

Annex 3

Guidelines on good manufacturing practices: validation, Appendix 7: non-sterile process validation¹

Background

The appendices of the *Supplementary guidelines on good manufacturing practices: validation* currently comprise the following:

Appendix 1. Validation of heating, ventilation and air-conditioning systems

Appendix 2. Validation of water systems for pharmaceutical use

Appendix 3. Cleaning validation

Appendix 4. Analytical method validation

Appendix 5. Validation of computerized systems

Appendix 6. Qualification of systems and equipment

Appendix 7. Non-sterile process validation – revised text reproduced in this Annex

1. Background and scope	76
2. Glossary	76
3. Introduction	78
4. Process design	80
5. Process qualification	81
6. Continued process verification	83
7. Change management	84
References	85

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).

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, 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 quality risk management (QRM) and quality by design principles 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 Technical Report Series, No. 957, Annex 2 (2) and WHO Technical Report Series, 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 QRM principles 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 (PAT), 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 (ICH Q8 (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 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 QRM 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 and 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.

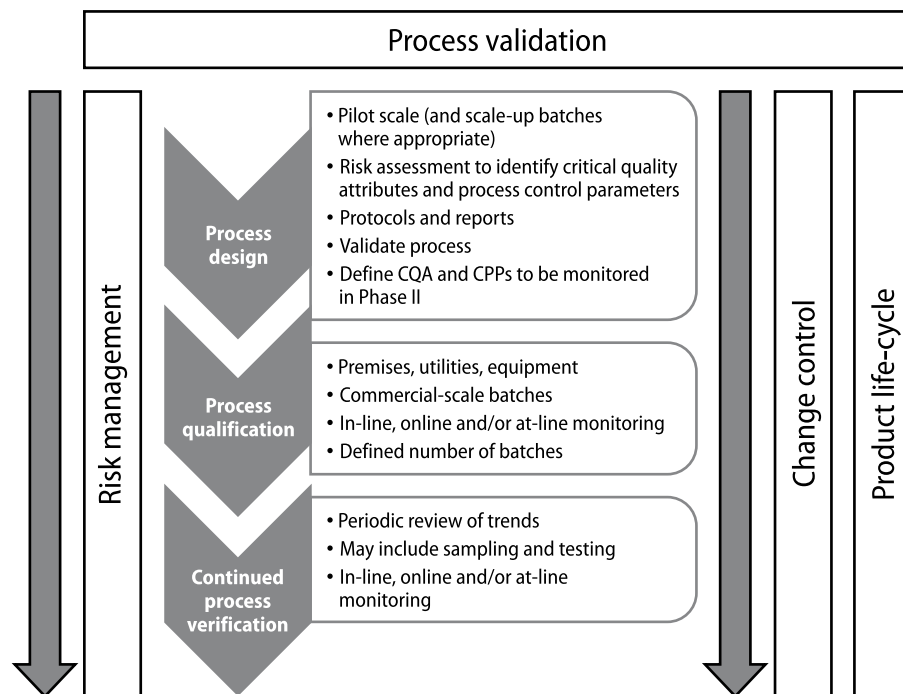
The validation should cover all manufactured strengths of a product and the extent of validation at each manufacturing site should be based on risk assessment. A matrix approach or bracketing may be acceptable and should also be based on appropriate risk assessment.

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.

Figure A3.1 shows the phases in the new approach to process validation.

Figure A3.1
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)), e.g. 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 QTPP, 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 (WHO Technical Report Series, No. 937, Annex 4 (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 which 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 (CPP) 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 2) 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 risk management principles.

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 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 required to the control strategy.

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 the implementation of the change.

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).
2. WHO good manufacturing practices for active pharmaceutical ingredients. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fourth report. Geneva: World Health Organization; 2010: Annex 2 (WHO Technical Report Series, No. 957).
3. WHO good manufacturing practices for sterile pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations: forty-fifth report. Geneva: World Health Organization; 2011: Annex 6 (WHO Technical Report Series, No. 961).
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Further reading

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