Australian Government
Department of Health
Therapeutic Goods Administration

Stability testing for prescription medicines

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TGA Health Safety Regulation

Contents

Introduction

This guidance applies to sponsors submitting applications to register a prescription medicine on the Australian Register of Therapeutic Goods (ARTG). It:

- identifies the European Union guidelines for stability testing that have been adopted by the TGA for testing the active substance and the drug product
- explains additional information that may be required to include in Module 3 of the Common Technical Document (CTD) to demonstrate stability of the medicines under Australian conditions.

The information requested in this guidance is to be included in the relevant CTD modules.

14.1 What medicines require stability testing

This guidance applies mainly to:

- prescription medicines containing active substances prepared by chemical synthesis
- prescription medicines containing active substances that are pure chemical entities isolated from a natural source (e.g. vincristine, digoxin)
- prescription medicines containing active substances produced by microbial fermentation (e.g. many antibiotics and some anticancer agents)
- radiopharmaceuticals
- biotechnological medicines
- biological medicines.

Note about Radionuclide generators

This guidance does not cover radionuclide generators.

Information required on the stability of radionuclide generators varies with each case. Advice on requirements for a particular generator system may be obtained from Australian Radiation Protection and Nuclear Safety Agency (ARPANSA).

14.2 General guidance

14.2.1 The purpose of stability testing

The purpose of stability testing is to determine how an active substance and a drug product vary with time under a variety of environmental conditions, including:

- high temperature
- high humidity
- exposure to light.

Stability testing is used to:

- establish the retest period for an active substance
- determine the appropriate storage conditions for a medicine
- establish the shelf life for a medicine.

Note

A medicine may be tested at any time during its period of use by either:

- the methods of the pharmacopoeia

  OR

- in the absence of a pharmacopoeial method, a suitable or alternative method that has been reviewed and approved by the TGA.

Advise manufacturers that they may need to apply more stringent test limits at the time of release of a batch of the medicine in order to ensure compliance throughout its shelf life.

Consolidated list of related European Union guidelines

- Note for guidance on stability testing: stability testing of new drug substances and products (CPMP/ICH/2736/99)
- Guideline on stability testing: stability testing of existing active substances and related finished products (CPMP/QWP/122/02, rev 1 corr)
- Quality of biotechnological products: stability testing of biotechnological/biological products (CPMP/ICH/138/95)
- Note for guidance on bracketing and matrixing designs for stability testing of drug substances and drug products (CPMP/ICH/4104/00)
- Photostability testing of new active substances and medicinal products (CPMP/ICH/279/95)
- Note for guidance on stability data package for registration in climatic zones III and IV (CPMP/ICH/421/02) (Adopted with annotations)
- Note for guidance on in-use stability testing of human medicinal products (CPMP/QWP/2934/99)
- Note for guidance on development pharmaceutics (CPMP/QWP/155/96)
- Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product (EMEA/CHMP/QWP/396951/2006).
- Note for guidance on maximum shelf life for sterile products after first opening or following reconstitution (CPMP/QWP/159/96 Corr).
- Note for guidance on evaluation of stability data (CPMP/ICH/420/02)
- Note for Guidance on Biotechnological/Biological Products Subject to Changes in their Manufacturing Process (CPMP/ICH/5721/03)

14.2.2 Active substance stability testing

Stability testing of active substances is required to establish:

- the inherent stability characteristics of the molecule, particularly the degradation pathways
- the identity of degradation products formed
- the suitability of proposed analytical procedures for quantification of both the active substance and degradation products.

14.2.3 Drug product stability testing

The design of the formal stability study for a drug product should be based on the known properties and stability of the active substance(s) at the intended storage conditions of the prescription medicine.

Australian climate: specific stability requirements

Major population centres in Australia experience a combination of high humidity and high temperature during the summer. These areas are classified as Zone IV regions.

- Ensure stability studies for medicines to be registered in Australia are performed under conditions representative of Zone IV regions.

Related information and European Union guidelines

- WHO Technical Report Series
- Note for guidance on stability data package for registration in climatic zones III and IV (CPMP/ICH/421/02) (Adopted with annotations)

Photostability studies

- Provide evidence to demonstrate that light exposure does not result in unacceptable changes to the medicine.

