Technical guidance on the interpretation of manufacturing standards

On-going stability testing for listed complementary medicines
Technical Working Group (TWG) on complementary medicines

Version 1.1, June 2013
About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, 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. 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 <http://www.tga.gov.au>.
## Version history

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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 1989*, and the Therapeutic Goods Regulations, 1990 for legislative requirements and the relevant Code of GMP or Quality Management System Standard for technical requirements.

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
Purpose

This guidance is intended to clarify the interpretation of the cGMP Standard requirements in relation to On-Going Stability Testing Requirements for Listed Complementary Medicines.

Scope

This guidance is relevant to Listed Complementary Medicines.

Definitions

Bulk product

Any product which has completed all processing stages up to, but not including, final packaging.

Intermediate product

Partly processed material which must undergo further manufacturing steps before it becomes a bulk product.

On-going stability

A programme to monitor the stability of a marketed product over its shelf life.
Flowchart for on-going stability programme

Finished packed product

2. Development of the stability protocol
The protocol for an on-going stability program should extend to at least the end of the shelf life period. Where herbal ingredients are present, chromatographic profiling should be considered for inclusion in the protocol. Minimum testing for a mineral in an organic form is start and end of the stability study. Relevant physical, chemical, biological and microbiological testing shall be included to support the marketed shelf life of the product as appropriate.

1. Method development and validation
Analytical methods must be validated and stability indicating. NB. Compendial methods may not fulfil this requirement. Methods are researched, developed and validated for the product or a group of products.

3. Full scale batch production
Production batches are manufactured and packed into selling units.

3 1. Stability protocol
The Stability Study Protocol is designed specifically for the finished product and the target market country. The testing requirements and storage conditions in the study design must meet the regulatory requirements of the country/s the product will be sold into. Validated analytical methods are used for testing the finished product.

4. On-going stability program
A minimum of one (1) production batch per product group per year should be placed on On-Going Stability under the predetermined study protocol.

4 1. Rework/reprocessing considerations
Any production batches which have undergone any significant change or significant deviation to the process or package, any rework, reprocessing or recovery operation should also be considered for inclusion on the On-Going Stability programme.

5. Monitoring the stability study
At each time point, the results of the stability study are reported and reviewed. Data should be reviewed to identify out of trend and out of specification results. All chromatographic data from the previous time point should be compared with the latest reports to identify any changes in the product. Microbiological testing should be considered throughout the study to support compliance with the expiry specifications, as a minimum at the start and end of the study and be consistent with the requirements of TGO 77 – Microbiological Standards for Medicines
Guidance

Introduction

Stability testing for complementary medicines is mandatory for compliance with the Australian Regulatory Guidelines for Complementary Medicines (ARGCM) and the Guide to GMP for Medicinal Products requirements. The Quality Control section of the Guide to GMP for Medicinal Products Part 1 titled On-Going Stability Programme from point 6.23 to 6.33 are the areas of compliance required.

One batch of a product of each group should be placed on the on-going stability programme each year.

Bulk and Intermediate products should also be considered as part of an on-going stability programme, particularly where bulk product is stored prior to being packaged and/or transported from a manufacturing site to a packaging site. The impact of storage of bulk and or intermediate products on the stability of the packaged product should also be evaluated and through a risk assessment process it should be determined whether further studies are deemed necessary.

General

The ongoing stability should be conducted in line with the regulatory guidelines for the country/s of destination and this should be considered when a sponsor first commences the stability program.

Conditions

Stability testing for complementary medicines should be conducted at real time at the storage conditions specified on the product label.

e.g.

- $30^\circ C \pm 2^\circ C / 65\% \pm 5\% RH$ when the label storage conditions are “store below $30^\circ C$” or
- $25^\circ C \pm 2^\circ C / 60\% \pm 5\% RH$ when the label storage conditions are “store below $25^\circ C$”, or
- $5^\circ C \pm 2^\circ C$ when the label storage condition is store below $8^\circ C$ (refrigerate).

Other incubation conditions may need to be considered for export countries depending on their regulatory requirements.

Groupings

In recognition of the reduced risk generally associated with complementary medicines a grouping approach can be undertaken with stability studies. Scientific justification of the rationale should be documented to establish product groupings.
Justifications should be based on groupings whereby products have similarly constructed formulations and with a similar method of manufacture. The packaging of the product as well as the dosage form should also be taken into consideration when putting together justifications for groupings.

Examples of groupings which may be used include but are not limited to:

1. **Different dose forms**
   - Solutions
   - Suspensions
   - Creams
   - Ointments
   - Tablets (via Direct Compression (DC) process)
   - Tablets (via Granulation process)
   - Capsules (two-piece, via Dry Mixing process)
   - Capsules (two piece, via Granulation process)
   - Soft Capsules (Softgels) containing solution fills
   - Soft Capsules (Softgels) containing suspensions fills, powder mixes

2. **Different formulation types**
   - Multi-component vitamin/mineral/herbal solid-dose tablet based on common formulation.
   - Vitamin tablet containing only one active, even if excipients similar to above.
   - Vitamin tablet containing same active, but sustained- rather than immediate-release.

