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Guideline on Process Validation

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This guideline replaces the Note for Guidance on Process Validation (CPMP/QWP/848/96, EMEA/CVMP/598/99)

Comments should be provided using this template. The completed comments form should be sent to qwp@ema.europa.eu

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Executive summary

This guideline replaces the previous guideline on process validation. The guideline is brought into line with ICH Q8, Q9 and Q10 documents and the possibility to use continuous process verification in addition to, or instead of, traditional process verification described in the previous guideline has been added. This guideline does not introduce new requirements on medicinal products already authorised and on the market, but clarifies how companies can take advantage of the new possibilities given when applying enhanced process understanding coupled with risk management tools under and efficient quality system as described by ICH Q8, Q9 and Q10.

1. Introduction (background)

Process validation can be defined as 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. Continuous process verification (CPV) has been introduced to cover an alternative approach to process validation based on a continuous monitoring of manufacturing performance. This approach is based on the knowledge from product and process development studies and / or previous manufacturing experience. CPV may be applicable to both a traditional and enhanced approach to pharmaceutical development. It may use extensive in-line, on-line or at-line monitoring and / or controls to evaluate process performance. It is intended that the combination of the guidance provided in the note for guidance on development pharmaceutics (CPMP/QWP/155/96) and the note for guidance on pharmaceutical development (ICH Q8R2) together with this guidance should cover all of the critical elements in manufacturing process for a pharmaceutical product for human use. For veterinary medicinal products, the applicable guidance is that provided in the note for guidance on development pharmaceutics for veterinary medicinal products (EMEA/CVMP/315/98) together with this guidance. Although the ICH Q8 guideline is not applicable to veterinary medicinal products the principles detailed in this guideline may be applied to veterinary medicinal products should an applicant choose to apply an enhanced approach to pharmaceutical development.

Process validation should not be viewed as a one-off event. A lifecycle approach should be applied linking product and process development, validation of the commercial manufacturing process and maintenance of the process in a state of control during routine commercial production.

2. Scope

This note for guidance is intended to apply to data generated to validate the manufacturing process of the intended commercial dosage form only. It is not directly relevant to the manufacture of the active substance or other starting materials, although it may contain information useful for such activities. It is intended to apply to medicinal products for human and veterinary use. The fundamental principles described in this document are applicable to biological products, however, these should be considered on a case-by-case basis in view of the complex nature and inherent variability of the biological substance. The document provides guidance on the information to be considered for dossier submission and as such is mainly aimed at industry and assessors; however the information may also be useful for inspectors.

3. Legal basis

This guideline has to be read in conjunction with the introduction and general principles section (4) of Annex I to Directive 2001/83/EC as amended and the introduction and general principles section (2) of Directive 2001/82/EC as amended.

4. General Considerations

Irrespective of whether a medicinal product is developed by a traditional approach or an enhanced approach, the manufacturing process should be validated before the product is placed on the market. In exceptional circumstances concurrent validation may be accepted. Process validation should confirm that the control strategy is sufficient to support the process design and the quality of the product. The validation should cover all manufactured strengths and all manufacturing sites used for production of the marketed product. A matrix approach may be acceptable.

Process validation can be performed in a traditional way as described below; however there is also the possibility to implement continuous process verification if 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. A combination of process validation and continuous process verification may be employed. The in-line, on-line or at-line monitoring that is often utilised for continuous process verification (discussed in section 5.2) provides substantially more information and knowledge about the process and might facilitate process improvements. When feed-forward or feedback loops are employed then it is possible to adjust the process during manufacture to maintain finished product quality.

5. Process validation

5.1. Traditional process validation

Process validation data should be generated for all products to demonstrate the adequacy of the manufacturing process at each site of manufacture. It is recognised that, at the time of submission, process validation data may not always be available. Nevertheless it is essential that valid manufacturing processes are always utilised. Validation should be carried out in accordance with GMP and data should be held at the manufacturing location and made available for inspection.

As part of the process validation lifecycle some process validation studies may be conducted on pilot scale batches if the process has not yet been scaled up to production scale. It should be noted that pilot batch size should correspond to at least 10% of the production scale batch (i.e. such that the multiplication factor for the scale-up does not exceed 10). For solid oral dosage forms this size should generally be 10% of the maximum production scale or 100,000 units whichever is the greater[1]. Where the intended batch size is less than 100,000 units, the predictive value of the pilot batches may be limited and a justified approach should be followed. The competent authority may decide on limitations for a post approval increase of the batch size.

