalification should be considered as part of the change control procedure.

Revalidation

11.17 Processes and procedures should be revalidated to ensure that they remain capable of achieving the intended results.

11.18 There should be periodic revalidation, as well as revalidation after changes. (See also points 5.2.5 above, point 11.21 below and section 12 below.)

11.19 Revalidation should be done in accordance with a defined schedule.

11.20 The frequency and extent of revalidation should be determined using a risk-based approach together with a review of historical data.

Periodic revalidation

11.21 Periodic revalidation should be performed to assess process changes that may occur gradually over a period of time, or because of wear of equipment.

11.22 The following should be considered when periodic revalidation is performed:

— master formulae and specifications;
— SOPs;
— records (e.g. of calibration, maintenance and cleaning); and
— analytical methods.

Revalidation after change

11.23 Revalidation should be performed following a change that could have an effect on the process, procedure, quality of the product and/or the product characteristics. Revalidation should be considered as part of the change control procedure.

11.24 The extent of revalidation will depend on the nature and significance of the change(s).

11.25 Changes should not adversely affect product quality or process characteristics.

11.26 Changes requiring revalidation should be defined in the validation plan and may include:

- changes in starting materials (including physical properties, such as density, viscosity or particle size distribution that may affect the process or product);
- change of starting material manufacturer;
- transfer of processes to a different site (including change of facilities and installations which influence the process);
- changes of primary packaging material (e.g. substituting plastic for glass);
- changes in the manufacturing process (e.g. mixing times or drying temperatures);
- changes in the equipment (e.g. addition of automatic detection systems, installation of new equipment, major revisions to machinery or apparatus and breakdowns);
- production area and support system changes (e.g. rearrangement of areas, or a new water treatment method);
- appearance of negative quality trends;
- appearance of new findings based on current knowledge, e.g. new technology;
- support system changes.

Changes of equipment which involve the replacement of equipment on a "like-for-like" basis would not normally require a revalidation. For example, installation of a new centrifugal pump to replace an older model would not necessarily require revalidation.

12. Change control

12.1 Changes should be controlled in accordance with a SOP as changes may have an impact on a qualified utility, system or piece of equipment, and a validated process and/or procedure.

12.2 The procedure should describe the actions to be taken, including the need for and extent of qualification or validation to be done.

12.3 Changes should be formally requested, documented and approved before implementation. Records should be maintained.

13. Personnel

13.1 Personnel should demonstrate that they are appropriately qualified, where relevant.

13.2 Personnel requiring qualification include, for example:

— laboratory analysts;
— personnel following critical procedures;
— personnel doing data entry in computerized systems; and
— risk assessors.

Appendix 1

Validation of heating, ventilation and air-conditioning systems

1. General
2. Commissioning
3. Qualification
4. Reference

1. General

1.1 The heating, ventilation and air-conditioning (HVAC) system plays an important role in the protection of the product, the personnel and the environment.

1.2 For all HVAC installation components, subsystems or parameters, critical parameters and non-critical parameters should be determined.

1.3 Some of the parameters of a typical HVAC system that should be qualified include:

— room temperature and humidity;
— supply air and return air quantities;
— room pressure, air change rate, flow patterns, particle count and clean-up rates; and
— unidirectional flow velocities and HEPA filter penetration tests.

2. Commissioning

2.1 Commissioning should involve the setting up, balancing, adjustment and testing of the entire HVAC system, to ensure that the system meets all the requirements, as specified in the user requirement specification, and capacities as specified by the designer or developer.

2.2 The installation records of the system should provide documented evidence of all measured capacities of the system.

2.3 The data should include items such as the design and measured figures for airflows, water flows, system pressures and electrical amperages. These should be contained in the operating and maintenance manuals (O & M manuals).

2.4 Acceptable tolerances for all system parameters should be specified prior to commencing the physical installation.

2.5 Training should be provided to personnel after installation of the system, and should include how to perform operation and maintenance.

2.6 O & M manuals, schematic drawings, protocols and reports should be maintained as reference documents for any future changes and upgrades to the system.

2.7 Commissioning should be a precursor to system qualification and validation.

3. Qualification

3.1 Manufacturers should qualify HVAC systems using a risk-based approach. The basic concepts of qualification of HVAC systems are set out in Fig. 1 below.

3.2 The qualification of the HVAC system should be described in a validation master plan (VMP).

3.3 The validation master plan should define the nature and extent of testing and the test procedures and protocols to be followed.

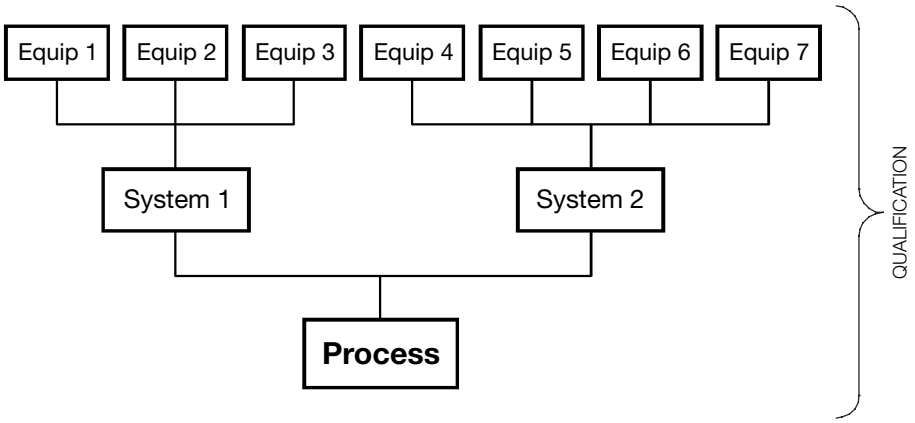
3.4 Stages of the qualification of the HVAC system should include design qualification (DQ), installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ).

3.5 Critical and non-critical parameters for all HVAC installation components, subsystems and controls should be determined by means of a risk analysis.

3.6 Any parameter that may affect the quality of the pharmaceutical product should be considered a critical parameter.

3.7 All critical parameters should be included in the qualification process.

Figure 1
Qualification is a part of validation



Note: A realistic approach to differentiating between critical and non-critical parameters is required, to avoid making the validation process unnecessarily complex.

Example:

- *The humidity of the room where the product is exposed should be considered a critical parameter when a humidity-sensitive product is being manufactured. The humidity sensors and the humidity monitoring system should, therefore, be qualified. The heat transfer system, chemical drier or steam humidifier, which is producing the humidity-controlled air, is further removed from the product and may not require operational qualification.*
- *A room cleanliness classification is a critical parameter and, therefore, the room air-change rates and high-efficiency particulate air (HEPA) filters should be critical parameters and require qualification. Items such as the fan generating the airflow and the primary and secondary filters are non-critical parameters, and may not require operational qualification.*

3.8 Non-critical systems and components should be subject to good engineering practice (GEP) and may not necessarily require full qualification.

3.9 A change control procedure should be followed when changes are planned to the HVAC system, its components, and controls, that may affect critical parameters.

3.10 Acceptance criteria and limits should be defined during the design stage.

3.11 The manufacturer should define design conditions, normal operating ranges, operating ranges, and alert and action limits.

3.12 Design condition and normal operating ranges should be identified and set to realistically achievable parameters.

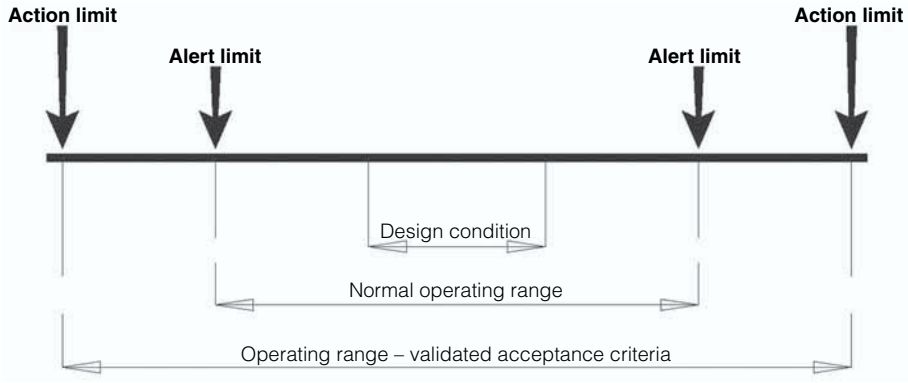
3.13 All parameters should fall within the design condition range during system operational qualification. Conditions may go out of the design condition range during normal operating procedures but they should remain within the operating range.

3.14 Out-of-limit results (e.g. action limit deviations) should be recorded and form part of the batch manufacturing records.

3.15 The relationships between design conditions, operating range and qualified acceptance criteria are given in Figure 2.

3.16 A narrow range of relative humidities coupled with a wide range of temperatures is unacceptable as changes in temperature will automatically give rise to variations in the relative humidity.

