



Information Letter – Implementation of New Manufacturing Principles

Dear Member,

This letter has been prepared by the Australian Self Medication Industry (ASMI) and the Complementary Healthcare Council (CHC) to make sponsors of medicines aware of imminent changes to the requirements for Good Manufacturing Practice. There are a number of implications for the responsibilities of both sponsors and manufacturers. Either your organisation directly, or your organisation's contract manufacturers (**NB in this document contract manufacturers also include contract packers**) will require additional information to achieve compliance with the new requirements. While this letter has been prepared with the best of intentions to assist our members with appropriate and timely information, please be aware that we are still working with the TGA to develop guidance on the interpretation of the new requirements. This letter provides initial information only on the changes. ASMI and CHC will endeavour to keep members informed as interpretive guidance is published by TGA.

Background

On 21 July 2009 a new legislative instrument titled "Therapeutic Goods (Manufacturing Principles) Determination No.1 of 2009" was gazetted. This document will commence operation from 1 July 2010. There are three important consequences of this new requirement that sponsors should note:

1. The manufacturer of your organisation's products will be audited to the revised Manufacturing Principle from that date.
2. This new Manufacturing Principle mandates the use of a new code of Good Manufacturing Practice (2009 GMP Guide) by adopting the PIC/S Guide for Good Manufacturing Practice for Medicinal Products – 15 January 2009 (PE 009-8) (Please note this Guide is only available on the TGA website <http://www.tga.gov.au/manuf/picsgmpmed.htm> as the Guide has been further updated by the PIC/S).
3. The adoption of this 2009 GMP Guide means that one standard will be applicable to all medicinal products including: Prescription medicines, OTC medicines, complementary medicines, Active Pharmaceutical Ingredients (APIs) and Sunscreens (revoking the Australian Code of GMP for Sunscreens products – February 1994). See <http://www.tga.gov.au/docs/html/gmpcodes.htm>

Please Note: for ease of understanding when reading the PIC/S Guide, it refers to:

- the 'sponsor' as the **Marketing** Authorisation (MA) Holder,
- the nominated licensed 'manufacturer' as the **Manufacturing** Authorisation Holder and
- the person responsible for final batch release for supply as the Authorised Person (AP)

What are the key changes from the current Code of GMP to the new GMP Guide?

The significant areas of change from the current Code are the requirements for:

1. **Product Quality Reviews (PQR)**, ref 1.4, – Documented regular periodic reviews and / or rolling reviews of all licensed medicinal products including but not limited to:
 - starting material trends,
 - in-process controls,
 - failed batches,
 - deviations,
 - non conformances including out of specification results,
 - effectiveness of corrective / preventive actions,
 - changes to process and / or analytical methods,
 - stability data,
 - complaints/returns/recalls,
 - validation status of equipment, facilities, and processes,
 - technical agreement status,
 - variations which have been submitted, granted or refused to or by TGA and
 - review of post marketing conditions of the MA.

The 2009 GMP Guide makes allowance for grouping of products by type (eg by dosage form) where this can be scientifically justified.

2. **Ongoing Stability**, ref 6.23 -6.33 –This is the requirement that ongoing stability testing (as distinct from, and in addition to, initial long-term stability testing) must be conducted to confirm that the product remains within its shelf-life specifications, under the labelled storage conditions, for its entire shelf life. The ongoing stability status of the product must also be made available to the Authorised Person (AP) who will be responsible for Release for Supply. Manufacturers and sponsors also need to consider the stability of intermediate, or partially-processed, materials and of bulk finished products when they are stored for extended periods of time.
3. **Quality Risk Management (QRM)** ref 1.5 & 1.6 and Annex 20 (which provides examples of QRM systems) – A system must be set up and documented to ensure the evaluation of risk to the quality of the product is based on scientific knowledge, experience with the process and links to the protection of the consumer. The aim is that the level of effort, formality & documentation of the QRM process is commensurate with the level of risk.
4. **Complaints and product recall**, ref 8.7, 8.8 and 8.16 – A new clause has been added to the Code which requires manufacturers to give special attention to establishing whether a product complaint was caused because of counterfeiting. Sponsors who use contract manufacturers need to investigate any concerns about counterfeiting in conjunction with their contract manufacturer(s). There is also a new clause requiring the effectiveness of recall arrangements to be evaluated regularly. Again, sponsors who use contract manufacturers need to consider recall arrangements in conjunction with their contract manufacturer(s).
5. **Release for Supply**, ref 1.4 and 6.31 – Release for Supply is the final step of manufacture where the Authorised Person (AP) must be satisfied that the medicine has been manufactured in accordance with the requirements of the Marketing Authorisation including those of the GMP guide. The AP will then release the product for supply to the market. Where the sponsor is not the Authorised Person, there are implications concerning both on-going stability studies and PQRs.

