GUIDELINES ON VALIDATION
(May 2016)

DRAFT FOR COMMENTS

Should you have any comments on the attached text, please send these to Dr S. Kopp, Group Lead, Medicines Quality Assurance, Technologies, Standards and Norms (kopps@who.int) with a copy to Ms Marie Gaspard (gaspardm@who.int) by 12 July 2016.

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**SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT**

**QAS/16.666:**

Guidelines on validation

<table>
<thead>
<tr>
<th>Activity</th>
<th>Dates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discussion of proposed need for revision in view of the current trends in validation during informal consultation on data management, bioequivalence, GMP and medicines’ inspection</td>
<td>29 June– 1 July 2015</td>
</tr>
<tr>
<td>Preparation of draft proposal for revision of the main text and several appendices by specialists in collaboration with the Medicines Quality Assurance Group and Prequalification Team (PQT)-Inspections, based on the feedback received during the meeting and from PQT-Inspections, draft proposals developed on the various topics by specialists, as identified in the individual working documents.</td>
<td>July 2015– April 2016</td>
</tr>
<tr>
<td>Presentation of the progress made to the fiftieth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>12–16 October 2015</td>
</tr>
<tr>
<td>Discussion at the informal consultation on good practices for health products manufacture and inspection, Geneva,</td>
<td>4–6 April 2016</td>
</tr>
<tr>
<td>Preparation of revision by Dr A.J. van Zyl, a participant at the above-mentioned consultation, based on his initial proposal and the feedback received during and after the informal consultation by the meeting participants and members of PQT-Inspections.</td>
<td>May 2016</td>
</tr>
<tr>
<td>Circulation of revised working document for public consultation</td>
<td>May 2016</td>
</tr>
<tr>
<td>Consolidation of comments received and review of feedback</td>
<td>August–September 2016</td>
</tr>
<tr>
<td>Presentation to the fifty-first meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>17–21 October 2016</td>
</tr>
<tr>
<td>Any other follow-up action as required</td>
<td>…</td>
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</table>
Background information

The need for revision of the published *Supplementary guidelines on good manufacturing practices: validation* (WHO Technical Report Series, No. 937, 2006, Annex 4) (1) had been identified by the Prequalification of Medicines Programme and a draft document was circulated for comment in early 2013. The focus of the revision was the Appendix on non-sterile process validation (Appendix 7), which had been revised and was adopted by the Committee at its forty-ninth meeting in October 2014.

The main text included in this working document constitutes the general principles of the new guidance on validation.

The draft on the specific topics, the appendices to this main text, will follow.

The following is an overview on the appendices that are intended to complement the text in this working document:

Appendix 1
*Validation of heating, ventilation and air-conditioning systems*
→ will be replaced by cross-reference to WHO Guidelines on GMP for HVAC systems for considerations in qualification of HVAC systems (update - working document QAS/15.639/Rev.1) (2)

Appendix 2
*Validation of water systems for pharmaceutical use*
→ will be replaced by cross-reference to WHO Guidelines on water for pharmaceutical use for consideration in qualification of water purification systems (3)

Appendix 3
*Cleaning validation* – consensus to retain

Appendix 4
*Analytical method validation* – update in process
Appendix 5
Validation of computerized systems – update in process

Appendix 6
Qualification of systems and equipment – update in process

Appendix 7
1. **INTRODUCTION**

1.1 Validation is an essential part of good practices including good manufacturing practices (GMP) (4) and good clinical practices (GCP). It is therefore an element of the pharmaceutical quality system. Validation, as a concept, incorporates qualification and should be applied over the life cycle of, e.g. the applicable product, process, system, equipment or utility.

1.2 These guidelines cover 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.

1.3 The following principles apply:

- the execution of validation should be in compliance with regulatory expectations;
- quality, safety and efficacy must be designed and built into the product;
- quality cannot be inspected or tested into the product;
- quality risk management principles should be applied in determining the need, scope and extent of validation;
- ongoing review should take place to ensure that the validated state is maintained and opportunities for continuing improvement are identified.

1.4 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, information technology, manufacturing and other disciplines, as appropriate.).

