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

(APRIL 2013) 

DRAFT FOR COMMENT 

Please address any comments on this proposal by 24 May 2013 to Dr S. Kopp, Medicines Quality Assurance Programme, World Health Organization, 1211 Geneva 27, Switzerland, fax: (+41 22) 791 4730 or e-mail: koppins@who.int with a copy to gaspardm@who.int.

We are sending out our working documents electronically only and they are also placed on the Medicines web site for comment. If you do not already receive our documents please let us have your e-mail address (to bonnyw@who.int) and we will add it to our electronic mailing list.
### SCHEDULE FOR THE PROPOSED ADOPTION PROCESS OF DOCUMENT QAS/13.527:

#### PROPOSAL FOR REVISION OF THE SUPPLEMENTARY GUIDELINE ON

**GOOD MANUFACTURING PRACTICES: VALIDATION, APPENDIX 7: NON-STERILE

**PROCESS VALIDATION**

<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for revision of published good manufacturing practices: validation identified by Prequalification of Medicines Programme</td>
<td>March 2013</td>
</tr>
<tr>
<td>Wide circulation of draft document for comment</td>
<td>April 2013</td>
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<tr>
<td>Compilation of feedback received</td>
<td>June 2013</td>
</tr>
<tr>
<td>Discussion of feedback during informal consultation on quality assurance guidelines</td>
<td>July 2013</td>
</tr>
<tr>
<td>Mailing of revision for comment</td>
<td>August 2013</td>
</tr>
<tr>
<td>Presentation to forty-eighth meeting of the WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>October 2013</td>
</tr>
<tr>
<td>Any further action as necessary</td>
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PROPOSAL FOR REVISION OF THE SUPPLEMENTARY GUIDELINE ON
GOOD MANUFACTURING PRACTICES: VALIDATION, APPENDIX 7: NON-STERILE
PROCESS VALIDATION

Note from Secretariat:
The current text of the Supplementary Guideline on Good Manufacturing Practices:
Validation (Ref: World Health Organization, WHO Technical Report Series, No. 937,
2006, Annex 4) is available on the following web site:
Moreover, comments are being sought at the same time, if the Appendix 3 on Cleaning
validation be revised 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

Appendix 2 -Validation of water systems for pharmaceutical use

Appendix 3 - Cleaning validation – need for revision?

Appendix 4 - Analytical method validation

Appendix 5 - Validation of computerized systems

Appendix 6 - Qualification of systems and equipment

Appendix 7 - Non-sterile process validation – proposed to be revised
Proposed for revision of the Supplementary Guideline on Good Manufacturing Practices: Validation, Appendix 7: Non-sterile process validation

Contents

1. Background and scope
2. Glossary
3. Introduction
4. Phase I. Process design
5. Phase II. Qualification and process verification
6. Phase III. Continued process verification
7. Change control
8. References

1. BACKGROUND AND SCOPE

Further to the Supplementary Guideline on good manufacturing practices: validation, as published in the World Health Organization (WHO) Technical Report, No. 937, additional guidelines to support current approaches in 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 applicable to non-sterile finished pharmaceutical dosage forms. Thorough knowledge of product and process development studies; previous manufacturing experience; and quality risk management (QRM) principles are essential in the all approaches to process validation as the focus is now on the life-cycle approach. The life-cycle approach

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links product and process development, validation of the commercial manufacturing process and maintenance of the process during routine commercial production.

A risk based approach to validation is recommended, linked to in-line or on-line controls and monitoring to ensure that a process is in a state of control during routine manufacture.

2. GLOSSARY

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)
Continued process verification (CPV) can be defined as continuous monitoring of manufacturing performance by using extensive in-line, on-line or at-line monitoring and/or controls to evaluate process performance. It is a science and risk-based real-time approach to verify and demonstrate that a process that operates within the predefined specified parameters consistently produces material which meets all its critical quality attributes (CQAs) and control strategy requirements.

continuous process verification
An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated.

critical process parameter (CPP)
A process parameter whose variability has an impact on a critical quality attribute and therefore should be monitored or controlled to ensure the process produces the desired quality.
critical quality attribute (CQA)
A physical, chemical, biological or microbiological property or characteristic that should be within an appropriate limit, range or distribution to ensure the desired product quality.

life-cycle
All phases in the life of a product from the initial development through marketing until the product’s discontinuation (ICH Q8).

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

process validation
Documented evidence which provides a high degree of assurance that a specific process will consistently result in a product that meets its predetermined specifications and quality characteristics.

3. INTRODUCTION

Process validation data should be generated for all products to demonstrate the adequacy of the manufacturing process at each site of manufacture. The validation should be carried out in accordance with good manufacturing practices (GMP) and data should be held at the manufacturing location and made available for inspection. Manufacturers should confirm that a manufacturing process is under control before a product is placed on the market.

Process validation is associated with the collection and evaluation of data, from the process design stage through commercial production, which provides scientific evidence that a process is capable of consistently delivering a quality product. Process validation provides documented evidence that a process is capable of reliably and repeatedly rendering a product of the required quality.

A risk assessment approach should be used 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 product and 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.

Where necessary, 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 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.

Different approaches can be followed when validating a process.

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 it is reproducible,
— the commercial manufacturing process is defined and controlled,
— ongoing assurance is gained to show that the process remains in a state of control.

