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Review Article

# A REVIEW ON LATEST GUIDELINES ON PROCESS VALIDATION OF EUROPEAN MEDICINES AGENCY

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**ABSTRACT**

Validation is an act of proving and documenting that a process functions efficiently. Process validation can be well-defined as documented proof that the process functions within established restrictions, can execute effectively and reproducibly to produce a pharmaceutical product meeting its determined conditions and quality features. The former note for guidance on process validation (1 March, 2001) of European Medicines Agency (EMA) emphasizes on traditional process validation. It describes the relationship between development studies and process validation data, connection between method of manufacture and process validation data, relationship between process validation and specification of the finished product. The latest draft of guidelines on process validation (29 march 2012) by EMA, is prepared based on the guidelines of ICH $Q_8$, $Q_9$, and $Q_{10}$. It describes the utility of continuous process verification principles to replace traditional process verification. Continuous process verification (CPV) has been presented to cover a substitute method to process validation centered on a continuous monitoring of manufacturing process. It is intended to apply to medicinal products for human and veterinary use. The document provides guidance on the information to be considered for dossier submission and as such is mainly aimed at industry and assessors.

**Keywords:** Critical process parameters, Critical quality attributes, Continued process verification, Continuous process verification, Process validation, Traditional process verification.

## INTRODUCTION

Process validation is defined as an act of creating a written evidence or proof regarding the ability of a process to produce a product which meeting its critical quality attributes.[1]

The present article is a compilation of different guiding principles on process validation by European medicines agency.

Based on the guiding principles on process validation by EMA, the approaches for process validations are as follows:

1. Traditional process validation
2. Continuous process verification
3. Hybrid approach
4. Continued process verification

## 1. TRADITIONALPROCESS VALIDATION

Process Validation documents should be created for all products to establish the capability of the manufacturing procedure at each onesite of production. It is recognized that, at the stage of market authorization proposal, process validation records may not always be available. However it is necessary that effective manufacturing procedures are continuously employed. The validation of the facility should be carried in accordance with GMP regulations and the data which is generated during the validation has to be maintained and reviewed further. In certain situations, where production scale has not been developed for a particular product, the validation data should be generated from pilot scale to produce the information in dossier. In such cases the pilot batch sizes are specified in this draft are as follows:

i. Pilot scale batch size should be at least 10% of the production scale.
e.g.: in case of solid oral dosages, if the production scale batch size is predicted as 1,000,000 the pilot scale batch size should be 100,000 i.e., $1/10^{th}$ of production scale.
ii. If the production batch size is less than 1,000,000 then the pilot scale batch size for that particular product is defined by experts and the value is extrapolated to 100,000 unit's size, and this approach is justified stating the reasons. Generally validation studies on pilot scale are not preferred. In such cases the validation is conducted on the subsequent production scale. The validation procedure description should be enclosed in the dossier.

The description should contain

- Manufacturing method
- Investigations to be performed
- Acceptance criteria
- Description of control strategy proposed to maintain the validation status.

It is necessary to produce the validation data on production scale in the dossier for the following situations:

- Production of biological / biotech products.
- Productions involving non-standard methods of sterilization
- Situations where extrapolation of pilot scale validation data can't resembles or represents the situation of production scale.
- Production of dedicated products.

Data submission requirements

i. For non-standard sterilization methods the number of batches depends on
- Process complexity
- Process unpredictability
- Production capability of the manufacturer.

The number of batches should be a minimum of 3. For other non-standard processes the validation should be generated from the at least 1-2 production scale batches, which is supported by pilot scale validation.[1]

Examples on non-standard methods:

**i. Pharmaceutical dosage forms**
- Metered dose inhalations, powder inhalers
- Emulsions, suspension and other liquid dispersed parenteral,
- Modified release dosage forms.
- Dosage forms containing the active pharmaceutical ingredient of ≤ 2%
- Other specialized dosage forms such as liposomal preparations, Nano particulate preparations, micellar preparations.[2]

**ii. Conventional manufacturing process involving new technologies**

The validation of the conventional manufacturing process is necessary when it incorporates new technologies into the process, which can affect the quality of the final product.
e.g.: generally the tablet manufacturing involves wet granulation method (conventional method). The incorporation of new drying

technology which is not often used in pharmaceutical industry can led to the validation of the whole conventional process. [2]

**iii. Specialized processes:**

- Processes involving special critical steps such as lyophilization, microencapsulation.
- In situations, where the active pharmaceutical ingredient and excipients will produce complications when scaled up to production batch size.[3]

**iv. Non-standard methods of sterilization (non-compendia)**

- Terminal sterilization by moist heat
- Terminal sterilization by irradiation.[4]

If a design space has been applied, the claimant should afford the validation strategy at production scale in order to assure that the models used at pilot scale to describe the design space are still valid at production scale. Validation at production scale may be directed step-wise when the manufacturer moves to different areas of the design space.