Figure 2
System operating ranges



3.17 Some of the typical HVAC system parameters that should be qualified for a pharmaceutical facility may include:

— temperature
— relative humidity
— supply air quantities for all diffusers
— return air or exhaust air quantities
— room air-change rates
— room pressures (pressure differentials)
— room airflow patterns
— unidirectional flow velocities
— containment system velocities
— HEPA filter penetration tests
— room particle counts
— room clean-up rates
— microbiological air and surface counts where appropriate
— operation of de-dusting
— warning/alarm systems where applicable.

3.18 The maximum time interval between tests should be defined by the manufacturer. The type of facility under test and the product level of protection should be considered.
Note: Table 1 gives intervals for reference purposes only. The actual test periods may be more or less frequent, depending on the product and process.

3.19 Periodic requalification of parameters should be done at regular intervals, e.g. annually.

3.20 Requalification should also be done when any change, which could affect system performance, takes place.

3.21 Clean-up times normally relate to the time it takes to "clean up" the room from one condition to another, e.g. the relationship between "at-rest"

Table 1.
Strategic tests (for reference purposes only)

Schedule of tests to demonstrate continuing compliance			
Test parameter	Clean area class	Max. time interval	Test procedure
Particle count test (verification of cleanliness)	All classes	6 months	Dust particle counts to be carried out and printouts of results produced. No. of readings and positions of tests to be in accordance with ISO 14644-1 Annex B
Air pressure difference (To verify absence of cross-contamination)	All classes	12 months	Log of pressure differential readings to be produced or critical plants should be logged daily, preferably continuously. A 15 Pa pressure differential between different zones is recommended. In accordance with ISO 14644-3 Annex B5
Airflow volume (To verify air change rates)	All classes	12 months	Airflow readings for supply air and return air grilles to be measured and air change rates to be calculated. In accordance with ISO 14644-3 Annex B13
Airflow velocity (To verify unidirectional flow or containment conditions)	All classes	12 months	Air velocities for containment systems and unidirectional flow protection systems to be measured. In accordance with ISO 14644-3 Annex B4

Source: ISO 14644 Standard, given for reference purposes only.

and "operational" conditions in the clean area may be used as the criteria for clean-up tests. Therefore, the clean-up time can be expressed as the time taken to change from an "operational" condition to an "at-rest" condition.

4. Reference

1. Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report.* Geneva, World Health Organization, 2006 (WHO Technical Report Series, No. 937), Annex 2.

Appendix 2

Validation of water systems for pharmaceutical use

1. General
2. Start-up and commissioning of water systems
3. Qualification
4. Reference

1. General

1.1 All water-treatment systems should be subject to planned maintenance, validation and monitoring.

1.2 Validation of water systems should consist of at least three phases: Phase 1: investigational phase; Phase 2: short-term control; and Phase 3: long-term control.

1.3 During the period following phase 3 (typically running for one year) the objective should be to demonstrate that the system is under control over a long period of time. Sampling may be reduced from, e.g. daily to weekly.

1.4 The validation performed and revalidation requirements should be included in the "Water quality manual".

2. Start-up and commissioning of water systems

2.1 Planned, well-defined, successful and well-documented commissioning is an essential precursor to successful validation of water systems. The commissioning work should include setting to work, system set-up, controls, loop tuning and recording of all system performance parameters. If it is intended to use or refer to commissioning data within the validation work then the quality of the commissioning work and associated data and documentation must be commensurate with the validation plan requirements.

3. Qualification

3.1 Water for pharmaceutical use (WPU), purified water (PW), highly purified water (HPW) and water for injections (WFI) systems are all considered to be direct impact, quality critical systems that should be qualified. The qualification should follow the validation convention of design review or design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

3.2 This guidance does not define the standard requirements for the conventional validation stages DQ, IQ and OQ, but concentrates on the particular PQ approach that should be used for WPU systems to demonstrate

their consistent and reliable performance. A three-phase approach should be used to satisfy the objective of proving the reliability and robustness of the system in service over an extended period.

Phase 1. A test period of 2–4 weeks should be spent monitoring the system intensively. During this period the system should operate continuously without failure or performance deviation. The following procedures should be included in the testing approach.

- Undertake chemical and microbiological testing in accordance with a defined plan.
- Sample the incoming feed-water to verify its quality.
- Sample after each step in the purification process daily.
- Sample at each point of use and at other defined sampling points daily.
- Develop appropriate operating ranges.
- Develop and finalize operating, cleaning, sanitizing and maintenance procedures.
- Demonstrate production and delivery of product water of the required quality and quantity.
- Use and refine the standard operating procedures (SOPs) for operation, maintenance, sanitization and troubleshooting.
- Verify provisional alert and action levels.
- Develop and refine the test-failure procedure.

Phase 2. A further test period of 2–4 weeks should be spent carrying out further intensive monitoring while deploying all the refined SOPs after the satisfactory completion of phase 1. The sampling scheme should be generally the same as in phase 1. Water can be used for manufacturing purposes during this phase. The approach should also:

— demonstrate consistent operation within established ranges; and
— demonstrate consistent production and delivery of water of the required quantity and quality when the system is operated in accordance with the SOPs.

Phase 3. Phase 3 typically runs for one year after the satisfactory completion of phase 2. Water can be used for manufacturing purposes during this phase which has the following objectives and features:

- Demonstrate extended reliable performance.
- Ensure that seasonal variations are evaluated.
- The sample locations, sampling frequencies and tests should be reduced to the normal routine pattern based on established procedures proven during phases 1 and 2.

Reference

1. *WHO good manufacturing practices: water for pharmaceutical use.* Geneva, World Health Organization 2005 (WHO Technical Report Series, No. 929), Annex 3.

Appendix 3

Cleaning validation

1. Principle
2. Scope
3. General
4. Cleaning validation protocols and reports
   - 4.1 Cleaning validation protocols
   - 4.2 Cleaning validation reports
5. Personnel
6. Equipment
7. Detergents
8. Microbiology
9. Sampling
   - 9.1 General
   - 9.2 Direct surface sampling (direct method)
   - 9.3 Rinse samples (indirect method)
   - 9.4 Batch placebo method
10. Analytical methods
11. Establishing acceptable limits

1. Principle

1.1 The objectives of good manufacturing practices (GMP) include the prevention of possible contamination and cross-contamination of pharmaceutical starting materials and products.

1.2 Pharmaceutical products can be contaminated by a variety of substances such as contaminants associated with microbes, previous products (both active pharmaceutical ingredients (API) and excipient residues), residues of cleaning agents, airborne materials, such as dust and particulate matter, lubricants and ancillary material, such as disinfectants, and decomposition residues from:

— product residue breakdown occasioned by, e.g. the use of strong acids and alkalis during the cleaning process; and
— breakdown products of the detergents, acids and alkalis that may be used as part of the cleaning process.

1.3 Adequate cleaning procedures play an important role in preventing contamination and cross-contamination. Validation of cleaning methods provides documented evidence that an approved cleaning procedure will provide clean equipment, suitable for its intended use.

1.4 The objective of cleaning validation is to prove that the equipment is consistently cleaned of product, detergent and microbial residues to an acceptable level, to prevent possible contamination and cross-contamination.

1.5 Cleaning validation is not necessarily required for non-critical cleaning such as that which takes place between batches of the same product (or different lots of the same intermediate in a bulk process), or of floors, walls, the outside of vessels, and following some intermediate steps.

1.6 Cleaning validation should be considered important in multiproduct facilities and should be performed among others, for equipment, sanitization procedures and garment laundering.

2. Scope

2.1 These guidelines describe the general aspects of cleaning validation, excluding specialized cleaning or inactivation that may be required, e.g. for removal of viral or mycoplasmal contaminants in the biological manufacturing industry.

2.2 Normally cleaning validation would be applicable for critical cleaning such as cleaning between manufacturing of one product and another, of surfaces that come into contact with products, drug products and API.

3. General

3.1 There should be written SOPs detailing the cleaning process for equipment and apparatus. The cleaning procedures should be validated.

3.2 The manufacturer should have a cleaning policy and an appropriate procedure for cleaning validation, covering:

- surfaces that come into contact with the product;
- cleaning after product changeover (when one pharmaceutical formulation is being changed for another, completely different formulation);
- between batches in campaigns (when the same formula is being manufactured over a period of time, and on different days);
- bracketing products for cleaning validation. (This often arises where products contain substances with similar properties (such as solubility) or the same substance in different strengths. An acceptable strategy is to first manufacture the more dilute form (not necessarily the lowest dose) and then the most concentrated form. There are sometimes "families" of products which differ slightly as to actives or excipients.); and
- periodic evaluation and revalidation of the number of batches manufactured between cleaning validations.

3.3. At least three consecutive applications of the cleaning procedure should be performed and shown to be successful to prove that the method is validated.