2. SCOPE

2.1 These guidelines focus mainly on the overall concept of validation and are not intended 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 starting materials and finished pharmaceutical products (FPPs), as well as other areas. Validation of specific processes and systems, 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 The general text in the main part of these guidelines may be applicable to validation and qualification of premises, equipment, utilities, systems, processes and procedures.

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.

**change control (including change management).** A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect a validated status. The intent is to determine the need for action that would ensure that the system is maintained in a validated state (reference working document QAS/15.639/Rev.1 - unpublished).

**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.

**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.

**computer validation (including computerized system validation).** Confirmation by examination and provision of objective documented evidence that computerized system specifications conform to user needs and intended uses, and that all requirements can be consistently fulfilled.
**concurrent validation.** Validation carried out during routine production of products intended for sale.

**design qualification.** Documented verification that the proposed design of facilities, systems and equipment is suitable for the intended purpose.

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

**installation qualification.** Documented verification that the installations (such as machines, computer system components, measuring devices, utilities and manufacturing areas) used in a processor system are appropriately selected and correctly installed in accordance with established specifications.

**operational qualification.** Documented verification that the system or subsystem operates as intended over all anticipated operating ranges.

**performance qualification.** Documented verification that the equipment or system performs consistently and reproducibly within defined specifications and parameters in its normal operating environment (i.e. in the production environment). (In the context of systems, the term “process validation” may also be used.)

**process validation.** The collection and evaluation of data, throughout the product life cycle, which provides documented scientific evidence that a process is capable of consistently delivering quality products.

**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.** Documented evidence that premises, systems or equipment are able to achieve the predetermined specifications 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.

**revalidation.** Repeated validation of a previously validated system (or a part thereof) to ensure continued compliance with established requirements.

**standard operating procedure.** 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 standard operating procedures 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 master plan.** The validation master plan 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.

**validation protocol.** A document describing the activities to be performed during a validation, including the acceptance criteria for the approval of a process or system – or a part thereof – for intended use.

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

**verification.** The application of methods, procedures, tests and other evaluations, in addition to monitoring, to determine compliance with established requirements and specifications.

**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

4.1 Qualification and validation are essentially the same. The term qualification is normally used for equipment and utilities, and validation for systems and processes. In this sense, qualification can be seen as part of validation.

4.2 Where the term “validation” is used in the document, the same principles may be applicable for “qualification”

5. VALIDATION

Approaches to validation

5.1 Manufacturers should organize and plan validation in a manner that will ensure product quality, safety and efficacy throughout its life cycle.

5.2 The scope and extent of qualification and validation should be based on risk management principles.

5.3 Statistical calculations should be applied, where appropriate, and provide scientific evidence that the process, system or other related aspect is appropriately validated.

5.4 Qualification and validation should be done in accordance with predetermined protocols, and the results appropriately documented, e.g. in reports.

5.5 There should be an appropriate and effective quality system ensuring the organization and management of validation.

5.6 Senior management should ensure that there are sufficient resources to perform validation in a timely manner. Management and persons responsible for quality assurance should be actively involved in
the process and authorization of protocols and reports.

5.7 Personnel with appropriate qualification and experience should be responsible for performing validation.

5.8 There should be a specific programme or schedule to support planning and execution of validation activities.

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

5.10 Qualification and validation should be performed:
   - for new premises, equipment, utilities and systems, and processes and procedures;
   - when changes are made, depending on the outcome of risk assessment;
   - where necessary or indicated based on the outcome of periodic review.

5.11 A written report on the outcome of the validation should be prepared.

5.12 The scope and extent of validation should be based on knowledge and experience, and the outcome of quality risk management principles as described in the World Health Organization (WHO) guidelines on quality risk management. Where necessary worst-case situations or specific challenge tests should be considered for inclusion in the validation, for example, stress load and volume verification in computer system validation.

