Australian Government

Department of Health and Ageing

Therapeutic Goods Administration

Technical Guidance on the Interpretation of Manufacturing Standards

SUPPLIER QUALIFICATION

Technical Working Groups (TWG) on Non-Sterile Medicines & 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 (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,* and the *Therapeutic Goods Regulations, 1990* for legislative requirements and the relevant Code of GMP or QMS Standard for technical requirements.

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Supplier Qualification

Purpose

This guidance document provides a formal and transparent process for the steps by which supplier qualification may be achieved. This should assist industry and regulators to work cohesively in order to improve industry implementation of the Code of Good Manufacturing Practice and enhance regulatory audit consistency in the application of this code.

This document does not cover the entire qualification process and is only intended to clarify the requirements of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products.

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

Scope

This guidance is relevant to Non-Sterile Medicines and Complementary Medicines

Definitions

Active Pharmaceutical Ingredient (API):	Any substance or mixture of substances intended to be used in the manufacture of a medicinal product and that, when used in the production of a medicinal product, becomes an active ingredient for that medicinal product. (Ref 1)
Approved Supplier:	The approved entity supplying packaging and/or starting material to the manufacturer of a medicinal product. This may be a broker or agent, or the actual manufacturer of the packaging or starting material.
Excipient:	An ingredient intended to be used in the manufacture of a medicinal product other than an active pharmaceutical ingredient
Finished Medicinal Product:	A medicinal product which has undergone all stages of production including packaging in its final container.
Medicinal Product Manufacturer:	Is a person who manufactures medicinal products, being a person who produces the product, or engages in any part of the process of producing the product or of bringing the product to its final state, including engaging in the processing, assembling, packaging, labelling, storage, sterilising, testing or releasing for supply of the product or of any component of ingredient of the product as part of that process. (Ref 2)
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. (Ref 2)
Qualified Supplier:	An entity supplying the packaging and/or starting material to the manufacturer of medicinal products who has undergone the process of supplier qualification. The supplier may be a broker or agent, or the actual manufacturer of the packaging or starting material. However brokers or agents supplying

packaging or starting materials could not be qualified where the source of manufacture is unknown or not qualified. Where a material is sourced through a supplier both the supplier and manufacturer would need to be qualified.

Starting Material: Any substance used in the production of a medicinal product, but excluding packaging materials.

Supplier: Any entity supplying the packaging and/or starting material to the manufacturer of medicinal product. This may be a broker or agent, or the actual manufacturer of the packaging or starting material.

Supplier Qualification: The process of further assessing the reliability of the supplier to consistently provide material of acceptable quality.
The qualification process should take account of at least the following aspects:

- nature and status of the manufacturer and of the supplier and their understanding of the GMP requirements of the Pharmaceutical Industry;
- the Quality Assurance system of the manufacturer of the starting material;
- the manufacturing conditions under which the starting material is produced and controlled;
- the nature of the starting material and the medicinal product in which it will be used

Supplier Qualification

The Supplier Qualification Process

Understanding the Nature of the Packaging or Starting Material

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Understanding the Nature of the Finished Medicinal Products

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Acquisition of Relevant Information on the Packaging or Starting Material Manufacturer

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Acquisition of Relevant Information on the Packaging and Starting Material Supply Chain

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Approval of Packaging or Starting Material Supplier

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Authorisation of the Packaging or Starting Material Specification

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Packaging or Starting Material Purchased and Used to Manufacture the Finished Medicinal Product

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Analysis and Trending of Data

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Reduced Sampling Considerations
(Refer Guideline for Reduced Sampling and Testing)

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Qualification of Packaging or Starting Material Supplier

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Reduced Testing Considerations
(Refer Guideline for Reduced Sampling and Testing)

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Periodic Review

Process Guidance

1. Understanding the Nature of the Packaging or Starting 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 qualification.

Items that may be considered when undertaking this step:

- Whether the packaging material is a pre-printed material, primary or secondary component.
- Whether the starting material is an active pharmaceutical ingredient, excipient or bulk material.
- Compliance to any international standard/s (e.g. BP, USP, FCC).
- The specific grade of the material required and its critical physical properties.
- Whether the material is of human, animal or biological origin.

2. Understanding the Nature of the Finished Medicinal Products

The nature of the finished products where the packaging and starting materials may be used can impact on the type and amount of information required from the supplier in order to undertake supplier qualification.

Items that may be considered when undertaking this step:

- The type of medicinal products (e.g. non-sterile, complimentary, herbal).
- Identification of potential finished product consumers.
- Other ingredients which may be used in the finished product formulations.
- Any potential stability issues with the finished products.
- Any potential manufacturing issues with the finished products.
- Consideration of the finished products indications and label claims.
- Identification of the finished product dosage instructions

3. Acquisition of Relevant Information on the Packaging or Starting Material Manufacturer

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

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

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

A copy of the Site Master File for the manufacturer can be useful.

This information may also help with the risk assessment that should be conducted prior to the introduction of reduced testing.