**a. Relationship between development studies and process validation data**

It is probable that all through the development period, the manufacturer of the product should generate appropriate evidence about the physical and chemical attributes of the drug substance, the composition of the manufactured goods in terms of active ingredient(s) and basic excipients and the manufacturing process to undoubtedly explain the critical steps in the manufacturing procedure. Critical parameters of the product should be recognized at an initial phase; for instance the dissolution rate of an active ingredient and the effect of the existence, type and extent of lubricant.

Evidence engendered during the development stage should consequently be used to recognize and assess the critical pharmaceutical process parameters which may need to be scrutinized and possibly organized in order to ensure batch to batch reproducibility. In order to delineate these critical parameters it may be compulsory to encounter the process by making deliberate alterations to endorse the robustness of the process and express the limits of tolerance. Such parameters will diverge depending upon the nature of the product, the composition and the offered method of manufacture.[1]

**b. Relationship between methods of manufacture and process validation data**

Having demarcated and justified a particular mode of manufacture based on a contemplation of the physical and chemical attributes of the active ingredient, the key excipients, the choice of formulation and the influence of processing on the product quality and stability, the claimant should progress to fully describe the manufacturing process.

Such a report should address also the need and importance of in-process controls and the manufacturer's methodology to process optimization.

The assessment of the process should provide satisfactory evidence of the practicability of the process at the production scale thus ensuring the reliable quality of the product in line with the approved specification.[1]

**c. Relationship between Process Validation and the Specification of the Finished Product**

Documents generated through process assessment or validation can be used to rationalize why certain test need not be conducted routinely on the finished product at issue. In such cases the claimant must explicate and justify such an approach in the dossier and in the adept report and should cross-refer to this methodology.[1]

## 2. CONTINUOUS PROCESS VERIFICATION

The new draft of EMA (29 march, 2012) on process validation suggests to use continuous process verification as a tool in replacement of traditional process validation, through which the manufacturing process in continuously monitored. [5]

The continuous process verification is a real-time scientific approach to monitor and evaluate the process in relation with the product critical quality attributes.

Continuous process verification can be implemented at any stage of the process, i.e.

- To prepare process validation protocol during early commercial production,
- For continual improvement of the process through life cycle,
- For revalidation at commercial production.

Continuous process verification involves extensive inline and at line studies to evaluate the process in accordance with critical quality attributes of a product by using process analytical technology as a tool for process evaluation.[6]

To perform continuous process verification, adept knowledge is required regarding

- the degree of process understanding
- supporting data from research and development studies
- process robustness
- level of automation of the process
- The manufacturing information for similar products.[5]

The continuous process verification should be documented and the data generated should be enclosed in the dossier. The data should be generated from at least lab or pilot scale. Actual data generated during the commercial production should be held at site for review.[7]

## 3. HYBRID APPROACH

For some complex processes involving vast number of critical steps, traditional process validation or continuous process verification can't serve as a sole validation tool. In such situations, a hybrid i.e., combination of traditional process validation and continuous process verification can be employed and this approach is justified by the claimant. The information regarding the implementation of hybrid validation approach and its stage of implementation is described in the dossier. [6]

## 4. CONTINUED PROCESS VERIFICATION DURING THE LIFECYCLE

The manufacturing process should be verified for its validity by examining the critical quality attributes of the end products. Quality of the incoming materials, out of specifications, non-conformances and faulty reporting should be examined and root cause should be determined and necessary changes has to be done to the control strategy to maintain the validation status of the process. This will ensure that the process is producing the product of desired quality. The dossier should include the continued process verification data for model verification during the life cycle. [5]

## DATA SUBMISSION

The validation documents, which are intended to submit to the regulatory authorities in the dossier should contain the data generated form laboratory scale, pilot scale and production scale. Where the manufacturing process utilizes non-standard methods, the data should be generated form at least 3 consecutive batches and the accuracy, robustness of the process has to be described. The extent of data given in to in the dossier will depend to a certain extent on

- The nature and complexity of the product and the active ingredient and
- The complexity, type and stage of development of the manufacturing process.