6. DOCUMENTATION

6.1 Qualification and validation should be done according to written procedures.

6.2 Documents associated with qualification and validation include:
   - validation master plan (VMP);
   - standard operating procedures (SOPs);
   - specifications;
   - protocols and reports;
7. VALIDATION MASTER PLAN

7.1 A manufacturer should have a VMP which reflects the key elements of validation. It should be concise and clear and contain at least the following:

- title page and authorization (approval signatures and dates);
- table of contents;
- abbreviations and glossary;
- validation policy;
- philosophy, intention and approach to validation;
- roles and responsibilities of relevant personnel;
- resources to ensure validation is done;
- outsourced services (selection, qualification, management through life cycle);
- deviation management in validation;
- change control in validation;
- risk management principles in validation;
- training;
- scope of validation;
- documentation required in qualification and validation such as procedures, certificates, protocols and reports;
- premises qualification;
- utilities qualification;
- equipment qualification;
- process validation;
- cleaning validation;
- personnel qualification such as analyst qualification;
7.2 The VMP should be reviewed at regular intervals and kept up to date according to current GMP.

8. QUALIFICATION AND VALIDATION PROTOCOLS

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

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

- the objectives;
- the site;
- the responsible personnel
- description of the standard operating procedures (SOPs) to be followed;
- equipment or instruments to be used;
- standards and criteria as appropriate;
- the stage of validation or qualification;
- the processes and/or parameters;
- sampling, testing and monitoring requirements;
- stress testing where appropriate;
- calibration requirements;
- predetermined acceptance criteria for drawing conclusions;
- review and interpretation of results;
- change control, deviations;
- archiving and retention.

8.3 There should be a description of the way in which the results will be analysed, including statistical analysis where appropriate.

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

9. QUALIFICATION AND VALIDATION REPORTS

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

9.2 Reports should reflect the protocols and procedures followed and include at least the title and objective of the study; make reference to the protocol; reference to the appropriate risk assessment; details of materials, equipment, programmes and cycles used; procedures and test methods with appropriate traceability.

9.3 Results should be recorded and be in compliance with good data and record management practices.

9.4 Results should be reviewed, analysed and compared against the justified predetermined acceptance criteria, interpreted and statistically analysed where appropriate.

9.5 Results should meet the acceptance criteria. Deviations, out-of-specification and out-of-limit results should be documented and investigated according to appropriate procedures. If these deviations are accepted, this should be justified. Where necessary, further studies should be performed.

9.6 The conclusion of the report should state whether or not the outcome of the qualification and/or validation was considered successful, and should make recommendations for future monitoring and setting of alert and action limits where applicable.

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

9.8 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.

9.9 Any deviations found during the validation process should be managed and documented. Corrective actions should be considered.
10. QUALIFICATION

10.1 There are different approaches in qualification and validation. The manufacturer should select an appropriate approach for the conduct thereof.

Figure 1. The V-model as an example of an approach to qualification and validation.

*Note. See text below for clarification on terms and stages

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

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

10.4 Normally, qualification should be completed before process validation is performed.

10.5 The process of qualification should be a logical, systematic process and should follow a logical flow from the premises, followed by utilities, equipment, to procedures and processes.

10.6 Stages of qualification should normally start with the preparation
of user requirement specifications (URS). Depending on the function and
operation of the utility, equipment or system, this is followed by, as
appropriate, different stages in qualification such as a factory acceptance
test (FAT), site acceptance test (SAT), design qualification (DQ),
installation qualification (IQ), operational qualification (OQ) and
performance qualification (PQ).

10.7 One stage of qualification should be successfully completed before
the next stage is initiated, e.g. from IQ to OQ.

10.8 In some cases, only IQ and 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.

Major equipment and critical utilities and systems, however, may require
URS, DQ, IQ, OQ and PQ.

10.9 Computerized systems, including equipment with software
component(s), require user and functional requirements specifications,
design and configuration specifications, development of SOPs, training
programmes for system use and administration, and an appropriate level of
IQ, OQ and PQ verification testing. This includes tests such as stress, load,
volume and other performance verification tests that mimic the live
production environment. It also includes user acceptance testing according
to draft SOPs and training as well as end-to-end business processes for
intended use.

(Note: See WHO Guidelines on computerized system validation for
details)

User requirement specifications
10.10 Manufacturers should prepare a document that describes, for
example, the utility or equipment to be sourced. The requirements and
specifications for the utility or equipment should be defined by the user
and documented in the URS.

