Guidance for Industry: Process Validation

Version 2.0

(Draft for Information)

Drug Office

Department of Health

Contents

1. Introduction

It is a GMP requirement that manufacturers control the critical aspects of their particular operations through qualification and validation over the life cycle of the product and process. Any planned changes to the facilities, equipment, utilities and processes, which may affect the quality of the product, should be formally documented and the impact on the validated status or control strategy assessed.

A quality risk management approach should be applied throughout the lifecycle of a medicinal product. As part of a quality risk management system, decisions on the scope and extent of qualification and validation should be based on a justified and documented risk assessment of the facilities, equipment, utilities and processes.

Process validation can be defined as documented evidence that the process, operated within established parameters, can perform effectively and reproducibly to produce a pharmaceutical product meeting its predetermined specifications and quality attributes.

It can include the collection and evaluation of data, from the process design stage throughout production, which establishes scientific evidence that a process is capable of consistently delivering a quality pharmaceutical product. The required level of quality assurance cannot be met through quality control testing alone.

This guideline is intended to provide general guidance on the interpretation of the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products* (the GMP Guide) and the relevant Annexes, in particular *Annex 15 Qualification and Validation* and *Annex 20 Quality Risk Management*, adopted by the Pharmacy and Poisons Board of Hong Kong with respect to process validation. It is not intended to create additional requirements and is not intended to form the basis for GMP inspections. There may be other acceptable approaches that provide an equivalent level of quality assurance.

2. Purpose

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

3. Scope

This guidance document is not intended to provide detailed guidance on topics already covered by other *PIC/S documents, e.g. Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation, Cleaning Validation, PI 006-3* and *Recommendation on the Validation of Aseptic Process, PI 007-6.*

These documents may be downloaded from the PIC/S website and should be consulted for detailed information. The general principles mentioned in these documents may also apply to other types of pharmaceutical products, e.g. biotechnological and biological products including advanced therapy products.

It is recognised that manufacturers may have further questions regarding process validation specific to their types of products. To address these, commonly asked questions and their corresponding answers are listed below.

4. Commonly Asked Questions and Answers

A. General Considerations

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

Process validation protocols in the traditional approach should include, but are not limited to the following:

- A short description of the process and a reference to the respective Master Batch Record;
- Functions and responsibilities;
- Summary of the critical quality attributes (CQAs) to be investigated;
- Summary of critical process parameters (CPPs) and their associated limits;
- Summary of other (non-critical) attributes and parameters which will be investigated or monitored during the validation activity, and the reasons for their inclusion;
- List of the equipment/facilities to be used (including measuring/monitoring/recording equipment) together with the calibration status;
- List of analytical methods and method validation, as appropriate;
- Proposed in-process controls with acceptance criteria and the reason(s) why each in-process control is selected;
- Additional testing to be carried out, with acceptance criteria;
- Sampling plan and the rationale behind it;
- Methods for recording and evaluating results;
- Process for release and certification of batches (if applicable).

4.2 How should the CQAs of products and CPPs for production processes that may affect quality of finished product be identified?

A CQA is 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. Relevant CQAs can be identified by an iterative process of quality risk management and experimentation that assesses the extent to which their variation can have an impact on the quality of the drug product.

A CPP is a process parameter whose variability has an impact on a CQA and therefore should be monitored or controlled to ensure the process produces the desired quality. For existing products all production processes should be documented and for each process all CPPs should be listed. A risk assessment should be completed to determine which of the process parameters are the CPPs for controlling the process.

The list of potential CQAs and CPPs can be modified when the formulation and manufacturing process are selected and as product knowledge and process understanding increase. CQAs and CPPs can also evolve throughout the product lifecycle, for example, when there is change of manufacturing process and subsequent knowledge gained throughout the lifecycle (e.g. material variability, pharmacovigilance, clinical trial experience, and product complaints).

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

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?

A process validation protocol should be prepared which defines the CPPs, CQAs and the associated acceptance criteria which should be based on development data or documented process knowledge.

Process validation acceptance criteria should also include 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?

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?

For the traditional approach of 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 is 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?

When there is a strong benefit-risk ratio for the patient, it may be acceptable not to complete a validation programme before routine production starts and concurrent validation could be used. However, the decision to carry out concurrent validation must be justified, documented in the validation master plan for visibility and approved by authorised personnel.

Below are 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);
- limited availability of the starting materials, as in the case of autologous ATP; 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.