Items that may be considered when undertaking this step:

- The site of manufacture of the material and alternative sites used.
- The GMP status of all manufacturing sites.
- The quality systems which the manufacturer has in place.
- Evaluation of the packaging or starting material manufacturer's CofA in regard to compendial and other company requirements.
- Who is the provider of the Certificate of Analysis (C of A) for the starting material . Note, it is unacceptable for results from the manufacturer's C of A to be transcribed from the original C of A to a supplier letter head. Acceptability of the 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 could be present as a result of the production process.
- Information on the relevant test methods used by the manufacturer.
- The actual provider of the testing which is documented on the Certificate of Analysis.
- "Free from" list, pesticide information, process validation and analytical method validation information.
- Confirmation that the manufacturer represents a single, specific source of the material. Should the manufacturer collect and blend materials from numerous sources, then supplier qualification in order to undertake reduced testing may not be appropriate.
- Stability attributes for starting materials and requirements of the material transportation.

4. Acquisition of Relevant Information on the Packaging and Starting Material Supply Chain

Each step in the supply chain may have the potential to impact on the quality of the packaging or starting material.

Identification of all interactions with the material between leaving the manufacturer's control and the final delivery to the finished medicinal product manufacturer can be useful.

<u>Items that may be considered when undertaking this step:</u>

- Manufacturer location.
- Supplier location.
- For herbal materials the harvesting location, time of harvest, identification of raw herbs and method of preparation (e.g. extraction).
- Whether the supplier/agent stores the material and the location and types of other materials stored next to the material of interest.
- Whether the supplier/agent repacks the material and the environment and manner in which this activity is conducted. (TGA license / GMP Clearance Certification)

- Whether the supplier has a Technical Agreement with the manufacturer and the content of the agreement (e.g. changes to the material, such as the method of manufacture or material supply).
- The number of intermediates and the control of the transportation pathway from the manufacturer to the finished medicinal product manufacturer.
- Any material specific storage requirements, such as cold chain requirements or humidity controls.
- The time taken typically for the starting material to be receipted on site.

5. Approval of Packaging or Starting Material Supplier

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

Items that may be considered when undertaking this step:

- When a starting material is supplied from a manufacturer that has a TGA licence or GMP Clearance issued by the TGA (Ref 3), then no further qualification of the manufacturer is required. The licence or certification must cover the manufacture of the specific material or bulk product and a GMP agreement should be established.
- For other suppliers a formal agreement covering all relevant issues is recommended.
- How your supplier approval system will classify the various levels or status of your approved and qualified suppliers.

6. Authorisation of the Packaging or Starting 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 material is supplied by a broker or agent, and if so has the manufacturer been identified and documented on the material specification.
- Whether the C of A provided clearly documents the test methods utilised, the acceptable specification limits and results obtained by the manufacturer.
- Whether all tests conducted by the manufacturer are compendial tests
- Whether any non-compendial tests are appropriately validated

7. Packaging or Starting Material Purchased and Used to Manufacture the Finished Medicinal Product

At this stage each delivery of specific lot numbers of the starting material would be approved by the Quality Unit after full sampling and full testing has been successfully undertaken.

Typically three lots of starting materials would be subjected to full sampling and testing, however specific starting material requirements may change this number.

Items that may be considered when undertaking this step:

- 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.

8. Analysis and Trending of Data

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.

Items that may be considered when undertaking this step:

- A review of the physical condition of each batch of the starting material.
- A review of the documentation which accompanied each batch of the starting material.
- Whether all results complied with specification requirements.
- A review of any out of specification or out of trend results and any subsequent investigations and their conclusions.
- Statistical comparison of in-house test results against starting material manufacturers C of A results where appropriate.

9. Reduced Sampling Considerations

For Complementary Medicines refer to Sampling and Testing of Complementary Medicines.

10. Qualification of Packaging or Starting Material Supplier

Assessment of all information collected on the packaging or starting material supplier.

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

The minimum information reviewed by the Quality Unit should include an appropriately completed supplier qualification questionnaire and where possible an on site audit of the starting material manufacturer.

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

Items that may be considered when undertaking this step:

- Assessment of the supplier qualification questionnaire.
- The evaluation of any other relevant information.
- Assessment via an on-site audit of the manufacturer and supplier as required.
- Whether appropriate measures are in place to ensure the source of material is known to help guard against counterfeit materials.

11. Reduced Testing Considerations

To be covered in detail in the guidance document for Reduced Sampling and Testing.

12. 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 packaging or starting material supplier and should prevent the use of reduced sampling and reduced testing until identified critical issues are satisfactorily resolved.

Items that may be considered when undertaking this step:

- The starting material manufacturer's quality systems.
- The supplier's quality systems.
- The quality of the batches of starting material received.
- Documentation reviews.
- Trend analysis.
- Information obtained form supplier questionnaires and on-site audits.

References

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

Sampling and Testing of Complementary Medicines. May 2009. Technical Working Group on Complementary Medicines