Annex 3

Good manufacturing practices: guidelines on validation

Background

The need for revision of the published World Health Organization (WHO) *Supplementary guidelines on good manufacturing practices: validation* (*1*) was identified by the Prequalification of Medicines Programme and a first draft document was circulated for comment in early 2013. The focus, at that time, was revision of the appendix on *Non-sterile process validation* (Appendix 7) (*2*), which had been revised and was adopted by the ECSPP at its Forty-ninth meeting in October 2014 (*3*).

The overarching text presented in this annex constitutes the general principles of the new guidance on validation.

The following appendices included in this annex address specific aspects of validation and are intended to complement the general text on validation:

- Appendix 1. Validation of heating, ventilation and air-conditioning systems (as cross-reference to TRS 1010, Annex 8 (*4*))
- Appendix 2. Validation of water systems for pharmaceutical use (as published in TRS 937, Annex 4, 2006 and as cross-reference to TRS 970, Annex 2, 2012 (*5*)
- Appendix 3. Cleaning validation (as published in TRS and TRS 937, Annex 4, 2006 and as cross-reference to TRS 970, Annex 2, 2012 (*5*)
- Appendix 4. Analytical procedure validation (adopted, subject to a review of the comments received by a subgroup of the Expert Committee)
- Appendix 5. Validation of computerized systems (adopted, subject to the changes discussed by the Expert Committee)
- Appendix 6. Guidelines on qualification (adopted, subject to a review of the comments received by a subgroup of the Expert Committee)
- Appendix 7. Non-sterile process validation (as published in TRS 992, Annex 3, 2015 (*3*)).

1. Introduction

1.1 Validation is an essential part of good practices, including good manufacturing practices (GMP) (*6*) 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, for example, a product, process, method, system, equipment or utility.

1.2 These guidelines cover the general principles of qualification and validation. In addition to the main text, appendices on some validation and qualification activities (such as applied to heating, ventilation and air-conditioning systems, water systems, cleaning, analytical methods, computerized systems, and non-sterile processes) are included.

1.3 The following principles apply:

1. the execution of qualification and validation should be in compliance with regulatory expectations (*7*);
2. quality must be designed and built into the product;
3. quality cannot be inspected or tested into the product;
4. principles of quality risk management (8) should be applied in determining the need, scope and extent of qualification and validation;
5. ongoing review should take place, to ensure that the qualified or validated state is maintained and opportunities for continuing improvement are identified.

1.4 Provision should be made for appropriate resources such as personnel, financing and time to organize, plan and execute qualification and validation.

2. Scope

2.1 These guidelines focus mainly on the overall concept of qualification and 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 production and control of starting materials and finished pharmaceutical products, as well as other areas such as GCP. Although the principles addressed in this guideline are applicable, qualification and validation of specific products, methods, processes and systems, such as bioanalytical methods, and manufacturing

processes for sterile products, may require other considerations 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 qualification and validation of premises, equipment, utilities, systems, methods, 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 (especially weighing), 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/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 the system is maintained in a validated state.

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.

computerized system validation. Confirmation by examination and provision of objective documented evidence that specifications for computerized systems 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.

installation qualification. Documented verification that the installations (such as machines equipment and instruments, computer system components, measuring devices, utilities and manufacturing) 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).

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 when properly installed, and/or work correctly and lead to the expected results.

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 that are 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. A high-level document that summarizes the manufacturer's overall philosophy and approach, to be used for establishing performance adequacy. It provides information on the manufacturer's qualification and validation work programme and defines details of and timelines for the 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 validation, including the acceptance criteria.

validation report. A document in which the records, results and evaluation of validation are documented and summarized. It should also contain a conclusion of the outcome of the validation.

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 standard operating procedures, 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 In general, qualification and validation follow similar underlying principles. The term "qualification" is normally used, for example, for equipment and utilities, and "validation", for example, for systems, methods and processes.

4.2 Qualification normally precedes validation.

5. Validation

Approaches to qualification and validation

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

5.2 Statistical evaluation should be applied, where appropriate, and provide scientific evidence that, for example, the process, system or other related aspect is appropriately qualified or validated.

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

5.4 There should be an appropriate and effective quality management system supporting the organization, planning, execution and management of qualification and validation.

5.5 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.

5.6 Personnel with appropriate education and experience should be responsible for qualification and validation.

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

5.8 Qualification and validation should be performed in a structured way, according to the documented protocols and procedures.

5.9 Qualification and validation (as appropriate), should be performed:

- for new premises, equipment and utilities;
- for new systems, methods, 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 (and may include requalification and revalidation).

5.10 The scope and extent of qualification and validation should be based on knowledge, experience and the outcome of principles of quality risk management, as described in the *WHO guidelines on quality risk management* (*8*).

5.11 Where necessary, worst-case situations or specific challenge tests should be considered for inclusion in the qualification and validation.

6. Documentation

6.1 Documents associated with qualification and validation may include:

- validation master plan;
- standard operating procedures (SOPs);
- specifications;
- protocols and reports;
- risk assessment outcomes;
- process flowcharts;
- operator manuals;
- training records;
- calibration procedures and records;
- sampling plans;
- testing plans and methods;
- statistical methods and results;
- history of qualification and validation;
- plan for ensuring maintaining a validated state including review of validation status.

7. Validation master plan

7.1 A manufacturer should have a validation master plan that reflects the key elements of validation. It should be concise and clear and at least contain reference to/have a short description of 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 that qualification and validation are done;
- outsourced services (selection, qualification, management through the life-cycle);
- scope of qualification and validation;
- documentation required in qualification and validation, such as procedures, certificates, protocols and reports;
- premises qualification, such as room verification where appropriate;
- qualification of utilities;
- equipment and instrument qualification;
- process validation;
- cleaning validation;
- personnel qualification (such as analyst qualification);
- analytical method validation;
- computerized system validation;
- establishment of acceptance criteria;
- life-cycle management, including retirement policy;
- requalification and revalidation;
- relationship with other quality management elements;
- validation matrix (such as a table indicating the history and status of qualification and validation on-site);
- retention of qualification and validation documentation;
- deviation management;
- change control;
- risk management principles;

- training;
- references.

7.2 The validation master plan 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 be appropriate for the qualification or validation to be executed, and may include the following significant background information:

- a unique document number and version number;
- the objective and scope;
- the site;
- the responsible personnel;
- reference to applicable standard operating procedures;
- equipment or instruments to be used;
- reference to standards, 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;
- change control, deviations;
- attachments and reference to attachments, including source data (where relevant);
- archiving and retention.

8.3 There should be a description of the procedure for review, evaluation and interpretation of results, including the application of statistical methods, where appropriate.

8.4 The protocol should be approved by responsible persons, including the quality unit, prior to use. Any changes to a protocol should be approved prior to implementation of the change.

8.5 The protocol should be executed by trained personnel. Records of the training and assessment should be retained.

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; reference to the protocol; reference to the appropriate risk assessment; details of materials, equipment, programmes and cycles used; procedures and test methods; data; changes and deviations; out-of-specification and non-conformance results, with appropriate traceability; and a conclusion.

9.3 Results should be recorded and be in compliance with good data and record management practices (*7*).

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

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

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 When appropriate, the quality assurance department should approve the report. The criteria for approval should be in accordance with the company's quality assurance system.

10. Qualification

10.1 There are different approaches in qualification. The manufacturer should select an appropriate approach for the conduct thereof (see Appendix 6).

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 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 design qualification (DQ), a factory acceptance test (FAT), site acceptance test (SAT), 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. For example, OQ normally follows IQ but, depending on the complexity of the equipment, it may be performed as a combined installation/operation qualification (IOQ). Conditional approval to proceed to the next qualification stage can be given where certain acceptance criteria or deviations have not been fully addressed and there is a documented assessment that there is no significant impact on the next activity.

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.

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

10.10 Computerized systems, including equipment with software component(s), should be appropriately qualified and validated (see Appendices 5 and 6).

User requirement specifications

10.11 Manufacturers should prepare a document that describes the requirements for the item (such as system(s) for a utility; or equipment) to be sourced.

The requirements may include specifications and should ensure that possible GMP risks are addressed; include technical requirements; and reference associated documentation.

10.12 The URS should be used when selecting the required item from an approved supplier, and to verify suitability throughout the subsequent stages of qualification.

Design qualification

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

Factory acceptance test and site acceptance test

10.14 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.

Installation qualification

10.15 IQ should provide documented evidence that the installation was complete and satisfactory, including supporting utilities, where appropriate.

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

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

10.18 Applicable control and measuring devices, identified through impact or risk assessment, should be calibrated.

Operational qualification

10.19 OQ should provide documented evidence that utilities, systems or equipment operate in accordance with operational specifications.

10.20 Tests should be designed to demonstrate satisfactory operation over the normal operating range, as well as at the limits of its operating conditions. Worst-case conditions may be included in the testing.

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

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

Performance qualification

10.23 Normally, PQ should be conducted prior to release of the utilities, systems or equipment. PQ should be performed under conditions simulating the intended use, to provide documented evidence that these can consistently perform in accordance with the specifications under routine use.