Together the sponsor and the AP must:

- Ensure that PQRs are conducted in a timely manner
- Identify where corrective actions, preventive actions or revalidation are necessary;
- Ensure that these are carried out and completed;
- Arrange access to information about ongoing stability and PQRs to the AP.

For a full summary of the changes to the Guide see

<http://www.tga.gov.au/manuf/mp2009requirements.pdf>

How are the TGA interpreting the new requirements?

Whilst the TGA is moving from a Code based on the 2002 PIC/S Guide to the January 2009 PIC/S Guide, most of the changes were introduced by the PIC/S in the 2007. As a result, manufacturers of most higher risk products (prescription and OTC medicines), have typically implemented these changes into their processes already, either because they may have multinational corporate requirements or in order to meet EU export requirements. Therefore, the greatest impact of mandating this new Guide is expected to occur where the Australian regulatory environment is significantly different to Europe. These differences affect complementary medicines, sunscreens and the areas of Release for Supply activities as described above.

TGA have committed to preparing and publishing Technical Guidance Documents on their website by the end of April 2010. These will provide interpretative guidance which will assist sponsors and manufacturers to implement the new 2009 GMP Guide. The Technical Guidance Documents can be found by using the following link:

<http://www.tga.gov.au/manuf/twg.htm#cmguides>

The aim of each of the Technical Guidance Documents is to provide an implementation approach that is commensurate to the risk category of the products.

Experts from industry representing ASMI and CHC are working with the TGA on the Complementary Medicine Technical Working Group to provide technical guidance on the interpretation of Ongoing Stability and Product Quality Reviews for listed complementary medicines. These documents are already in draft form; they will also provide guidance on the concept of groupings of products and the circumstances where groupings might be scientifically justified to reduce the cost burden.

Additionally, the need for Technical Guidance Documents has been identified for Release for Supply and Quality Risk Management requirements for all medicinal products as well as a general interpretive guidance for Sunscreen products.

ASMI and CHC have raised concerns with the TGA regarding the challenges of implementation of the Release for Supply requirements where the sponsor is not also the AP. Companies consider the stability and PQR data as highly confidential proprietary information, as it summarises all the significant details for manufacture of their stable medicine.

Currently in Australia under these circumstances release of each step in manufacture of the product culminates in the final step which is release for supply. At each step an appropriate person confirms the release of the previous step(s) along with the current step. The final release for supply reviews and confirms all steps in manufacture for conformance of the product to the marketing authorisation details.

It is recognised that without technical guidance around release for supply, any change to the current scenario described above could create a series of complex and burdensome commercial implications. The CM TWG will be working to produce guidance that addresses this issue.

The finer detail of what will be considered compliant on 1 July 2010 is yet to be finalised in consultation between ASMI/CHC and TGA. It is expected, however, that following mandatory commencement of the 2009 GMP Guide, TGA auditors will expect to see defined and documented plans are in place for compliance. TGA recognise that the implementation of this change from planning to a satisfactory level of compliance could take up to 2 years.

We will provide more information as it becomes available, through industry newsletters and bulletins.

What are the implications to me as a Sponsor of Listed Complementary Medicines?

