GUIDELINES ON QUALIFICATION - APPENDIX 6
VALIDATION

(September 2018)

DRAFT FOR COMMENTS

Please forward any comments you may have on the attached text to Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies, Standards and Norms (kopps@who.int) with a copy to Mrs Xenia Finnerty (finnertyk@who.int) by 15 November 2018.

Medicines Quality Assurance working documents will only be sent out electronically and will also be placed on the Medicines website for comments under “Current projects”. If you have not already received our draft working documents, please send your email address (to jonessi@who.int) and we will add it to our electronic mailing list.

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SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/16.673/Rev.2: GUIDELINES ON QUALIFICATION - APPENDIX 6 VALIDATION

<table>
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<tr>
<th>Discussion of proposed need for revision in view of the current trends in validation during informal consultation on data management, bioequivalence, good manufacturing practices (GMP) and medicines’ inspection.</th>
<th>29 June – 1 July 2015</th>
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<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>
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<td>Presentation of the progress made to the fiftieth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP).</td>
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<td>Discussion at the informal consultation on good practices for health products manufacture and inspection, Geneva.</td>
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<td>Preparation of revised text by Dr A.J. van Zyl, participant at the above-mentioned consultation, based on the feedback received during and after the informal consultation by the meeting participants and members of PQT-Inspections.</td>
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<td>Presentation to the fifty-first meeting of the ECSPP.</td>
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<td>Preparation of revised text by Dr A.J. van Zyl based on the feedback received during the public consultation and the fifty-first ECSPP meeting.</td>
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<td>Circulation of revised working document for public consultation.</td>
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<td>Discussion at the informal consultation on GMP and inspection, Geneva.</td>
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<td>Cleaning-up of the changes agreed during the consultation and circulation of revised working document for another round of public consultation.</td>
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<td>Presentation to the fifty-third meeting of ECSPP.</td>
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<td>Any other follow-up action as required.</td>
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BACKGROUND INFORMATION

The need for revision of the published *Supplementary guidelines on good manufacturing practices: validation* (World Health Organization (WHO) Technical Report Series, No. 937, 2006, Annex 4) was identified by the Prequalification of Medicines Programme and a draft document was circulated for comments 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 WHO Expert Committee on Specifications for Pharmaceutical Preparations (ECSPP) at its forty-ninth meeting in October 2014.

The main text was sent out for consultation as a *working document QAS/15.639* entitled *Guidelines on validation* which constitute the general principles of the new guidance on validation.

The draft on the specific topics, the appendices to this main text, will follow. One of them, the *Validation on qualification of systems, utilities and equipment*, newly entitled *Guidelines on qualification*, constitutes this working document.

The following is an overview on the appendices that are intended to complement the general text on validation:

**Appendix 1**
*Validation of heating, ventilation and air-conditioning systems (HVAC)*

will be replaced by cross-reference to the WHO Guidelines on GMP for HVAC systems for considerations in qualification of HVAC systems

(— Annex 8 in TRS 1010, 2018)

**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*

**Appendix 3**

*Cleaning validation* – consensus to retain

**Appendix 4**

*Analytical method validation*

→ will be replaced by update – working document QAS/16.671

**Appendix 5**

*Validation of computerized systems*

→ will be replaced by update – working document QAS/16.667

**Appendix 6**

*Guideline on Qualification – updated text proposed in this working document*  
(new title)

**Appendix 7**


**Brief background on the changes in this document**

There was some confusion regarding the title. It is therefore suggested to change the title to GUIDELINES ON QUALIFICATION. In this way, the general principles in qualification are addressed which can be applied for systems, equipment, and so on.

Based on the comments, the general chapters on objective and scope were written to make it clear that the guidelines address principles of qualification that can be applied, as appropriate, to
premises, systems, utilities and equipment and to include the application of risk management principles.

Moreover, duplication was removed, logical flow of concepts addressed and aligned with international texts and the comments. The V Model has been removed based on the feedback received. In the former published text on qualification, protocol formats were included. These protocol formats were extracted from training materials and were intended to serve as examples. In view of the feedback that seemingly manufacturers took them as absolute examples to be used, these examples have been removed in the current version.
APPENDIX 6
GUIDELINES ON QUALIFICATION

1. Principle
2. Scope
3. Glossary
4. General
5. User requirement specifications
6. Design qualification
7. Factory acceptance test and site acceptance test
8. Installation qualification
9. Operational qualification
10. Performance qualification
11. Periodic review and requalification

1. PRINCIPLE

1.1 In principle, premises, systems, utilities and equipment should be appropriately designed, installed, qualified, operated, cleaned and maintained to suit their intended purpose.
1.2 Quality management systems should be in place to ensure that these remain in a qualified state throughout their life cycle.
1.3 Products should be manufactured on qualified equipment.
1.4 Manufacturers who may use an alternative verification framework to achieve qualification should ensure the qualification expectations within this guide are satisfied.
2. SCOPE

2.1 These guidelines describe the general approach to qualification, for example, premises, systems, computerized system, utilities and equipment.