Requalification

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

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

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

10.27 The scope and extent of requalification should be determined when components or parts are replaced.

10.28 Where a system or 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.

11. Revalidation

11.1 Systems should be in place to ensure that procedures, processes and methods remain in a validated state, for example, through periodic review or verification (e.g. in cleaning validation and analytical method validation).

11.2 Revalidation should be done based on the identified need and principles of risk management.

11.3 Any changes made to, for example, procedures, processes and methods, should be managed through the change-control procedure. The extent of validation or revalidation as a result of such a change should be determined based on principles of risk management.

11.4 Where appropriate, periodic revalidation may be performed.

12. Process validation

For recommendations on process validation, see reference (*3*).

13. Change management

13.1 Changes should be controlled in accordance with the appropriate quality management system.

13.2 When a change is initiated, consideration should be given to previous changes and the impact of the cumulative effect of the changes. The scope and extent of qualification and validation should be determined based on risk management principles.

14. Deviation management

14.1 Any deviation during qualification and validation should be appropriately managed (e.g. investigated, evaluated, the impact assessed, and documented) through an appropriate quality management system.

14.2 Corrective actions should be considered.

15. Calibration and verification

15.1 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.

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

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

15.4 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.

15.5 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, for example, standards used, acceptance limits, uncertainty where applicable, range, calibration due date.

15.6 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.

15.7 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.

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

15.9 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

1. Supplementary guidelines on good manufacturing practices: validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937; http://apps.who.int/medicinedocs/documents/s20108en/s20108en.pdf, accessed 9 February 2019).
2. Appendix 7: Non-sterile process validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937; http://apps.who.int/medicinedocs/documents/s20108en/s20108en.pdf, accessed 9 February 2019).
3. Guidelines on good manufacturing practices: validation. Appendix 7: Non-sterile process validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-ninth report. Geneva: World Health Organization; 2015: Annex 3 (WHO Technical Report Series, No. 992; https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex3-TRS992.pdf, accessed 8 February 2019).

4. Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization; 2018: Annex 8 (WHO Technical Report Series, No. 1010; http://apps.who.int/medicinedocs/documents/s23455en/s23455en.pdf, accessed 9 February 2019).
5. WHO good manufacturing practices: water for pharmaceutical use. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-sixth report. Geneva: World Health Organization; 2012: Annex 2 (WHO Technical Report Series, No. 970; Geneva, World Health Organization 2012 (WHO Technical Report Series, No. 970; http://apps.who.int/medicinedocs/documents/s19464en/s19464en.pdf, accessed 11 February 2019).
6. World Health Organization. Quality assurance of pharmaceuticals. WHO guidelines, good practices, related regulatory guidance and GXP training materials. CD-ROM, update 2018 (http://digicollection.org/whoqapharm/, accessed 8 February 2019).
7. Guidance on good data and record management practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fiftieth report. Geneva: World Health Organization; 2016: Annex 5 (WHO Technical Report Series, No. 966; https://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf, accessed 8 February 2019).
8. WHO guidelines on quality risk management. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-seventh report. Geneva: World Health Organization; 2013: Annex 2 (WHO Technical Report Series, No. 981; https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex2TRS-981.pdf, accessed 8 February 2019).

Appendix 1

Validation of heating, ventilation and air-conditioning systems

For details on the validation of heating, ventilation and air-conditioning systems, please see:

- Appendix 1: Guidelines on heating, ventilation and air-conditioning systems for non-sterile pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fifty-second report. Geneva: World Health Organization; 2018: Annex 8 (WHO Technical Report Series, No. 1010; http://apps.who.int/medicinedocs/documents/s23455en/s23455en.pdf).

Appendix 2

Validation of water systems for pharmaceutical use

The text of this appendix was previously published as:

- Appendix 2: Validation of water systems for pharmaceutical use. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937; https://www.who.int/medicines/areas/quality_safety/quality_assurance/SupplementaryGMPValidationTRS937Annex4.pdf?ua=1).

For details on the validation of water systems for pharmaceutical use, please see:

- WHO good manufacturing practices: water for pharmaceutical use. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-sixth report. Geneva: World Health Organization; 2012: Annex 2 (WHO Technical Report Series, No. 970; Geneva, World Health Organization 2012 (WHO Technical Report Series, No. 970; http://apps.who.int/medicinedocs/documents/s19464en/s19464en.pdf).

Appendix 3

Cleaning validation

The text of this appendix was previously published as:

- Appendix 3: Cleaning validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937; https://www.who.int/medicines/areas/quality_safety/quality_assurance/SupplementaryGMPValidationTRS937Annex4.pdf?ua=1).

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 [APIs] 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, for example, the use of strong acids and alkalis during the cleaning process;
- 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, for example, 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 APIs.

3. General

3.1 There should be written standard operating procedures (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.);
- 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

Cleaning validation protocols

4.1 Cleaning validation should be described in cleaning validation protocols, which should be formally approved, for example, by the quality control or quality assurance unit.

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

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

4.3 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 (the 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, for example, 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;

- Documentation of the choice of cleaning agent and approval by the quality unit, which should be scientifically justified on the basis of, for example:
  - 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;
  - the manufacturer's recommendations;
- revalidation requirements.

4.4 Cleaning procedures for products and processes that 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.

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

4.6 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.

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

4.8 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.

Cleaning validation reports

4.9 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 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 the 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 that are difficult to clean, equipment that is difficult to clean, or 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 manufactured, 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, for example, 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

General

9.1 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.

9.2 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.

9.3 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.

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 (e.g. the adhesive used in swabs has been found to interfere with the analysis of samples).

9.4 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.

9.5 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.

9.6 Critical areas, that is, those that are hardest to clean, should be identified, particularly in large systems that employ semi-automatic or fully automatic clean-in-place systems.

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

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, for example, detergents.

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

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

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.

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

9.11 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;
- limit of quantitation;
- recovery, by spiking with the analyte;
- 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 chromatography; gas chromatography; and high pressure thin-layer chromatography). Other methods may include (alone or in combination) measurement of total organic carbon, pH, or conductivity; ultraviolet spectroscopy; and enzyme-linked immunosorbent assay.

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, for example, 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 (parts per million – ppm), limit per surface area (µg/cm2), 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);
- 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 manufacture and processing of such products.)

Appendix 4

Analytical procedure validation

Background

This is a revision of the previous publication:

- Supplementary guidelines on good manufacturing practices: validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Appendix 4: Analytical method validation. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937; http://apps.who.int/medicinedocs/documents/s20108en/s20108en.pdf).

1. Principle

1.1 This appendix presents some information on the principles and characteristics that should be considered during validation and life-cycle management of analytical procedures. 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. Owing to their complex nature, analytical procedures for biological and biotechnological products may, in some cases, be approached differently than is indicated in this document.

1.2 Validation is the documented evidence that the analytical procedure is suitable for its intended purpose.

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

1.4 Analytical procedures should be validated before being used for quality control purposes.

1.5 The recommendations as provided for in good practices (GXP) for pharmaceutical quality control laboratories (*1*), guidance on good data and record management practices (*2*) and guidelines for transfer of technology (*3*) should be followed, where applicable, when analytical procedure validation is organized and planned.

2. General

2.1 There should be specifications (a list of tests, references to analytical procedures and appropriate acceptance criteria) for both materials and products. The tests to be performed should be described in the documentation.

2.2 Acceptance criteria and test methods described in pharmacopoeias ("pharmacopoeial methods"), or suitably developed acceptance criteria or test methods ("non-pharmacopoeial methods"), as approved by the national regulatory authority (NRA), may be used.

2.3 Well-characterized reference standards, with documented suitability for the intended use, should be used in validation studies as well as in analysis.

2.4 The results of analytical procedures should be reliable, that is, attributable, legible, contemporaneous, original, accurate and reproducible.

2.5 The procedure should be followed, to continually assure that it meets the predefined criteria over its life-cycle.

2.6 Trend analysis and risk assessment should be considered at intervals, to ensure that the procedure is appropriate for its intended application.

2.7 Changes to procedures should be managed in accordance with the authorized change-control procedure. When analytical procedures are to be used by another laboratory and method transfer is not possible, the variability of reference standards and other factors, such as changes in the process for synthesis of the drug substance, changes in the composition of the finished product, changes in the analytical procedure, or changes to major pieces of equipment or instruments, should be considered. These should be understood, controlled and, where possible, reduced. Verification or revalidation should be considered, where appropriate.

2.8 The need and scope of verification or degree of revalidation depend on the nature of the change(s) and the outcome of risk assessment.

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

2.10 The data obtained during procedure validation and verification (including their associated metadata) should be considered covered by GXP requirements and are expected to follow the principles of GXP for data and record management (*2*).

2.11 When computerized systems are used to obtain and process data relating to procedure validation and verification, they should comply with the principles enunciated in *Appendix 5. Validation of computerized systems*.