Related European Union guidelines

- Photostability testing of new active substances and medicinal products (CPMP/ICH/279/95)

14.2.4 In-use stability testing on medicines for multi-dose use

For medicines intended for multi-dose use:

- provide evidence that repeated access (i.e. opening and closing) does not affect the physical, chemical or microbiological quality of the medicine.

For bottles containing solid dosage units (e.g. capsules) that are to be refrigerated provide information or a justification that addresses:

- the possibility of moisture condensation after repeated openings and closings of the bottle
- effects of condensation on the medicine.

Related European Union guidelines

- Note for guidance on in-use stability testing of human medicinal products (CPMP/QWP/2934/99)

14.2.5 Reconstituted and/or diluted prescription medicines

For medicines that may be diluted or reconstituted with a range of solutions, for example a parenteral medicine that is diluted for intravenous infusion:

- provide stability data that establishes compatibility with each recommended diluent at the extremes of the recommended dilution ratios for the permitted duration of storage. Testing of reconstituted and /or diluted solutions include:
  - pH
  - clarity/particulate matter
  - assay and (if assay sensitivity allows)
  - degradation products.

Where storage at 2-8 °C is not possible because of adverse effects on the medicine:

- specify and justify the maximum time for storage at room temperature (not more than 6 hours).

If the reconstituted and/or diluted medicine may be kept for longer than 24 hours at 2-8 °C (or 6 hours at >8 °C):

- provide data to show that when the medicine is presented with a microbial challenge (similar to a preservative efficacy test), ideally there is evidence of microbial death. However the minimum requirement is demonstrating stasis (i.e. not more than 0.5 $\log_{10}$ units higher than the initial value of the inoculum) over the proposed storage period.

The Product Information (PI) for injections that are intended to be reconstituted or diluted should include the direction:

> 'To reduce microbiological hazard, use as soon as practicable after reconstitution/preparation. If storage is necessary, hold at 2–8 °C for not more than 24 hours'

or words to that effect.

14.2.6 Container, container closure and delivery device effects on liquids

The stability of liquid medicines may be affected by the components of the storage containers, container closures and delivery devices.

For parenteral, ophthalmic, inhalation medicines, and medicines used with a delivery device (such as infusion pump) provide data on investigations relating to the possibility of substances leaching from the container or device into the medicine.

Pay particular attention to:

- extractable substances leaching from outside the primary container, if manufactured from semi permeable materials, into the medicine (e.g. adhesives used to affix labels to the bottle)
- additives in plastics and elastomers, and their possible degradation products that may form during the manufacturing steps, especially during filling and sterilisation steps and storage
- plastic components of metered-dose aerosols
- injectables and opthalmics supplied in non-glass containers, with a plastic or rubber stopper.

To determine whether contact with the container closure affects the container integrity and/or the stability of liquid medicines in containers (other than ampoules):

- provide the stability data conducted with the liquid medicine stored in the inverted position to maximise contact with all parts of the container, the container closure (e.g. rubber stopper) and/or delivery device.

Related guidance

- Inhalation and nasal medicines

14.2.7 Preservative efficacy

Stability testing for a preserved medicine includes testing of the physical, chemical, biological and microbiological attributes and preservative content of the medicine that are susceptible to change during storage are likely to influence quality, safety or efficacy.

Related European Union guidelines

For guidance on the stability testing for a preserved medicine:

- Note for guidance on stability testing: Stability testing guidelines: stability testing of new drug substances and products (CPMP/ICH/2736/99)

For guidance on preservatives in liquid and semisolid formulations that are not self-preserving, refer to the European Union guideline:

- Note for guidance on development pharmaceutics (CPMP/QWP/155/96)
- Guideline on excipients in the dossier for application for marketing authorisation of a medicinal product (EMEA/CHMP/QWP/396951/2006).

For guidance on:

- the requirements of the PI for a sterile medicine to include information on how long the medicine may be used after opening
- the requirements for a microbiological simulated in-use study to justify the open shelf life for certain dosage forms, such as injectables and eyedrops. The chemical stability of the preservative over the open shelf life should also be demonstrated

Refer to:

- Note for guidance on maximum shelf life for sterile products after first opening or following reconstitution (CPMP/QWP/159/96 Corr).