There are two types of sponsors responsible for ensuring that the new requirements are carried out.

The table below lays out the new requirements for the situation in which the:

1. Sponsor is also the licensed/certified manufacturer (Sponsor/Manufacturer); and
2. Sponsor who contracts the manufacture of all steps of manufacture to one or more contract manufacturers (Sponsor only).

New requirements	Sponsor/Manufacturer situation	Sponsor only situation NB. The contracts between sponsors and their contract manufacturers will need to reflect these changes (see below)
Product Quality Review	See Appendix A and 2009 GMP Guide clause 1.4 and the CM TWG Technical Guidance draft for Product Quality Reviews.	See Appendix A
Ongoing Stability	See Appendix A (7c) and 2009 GMP Guide clauses 6.23 – 6.33 and the CM TWG Technical Guidance draft for On-Going Stability for Listed Medicines	See Appendix A (7c) as per 2009 GMP Guide clauses 6.23 – 6.33
Quality Risk Management (QRM)	See 2009 GMP Guide clauses 1.5 and 1.6 as well as information in Annex 20	Each of the parties involved need to have their own QRM process in place with the sponsor taking the coordinating role
Complaints & Product Recall	See 2009 GMP Guide clauses 8.7, 8.8 and 8.16	With the sponsor taking a coordinating role, each of the parties need to take responsibilities for the relevant actions in complaint clauses 8.7 and 8.8. The sponsor should take responsibility for the recall, clause 8.16.
Release for Supply	See 2009 GMP Guide clause 1.4 and 6.31	A coordinated approach will need to be established to ensure the person conducting Release for Supply has the appropriate information from the agreed responsible parties in a timely fashion with respect to 6.31 – Ongoing Stability and 1.4 – PQR.

If you are a Sponsor/manufacturer, you will be manufacturing your own products. All these new requirements will be performed in house. The new requirements will need management careful oversight to achieve compliance.

However, if you as the Sponsor use one or more contract manufacturers (including contract laboratories or packers), you will need to review the Technical Agreements you hold with them to manufacture, pack or test starting materials and/or finished products. The Agreements will need to specify who will be responsible for the provision of what pieces of data to whom, in order to achieve compliance with the new requirements. For example - If the ongoing stability testing of the finished product is not conducted by the manufacturer who conducts your Release for Supply, you will need an agreement to provide appropriate information about that data.

During negotiation of revised Agreements, sponsors will need to be mindful of the intellectual property implications surrounding PQR and Ongoing Stability for the activity of Release for Supply.

It is anticipated that there will be additional cost associated with the collection and statistical analysis of the data, report preparation and review to conduct a PQR. Your contract manufacturer/s may therefore propose to renegotiate your commercial agreement/s with them for supply of your product.

What should I expect as the next steps/timings to implement these changes?

The TGA published the new Manufacturing Principles in July 2009 and it is expected that the Technical Guidance Documents for interpretive guidance will be available from the TGA website by end of April 2010. As a result there is little time remaining for the preparation of plans to achieve compliance before July 2010. Once the guidances are available, manufacturers should establish a planned approach as quickly as possible to implement the changes into their Quality Management System.

If you are a sponsor who manufactures your own products, you will be doing all these activities in house with the objective of having a documented plan in place by 1 July 2010.

If you are using a contract manufacturer, that organisation should be approaching your company with the aim of renegotiating the Technical Agreements. Where your organisation uses more than one contractor to produce your product, you will need to coordinate the specific responsibilities in the Technical Agreements to ensure each step of manufacture can be achieved efficiently.

Where there are gaps in the data requirements to achieve compliance, you will need to establish plans with your contract manufacturer or another licensed contractor to fill those gaps. Plans for compliance will need to be communicated to and coordinated with the Authorised Person who will be conducting Release for Supply. This may include providing the AP with rolling progress reports.

What if I am unable to establish or agree upon plans for compliance with my contract manufacturer(s)?