2.2 The principles in these guidelines may also be applied to the qualification of instruments, analytical instruments and testing devices, where appropriate.

2.3 These may include and are not limited to: certain rooms; water purification systems; cleaning systems; heating, ventilation and air conditioning systems; compressed air systems; gas systems; steam systems; as well as production equipment and analytical instruments.

2.4 Separate guidelines in this series address other principles in validation such as process validation and cleaning validation (see references at the end of this document).

2.5 The principle can be used when de-commissioning equipment to show that it remains fit for its purpose throughout the life cycle.

3. GLOSSARY

computerized system. A computerized system collectively controls the performance and execution of one or more automated processes and/or functions. It includes computer hardware, software, peripheral devices, networks and documentation, for example, manuals and standard operating procedures (SOPs), as well as personnel interacting with hardware and software.

design qualification. Documented evidence that, for example, the premises, supporting systems, utilities and equipment have been designed for their intended purposes and in accordance with the requirements of good manufacturing practices (GMP).
factory acceptance test. A test conducted, usually at the vendor’s premises, to verify that the system, equipment or utility, as assembled or partially assembled, meets approved specifications. *(new)*

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

performance qualification. 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.)

site acceptance test. A test conducted at the site of use to verify that the system, equipment or utility, as assembled or partially assembled meets approved specifications. *(new)*

system. A regulated pattern of interacting activities and techniques that are united to form an organized whole.

user requirement specifications. An authorized document that defines the requirements for use of the system, equipment or utility in its intended production environment. *(amended)*

utility. A system consisting of one or more components to form a structure designed to collectively operate, function or perform and provide a service such as electricity, water, ventilation or other. *(new)*
4. GENERAL

Note: The remainder of the text in these guidelines will refer to utilities and equipment as examples, even though the principles may be applicable to others such as premises and systems.

4.1 The validation master plan, or other relevant document, should specify the policy, organization, planning, scope and stages applied in qualification on site, and should cover, for example, production, quality control and engineering.

4.2 Quality risk management principles should be applied in qualification. These include:

- A clear understanding of the system, and the role it plays in establishing/protecting the process and quality and all of the potential ways (risks) the process or quality could be impacted by failures, events, errors, or time/use-based factors (deterioration, out of tolerance instruments, wear and tear, and so on);
- Defining all of the Design, Procedural and/or Quality System Controls required to protect against these potential risks. These controls either mitigate/reduce the risks and/or detect the impact to quality or process – should the risk occur. (To ensure the “failure” does not impact final product quality);
- Compiling evidence during the design, engineering, commissioning and qualification to demonstrate that all of these required “controls” have been properly implemented and verified. (Including “function” where applicable – such as alarms on operating parameters);
- Appropriate control and oversight of change once the controls have been verified.

4.3 The scope and extent of qualification and requalification should be determined based on the principles of impact assessment and risk management principles.

4.4 Qualification should be executed by trained personnel. Training records should be maintained.
4.5 Where appropriate, new premises, systems, utilities and equipment should be subjected to all stages of qualification. This includes the preparation of user requirement specifications (URS), design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

4.6 Justification should be provided where it is decided that not all stages of qualification are required.

4.7 Qualification should be done in accordance with predetermined and approved qualification protocols. The protocol should specify the prerequisites and test details, including acceptance criteria.

4.8 The results of the qualification should be recorded and reflected in qualification reports.

4.9 A qualification report prepared at the completion of each protocol or stage of qualification (Installation/Operational/Performance) should include, or reference as appropriate, the following:

- test results, including supporting calculations, documentation and raw/original data,
- test failures,
- protocol departures,
- recommendations and justification for issue resolution, and
- conclusions.

4.10 There should be a logical sequence for executing qualification, such as premises (rooms), then utilities and equipment.

4.11 Normally, qualification stages should be sequential. (For example, operational qualification should follow after the successful completion of installation qualification.) In some
cases, different stages of qualification may be executed concurrently. This should be justified and documented in the validation master plan (or qualification protocol).

4.12 Equipment should be released for routine use only once there is documented evidence that the qualification has been successful.

4.13 Certain stages of the qualification may be done by a supplier or a third party, subject to the conditions and responsibilities as defined in a written agreement between the parties. The contract giver remains responsible to ensure that the qualification is done in accordance with the principles of GMP.

4.14 The relevant documentation associated with qualification, including SOPs, specifications and acceptance criteria, certificates and manuals, should be available.

4.15 Utilities and equipment should be maintained in a qualified state and should be periodically reviewed for the need for requalification. Requalification should be considered when changes are made.

5. USER REQUIREMENT SPECIFICATIONS

5.1 URS should be prepared for, but not limited to, utilities and equipment, as appropriate.

5.2 URS should be used at later stages in qualification to verify that the purchased and supplied utility or equipment is in accordance with the user’s needs.

6. DESIGN QUALIFICATION

6.1 DQ should demonstrate that the system, as designed, is appropriate for its intended use as defined in the URS.
6.2 A suitable supplier should be selected and approved for the relevant utility or equipment.