Where a concurrent validation approach has been adopted, there should be sufficient data to support a conclusion that any given batch of product is uniform and meets the defined acceptance criteria. The results and conclusion should be formally documented and available to the Authorised Person prior to certification of the batch.

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

Starting from version 12, *Annex 15 Qualification and Validation* of the PIC/S GMP Guide effectively defines the traditional approach (i.e. 3 manufacturing batches) and the approach of continuous process verification.

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?

Manufacturers should monitor product quality to ensure that a state of control is maintained throughout the product lifecycle with the relevant process trends evaluated.

Ongoing process verification should be conducted under an approved protocol or equivalent documents (for example, annually as part of periodic product review) to establish that they remain in a validated state. Statistical tools should be used, where appropriate, to support any conclusions with regard to the variability and capability of a given process. Depending on risk, it may be appropriate to perform evaluations more frequently.

4.10 What changes are considered significant and require a revalidation?

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 and starting materials;
- Change of raw and 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?

Annex 15 Qualification and Validation of the GMP Guide requires a risk based approach to determining the extent and scope of validation.

Appendix ll to *Annex 20 Quality Risk Management of the GMP Guide* 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 re-validation); 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.

Various models and tools for risk management are described in *Appendix I to Annex 20 Quality Risk Management of the GMP Guide*.

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

A bracketing approach is a validation 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.

Bracketing could be justified for new products based on extensive process knowledge from the development stage in conjunction with an appropriate ongoing verification programme.

For the process validation of products, which are transferred from one site to another or within the same site, the number of validation batches could be reduced by the use of a bracketing approach. However, existing product knowledge, including the content of the previous validation, should be available.

4.13 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 parameters or variables must be assessed to identify the "worst case" or "extreme" conditions for a combination of parameters or variables. These conditions are used during validation of the process, rather than validating all possible combinations.

Because the combination contains overlap in the parameters or 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.

4.14 What precautions should be taken when a bracketing/matrix approach is adopted?

The use of a bracketing or 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 extensive process knowledge from the development stage in conjunction with an appropriate ongoing verification programme involved and the risks being assumed.

The use of a bracketing design or matrix approach would not be considered appropriate if it is not possible to demonstrate that the extremes are limited to the batches, products, strengths, container sizes or fills. For those excluded from the exercise there should be no risk to process capability.

4.15 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 *Cpk* (process capability adjusted for centeredness).

A Cpk 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 Cpk $\geq$ 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.

4.16 Is performance qualification (PQ) required to be carried out for each piece 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.

PQ should normally follow the successful completion of installation qualification (IQ) and operational qualification (OQ). However, it may in some cases be appropriate to perform it in conjunction with OQ or process validation.

B. Advanced Therapy Products (ATPs)

ATPs are specific types of biological pharmaceutical products majority of which cannot be terminally sterilised. In such cases, the manufacturing process should be conducted aseptically (i.e. under conditions which prevent microbial contamination). The requirements under Annex 1 *Manufacture of sterile medical product* and Annex 2 *Manufacture of biological medicinal substances and products for human use* of the GMP Guide should generally apply.

Some questions specific to these types of products and their corresponding answers are given below.

4.17 What risks should be considered during the process development of cell-based ATPs?

The risk posed by the administration of a cell-based pharmaceutical product is highly dependent on the origin of the cells, the manufacturing process, the non-cellular components and on the specific therapeutic use.

Comprehensive risk analysis should be used to justify the product development and the results should be used:

- to identify risk factors associated with the quality and safety of the product;
- to determine the extent and focus of the data required during non-clinical and clinical development;
- when establishing the need for risk minimisation activities;
- when determining the post market risk management activities specified in the pharmacovigilance plan.

Risk criteria used in the estimation of the overall risk of the product should include, but not be limited to:

- origin (autologous or allogeneic)
- ability to proliferate and/or differentiate
- ability to initiate an immune response (as target or effector)
- level of cell manipulation (in vitro or ex vivo expansion; activation; differentiation; genetic manipulation; cryo-conservation)
- mode of administration (e.g. ex vivo perfusion, local or systemic surgery)
- duration of exposure or culture (short to permanent) or life span of cell
- combination product (cells and bioactive molecules or structural materials);
- availability of clinical data on or experience with similar products.

