Australian Government
Department of Health
Therapeutic Goods Administration

Process validation for listed and complementary medicines

Technical guidance on the interpretation of the PIC/S Guide to GMP

Version 2.0, January 2019

TGA Health Safety Regulation

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About this guidance

This guidance is for manufacturers of listed and complementary medicines manufactured according to the *PIC/S Guide to Good Manufacturing Practice for Medicinal Products* (PIC/S Guide to GMP).

This guidance is **only applicable** to manufacturers and sponsors of listed medicines and complementary medicines (including registered complementary medicines).

This guidance does **not** apply to medicines listed for export-only when the medicine would not be a listed or complementary medicine if supplied in Australia.

Purpose

This guidance is intended to clarify the interpretation of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products (PIC/S Guide to GMP) in relation to process validation for listed and complementary medicines.

Process validation is a critical step in assuring the quality of medicinal products.

This guidance addresses compliance with the 'Process validation' section of Annex 15 – Qualification and Validation of the PIC/S Guide to GMP.

Development of this guidance

This guidance was developed in collaboration with the complementary medicine technical working group. Technical working groups comprise TGA and industry subject matter experts and have been established to develop, consider and review GMP guidelines.

This document is provided for **guidance only** and has been developed on the basis of current knowledge of the subject matter. It should not be relied upon to address every aspect of the relevant legislation. Please also refer to the *Therapeutic Goods Act 1989* and the *Therapeutic Goods Regulations 1990* for legislative requirements and the current version of the PIC/S Guide to GMP.

Disclaimer

This guidance is not mandatory or enforceable under law. It is not intended to be restrictive. We recommend following this guidance document to facilitate regulatory obligations being met. The guidance describes a way that a manufacturer may operate to demonstrate compliance with the relevant manufacturing principles (PIC/S Guide to GMP).

Guidance documents are not intended to establish a minimum standard of practice for inspection purposes. Guidance documents are not enforceable.

Related guidance

The following guidance is relevant:

- TGA interpretation and expectations for demonstrating compliance with the PIC/S guide to GMP

Definitions

Definitions of qualification and validation terms can be found in the Glossary of Annex 15 - Qualification and Validation, of the PIC/S Guide to GMP.

Principles for process validation

Process validation is 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.

Process validation for listed and complementary medicines should:

- be risk-based
- follow the general principles contained in the PIC/S Guide to GMP
- be consistent with Annex 20 – Quality Risk Management

Equipment qualifications before process validation

Prior to process validation, conduct the following qualifications of manufacturing equipment.

- Appropriate equipment qualification
- installation qualification
- operational qualification
- performance qualification

Note that performance qualification may be performed in conjunction with operational qualification and process validation.

Validate test methods to be used in process validation.

Concurrent or prospective process validation

Use concurrent or prospective process validation.

- Concurrent validation is carried out during routine production of batches intended for supply.
- Prospective validation is carried out before routine production of products intended for supply.

Concurrent process validation is acceptable for listed and complementary medicines, because of the lower risk generally associated with these medicines.

Release for supply of validation batches

If a batch used for process validation meets release specifications, then it can be released for supply.

It is not a requirement for listed and complementary medicines that the validation batch be held in quarantine until process validation results are obtained for the remaining validation batches.

Retrospective process validation no longer permitted

Retrospective validation is no longer an acceptable approach.

- Retrospective validation is carried out after a product has been marketed, based upon accumulated manufacturing, testing and control batch data.

Any existing validations based on retrospective validation will be accepted; however, any new products, processes, updates or changes to existing processes are expected to undergo full concurrent or prospective process validation.

When Annex 15 was originally published in 2001 the provision for retrospective validation was given to provide a means by which existing products could be validated. As the process validation requirements of Annex 15 have been in place for over 15 years, the provision for retrospective validation is no longer applied.

Process validation requirements

Protocol design

Before validation activities commence, appropriate quality personnel are required to formally approve the process validation protocol.

Prepare a process validation protocol in advance, specifying:

- how the process validation will be conducted using a quality risk management approach
- the critical process parameters (CPP), critical quality attributes (CQA) and the associated acceptance criteria
- what parameters will be monitored
- what samples will be taken for testing purposes
- acceptance criteria: the results that will be accepted (for example range & %RSD or acceptable statistical analysis) and result in a process validation being considered acceptable or 'passing'

Acceptance criteria

Targeted acceptance criteria limits should reflect a plus and minus percentage of the added dose. Choose limits to demonstrate the robustness of the process. Tighter limits are generally applied to a process validation than for product release.

Overages included into the manufacturing process (for example for stability purposes) must also be included in the target assay for the purposes of process validation. For example, if a tablet containing 1000 mg Ascorbic acid has a 20% overage added for stability purposes, use an ascorbic acid content of 1200 mg per tablet for the purpose of assays conducted for process validation.

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 approved limit, range or distribution to ensure the desired product quality. (ICH Q8)

Sampling

Take sufficient samples for any process validation study to permit statistical analysis.

It may be possible to justify collecting samples for a listed and complementary medicine process validation from the unit dose stage of manufacture, final filling stage or final manufacturing step.

If testing is conducted on the finished product, samples could be taken throughout the filling and/or packaging run, as these samples may be more representative of the final product than samples taken from a manufacturing tank or mixer.

