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Committee for Medicinal Products for Human Use (CHMP)
Committee for Medicinal Products for Veterinary Use (CVMP)

Guideline on process validation for finished products - information and data to be provided in regulatory submissions

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This guideline replaces the note for guidance on process validation (CPMP/QWP/848/96, EMEA/CVMP/598/99) including annex II – non-standard processes (CPMP/QWP/2054/03).

Keywords	***Process validation, continuous process verification, on-going process verification, critical process parameter, critical quality attribute, lifecycle, change control***

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Executive summary

This guideline replaces the previous note for guidance on process validation (CPMP/QWP/848/96, EMEA/CVMP/598/99). 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 validation described in the previous guideline has been added and is encouraged. 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 an 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 (ICH Q7). Continuous process verification 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. Continuous process verification 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 advice 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 guideline should cover all of the critical elements in manufacturing process for inclusion in the dossier for regulatory submission 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 guideline. 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 and process validation.

Process validation should not be viewed as a one-off event. Process validation incorporates a lifecycle approach 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 document is intended to provide guidance on the process validation information and data to be provided in regulatory submissions for the finished dosage forms of chemical medicinal products for human and veterinary use. The general principles also apply to active substances. However, information on validation of non-sterile active substances is not required in the dossier. In addition, expectations for active substances are contained in ICH Q11 and so the information is not repeated in this document.

The principles described are also applicable to biological medicinal 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.

It is expected that the information / data requested in this guideline be present in the dossier at the time of regulatory submission.

This document provides guidance on the validation of the manufacturing process, which can be considered as the second stage in the product lifecycle. The first stage (process design) is covered in the note for guidance on pharmaceutical development (ICH Q8R2/ EMEA/CVMP/315/98) and the third stage (on-going process verification) is covered under GMP (Annex 15).

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 Annex I to 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. Please refer to GMP Annex 15 for further guidance.

Process validation should confirm that the control strategy is adequate to 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 bracketing approach may be acceptable for different strengths, batch sizes and pack sizes. However, validation must cover all proposed sites. Process validation data should be generated for all products to demonstrate the adequacy of the manufacturing process at each site of manufacture. Validation should be carried out in accordance with GMP and data should be held at the manufacturing location and made available for inspection if not required in the dossier (see section 8).

Process validation can be performed in a traditional way, as described below, regardless of the approach to development taken. However, there is also the possibility to implement continuous process verification if an enhanced approach to development has been performed or where a substantial amount of product and process knowledge and understanding has been gained through historical data and manufacturing experience. A combination of traditional 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.

5. Process validation

5.1. Traditional process validation

Traditional process validation is normally performed when the pharmaceutical development and/or process development is concluded, after scale-up to production scale and prior to marketing of the finished product. 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. For other dosage forms the pilot batch size should be justified taking into account risk to the patient of failure of the dosage form. 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 production scale; bracketing may be acceptable. 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 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.

In certain cases however, it is considered necessary to provide production scale validation data in the marketing authorisation dossier at the time of regulatory submission, for example when the product is a biological / biotech product or where the applicant is proposing a non-standard method of manufacture (see section 8 and Annex II). In these cases, data should be provided in the dossier on a number of consecutive batches at production scale prior to approval. The number of batches should be based on the variability of the process, the complexity of the process / product, process knowledge gained during development, supportive data at commercial scale during technology transfer and the overall experience of the manufacturer. Data on a minimum of 3 production scale batches should be submitted unless otherwise justified. Data on 1 or 2 production scale batches may suffice where these are supported by pilot scale batches and a justification as highlighted above.

The studies should address critical steps of manufacture, by conducting additional testing as necessary.

5.2. Continuous process verification

Continuous process verification is an alternative approach to traditional process validation in which manufacturing process performance is continuously monitored and evaluated (ICH Q8). Continuous process verification can be used in addition to, or instead of, traditional process validation.

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, on-line or at-line controls and monitor process performance and product quality on each batch. Relevant data on 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

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

technology (PAT) 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;
- for legacy products, with reference to the product lifecycle, process robustness and manufacturing history since point of commercialization as appropriate.

A discussion on the appropriateness and feasibility of the continuous process verification strategy should be included in the development section of the dossier and should be supported with data from at least laboratory or pilot scale batches. A description of the continuous process verification 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 to the validation section of the dossier. Actual data generated during continuous process verification at production scale should be available at the site for inspection. The applicant should define the stage at which the process is considered to be under control and the validation exercise completed prior to release of the product to the market, and the basis on which that decision will be made. The discussion should include a justification for the number of batches to be used based on the complexity and expected variability of the process and existing manufacturing experience of the manufacturing site. Continuous process verification would be considered the most appropriate method for validating continuous processes.

Continuous process verification can be introduced at any time in the lifecycle of the product. It can be used for the initial commercial production, to re-validate commercialised products as part of process changes or to support continual improvement.

Continuous process verification is dependent 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 as 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. It should be clear in the dossier which approach to validation has been taken for which steps in 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) if continuous process verification does not address the critical unit

operation(s) the process validation requirements highlighted in section 5.1 should be applied unless otherwise justified.

5.4. Design space verification

A design space will normally be developed at laboratory or pilot scale. During scale-up the commercial process is generally conducted and validated in a specific area of the design space, defined as the target interval or Normal Operating Range (NOR). During the product lifecycle, moving from one area to another within the design space (i.e. change in the NOR) may represent higher or unknown risks not previously identified during initial establishment of the design space. For this reason and depending on how the design space was originally established and how the process was validated, there will be situations where it will be necessary to confirm the suitability of the design space and verify that all product quality attributes are still being met in the new area of operation within the design space. This is termed 'design space verification'.