Since it is not generally considered useful to conduct full validation studies on pilot scale batches, the process validation scheme outlined in Annex I of this guideline should be completed for each product for subsequent execution at the production scale. The process validation scheme to be followed should be included in the dossier. The scheme should include a description of the manufacturing process, the tests to be performed and acceptance criteria, a description of the additional controls in place and the

[1] In the case of veterinary medicinal products, the minimum pilot batch size may be smaller than 100,000 units where justified.

data to be collected. A justification for the chosen process validation scheme should be presented in Module 3 and the Quality Overall Summary for human medicines and in Part 2.B and the Pharmaceutical Detailed and Critical Summary for veterinary medicines.

Process validation should focus on the control strategy, which primarily includes critical process parameters, and other relevant studies demonstrating that the process is capable of delivering the desired product quality.

In certain cases however, it is considered necessary to provide production scale validation data in the marketing authorisation dossier, e.g. in those circumstances where the product is a biological / biotech product, where the applicant is proposing a non-standard method of manufacture, where pilot scale data may not be predictive of production scale, or for specialised products such as certain modified release preparations (for medicinal products for human use, see the Note for guidance on quality of Modified release products; for those for veterinary use, see the Note for guidance on the Quality of Modified Release Dosage Forms for Veterinary Use). Where non-standard sterilisation methods or aseptic processing are employed, data should be provided on a number of consecutive batches at production scale prior to approval. The number of batches (minimum of 3) should be based on the variability of the process, the complexity of the process / product and the experience of the manufacturer. For other specialised non-standard processes (described in section 8), data on 1 or 2 production scale batches may suffice where these are supported by pilot scale batches, and by a history of consistent manufacture of products by essentially equivalent processes.

The studies should address those phases of manufacture, in particular the critical phases which would not necessarily be adequately addressed by application of the finished product specification alone, by conducting additional testing as necessary. A justification for the chosen process validation studies should be presented in Module 3 and the Quality Overall Summary for human medicines, and in Part 2.B and the Pharmaceutical Detailed and Critical Summary for veterinary medicines.

If a design space has been implemented, the applicant should provide the validation strategy at production scale in order to confirm that the models used at pilot scale to define the design space are still valid at production scale. Validation at production scale may be conducted step-wise when the manufacturer moves to different areas of the design space.

5.2. Continuous process verification

Continuous Process Verification (CPV) is an alternative approach to traditional process validation in which manufacturing process performance is continuously monitored and evaluated (ICH Q8).

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. In order to enable continuous process verification, companies should perform, as relevant, extensive in-line or at-line controls and 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 such as NIR spectroscopy with or without feedback loop (e.g. end point determination of blend homogeneity, determination of granules surface area, determination of content uniformity with large sample size) and multivariate statistical process control (MSPC) can be viewed as enablers for continuous process verification.

Sufficient knowledge and understanding of the process is required in order to support continuous process verification. However, 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;
- With reference to the product lifecycle, process robustness and manufacturing history since point of commercialization as appropriate.

The process should be verified on commercial scale batches prior to marketing.

If a design space has been implemented continuous process verification may contribute to ensuring its validity throughout the product lifecycle.

A discussion on the appropriateness and feasibility of the CPV strategy should be included in the development section of the dossier and should be supported with data from at least lab or pilot scale batches. A description 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 should be included as described in Annex 1, with cross reference in the validation section of the dossier. Actual data generated during continuous process verification at commercial scale should be held at the site for inspection. The applicant should define the stage at which the product is considered to be validated and the basis on which that decision was made. The discussion should include a justification for the number of batches used based on the complexity and expected variability of the process and existing manufacturing experience of the company.

Continuous process verification can be introduced at any time of the lifecycle of the product: it can be used to design process validation protocols for the initial commercial production, to re-validate commercialised products as part of process changes or to support continual improvement throughout the remainder of the lifecycle.

Continuous process verification performance depends strongly on compliance with GMP principles and requirements. Pharmaceutical quality systems (PQS) as described in ICH Q10 can complement GMP requirements, however GMP matters and PQS should not be included in the submission. They are assessed and handled by GMP inspectors as appropriate.

5.3. Hybrid approach

It may be necessary to use either the traditional process validation or the continuous process verification approach for different steps within the manufacturing process. A justification for using this hybrid approach should be presented in the dossier and it should be clear which approach to validation has been taken for which part of the manufacturing process. The validation requirements in terms of batch size and number of batches would depend on the extent to which continuous process verification has been used. For non-standard processes (as defined in section 8) the process validation requirements highlighted in section 5.1 should be applied unless otherwise justified.

