Technical Guidance on the Interpretation of Manufacturing Standards

PROCESS VALIDATION FOR LISTED COMPLEMENTARY MEDICINES

Technical Working Group (TWG) on Complementary Medicines

Issue 1 – 9/2/2010
Technical Working Groups

Technical Working Groups have been established by the TGA’s Office of Manufacturing Quality (OMQ) to bring together manufacturing technical expertise from industry and the regulator to address the application of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products January 2009 (adopted under transitional arrangements 31 July 2009 by Therapeutic Goods (Manufacturing Principles) Determination No 1 of 2009, as the Australian Code of Good Manufacturing Practice (GMP), becoming mandatory 1 July 2010).

The aim of the Technical Working Groups is to:

- Establish a formal and transparent forum for industry and the regulator to work cohesively in order to provide advice on the application of Manufacturing Standards.
- Improve and foster industry implementation of Manufacturing Standards, and enhance regulatory audit consistency in the application of Manufacturing Standards.
- Identify and discuss key areas of concern, and address emerging issues relevant to the interpretation and application of Manufacturing Standards.
- Develop specific guidance documents as appropriate.

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

About this Guidance

This Guidance is not mandatory or enforceable under law. It is not intended to be restrictive. It describes a way that a manufacturer may operate to demonstrate compliance with the relevant Code of Good Manufacturing Practice for Medicinal Products.
Disclaimer

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 PIC/S Guide to Good Manufacturing Practice for Medicinal Products January 2009.

Further Information

The Office of Manufacturing Quality of the Therapeutic Goods Administration (TGA) can be contacted by:

Email:
- General & Australian manufacturing enquiries: gmp@tga.gov.au
- Overseas manufacturing enquiries: gmpclearance@tga.gov.au

Phone:
- 02 6232 8156
- 1800 446 443 (freecall)
- Users who are deaf or have a hearing or speech impairment can call through the National Relay Service:
  - TTY or computer with modem users phone 1800 555 677 then ask for 1800 020 653
  - Speak and listen (speech to speech relay) users phone 1800 555 727 then ask for 1800 020 653

Fax:
- 02 6232 8426

Post:
- Office of Manufacturing Quality, TGA, PO Box 100, Woden ACT 2606, Australia

Website:

Copyright
© Commonwealth of Australia 2010

This work is copyright. Apart from any use as permitted under the Copyright Act 1968, no part may be reproduced by any process without prior written permission from the Commonwealth. Requests and inquiries concerning reproduction and rights should be addressed to the Commonwealth Copyright Administration, Attorney General’s Department, Robert Garran Offices, National Circuit, Barton ACT 2600 or posted at <http://www.ag.gov.au/cca>
# Table of Contents

Technical Working Groups........................................................................................................ 2  
About this Guidance.................................................................................................................. 2  
Disclaimer ................................................................................................................................. 3  
Further Information ................................................................................................................ 3  
Copyright ................................................................................................................................ 3  
Purpose ................................................................................................................................... 5  
Scope ..................................................................................................................................... 5  
Definitions .............................................................................................................................. 5  
General Principles.................................................................................................................. 5  
Validation Requirements........................................................................................................ 6  
References ............................................................................................................................... 9
Process Validation for Listed Complementary Medicines

Purpose

This guidance is intended to clarify the interpretation of the cGMP Standard requirements in relation to Process Validation of Listed Complementary Medicines.

Scope

This guidance is relevant to Listed Complementary Medicines.

Definitions

Process Validation (PV)

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.

Installation Qualification (IQ)

The documented verification that the facilities, systems and equipment, as installed and modified, comply with the approved design and the manufacturer’s recommendations.

Operational Qualification (OQ)

The documented verification that the facilities, systems and equipment, as installed and modified, perform as intended throughout the intended operating ranges.

Performance Qualification (PQ)

The documented verification that the facilities, systems and equipment, as connected together, can perform effectively and reproducibly, based on the approved process method and product specification.

Concurrent Validation

Validation carried out during routine production of batches intended for sale.

Retrospective Validation

Validation of a process for a product which has been marketed, based upon accumulated manufacturing, testing and control batch data.

Note: The above definitions are reproduced here for ease of reference from Annex 15 - Qualification and Validation, of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products January 2009.

General Principles

Introduction

Process Validation for Listed Complementary Medicines should follow the general principles contained in the current Australian Code of GMP. Any approach to the Process Validation of Listed Complementary Medicines should be risk-based and consistent with Annex 20 – Quality Risk Management, of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products January 2009.
Prior to validation it is expected that manufacturing equipment will have been appropriately qualified and that Installation Qualification (IQ), Operational Qualification (OQ) and Performance Qualification (PQ) will have been conducted, to determine appropriate validation parameters (e.g. batch sizes, mixing times and speeds), prior to any formal Process Validation studies being conducted for specific Listed Complementary Medicine products. Test methods employed during Process Validation should be appropriately validated.

However in recognition of the reduced risk generally associated with Listed Complementary Medicines and in acknowledgement that manufacturers may be manufacturing a large number of products with only minor differences in formulation, Process Validation requirements for Listed Complementary Medicines are not generally as stringent as for registered OTC and Prescription Medicines and Concurrent Validation is generally accepted for Listed Complementary Medicines.

Such justifications may be based on ‘groupings’ whereby products which have similarly constructed formulations and are manufactured on similar equipment are placed in a group. Process Validation conducted on a product or formulation demonstrated or justified as being representative of the group may be acceptable as evidence of validation for all products in that group.

Consequently a reduced number of Process Validations and / or a reduced number of assays per validation may be acceptable for formulations or products which a manufacturer / sponsor can demonstrate or justify as being in a designated group.