4. Cleaning validation protocols and reports

4.1 Cleaning validation protocols

4.1.1 Cleaning validation should be described in cleaning validation protocols, which should be formally approved, e.g. by the quality control or quality assurance unit.

4.1.2 In preparing the cleaning validation protocol, the following should be considered:

— disassembly of system;
— precleaning;
— cleaning agent, concentration, solution volume, water quality;
— time and temperature;
— flow rate, pressure and rinsing;
— complexity and design of the equipment;
— training of operators; and
— size of the system.

4.1.3 The cleaning validation protocol should include:

- the objectives of the validation process;
- the people responsible for performing and approving the validation study;
- the description of the equipment to be used, including a list of the equipment, make, model, serial number or other unique code;
- the interval between the end of production and the commencement of the cleaning procedure (interval may be part of the validation challenge study itself)
  — the maximum period that equipment may be left dirty before being cleaned as well as the establishment of the time that should elapse after cleaning and before use;
- the levels of microorganisms (bioburden);
- the cleaning procedures (documented in an existing SOP, including definition of any automated process) to be used for each product, each manufacturing system or each piece of equipment;
- all the equipment used for routine monitoring, e.g. conductivity meters, pH meters and total organic carbon analysers;
- the number of cleaning cycles to be performed consecutively;
- the sampling procedures to be used (direct sampling, rinse sampling, in-process monitoring and sampling locations) and the rationale for their use;
- the data on recovery studies (efficiency of the recovery of the sampling technique should be established);
- the analytical methods (specificity and sensitivity) including the limit of detection and the limit of quantification;
- the acceptance criteria (with rationale for setting the specific limits) including a margin for error and for sampling efficiency;

- the choice of the cleaning agent should be documented and approved by the quality unit and should be scientifically justified on the basis of, e.g.
  - — the solubility of the materials to be removed;
  - — the design and construction of the equipment and surface materials to be cleaned;
  - — the safety of the cleaning agent;
  - — the ease of removal and detection;
  - — the product attributes;
  - — the minimum temperature and volume of cleaning agent and rinse solution; and
  - — the manufacturer's recommendations;
- revalidation requirements.

4.1.4 Cleaning procedures for products and processes which are very similar do not need to be individually validated. A validation study of the "worst case" may be considered acceptable. There should be a justified validation programme for this approach referred to as "bracketing", addressing critical issues relating to the selected product, equipment or process.

4.1.5 Where "bracketing" of products is done, consideration should be given to type of products and equipment.

4.1.6 Bracketing by product should be done only when the products concerned are similar in nature or property and will be processed using the same equipment. Identical cleaning procedures should then be used for these products.

4.1.7 When a representative product is chosen, this should be the one that is most difficult to clean.

4.1.8 Bracketing by equipment should be done only when it is similar equipment, or the same equipment in different sizes (e.g. 300-l, 500-l and 1000-l tanks). An alternative approach may be to validate the smallest and the largest sizes separately.

4.2 Cleaning validation reports

4.2.1 The relevant cleaning records (signed by the operator, checked by production and reviewed by quality assurance) and source data (original results) should be kept. The results of the cleaning validation should be presented in cleaning validation reports stating the outcome and conclusion.

5. Personnel

5.1 Personnel or operators who perform cleaning routinely should be trained and should be effectively supervised.

6. Equipment

6.1 Normally only procedures for the cleaning of surfaces of the equipment that come into contact with the product need to be validated. Consideration should be given to "non-contact" parts of the equipment into which product or any process material may migrate. Critical areas should be identified (independently from method of cleaning), particularly in large systems employing semi-automatic or fully automatic clean-in-place systems.

6.2 Dedicated equipment should be used for products which are difficult to clean, equipment which is difficult to clean, or for products with a high safety risk where it is not possible to achieve the required cleaning acceptance limits using a validated cleaning procedure.

6.3 Ideally, there should be one process for cleaning a piece of equipment or system. This will depend on the products being produced, whether the cleaning occurs between batches of the same product (as in a large campaign) or whether the cleaning occurs between batches of different products.

6.4 The design of equipment may influence the effectiveness of the cleaning process. Consideration should therefore be given to the design of the equipment when preparing the cleaning validation protocol, e.g. V-blenders, transfer pumps or filling lines.

7. Detergents

7.1 Detergents should facilitate the cleaning process and be easily removable. Detergents that have persistent residues such as cationic detergents which adhere very strongly to glass and are difficult to remove, should be avoided where possible.

7.2 The composition of the detergent should be known to the manufacturer and its removal during rinsing, demonstrated.

7.3 Acceptable limits for detergent residues after cleaning should be defined. The possibility of detergent breakdown should also be considered when validating cleaning procedures.

7.4 Detergents should be released by quality control and, where possible, should meet local food standards or regulations.

8. Microbiology

8.1 The need to include measures to prevent microbial growth and remove contamination where it has occurred should be considered.

8.2 There should be documented evidence to indicate that routine cleaning and storage of equipment does not allow microbial proliferation.

8.3 The period and conditions for storage of unclean equipment before cleaning, and the time between cleaning and equipment reuse, should form part of the validation of cleaning procedures.

8.4 Equipment should be stored in a dry condition after cleaning. Stagnant water should not be allowed to remain in equipment after cleaning.

8.5 Control of the bioburden through adequate cleaning and appropriate storage of equipment is important to ensure that subsequent sterilization or sanitization procedures achieve the necessary assurance of sterility, and the control of pyrogens in sterile processing. Equipment sterilization processes may not be adequate to achieve significant inactivation or removal of pyrogens.

9. Sampling

9.1 General

9.1.1 Equipment should normally be cleaned as soon as possible after use. This may be especially important for operations with topical products, suspensions and bulk drug or where the drying of residues will directly affect the efficiency of a cleaning procedure.

9.1.2 Two methods of sampling are considered to be acceptable. These are direct surface sampling and rinse samples. A combination of the two methods is generally the most desirable.

9.1.3 The practice of resampling should not be used before or during cleaning and operations and is acceptable only in rare cases. Constant retesting and resampling can show that the cleaning process is not validated because these retests actually document the presence of unacceptable residue and contaminants resulting from an ineffective cleaning process.

9.2 Direct surface sampling (direct method)

Note: This method of sampling is the most commonly used and involves taking an inert material (e.g. cotton wool) on the end of a probe (referred to as a "swab") and rubbing it methodically across a surface. The type of sampling material used and its potential impact on the test data is important as the sampling material may interfere with the test. (For example, the adhesive used in swabs has been found to interfere with the analysis of samples.)

9.2.1 Factors that should be considered include the supplier of the swab, area swabbed, number of swabs used, whether they are wet or dry swabs, swab handling and swabbing technique.

9.2.2 The location from which the sample is taken should take into consideration the composition of the equipment (e.g. glass or steel) and the

location (e.g. blades, tank walls or fittings). Worst case locations should be considered. The protocol should identify the sampling locations.

9.2.3 Critical areas, i.e. those hardest to clean, should be identified, particularly in large systems that employ semi-automatic or fully automatic clean-in-place systems.

9.2.4 The sampling medium and solvent used should be appropriate to the task.

9.3 Rinse samples (indirect method)

Note: This method allows sampling of a large surface, of areas that are inaccessible or that cannot be routinely disassembled and provides an overall picture. Rinse samples may give sufficient evidence of adequate cleaning where accessibility of equipment parts can preclude direct surface sampling, and may be useful for checking for residues of cleaning agents, e.g. detergents.

9.3.1 Rinse samples should be used in combination with other sampling methods such as surface sampling.

9.3.2. There should be evidence that samples are accurately recovered. For example, a recovery of > 80% is considered good, > 50% reasonable and < 50% questionable.

9.4 Batch placebo method

Note: This method relies on the manufacture of a placebo batch which is then checked for carry-over of the previous product. It is an expensive and laborious process. It is difficult to provide assurance that the contaminants will be dislodged from the equipment surface uniformly. Additionally, if the particles of the contaminant or residue are large enough, they may not be uniformly dispersed in the placebo batch.

9.4.1 The batch placebo method should be used in conjunction with rinse and/or surface sampling method(s).

9.4.2 Samples should be taken throughout the process of manufacture. Traces of the preceding products should be sought in these samples. (Note that the sensitivity of the assay may be greatly reduced by dilution of the contaminant.)

10. Analytical methods

10.1 The analytical methods should be validated before the cleaning validation is performed.

10.2 The methods chosen should detect residuals or contaminants specific for the substance(s) being assayed at an appropriate level of cleanliness (sensitivity).

10.3 Validation of the analytical method should include as appropriate:

— precision, linearity and selectivity (the latter if specific analytes are targeted);
— limit of detection (LOD);
— limit of quantitation (LOQ);
— recovery, by spiking with the analyte; and
— reproducibility.

10.4 The detection limit for each analytical method should be sufficiently sensitive to detect the established acceptable level of the residue or contaminants.