5.4. Continued Process Verification during the Lifecycle

Subsequent to process validation and during commercial manufacture, companies should monitor product quality to ensure a state of control is maintained throughout the commercial part of the product lifecycle. This will provide assurance of the continued capability of the process and controls to produce product that meets the desired quality and to identify changes that may improve product quality or performance. Relevant process trends e.g. quality of incoming materials or components, in-process and finished product results, non-conformances and defect reporting 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 lifecycle considering the level of process understanding and process performance at any point in time. Hence, if appropriate, the product may benefit from a defined period of enhanced sampling and monitoring to help increase process understanding as part of continuous improvement. If high impact models are used as part of continued process verification during the lifecycle a general discussion of the process for model verification during the lifecycle should be included in the dossier.

6. Scale up

In order to avoid the repetition of lengthy and costly tests, it is necessary to gather information during properly designed development and process optimisation studies, when scaling up from laboratory through pilot to production scale. Such information provides the basis for justification that scale-up can be achieved without a consequent loss in quality. Those parts of the process likely to be critical in scale-up should be identified in section 3.2.P.2 (Veterinary Part 2.A.4) and defined in section 3.2.P.3 (Veterinary Part 2.B) of the dossier.

Where ranges of batch sizes are proposed, it should be shown that variations in batch size would not adversely alter the characteristics of the finished product. It is envisaged that those parameters listed in the process validation scheme (Annex I of this guideline) will need to be re-validated once further scale-up is proposed post-authorisation unless the process has been proven to be scale independent.

7. Post approval change control

Clearly defined procedures are needed to control changes proposed in production processes. These procedures are part of GMP and would not normally be specified in the dossier. Such procedures should tightly control planned changes, ensure that sufficient supporting data are generated to demonstrate that the revised process will result in a product of the desired quality, consistent with the approved specification and ensure that all aspects are thoroughly documented and approved including whether regulatory approval is needed by way of variation.

Refer to the European Commission guidance on Type I and Type II variations (Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products) and Regulation 1234/2008/EC for details on the changes which would require a variation.

8. Standard vs. non-standard methods of manufacture

This section is only relevant for processes which have not been validated using continuous process verification (see sections 5.1 and 5.2).

For the purposes of this guideline the designation of a process as non-standard is determined by a combination of the nature of the drug substance, the nature of the product, the actual process itself and the production experience of the manufacturer. Non-standard methods of manufacture could include non-standard methods of sterilisation and, aseptic processing, or processes with critical steps such as lyophilisation, micro-encapsulation, certain mixing, coating processes and other specialised processes.

The following categories are examples of products or processes which could be considered as non-standard, and for which production scale validation data might need to be provided in the marketing authorisation application dossier, unless otherwise justified:

1. The manufacture of specialised pharmaceutical dose forms;
2. The incorporation of some new technology into a conventional process;
3. (Highly) Specialised processes involving new technologies or an established process known, or likely, to be complex and therefore to require particular care;
4. Non-standard methods of sterilisation.

In addition a manufacturing process type not previously approved for pharmaceutical products within the EU is usually considered a non-standard process. However it should be noted that a manufacturer's own experience in the manufacture of specialised products or use of processes which might otherwise be considered "non-standard", might exempt them from the need to provide production scale process validation data at the time of submission provided sufficient supporting data are provided. This needs to be justified on a "case-by-case" basis, on the basis of appropriate pharmaceutical development data or by reference to similar products.

The applicant should clearly state (in section 3.2.P.3.5 of the dossier for human medicines, in section 2.B of the dossier for veterinary medicines) whether they consider the manufacturing process to be standard or non-standard and the justification for their decision should be presented. The data required to be presented in the dossier are detailed in section 5.1.

1. <u>Specialised Pharmaceutical Dose Forms</u>

A non exhaustive list of types of products which might be considered as "specialised" is provided below for illustrative purposes.

- Preparations for metered dose inhalation in the lungs e.g., pressurised metered dose inhaler (MDI's) and dry powder inhalers (DPI's);
- Suspension, emulsions or other liquid dispersed Parenterals;
- Modified release preparations;
- Unit dose products containing drugs in low content (≤2% of composition);
- Other specialised dose forms e.g., parenteral depot preparations based on biodegradable polymers; liposomal preparations; micellar preparations, nanoparticulate preparations.