2.12 Adequate attention should be paid to sample preparation. The description of this step should be as detailed as possible, especially if it can have a significant impact on test results (e.g. particular attention should be paid to details such as sonication time, sonication bath temperature and mixing, conditions of shaking, type of a shaker, and samples where demixing is known to occur). As sample preparation is an integral part of the analytical procedures, this step should be incorporated in the validation experiments as appropriate.

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 – see Section 6).

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 product under consideration (no placebo interference).

4. Non-pharmacopoeial methods

4.1 Non-pharmacopoeial methods should be appropriately validated.

5. Procedure 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.

5.3 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, sample preparation, reference standards, the formulae for the calculation of results and system suitability tests.

6. Procedure verification

6.1 Procedure verification consists of partial validation. It should be performed for already validated analytical procedures under the following circumstances:

- when an already validated procedure is used on a product for the first time (e.g. in case of a change in active pharmaceutical ingredient [API] supplier, change in the method of synthesis or after reformulation of a drug product);

- when an already validated procedure is used for the first time in a laboratory that is different from the one that validated the procedure (in some cases, method transfer may be preferable).

6.2 Procedure verification may include only the validation characteristics of relevance to the particular change. The selection of characteristics for verification depends on the procedure and its intended use and should be justified. For instance, in the case of a change in API supplier, the only expected difference would be in the impurity profile or solubility of the API, and therefore, for a procedure for related substances, there should be an appropriate verification that the procedure is able to detect and quantitate all potential impurities, even the late-eluting ones. Specificity should be among the tests considered (see Sections 9 for more detail).

6.3 Procedure verification is suitable in lieu of validation for pharmacopoeial methods.

7. Procedure revalidation

7.1 Procedures should be maintained in a validated state over the life-cycle of the procedure (see point 2.5). Whenever there are changes made to the analytical procedure, the impact assessment should be conducted and revalidation of the procedure should be considered. For example for a high-performance liquid chromatography (HPLC) method, changes requiring revalidation may include (please refer to *The International Pharmacopoeia* (*4*) and other pharmacopoeias for the acceptance limits beyond which revalidation must be performed):

- changes to the mobile phase;
- changes to the column;
- changes to the temperature of the column;
- changes to the concentration/composition of the samples and standards;
- changes to the detector (change in detector type, for example, if going from ultraviolet-visible detection to fluorimetry, or wavelength of detection).

7.2 In the case of repeated system suitability failures or when obtaining doubtful results, an investigation of the root cause should be performed. In the case that the procedure is identified as being the root cause, the appropriate changes should be made and the procedure revalidated.

7.3 Periodic revalidation of analytical procedures should be considered and the interval should be scientifically justifiable.

7.4 It is acceptable for revalidation to include only the validation characteristics of relevance to the particular change and procedure.

8. Method transfer

8.1 During method transfer, documented evidence should be established to prove that a method has equivalent performance when used in a laboratory that is different from the one where it has been validated.

8.2 Generally, it should be performed by comparing a set of results obtained by one laboratory to those obtained by another laboratory to which the method is being transferred.

8.3 The two sets of results should be compared and the differences between them should be within an acceptable range, which is predefined in the transfer protocol.

8.4 Method transfer should be performed before the testing of samples, with a view to obtaining critical data for a dossier, such as process validation or stability studies, or before being applied for routine use.

8.5 A predefined protocol should be followed, which includes at least: a title, objective, scope, responsibilities of the sending unit and the receiving unit; a specification of materials and methods; the experimental design and acceptance criteria; documentation (including information to be supplied with the results, and report forms to be used, if any); procedure for the handling of deviations; references; and details of reference samples (starting materials, intermediates and finished products). The protocol should be authorized and dated.

8.6 In the case of independent testing by a separate entity, such as a national quality control testing laboratory that is testing samples on its market, method transfer is not always possible. It is not considered an obligation but may be considered as an optional step when encountering difficulties in applying any particular method. See *WHO guidelines on transfer of technology in pharmaceutical technology* (*3*) for further reference.

9. Characteristics of analytical procedures

9.1 Characteristics that should be considered during validation of analytical procedures include:

- accuracy;
- precision;
- robustness;
- linearity;
- range;
- specificity;
- detection limit;
- quantitation limit.

This list should be considered typical but occasional exceptions should be dealt with on a case-by-case basis.

9.1.1 *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, for example, three concentrations/three replicates each.

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

9.1.2 *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 is usually expressed as the standard deviation or relative standard deviation.

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

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

Reproducibility expresses precision between laboratories.

9.1.3 *Robustness* 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.

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

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

The variation of extraction time and stability of analytical solutions are of particular importance.

9.1.4 *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. If linearity is not attainable, a nonlinear model may be used.

9.1.5 *Range* is an expression of the lowest and highest levels of analyte for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy and linearity. The specified range is normally derived from linearity studies.

9.1.6 *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 the assay. The procedures used to demonstrate specificity depend on the intended objective of the analytical procedure.

9.1.7 *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;
- calibration curve.

9.1.8 *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;
- calibration curve.

9.2 *Characteristics* (*including tests*) that should be considered when using different types of analytical procedures are summarized in Table A3.4.1. More details can be found in the guidelines listed in the Further reading section at the end of this appendix.

Table 3.4.1
Characteristics to consider during analytical validation

Type of analytical procedure		Testing for impurities		
Characteristics	**Identification**	**Quantitative tests**	**Limit tests**	**Assay[a]**
Accuracy	—	+	—	+
Precision				
Repeatability	—	+	—	+
Intermediate precision[b]	—	+	—	+
Specificity	+	+	+	+
Detection limit	—	—[c]	+	—

Table 3.4.1 *continued*

Type of analytical procedure		Testing for impurities		
Characteristics	**Identification**	**Quantitative tests**	**Limit tests**	**Assay[a]**
Quantitation limit	—	+	—	—
Linearity	—	+	—	+
Range	—	+	—	+

— Characteristic is not normally evaluated; + characteristic should normally be evaluated.

[a] dissolution (measurement only) or content/potency.

[b] In cases where a reproducibility study has been performed, intermediate precision is not needed.

[c] May be needed in some cases.

9.3 Statistical analysis used to evaluate validation characteristics against predetermined acceptance criteria should be appropriate for the intended evaluation. Statistical analysis should be performed using appropriately validated software. Alternatively, if validated software is not used, the calculations must be verified to be correct. An appropriate number of samples to provide adequate statistical power and range should be considered.

10. System suitability testing

Note: 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.

10.1 System suitability testing should be done as appropriate and defined in the test procedure.

10.2 System suitability runs should include only reference standards or established standards of known concentration, to provide an appropriate comparator for the potential variability of the instrument. The sample material or product under test should not be used as a standard to evaluate the suitability of the system (see *General guidelines for the establishment, maintenance and distribution of chemical reference substances* (*5*)).

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2. Guidance on good data and record management practices. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fiftieth report. Geneva: World Health Organization; 2016: Annex 5 (WHO Technical Report Series, No. 966; https://www.who.int/medicines/publications/pharmprep/WHO_TRS_996_annex05.pdf, accessed 8 February 2019).
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5. General guidelines for the establishment, maintenance and distribution of chemical reference substances. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-first report. Geneva: World Health Organization; 2007: Annex 3 (WHO Technical Report Series, No. 943; http://apps.who.int/medicinedocs/documents/s21438en/s21438en.pdf, accessed 12 February 2019).

Further reading

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Appendix 5

Validation of computerized systems

Background

This is a revision of the previous publication:

- Supplementary guidelines on good manufacturing practices: validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Appendix 5: Validation of computerized systems. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937; http://apps.who.int/medicinedocs/documents/s20108en/s20108en.pdf).

1. Introduction and scope

1.1 Computerized systems should be validated in accordance with the principles of quality risk management and the level of validation should be commensurate with the identified risks, complexity and intended use. This guide applies to systems used in good manufacturing practices (GMP) (*1*) but may be extended to systems used in all good practices (GXP) activities, as appropriate.

1.2 The purpose of validation is to confirm that the specifications of a computerized system conform to the user's needs and are fit for intended use, by examination and provision of documented and objective evidence that the particular requirements can be consistently fulfilled. Validation should establish confidence in the accuracy, reliability and consistency in the performance of the system, and should also ensure that all necessary technical and procedural controls are implemented, confirming compliance with good documentation practices for electronic data generated by the system (*1*).

1.3 System elements that need to be considered in validation of a computerized system include computer hardware and software, and related equipment, IT infrastructure and operating system environment, and documentation of procedures and systems, as appropriate, including user manuals. Persons should be appropriately trained and qualified, including but not limited to, developers, end-users, system application administrators, network engineers, database administrators and data managers. Computerized system validation activities should address both system functionality and configuration, as well as any custom-developed elements.

1.4 Computerized systems should be maintained throughout the system life-cycle, in a validated state, with risk-based controls for the operational phase, which may include, but are not limited to, system planning; preparation and verification of standard operating procedures (SOPs) and training programmes; system operation and maintenance, including handling of software and hardware updates; monitoring and review; change management; and incident reporting, followed by system retirement.

1.5 Depending on the types of systems or typical applications, such as process control systems (distributed control system [DCS], programmable logic controller [PLC], supervisory control and data acquisition [SCADA]); laboratory information management systems (LIMS); laboratory instrument control systems; and business systems (enterprise resource planning [ERP], manufacturing resource planning [MRP II]) used by the manufacturer.

