



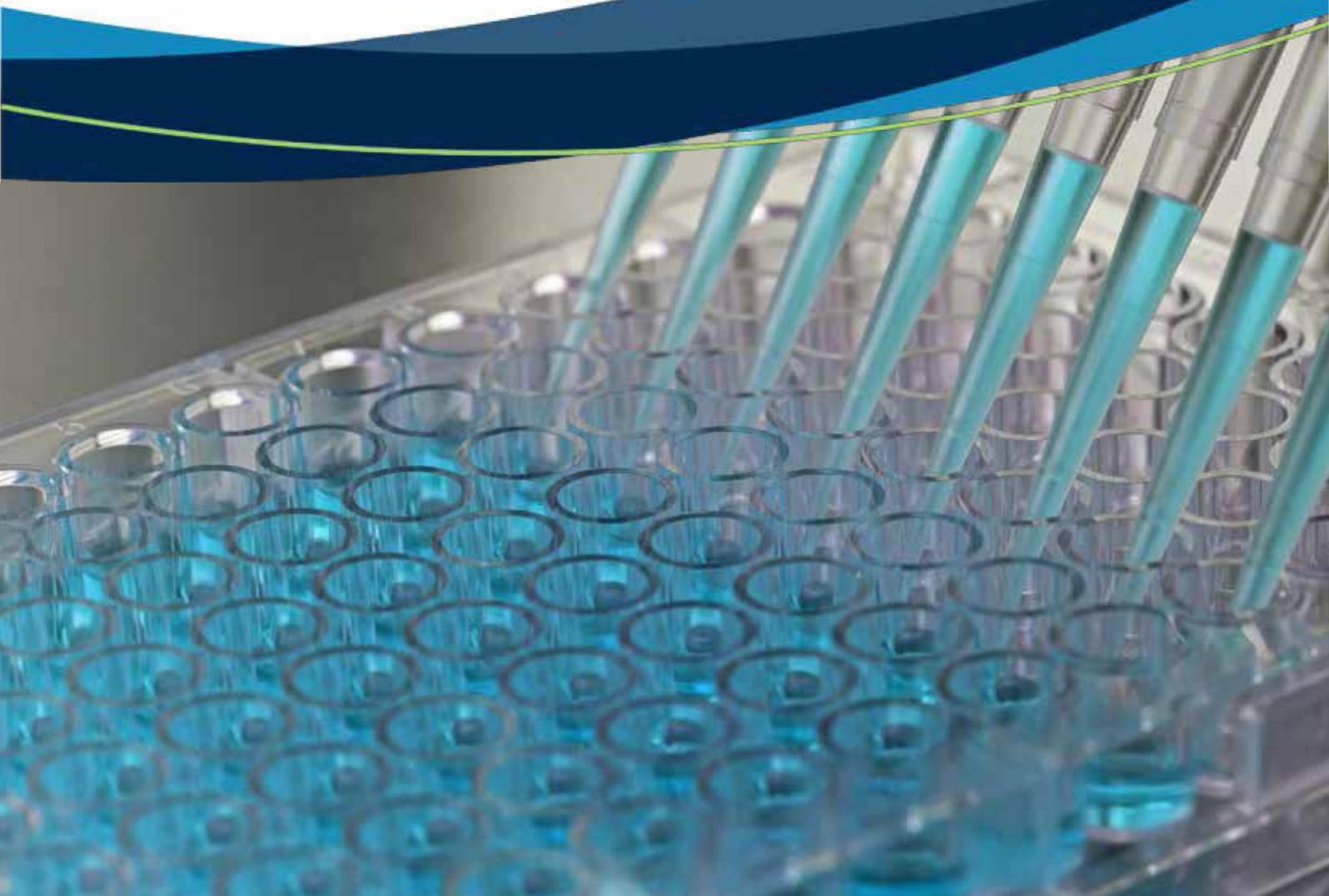
Australian Government
Department of Health
Therapeutic Goods Administration

Ongoing stability testing 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



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About this guidance

This guidance is for manufacturers and sponsors of listed and complementary medicines manufactured according to the PIC/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 ongoing stability testing requirements for listed and complementary medicines.

