



**Australian Government**  
**Department of Health and Ageing**  
**Therapeutic Goods Administration**

## **Technical Guidance on the Interpretation of Manufacturing Standards**

### ***SAMPLING AND TESTING OF COMPLEMENTARY MEDICINES***

**Technical Working Group on  
Complementary Medicines**



***Issue 1 – 12 May 2009***

# ***Sampling and Testing of Complementary Medicines***

## ***Technical Working Groups***

Technical Working Groups have been established by the TGA's OMQ to bring together manufacturing technical expertise from industry and the regulator to address the standards for the application of Manufacturing Standards.

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 use to demonstrate compliance with the relevant Code of GMP or QMS Standard.

## **Sampling and Testing of Complementary Medicines**

### **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*, and the *Therapeutic Goods Regulations, 1990* for legislative requirements and the relevant Code of GMP or Quality Management System Standard for technical requirements.

### **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](mailto:gmp@tga.gov.au)
- Overseas manufacturing enquiries: [gmpclearance@tga.gov.au](mailto:gmpclearance@tga.gov.au)

Phone:

- 02 6232 8156
- 1800 446 443 (free call)
- 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:

- <http://www.tga.gov.au/manuf/index.htm>

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# Sampling and Testing of Complementary Medicines

## Purpose

This guidance is intended to clarify the interpretation of the Australian Code of GMP for Medicinal Products in relation to the sampling and testing of complementary medicines.

It covers the sampling and testing requirements for raw materials used in the manufacture of complementary medicines and complementary medicines, whether in the form of intermediate, bulk or finished products.

It also describes a plan for reduced sampling and testing once an approved supplier has been qualified.

## Scope

This guidance is relevant to complementary medicines.

## Glossary

**Intermediate Product:** Partly processed material which must undergo further manufacturing steps before it becomes a bulk product.

**Bulk Product:** Any product that has completed all processing steps up to, but not including, final packaging.

**Finished Product:** Any medicinal product which has undergone all stages of production including packaging in the final container.

**Certificate of Analysis (C of A):** A certificate issued by the manufacturer of the product reporting the test results obtained for the specified lot(s) of product supplied.

## Guidance

### SAMPLING:

Criteria – Pre Qualification	Post Qualification
<b>Excipients – Raw Materials</b>	
<ul style="list-style-type: none"><li>Guideline currently allows <math>\sqrt{n} + 1</math></li></ul>	<ul style="list-style-type: none"><li>Apply <math>\sqrt{n} + 1</math> or reduced sampling plan if material is from a site that manufactures only one product, eliminating product mix-up possibilities. Further reduced sampling or alternative sampling plans may be justified.</li></ul>

## **Sampling and Testing of Complementary Medicines**

<b>Actives – Raw Material</b>	
<ul style="list-style-type: none"> <li>All containers to be sampled</li> </ul>	<ul style="list-style-type: none"> <li>Apply <math>\sqrt{n+1}</math> or reduced sampling plan</li> </ul>
<b>Intermediate Product</b>	
<ul style="list-style-type: none"> <li>All intermediate products must be sourced from manufacturers that are either TGA licensed or have a TGA GMP clearance. All containers to be sampled, with the exception of solid dosage forms transported for coating.</li> </ul>	<ul style="list-style-type: none"> <li>Apply <math>\sqrt{n+1}</math> or reduced sampling plan.</li> </ul>
<b>Bulk Product</b>	
<ul style="list-style-type: none"> <li>All bulk products, including solid dosage forms transported for coating, must be sourced from manufacturers that are either TGA licensed or have a TGA GMP clearance. As such, pre-qualification does not apply.</li> </ul>	<ul style="list-style-type: none"> <li>Container must have some form of integrity sealing; otherwise sample every container.</li> <li>Containers should be numbered and the quantity reconciled.</li> <li>If integrity seals are intact, sample 1 container from each pallet or the <math>\sqrt{n+1}</math> of all containers, whichever is less.</li> <li>If integrity seals are compromised on any container then an investigation should be documented by the Quality Unit.</li> </ul>
<b>Finished Product</b>	
	<ul style="list-style-type: none"> <li>If testing occurs on the finished pack for release purposes, samples must be taken throughout the run and be representative of the entire batch.</li> <li>Additional sampling of finished packs is not required by the sponsor if retention samples are held by the contract manufacturer.</li> <li>Sufficient retention samples should be held to allow two times full testing of the product.</li> </ul>