Where a contract manufacturer or a separate agent responsible for conducting Release for Supply of your product or other steps in Manufacture has not been able to establish a satisfactory plan to ensure that compliance with these new requirements can be implemented in a timely manner, they may be unable to accept the risk of continuing to manufacture, pack and/or release your product for supply. To do so would jeopardise their licence.

If a contract manufacturer were to take the risk of releasing your product without satisfactory proof of compliance, TGA auditors would report this as a deficiency against the organisation. Should the auditors have serious concerns, they may notify the post market surveillance section of the TGA, who could then issue you, the sponsor with a Section 31 Notice requesting that you submit your product data for review. If for any reason you could not provide this, or it was found to be inadequate, you would be required to take remedial action.

Where can I get more information?

1. Talk to your manufacturer/packer so that you understand their plans to comply with these new requirements.
2. Talk to your industry association who can assist you with information and if necessary identify consultants and/or licensed stability testing facilities to help you prepare for the changes.
3. Contact the Office of Manufacturing Quality, TGA, PO Box 100, Woden ACT 2606.

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Phone: 02 6232 8156

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Yours sincerely



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Appendix A Matrix of Product Quality Review Activities and Suggested Responsibilities for Sponsors who use contract manufacturers

(Note: if your organization makes and releases its own products then you have all the responsibilities in the first, second and third columns of this Appendix table).

RFS: Release for Supply

Note: The responsibilities may be re-assigned to each other or shared but must be clearly detailed in the GMP/Technical/Quality Agreement.

Note: the following table has separated out the responsibilities of the packer and the release for supply which is combined in the technical guidance draft for both On-going stability and Product Quality Review. This has been done to assist industry's understanding.

Details of Clause 1.4 area	Bulk Manufacturer	Packer	RFS	Sponsor
1a Review starting materials used in bulk manufacture, especially those from new sources	Responsible			
1b Review starting materials used in packing activity, especially those from new sources		Responsible		
2a Review critical in-process controls in bulk manufacture	Responsible			
2b Review finished product results	Responsible			
2c Review critical in-process controls in packing		Responsible		
3a Review of all bulk batches that fail to meet established specifications and their investigation	Responsible			
3b Review of all packed batches that fail to meet established specifications and their investigation		Responsible		
4a Review all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken regarding bulk manufacture	Responsible			
4b Review all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken regarding testing	Responsible			
4c Review all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventative actions taken regarding packing activities		Responsible		
5a A review of all changes carried out to the bulk manufacturing processes	Responsible			
5b A review of all changes carried out to analytical (<i>and other</i>) testing methods	Responsible			
5c A review of all changes carried out to the processes involved in the packing activity		Responsible		

Details of Clause 1.4 area	Bulk Manufacturer	Packer	RFS	Sponsor
6 Review the Marketing Authorisation variations submitted/granted/refused, including those for third country (export only) dossiers			Responsible	Responsible
7a Review the results of the initial long term stability of the bulk product monitoring program and any adverse trends	Responsible			
7b Review the results of the initial long term stability of the market product monitoring program and any adverse trends			Responsible	Responsible
7c Review the results of the ongoing stability of the market product monitoring program and any adverse trends			Responsible	Responsible
8 Review all quality-related returns, complaints and recalls and the investigations performed at the time			Responsible	Responsible
9a Review the adequacy of any previous product process or equipment corrective actions relating to manufacture of the bulk product	Responsible			
9b 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 authorisations and variations to marketing authorisations			Responsible	Responsible
11a Review the qualification status of relevant equipment and utilities eg HVAC, water, compressed gases relating to manufacture of the bulk product.	Responsible			
11b 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 review.		Responsible		
12a Review any contractual arrangements relating to the manufacture of the bulk product as defined in Chapter 7 (<i>of the code</i>) to ensure that they are up to date	Responsible		Responsible	Responsible
12b Review any contractual arrangements relating to the manufacture of the market product as defined in Chapter 7 (<i>of the code</i>) to ensure that they are up to date		Responsible		Responsible
13 Overview review of the Product Quality Review programs			Responsible	Responsible