Specific guidance related to Biotechnological products:

- Quality of biotechnological products: stability testing of biotechnological/biological products (CPMP/ICH/138/95)

Related guidance

- Microbial quality of prescription and over-the-counter medicines

14.2.8 Presenting data in a registration application

- Include, where possible, quantitative results rather than a statement that the medicine complies with a particular specification.
- Discuss all results.
- Give explanations where necessary, for example:
  - for anomalous or unusual results
  - for change in analytical methods
  - change in appearance
  - whether mass balance has (or has not) been achieved with respect to assay and degradation products.

14.3 Chemically derived medicines: specific requirements

14.3.1 Predicting shelf life from stability data

The maximum shelf life for chemically derived medicines is normally five years.

- Provide the stability data to support the proposed retest period for active substances and shelf life for a medicine.
- Justify any extrapolation beyond the period covered by available data.
- Take into account the worst-case situation at batch release. For example:
  - For medicine that has a lower assay release limit of 95 per cent and a lower assay expiry limit of 90 per cent, the maximum decrease in assay allowed over the shelf-life is 5 per cent.
  - Similarly, for a medicine that has a release limit for an individual impurity of 0.2 per cent and an expiry limit of 0.5 per cent, the maximum increase in the impurity allowed over the shelf life is 0.3 per cent.
  - For the same medicine, if the actual release assay result is 101 per cent, then the shelf life should be determined at the time the medicine (or confidence interval of the regression line) decreases by 5 per cent and reaches 96 per cent, rather than the expiry limit (90 per cent). This takes into account the possibility of batches being released at the lower release limit (i.e. 95 per cent) and ensures they will comply with the expiry limit throughout the shelf life.

- Similarly, if the actual impurity content is 0.1 per cent at batch release, the shelf life should be determined as the time the 95 per cent confidence interval reaches 0.4 per cent (i.e. increases by 0.3 per cent).

Maximum extrapolated shelf life for a medicine

The maximum extrapolated shelf life is normally three years.

For a shelf life longer than three years:

- include real-time data on production batches stored under the maximum recommended storage conditions for the duration of the proposed shelf life.

Related European Union guidelines

- Note for guidance on evaluation of stability data (CPMP/ICH/420/02)

14.3.2 Extending the shelf life of individual batches of chemically derived medicines

The TGA may approve a limited extension of shelf life for individual batches of chemically derived medicines that are approaching their expiry date.

The prerequisites for this approval include:

- the existing shelf life should be at least two years
- real-time stability data that either
  - validate the existing shelf life and show no significant deterioration of the medicine during this period
  - extrapolation of stability data shows that the medicine will comply with the expiry specification after storage at the maximum recommended storage temperature for the duration of the proposed extension period
- a certificate of analysis that is less than two months old at the time of application showing compliance with specifications for the batch near its expiry date, together with the results obtained at batch release
- an assurance that a stability study to validate a permanent extension of the shelf life has or will commence, if relevant.

Note

Prospective extensions of more than six months or extensions that result in a shelf life of more than five years are not normally acceptable. If there are extenuating circumstances include a justification for consideration.

14.3.3 Self-assessable request for shelf-life extensions

This relates to variations for a registered prescription medicine.

The shelf-life of a medicine may be extended through the self-assessable request (SAR) process. Amongst other requirements for a shelf-life extension, ensure that the supporting stability has been generated using a stability testing protocol explicitly approved for this purpose by the TGA.

Approval of such a protocol may be applied for at the time of product registration or subsequent to registration. For the proposed protocol include all of the following:

- included in the stability trial at least three production batches of the registered product in the marketing container/closure system
- state the storage conditions and duration of tests
- state details of the tests to be performed and the test methods to be used
- state acceptance criteria for the tests performed. This should generally be tighter than the approved expiry limits, particularly for quantifiable test parameters such as assay, degradation products, dissolution, disintegration etc. (this is to provide a safety margin for sponsor self-assessment of the test results)
- provide a matrix indicating the time stations at which testing will be conducted.