Documentation covering, but not limited to, the following information and supporting process should be accessible on-site for review:

- purpose and scope;
- roles and responsibilities;
- validation approach;
- risk management approach;
- approved system requirement/specifications;
- system acceptance criteria;
- supplier selection and assessment;
- configuration management and change-control procedures;
- backup and recovery (application and data);
- error handling and corrective action;
- business continuity plan and disaster recovery;
- maintenance and support;
- data security, including cybersecurity;
- validation deliverables and documentation.

2. Glossary

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

archiving. Archiving is the process of protecting records from the possibility of being further altered or deleted, and storing these records under the control of independent data management personnel throughout the required retention period. Archived records should include, for example, associated metadata and electronic signatures.

audit trail. The audit trail is a form of metadata that contains information associated with actions that relate to the creation, modification or deletion of GXP records. An audit trail provides for secure recording of life-cycle details, such as creation, additions, deletions or alterations of information in a record, either paper or electronic, without obscuring or overwriting the original record. An audit trail facilitates the reconstruction of the history of such events relating to the record, regardless of its medium, including the "who", "what", "when" and "why" of the action. For example, in a paper record, an audit trail of a change would be documented via a single-line cross-out that allows the original entry to remain legible and documents the initials of the person making the change, the date of the change and the reason for

the change, as required to substantiate and justify the change. In electronic records, secure, computer-generated, time-stamped audit trails should allow for reconstruction of the course of events relating to the creation, modification and deletion of electronic data. Computer-generated audit trails should retain the original entry and document the user identification and the time/date stamp of the action, as well as the reason for the change, as required to substantiate and justify the action. Computer-generated audit trails may include discrete event logs, history files, database queries or reports, or other mechanisms that display events related to the computerized system, specific electronic records or specific data contained within the record.

automatic or live update. A process used to bring up-to-date software and system functionalities in a silent or announced way. More specifically, the update takes place automatically with or without the user's knowledge.

backup. A backup means a copy of one or more electronic files created as an alternative in case the original data or system are lost or become unusable (e.g. in the event of a system crash or corruption of a disk). It is important to note that backup differs from archiving, in that backup copies of electronic records are typically only temporarily stored for the purposes of disaster recovery and may be periodically overwritten. Such temporary backup copies should not be relied upon as an archiving mechanism.

business continuity plan. A documented plan that defines the ongoing process supported by management and funded to ensure that the necessary steps are taken to identify the impact of potential losses, maintain viable recovery strategies and recovery plans, and assure continuity of services through personnel training, plan testing and maintenance.

cloud based. A model for enabling on-demand network access to a shared pool of configurable computing resources that can be rapidly provisioned and released with minimal management effort or service provider interaction. These computing resources should be appropriately qualified.

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, as well as personnel interacting with hardware and software.

computerized systems validation. Confirmation by examination and provision of objective and documented evidence that a computerized system's predetermined specifications conform to user needs and intended use and that all requirements can be consistently fulfilled.

commercial off-the-shelf software (COTS). A vendor-supplied software component of a computerized system for which the user cannot claim complete control of the software life-cycle.

configuration management. A discipline applying technical and administrative direction and surveillance to identify and document the functional and physical characteristics of a configuration item, control changes to those characteristics, record and report change processing and implementation status, and verify compliance with specified requirements.

data. All original records and true copies of original records, including source data and metadata, and all subsequent transformations and reports of these data, which are generated or recorded at the time of the GMP activity and allow full and complete reconstruction and evaluation of the GMP activity. Data should be accurately recorded by permanent means at the time of the activity. Data may be contained in paper records (such as worksheets and logbooks), electronic records and audit trails, photographs, microfilm or microfiche, audio or video files or any other media whereby information related to GMP activities is recorded.

data integrity. The degree to which data are complete, consistent, accurate, trustworthy and reliable and to which these characteristics of the data are maintained throughout the data life-cycle. The data should be collected and maintained in a secure manner, such that they are attributable, legible, contemporaneously recorded, original or a true copy and accurate. Assuring data integrity requires appropriate quality and risk management systems, including adherence to sound scientific principles and good documentation practices (*1*).

data life-cycle. All phases of the process by which data are created, recorded, processed, reviewed, analysed and reported, transferred, stored and retrieved and monitored, until retirement and disposal. There should be a planned approach to assessing, monitoring and managing the data and the risks to those data, in a manner commensurate with potential impact on patient safety, product quality and/or the reliability of the decisions made throughout all phases of the data life-cycle.

disaster recovery. A documented process or set of procedures to recover and protect a business IT infrastructure in any event causing the system to be unavailable. It appropriately defines resources and actions to be taken before, during and after a disaster, to return the system to operational use.

functional specifications. The functional specifications define functions and technological solutions that are specified for the computerized system, based upon technical requirements needed to satisfy user requirements (e.g. specified bandwidth required to meet the user requirement for anticipated system usage).

legacy system. This refers to a mature computer system, programming language, application software, or processes that are used instead of available upgraded versions, and that have not been qualified according to current regulatory requirements.

master data. A single source of business data used across multiple systems, applications and processes and subject to change control to ensure accuracy throughout the data life-cycle.

metadata. Metadata are data about data that provide the contextual information required to understand those data. These include structural and descriptive metadata. Such data describe the structure, data elements, interrelationships and other characteristics of data. They also permit data to be attributable to an individual. Metadata necessary to evaluate the meaning of data should be securely linked to the data and subject to adequate review. For example, in weighing, the number 8 is meaningless without metadata, such as, the unit, milligram, gram, kilogram, etc. Other examples of metadata include the time/date stamp of an activity, the operator identification (ID) of the person who performed an activity, the instrument ID used, processing parameters, sequence files, audit trails and other data required to understand data and reconstruct activities.

production environment. For regulated computerized systems, the production environment is the business and computing operating environment in which the computerized system is being used for GMP-regulated purposes.

regression analysis and testing. A documented software verification and validation task to determine the extent of verification and validation analysis and testing that must be repeated when changes are made to any previously examined software component or system.

system life-cycle. The period of time that starts when a computerized system is conceived and ends when the system is retired and decommissioned, taking into consideration regulatory requirements. The system life-cycle typically includes a planning phase; a development phase that includes a design phase and a programming and testing phase; a qualification and release phase that includes a system integration and testing phase; a validation phase; a release phase; an operation and maintenance phase; and, finally, a system retirement phase.

user acceptance testing. Verification of the fully configured computerized system installed in the production environment (or in a test environment equivalent to the production environment) to perform, as intended, in the business process when operated by end-users trained in end-user SOPs that define system use and control. User acceptance testing (UAT) may be a component of the performance qualification (PQ) or a validation step separate from the PQ.

user requirements specification. The user requirements specification (URS), if prepared as a separate document, is a formal document that defines the requirements for use of the computerized system in its intended production environment.

3. Computerized system validation protocols and reports

3.1 A computerized system needs to be validated according to an approved protocol and a final report including results and conclusions, prior to routine use. All validation documentation should be appropriately retained.

Validation protocol

3.2 Validation should be executed in accordance with the validation protocol and applicable written procedures.

3.3 A validation protocol should define the objectives and the validation strategy, including roles and responsibilities and documentation and activities to be performed. The protocol should at least cover the scope, risk management approach, specification, acceptance criteria, testing, review, personnel training and release of the computerized system for GMP use.

3.4 The validation protocol should be tailored to the system type, impact, risks and requirements applicable to the system for which it governs validation activities.

Validation report

3.5 A validation report should be prepared, summarizing system validation activities.

3.6 The report should make reference to the protocol, outline the validation process, and include an evaluation and conclusion of results. Any changes or deviations from the validation protocol and applicable written procedures should be described and assessed, and justification for their acceptance or rejection should be documented. Deviations should be investigated and a root cause determined. A validation report should also include a summary of procedures and training.

3.7 Test results should be recorded, reviewed, analysed and compared against the predetermined acceptance criteria. All critical and major test discrepancies that occurred during the verification/validation testing should be investigated and resolved. If critical and major test discrepancies are accepted after investigation, they should be appropriately justified.

3.8 The conclusion of the report should state whether or not the outcome of the validation was considered successful and should make recommendations for future monitoring where applicable. The report should be approved after appropriately addressing any issue identified during validation, and the system should then be released for routine GMP use.

4. Supplier management

4.1 When third parties (e.g. suppliers, service providers) are used, such as to provide, install, configure, validate, maintain, modify or retain a computerized system or related service, or for data processing or system components, including cloud-based systems, an evaluation of the supplier, supplied system or service, and the supplier's quality systems should be conducted and recorded. The scope and depth of this evaluation should be based upon risk management principles.