As the manufacturing process is developed, data will be created on different scales such as laboratory, pilot and production scales.

**i. Laboratory Scale Batches**

This data is generated during the research and early development laboratory stage. The batch size may be of very small size (e.g. 100-1000x less than large scale production). These batches may find several uses, for instance to support preparation and packing

development, clinical and/or pre- clinical studies. The data resulting from these batches support in the evaluation and definition of critical product performance characteristics and thereby enables the choice of the appropriate manufacturing process.

**ii. Pilot Batches**

These may be used in the process development or optimization stage, may be used to support formal stability studies and also to support pre-clinical and clinical evaluation. The pilot batch size should be at least $1/10^{th}$ of that of the production batch size, or 100,000 units, whichever is greater in case of solid oral dosage forms.[6]The role of pilot scale batches is to provide data predictive of the production scale product. It may be necessary to further develop and optimize the manufacturing process using pilot scale.[6]

**Scale Up**

In order to avoid the repetition of lengthy and expensive tests, it is necessary to gather information during properly designed development and process optimization studies, when scaling up from laboratory through pilot to production scale. Such evidence provides the source for justification that scale-up can be achieved without a consequent loss in quality.[7]When the manufacturing involves production of a wide range of batch sizes, measures should be taken to avoid deviations in finished product due to variability in batch sizes. During the post authorization scale-up and it should be proven that the process is scale independent. [1]

**Change Control**

The changes the manufacturing process controlled by clearly defined procedure. The procedures should control the changes but should not lead to any other out of specifications and non-conformance. Data should be generated and documented to ensure that the changes proposed will produce a product of desired quality. Such actions are profoundly part of GMP but may result in the need for variation in the marketing authorization dossier requiring regulatory authority approval before implementation. Minor changes in SOP's, equipment, environment etc. which can be made known not to have an impact on the quality of the final product are unlikely to need regulatory approval. However, significant changes to processes (e.g. mixing times, drying temperatures), new equipment involving different design and functional parameters, which are likely to effect on product quality are likely to need prior regulatory authority authorization, and the proper supportive data should be submitted by way of a variation to the marketing authorization. In general terms very detailed description of processing instructions and equipment design need not be included in the dossier, if notearlier approval by variation will be necessary before they can be altered.[7]

**CONCLUSION**

As mentioned in above draft of guidelines on process validation by EMA, the approach for validating the pharmaceutical establishments was basic stereotype traditional validation.

Eventually the need for producing extremely accurate and precise dosages was on high. Hence the basic traditional process verification was replaced by Continual and Continued process verification.Any further changes will be controlled by change control methodology. Ultimately the validation data will be included in marketing authorization dossier.

**REFERENCES**

1. Note for Guidance on Process Validation, CPMP/QWP/96, EMEA/CVMP/598/99, 1 March, 2001.
2. Draft: Annexure I: Note For Guidance on Process Validation - Non Standard Processes, CPMP/QWP/2054/03, EMEA/CVMP/395/03, 3 April, 2003.
3. Annexure II: Note For Guidance in Process Validation, CHMP/CQWP/848/99 and EMEA/CVMP/598/99, nonstandard processes, CPMP/QWP/2054/03, EMEA/CVMP/395/03, 10 AUGUST, 2003.
4. Van Amsterdam, Peter, Companjen, Arjen, The European Bioanalysis Forum community's evaluation, interpretation and implementation of the European Medicines Agency guideline on Bioanalytical Method Validation. Database: Journals@Ovid Full Text, Accession No.: 01436926-201303010-00008.
5. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use ICH Harmonised Tripartite Guideline, Pharmaceutical Development, Q8 (R2), Current *Step 4* Version, Dated August 2009.
6. Guideline on Process Validation, EMA/CHMP/CVMP/QWP/70278/2012-Rev1, Draft, 29 March 2012.
7. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Quality Risk Management, Q9, Current *Step 4* Version, Dated 9 November 2005.
8. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Pharmaceutical Quality System, Q10, Current *Step 4* Version, Dated 4 June 2008.