This guidance addresses compliance with the 'On-going stability programme' section of Chapter 6 – Quality Control in Part 1 of the PIC/S Guide to GMP.

Evidence for the stability of medicines is an important part of quality control and is used to justify shelf life and storage conditions.

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.

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.

Related guidance

The following guidance is relevant:

- [Stability testing of listed complementary medicines](#)
- [Stability testing for sunscreens](#)
- [Conducting on-going stability studies](#)

The TGA has adopted a number of [EU guidelines on stability testing](#).

Responsibility for the ongoing stability program

Stability testing for listed and complementary medicines is mandatory. All responsibilities related to ongoing stability testing should be defined in a GMP agreement (unless the sponsor, manufacturer and authorised person conducting release for supply are all from the same entity).

The sponsor needs to:

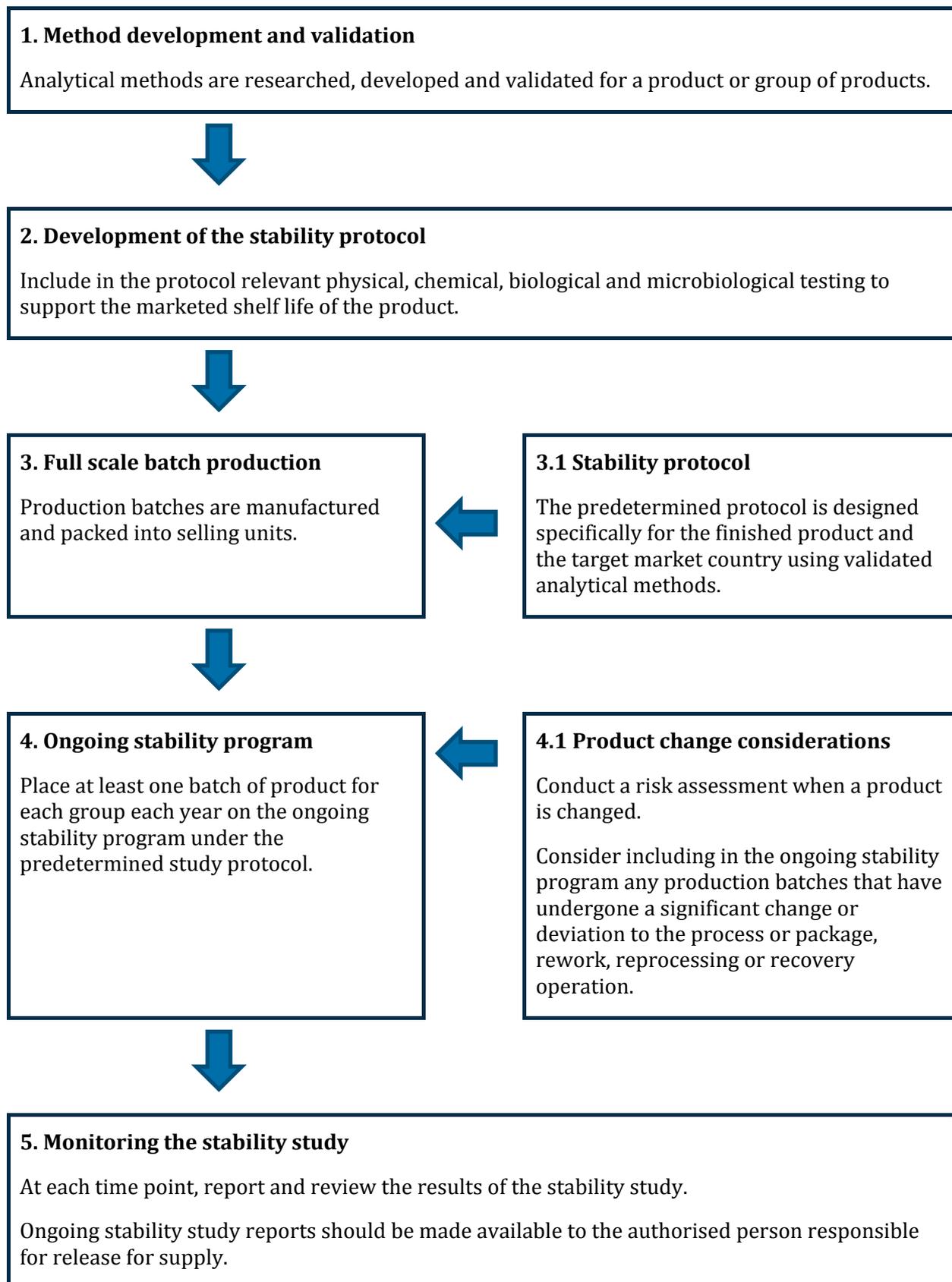
- ensure that there is stability data to support the shelf life of the product
- have access to the laboratory results