7. FACTORY ACCEPTANCE TEST AND SITE ACCEPTANCE TEST

7.1 Where a utility or equipment is assembled, or partially assembled at a site other than that of the purchaser or end-user, testing and verification may be done, based on quality risk management principles, to ensure that it is appropriate and ready for dispatch.

7.2 The checks and tests during factory acceptance test (FAT) should be recorded.

7.3 The acceptability of the assembly and overall status of the utility or equipment should be described in a conclusion of the report for the FAT, prior to shipment.

7.4 Tests, based on quality risk management principles, may be performed to verify the acceptability of the utility or equipment when it is received at the end-user. This is a site acceptance test (SAT).

7.5 The results of the tests should be evaluated and the outcome of the acceptability of the utility or equipment should be recorded in the conclusion section of the report for the SAT.

8. INSTALLATION QUALIFICATION

8.1 Utilities and equipment should be correctly installed, in an appropriate location.

8.2 There should be documented evidence of the installation. This should be in accordance with the IQ protocol which contains all the relevant details.

8.3 IQ should include identification and installation verification of relevant components identified, e.g. services, controls and gauges.
8.4 Identified measuring, control and indicating devices, should be calibrated on site unless otherwise appropriately justified. The calibration should be traceable to national or international standards. Traceable certificates should be available.

8.5 Deviations and non-conformances, including those from URS, DQ and acceptance criteria specified and observed during installation, should be recorded, investigated, and corrected or justified.

8.6 Normally, the outcome of the IQ should be recorded in the conclusion of the report, before OQ is started.

9. OPERATIONAL QUALIFICATION

9.1 Requirements and procedures for operation (or use), calibration, maintenance and cleaning should normally be prepared normally before OQ and approved prior to PQ.

9.2 Utilities and equipment should operate correctly and their operation should be verified in accordance with an OQ protocol. OQ normally follows IQ but, depending on the complexity of utility or equipment, it may be performed as a combined installation/operation qualification (IOQ). This should be justified and documented in the validation master plan (or qualification protocol).

9.3 OQ should include, but is not limited to, the following:

- tests that have been developed from the knowledge of processes, systems and equipment to ensure the utility or equipment is operating as designed; and

- tests to confirm upper and lower operating limits, and/or “worst case” conditions.
9.4 Training of operators for the utilities and equipment should be provided and training records maintained.

9.5 Calibration, cleaning, maintenance, training and related tests and results should be verified to be acceptable.

9.6 Deviations and non-conformances observed should be recorded, investigated and corrected or justified.

9.7 The results for the verification of operation should be documented in the OQ report.

The outcome of the OQ should be recorded in the conclusion of the report, normally before PQ is started.

10. PERFORMANCE QUALIFICATION

10.1 PQ should normally follow the successful completion of IQ and OQ. In some cases, it may be appropriate to perform PQ in conjunction with OQ or process validation. This should be justified and documented in the validation master plan (or qualification protocol).

10.2 PQ should include, but is not limited to, the following:

- tests using production materials, qualified substitutes or simulated products proven to have equivalent behaviour under normal operating conditions with worst case scenario and batch sizes where appropriate; and
- tests should cover the intended operating range.

10.3 Utilities and equipment should consistently perform in accordance with their design specifications and URS. The performance should be verified in accordance with a PQ protocol.
10.4 There should be records (for example, a PQ report) for the PQ to indicate the satisfactory performance over a predefined period of time. Manufacturers should justify the period over which PQ is done.

11. PERIODIC REVIEW AND REQUALIFICATION

11.1 Utilities and equipment should be maintained in a qualified state through the life cycle of the utility or equipment.

11.2 Utilities and equipment should be reviewed periodically to confirm that they remain in a qualified state or to determine the need for requalification.

11.3 Where the need for requalification is identified, this should be performed.

11.4 Risk management principles should be applied in the review and requalification and the possible impact of small changes over a period of time should further be considered (such as, through change control).

11.5 Risk management principles may include factors such as calibration, verification, maintenance data and other information.

11.6 The qualification status and requalification due dates should be documented, for example, in a qualification matrix, schedule or plan.

11.7 In case a utility or equipment in use is identified, where it had not been subjected to qualification, a qualification protocol should be prepared where elements of URS, design specifications, operation and performance are verified for acceptability. The outcome of this qualification should be recorded in a report.
Reference documents for additional reading

[Note from the Secretariat: The references below will be updated upon finalization of the related texts.]

See WHO TRS 970, 2012, Annex 2, for aspects to be considered for inclusion in qualification of water purification systems.

See WHO TRS 1010, 2018, Annex 8, for aspects to be considered for inclusion in qualification of heating, ventilation and air-conditioning (HVAC) systems.

See WHO TRS XXX for aspects to be considered for inclusion in qualification and validation of computerized systems (QAS working document QAS/16.677).

See WHO TRS 992, 2015, Annex 3, for aspects to be considered in process validation.

See WHO TRS XXX for aspects to be considered in analytical method validation (QAS working document QAS/16.671).

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