A mechanism should be in place to evaluate what Process Validation is required for new product introductions. For existing, well-established products, retrospective validation could be considered. However concurrent or prospective validation is preferred and would normally be expected for new products.

**Validation Requirements**

**The Protocol Design**

A Process Validation Protocol should be prepared in advance, specifying how the Process Validation will be conducted, identifying critical steps, what parameters will be monitored, what samples will be taken for testing purposes and what results will be accepted (for example range & %RSD or acceptable statistical analysis); resulting in a Process Validation being considered acceptable or ‘passing’. These are generally described as the ‘Acceptance Criteria’ for the Process Validation. It is recognized that limits applied for a Process Validation will generally be tighter than limits applied for Product Release.

Oversages which are included into the manufacturing process (e.g. for stability purposes) should be included in the target assay for the purposes of Process Validation. When designing the Process Validation acceptance criteria, the targeted limits should reflect a plus and minus percentage of the added dose and should be chosen to demonstrate the robustness of the process. For example, if a tablet containing 1000 mg Ascorbic acid had a 20% overage added for stability purposes, assays conducted for Process Validation purposes should be based on an Ascorbic acid content of 1200 mg per tablet.

A Process Validation may also 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.
The Process Validation Protocol should be formally approved by appropriate senior personnel, including QA, before validation activities commence.

**Analytical Considerations**

For Listed Complementary Medicines that are (complex) mixtures of vitamins &/or minerals &/or herbs, the Process Validation Protocol should specify which ingredients will be tested as part of the Process Validation. To confirm the effectiveness of the process it may not be necessary to test all vitamin or mineral ingredients in the same product, as results on multiple ingredients do not generally provide a lot of additional assurance that the manufacturing process is valid. Selection of at least two ingredients that can be readily tested without interference from other components is generally acceptable for Listed Complementary Medicines.

When deciding what ingredients to assay for, there may be little benefit in assaying for a Process Validation an ingredient in a product that constitutes more than 50% of the dose unit.

Selection of an ingredient such as 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. In choosing ingredients for assay during a Process Validation, consideration should be given to selecting ingredients for which safety issues may result from over-dosage, such as Chromium or Selenium.

Selection of both a vitamin and a mineral may provide additional assurance compared to selecting for assay only two vitamins or only two minerals. When selecting ingredients for assay, the physical characteristics of a particular ingredient may need to be considered to ensure issues such as homogeneity are addressed.

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

Where the assay technique used (e.g. AA / ICP for minerals or HPLC / UPLC for B-group vitamins) allows the simultaneous assay of multiple ingredients in a product, these results should be evaluated during the Process Validation and not excluded from consideration.

The Process Validation Protocol should specify how many batches will be assessed during the Process Validation. 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.

It is recognised that a second batch may not be scheduled for manufacturing and available for Process Validation until a considerable period after manufacture of the first batch. It may be acceptable to use batches of other products that are similar but not identical to the first batch to complete a Process Validation.

**Grouping**

Listed Complementary Medicine Products manufactured in the same plant may be ‘grouped’ for the purpose of Process Validation. If Process Validation is successfully conducted on one product in a ‘group’, that validation data may be used in support of other products in the ‘group’. Process Validation must be conducted on a ‘worst case’ or more complex product in a ‘group’, such as a product with a larger number of ingredients and,
where justified on scientific grounds, this may be used to support less complex products with fewer ingredients.

When considering groupings, the formulation and mode of manufacturing should be assessed when placing products in a ‘group’. A group should be restricted to products manufactured by a similar equipment train and having similar formulations. In general, products manufactured via a straight powder mix process should never be placed in the same group as products where the manufacturing process involves granulation.

Validation groups which would require separate validation studies include but are not limited to:

1. Different Dose Forms

   Solutions
   Suspensions
   Creams
   Ointments
   Tablets (via Direct Compression (DC) 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. Equipment Trains

Some examples of ‘groupings’ of products for equipment train used in manufacture where separate Process Validation studies would be required are (but not limited to):

   Powder Mixer - granulator bowl with rotor & chopper (e.g. Diosna, Fielder, etc.)
   Powder Mixer - rotating drum or cube
   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)

   Vacuum powder transfer system
   Manual powder transfer system

   Liquid solution manufacturing & filling equipment
   Liquid suspension manufacturing & filling equipment

Some examples of ‘groupings’ of products for formulation where separate Process Validation studies would be required are:

3. 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.
**Process Validation for Listed Complementary Medicines**

**Sampling**

Sufficient samples should be taken for any Process Validation study to permit statistical analysis.

It may be possible to justify collecting samples for a Listed 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. This is particularly appropriate for liquid suspensions & semi-solids and for solid dose forms (compression / encapsulation).

**Release for Supply of Validation Batches**

‘Release for Supply’ of a batch used for a Process Validation is acceptable if the batch meets release specifications, to ensure that the product remains within the expiry specifications for the term of the shelf life. It will not be a requirement for Listed Complementary Medicines that the batch be held in quarantine until Process Validation results are obtained for other batches.

**Validation Report**

A final Process Validation Report should reference acceptance criteria from the protocol, clearly stating what conclusions are drawn regarding the acceptability of the results generated during the Process Validation study and what products or product groupings the Process Validation study supports. The Process Validation Report should be signed by appropriate senior personnel, whose signatures ratify the conclusions drawn in the report. Dates adjacent to the signatures should demonstrate the timely closure of the Process Validation study.

**References**

PIC/S Guide to Good Manufacturing Practice for Medicinal Products January 2009, including Annexes