The individuals conducting release for supply need to:

- have adequate information to support the shelf life of the product being released
- have adequate information to confirm that the batch meets the requirements for marketing authorisation

The stability testing program can be contracted out to third parties. This can include physical storage under the specified controlled conditions and undertaking the testing at the specified time points.

Flowchart for ongoing stability program



1. Method development and validation

Analytical methods are researched, developed and validated for a product or group of products.

The methods used for the stability testing of products need to be **stability-indicating**. Please note that not all compendial methods are stability-indicating.

As a minimum, validate methods for specificity and robustness in accordance with the TGA's [Finished product \(medicine\) analytical procedure validation for complementary medicines](#).

It is unnecessary to monitor the level of impurities for listed and complementary medicines.

2. Development of the stability protocol

The initial stability study shall be conducted in accordance with a predetermined protocol, which should be in line with the ICH Guideline time points for stability testing. Ongoing stability studies may use different time points as the data is used to confirm that the product remains stable over its shelf life if the initial studies have already been confirmed as acceptable.

Include in the protocol relevant physical, chemical and microbiological testing to support the marketed shelf life of the product. The protocol for an ongoing stability program should extend to at least the end of the shelf life period.

Target market countries

Conduct the ongoing stability program in line with the regulatory guidelines for the countries of destination. The testing requirements and storage conditions in the study design must meet the regulatory requirements of the countries the product will be sold into.

The different regulatory requirements of different countries need to be considered when a sponsor first commences the stability program.

Conditions

Conduct stability testing in real time at the storage conditions specified on the product label.

For example, when the label storage conditions are:

- 'store below 30°C', conduct studies at $30 \pm 2^\circ\text{C}$ and $65 \pm 5\%$ relative humidity
- 'store below 25°C', conduct studies at $25 \pm 2^\circ\text{C}$ and $60\% \pm 5\%$ relative humidity
- 'store below 8°C (refrigerate)', conduct studies at $5 \pm 2^\circ\text{C}$

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

Types of product

Ongoing stability testing is of the finished packed product.

Consider whether [bulk product](#) or [intermediate product](#) should also be part of the ongoing stability program, particularly where bulk product is stored prior to being packaged or transported from a manufacturing site to a packaging site. To determine whether further studies are necessary, use a risk assessment process to evaluate the impact of storage of bulk and intermediate products on the stability of the packaged product.

In general, further studies may be appropriate if storage is more than:

- 1 month for liquids
- 3 months for solids

Types of testing

Physical testing parameters

Include physical testing parameters specific to the medicinal product, including pack integrity.

Microbiological testing

Consider microbiological testing throughout the study to support compliance with the expiry specifications. At a minimum, conduct microbiological testing at the initial and the end time points of the study.

Types of active ingredients

Active ingredients labelled quantitatively

Test the active ingredients that are claimed on the label quantitatively throughout the study using validated stability-indicating methods.

