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PROPOSAL FOR REVISION OF THE SUPPLEMENTARY GUIDELINES ON GOOD MANUFACTURING PRACTICES: VALIDATION, APPENDIX 7:NON-STERILE PROCESS VALIDATION

(APRIL 2014)

DRAFT FOR COMMENT

Should you have any comments on the attached text, please send these to:
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Working documents are sent out electronically and they will also be placed on the Medicines website for comment. If you do not already receive directly our draft guidelines please let us have your email address (to bonnyw@who.int) and we will add it to our electronic mailing list.

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SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/13.527: PROPOSAL FOR REVISION OF THESUPPLEMENTARY GUIDELINE ON GOOD MANUFACTURING PRACTICES: VALIDATION, APPENDIX 7: NON-STERILE PROCESS VALIDATION

Need for revision of published good manufacturing practices: validation identified by Prequalification of Medicines Programme	March 2013
Wide circulation of draft document for comment	April 2013
Compilation of feedback received	June 2013
Discussion of feedback during informal consultation on quality assurance guidelines	July 2013
Mailing of revision for comment	August 2013
Presentation to forty-eighth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations	October 2013
Recirculation of working document for comments	March 2014
Compilation of comments	April 2014
Discussion of feedback during informal consultation on medicines quality: GXPs, inspection guides and risk management	28-30 April 2014
Recirculation of updated working document	May 2014
Compilation of comments and evaluation of feedback received	July 2014
Presentation to forty-ninth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations	October 2014
Further follow-up action as required	…

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PROPOSAL FOR REVISION OF THESUPPLEMENTARY GUIDELINE ON GOOD MANUFACTURING PRACTICES: VALIDATION, APPENDIX 7: NON-STERILE PROCESS VALIDATION

Note from the Secretariat:

The current text of the Supplementary guideline on good manufacturing practices: validation (World Health Organization, WHO Technical Report Series, No. 937, 2006, Annex 4) is available on the following website:
http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/index.html

Moreover, comments are being sought at the same time as to whether the Appendix 3 on *Cleaning validation* be revised to be in line with the current developments on setting health-based exposure limits for use in risk identification in the manufacture of different medicinal products in shared facilities; if yes, concrete proposals for revision would be appreciated.

The Appendixes of the *Supplementary guideline on good manufacturing practices: validation* **are currently as follows:**

Appendix 1. Validation of heating, ventilation and air-conditioning systems – TO BE REVISED

Appendix 2. Validation of water systems for pharmaceutical use – TO BE REVISED

Appendix 3. Cleaning validation – TO BE REVISED

Appendix 4. Analytical method validation

Appendix 5. Validation of computerized systems – TO BE REVISED

Appendix 6 - Qualification of systems and equipment – TO BE REVISED

Appendix 7. Non-sterile process validation – proposed to be revised

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Proposal for revision of the

Supplementary Guideline on Good Manufacturing Practices: Validation

Appendix 7: Non-sterile process validation

Contents

1. BACKGROUND AND SCOPE

Further to the *Supplementary guideline 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 in good manufacturing practices (GMP) are published herewith to further support the scope of process validation (also referred to as process qualification) linked to quality risk management and quality by design principles as described by WHO and the International Conference on Harmonisation (ICH).

This guideline allows for different approaches in process validation. The principles described in this guideline 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 and WHO Technical Report Series, No. 961, Annex 6.)

[1]Supplementary guidelines on good manufacturing practices: validation. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report*. Geneva, World Health Organization. WHO Technical Report Series, No. 937 (Annex 5), 2006.

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Thorough knowledge of product and process development studies; previous manufacturing experience; and quality risk management (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.

A risk-based approach in validation is recommended. The use of in-line, online and/or at-line controls and monitoring are recommended to ensure that a process is in a state of control during manufacture

2. GLOSSARY

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.

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 drug substance and 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 (CPV)

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

critical process parameter (CPP)

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

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desired quality.

critical quality attribute (CQA)
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 and 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).

matrix approach

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

process analytical technology (PAT)
PAT is a system for designing, analysing and controlling manufacturing through timely measurements (i.e. during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality. It includes chemical, physical, microbiological, mathematical and risk analysis conducted in an integrated manner.

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

process qualification

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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 documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a medicinal product meeting its predetermined specifications and quality attributes.

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 be available for inspection. Manufacturers should confirm that a manufacturing process is under control before a product is placed on the market. (Clarify 'under control'?)

Process validation is associated with the collection and evaluation of data over the life-cycle of a product – from the process design stage through 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 parameters (e.g. those that may have an impact on the quality of the product) in the process of manufacturing a pharmaceutical productand other relevant studies demonstrating that the process is capable of delivering the desired product quality should be identified and documented and be based on knowledge of the product or processes concerned, according to the stage of the product life-cycle. Process validation should cover at least these critical steps and parameters.

A flow diagram may be helpful, covering all operations and controls in the process to be validated. When applying QRM to a given operation, the steps preceding and following that

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operation should also be considered. Amendments to the flow diagram may be made where appropriate and should be documented as part of the validation documentation.

Manufacturers should ensure that the principles of process validation described in this guideline are implemented. These include and cover phases of validation during process design, scale up, qualification of premises, utilities and equipment, process performance verification and ongoing monitoring of batches manufactured for commercial supply 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;

— ongoing assurance is gained 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 may be acceptable based on appropriate risk assessment.