10.5 Suitable methods that are sensitive and specific should be used where possible and may include chromatographic methods (e.g. high pressure liquid chromotography (HPLC), gas chromotography (GC), and high pressure thin-layer chromatography (HPTLC)). Other methods may include (alone or in combination) measurement of total organic carbon (TOC), pH, or conductivity; ultraviolet (UV) spectroscopy; and enzyme-linked immunosorbent assay (ELISA).

11. Establishing acceptable limits

Note: uniform distribution of contaminants is not guaranteed.

11.1 The acceptance criteria established for contaminant levels in the sample should be practical, achievable and verifiable. The rationale for the residue limits established should be logical, and based on the knowledge of the materials involved.

11.2 Each situation should be assessed individually. The manner in which limits are established should be carefully considered. In establishing residual limits it may not be adequate to focus only on the principal reactant, because other chemical variations may be more difficult to remove.

11.3 Where necessary, screening using thin-layer chromatography should be performed in addition to chemical analyses.

11.4 There should be no residue from the previous product, from reaction by-products and degradants, or from the cleaning process itself (e.g. detergents or solvents).

11.5 The limit-setting approach can:

- be product-specific;
- group products into families and choose a worst case product;

- group products into groups according to risk, e.g. very soluble products, products with similar potency, highly toxic, or difficult to detect products;
- use different safety factors for different dosage forms based on physiological response (this method is essential for potent materials).

11.6 Limits may be expressed as a concentration in a subsequent product (ppm), limit per surface area (mcg/cm^2), or in rinse water as ppm.

11.7 The sensitivity of the analytical methods should be defined to enable reasonable limits to be set.

11.8 The rationale for selecting limits for carry-over of product residues should meet defined criteria.

11.9 The three most commonly used criteria are:

- visually clean. (No residue should be visible on equipment after cleaning.) Spiking studies should determine the concentration at which most active ingredients are visible. This criterion may not be suitable for high-potency, low-dosage drugs;
- no more than 10 ppm of one product will appear in another product (basis for heavy metals in starting materials); and
- no more than 0.1% of the normal therapeutic dose of one product will appear in the maximum daily dose of a subsequent product.

11.10 The most stringent of three options should be used.

11.11 Certain allergenic ingredients (e.g. penicillins and cephalosporins) and highly potent material (e.g. anovulent steroids, potent steroids and cytotoxics) should be undetectable by the best available analytical methods. (In practice this may mean that dedicated manufacturing facilities should be used for the manufacturing and processing of such products.)

Appendix 4

Analytical method validation

1. Principle
2. General
3. Pharmacopoeial methods
4. Non-pharmacopoeial methods
5. Method validation
6. Characteristics of analytical procedures

1. Principle

1.1 This appendix presents some information on the characteristics that should be considered during validation of analytical methods. Approaches other than those specified in this appendix may be followed and may be acceptable. Manufacturers should choose the validation protocol and procedures most suitable for testing of their product.

1.2 The manufacturer should demonstrate (through validation) that the analytical procedure is suitable for its intended purpose.

1.3 Analytical methods, whether or not they indicate stability, should be validated.

1.4 The analytical method should be validated by research and development before being transferred to the quality control unit when appropriate.

2. General

2.1 There should be specifications for both, materials and products. The tests to be performed should be described in the documentation on standard test methods.

2.2 Specifications and standard test methods in pharmacopoeias ("pharmacopoeial methods"), or suitably developed specifications or test methods ("non-pharmacopoeial methods") as approved by the national drug regulatory authority may be used.

2.3 Well-characterized reference materials, with documented purity, should be used in the validation study.

2.4 The most common analytical procedures include identification tests, assay of drug substances and pharmaceutical products, quantitative tests for content of impurities and limit tests for impurities. Other analytical procedures include dissolution testing and determination of particle size.

2.5 The results of analytical procedures should be reliable, accurate and reproducible. The characteristics that should be considered during validation of analytical methods are discussed in paragraph 6.

2.6 Verification or revalidation should be performed when relevant, for example, when there are changes in the process for synthesis of the drug substance; changes in the composition of the finished product; changes in the analytical procedure; when analytical methods are transferred from one laboratory to another; or when major pieces of equipment instruments change.

2.7 The verification or degree of revalidation depend on the nature of the change(s).

2.8 There should be evidence that the analysts, who are responsible for certain tests, are appropriately qualified to perform those analyses ("analyst proficiency").

3. Pharmacopoeial methods

3.1 When pharmacopoeial methods are used, evidence should be available to prove that such methods are suitable for routine use in the laboratory (verification).

3.2 Pharmacopoeial methods used for determination of content or impurities in pharmaceutical products should also have been demonstrated to be specific with respect to the substance under consideration (no placebo interference).

4. Non-pharmacopoeial methods

4.1 Non-pharmacopoeial methods should be appropriately validated.

5. Method validation

5.1 Validation should be performed in accordance with the validation protocol. The protocol should include procedures and acceptance criteria for all characteristics. The results should be documented in the validation report.

5.2 Justification should be provided when non-pharmacopoeial methods are used if pharmacopoeial methods are available. Justification should include data such as comparisons with the pharmacopoeial or other methods.

5.3 Standard test methods should be described in detail and should provide sufficient information to allow properly trained analysts to perform the analysis in a reliable manner. As a minimum, the description should include the chromatographic conditions (in the case of chromatographic tests), reagents needed, reference standards, the formulae for the calculation of results and system suitability tests.

6. Characteristics of analytical procedures

6.1 Characteristics that should be considered during validation of analytical methods include:

— specificity
— linearity
— range
— accuracy
— precision
— detection limit
— quantitation limit
— robustness.

6.1.1 *Accuracy* is the degree of agreement of test results with the true value, or the closeness of the results obtained by the procedure to the true value. It is normally established on samples of the material to be examined that have been prepared to quantitative accuracy. Accuracy should be established across the specified range of the analytical procedure.

Note: it is acceptable to use a "spiked" placebo where a known quantity or concentration of a reference material is used.

6.1.2 *Precision* is the degree of agreement among individual results. The complete procedure should be applied repeatedly to separate, identical samples drawn from the same homogeneous batch of material. It should be measured by the scatter of individual results from the mean (good grouping) and expressed as the relative standard deviation (RSD).

6.1.2.1 *Repeatability* should be assessed using a minimum of nine determinations covering the specified range for the procedure e.g. three concentrations/three replicates each, or a minimum of six determinations at 100% of the test concentration.

6.1.2.2 *Intermediate precision* expresses within-laboratory variations (usually on different days, different analysts and different equipment). If reproducibility is assessed, a measure of intermediate precision is not required.

6.1.2.3 *Reproducibility* expresses *precision* between laboratories.

6.1.3 *Robustness* (or *ruggedness*) is the ability of the procedure to provide analytical results of acceptable accuracy and precision under a variety of conditions. The results from separate samples are influenced by changes in the operational or environmental conditions. Robustness should be considered during the development phase, and should show the reliability of an analysis when deliberate variations are made in method parameters.

6.1.3.1 Factors that can have an effect on robustness when performing chromatographic analysis include:

— stability of test and standard samples and solutions;
— reagents (e.g. different suppliers);
— different columns (e.g. different lots and/or suppliers);
— extraction time;
— variations of pH of a mobile phase;
— variations in mobile phase composition;
— temperature; and
— flow rate.

6.1.4 *Linearity* indicates the ability to produce results that are directly proportional to the concentration of the analyte in samples. A series of samples should be prepared in which the analyte concentrations span the claimed range of the procedure. If there is a linear relationship, test results should be evaluated by appropriate statistical methods. A minimum of five concentrations should be used.

6.1.5 *Range* is an expression of the lowest and highest levels of analyte that have been demonstrated to be determinable for the product. The specified range is normally derived from linearity studies.

6.1.6 *Specificity* (*selectivity*) is the ability to measure unequivocally the desired analyte in the presence of components such as excipients and impurities that may also be expected to be present. An investigation of specificity should be conducted during the validation of identification tests, the determination of impurities and assay.

6.1.7 *Detection limit* (*limit of detection*) is the smallest quantity of an analyte that can be detected, and not necessarily determined, in a quantitative fashion. Approaches may include instrumental or non-instrumental procedures and could include those based on:

— visual evaluation;
— signal to noise ratio;
— standard deviation of the response and the slope;
— standard deviation of the blank; and
— calibration curve.

6.1.8 *Quantitation limit* (*limit of quantitation*) is the lowest concentration of an analyte in a sample that may be determined with acceptable accuracy and precision. Approaches may include instrumental or non-instrumental procedures and could include those based on:

— visual evaluation;
— signal to noise ratio;
— standard deviation of the response and the slope;

— standard deviation of the blank; and
— calibration curve.

6.2 Characteristics (including tests) that should be considered when using different types of analytical procedures are summarized in Table 1.