Reduced ongoing stability testing may be acceptable, with a documented risk assessment and justification, if full stability data for the support of the product listing shelf life is available for all active ingredients as per the label claim.

Mineral actives

For mineral active ingredients in an organic form, when possible, choose test methods specific for the organic form of the mineral. If this is not done, or an alternative test method is used, provide a justification. As a minimum, test minerals in an organic form at the initial time point and at the end of the ongoing stability study.

For mineral actives ingredients that are not in an organic form, the content of inorganic salts is expected not to vary over the shelf life of the product, after quality control release testing has been completed.

Herbal ingredients

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.

3. Full scale batch production

In full scale batch production, batches are manufactured and packed into finished product packaging.

3.1 Stability protocol

The predetermined protocol is designed specifically for the finished product and the target market country using stability-indicating validated analytical methods.

4. Ongoing stability program

At least one batch of product from each group each year should be placed on the ongoing stability program under the predetermined study protocol.

Grouping

A grouping approach can be undertaken with stability studies of listed and complementary medicines, because of the lower risk generally associated with these medicines. Document the scientific justification of the rationale used to establish product groupings.

Base your justifications on the products having similarly constructed formulations, the same dosage form, method of manufacture and primary packaging materials.

Groups that require separate stability studies

Groups that may require separate stability studies include, but are not limited to:

1. different dose forms
 - solutions
 - suspensions
 - creams
 - ointments
 - tablets
 - two-piece capsules
 - 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

3. different packaging
 - glass bottle
 - specific type of plastic bottle
 - blister platform
 - laminated tube

Representative products

Document the justification for a particular product being representative of the group.

- A product with a complex formulation containing multiple active ingredients with a generic base could be selected as the worst case to represent a group of products that contain one of the active ingredients with the same or similar base formulation.

The ongoing stability program for the group commences when a representative product is placed on the stability program.

You can also rotate products within the group, provided that a documented justification is signed off prior to the batch being placed on the stability program.

Confidentiality issues

All parties involved should consider confidentiality issues when:

- a sponsor uses several manufacturers and a product is being manufactured and packaged by more than one company
- a manufacturer has several sponsors with similar formulations that could theoretically be grouped for stability purposes

4.1 Product change considerations

Conduct a risk assessment when a product is changed, to determine whether a new stability study is required to confirm that the change has not impacted the product adversely.

Consider including in the ongoing stability program any production batches that have undergone a significant change or deviation to the process or package, rework, reprocessing or recovery operation.

The *On-going stability programme section* in Chapter 6 of the PIC/S Guide to GMP states that:

- an ongoing stability study should be conducted after any significant change or significant deviation to the process or package
- any reworking, reprocessing or recovery operation should also be considered for inclusion

5. Monitoring the stability study

At each time point, report and review the results of the stability study. Review the data to identify [out-of-trend \(OOT\)](#) and [out-of-specification \(OOS\)](#) results.

Compare all data from the previous time point with the latest reports to identify any significant changes in the product.

Documentation

Maintain a written summary of all the data generated, including any interim conclusions on the program. Review this summary periodically.

- Where analytical data is found to be OOS or where an atypical trend is observed, conduct a formal investigation.
- Where the shelf life of the product could be compromised, perform a risk assessment. Label subsequent production batches with a reduced shelf life to reflect the actual shelf life achievable.

Ongoing stability study reports

Ongoing stability study reports should be available to:

- the authorised person responsible for release for supply
- the sponsor
- the TGA for review when requested

Ongoing 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.

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: on-going stability testing for listed complementary medicines – Technical Working Group (TWG) on complementary medicines'	Office of Manufacturing Quality	30/06/2010
V1.1	Template change	Office of Manufacturing Quality	02/06/2013
V2.0	Change in title and scope Restructured and updated to be consistent with PE009-13, PIC/S Guide to GMP	Manufacturing Quality Branch Regulatory Guidance Team	16/01/2019

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