There are different 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 approach described in this guideline.

Historical data should be available in cases where there have been changes to the process.

Manufacturers should plan towards implementing the new approach in process validation that covers process design, process qualification and continued process verification in the product life-cycle.

Table 1 shows different phases in the new approach in process validation

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Table1. New approach to process validation

Product life-cycle		
Process validation		
Process design	Process qualification	Continued process verification
-Pilot scale (and scale-up batches where appropriate) -Risk assessment to identify critical quality attributes and process control parameters -Protocols and reports -Validate process -Define CQA and CPPs to be monitored in Phase II	-Premises -Utilities -Equipment -Commercial-scale batches -In-line, online and/or at-line monitoring -Defined number of batches	-Periodic review of trends -May include sampling and testing -In-line, online and/or at-line monitoring
Change control		
GMP		

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, clinical manufacturing, 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.

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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. In case of smaller batch size and/or where the process is tailored to the geometry and capacity of 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 the batch used for bioequivalence testing (biobatch).

The number of batches included in the process design stage of validation should be appropriate and sufficient to include (but not be limited to) challenging the variations for materials, the suitability of the equipment and manufacturing technology.

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 document(s) may include information such as 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.

The goal is to design a suitable process for routine commercial manufacturing that can consistently deliver a product that quality attributes.

5. PROCESS QUALIFICATION

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Personnel, premises, utilities, support systems and equipment should be appropriately qualified before processes are validated. Materials, environmental controls, measuring systems/apparatus and methods should be considered during validation. Stages of qualification of equipment may include design, installation, operation and performance of equipment (for more details see WHO Technical Report Series, No. 970, Annex 2)

Traditionally three batches have been considered the minimum number for process validation; however, the number of batches should be based on risk assessment that includes, e.g. 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 product is considered to be validated and the basis on which that decision was made. It should include a justification for the number of batches used based on the complexity and expected variability of the process.

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 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 it will be evaluated;
- the type of testing/monitoring to be performed (in-process, release, characterization) and acceptance criteria for each significant processing step;
- the 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;
- statistical models or tools used should be described;
- 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;

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- 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/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 reflected in process validation reports. The report should reflect the validation protocol. A dual protocol report can be used; however, these 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 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.

A risk assessment should be performed for the change in batch size from scale up to commercial batch size

Process qualification should confirm that scale up in batch size did not adversely affect the characteristics of a product and that a process that operates within the predefined specified parameters consistently produces a product which meets all its critical quality attributes (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 should be used to monitor process performance and product quality in a timely manner. Results of 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

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assessment of CQA and critical process parameter (CPP) trends. Process analytical technology applications and multivariate statistical process control (MSPC) can be used.

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 manufacturing knowledge from 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;
– process robustness and manufacturing history since 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 number of batches for which monitoring is proposed;
– the type of testing/monitoring to be performed;
– the acceptance criteria to be applied;
– how the data will be evaluated.

Any statistical models or tools used should be described. If continuous processing is employed, the stage where the commercial process is considered to be validated should be

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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. 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 in order to verify the validity of the original process validation or to identify required changes to the control strategy.

The extent and frequency of continued process verification should be reviewed periodically and modified if appropriate throughout the product life-cycle.

7. CHANGE MANAGEMENT

Changes during the life-cycle of a product should be managed through a change control procedure. Sufficient data should be generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specification.

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

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

– changes in the master formula, methods, starting material manufacturer;
– changes in the equipment or instruments (e.g. addition of automatic detection systems);
– equipment calibrations and preventive maintenance carried out;
– 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);

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– 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 (SOPs);
– changes to cleaning and hygiene programmes.

REFERENCES

1. Guideline on Process Validation, 29 March 2012 EMA/CHMP/CVMP/QWP/70278/2012-Rev1 , Committee for Medicinal Products for Human Use (CHMP), Committee for Medicinal Products for Veterinary Use (CVMP) www.ema.europa.**eu**/…uideline/2012/04/WC500125399.pdf.

2. Guidance for Industry, Process Validation: General Principles and Practices, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Veterinary Medicine (CVM), January 2011, Current Good Manufacturing Practices (CGMP) Revision 1.

3. ICH Harmonised Tripartite Guideline, Pharmaceutical Development Q8(R2), Current *Step 4* version, dated August 2009.

4. ICH Harmonised Tripartite Guideline, Quality Risk Management, Q9, Current *Step 4* version, dated 9 November 2005.

5. ICH Harmonised Tripartite Guideline, Pharmaceutical Quality System, Q10, Current *Step 4* version, dated 4 June 2008 http://www.ich.org/products/guidelines/quality/article/quality-guidelines.html

6. Quality assurance of pharmaceuticals. *WHO guidelines, related guidance and GXP training materials*. Geneva, World Health Organization, 2013 (CD-ROM).

Draft for comment

7. WHO good manufacturing practices: main principles for pharmaceutical products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-fifth report*. Geneva, World Health Organization. WHO Technical Report Series, No. 961 (Annex 3), 2011 (WHO good manufacturing practices: main principles for pharmaceutical products).

8. WHO guidelines on quality risk management. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty-seventh report*. Geneva, World Health Organization. WHO Technical Report Series, No. 981 (Annex 2), 2013 (in press).

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