4.2 The competence and reliability of a supplier are key factors when selecting a product and/or service provider. Supplier management is an ongoing process that requires periodic assessment and review of the system or service provided. Supplier evaluation activities may include, but are not limited to: completion of a quality-related questionnaire by the supplier; gathering of supplier documentation related to system development, testing and maintenance, including supplier procedures, specifications, system architecture diagrams, test evidence, release notes and other relevant supplier documentation; an on-site audit of the supplier's facilities, which may be conducted based on risk principles to evaluate the supplier's system life-cycle control procedures, practices and documentation.

4.3 A contract should be in place between the manufacturer and the supplier and/or the service provider, defining the roles and responsibilities and quality procedures for both parties, throughout the system life-cycle. The contract acceptor should not pass to a third party any of the work entrusted to her/him under the contract, without the manufacturer's prior evaluation and approval of the arrangements.

5. Requirements specifications

5.1 Requirements specifications should be written to document user requirements and functional or operational requirements and performance requirements. Requirements may be documented in separate user requirements specification (URS) and functional requirements specifications (FRS) documents, or in a combined document.

User requirements specifications

5.2 The authorized URS document, or equivalent, should describe the intended uses of the proposed computerized system and should define critical data and data life-cycle controls that will assure consistent and reliable data throughout the processes by which data are created, processed, transmitted,

reviewed, reported, retained and retrieved and eventually disposed. The URS should be written in a way to ensure that the data will meet regulatory requirements, such as the World Health Organization (WHO) *Guidance on good data and record management practices* (*1*).

5.3 Other aspects to be included in the URS may include, but are not limited to:

- the transaction or data to be entered, processed, reported, stored and retrieved by the system, including any master data and other data considered to be the most critical to system control and data output;
- the flow of data, including that of the business process(es) in which the system will be used, as well as the physical transfer of the data from the system to other systems or network components. Documentation of data flows and data process maps is recommended, to facilitate the assessment and mitigation and control of data integrity risks across the actual, intended data process(es);
- networks and operating system environments that support the data flows;
- the system interfaces with other systems and the overall security;
- the operating program;
- synchronization and security controls of time/date stamps;
- controls of both the application software as well as operating systems, to assure system access only to authorized persons;
- controls to ensure that data will be attributable to unique individuals (e.g. to prohibit use of shared or generic log-in credentials);
- controls to ensure that data related to GMP purposes is legibly and contemporaneously recorded to durable ("permanent") media at the time of each step and event, and controls that enforce the sequencing of each step and event (e.g. controls that prevent alteration or deletion of data in temporary memory in a manner that would not be documented);
- controls that assure that all steps that create, modify or delete electronic data related to GMP purposes will be recorded in independent, computer-generated audit trails or other metadata, or alternate documents that record the "what" (e.g. original entry), "who" (e.g. user ID), "when" (e.g. time/date stamp) and "why" (e.g. reason) of the action;
- backups and the ability to restore the system and data from backups;
- the ability to archive and retrieve the electronic data in a manner that assures that the archive copy preserves the full content of the

original electronic data set, including all metadata needed to fully reconstruct the GMP activity. The archive copy should also preserve the meaning of the original electronic data set;

- input/output checks, including implementation of procedures for the review of original electronic data and metadata, such as audit trails;
- electronic signatures;
- alarms and flags that indicate alarm conditions and invalid and altered data, in order to facilitate detection and a review of these events;
- system documentation, including system specifications documents, user manuals and procedures for system use, data review and system administration;
- system capacity and volume requirements, based upon the predicted system usage and performance requirements;
- performance monitoring of the system;
- controls for orderly system shutdown and recovery;
- business continuity.

5.4 The extent and detail of the requirements should be commensurate with the operational risk and the complexity of the computerized system. User requirements should be specific and phrased in a way that supports their testing or verification within the context of the computerized system.

Functional specifications

5.5 Functional specifications should describe in detail the functions, performance and interfaces of the computerized system, based upon the technical requirements needed to satisfy user requirements, and should be linked to user specifications.

5.6 The functional specifications provide a basis for the system design and configuration specifications. Functional specifications should consider requirements for operation of the computerized system in the intended computing environment, such as functions provided by supplier-provided software, as well as functions required for user business processes that are not met by commercial off-the-shelf software (COTS) functionality, and default configurations that will require custom code development. Network infrastructure requirements should also be taken into account. Each described function should be verifiable.

5.7 Personnel access roles that provide the ability and/or authorization to write, alter or access programs or configuration should be defined and qualified.

There should be appropriate segregation of roles between personnel responsible for the business process and personnel for system administration and maintenance.

6. System design and configuration specifications

6.1 System design and configuration specifications should be developed based on user and functional requirements. Specification of design parameters and configuration settings (separate or combined) should ensure data integrity and compliance with the WHO *Guidance on good data and record management practices* (*1*).

6.2 System design and configuration specifications should provide a high-level system description, as well as an overview of the system's physical and logical architecture, and should map out the system business process and relevant work flows and data flows if these have not already been documented in other requirements specifications documents.

6.3 The system design and configuration specifications may include, as applicable, a software design specification, in case of code development, and configuration specifications of the software application parameters, such as security profiles, audit trail configuration, data libraries and other configurable elements.

6.4 In addition, the system design and configuration specifications may also include, based upon risk, the hardware design and its configuration specifications, as well as that of any supporting network infrastructure.

6.5 System design and configuration specifications should include secure, protected, independent computer-generated audit trails to track configuration changes to critical settings in the system.

7. Design qualification

7.1 Following design qualification (DQ), a review should be conducted to verify that the proposed design and configuration of the system is suitable for its intended purpose and will meet all applicable user and functional specifications.

7.2 It may include a review of supplier documentation, if applicable, and verification that requirements specifications are traceable to proposed design and configuration specifications. The DQ review should be documented.

8. System development and project implementation

8.1 Once the system requirements and the system design and configuration are specified and verified, where applicable, system development activities may begin. The development activities may occur as a dedicated phase following completion of specification of system requirements, design and configuration. Alternatively, development activities may occur iteratively as requirements are specified and verified (such as when prototyping or rapid-development methodologies are employed).

Supplier-provided systems

8.2 For supplier-provided systems, the development controls for the supplier-provided portion of the computerized system should be assessed during the supplier evaluation or supplier qualification. For supplier-provided systems that include custom components (such as custom-coded interfaces or custom report tools) and/or require configuration (such as configuration of security profiles in the software or configuration of the hardware within the network infrastructure), the system should be developed under an appropriate documented quality management system.

Custom-developed systems

8.3 For custom-developed and configurable systems, the system should be developed under an appropriate documented quality system. For these systems or modules, the quality management system controls should include development of code in accordance with documented programing standards, review of code for adherence to programing standards, and design specifications and development testing that may include unit testing and module/integration testing.

8.4 System prototyping and rapid, agile development methodologies may be employed during the system build and development testing phase. There should be an adequate level of documentation of these activities.

Preparation for the system qualification phase

8.5 The system development and build phase should be followed by the system qualification phase. This typically consists of installation, operational and performance testing. The actual qualification required may vary depending on the scope of the validation project, as defined in the validation protocol and based upon a documented and justified risk assessment.

8.6 Prior to the initiation of the system qualification phase, the software program and requirements and specifications documents should be finalized and subsequently managed under formal change control.

8.7 Persons who will be conducting the system qualification should be trained to adhere to the following requirements for system qualification:

- test documentation should be generated to provide evidence of testing;
- test documentation should comply with good documentation practices;
- any discrepancies between actual test results and expected results should be documented and adequately resolved, based upon risk prior to proceeding to subsequent test phases.

9. Installation qualification

9.1 Installation qualification (IQ) – also referred to as installation verification testing – should provide documented evidence that the computerized system, including software and associated hardware, is installed and configured in the intended system test and production environments, according to written specifications.

9.2 The IQ will verify, for example, that the computer hardware on which the software application is installed has the proper firmware and operating system, that all components are present and in the proper condition, and that each component is installed per the manufacturer or developer instructions.

9.3 IQ should include verification that configurable elements of the system are appropriately set as specified. Where appropriate, this could also be done during operational qualification (OQ).

10. Operational qualification

10.1 The OQ – or operational/functional verification testing – should provide documented evidence that software and hardware function as intended over anticipated operating ranges.

10.2 Functional testing should include, based upon risk:

- challenges on the system's ability to do what it should do, including verification that significant alerts and error messages are raised based upon alarm conditions and according to specifications;

- an appropriate degree of testing (such as boundary, range, limit, and nonsense entry testing), to verify that the system appropriately handles erroneous entries or erroneous use.

11. Standard operating procedures and training

11.1 Prior to conducting of the PQ and UAT, and prior to release of the computerized system, there should be adequate written procedures and documents and training programmes created defining system use and control. These may include supplier-provided user manuals as well as SOPs and training programmes developed in house.

11.2 Procedures and training programmes that should be developed include, but are not necessarily limited to:

- system use procedures that address:
  - routine operation and use of the system in the intended business process(es);
  - review of the electronic data and associated metadata (such as audit trails) and how the source electronic records will be reconciled with printouts, if any;
  - mechanisms for signing electronic data;
  - system training requirements prior to being granted system access;
- system administration procedures that address:
  - granting disabling and review of user access and maintaining security controls;
  - backup/restore;
  - archiving/retrieval;
  - disaster recovery and business continuity;
  - change management;
  - incident and problem management;
  - system maintenance.

