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1. **Introduction**

This guideline is intended to provide general guidance on the interpretation of the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products* (PIC/S Guide to GMP) with respect to process validation. It is not intended to create additional requirements and is not intended to form the basis for GMP inspections.

Process validation demonstrates, through scientific evidence, that a process is capable of consistently producing a product that meets desired quality attributes. The required level of quality assurance cannot be met through quality control testing alone.

2. **Purpose of this document**

To provide guidance to industry on process validation requirements for non-sterile pharmaceutical product manufacture.

3. **Scope**

This guidance document is not intended to provide detailed guidance on topics already covered by the *PIC/S Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation, PI 006-3*. That document may be downloaded from the PIC/S website and should be consulted for detailed information.

It is recognised that manufacturers may have further questions regarding non-sterile process validation. To address these, commonly asked questions and their corresponding answers are listed below.

4. **Commonly asked questions and answers**

4.1 **What elements should be included in a process validation protocol?**

*PIC/S PI006-3* Section 6.3.3 describes the mandatory, minimum requirements for process validation protocols:

- A description of the process;
- A description of the experiment;
- Details of the equipment/facilities to be used (including measuring/recording equipment) together with calibration status;
- The variables to be monitored;
- The samples to be taken - where, when, how and how many;
- The product performance characteristics/attributes to be monitored, together with the test methods;
- The acceptance criteria/limits;
- Time schedules;
- Personnel responsibilities; and
- Details of methods for recording and evaluating results, including statistical analysis.
4.2 How should the critical factors/parameters for production processes that may affect quality of finished product be identified?

Refer to PIC/S PI006-3 Section 6.3.1 and 6.3.2. For existing products all production processes should be documented and for each process all variables and control points should be listed.

A risk assessment should be completed to determine which of these variables and control points are the critical factors/parameters for controlling the process. When the process is controlled and stable, then it will consistently produce a product that meets specifications.

4.3 What considerations have to be taken when deciding the sample plan of a process validation protocol?

Refer to PIC/S PI006-3 Section 6.3.3. Samples should be representative of the population. Some materials may not be homogenous due to segregation that occurs during transport, handling, variability occurring during the manufacturing process, and other factors impacting a representative sample.

Samples or sampling plans should be based on statistical criteria where possible. Each sampling plan should be developed to consider the specific attributes being measured and the risks associated with accepting an out-of-specification lot.

Sampling locations with the highest risk of out-of-specification results (worst case locations) should be included in the sampling plan.

Sufficient reserve sample should be collected, when possible, to support potential investigation.

4.4 What considerations should be taken when deciding the acceptable limits of a process validation protocol?

Process validation acceptance criteria should include process output specifications (e.g. product specifications), as well as in-process testing limits.

Any other measurements which confirm acceptable performance should also be considered for inclusion in process validation acceptance criteria.

It is a good practice, but not a requirement, that acceptance limits set for process validation are tighter than routine specification limits. This allows additional confidence that the process is consistent and reliable.

4.5 What elements should be included in process validation report?

Refer to PIC/S PI006-3, Section 6.3.9. The following items should be included in the validation report:

- A description of the process - Batch/Packaging Document, including details of critical steps;
- A detailed summary of the results obtained from in-process and final testing, including data from failed tests. When raw data are not included reference should be made to the sources used and where it can be found;
- Any work done in addition to that specified in the protocol or any deviations from the protocol should be formally noted along with an explanation;
- A review and comparison of the results with those expected; and
- Formal acceptance/rejection of the work by the team/persons designated as being responsible for the validation, after completion of any corrective action or repeated work.

The report must include formal conclusions regarding the validated state of the process, as well as any recommendations to be implemented.
4.6 For prospective validation, is the “three consecutive batches/run approach” still acceptable?

Refer to PIC/S PI006-3, Section 6.3.6 and PIC/S Guide to GMP Annex 15, Clause 25. Under current PIC/S GMP guidelines on prospective validation, it is generally considered acceptable that three consecutive batches/runs within the finally agreed parameters, would constitute a validation of the process.

However, there may be situations where additional process runs are warranted to prove consistency of the process. The appropriate number of process validation batches depends on several factors including, but not limited to:

- The complexity of the process being validated;
- The level of process variability; and
- The amount of experimental data and/or process knowledge available on the specific process.

4.7 For concurrent validation, what are the examples of “exceptional circumstances”? What level of documentation is expected to justify a concurrent validation?

PIC/S PI006-3, Sections 6.4.1 and 6.4.2, provide some examples of circumstances where concurrent validation may be justified:

- process undergoing transfer to third party;
- where the product is a different strength of a previously validated product;
- where the product is a different tablet shape; and
- where the process is well understood.

The following are also generally regarded as examples of exceptional circumstances when considering concurrent validation:

- Limited demand (e.g. orphan drugs); and
- Very short shelf life products (e.g. radiopharmaceuticals).

The use of concurrent validation is usually justified within rationale statements in validation plans and protocols and should rely on prior process experience and validation, as well as risk to the product.

4.8 What are Department of Health’s views on “Traditional Approach” and the new “Continuous Process Verification Approach”? Are both approaches acceptable?

New guidance for process validation methodology allows manufacturers to choose between the tradition process validation methods or the new approach published in the FDA Process Validation Guidance for Industry, 2011.

Currently manufacturers subject to PIC/S and EMA GMP regulations must still comply with a version of Annex 15 which dates back to 2000. Annex 15 effectively defines the traditional approach (i.e. 3 manufacturing batches). However, PIC/S and EMA are developing new guidance and rules for validation.