If the parameters investigated during development of the design space have not been shown to be scale independent and the process has been validated using traditional process validation, design space verification would be required and a verification protocol should be provided in the dossier. If continuous process verification has been utilised, this may contribute towards ensuring the validity of the design space throughout the product lifecycle. In this case, a design space verification strategy should be included as part of the continuous process verification strategy.

Depending on the change and the extent of movement within the design space (i.e. distance from validated target/NOR or new area of design space with higher or unknown risk) protocols for verification may include controls of quality attributes (QA's) and process parameters (PP's) not included in the routine control system (e.g. monitoring or testing of QA's and PP's that are expected to be scale dependant and when applicable, equipment dependant). It is not necessary to verify entire areas of the Design Space or the edge of failure. In principle more than one area of the design space should be verified but a stepwise approach taking into consideration the need to adjust the NOR within the approved design space during product lifecycle is acceptable.

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 justified that variations in batch size would not adversely alter the CQAs 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 or continuous process verification is employed.

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 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 control strategy 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 (Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No. 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures) and Regulation 712/2012/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 been validated using traditional process validation. It is not relevant for those processes where continuous process verification is employed (see sections 5.1 and 5.2). According to section 5.1, full production-scale data should be provided in the dossier for non-standard products or processes which were validated using traditional process validation. It is possible for the applicant to justify that the product process can be considered standard for a particular manufacturer / site taking into account the risk to the patient of failure of the product or process. Such justifications are assessed on a case by case basis, but the information provided by the applicant (for each manufacturing site) should include:

- experience with the same or essentially similar product or process (number of products authorised / marketed in the EU/EEA and number of batches (including information on scale) manufactured);
  - the names/ marketing authorisation numbers in the relevant EU/EEA member state should be provided.
- amount of knowledge gained during the development of the product (number and scale of batches manufactured at each manufacturing site involved);
- history of GMP compliance of manufacturing sites for that type of process 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 for new marketing authorisation applications.

Please see Annex II for further information on products / processes considered to be non-standard.

Definitions

At-line:

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

Bracketing approach:

A validation scheme / protocol designed such that only batches on the extremes of certain predetermined and justified design factors, e.g., strength, batch size, pack size are tested during process validation. The design assumes that validation of any intermediate levels is represented by the validation of the extremes. Where a range of strengths is to be validated, bracketing could be applicable if the strengths are identical or very closely related in composition (e.g., for a tablet range made with different compression weights of a similar basic granulation, or a capsule range made by filling different plug fill weights of the same basic composition into different size capsule shells). Bracketing can be applied to different container sizes or different fills in the same container closure system.

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 active substance and finished 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)

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)

Enhanced approach:

A development approach where risk management and scientific knowledge is used to identify and understand the material attributes and process parameters which influence the critical quality attributes of a product.

In-line:

Measurement where the sample is analysed within the process stream and not removed from it.

Lifecycle:

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

Ongoing process verification:

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

On-line:

Measurement where the sample is diverted from the manufacturing process and not returned to the process stream.

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.

Traditional approach:

A product development approach where set points and operating ranges for process parameters are defined to ensure reproducibility.

References

Commission Regulation (EC) No 712/2012 of 3 August 2012 amending Regulation (EC) No 1234/2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products.

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.

Directive 2001/82/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to veterinary medicinal products.

Eudralex volume 4 (GMP guidelines), Annex 15 (Qualification and validation).

Guidelines on the details of the various categories of variations, on the operation of the procedures laid down in Chapters II, IIa, III and IV of Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of variations to the terms of marketing authorizations for medicinal products for human use and veterinary medicinal products and on the documentation to be submitted pursuant to those procedures.

ICH Q8 (R2) (Pharmaceutical development).

ICH Q9 (Quality risk management).

ICH Q10 (Pharmaceutical quality system).

ICH Q11 (Development and manufacture of drug substances (chemical entities and biotechnological / biological entities).

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).

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 process parameters to be monitored during validation;
- finished product release specification (references to the dossier);
- 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 proposed changes to the manufacturing process should receive appropriate regulatory approval by way of variation.

Continuous process verification

In cases where continuous process verification is proposed (as described in section 5.2) a continuous process validation scheme should be submitted by the applicant. This should outline the monitoring to be performed on production scale batches. The information obtained will be

available for verification post authorisation by the supervisory authority. The continuous process verification scheme should be submitted in the marketing authorisation dossier and should include, as appropriate, the following information on the monitoring proposed:

- details of on-line / in-line / at-line monitoring including parameters tested, number of samples, size of samples and frequency of monitoring
- details of Analytical Methods (References to the dossier);
- acceptance criteria;
- information/ data including, as appropriate, information on statistical models or tools used to determine whether the continuous verification data supports the ability of the process and controls to produce reproducible product at a commercial scale;
- if a design space has been developed, how the proposed monitoring will contribute to design space verification.

Annex II: Standard/non-standard processes

For the purposes of this guideline the designation of a process as non-standard is determined by a combination of the nature of the active substance, the nature of the finished product, the actual process itself and the production experience of the manufacturer. All biological products are considered to be non-standard.

The following categories are examples of products or processes which could be considered as non-standard, and for which production scale validation data should 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.

1. Specialised pharmaceutical dose forms

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);
- suspensions, emulsions or other liquid dispersed sterile products;
- 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. Conventional pharmaceutical processes incorporating new technologies

A conventional process is well established and approved, and could, for example, 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;
- 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.