Note

The stability data generated according to such a protocol may be self-assessed against the acceptance criteria stated in the protocol. If all test results are within the limits, the product shelf-life may be extended using the SAR process stated in Minor variations to registered prescription medicines: Chemical entities.

If some of the test results are outside the approved protocol limits but within the registered expiry limits, the stability data may be submitted as a minor variation application to the TGA.

- Include a justification as to why the shelf-life should be extended.

14.4 Biological medicines: specific requirements

14.4.1 Biological medicine stability testing

We evaluate stability data for biological medicines on a case-by-case basis, with regard to:

- the nature of the medicine
- the methods of analysis (physical, chemical, biological) that are appropriate for that medicine:
  - it may not always be possible to establish degradation pathways and identify decomposition products formed in significant amounts
  - the use of only compendial methods is not acceptable unless it has been demonstrated that the methods used are able to detect critical degradation pathways for that product
  - use of only physicochemical assay techniques, such as chromatographic methods for decomposition products, may not always be appropriate for biological medicines.

14.4.2 Predicting shelf life of biological medicines from stability data

The maximum shelf life permitted by the TGA for biological medicines is normally three years, but longer may be justified by supportive data.

The degradation of biological medicines is not usually amenable to kinetic analysis and extrapolation from accelerated testing. All biological medicines require real-time stability data. All approved shelf lives will be no longer than the real-time data submitted to support them.

Trend analysis (either linear or exponential nonlinear regression) may be done by the TGA on consolidated real time datasets, and the overall trend is regarded as more important than the individual data points.

Example

For example, consider a medicine that loses a mean of 6 per cent potency each year and whose label claims a lower expiry specification of 90 per cent. All batches in the stability study have an initial potency of 105 per cent (without an approved overage), therefore all batches appear to comply over the proposed shelf life of 24 months. However, the approved shelf life will be 18 months because, if the medicine is filled to target (100 per cent) potency and loses 6 per cent potency each year, it is likely to reach its expiry specification after only 19.2 months.

14.4.3 Stability data for biological medicine applications

For biological medicines:

- Provide stability data generated from at least three batches manufactured using the commercial process or earlier processes unchanged in scale and method from the commercial scale.
- A content assay (e.g. HPLC, ELISA) is not sufficient unless the content assay is a pharmacopoeial activity assay (e.g. insulin or somatropin).
- For medicines with two storage temperatures (e.g. 1 month at <25 °C and 23 months at 2-8°C), provide a study using both temperatures in a worst-case scenario (e.g. high temperature first, then low temperature).
- For time out of refrigeration (TOR), sponsors should define and justify the time the medicines are out of recommended storage conditions during manufacture, up to the point of return to the recommended storage conditions. Justification should include real-time data to support the TOR worst case scenario.

14.4.4 Shipping and stability data

Stability data are required to indicate acceptable duration and magnitude of temperature excursions during shipping.

Real time data should be provided to support the proposed shipping method.

- Include a justification of how the proposed shipping conditions represent the worst case shipping scenario (based on both time and likely external temperature exposure) for product being imported into Australia.
- Validation of shipping containers should also cover the worst case shipping scenario.

- Ensure the data for justifying any temperature excursions during shipping includes real time studies of the proposed excursion, followed by return to the normal storage conditions for the remainder of the shelf life.

Deviations to storage conditions

A biological medicine that has undergone a deviation to the recommended storage conditions may only be supplied if the TGA has assessed the data to support the release. This data may be submitted:

- as part of an initial application for registration under s25 of the Act or
- as a variation under s9D of the Act to permanently allow ongoing release within defined conditions (e.g. Store at 2-8°C with no more than 72h at <30°C and 6h at -5°C).

In either case, the approved excursions will be recorded in the ARTG and in the Certified Product Details.

Where possible, include a temperature cycling study. Structure cycling stability studies as follows:

- Preferably, include three batches of commercial scale product.
- Include at least one cycle above (and if desired, below) the storage conditions of sufficient magnitude as to cover the majority of projected excursion likely to occur (e.g. -5°C and +30°C). Multiple cycles may be included if desired.
- The duration of the cycle should mimic or exceed the maximum likely duration of a shipping excursion (e.g. 3 days or 72 h for air freight or 3-6 weeks for sea freight)
- Conduct the cycles at the beginning of shelf life and store the samples at the approved or proposed long-term storage conditions for the remainder of the shelf life. Carry out a stability assessment at the end of the shelf life, because biological medicines (particularly those that are complex mixtures extracted from human or animal sources) are sometimes subject to multiphasic and non-linear degradation.
- Apply appropriate stability testing techniques, specifications and intervals.
- For already-registered products, you may incorporate this type of stability study into the design of the annual stability study required under GMP.