Batches to be used

Specify how many batches will be assessed during the process validation in the process validation protocol. In general, if three batches are shown to have results meeting the acceptance criteria specified in the validation protocol, the process validation may be formally approved as passing.

Process validation may be conducted on three batches of different batch sizes, provided the same equipment is used, if these batch sizes are typical of the batch sizes that will be manufactured for a specific product or product group.

It would be acceptable to use batches of other products that are similar but not identical to the first batch to complete the process validation if they are grouped (see grouping). This would enable completion in a timely manner when a second batch is not scheduled for manufacturing until a considerable period after manufacture of the first batch.

Analytical considerations

Complex mixtures

The process validation protocol needs to specify the ingredients that will be tested as part of the process validation.

There is little benefit in assaying for process validation an ingredient constituting more than 50% of the dose unit.

Select a minimum of two ingredients that can be readily tested without interference from other components, and justify this selection. Consider microdose ingredients as part of the choice of ingredients.

Vitamin or mineral ingredients

It may not be necessary to test all vitamin or mineral ingredients in the same product to confirm the effectiveness of the process. Results on multiple ingredients do not generally provide a lot of additional assurance that the manufacturing process is valid.

Selection of a vitamin or mineral present at a low level and another vitamin or mineral present at a higher level would provide acceptable evidence that the manufacturing process was valid. Selection of both a vitamin and a mineral may provide additional assurance compared to selecting for assay only two vitamins or only two minerals.

In choosing ingredients for assay during a process validation, consider:

- selecting ingredients for which safety issues may result from over-dosage, such as chromium or selenium
- the physical characteristics of the ingredients, to address issues such as homogeneity

Herbal ingredients

In general, herbal ingredients may not be suitable for assay during a process validation, as it may be difficult to assay herbs once mixed with other ingredients in a product (other than standardised herbal extracts). For herbal products where no actives are tested in the final formulation, it is acceptable to monitor only physical parameters of the dosage form, such as:

- visual examination of colour distribution
- uniformity of weight

Assay techniques

Where the assay technique used allows for simultaneous assay of multiple ingredients in a product (for example ICP for minerals or HPLC or UPLC for B-group vitamins), evaluate assay results during the process validation; do not exclude results from consideration.

The report

Appropriate senior personnel sign the process validation report. Their signatures ratify the conclusions drawn in the report. Dates adjacent to the signatures demonstrate the timely closure of the process validation study.

In the final process validation report:

- State what products or product groupings the process validation study supports.
- Reference acceptance criteria from the protocol.
- Clearly state what conclusions are drawn regarding the acceptability of the results generated during the process validation study.

Grouping

A grouping approach can be undertaken with process validation for listed and complementary medicines, because of the lower risk generally associated with these medicines. Document the scientific justification of the rationale used to establish product groupings.

The whole group must be manufactured at the same plant for process validation.

Base your justifications for grouping on the products having the same dosage form and a similar method of manufacture using a similar equipment train at the same manufacturing plant.

Groups that require separate validation studies

Groups that may require separate validation studies include, but are not limited to:

1. different dose forms
    - solutions
    - suspensions
    - creams
    - ointments
    - tablets via direct compression process
    - tablets via granulation process
    - capsules: two-piece, via dry mixing process
    - capsules: two-piece, via granulation process
    - soft capsules (softgels) containing solution fills
    - soft capsules (softgels) containing suspensions fills, powder mixes

2. different formulation types
   - multi-component vitamin/mineral/herbal solid-dose tablet based on common formulation
   - vitamin tablet containing only one active, even if similar excipients to above
   - vitamin tablet containing same active, but sustained- rather than immediate-release
3. different equipment trains
   - powder mixer - granulator bowl with rotor & chopper (e.g. Diosna, Fielder, etc.)
   - powder mixer - rotating drum or bin
   - powder mixer - ribbon blender
   - fluid bed dryer (drying process includes mixing process to ensure uniformity)
   - oven dryer (drying process does not include mixing to ensure uniformity)
   - liquid solution manufacturing & filling equipment
   - liquid suspension manufacturing & filling equipment

Packaging process validation

For packaging process validation, the type of packaging is an important consideration for process validation groupings, for example a bottle or blister platform. However, minor differences in the packaging material construction may also be able to be included in a group. Use risk assessment principles to determine and justify your grouping.

Representative products

For manufacturing process validation, you may choose the 'worst case', more difficult product to manufacture, to represent a dosage form family. The product might have physical characteristics that make it more difficult to manufacture, for example viscosity, a liquid suspension, sticky or fluffy powders for compression and difficult to encapsulate slurry medicine fills.

Document the scientific justification for a particular product being representative of the group.

If process validation is successfully conducted on a representative product, that validation data can be used in support of other products in the group. Consequently, a reduced number of process validations or a reduced number of assays per validation may be acceptable for other products in the group.

Further information

For further information, see contact details for enquiries about manufacturing therapeutic goods.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication: 'Technical guidance on the interpretation of manufacturing standards: process validation for listed complementary medicines – Technical Working Group (TWG) on complementary medicines'	Office of Manufacturing Quality	09/02/2010
V1.1	Template update	Office of Manufacturing Quality	01/07/2013
V2.0	Change in title and scope Restructured and updated to be consistent with PE009-13, PIC/S Guide to GMP	Manufacturing Quality Branch Regulatory Guidance Team	16/01/2019

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Reference/Publication #