Australian Government
Department of Health
Therapeutic Goods Administration

Supplier assessment, approval and qualification 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 and sponsors of listed and complementary medicines manufactured according to the P*IC/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 a medicine 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 assessment, approval and qualification of suppliers of starting and packaging materials used in the manufacture of listed and complementary medicines.

This document does not cover the entire supplier qualification process and is only intended to clarify the requirements of the PIC/S Guide to GMP.

All suppliers should be approved before materials and products are used. A separate guidance document covers reduced sampling and testing, which may be considered after supplier qualification.

Supplier

Any entity supplying the 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.

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.

Related guidance

The following guidance is relevant:

- TGA interpretation and expectations for demonstrating compliance with the PIC/S guide to GMP
- Sampling and testing for listed and complementary medicines

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.

The process

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Qualification of the supplier

Introduction of reduced sampling plan and testing as applicable to qualified suppliers (Refer to guidance: Sampling and testing for listed and complementary medicines)

Periodic Review

Process guidance

Understanding the nature of the starting or packaging material

The nature of the packaging or starting material can impact on the type and amount of information required from the supplier in order to undertake supplier approval and qualification.

Items that may be considered when undertaking this step:

- whether the starting material is an active substance, excipient or packaging material
- compliance to any required international standard(s) (e.g. BP, EP, USP, FCC)
- the specific grade of the material required and any critical physical properties
- whether the origin of material results in any specific requirements, for example, TSE, allergen-free, heavy metals, pesticides etc.
- whether the packaging material is a pre-printed material, primary or secondary component

Starting material

Any substance (active or excipient) used in the production of a medicinal product, excluding packaging materials.

Packaging material

Any material employed in the packaging of a medicinal product, excluding any outer packaging used for transportation or shipment. Packaging materials are referred to as primary or secondary according to whether or not they are intended to be in direct contact with the product.

Establishing a GMP or technical agreement is not required

For listed and complementary medicines, it is not required to establish a formal GMP or technical agreement for suppliers and manufacturers of raw materials, packaging materials and printed artwork.

These are controlled by having the following information:

- approved specifications
- Certificate of Analysis (C of A) from manufacturing site
- a system of vendor qualification

Understanding the nature of the finished product

The nature of the finished product for which the starting or packaging materials will be used can impact on the type and amount of information required from the supplier, in order to undertake supplier approval and qualification.

Items that may be considered when undertaking this step:

- the type of medicinal product (e.g. listed or registered, complementary, herbal)
- other ingredients that may be used in the finished product formulations
- any potential stability issues with the finished product
- any potential manufacturing issues with the finished product
- consideration of the finished product indications and label claims

Obtaining information on the supplier

Acquisition of relevant information, including the identification of the manufacturer of the starting or packaging material, is required in order to undertake supplier approval and qualification.

It may not be possible to deal directly with the starting or packaging material manufacturers. If this situation occurs, it may be possible to gain information about the manufacturer through the agent or broker.

A questionnaire or standard form to collect this type of information may be employed.

Two industry associations, ASMI (Australian Self Medication Industry) and CMA (Complementary Medicines Australia), have worked together to develop vendor qualification questionnaires and:

- an industry guideline on good supplier practice
- CMA guideline for the quality and safety of raw materials used in complementary medicines

The TGA was not involved in the development of the industry guideline or the associated questionnaires and cannot guarantee that their use will enable you to meet all relevant TGA regulatory requirements. However, you might find the guideline and questionnaires useful.

A copy of a Site Master File (or any comparable document) for the manufacturer can be useful.

This information may also help with the assessment conducted prior to the introduction of reduced sampling and/or testing.

Items that may be considered when undertaking this step:

- the site of manufacture of the material and (any) alternative sites used
- the GMP status of all manufacturing sites
- the quality systems that the manufacturer has in place

- evaluation of the packaging or starting material manufacturer's C of A, in regard to compendial and other company requirements
- the provider of the C of A for the starting material: note that it is unacceptable for results from the material manufacturer's C of A to be transcribed to a broker or agent letterhead
- acceptability of any sample(s) supplied with reference to chemical, microbiological and physical attributes
- whether the site of manufacture has been audited and by whom
- whether the manufacturer has been dealt with on prior occasions, or other materials are being sourced from this manufacturer
- any other materials being produced on the manufacturing site
- information about how the material is produced and what impurities, allergens and substances of concern could be present
- information on the relevant test methods used by the manufacturer
- the actual provider of the testing documented on the C of A
- confirmation that the manufacturer represents a single, specific source of the material
- stability attributes for starting materials and requirements for the material transportation

Obtaining information on the supply chain

Each step in the supply chain may have the potential to impact on the quality of the starting or packaging material. Identification of all interactions with the starting or packaging material between leaving the manufacturer's control and the final delivery to the finished product manufacturer can be useful.