It is recognised that successful manufacture of three consecutive batches may not necessarily provide assurance of process reproducibility. The FDA guidance on process validation does not define the regulatory expectation of the number of process validation batches. It is expected that the manufacturers make a rational decision for number of validation batches and design of the validation study based on product knowledge and process understanding.

The new approach incorporates all of the traditional elements but also involves:
a. Appropriate documentation and assessment of the product development phase to ensure that the process is well defined and understood, as well as providing scientific basis for decisions on later testing requirements;
b. Design, specification and qualification with less emphasis on separate phases (DQ, IQ, OQ, PQ), provided appropriate specification and qualification is performed;
c. Integrated testing of the facilities, equipment and systems in commercial manufacture with emphasis on statistical confidence of process performance, rather than a specific number of batches; and
d. Continued process verification with data from each new batch being collated to form a picture of a continually valid process.

It is considered that the new continuous process verification approach will provide at least an equivalent level of quality assurance as the traditional approach currently described in Annex 15 – consequently, either approach will be acceptable.

4.9 How often should a production process be re-validated periodically if there is no significant change? How frequently should processes be evaluated to confirm they remain valid?

Revalidation is mentioned in both PIC/S Guide to GMP Annex 15 (Clause 45) and PI006-3 (Section 6.6 and 6.7). Revalidation does not mean that all processes and equipment need to be undergo routine retesting. In both documents, the term revalidation is intended to prompt assessment of when such retesting may be appropriate.

If there is no significant change to a process, and the process is regularly evaluated as remaining valid, there is usually no need to routinely re-validate periodically.

For most processes, it is a requirement that processes be evaluated routinely (for example, annually as part of periodic product review) to establish that they remain in a validated state. Depending on risk, it may be appropriate to perform evaluations more frequently.
4.10 What changes are considered significant and require a revalidation?

Refer to PIC/S Guide to GMP Annex 15 (Clause 43 and 44) and PI006-3 (Section 6.7.4). The need for revalidation should be considered when change is proposed to a starting material, product component, process equipment, process environment (or site), method of production or testing or any other change that may affect product quality or reproducibility of the process.

The likely impact of the change on the product should be evaluated, including risk analysis and the need for, and the extent of, requalification and revalidation should be determined.

Changes that are likely to require revalidation include:

- Changes of raw materials (physical properties such as density, viscosity, particle size distribution may affect the process or product);
- Change of starting material manufacturer;
- Changes of packaging material (e.g. substituting plastic for glass);
- Changes in the process (e.g. mixing times, drying temperatures);
- Changes in the equipment (e.g. addition of automatic detection systems). Changes of equipment which involve the replacement of equipment on a 'like for like' basis would not normally require a revalidation;
- Production area and support system changes (e.g. rearrangement of areas, new water treatment method);
- Transfer of processes to another site; and
- Unexpected changes (e.g. those observed during self-inspection or during routine analysis of process trend data).

4.11 What type of quality risk management is expected for process validation?

PIC/S Guide to GMP Annex 15, Clause 1 requires a risk based approach to determining the extent and scope of validation.

PIC/S Guide to GMP Annex 20, Appendix II, Section II.6 provides guidance on the application of risk management to validation:

- To identify the scope and extent of verification, qualification and validation activities (e.g. analytical methods, processes, equipment and cleaning methods);
- To determine the extent for follow-up activities (e.g., sampling, monitoring and revalidation); and
- To distinguish between critical and non-critical process steps to facilitate design of a validation study.

A risk assessment should form part of all validation projects and include:

- Significance/severity and likelihood/probability of a failure;
- Consequences (associated risk to product quality);
- Other factors (as applicable), including the level of risk due to:
  - level of process knowledge,
  - level of product knowledge,
  - thoroughness of control strategy,
  - novelty of process / unit operations,
  - level of process fit with facility/equipment; and
- Potential for reoccurrence of the non-conformity.

The outcomes of the risk assessment should form a basis for process validation planning, testing requirements and acceptance criteria.

Changes to validated processes should also be assessed for risk as part of the change control process (PI006-3, Section 6.7.2).
Various models and tools for risk management are described in PIC/S Guide to GMP Annex 20, Appendix I.

4.12 When can a matrix approach be used in process validation?

A matrix approach is where multiple similar products, presentations or equipment are grouped together within one validation exercise to reduce the overall testing requirements. All variables must be assessed, however, because the group contains overlap in the variables for each product/presentation/equipment, the validation effort may be reduced. This approach assumes that there is minimal variation in the process from product type to product type.

The use of a matrix approach for the process validation of a manufacturing process across different products should be approached with caution because of the risk of overlooking other possible sources of variation. This type of approach requires a good understanding of the processes involved and the risks being assumed.

4.13 How is process capability determined?

Many product non-conformities are not due to errors but are a result of excessive variation and off-target processes. Reducing variation and proper targeting of a process requires identifying the key input variables and establishing controls on these inputs.

A capability study may be used to demonstrate that the process consistently conforms to requirements and is appropriate for measuring characteristics where non-conformities are due to variation and off-target conditions.

There are several statistics that can be used to measure the capability of a process - the most commonly used is \( C_{pk} \) (process capability adjusted for centeredness).

A \( C_{pk} \) of 1 implies that 99.7% of all data points will occur within the specification limits. The most common acceptance criterion for a capable process is \( C_{pk} \geq 1.33 \), which implies that 99.99% of all data points will occur within the specification limits. The specific method for determining process capability is available in texts and online.

Most capability indices estimates are valid only if the sample size used is large enough. ‘Large enough’ is generally thought to be about 50 independent data values.

4.14 Is performance qualification (PQ) required to be carried out for each item of critical process equipment, if process validation is to be performed on the same equipment?

Yes. Performance qualification and process validation do not have the same objectives. Refer to Question 3.8 for further information.
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References

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