10.11 The URS should be used when selecting the required utility or
equipment from an approved supplier, and to verify suitability throughout
the subsequent stages of qualification.
Factory acceptance test and site acceptance test
10.12 Where appropriate, FAT and SAT should be performed to verify the suitability of the system at site, prior to the subsequent stages of qualification. This should be appropriately documented.

Design qualification
10.13 DQ should provide documented evidence that the design specifications were met and are in accordance with the URS.

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

10.15 The design specifications, including purchase specifications, drawings, manuals, spare parts lists and vendor details should be verified during IQ as should the configuration specifications for the intended operational environment.

10.16 Components installed should be verified and documented evidence should be provided that components meet specifications, are traceable and are of the appropriate material of construction.

10.17 Control and measuring devices should be calibrated.

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

10.19 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).

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

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

Performance qualification
10.22 PQ should be conducted prior to release of the utilities,
systems or equipment under conditions simulating conditions of intended use
to provide documented evidence that utilities, systems or equipment and
all its components can consistently perform in accordance with the
specifications under routine use.

10.23 Test results should also be collected over a suitable period of time
during continuous process verification and/or periodic review and
monitoring of the utilities, systems and equipment to prove consistency.

Requalification

10.24 Utilities, systems and equipment should be maintained in a validated
state. Any changes made to these should be managed through the change
control procedure. The extent of validation or qualification as a result of
such a change should be determined based on risk management principles.

10.25 Requalification should be done based on the identified need. The
requalification should be considered based on risk management principles.
Factors such as the frequency of use, breakdowns, results of operation,
criticality, preventive maintenance, repairs, calibration, verification may
be considered.

10.26 Requalification should also be considered after cumulative /
multiple changes.

10.27 Changes of equipment which involve the replacement of
equipment on a “like-for-like” basis will require requalification.
Replacement of parts may not require full requalification.

10.28 Where a system, utility or equipment has not been used for an
extended period of time, requalification may have to be considered.

10.29 Where appropriate, periodic requalification may be performed.

Revalidation

10.30 Systems should be in place to ensure that procedures remain in a
validated state, e.g. such as through verification in cleaning validation and
analytical method validation.

10.31 Revalidation should be done when the need is identified.
10.32 Where periodic revalidation is done, this should be done in accordance with a defined schedule to ensure that the validated state is maintained.

10.33 Periodic revalidation should be considered as some process changes may occur gradually over a period of time, or because of wear of equipment.

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

**Process validation**

“New approach”

10.35 It is recommended that manufacturers implement the new approach in process validation. See *Guidelines on process validation*.

“Traditional approach”

10.36 Where the “traditional approach” in process validation is followed, the need for validation should be considered, e.g. through product quality review.

11. **CHANGE MANAGEMENT**

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

11.2 When a change is initiated, consideration should be given to previous changes and whether requalification and/or revalidation is needed as a result of the cumulative effect of the changes.

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

12. **DEVIATION MANAGEMENT**

12.1 Deviations during validation and qualification should be documented and investigated, through the deviation management procedure.
13. CALIBRATION AND VERIFICATION

13.1 Calibration and verification of equipment, instruments and other devices, as applicable, should be initiated during installation qualification to ensure that the system operates according to the described specifications and because the calibration status could have been affected during transport and installation.

13.2 Thereafter, it should be performed at regular intervals in accordance with a calibration programme and SOPs.

13.3 Personnel who carry out calibration and preventive maintenance should have an appropriate qualification and training.

13.4 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.

13.5 There should be traceability to standards (e.g. national, regional or international standards) used in the calibration. A valid certificate of calibration should be maintained which is dated and includes reference to and traceability to, e.g. standards used, acceptance limits, uncertainty where applicable, range, calibration due date.

13.6 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.

13.7 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.

13.8 Equipment, instruments and other devices should be calibrated before or on the due date for calibration to ensure that they remain in a calibrated state.

13.9 Where instruments and devices are identified as critical or non-critical, or impacting and non-impacting for the purpose of calibration, documented evidence of the decision making process should be available.
This should include impact and or risk assessment.

References


2. Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms (working document QAS/15.639/Rev.1) (*Appendix 1*).


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