Table 1
Characteristics to consider during analytical validation

Type of analytical procedure	Identification	Testing for impurities	Testing for impurities	Assay — dissolution (measurement only) — content/potency
Characteristics		Quantitative tests	Limit tests	
Accuracy	–	+	–	+
Precision				
Repeatability	–	+	–	+
Intermediate precision[a]	–	+	–	+
Specificity	+	+	+	+
Detection limit	–	–[b]	+	–
Quantitation limit	–	+	–	–
Linearity	–	+	–	+
Range	–	+	–	+

– Characteristic is normally not evaluated;
+ Characteristic should normally be evaluated.
[a] In cases where a reproducibility study has been performed, intermediate precision is not needed.
[b] May be needed in some cases.

6.3 System suitability testing

System suitability testing is an integral part of many analytical procedures. The tests are based on the concept that the equipment, electronics, analytical operations and samples to be analysed constitute an integral system that can be evaluated as such. System suitability test parameters that need to be established for a particular procedure depend on the type of procedure being evaluated, for instance, a resolution test for an HPLC procedure.

Appendix 5

Validation of computerized systems

1. General
2. System specification
3. Functional specification
4. Security
5. Back-ups
6. Validation
7. Validation of hardware and software
   7.1 Hardware
   7.2 Software

1. General

1.1 Computer systems should be validated at the level appropriate for their use and application. This is of importance in production as well as in quality control.

1.2 The use of a computer system includes different stages. These are planning, specification, programming, testing, commissioning, document operation, monitoring and modifying.

1.3 The purpose of validation of a computer system is to ensure an acceptable degree of evidence (documented, raw data), confidence (dependability and thorough, rigorous achievement of predetermined specifications), intended use, accuracy, consistency and reliability.

1.4 Both the system specifications and functional specifications should be validated.

1.5 Periodic (or continuous) evaluation should be performed after the initial validation.

1.6 There should be written procedures for performance monitoring, change control, programme and data security, calibration and maintenance, personnel training, emergency recovery and periodic re-evaluation.

1.7 Aspects of computerized operations that should be considered during validation include:

— networks
— manual back-ups
— input/output checks
— process documentation
— monitoring
— alarms
— shutdown recovery.

2. System specification

2.1 There should be a control document or system specification. The control document should state the objectives of a proposed computer system, the data to be entered and stored, the flow of data, how it interacts with other systems and procedures, the information to be produced, the limits of any variable and the operating programme and test programme. (Examples of each document produced by the programme should be included.)

2.2 System elements that need to be considered in computer validation include hardware (equipment), software (procedures) and people (users).

3. Functional specification

3.1 A functional or performance specification should provide instructions for testing, operating, and maintaining the system, as well as names of the person(s) responsible for its development and operation.

3.2 The following general aspects should be kept in mind when using computer systems:

— location
— power supply
— temperature, and
— magnetic disturbances.

Fluctuations in the electrical supply can influence computer systems and power supply failure can result in loss of memory.

3.3 The following general good manufacturing practice (GMP) requirements are applicable to computer systems.

- *Verification and revalidation.* After a suitable period of running a new system it should be independently reviewed and compared with the system specification and functional specification.
- *Change control.* Alterations should only be made in accordance with a defined procedure which should include provision for checking, approving and implementing the change.
- *Checks.* Data should be checked periodically to confirm that they have been accurately and reliably transferred.

4. Security

4.1 This is of importance in production as well as in quality control.

4.2 Data should be entered or amended only by persons authorized to do so. Suitable security systems should be in place to prevent unauthorized entry or manipulation of data. The activity of entering data, changing or

amending incorrect entries and creating back-ups should all be done in accordance with written, approved standard operating procedures (SOPs).

4.3 The security procedures should be in writing. Security should also extend to devices used to store programmes, such as tapes, disks and magnetic strip cards. Access to these devices should be controlled.

4.4 Traceability is of particular importance and it should be able to identify the persons who made entries/changes, released material, or performed other critical steps in manufacture or control.

4.5 The entry of critical data into a computer by an authorized person (e.g. entry of a master processing formula) requires an independent verification and release for use by a second authorized person.

4.6 SOPs should be validated for certain systems or processes, e.g. the procedures to be followed if the system fails or breaks down should be defined and tested. Alternative arrangements should be made by the validation team, and a disaster recovery procedure should be available for the systems that need to be operated in the event of a breakdown.

5. Back-ups

5.1 Regular back-ups of all files and data should be made and stored in a secure location to prevent intentional or accidental damage.

6. Validation

6.1 Planning, which should include the validation policy, project plan and SOPs, is one of the steps in the validation process.

6.2 The computer-related systems and vendors should be defined and the vendor and product should be evaluated. The system should be designed and constructed, taking into consideration the types, testing and quality assurance of the software.

6.3 After installation of the system it should be qualified. The extent of the qualification should depend on the complexity of the system. The system should be evaluated and performance qualification, change control, maintenance and calibration, security, contingency planning, SOPs, training, performance monitoring and periodic re-evaluation should be addressed.

7. Validation of hardware and software

Table 1 indicates aspects of computer systems that should be subjected to validation.

Table 1
Summary of validation requirements for computer systems

Hardware	Software
1. Types 1.1 Input device 1.2 Output device 1.3 Signal converter 1.4 Central processing unit (CPU) 1.5 Distribution system 1.6 Peripheral devices	1. Level 1.1 Machine language 1.2 Assembly language 1.3 High-level language 1.4 Application language
2. Key aspects 2.1 Location environment distance input devices 2.2 Signal conversion 2.3 I/O operation 2.4 Command overrides 2.5 Maintenance	2. Software identification 2.1 Language 2.2 Name 2.3 Function 2.4 Input 2.5 Output 2.6 Fixed set point 2.7 Variable set point 2.8 Edits 2.9 Input manipulation 2.10 Programme overrides
3. Validation 3.1 Function 3.2 Limits 3.3 Worst case 3.4 Reproducibility/consistency 3.5 Documentation 3.6 Revalidation	3. Key aspects 3.1 Software development 3.2 Software security
	4. Validation 4.1 Function 4.2 Worst case 4.3 Repeats 4.4 Documentation 4.5 Revalidation

I/O, Input/output.

7.1 Hardware

7.1.1 As part of the validation process appropriate tests and challenges to the hardware should be performed.

7.1.2 Static, dust, power-feed voltage fluctuations and electromagnetic interference could influence the system. The extent of validation should depend on the complexity of the system. Hardware is considered to be equipment, and the focus should be on location, maintenance and calibration of hardware, as well as on validation/qualification.

7.1.3 The validation/qualification of the hardware should prove:

- that the capacity of the hardware matches its assigned function (e.g. foreign language);

- that it operates within the operational limits (e.g. memory, connector ports, input ports);
- that it performs acceptably under worst-case conditions (e.g. long hours, temperature extremes); and
- reproducibility/consistency (e.g. by performing at least three runs under different conditions).

7.1.4 The validation should be done in accordance with written qualification protocols and the results should be recorded in the qualification reports.

7.1.5 Revalidation should be performed when significant changes are made.

7.1.6 Much of the hardware validation may be performed by the computer vendor. However, the ultimate responsibility for the suitability of equipment used remains with the company.

7.1.7 Hardware validation data and protocols should be kept by the company. When validation information is produced by an outside firm, e.g. computer vendor, the records maintained by the company need not include all of the voluminous test data; however, such records should be sufficiently complete (including general results and protocols) to allow the company to assess the adequacy of the validation. A mere certification of suitability from the vendor, for example, will be inadequate.

7.2 Software

7.2.1 Software is the term used to describe the complete set of programmes used by a computer, and which should be listed in a menu.

7.2.2 Records are considered as software; focus is placed on accuracy, security, access, retention of records, review, double checks, documentation and accuracy of reproduction.

Identification

7.2.3 The company should identify the following key computer programmes: language, name, function (purpose of the programme), input (determine inputs), output (determine outputs), fixed set point (process variable that cannot be changed by the operator), variable set point (entered by the operator), edits (reject input/output that does not conform to limits and minimize errors, e.g. four- or five-character number entry), input manipulation (and equations) and programme overrides (e.g. to stop a mixer before time).

7.2.4 The personnel who have the ability and/or are authorized to write, alter or have access to programmes should be identified.

7.2.5 Software validation should provide assurance that computer programmes (especially those that control manufacturing and processing) will consistently perform as they are supposed to, within pre-established limits.

When planning the validation, the following points should be considered.

- Function: does the programme match the assigned operational function (e.g. generate batch documentation, different batches of material used in a batch listed)?
- Worst case: perform validation under different conditions (e.g. speed, data volume, frequency).
- Repeats: sufficient number of times (replicate data entries).
- Documentation: protocols and reports.
- Revalidation: needed when significant changes are made.