An on-going stability programme commences when a batch of product within a group is placed on the stability programme, providing that the justification is documented for this particular product being representative of the grouping. Rotating of products within a group would also be acceptable providing that a documented justification is signed off prior to the batch commencing on the on-going stability programme.

Where there are several manufacturer/s used by a sponsor and a product is being manufactured and packaged with more than one company or if a manufacturer has several sponsors which have similar formulations which could theoretically be grouped for stability purposes then consideration should be given to confidentiality issues by all parties involved. Individuals conducting Release for Supply need to have adequate information to support the shelf life of the product being released.

**Test methods**

Test methods used for the stability testing of products need to be stability indicating and be validated to a standard consistent with the requirements of the TGA's Finished Product (Medicine) Analytical Procedure Validation for Complementary Medicines. It should be noted that not all compendial methods are stability indicating.
However it is not necessary to monitor the level of impurities for Complementary Medicines.

Methods should be validated for specificity and robustness as a minimum and in accordance with the TGA's Finished Product (Medicine) Analytical Procedure Validation for Complementary Medicines.

**Design of stability protocol**

A stability protocol should be designed to incorporate the following factors for stability testing:

- Physical testing parameters specific to the medicinal product including pack integrity.
- Active ingredients which are claimed on the label quantitatively will be tested throughout the study by validated stability-indicating methods. Should full stability data for the support of the product listing shelf life be available for all active ingredients as per the label claim then reduced testing may be considered with a documented risk assessment and justification for reduced ongoing stability testing. If product groupings for stability are being utilised then reduced testing for on-going stability needs to be in accordance with shelf-life stability testing.
- For mineral actives ingredients the content of inorganic salts is expected not to vary over the shelf life of the product, after QC release testing has been completed. Mineral active ingredients only need to be tested during on-going stability where the mineral is present in an organic form, unless otherwise justified. Testing of minerals in an organic form should be conducted at the initial time point and at the end of the study as a minimum.
- Microbiological testing should be conducted at the initial and the end time points of the study as a minimum, including Preservative Efficacy Testing (PET) as necessary (e.g. liquids and semi-solids).
- Biological testing (e.g. enzymes, probiotics) shall be tested throughout the study.
- Products which contain herbal ingredients where no standardised component is claimed should be considered for chromatographic profiling, based on the ingredients added to the individual batches. For complex products containing multiple herbal ingredients it may be useful as part of the stability development stage to monitor chromatographic changes in individual herbal ingredient profiles.
- The stability study shall be conducted in accordance with the predetermined protocol, which should be in line with the ICH Guideline time points for stability testing.

**Product change / regulatory considerations**

If a product is changed, then a risk assessment should be conducted to determine whether a new stability study is required to confirm that the change has not impacted the product adversely. Some points of change to consider would be as follows:

- The type of active e.g. herbal active which has been manufactured with different solvents of extraction (excluding permitted variations in solvent mixture ratios), changing from an extract to a dried herb, or simply a different type of herb whereby the ARTG entry would need to be amended to create a separate and distinct good.
• Mineral constituents changing from one form to another e.g. oxide to chelated mineral.

• Naturally derived actives e.g. Glucosamine HCl to Glucosamine sulphate 2KCl or simply a change from one manufacturer to another.

• Changing from a granulated product to a dry mix formulation or from a liquid to a gel.

• Significant changes to excipients which may impact on product specifications e.g. Lubricant, binders, disintegrants, suspension agents, gelling agents, sweetners, colours, flavours, emollients, preservatives which may impact on the availability of the active ingredients.

• Any production batches which have undergone any significant change or significant deviation to the process or package, any rework, reprocessing or recovery operation should also be considered for inclusion on the On-Going Stability programme.

• Packaging type changes e.g. changing from a blister pack to a HDPE bottle with induction sealing.

**Documentation**

A summary of all the data generated, including any interim conclusions on the programme, should be written and maintained. This summary should be subjected to periodic review.

Where analytical data is found to be out of specification or where an atypical trend is observed a formal investigation should be conducted and where the shelf life of the product could be compromised, a risk assessment should be performed.

Subsequent production batches should be labelled with a reduced shelf life to reflect the actual shelf life achievable.

On-going stability study reports should be made available to the Authorised Person responsible for product release and be available to the TGA for review when requested.

On-going stability reports should be summarised and authorised by a suitably experienced and qualified individual with a quality and/or technical and/or regulatory background for inclusion in the Product Quality Review.

**Monitoring the stability study**

At each time point, the results of the stability study are reported and reviewed. Data should be reviewed to identify out of trend and out of specification results. All chromatographic data from the previous time point should be compared with the latest reports to identify any changes in the product. Microbiological testing should be considered throughout the study to support compliance with the expiry specifications, as a minimum at the start and end of the study and be consistent with the requirements of TGO 77 – Microbiological Standards for Medicines.

**References**

• *PIC/S Guide to Good Manufacturing Practice for Medicinal Products- 15 January 2009, including Annexes*
• *Australian Regulatory Guidelines for Complementary Medicines*

• *Finished Product (Medicine) Analytical Procedure Validation for Complementary Medicines March 2006*

• *Therapeutic Goods Order 77 Microbiological Standard for Medicines*

• *Therapeutic Goods Order 78 Standard for Tablets and Capsules*