The validation should cover all manufactured strengths and all manufacturing sites used for production of the marketed product. A matrix approach may be acceptable based on appropriate risk assessment.

There are different approaches to process validation which include traditional process validation with prospective and concurrent validation, continuous process performance verification (where an enhanced approach to development has been employed or where a
substantial amount of product and process knowledge and understanding has been gained through historical data and manufacturing experience) and a combination of traditional process validation and continuous process verification.

Continued process verification is considered as a third phase in process validation.

Manufacturers should plan towards implementing the new approach in process validation that should consist of three phases in the product life-cycle.

Phase I. Process design
Phase II. Qualification and process verification
   Phase IIA. Qualification
   Phase IIB. Continuous process performance verification
Phase III. Continued process verification

4. PHASE I. PROCESS DESIGN

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 certain cases, however, it may be necessary to provide production-scale validation data. The number of batches (minimum of three) should be based on the variability of the process, the complexity of the process/product and the experience of the manufacturer.

The number of batches produced in this validation exercise should be sufficient to allow the normal extent of variation and trends to be established and to provide sufficient data for evaluation. Extensive testing should be performed on the product at various stages during the manufacturing process of the batches.

 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. Data should be collected and reviewed against predetermined acceptance criteria, and reflected in process validation reports.

The protocol should include:
- a description of the process;
- a description of the experiment;
- 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;
- the samples to be taken – 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;
- time schedules;
- personnel responsibilities;
- details of methods for recording and evaluating results, including statistical analysis.

The results should be documented in the validation report which reflects the validation protocol.

A conclusion and recommendation should be made on the extent of monitoring and the in-process controls necessary for routine production, on the basis of the results obtained.

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.
5. PHASE II. QUALIFICATION AND PROCESS VERIFICATION

Process verification is divided into two phases. These phases include qualification of premises, utilities and equipment where commercial scale batches will be manufactured and continuous process performance verification.

Phase IIA. Qualification

Premises, utilities, support systems and equipment should be appropriately qualified before process performance verification (as part of validation) is started.

In a traditional approach, stages of qualification may include design, installation, operational and performance qualification.

In some cases process validation may be conducted concurrently with performance qualification.

Phase IIB. Continuous process performance verification

After completion of qualification, commercial batches should be subjected to continuous process performance verification as part of process validation. It should confirm that scale up in batch size did not adversely affect the characteristics of a product.

CPV demonstrates 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 or at-line controls should be used to monitor process performance and product quality in a timely manner. Relevant process 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 (MSPC) can be used.

The scope and extent of continuous 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 CPV strategy including the process parameters and material attributes that will be monitored as well as the analytical methods that will be employed.

Continuous process verification can be introduced at any time of the life-cycle of the product:
— it can be used to design process validation protocols for the initial commercial production;
— to revalidate commercialized products as part of process changes;
— to support continual improvement throughout the remainder of the life-cycle.

It is expected that additional monitoring for the first commercial batches should be done where continuous process verification is implemented.

Manufacturers should define:
— the number of batches for which additional monitoring is proposed;
— the type of testing/monitoring to be performed;
— the acceptance criteria to be applied;
— how the data will be evaluated.

Statistical models or tools used should be described.
Manufacturers should monitor product quality of commercial batches after completion of Phase I and Phase II of process validation. This will provide evidence that a state of control is maintained throughout the product life-cycle.

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 ongoing process validation should be reviewed periodically and modified if appropriate throughout the product life-cycle.

Continued process validation (CdPV) should not be confused with product quality review.

Table 2 provides a summary of the new approach to process validation.

<table>
<thead>
<tr>
<th>Product life-cycle</th>
<th>Process validation</th>
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<tbody>
<tr>
<td><strong>Phase I</strong></td>
<td><strong>Phase II</strong></td>
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<tr>
<td>Process design</td>
<td>Qualification</td>
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<tr>
<td>- Pilot scale (and scale-up batches where appropriate)</td>
<td>- Premises - Utilities - Equipment</td>
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<tr>
<td>- Risk assessment to identify critical quality attributes and process control parameters</td>
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7. CHANGE CONTROL

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.

Changes that are likely to require revalidation may include:

— changes in the manufacturing process (e.g. mixing times, drying temperatures);
— changes in the equipment (e.g. addition of automatic detection systems);
— production area and support system changes (e.g. rearrangement of areas or a new water treatment method);
— transfer of processes to another site;
— unexpected changes (e.g. those observed during self-inspection or during routine analysis of process trend data).

Based on risk assessment, revalidation should be considered in the case of:

— changes in the master formula, methods, starting material manufacturer, equipment and/or instruments;
— equipment calibrations and preventive maintenance carried out;
— changes to standard operating procedures (SOPs);
— changes to cleaning and hygiene programmes.

REFERENCES

   EMA/CHMP/CVMP/QWP/70278/2012-Rev1, Committee for Medicinal Products for
   Human Use (CHMP), Committee for Medicinal Products for Veterinary Use (CVMP)

   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

5. ICH Harmonised Tripartite Guideline, Pharmaceutical Quality System, Q10, Current
   Step 4 version, dated 4 June 2008

6. Quality Assurance of pharmaceuticals. WHO guidelines, related guidance and


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