Appendix 6

Qualification of systems and equipment

1. Principle
2. Scope
3. General
4. Design qualification
5. Installation qualification
6. Operational qualification
7. Performance qualification
8. Requalification
9. Qualification of “in use” systems and equipment

1. Principle

1.1 Systems and equipment should be appropriately designed, located, installed, operated and maintained to suit their intended purpose.

1.2 Critical systems, i.e. those whose consistent performance may have an impact on the quality of products, should be qualified. These may include, where appropriate, water purification systems, air-handling systems, compressed air systems and steam systems.

1.3 The continued suitable performance of equipment is important to ensure batch-to-batch consistency. Critical equipment should therefore be qualified.

2. Scope

2.1 These guidelines describe the general aspects of qualification for systems and equipment.

2.2 Normally qualification would be applicable to critical systems and equipment whose performance may have an impact on the quality of the product.

3. General

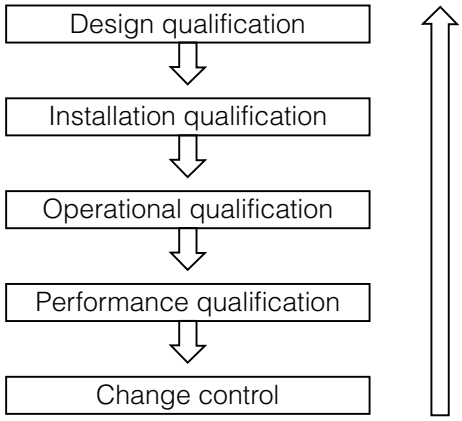
3.1 The manufacturer should have a qualification policy for systems and equipment.

3.2 Equipment (including instruments) used in production and quality control should be included in the qualification policy and programme.

3.3 New systems and equipment should pass through all stages of qualification including design qualification (DQ), installation qualification (IQ),

operational qualification (OQ) and performance qualification (PQ) as appropriate (Fig. 1).

Figure 1
Stages of qualification



3.4 In some cases, not all stages of qualification may be required. See also the guidelines on the qualification of water purification systems in Appendix 2 and heating, ventilation and air-conditioning (HVAC) in Appendix 1.

3.5 Systems should be qualified before equipment.

3.6 Equipment should be qualified prior to being brought into routine use to provide documented evidence that the equipment is fit for its intended purpose.

3.7 Systems and equipment should undergo periodic requalification, as well as requalification after change.

3.8 Certain stages of the equipment qualification may be done by the supplier or a third party.

3.9 The relevant documentation associated with qualification including standard operating procedures (SOPs), specifications and acceptance criteria, certificates and manuals should be maintained.

3.10 Qualification should be done in accordance with predetermined and approved qualification protocols. The results of the qualification should be recorded and reflected in qualification reports.

3.11 The extent of the qualification should be based on the criticality of a system or equipment (e.g. blenders, autoclaves or computerized systems).

4. Design qualification

Note: see also "Supplementary guidelines on good manufacturing practices (GMP): validation".

4.1 User requirements should be considered when deciding on the specific design of a system or equipment.

4.2 A suitable supplier should be selected for the appropriate system or equipment (approved vendor).

5. Installation qualification

Note: see also "Supplementary guidelines on good manufacturing practices (GMP): validation".

5.1 Systems and equipment should be correctly installed in accordance with an installation plan and installation qualification protocol.

5.2 Requirements for calibration, maintenance and cleaning should be drawn up during installation.

5.3 Installation qualification should include identification and verification of all system elements, parts, services, controls, gauges and other components.

5.4 Measuring, control and indicating devices should be calibrated against appropriate national or international standards, which are traceable.

5.5 There should be documented records for the installation (installation qualification report) to indicate the satisfactoriness of the installation, which should include the details of the supplier and manufacturer, system or equipment name, model and serial number, date of installation, spare parts, relevant procedures and certificates.

Format for an installation qualification protocol and report[a]

Validation protocol _____ Installation Qualification _____ Page _____ of _____

Title: _____ Name and address of site: _____

_____

Validation Protocol # _____ IQ Protocol number: _____

Title: _____

Protocol written by: _____

Protocol approved by: _____ Date: _____

QA Approval: _____ Date: _____

Objective

To ensure that _____ (system/equipment) installed conforms to the purchase specifications and the manufacturer details and literature, and to document the information that _____ (system/equipment) meets its specifications.

Equipment inventory number: _____

Scope

To perform installation qualification as described in this IQ protocol at the time of installation, modification and relocation.

Responsibility

_____ (post/person) overseeing the installation will perform the qualification and records results.

_____ (post/person) will verify results and write the report.

Quality Assurance will review and approve the IQ protocol and report.

[a] This format is used for training purposes and reflects some of the possible contents for an installation qualification protocol.

Format for an installation qualification protocol and report (continued)[a]

Validation protocol _____ Installation Qualification _____ Page _____ of _____

Title: _____ Name and address of site: _____

_____

System/Equipment _____ Code no.: _____

a. Description of the system/equipment being installed: general description of the function and the main components.

_____

_____

_____

b. List of the main components:

1. _____ Code no.: _____
2. _____ Code no.: _____
3. _____ Code no.: _____
4. _____ Code no.: _____

c. Description of supporting utilities (e.g. piping, connections, water supply)

1. _____ Code no.: _____
2. _____ Code no.: _____
3. _____ Code no.: _____
4. _____ Code no.: _____

Procedure

1. Prepare a checklist of all components and parts, including spare parts according to the purchase order and manufacturer's specifications.
2. Record the information for each actual part, component, item of auxiliary equipment, supporting facilities, and compare with the manufacturer's specifications.
3. Record any deviations to the system/equipment.
4. Prepare a deviation report including justification of acceptance and impact on the function.
5. Prepare an IQ report.[b]
6. Submit the report to QA for review and approval.

[a] This format is used for training purposes and reflects some of the possible contents for an installation qualification protocol.

[a] As a minimum, the IQ report should include the date of initiation of the study, date completed, observations made, problems encountered, completeness of information collected, summary of deviation report, results of any tests, sample data (if appropriate), location of original data, other information relevant to the study, and the conclusion on the validity of the installation.

Format for an installation qualification protocol and report (continued)[a]

Validation protocol _____ **Installation Qualification** _____ **Page** _____ **of** _____

Title: _____ **Name and address of site:** _____

_____

Checklist for component no. _____

Name: _____ Code no.: _____

Component function: _____

		Require/order	**Actual**	**Deviations**
1	Model/serial no.			
2	Specification			
3	Manual			
4	Drawing			
5	Wiring/cabling			
6	Power, fusing			
7	SOP (operation) SOP (maintenance) SOP (calibration)			
8	Input/output control			
9	Environment			
10	Test equipment or instruments			
11	Utilities and service			
12	Spare parts list, part number and supplier			
13	Other			

Performed by: _____ **Date:** _____

Deviations: _____ **Date:** _____

Verified by: _____ **Date:** _____

[a] This format is used for training purposes and reflects some of the possible contents for an installation qualification protocol.

Format for an installation qualification protocol and report (continued)[a]

Validation protocol _____ Installation Qualification _____ Page _____ of _____

Title: _____ Name and address of site: _____

_____

Deviation report

Deviations: _____

_____

_____

_____

_____

_____

_____

Justification for acceptance

_____

_____

_____

_____

_____

_____

_____

_____

Impact on operation:

_____

_____

_____

_____

_____

_____

_____

_____

Report written by: _____ Date: _____

[a] This format is used for training purposes and reflects some of the possible contents for an installation qualification protocol.

Format for an installation qualification protocol and report (continued)[a]

Validation protocol _____ **Installation Qualification** _____ **Page** _____ **of** _____ **Title:** _____ **Name and address of site:** _____ _____
Installation qualification report Results: _____ _____ _____ _____ _____ **Conclusions:** _____ _____ _____ _____ _____ _____ _____ _____ _____
Report written by: _____ **Date:** _____ **QA approved by:** _____ **Date:** _____

[a] This format is used for training purposes and reflects some of the possible contents for an installation qualification protocol.

6. Operational qualification

Note: see also "Supplementary guidelines on good manufacturing practices (GMP): validation".

6.1 Systems and equipment should operate correctly and their operation should be verified in accordance with an operational qualification protocol.

6.2 Critical operating parameters should be identified. Studies on the critical variables should include conditions encompassing upper and lower operating limits and circumstances (also referred to as "worst case conditions").

6.3 Operational qualification should include verification of operation of all system elements, parts, services, controls, gauges and other components.

Format for an operational qualification protocol[a]

Validation protocol _____ **Operational Qualification** _____ **Page** _____ **of** _____

Title: _____ **Name of Facility:** _____

_____

Validation Protocol # _____ Operational Qualification _____

Title _____

_____

Protocol written by _____

Departmental Approval by _____ Date _____

QA Approval by _____ Date _____

Objective

To determine that the system/equipment operates according to specifications, and to record all relevant information and data to demonstrate that the system/equipment functions as expected.