2. <u>Conventional pharmaceutical processes incorporating new technologies</u>

A conventional process is well established and approved, and for example could include such activities as tabletting using wet granulation. However the introduction of a new technology into such a conventional process e.g., a new drying technology not commonly used by the pharmaceutical industry, might result in the need for full-scale validation data based on a case-by-case consideration of the product and process development studies.

3. Specialised processes or established processes known to be complex

- Processes with critical steps such as lyophilisation, microencapsulation;
- Processes where the physicochemical properties of the active substance or a key excipient (e.g., lubricant, coating agent) may give rise to processing or scale up difficulties, or stability problems during manufacture at larger scale for related products;
- Any request for real time release testing;
- Aseptic processing.

4. Non-standard methods of sterilisation

- Terminal sterilisation by moist heat using conditions other than pharmacopoeial reference conditions;
- Terminal sterilisation by irradiation using less than 25 KGy.

Definitions

Control Strategy:

A planned set of controls, derived from current product and process understanding that ensures process performance and product quality. The controls can include parameters and attributes related to drug substance and drug 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. (ICH Q10)

Continued Process Verification:

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

Continuous Process Verification:

An alternative approach to process validation in which manufacturing process performance is continuously monitored and evaluated. (ICH Q8)

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. (ICH Q8)

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. (ICH Q8)

Design Space:

The multidimensional combination and interaction of input variables (e.g., material attributes) and process parameters that have been demonstrated to provide assurance of quality. Working within the design space is not considered as a change. Movement out of the design space is considered to be a change and would normally initiate a regulatory post approval change process. Design space is proposed by the applicant and is subject to regulatory assessment and approval. (ICH Q8)

High impact models:

A model can be considered high impact if prediction from the model is a significant indicator of quality of the product (e.g. a chemometric model for product assay, a surrogate model for dissolution).

Lifecycle:

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. (ICH Q10)

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.

References

Note for Guidance on Development Pharmaceutics (CPMP/QWP/155/96)

Note for Guidance on Development Pharmaceutics for Veterinary Medicinal Products (EMEA/CVMP/315/98)

Note for Guidance on Quality of Modified Release Products (CPMP/QWP/604/96)

Note for Guidance on the Quality of Modified Release Dosage Forms for Veterinary Use (EMEA/CVMP/680/02)

ICH Q8 (R2) (Pharmaceutical Development)

ICH Q9 (Quality Risk Management)

ICH Q10 (Pharmaceutical Quality System)

Guideline on the details of the various categories of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products

Commission Regulation (EC) No 1234/2008

ANNEX I: Process validation scheme

Traditional process validation

Where validation data on production scale batches are not provided with the application and traditional process validation as described in section 5.1 is proposed, the process validation scheme described below should be submitted by the applicant. This should outline the formal process validation studies to be conducted on production scale batches (the number of batches used would depend on the variability of the process, the complexity of the process / product and the experience of the manufacturer, but would usually be a minimum of 3 consecutive batches). The information from these studies will be available for verification post authorisation by the supervisory authority. The process validation scheme should be submitted in the marketing authorisation dossier and should include the following information as a minimum:

- Short description of the process with a summary of the critical processing steps or critical parameters to be monitored during validation;

- Finished Product Specification (release);
- Details of Analytical Methods (References to the dossier);
- In-Process Controls proposed with Acceptance Criteria;
- Additional testing intended to be carried out (e.g. with proposed acceptance criteria and analytical validation as appropriate);
- Sampling plan - where, when and how the samples are taken;
- Details of methods for recording and evaluation of results;
- Proposed Timeframe.

Following completion of the scheme, a report containing the following information and signed by the appropriate authorised person should be generated and made available for inspection:

- Batch Analytical Data;
- Certificates of Analysis;
- Batch Production Records;
- Report on unusual findings, modifications or changes found necessary with appropriate rationale;
- Conclusions.

Where the results obtained show significant deviations from those expected, the regulatory authorities need to be informed immediately. In such cases corrective actions should be proposed and any changes proposed in the manufacturing process should receive prior regulatory approval by way of variation.

Continuous process verification

In cases where continuous process verification is proposed (as described in section 5.2) additional monitoring would be expected for the first commercial batches. The process validation scheme should provide details on the number of batches for which additional monitoring is proposed, the type of testing / monitoring to be performed, the acceptance criteria to be applied and 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 stated based on the complexity of the process, expected variability and manufacturing experience of the company.