4.18 What processes should be validated for cell-based ATPs?

Given the complexity of the process, the entire manufacturing process, including cell harvesting, cell manipulation processes, maximum number of cell passages, combination with other components of the product, filling, packaging, transport, storage etc., should be validated. Any preservation steps, holding periods and/or transportations of the active substance, final product, supportive structures or intermediate products during the manufacturing process should also be validated.

Validation of the production process of a combined product should encompass all steps from separate components up to the final combination to ensure consistent production.

For products containing genetically modified cells, the genetic modification of the cells is a manufacturing step that is affected by a variety of inputs and therefore its control is critical.

4.19 What aspects should be addressed during the design of the manufacturing process of ATPs?

A detailed description of the manufacture of the active substance and of the finished product should be provided. A flow diagram of the entire process starting from biological fluid, tissue or organ, from cell banks, or from the purified active substance up to the product in its primary packaging, should be prepared indicating critical steps and intermediate products (e.g. intermediate cell batches), as well as operating parameters, in-process controls and acceptance criteria.

Manufacture of combined products consisting of cells and matrices/devices/scaffolds, require additional consideration regarding the cell-matrix/scaffold interactions and quality issues raised there from.

For products that are cell-based, the following aspects should be addressed:

- cell preparation procedures including organ/tissue dissociation, isolation of the cell population of interest, cell culture, cell modification, etc
- in-process controls
- batch definition
- container and closure system

For products containing genetically modified cells, additional aspects to be addressed should include:

- gene modification
- further manufacturing steps after the gene modification procedure, e.g. washing, enrichment, isolation, purification, selection and culture for further expansion

4.20 What are the specific aspects that should be addressed in the process validation of products containing genetically modified cells?

The following aspects should be addressed, as applicable:

- absence of adventitious viruses
- absence of modifying enzymes and nucleic acids
- removal of infectious particles
- release of vector from transduced cells
- transduction efficiency
- vector copy number
- transgene identity and integrity (and of other regions as needed)
- level of transgene expression
- structure and function of the expressed molecule(s)
- removal or elimination of the desired nucleic acid sequences when appropriate
- removal or reduction of impurities associated with the genetic modification

4.21 Should all processes involved in the manufacture of ATPs be validated when there is limited availability of the cells or tissues involved?

As for the manufacture of other types of pharmaceutical products, process validation of ATPs should establish whether all quality attributes and process parameters, which are considered important for ensuring the validated state and acceptable product quality, can be consistently met by the process.

The limited availability of the cells or tissues which is typical for most ATPs requires the development of pragmatic approaches. The approach to process validation should take into account the quantities of tissue or cells available and should focus on gaining maximum experience of the process from each batch processed. Reduced process validation should, where possible, be offset by additional in-process testing to demonstrate consistency of production.

4.22 Can surrogate materials be used in process validation?

The use of surrogate material may be acceptable when there is shortage of the starting materials, e.g. autologous ATPs or allogeneic in a matched-donor scenario. The representativeness of surrogate starting material should be evaluated, including, e.g. donor age, use of materials from healthy donors, anatomical source or other different characteristics.

Where possible, consideration should be given to complementing the use of surrogate materials with samples from the actual starting materials for key aspects of the manufacturing process. For instance, in the case of an ATP based on modification of autologous cells to treat a genetic disorder, process validation using the autologous cells (affected by the condition) may be limited to those parts of the process that focus on the genetic modification itself. Other aspects could be validated using a representative surrogate cell type.

4.23 Can the validation efforts be reduced for closely related products?

The approach of validation should always be based on the extent of process knowledge and the application of quality risk management.

Where the same manufacturing platform is used for a number of closely related products, e.g. genetically modified cells where viral vectors are manufactured according to the same manufacturing process, the extent of validation work for each new product should be based on a justified and documented risk assessment of the process. If the other manufacturing steps remain the same, it may be possible to limit the validation to only the steps that are new to the process.

4.24 How should the validation of aseptic processing of ATPs be conducted?

This can be done by means of a process simulation test to study the performance of the manufacturing process using a sterile microbiological growth medium and/or placebo (e.g. culture media of cells which is demonstrated to support the growth of bacteria) to test whether the manufacturing procedures are adequate to prevent contamination during production.

4.25 What aspects should be considered in designing a process simulation test for validating the aseptic processing of ATPs?

Guidance in *Recommendation on the Validation of Aseptic Process, PI 007-6* may also apply to the validation of the processing of ATPs.