Scope

To be performed after installation, modification or relocation, after the Installation Qualification has been completed.

Responsibility

Person responsible for operating the system/equipment will perform the qualification and record the information.

The supervisor will supervise the study, verify the completion of the records, write the deviation report and the Operational Qualification (OQ) Report.

Qualify Assurance will review and approve the OQ protocol and report.

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

6.4 There should be documented records for the verification of operation (operational qualification report) to indicate the satisfactory operation.

6.5 Standard operating procedures for the operation should be finalized and approved.

6.6 Training of operators for the systems and equipment should be provided, and training records maintained.

6.7 Systems and equipment should be released for routine use after completion of operational qualification, provided that all calibration, cleaning, maintenance, training and related tests and results were found to be acceptable.

Format for an operational qualification protocol (continued)[a]

Validation protocol _____ Operational Qualification _____ Page _____ of _____

Title: _____ Name of Facility: _____

_____

Materials, Equipment, Documents

List of calibration equipment required (Chart 1).

Materials or supplies needed to perform the Operational Qualification

1 _____ Code # _____

2 _____ Code # _____

3 _____ Code # _____

4 _____ Code # _____

5 _____ Code # _____

6 _____ Code # _____

SOPs and datasheets for normal operations of the system under test (Chart 2).

Training records documenting that operators have been trained (Chart 2).

Manuals for equipment (Chart 2).

Procedure

Test and record calibration data for calibrating apparatus and instruments (Chart 1).

Test and record operative condition of control points and alarms (Chart 3).

Test and record outputs (Chart 4).

List of calibration requirements for the system under test and records of the calibration of the system (Chart 5).

Measure and record the results of specific challenge to the system in normal and worst case situation where appropriate (Chart 6).

Record any deviations to the procedures performed.

Prepare a Deviation Report including the justification of acceptance and impact on the operation.

Prepare an Operational Qualification Report. This should include date study initiated; date completed; observations made; problems encountered; completeness of information collected; summary of deviation report; results of control/alarm tests; sample data if appropriate; location of original data; other information relevant to the study; and conclusions on the validity of the equipment/system operations.

Submit QA for review and approval.

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

Format for an operational qualification protocol (continued)[a]

Validation protocol _____ Operational Qualification _____ Page _____ of _____

Title: _____ Name of Facility: _____

_____

Preparation

Chart 1: Calibrating apparatus and instruments.

Apparatus/Instrument	Calibration method	Calibration date
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Performed by: _____ Date _____

Deviations: _____

_____

_____

_____

Verified by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

Format for an operational qualification protocol (continued)[a]

Validation protocol _____ Operational Qualification _____ Page _____ of _____

Title: _____ Name of Facility: _____

_____

Preparation

Chart 2: Document check

SOP Title and number	File location	QA/QC approval date
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Training Records

Course on SOP #	Staff name	Date
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Equipment Make and Model	Manual Available
_____	Y [ ] N [ ]
_____	Y [ ] N [ ]
_____	Y [ ] N [ ]

Performed by: _____ Date _____

Deviations: _____

_____

_____

Verified by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

Format for an operational qualification protocol (continued)[a]

Validation protocol _____ Operational Qualification _____ Page _____ of _____

Title: _____ Name of Facility: _____

_____

Results

Chart 3: Control points and alarms.

Control point/Alarm	Results	Date
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____
_____	_____	_____

Performed by: _____ Date _____

Deviations: _____

_____

_____

Verified by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

Format for an operational qualification protocol (continued)[a]

Validation protocol _____ Operational Qualification _____ Page _____ of _____

Title: _____ Name of Facility: _____

_____

Results

Chart 4: Outputs

Outputs	Results	Date

Performed by: _____ Date _____

Deviations: _____

_____

_____

Verified by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

Format for an operational qualification protocol (continued)[a]

Validation protocol _____ Operational Qualification _____ Page _____ of _____

Title: _____ Name of Facility: _____

_____

Chart 5: Calibration of Equipment/System

Calibration SOP (short title and #)	Result	Date

Performed by: _____ Date _____

Deviations: _____

_____

_____

Verified by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

Format for an operational qualification protocol (continued)[a]

Validation protocol _____ Operational Qualification _____ Page _____ of _____

Title: _____ Name of Facility: _____

_____

Chart 6: Specific challenge of the equipment or system

Test in normal conditions:

Test of worst case situation:
(e.g. start-up after shutdown, temperature recovery time, centrifuge imbalance)

Performed by: _____ Date _____

Deviations: _____

_____

_____

Verified by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

Format for an operational qualification protocol (continued)[a]

Validation protocol _____ Operational Qualification _____ Page _____ of _____

Title: _____ Name of Facility: _____

_____

Deviation Report

Deviation(s):

Justification for acceptance:

Impact on operation:

Written by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

Format for an operational qualification protocol (continued)[a]

Validation protocol _____ Operational Qualification _____ Page _____ of _____

Title: _____ Name of Facility: _____

_____

Operational Qualification Report

Results:

Conclusions:

Written by: _____ Date _____

QA approved by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for an operational qualification protocol.

7. Performance qualification

Note: see also "Supplementary guidelines on good manufacturing practices (GMP): validation".

7.1 Systems and equipment should consistently perform in accordance with design specifications. The performance should be verified in accordance with a performance qualification protocol.

7.2 There should be documented records for the verification of performance (performance qualification report) to indicate the satisfactory performance over a period of time. Manufacturers should justify the selected period over which performance qualification is done.

Format for a performance qualification protocol[a]

Validation protocol _____ **Performance Qualification** _____ **Page** _____ **of** _____ **Title:** _____ **Name of facility:** _____ _____
Validation Protocol # _____ Performance Qualification Title _____ _____ Protocol written by _____ Departmental Approval by _____ Date _____ QA Approval by _____ Date _____
Objective To determine that the systems/equipment perform as intended by repeatedly running the system on its intended schedules and recording all relevant information and data. Results must demonstrate that performance consistently meets pre-determined specifications under normal conditions, and where appropriate for worst case situations.
Scope To be performed after the Installation and Operational Qualification have been completed and approved. To be performed after installation, modification or relocation and for re-validation at appropriate intervals. Each piece of equipment must be validated before it serves another piece of equipment/ system during validation of the latter (e.g. water system before steam generator; steam generator before autoclave).

[a] This format is used for training purposes and reflects some of the possible contents for a performance qualification protocol.

Format for a performance qualification protocol (continued)[a]

Validation protocol _____ Performance Qualification _____ Page _____ of _____

Title: _____ Name of facility: _____

_____

Responsibility

Person responsible for operating the system or equipment will perform the qualification and record the information.

The supervisor will supervise the study, verify the completion of the records and write the Deviation Report and the Performance Qualification Report.

Qualify Assurance will review and approve the Performance Qualification Protocol and Report.

Materials, Equipment, Documents

SOPs for normal operations of the equipment or system under test (including data record forms, charts, diagrams materials and equipment needed). Attach copies.

SOP list:

_____

_____

_____

_____

_____

_____

SOPs specific for performance tests (including data record forms, charts, diagrams, materials and equipment needed, calculations and statistical analyses to be performed, and pre-determined specifications and acceptance criteria). Attach copies.

SOP list:

_____

_____

_____

_____

_____

_____

[a] This format is used for training purposes and reflects some of the possible contents for a performance qualification protocol.

Format for a performance qualification protocol (continued)[a]

Validation protocol _____ Performance Qualification _____ Page _____ of _____

Title: _____ Name of facility: _____

_____

Procedure

Equipment: Run normal procedure three times for each use (configuration or load) and record all required data and any deviations to the procedure.

Systems: Run for 20 consecutive working days, recording all required data and any deviations to the procedure.

Prepare the Summary Data Record Form(Chart 1).

Evaluation

Attach all completed, signed data record forms.

Complete the Summary Data Record Form (Chart 1).

Perform all required calculations and statistical analyses (Chart 2).

Compare to acceptance criteria (Chart 3).

Prepare Deviation Report including the justification of acceptance and impact on the performance.

Prepare a Performance Qualification Report: This should include: date study initiated; date completed; observations made; problems encountered; completeness of information collected; summary of deviation report; results of any tests; do results meet acceptance criteria; location of original data; other information relevant to the study; and conclusions on the validity of the equipment/system.

Submit Performance Qualification Document to QA for review and approval.

[a] This format is used for training purposes and reflects some of the possible contents for a performance qualification protocol.

Format for a performance qualification protocol (continued)[a]

Validation protocol _____ Performance Qualification _____ Page _____ of _____

Title: _____ Name of facility: _____

_____

Chart 1: Summary Data Record
(To be prepared for the specific procedure being tested)

Performed by: _____ Date _____

Verified by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for a performance qualification protocol.