Items that may be considered when undertaking this step:

- manufacturer location
- agent or broker location
- for herbal materials, the harvesting location, time of harvest, identification of raw herbs and method of preparation (e.g. extraction)
- whether the broker or agent stores the material and the location and types of other materials stored next to the material of interest
- whether the broker or agent repacks the material and if so the manner in which this activity is conducted (TGA licence or GMP clearance certification)
- control of the transportation pathway from the material manufacturer to the finished product manufacturer
- any material-specific storage requirements, such as cold chain requirements or humidity controls

Approval of the supplier

Information obtained in the previous steps is assessed by the Quality Unit and, if acceptable, the supplier can be approved.

The approval process should take account of at least the following aspects:

- nature and status of the manufacturer and of the supplier and their understanding of GMP requirements
- the Quality System of the manufacturer of the starting material
- the manufacturing conditions under which the starting material is produced and controlled

This approval process will normally take the form of the supplier providing information, by completion of a questionnaire or by other suitable means. This allows an assessment to be made of the suitability of the supplier to provide the starting and/or packaging material to the manufacturer of a medicinal product.

When a starting material is supplied from a manufacturer that has a TGA licence or GMP clearance issued by the TGA, a GMP agreement should be established.

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.

Authorisation of the starting or packaging material specification

The specification should be based on an applicable monograph, if available, and any relevant information supplied by the manufacturer.

Items that may be considered when undertaking this step:

- whether the manufacturer of the material is clearly identified and documented on the material specification
- whether the C of A provided clearly documents the test methods used, the acceptable specification limits and results obtained by the manufacturer
- whether any tests conducted by the manufacturer are compendial tests

Full sampling and testing until supplier qualified

Conduct full sampling and testing on three (or as otherwise justified) different specific manufacturer's lots of starting or packaging material.

Items that may be considered when making this qualification decision:

- the standards that exist for the starting material
- number of deliveries received per year
- number of different manufacturer's lot numbers received per year
- supplier history
- starting material manufacturer history

Until qualified, each delivery of the starting material would be approved by the Quality Unit after full sampling and full testing has been successfully undertaken.

Analysis and trending of actual test or inspection results

Review the results reported by the supplier, provided on the C of A, against actual test or inspection results obtained. Perform an analysis of the data and the trends.

All relevant data may be reviewed against compliance to the defined acceptance criteria.

The information can be used to support a documented justification for reduced sampling and testing.

Items that may be considered when undertaking this step:

- a review of the physical condition of each delivery of the starting material
- a review of the documentation that accompanied each lot of the starting material
- whether all results complied with specifications
- a review of any out-of-specification (OOS) or out-of-trend (OOT) results and any subsequent investigations and their conclusions.
- Statistical comparison of in-house test results against starting material manufacturer's C of A results, where appropriate.

out-of-specification (OOS)

Test results that fall outside the specifications or acceptance criteria that have been specified.

out-of-trend (OOT)

Test results that are within specification or acceptance criteria, but fall outside the range of values expected, when viewed alongside historical results or results obtained for comparable lots of material.

Qualification of the supplier

Assessment of all information collected on the starting or packaging material supplier, including actual test or inspection results obtained from initial deliveries.

This assessment should be carried out by authorised Quality Unit personnel and may be achieved by using documentation reviews, questionnaires and/or audits.

The minimum information reviewed by the Quality Unit should include an appropriately completed supplier questionnaire and if considered additionally necessary, an onsite audit of the starting or printed packaging material manufacturer.

This information can be used to support qualification of the supplier.

Items that may be considered when undertaking this step:

- a review of actual test or inspection results obtained from initial deliveries (normally at least three specific lots) of the starting or packaging material
- the condition of the initial deliveries upon receipt by the medicinal product manufacturer
- a review of results reported by the supplier, provided via a C of A, against the actual test or inspection results obtained

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.

Reduced sampling plan and testing considerations

Refer to Sampling and testing for listed and complementary medicines.

Periodic review

As part of the qualification process, a program for periodic review should be established. This program should include a mechanism for removing the qualified status of a starting or packaging material supplier and should prevent the use of reduced sampling and reduced testing until any identified critical issues are satisfactorily resolved.

Items that may be considered when undertaking this step:

- trend analysis
- any issues with other materials from the same supplier (e.g. microbiological alerts)

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: supplier qualification – Technical Working Group (TWG) on non-sterile medicines & complementary medicines'	Office of Manufacturing Quality	01/09/2010
V1.1	Template change	Office of Manufacturing Quality	01/06/2013
V2.0	Change in title and scope Restructured and updated to be consistent with PE 009-13, PIC/S Guide to GMP	Manufacturing Quality Branch Regulatory Guidance Team	17/01/2019

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