12. Performance qualification and user acceptance testing

12.1 PQ, which includes UAT, should be conducted to verify the intended system use and administration defined in the URS and DQ, or equivalent document.

12.2 The PQ should be conducted in the live environment (controls for restricted release for GMP use may be necessary) or in a test environment that is functionally equivalent to the live environment in terms of overall software and hardware configuration.

12.3 PQ testing should also include, as applicable, an appropriate degree of stress/load/volume testing, based upon the anticipated system use and performance requirements in the production environment. Such testing may also be performed during OQ if appropriately justified.

12.4 In addition, an appropriate degree of end-to-end or regression testing of the system should be conducted to verify the system performs reliably when system components are integrated in the fully configured system deployed in the production environment.

12.5 UAT should be conducted by system users, to verify the adequacy of the system, use of SOPs and training programmes. The UAT should include verification of the ability to generate and process only valid data within the computerized system, including the ability to efficiently review electronic data and metadata, such as audit trails. SOPs should be finalized and approved upon completion of performance qualification.

Legacy systems

12.6 The continued use of a legacy system should be justified by demonstrating the system continues to be relevant to the GMP process being supported and by ensuring adequate validation of the system (i.e. hardware, software, peripheral devices, networks) has been performed.

12.7 The validation approach to be taken should aim at providing data and information to justify and support the retrospective qualification of the system. It should demonstrate that the system remains in a state of control and is fit for its intended use and, where necessary, it should include an approach for retrospective qualification of the system with relevant evidence.

12.8 A risk assessment should be undertaken to determine the criticality of the system to the process or operation being supported, and a gap analysis should identify the level of completeness of existing qualification documentation (e.g. URS, IQ/OQ/PQ, SOPs) and state of system control, operation and maintenance.

12.9 For legacy systems, development documentation and records appropriate for validation may not be available. Nevertheless, the strategy should be consistent with validation principles where assurance is established, based

on compilation and formal review of the history of use, maintenance, error report and change-control system records. These activities should be based on documented URS. If historical data do not encompass the current range of operating parameters, or if there have been significant changes between past and current practices, then retrospective data would not of themselves support validation of the current system.

12.10 The validation exercise should demonstrate that user requirements and system description have been appropriately established, as well as providing evidence that the system (i.e. hardware, software, peripheral devices, networks, processes) has been qualified and accepted and that GMP requirements are met.

13. System operation and maintenance

Security and access control

13.1 Manufacturers should have systems and procedures in place to ensure data integrity and access control to computerized systems, and these measures should be commensurate with identified risks

13.2 Suitable security measures should be in place to prevent unauthorized entry or manipulation or deletion of data through the application software, as well as in operating system environments in which data may be stored or transmitted. Data should be entered or amended only by persons who are qualified and authorized to do so.

13.3 The activity of entering data, changing or amending incorrect entries, or creating backups should be done in accordance with SOPs.

13.4 Security should extend to devices used to store programs and data. Access to these devices should be controlled.

13.5 Measures for protecting audit trails from alteration or unauthorized deletion should be in place. Procedures for review of audit trails, and when necessary metadata, should define the frequency, roles and responsibilities and nature of these reviews.

13.6 Operation of the system and acquisition of data should be traceable and should identify the persons who made entries and/or changes, approved decisions or performed other critical steps in system use or control.

13.7 Details of user profiles and access rights to systems, networks, servers, computerized systems and software should be documented and reviewed periodically. An up-to-date list on the individual user rights for the

software, individual computer systems and networks should be maintained and subjected to change control. The level of detail should be sufficient to enable computer system validation personnel, as well as IT personnel/ any external auditor/inspector, to ascertain that security features of the system and of software used to obtain and process critical data cannot be circumvented.

13.8 All GMP computerized systems, either stand-alone or in a network, should have a system that is commensurate with identified risks for monitoring through an audit trail of events that are relevant. These events should include all elements that need to be monitored to ensure that the integrity (*1*) of the data could not have been compromised without leaving a trace, such as, but not limited to, changes in or deletion of data; changes in dates, times, backups, archives or user access rights; and addition/deletion of users and log-ins, in accordance with WHO *Guidance on good data and record management practices* (*1*). The configuration and archiving of these audit trails should be documented and also be subjected to change control. These audit trails should be system generated, accurate, consistent, secure, available and convertible to a generally intelligible form throughout the retention period, and their generation appropriately qualified.

Operation and maintenance

13.9 Entry of GMP-related data into a computerized system should be verified by an independent authorized person and locked before release for routine use.

13.10 Validated computerized systems should be maintained in a validated state once released to the GMP production environment.

13.11 There should be written procedures governing system operation and maintenance, including, for example:

- performance monitoring;
- change management and configuration management;
- problem/incident management;
- program and data security;
- program and data backup/restore and archiving/retrieval;
- system administration and maintenance;
- data flow and data life-cycle;
- system use and review of electronic data and metadata (such as audit trails);

- personnel training;
- disaster recovery and business continuity;
- availability of replacement parts and technical support;
- periodic re-evaluation.

13.12 Automatic or live updates should be subject to review prior to becoming effective.

Data migration

13.13 Where electronic data are transferred from one system to another, it should be demonstrated that data are not altered during the migration process. Conversion of data to a different format should be considered as data migration. Where data are transferred to another medium, they must be verified as an exact copy, prior to any destruction of the original data.

13.14 Procedures for data migration may vary greatly in complexity, and measures to ensure appropriate transfer of data should be commensurate with identified risks. Migrated data should remain usable and should retain their content and meaning. The value and/or meaning of and links between a system audit trail and electronic signatures should be ensured in a migration process.

Periodic review

13.15 Computerized systems should be periodically reviewed to determine whether the system remains in a validated state or whether there is a need for revalidation. The scope and extent of the revalidation should be determined using a risk-based approach. The review should at least cover:

- system performance and functionality;
- security;
- maintenance;
- review of changes including upgrades;
- review of deviations;
- review of incidents/events (including review of audit trail);
- systems documentation;
- procedures;
- training;
- effectiveness of corrective and preventive action.

13.16 Corrective and preventive action should be taken where indicated as a result of the periodic review.

14. System retirement

14.1 System retirement should be considered as a system life-cycle phase. It should be planned, risk based and documented. If migration or archiving of GMP-relevant data (*1*, *2*) is necessary, the process must be documented.

14.2 Once the computerized system or components are no longer needed, the system or components should be retired and decommissioned, in accordance with established authorized procedures, including a change-control procedure and a formal plan for retirement.

14.3 Records should be archived in a readable form and in a manner that preserves the accessibility, readability and integrity of the data of the source electronic records throughout the required records retention period.

14.4 The outcome of the retirement activities, including traceability of the data and computerized systems, as well as the ability to retrieve the data, should be tested and documented in a report.

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Appendix 6

Guidelines on qualification

Background

There was some confusion regarding the title of this appendix. It was therefore suggested to change the previous title *Validation on qualification of systems, utilities and equipment to Guidelines on qualification*. In this way, the general principles of qualification are addressed, which can be applied for systems, equipment, and so on.

Based on the comments, the general sections 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 and logical flow of concepts addressed and aligned with international texts and the comments. Discussion of the V Model has been removed, based on the feedback received. In the former published text on qualification (see reference below), 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 manufacturers seemingly took them as absolute examples to be used, these examples have been removed in the current version.

This is a revision of the previous publication:

- Supplementary guidelines on good manufacturing practices: validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, fortieth report. Appendix 6: Qualification of systems and equipment. Geneva: World Health Organization; 2006: Annex 4 (WHO Technical Report Series, No. 937; http://apps.who.int/medicinedocs/documents/s20108en/s20108en.pdf).

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 produced and controlled using qualified equipment and instruments.

1.4 Manufacturers who may use an alternative verification framework to achieve qualification should ensure the qualification expectations within these guidelines are satisfied.

2. Scope

2.1 These guidelines describe the general approach to qualification of, for example, premises, systems, 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, but are not limited to: certain rooms; water purification systems; cleaning systems; heating, ventilation and air-conditioning systems; compressed air systems; gas systems; and 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 Appendices 1–5 and 7).

2.5 The principle should be applied that a qualified state is maintained throughout the life-cycle.

3. Glossary

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

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, 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.

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.

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.

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.

site acceptance test. A test conducted at the manufacturer's site of use, to verify that the system, equipment or utility, as assembled or partially assembled, meets approved specifications.

user requirements specification. An authorized document that defines the requirements for use of the system, equipment or utility in its intended production environment.

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.

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 Principles of quality risk management 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.

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 requirements specification (URS), design qualification (DQ), installation qualification (IQ), operational qualification (OQ) and performance qualification (PQ).

4.6 Where it is decided that not all stages of qualification are required, justification should be provided.

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;
- 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 (e.g. 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 writing and agreed between the parties. The contract giver remains responsible to ensure that the qualification is done in accordance with the principles of good manufacturing practices.