The following aspects should be considered during the design of a process simulation for validation of the aseptic processing of ATPs:

- It should follow as closely as possible the routine manufacturing process;
- It should be conducted in the same locations where the production occurs;
- The process simulation should focus on all operations carried out by operators involving open process steps;
- All potential interventions and challenges to the process (e.g. work overnight) should be considered;
- An appropriate simulated model (e.g. use of alternative tools to the manufacturing kit ("mock materials") may be acceptable provided that this is duly justified;
- The simulation of reduced times for certain activities (e.g. centrifugation, incubation) should be justified having regard to the risks;
- It may also be acceptable, in some cases, to split the process into key stages which are simulated separately provided that the transitions between each stage are also evaluated;
- When a closed system is used for the manufacturing of an ATP, the process simulation should focus on the steps related to the connections to the closed system;
- The selection of the incubation duration and temperature should be justified and appropriate for the process being simulated and the selected media/placebo.

4.26 When can a bracketing/matrix approach be used in aseptic process validation?

Under a bracketing approach, only samples on the extremes of certain design factors would undergo a full process simulation. This approach can be accepted if the handling of different products is similar (same equipment and processing steps).

Under a matrix approach, it may be possible to combine media fills for different ATPs sharing similar processing steps, provided that the worst case is covered by the matrix approach.

The use of bracketing and matrixing together should be duly justified.

4.27 How many filled containers should be incubated during a process simulation test?

If batches smaller than 3000 units are produced, the minimum number of containers used for the process simulation should be equal to that of the batch size.

4.28 How should the results of process simulation test be interpreted?

All contaminants from the filled containers should be identified. The results should be assessed, in particular in relation to the overall quality of the product and the suitability of the production process. The target should be zero growth. Any growth detected should be investigated. If the growth detected is indicative of potential systemic failure, the potential impact on batches manufactured since the last successful process simulation test should be assessed and adequate corrective and preventive actions should be taken.

4.29 How often should the validation of aseptic processing by process simulation test be conducted?

Process simulation test to support initial validation of aseptic processing should be performed with three consecutive satisfactory simulation tests per production process.

One run should be repeated periodically to provide ongoing assurance of the ability of the process and the staff to ensuring aseptic manufacturing. The frequency should be determined based on a risk assessment but should generally not be lower than once every six months for each production process.

The relevance of the process simulation test for the training of operators and their ability to operate in an aseptic environment should be considered when considering the frequency of the simulation test.

A process simulation should also be conducted in cases when there is any significant change to the process (e.g. modification of HVAC system, equipment, etc). In this case, three runs are required.

4.30 Can process simulation test be done just before the manufacturing of the next batch instead of repeating once every six months?

In the case of infrequent production, i.e. if the interval between the production of two batches is more than six months, it is acceptable that the process simulation test is done just before the manufacturing of the next batch, provided that the results of the process simulation test are available before production is started.

In cases of long periods of inactivity, i.e. over one year, the validation prior to restart of production should be done with three runs.

C. Investigational Pharmaceutical Products

An investigational pharmaceutical product is a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorisation when used or assembled (formulated or packaged) in a way different from the authorised form, or when used for an unauthorised indication, or when used to gain further information about the authorised form.

It should be produced in accordance with the principles of GMP so as to ensure that trial subjects are not placed at risk, and that the results of clinical trials are unaffected by inadequate safety, quality or efficacy arising from unsatisfactory manufacture.

Equally, the application of GMP is intended to ensure that there is consistency between batches of the same investigational pharmaceutical product used in the same or different clinical trials, and that changes during the development of an investigational medicinal product are adequately documented and justified.

Specific requirements for the production of investigational pharmaceutical products are provided in *Annex 13 Manufacture of Investigational Medicinal Products* of the GMP Guide. Some questions specific to investigational ATPs and their corresponding answers are given below.

4.31 Should the manufacturing process for investigational ATPs be validated?

The manufacturing process for investigational ATPs is not expected to be validated but appropriate monitoring and control measures should be implemented to ensure compliance with the requirements in the clinical trial authorisation.

4.32 Should the aseptic processes of the manufacture of investigational ATP be validated?

As for other investigational pharmaceutical products, it is expected that the aseptic processes of investigational ATPs have been validated.

Document Information

Version	Date	Description of Change
1.0	27 Dec 2013	First version
2.0	02 Jul 2019	Second version (Draft for information) ● Extended the scope to address the special considerations for advanced therapy products and investigational pharmaceutical products ● Restructured and updated to be consistent with PIC/S Guide to GMP and relevant annexes.

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