Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Technical Guidance on the Interpretation of Manufacturing Standards

Product quality review for listed Complementary Medicines

Technical Working Group (TWG) on Complementary Medicines

Issue 9 - 4/3/2010

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. The TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

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:

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

Contents

Purpose

This guidance is intended to clarify the interpretation of the PIC/S Guide to Good Manufacturing Practice for Medicinal Products in relation to the conducting of Product Quality Reviews for Listed Complementary Medicines.

Product Quality Reviews have become an accepted part of GMP requirements internationally and may provide useful information and additional controls over manufacturing processes and quality requirements for products. Product Quality Reviews will also provide a mechanism to ensure on-going stability studies are conducted by sponsors, as verified during an audit of a manufacturer by reviewing the information available to the authorised person releasing product for supply to the market.

Scope

This guidance is relevant to Listed Complementary Medicines.

Definitions

Refer to glossary in PIC/S Guide to Good Manufacturing Practice for Medicinal Products

CAPA Corrective And Preventative Action – A documented course of action intended to rectify a situation and prevent its recurrence.

RFS Release for Sale / Supply

Flowchart

[A Flowchart may be added later]

Guidance

The introduction of the PIC/S Guide to GMP for Medicinal Products in July 2009 and its implementation by 1 July 2010 has introduced some changes from the requirements of the 2002 PIC/S Code previously in force in Australia. One significant change is Section 1.4 Product Quality Review which requires regular reviews (usually annually) of all medicinal products.

The authorised person responsible for final batch certification together with the marking authorisation holder (Sponsor) should ensure that the Product Quality Review is performed in a timely manner and is accurate. For those manufacturers that are also the Sponsor of the product, a delineation of responsibility between the Manufacturer and the Sponsor is not an issue. However when a contract manufacturer (or manufacturers) make(s) a product on behalf of a Sponsor the responsibilities of each party in the Product Quality Review Process shall be documented in the Technical Agreement or GMP Agreement, a copy of which shall be held by the Authorised Person who conducts Release for Supply.

Relevant objective evidence will be expected to be available for review, at the time of audit of licensed premises, to demonstrate that manufacturers have undertaken their respective responsibilities in regard to Product Quality Reviews as defined in the Technical or GMP agreements. For guidance on allocation of responsibilities please refer to Table 1 in this document. Manufacturers can not delegate inherent responsibilities for the steps that they are licensed to undertake to non licensed parties. The Authorised Person conducting the release for supply step must hold complete copies of the Product Quality Reviews. These documents will be auditable by the TGA at licensed premises.

This document will look at each part of Section 1.4 and offer guidance for manufacturers of Listed Complementary Medicines. Excerpts from the PIC/S Guide to GMP for Medicinal Products are in bold type, with comments under each paragraph.

1.4 "Regular periodic or rolling quality reviews of all licensed medicinal products, including export only products, should be conducted with the objective of verifying the consistency of the existing process, the appropriateness of existing specifications for both starting materials and finished products, to highlight any trends and to identify product and process improvements. Such reviews should normally be conducted and documented annually, taking into account previous reviews and should include at least:"

Reviews are to be conducted annually, unless 2 or less batches have been manufactured in the year, in which case a review shall be conducted every 2 years.

1.4 (i – xii)

The respective responsibilities of the various parties in conducting the Product Quality Review is set out in Table 1.

Table 1 is intended to provide guidance as to which party is most likely to hold the relevant information and to conduct that part of the Product Quality Review. However Table 1 is not to be read as specifying that these particular parties must hold the relevant information or conduct that part of the Product Quality Review. The Technical Agreement or GMP Agreement will normally specify in each particular situation which party will be responsible for each area described in Table 1.

Details of Section 1.4 of PIC/S Code January 2009	Bulk Manufacturer	Packer / RFS	Sponsor
1 a Review starting materials used in bulk manufacture, especially those from new sources	Responsible		
1 b Review starting materials used in packing activity, especially those from new sources		Responsible	
2 a Review critical in-process controls in bulk manufacture	Responsible		
2 b Review finished product results This would normally be conducted by the bulk manufacturer unless QC testing is carried out on the packed product.	Responsible		
2 c Review critical in-process controls in packing		Responsible	
3 a Review of all bulk batches that fail to meet established specifications and their investigation	Responsible		
3 b Review of all packed batches that fail to meet established specifications and their investigation		Responsible	
4 a Review all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken regarding bulk manufacture	Responsible		
4 b Review all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken regarding testing	Responsible		
4 c Review all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken regarding packing activities		Responsible	
5 a A review of all changes carried out to the bulk manufacturing processes	Responsible		
5 b A review of all changes carried out to analytical *(and other testing)* methods	Responsible		