4.14 The relevant documentation associated with qualification, including standard operating procedures, 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 requirements specification

5.1 URS documentation 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 principles of quality risk management, to ensure that it is appropriate, as described in the URS, and ready for dispatch.

7.2 The checks and tests conducted during the 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 principles of quality risk management, 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 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 be prepared 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 the 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;
- tests over the operating limits.

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.

9.8 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 operating conditions, with batch sizes where appropriate;
- tests covering 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 the PQ (e.g. a PQ report), 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 throughout 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 Principles of risk management 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 Principles of risk management may include factors such as calibration, verification, maintenance data and other information.

11.6 The qualification status and periodic 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 that has 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.

Appendix 7

Non sterile process validation

Background

The text of this appendix was previously published as:

- Guidelines on good manufacturing practices: validation. Appendix 7: Non-sterile process validation. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations, forty-ninth report. Geneva: World Health Organization; 2015: Annex 3 (WHO Technical Report Series, No. 992; https://www.who.int/medicines/areas/quality_safety/quality_assurance/Annex3-TRS992.pdf).

1. Background and scope

Further to the *Supplementary guidelines on good manufacturing practices: validation*, as published in the World Health Organization (WHO) Technical Report Series (TRS), No. 937 (*1*), additional guidelines to support current approaches to good manufacturing practices (GMP) are published here. These guidelines are intended to further support the concept of process validation linked to principles of quality risk management and quality by design, as described by WHO and the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).

These guidelines allow for different approaches to process validation. The principles described are mainly applicable to non-sterile finished pharmaceutical dosage forms. Similar approaches may be applicable to active pharmaceutical ingredients (APIs) and sterile products. (See also recommendations in WHO TRS No. 957, Annex 2 (*2*) and WHO TRS No. 961, Annex 6 (*3*).)

A risk-based and life-cycle approach to validation is recommended.

Thorough knowledge of product and process development studies; previous manufacturing experience; and principles of quality risk management are essential in all approaches to process validation, as the focus is now on the life-cycle approach. The life-cycle approach links product and process development, validation of the commercial manufacturing process and maintaining the process in a state of control during routine commercial production. The use of process analytical technology, which may include in line, online and/or at-line controls and monitoring, is recommended, to ensure that a process is in a state of control during manufacture.

2. Glossary

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

at-line. Measurement where the sample is removed, isolated from, and analysed in close proximity to the process stream.

concurrent validation. Validation carried out during routine production of products intended for sale in exceptional circumstances when data from replicate production runs are unavailable because only a limited number of batches have been produced, batches are produced infrequently or batches are produced by a validated process that has been modified. Individual batches may be evaluated and released before completion of the validation exercise, based on thorough monitoring and testing of the batches.

control strategy. A planned set of controls, derived from current product and process understanding that assures process performance and product quality.

The controls can include parameters and attributes related to API and finished pharmaceutical product materials and components, facility and equipment operating conditions, in-process controls, finished product specifications and the associated methods and frequency of monitoring and control.

continued process verification. Documented scientific evidence that the process remains in a state of control during commercial manufacture.

critical process parameter. A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored and/or controlled to ensure the process produces the desired quality.

critical quality attribute. A physical, chemical, biological or microbiological property or characteristic of materials or products that should be within an appropriate limit, range or distribution to ensure the desired product quality.

in-line. Measurement where the sample is not removed from the process stream: can be invasive or non-invasive.

life-cycle. All phases in the life of a product from the initial development through marketing until the product's discontinuation (*4*).

matrix approach or bracketing. Bracketing is the assessment of a single parameter or variable by identifying the edge(s) of the range of conditions for the parameter or variable and assessing these during validation, to span the possible range of that parameter or variable. For example, bracketing can be applied to process parameters, multiple pieces of identical equipment and/or different size considerations for the same product. The rationale for using this strategy should be justified, documented and approved.

Matrixing involves the assessment of the effect of more than one parameter or variable by using a multidimensional matrix to identify the "worst-case" or "extreme" conditions for a combination of parameters or variables. These conditions are used during validation of the process, rather than validating all possible combinations. Matrixing is typically used when there are significant similarities between products in a product family (e.g. the same product with different strengths in the manufacturing stage or different products with a similar container-closure in the packaging stage). The rationale for using this strategy should be justified, documented and approved.

The use of a matrix approach or bracketing design would not be considered appropriate if it is not possible to demonstrate that the extremes are limited to the batches, products, strengths, container sizes or fills. For those excluded from the exercise, there should be no risk to process capability.

online. Measurement where the sample is diverted from the manufacturing process, and may be returned to the process stream.

pharmaceutical quality system. Management system to direct and control a pharmaceutical company with regard to quality.

process qualification. Process qualification combines the actual facility, utilities, equipment (each now qualified) and the trained personnel with the commercial manufacturing process, control procedures and components to produce commercial batches; confirms the process design; and demonstrates that the commercial manufacturing process performs as expected.

process validation. The collection and evaluation of data, from the process design stage through to commercial production, which establishes scientific evidence that a process is capable of continuously delivering the finished pharmaceutical product, meeting its predetermined specifications and quality attributes.

quality target product profile (QTPP). A prospectively documented summary of the quality characteristics of a finished pharmaceutical product (FPP) that ideally will be achieved to ensure the desired quality, taking into account safety and efficacy of the FPP. The QTPP forms the basis of design for the development of the product and typically would include:

- intended use in a clinical setting, route of administration, dosage form, delivery systems;
- dosage strength(s);
- container-closure system;
- therapeutic moiety release or delivery and attributes affecting pharmacokinetic characteristics (e.g. dissolution, aerodynamic performance) appropriate to the FPP dosage form being developed;
- FPP quality criteria (e.g. sterility, purity, stability and drug release) appropriate for the intended marketed product.

real-time release testing. The ability to evaluate and ensure the quality of in-process and/or final product, based on process data, which typically include a valid combination of measured material attributes and process controls.

state of control. A condition in which the set of controls consistently provides assurance of continued process performance and product quality.

3. Introduction

Process validation data should be generated for all products, to demonstrate the adequacy of the manufacturing process. The validation should be carried out in accordance with GMP and data should be held at the manufacturing location whenever possible and should be available for inspection.

Process validation is associated with the collection and evaluation of data throughout the life-cycle of a product – from the process design stage through to commercial production – and provides scientific evidence that a process

is capable of consistently delivering a quality product. A risk-assessment approach should be followed, to determine the scope and extent to which process(es) and starting material variability may affect product quality. The critical steps and critical process parameters should be identified, justified and documented and based on relevant studies carried out during the design stage and on process knowledge, according to the stages of the product life-cycle. During process validation and qualification, the critical process parameters should be monitored. It may be helpful to use a flow diagram depicting all the operations and controls in the process to be validated.

When applying quality risk management to a given operation, the steps preceding and following that operation should also be considered. Amendments to the flow diagram may be made where appropriate, and should be recorded as part of the validation documentation. Manufacturers should ensure that the principles of process validation described in these guidelines are implemented. These cover the phases of validation during process design; scale-up; qualification of premises, utilities and equipment; process performance qualification; and continuous process verification to ensure that the process remains in a state of control.

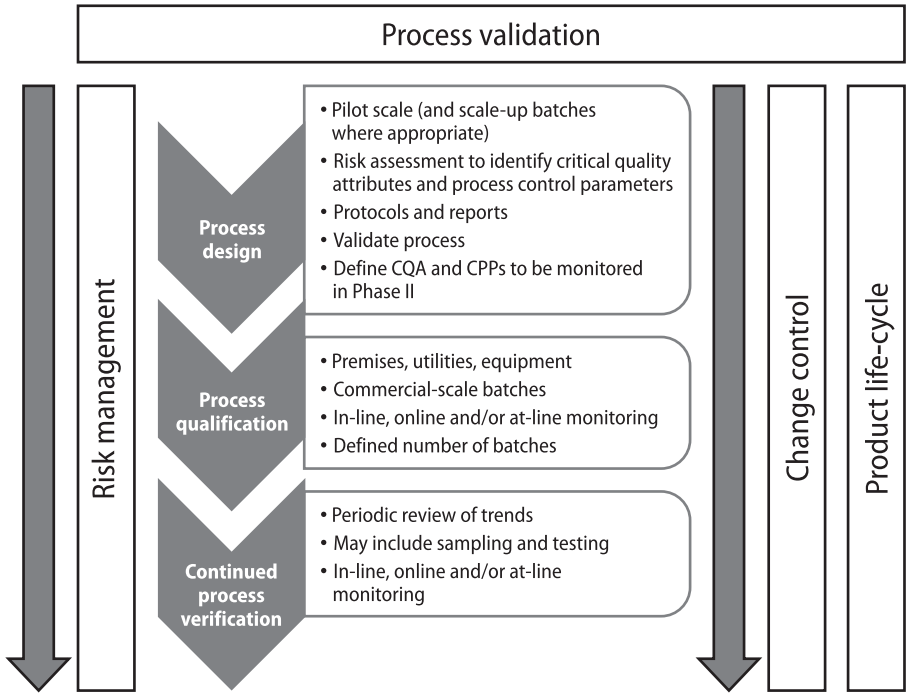
The objectives of process validation include ensuring that:

- the process design is evaluated to show that the process is reproducible, reliable and robust;
- the commercial manufacturing process is defined, monitored and controlled;
- assurance is gained on a continuous basis to show that the process remains in a state of control.

