Australian Government
Department of Health
Therapeutic Goods Administration

Sampling and testing 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

Contents

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 the sampling and testing requirements for starting materials (active substances and excipients), packaging materials, intermediate products and bulk products used in the manufacture of listed and complementary medicines.

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

This guidance addresses compliance with the sections of the PIC/S guide related to sampling and testing, which is part of quality control, addressed in Part 1 in Chapter 1 (Pharmaceutical Quality System), Chapter 2 (Personnel), Chapter 3 (Premise and equipment), Chapter 4 (Documentation), Chapter 5 (Production) and Chapter 6 (Quality Control).

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, including Sampling of starting and packaging material (Annex 8)

Sampling environment

Depending on the manufacturing stage sampled, the sampling environment requirements differ.

Starting material

In order to protect the sampled material from contamination, this sampling would be expected to be carried out in a separate room, or appropriately qualified sampling hood, that supplies air of a quality and cleanliness equivalent to that used in the manufacturing area where the material is exposed. The sampling area would also be expected to be designed with dust extraction or equivalent controls to prevent contamination from adjacent areas.

Sampling hoods may be used provided there are adequate controls in place to ensure that materials are contained. Consideration should be given to:

- the use of appropriate extraction and de-dusting facilities
- the qualification of the hood
- the possibility of contaminating the sampled material and the adjacent storage area
- whether materials sampled are hazardous

Areas for the sampling of starting materials should be supplied with air filtered to remove 85% of particles above 1 micron, or EU 7 standard. There needs to be a pressure differential to prevent the ingress of unfiltered air.

Primary packaging

The sampling environment for primary packaging materials:

- is to adequately protect the packaging material from contamination
- does not require filtered air supply
- is not to be performed in a warehouse environment

Secondary packaging

There are no specific requirements for the sampling environment for secondary packaging materials.

Sampling starting materials and intermediate products

For starting materials and intermediate products, there are different sampling requirements depending on whether the supplier has been qualified or not.

Approved supplier

The approved entity supplying starting and/or packaging material to the manufacturer of a medicinal product. This entity should normally be the actual manufacturer of the starting or packaging material, rather than a broker or agent. However brokers or agents may be additionally approved if they play significant roles in the supply chain other than merely on-selling the starting or packaging materials.

Qualified supplier

An approved supplier, supplying the starting and/or packaging material to the manufacturer of medicinal products, who has undergone the process of supplier qualification. The supplier should normally be the actual manufacturer of the starting or packaging material, not a broker or agent.

Supplier qualification

The process of establishing confidence in the reliability of the supplier to consistently provide material of acceptable quality.

Sampling requirements pre- and post- supplier qualification

Type of material	Pre-qualification	Post qualification
Excipients – starting materials	Apply $\sqrt{n}+1$	• Apply $\sqrt{n}+1$ OR • reduced sampling plan if: – material is from a site that manufactures only one product, eliminating product mix-up possibilities – there is another justification
Actives – starting materials	Sample all containers.	

Sampling intermediate and bulk product

Pre-qualification does not apply to intermediate or bulk products. All intermediate and 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.

Intermediate product

Partly processed material from a manufacturer with a current TGA licence or GMP clearance that 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, primary packaging.

All containers are to be numbered and the quantity reconciled.

Containers should be undamaged, intact and sealed:

- If seals are undamaged and intact, sample one container.
- If seals are compromised on any container the Quality Unit should conduct and document an investigation. Additional containers may need to be sampled.

Sampling packaging

For sampling plans based on known manufacturing processes, take one sample:

- from each roll of labels
- printed foil or printed cartons
- other pre-printed materials
- container
- container closure

Multiple samples may not provide any additional assurance where all packaging materials come from the same manufacturing process.

Testing samples

Rotational testing

A qualified supplier will revert to a non-qualified status if a quality issue results in rejection of any material.

Rotational testing may be used for material from a qualified a supplier.

Rotational testing follows the process below:

- Perform critical tests on each delivery plus one non-critical test.
- Rotate through all non-critical tests:
  - Do not skip any non-critical tests without adequate justification.

Starting materials

Starting material grade

It is expected that starting materials will comply with the applicable pharmacopoeial requirements as specified in the *Therapeutic Goods Act 1989*.

Excipients

Verify that each delivery is from the approved supplier (Chapter 1, Part 1, PIC/S Code of GMP). This usually involves receipt of the original Certificate of Analysis.

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

Perform identity testing individually on all sampled containers for each delivery. Samples for other tests can be composite samples. Define the number of samples within a composite and provide a justification if the number is greater than ten.

Test samples on all deliveries for critical parameters. Any particular test may be considered critical depending on the circumstances. For example, moisture may be critical, depending on the starting material risk analysis and the finished product it is used in.

All other tests can be rotated.

Preservatives in starting materials

Preservatives in starting materials are incidental minor excipients, and testing is not required.

Actives

Perform identity testing on all sampled containers. Identity testing on a composite sample is not permitted. Other tests can be conducted on a composite sample.

Test samples on all deliveries for critical parameters. An assay is critical if it is part of release specifications. Moisture and related substances may be critical, depending on starting material.

All other tests may be rotated.

Herbs and herbal extracts

Critical testing includes:

- identification
- active component, if the component is reported on finished product label

Testing performed, as required, includes:

- microbiological testing
- heavy metals testing
- residual solvent testing

Using C of A results is acceptable for other criteria, including pesticides and residual solvents (where relevant).

Herbal extracts based on the C of A may be accepted without further testing when sourced from a manufacturer with a current TGA licence or GMP clearance, if you:

- qualify the manufacturer
- examine the packaging for integrity of seal

Intermediate products

Verify that each delivery is from an approved manufacturer with a current TGA licence or GMP clearance (Chapter 1, Part 1, PIC/S Code of GMP). This usually involves receipt of the manufacturer's C of A.

Conduct sufficient testing to ensure quality of the product.

Premixes

Test all multi-active ingredients, where possible, e.g. vitamin premixes.

Material may be acceptable based on the C of A, without further testing, when sourced from a manufacturer with a current TGA licence or GMP clearance.

Multi herb materials

Each herb must able to be uniquely identified in the material.

Material may be acceptable based on the C of A, without further testing, when sourced from a manufacturer with a current TGA licence or GMP clearance.

Bulk products

Verify that each delivery is from the approved manufacturer (Chapter 1, Part 1, PIC/S Code of GMP). This usually involves receipt of the manufacturer's C of A.

Bulk products may be accepted based on a C of A from a manufacturer with a current TGA license or GMP clearance without further testing, if you:

- confirm manufacturer
- examine the packaging for integrity of seal
- visually inspect individual samples
- visually identify bulk materials by comparing against an internal reference or reference standard

Packaging

Compare all pre-printed packaging material samples against packaging and labelling specifications or against approved artwork.

Compare primary packaging material samples against packaging specifications or reference sample. Conduct functional testing of containers and closures if appropriate.

Extension of assigned expiry dates

For starting materials

Extensions of assigned expiry date for starting materials are permitted.

Extensions beyond the manufacturer's recommended expiry date for starting materials require data (e.g. assay and impurity testing) clearly justifying the extension.

For bulk product

Extensions of assigned expiry date for bulk product:

- ü are permitted provided data (e.g. stability data) are available supporting the extension
- û not permitted beyond 5 years from original date of manufacture

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: sampling and testing of complementary medicines – Technical Working Group (TWG) on complementary medicines'	Office of Manufacturing Quality	12/05/2009
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 #