Details of Section 1.4 of PIC/S Code January 2009	Bulk Manufacturer	Packer / RFS	Sponsor
5 c A review of all changes carried out to the processes involved in the packing activity		Responsible	
6 Review the Marketing Authorisation variations submitted/granted/refused, including those for third country (export only) dossiers			Responsible
7 a Review the results of the initial long term stability of the bulk product monitoring program and any adverse trends	Responsible		
7 b Review the results of the initial long term stability of the market product monitoring program and any adverse trends			Responsible
7 c Review the results of the ongoing stability of the market product monitoring program and any adverse trends			Responsible
8 Review all quality-related returns, complaints and recalls and the investigations performed at the time			Responsible
9 a Review the adequacy of any previous product process or equipment corrective actions relating to manufacture of the bulk product	Responsible		
9 b Review the adequacy of any previous product process or equipment corrective actions relating to packing of the market product		Responsible	
10 Review post marketing commitments to new marketing authorizations and variations to marketing authorisations			Responsible
11 a Review the qualification status of relevant equipment and utilities eg HVAC, water, compressed gases relating to manufacture of the bulk product. NB Qualification of equipment and utilities can be reviewed as part of the Validation Master Plan schedule and not for each Product Quality Review.	Responsible		

Details of Section 1.4 of PIC/S Code January 2009	Bulk Manufacturer	Packer / RFS	Sponsor
11 b Review the qualification status of relevant equipment and utilities eg HVAC, water, compressed gases relating to packing of the market product. NB Qualification of equipment and utilities can be reviewed as part of the Validation Master Plan schedule and not for each Product Quality Review.		Responsible	
12 a Review any contractual arrangements relating to the manufacture of the bulk product as defined in Chapter 7 *(of the code)* to ensure that they are up to date	Responsible		Responsible
12 b Review any contractual arrangements relating to the manufacture of the market product as defined in Chapter 7 *(of the code)* to ensure that they are up to date		Responsible	Responsible

"The manufacturer and market authorisation holder should evaluate the results of this review and an assessment made of whether corrective and preventative action or any revalidation should be undertaken. Reasons for such corrective actions should be documented. Agreed corrective and preventive actions should be conducted in a timely and effective manner. There should be management procedures for the ongoing management and review of these actions and the effectiveness of these procedures verified during self inspection. Quality reviews may be grouped by product type, e.g. solid dosage forms, liquid dosage forms, sterile products, etc. when scientifically justified."

- Product Quality Reviews to be evaluated by both Manufacturer and Sponsor.
- Product Quality Reviews should assess any CAPAs and need for revalidation.
- A management procedure should be in place to monitor any CAPAs and revalidations resulting from Product Quality Reviews.
- Internal audits must cover Product Quality Reviews.
- Product Quality Reviews can be grouped into product types, where scientifically justified. A similar justification which would apply to process validation and or stability testing grouping would be appropriate, considering such areas as dosage type, equipment train, ingredient matrix and active quantities.

"Where the market authorisation holder is not the manufacturer, there should be a technical agreement in place between the various parties that defines their respective responsibilities in producing the quality review. The authorised person responsible for final batch

certification together with the market authorisation holder should ensure that the quality review is performed in a timely manner and is accurate."

- The TGA will expect to see during audits that Product Quality Reviews have been conducted and that copy/s are held by Authorised Person/s.
- For contract manufacturers a Technical Agreement or GMP Agreement should be in place defining who does what in the Product Quality Review. This could be an extension to the normal GMP Agreement.
- Responsibility for ensuring the Product Quality Review is conducted is held jointly by both the person releasing the product (Authorised Person) and the market authorisation holder (Sponsor). Assigning responsibility in a GMP Agreement to one party only will not be acceptable.
- Grouping is to be established by the Manufacturer, in conjunction with the Sponsor's input. Once the grouping is established, then a list of all batches manufactured and packed during the review period is to be identified for the products in this grouping.
- Manufacturer/s to compile a list of significant non-conformances, deviations and CAPAs for equipment, process and products, as well as results of internal audits.
- Sponsor to provide details of complaints, investigations of these by the relevant manufacturer(s), close out of complaints and trending (complaint history).
- Sponsor and/or manufacturer to review the stability monitoring program and to document any adverse trends.
- Batch documentation does not need to be routinely assessed in conducting a Product Quality Review, However if an assessment of deviations, non-conformances, or internal audit findings indicates serious issues , then batch documentation may need to be reviewed, but only as required and deemed necessary by the Sponsor and Manufacturer/s conducting the Product Quality Review.
- Sponsor to review the ARTG entry changes and post-marketing commitments, to determine if any outstanding issues need to be addressed and their impact on the products being reviewed in this grouping. This will include any variations submitted / granted / refused, including those for export only products.
- Test results (chemical & microbiological) to be compiled by the testing laboratory (contract or manufacturer) for all batches and products in the grouping, for bulk and finished products where appropriate. Should there be any issues found during this review, then in-process testing results for the relevant batches may need to be reviewed, to ascertain clarity of results obtained during production runs.

References

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

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 02 6232 8444 Fax: 02 6232 8605
www.tga.gov.au

Reference/Publication #