The validation should cover all manufactured strengths of a product, and the extent of validation at each manufacturing site should be based on risk assessment.

A matrix approach or bracketing may be acceptable and should also be based on appropriate risk assessment. There are various approaches to process validation, which include: traditional process validation (consisting of prospective and concurrent validation); process design followed by process qualification and continued process verification; or a combination of traditional process validation and the new approach described in these guidelines. Historical data should be evaluated in cases where there have been changes to the process. Manufacturers should plan to implement the new approach to process validation, which covers process design, process qualification and continued process verification throughout the product life-cycle. Fig. A3.7.1 shows the phases in the new approach to process validation.

Fig. A3.7.1
Phases of process validation



CQA: critical quality attribute; CPPs: critical process parameters.

4. Process design

Under the life-cycle approach, the focus of validation is shifted from commercial-scale batches to development. Product development activities provide key inputs to the process design stage, such as the intended dosage form, the quality attributes and a general manufacturing pathway. Laboratory or pilot-scale models designed to be representative of the commercial process can be used to estimate variability.

Process design should normally cover design of experiments, process development, the manufacture of products for use in clinical trials, pilot-scale batches and technology transfer. Process design should be verified during product development. Process design should cover aspects for the selection of materials; expected production variation; selection of production technology/process and qualification of the unitary processes that form the manufacturing process as a whole; selection of in-process controls; tests; inspection; and its suitability for the control strategy.

As part of the process validation life-cycle, some process validation studies may be conducted on pilot-scale batches (corresponding to at least 10% or 100 000 units, whichever is the greater) of the production scale. Where the batch size is smaller and/or where the process is tailored to the geometry and capacity of specific equipment, it may be necessary to provide production-scale validation data.

Process qualification and continued process verification should always be linked to process design and be referenced to those specific batches used in studies critical to the development of the product, for example, the batch(es) used for pivotal clinical assessments (biobatch(es)), for example, bioequivalence testing in the case of multisource products, and toxicological studies. The number of batches included in the process design stage of validation should be appropriate and sufficient to include (but not be limited to) the expected variations in starting materials, and confirm the suitability of the equipment and manufacturing technology.

A statistically based design of experiment approach can be helpful during this stage. Processes and results should be appropriately documented. A development report and/or a technology transfer document, formally reviewed and approved by research and development personnel, and formally accepted by manufacturing, engineering and quality personnel, should be prepared. Such a document may include information such as a quality target product profile, desired clinical performance, bills of materials, approved suppliers, finished product specifications and test methods, in-process testing specifications, equipment recommendations, master batch production records, master batch packaging records, stability reports, critical quality attributes, critical process parameters, batch comparisons, data on formulation batches, stability batches, clinical/biobatches and scale-up batches. These documents should be readily available to the manufacturing site. The goal is to design a suitable process for routine commercial manufacturing that can consistently deliver a product that meets its required quality attributes.

5. Process qualification

Personnel, premises, utilities, support systems and equipment should be appropriately qualified before manufacturing processes are validated. Materials, environmental controls, measuring systems, apparatus and methods should be considered during validation. The stages of qualification of equipment may include design, installation, operation and performance of equipment (for more details see reference (*1*)).

Traditionally, three batches have been considered the normal and acceptable number for process validation; however, the number of batches should

be justified and based on a risk assessment that includes, for example, variability of results from the process design stage, variability of materials, product history, where the product is being transferred from and where it will be produced. Manufacturers should define the stage at which the process is considered to be validated and the basis on which that decision was made. The decision should include a justification for the number of batches used based on the complexity and expected variability of the process and critical quality attributes (CQAs).

Successful completion of process performance qualification stage of the life-cycle is required for commercial distribution. A risk assessment should be performed for the change from scale-up to commercial batch size. Process qualification should confirm that scale-up in batch size did not adversely affect the characteristics of the product and that a process that operates within the predefined specified parameters consistently produces a product that meets all its CQAs and control strategy requirements. The process should be verified on commercial-scale batches prior to marketing of the product.

Extensive in-line and/or online and/or at-line controls may be used to monitor process performance and product quality in a timely manner. Results on relevant quality attributes of incoming materials or components, in-process material and finished products should be collected. This should include the verification of attributes, parameters and end-points and assessment of CQA and critical process parameter trends. Process analytical technology applications and multivariate statistical process control can be used. Manufacturers are encouraged to implement the new validation approach to ensure that processes are of known and acceptable capability. As full implementation of this approach may take time, the traditional approach of prospective validation and concurrent validation (used infrequently and restricted to the scenarios described in Section 3) may be acceptable in the interim. A combination of elements of the traditional process validation approach and the new continuous process verification approach may be considered appropriate, subject to appropriate controls being in place, based on scientific justification and principles of risk management.

Validation should be done in accordance with process validation protocols. A written protocol is essential for this stage of process validation. The protocol should include or reference at least the following elements:

- the manufacturing conditions, including operating parameters, processing limits and component (raw material) inputs;
- the data to be collected and when and how they will be evaluated;
- the type of testing or monitoring to be performed (in-process, release, characterization) and acceptance criteria for each significant processing step;

- the scientifically justified sampling plan, including sampling points, number of samples and the frequency of sampling for each unit operation and attribute;
- the number of batches for which additional monitoring is proposed;
- status of the validation of analytical methods used in measuring the process, in-process materials and the product;
- a description of the statistical models or tools used;
- review and approval of the protocol by appropriate departments and the quality unit;
- a description of the process;
- 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, with appropriate justification;
- the samples to be taken
- "who", "where", "when", "how", "how many" and "how much" (sample size);
- the product performance characteristics or attributes to be monitored, together with the test methods;
- the acceptable limits;
- personnel responsibilities;
- details of methods for recording and evaluating results, including statistical analysis. Data should be collected and reviewed against predetermined acceptance criteria and fully documented in process validation reports.

The report should reflect the validation protocol. A dual protocol report can be used; however, such reports must be designed to ensure clarity and sufficient space for recording of results. The outcome should confirm that the acceptance criteria have been met. Any deviations (including abandoned studies) should be explained and justified. The planned commercial production and control records, which contain the operational limits and overall strategy for process control, should be carried forward to the next phase for confirmation.

6. Continued process verification

Manufacturers should monitor the product quality of commercial batches after completion of process design and process qualification. This will provide evidence that a state of control is maintained throughout the product life-cycle.

The scope and extent of process verification will be influenced by a number of factors, including:

- prior development and knowledge of the manufacturing of similar products and/or processes;
- the extent of process understanding gained from development studies and commercial manufacturing experience;
- the complexity of the product and/or manufacturing process;
- the level of process automation and analytical technologies used;
- for legacy products, with reference to the product life-cycle process, robustness and manufacturing history since the point of commercialization, as appropriate.

Manufacturers should describe the appropriateness and feasibility of the verification strategy (in the protocol), including the process parameters and material attributes that will be monitored, as well as the validated analytical methods that will be employed.

Manufacturers should define:

- the type of testing or monitoring to be performed;
- the acceptance criteria to be applied;
- how the data will be evaluated and the actions to be taken.

Any statistical models or tools used should be described. If continuous processing is employed, the stage at which the commercial process is considered to be validated should be stated, based on the complexity of the process, expected variability and manufacturing experience of the company. Periods of enhanced sampling and monitoring may help to increase process understanding as part of continuous improvement. Information on process trends, such as the quality of incoming materials or components, in process and finished product results and non-conformances, should be collected and assessed to verify the validity of the original process validation or to identify changes to the control strategy required. The scope of continued process verification should be reviewed periodically, and modified if appropriate, throughout the product life-cycle.

7. Change management

Manufacturers should follow change-control procedures when changes are planned to existing systems or processes. The change-control procedure and records should ensure that all aspects are thoroughly documented and approved, including regulatory approval where appropriate (variation).

Sufficient data should be generated to demonstrate that the revised process will result in a product of the desired quality, consistent with approved specifications.

Validation should be considered when changes to production and/or control procedures are planned. Based on risk assessment, changes that may require revalidation could include (but are not limited to):

- changes in the master formula, methods, starting material manufacturer, starting material manufacturing process, excipient manufacturer, excipient manufacturing process;
- changes in the equipment or instruments (e.g. addition of automatic detection systems);
- changes associated with equipment calibrations and the preventive maintenance carried out, which may impact the process;
- production area and support system changes (e.g. rearrangement of areas or a new water-treatment method);
- changes in the manufacturing process (e.g. mixing times, drying temperatures);
- transfer of processes to another site;
- unexpected changes (e.g. those observed during self-inspection or during routine analysis of process trend data);
- changes to standard operating procedures;
- changes to cleaning and hygiene programmes.

Depending upon the nature of the change being proposed, the change-control process should consider whether existing approved specifications will be adequate to control the product subsequent to implementation of the change.

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Further reading

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