## **Sampling and Testing of Complementary Medicines**

### **TESTING:**

<b>Raw Materials</b>	
	<p><b>Excipients:</b></p> <ul style="list-style-type: none"> <li>• Identity testing performed individually on all sampled containers, each delivery.</li> <li>• Composite of all samples for other tests.</li> <li>• Critical tests on composite samples on all deliveries. Assay may / may not be considered critical. Moisture may be critical depending on the raw material risk analysis and finished product it's used in.</li> <li>• All other tests can be rotated.</li> </ul>
	<p><b>Actives:</b></p> <ul style="list-style-type: none"> <li>• Identity testing performed individually on all sampled containers, each delivery.</li> <li>• Composite all samples for other tests.</li> <li>• Critical tests on composite samples on all deliveries. Assay considered critical if part of release specification.</li> <li>• Minerals should not be excluded from critical assay. Moisture and related substances may be critical depending on the raw material.</li> <li>• All other tests maybe rotated.</li> </ul>
<b>Intermediate Product</b>	
	Sufficient testing should be conducted to ensure quality of the product.
<b>Bulk Product</b>	
	<b>Single Active Products</b>
	<ul style="list-style-type: none"> <li>• Sufficient testing, including active ingredient assay where possible and Uniformity of Content testing (if required), should be conducted to the quality of the product.</li> <li>• Customers can accept C of A from TGA licensed or GMP clearance issued manufacturers without further testing if the following issues are addressed:             <ol style="list-style-type: none"> <li>1. Verification of supply chain (may be included in supplier qualification).</li> <li>2. Examination of packaging for integrity of seal.</li> <li>3. Individual samples visually inspected.</li> <li>4. Visual comparison of bulk materials against an internal reference standard for identification purposes.</li> </ol> </li> </ul>

## **Sampling and Testing of Complementary Medicines**

	<b>Multi Active Products</b>
	<ul style="list-style-type: none"> <li>• Sufficient testing should be conducted to ensure the quality of the product. Reduced and/or rotational testing may be used where justified.</li> <li>• Customers can accept C of A from TGA licensed or GMP clearance issued manufacturers without further testing if the following issues are addressed:               <ol style="list-style-type: none"> <li>1. Verification of supply chain (may be included in supplier qualification).</li> <li>2. Examination of packaging for integrity of seal.</li> <li>3. Individual samples visually inspected.</li> <li>4. Visual comparison of bulk materials for identification purposes.</li> </ol> </li> </ul>
<b>Finished Product</b>	
	<ul style="list-style-type: none"> <li>• If testing occurring at this stage, same protocol to be followed as for bulk product.</li> <li>• No need for repeat chemical testing if already performed on bulk product.</li> <li>• Micro testing on finished pack for liquids and semi solids if applicable.</li> </ul>

### **FURTHER ITEMS FOR CLARIFICATION:**

#### **Extension of Assigned Expiry Date for Raw Materials:**

Extensions of assigned expiry date are permitted up to the manufacturer's recommended expiry date. Extensions beyond the manufacturer's recommended expiry date require data (e.g. assay and impurity testing) clearly justifying the extension.

#### **Extension of Assigned Expiry Date for Bulk and Finished Goods:**

Extensions of assigned expiry date are permitted provided data (e.g. stability data) is available supporting the extension. Extension beyond 5 years from original date of manufacture is not permitted. Any extension to the expiry date of the finished goods must be based on stability data.

#### **Premixes:**

Multi active ingredients eg vitamin premixes: Test all ingredients where possible.

## ***Sampling and Testing of Complementary Medicines***

### **Preservatives in Raw materials:**

Testing of preservatives not required

### **Herbs and Herbal Extracts:**

Identification testing is critical. Active component testing is critical if component reported on label. Microbiological testing as required. Heavy metals tested on a rotational basis. C of A result acceptable for other criteria, including pesticides and residual solvents (where relevant).

If herbal extracts are sourced from a manufacturer that is either TGA licensed or has a TGA GMP clearance then extracts can be accepted on a C of A without further testing if the following issues are addressed:

- Verification of supply chain (may be included in supplier qualification).
- Examination of packaging for integrity of seal.

### **Multi Herb Materials**

Must be able to uniquely identify each herb in the material. If multi herb materials are sourced from a manufacturer that is either TGA licensed or has a GMP clearance then multi herb materials can be accepted on a C of A without further testing.

### **Rotational Testing**

May be implemented once supplier qualified. Any rejected material relating to quality issue from supplier, should result in reverting status back to non-qualified.

Rotational testing is considered to follow the process below:

- Perform critical tests on each delivery plus one non critical test
- Non critical test are rotated. It is expected that all test are to be done and none are skipped without adequate justification.

### **Starting Material Grade**

It is expected that starting materials will comply with the applicable pharmacopoeial requirements as specified in the Therapeutic Goods Act.

## ***Sampling and Testing of Complementary Medicines***

### ***References***

Australian Code of GMP for Medicinal Products

Application of the Australian Code of GMP for Medicinal Products 16 August 2002 to the Manufacture of Complementary Medicines

TGO 69 – General Requirements for Labels for Medicines

TGO 78 – General Requirements for Tablets and Capsules