Format for a performance qualification protocol (continued)[a]

Validation protocol _____ **Performance Qualification** _____ **Page** _____ **of** _____

Title: _____ **Name of facility:** _____

_____

Chart 2: Calculations and Statistical Analyses

Performed by: _____ **Date** _____

Verified by: _____ **Date** _____

[a] This format is used for training purposes and reflects some of the possible contents for a performance qualification protocol.

Format for a performance qualification protocol (continued)[a]

Validation protocol _____ **Performance Qualification** _____ **Page** _____ **of** _____

Title: _____ **Name of facility:** _____

_____

Chart 3: Acceptance Criteria vs. Performance Test Results

Criteria	Results	Pass/Fail

Performed by: _____ **Date** _____

Verified by: _____ **Date** _____

[a] This format is used for training purposes and reflects some of the possible contents for a performance qualification protocol.

Format for a performance qualification protocol (continued)[a]

Validation protocol _____ **Performance Qualification** _____ **Page** _____ **of** _____

Title: _____ **Name of facility:** _____

_____

Deviation Report

Deviation(s):

Justification for acceptance:

Impact on operation, function or process:

Written by: _____ **Date** _____

Verified by: _____ **Date** _____

[a] This format is used for training purposes and reflects some of the possible contents for a performance qualification protocol.

Format for a performance qualification protocol (continued)[a]

Validation protocol _____ Performance Qualification _____ Page _____ of _____

Title: _____ Name of facility: _____

_____

Performance Qualification Report

Results:

Conclusions:

Written: _____ Date _____

Verified by: _____ Date _____

[a] This format is used for training purposes and reflects some of the possible contents for a performance qualification protocol.

8. Requalification

Note: see also "Supplementary guidelines on good manufacturing practices (GMP): validation".

8.1 Requalification of systems and equipment should be done in accordance with a defined schedule. The frequency of requalification may be determined on the basis of factors such as the analysis of results relating to calibration, verification and maintenance.

8.2 There should be periodic requalification.

8.3 There should be requalification after changes. The extent of requalification after the change should be justified based on a risk-assessment of the change. Requalification after change should be considered as part of the change control procedure.

9. Qualification of "in-use" systems and equipment

9.1 There should be data to support and verify the suitable operation and performance of systems and equipment that have been "in use" for a period of time, and which had not been subjected to installation and or operational qualification.

9.2 These should include operating parameters and limits for critical variables, calibration, maintenance and preventive maintenance, standard operating procedures (SOPs) and records.

10. Reference

A WHO guide to good manufacturing practice (GMP) requirements. Part 2: Validation. Geneva, Global Programme for Vaccines and Immunization, Vaccine Supply and Quality, Global Training Network, World Health Organization, 1997 (WHO/VSQ/97.02).

Appendix 7

Non-sterile process validation

1. Principle
2. Scope
3. General
4. Prospective validation
5. Concurrent validation
6. Retrospective validation
7. Revalidation
8. Change control

1. Principle

1.1 Process validation provides documented evidence that a process is capable of reliably and repeatedly rendering a product of the required quality.

1.2 The principles of planning, organizing and performing process validation are similar to those for qualification. It should be done in accordance with process validation protocols, data should be collected and reviewed against predetermined acceptance criteria, and reflected in process validation reports.

2. Scope

2.1 These guidelines describe the general aspects of process validation for the manufacture of non-sterile finished products.

2.2 Normally process validation should cover at least the critical steps and parameters (e.g. those that may have an impact on the quality of the product) in the process of manufacturing a pharmaceutical product.

3. General

3.1 The policy and approach to process validation should be documented, e.g. in a validation master plan, and should include the critical process steps and parameters.

3.2 Process validation should normally begin only once qualification of support systems and equipment is completed. In some cases process validation may be conducted concurrently with performance qualification.

3.3 Process validation should normally be completed prior to the manufacture of finished product that is intended for sale (*prospective validation*). Process validation during routine production may also be acceptable (*concurrent validation*).

4. Prospective validation

4.1 Critical factors or parameters that may affect the quality of the finished product should be identified during product development. To achieve this, the production process should be broken down into individual steps, and each step should be evaluated (e.g. on the basis of experience or theoretical considerations).

4.2 The criticality of these factors should be determined through a "worst-case" challenge where possible.

4.3 Prospective validation should be done in accordance with a validation protocol. The protocol should include:

— a description of the process;
— a description of the experiment;
— details of the equipment and/or facilities to be used (including measuring or recording equipment) together with its calibration status;
— the variables to be monitored;
— the samples to be taken — where, when, how, how many and how much (sample size);
— the product performance characteristics/attributes to be monitored, together with the test methods;
— the acceptable limits;
— time schedules;
— personnel responsibilities; and
— details of methods for recording and evaluating results, including statistical analysis.

4.4 All equipment, the production environment and analytical testing methods to be used should have been fully validated (e.g. during installation qualification and operational qualification).

4.5 Personnel participating in the validation work should have been appropriately trained.

4.6 Batch manufacturing documentation to be used should be prepared after these critical parameters of the process have been identified, and machine settings, component specifications and environmental conditions have been determined and specified.

4.7 A number of batches of the final product should then be produced. The number of batches produced in this validation exercise should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation.

4.8 Data within the finally agreed parameters, from at least three consecutive batches, giving product of the desired quality may be considered to constitute a proper validation of the process.

4.9 The batches should be of the same size, and should be the same as the batch size intended in full-scale production. Where this is not possible, the reduced batch size should be considered in the design of the protocol and when full-scale production starts, the validity of any assumptions made should be demonstrated.

4.10 Extensive testing should be performed on the product at various stages during the manufacturing process of the batches, including on the final product and its package.

4.11 The results should be documented in the validation report. As a minimum, the report should include:

- a description of the process: batch/packaging document, including details of critical steps;
- a detailed summary of the results obtained from in-process and final testing, including data from failed tests. When raw data are not included, reference should be made to the sources used and where it can be found;
- any work done in addition to that specified in the protocol, or any deviations from the protocol should be formally noted along with an explanation;
- a review and comparison of the results with those expected; and
- formal acceptance or rejection of the work by the team or persons designated as being responsible for the validation, after completion of any corrective action or repeated work.

4.12 A conclusion and recommendation should be made on the extent of monitoring and the in-process controls necessary for routine production, on the basis of the results obtained.

4.13 The conclusion and recommendation should be incorporated into the batch manufacturing and batch packaging documents and/or standard operating procedures (SOPs) for routine use. Limits and frequencies of testing and monitoring should be specified. Actions to be taken in the event of the limits being exceeded should be specified.

4.14 Batches manufactured as part of the validation exercise, and intended to be sold or supplied, should have been manufactured under conditions that comply fully with the requirements of good manufacturing practice and the marketing authorization (where applicable).

5. Concurrent validation

5.1 In certain cases, it may be appropriate to validate a process during routine production, e.g. where the product is a different strength of a previously validated product, a different tablet shape or where the process is well understood.

5.2 The decision to carry out concurrent validation should be made by appropriately authorized personnel.

5.3 It is essential that the premises and equipment to be used during concurrent validation have been previously qualified.

5.4 Prospective validation should be done in accordance with a validation protocol.

5.5 The results should be documented in the validation report.

6. Retrospective validation

6.1 Retrospective validation is based on a comprehensive review of historical data to provide the necessary documentary evidence that the process is doing what it is believed to do. This type of validation also requires the preparation of a protocol, the reporting of the results of the data review, a conclusion and a recommendation.

6.2 Retrospective validation is not the preferred method of validation and should be used in exceptional cases only. It is acceptable only for well-established processes and will be inappropriate where there have been changes in the composition of the product, operating procedures or equipment.

6.3 Sufficient data should be reviewed to provide a statistically significant conclusion.

6.4 When the results of retrospective validation are considered satisfactory, this should serve only as an indication that the process does not need to be subjected to validation in the immediate future.

7. Revalidation

Note: see main text on "Validation". The need for periodic revalidation of non-sterile processes is considered to be a lower priority than for sterile processes.

7.1 In the case of standard processes using conventional equipment, a data review similar to that which would be required for retrospective validation may provide an adequate assurance that the process continues to be under control. The following points should also be considered:

— the occurrence of any changes in the master formula, methods, starting material manufacturer, equipment and/or instruments;
— equipment calibrations and preventive maintenance carried out;
— standard operating procedures (SOPs); and
— cleaning and hygiene programme.

8. Change control

Note: see main text on "Validation".

8.1 Products manufactured by processes that have been subjected to changes should not be released for sale without full awareness and consideration of the change and its impact on the process validation.

8.2 Changes that are likely to require revalidation may include:

— changes in the manufacturing process (e.g. mixing times, drying temperatures);
— changes in the equipment (e.g. addition of automatic detection systems);
— production area and support system changes (e.g. rearrangement of areas or a new water treatment method);
— transfer of processes to another site; and
— unexpected changes (e.g. those observed during self-inspection or during routine analysis of process trend data).