Where a cycling study is not available, the sponsor will need to provide a justification, with sufficient supporting evidence, why the product quality has not be impacted.

Reason for approach

We take this approach because most biological medicines are temperature-sensitive and are required to be shipped at the approved storage temperature, which usually means the maintenance of a cold chain**.** Biological medicines manufactured in Europe and the USA are shipped to Australia after release for supply.

- Shipping is always lengthy due to the distances involved and crosses the equatorial region (Zone IV[1]) of the globe.

[1] ICH Q1F Stability Data Package for Registration in Climatic Zones III and IV. <https://www.tga.gov.au/sites/default/files/ich042102.pdf>

- It is not uncommon that during shipping, excursions from approved storage conditions of extensive duration occur that reach temperatures capable of denaturing proteins.
- Deviations from approved storage conditions may cause a biological medicine to be of unacceptable quality and therefore not suitable for supply.

14.4.5 Manufacturing variations and stability data

Any change in the manufacturing process has the potential to impact the quality of the active substance and/or drug product. Therefore, the impact of the change on quality characteristics and stability has to be assessed, because these are integral to the overall assessment of comparability of biological medicines before and after changes are made in the manufacturing process.

In addition to other comparability or characterisation studies of quality aspects, for manufacturing changes that might lead to changes in the protein structure, purity, impurities profiles and potency:

- Conduct a real-time stability study on the active substance or the drug product, depending on the point at which the change in the manufacturing process takes place.
- Justify the number of batches included in the stability study.
- Design the stability studies to cover the entire duration of the approved shelf life.

Example

For example, a change in the manufacturing process during production of the active substance will require that a stability study be conducted, at the minimum, on the active substance. Where the change occurs after the manufacture of the active substance, that is during the manufacture of the drug product, stability study on the final drug product will be required. Additional stability studies, on the active substance or drug product in each of the cases above, may be conducted to provide further support for the proposed change, if you consider this necessary.

Recommended batch number and study duration

Data submitted to support major manufacturing changes (e.g., establishment of a new host cell line, change to a critical raw material, change of a critical step etc.) should include stability data using at least three batches of the drug product and conducted for the length of the approved shelf life. Comparability of the pre- and post-change stability data should be provided.

The stability study may be conducted with reduced number of batches when the sponsor can demonstrate all of the following:

- that there is a history of the active substance or drug product stability
- that the manufacturing changes are deemed minor

  AND

- with appropriate validation and specifications data that the active substance or product are unaffected by the change.

The applicant may submit an available stability study that does not cover the entire duration of the shelf life for evaluation provided that robust comparability data that permits trend analyses is submitted. This should be accompanied by a commitment to complete the ongoing stability

study and report any confirmed out of specification results to the TGA. Acceptability of these abridged stability studies will be considered on a case-by-case basis.

Related European Union guidelines

- Note for guidance on biotechnological/biological products subject to changes in their manufacturing process (CPMP/ICH/5721/03)

14.5 Common deficiencies in stability data and trial design

These common issues may lead to requests for further information and delays in approval of a shelf life for medicines.

14.5.1 Batch information issues

Did not:

- specify the formulations used in the trial, and which batches are identical to the formulation that will be registered in Australia
- state the size or scale of the batches used in the trial
- identify the active substance batches used to manufacture the batches of medicines used in the trial
- describe the packaging used in the trial and to confirm whether it is identical to the pack that will be used in Australia.

14.5.2 Stability trial conditions and/or design issues

Did not:

- accumulate stability data on more than one batch of each strength of the medicine
- accurately define the temperature, lighting and humidity conditions applied during the trial
- reconstitute radiopharmaceuticals at the activities and radioactive concentrations that would be used in a clinical situation
- include stability studies under conditions of high humidity for medicines that are to be registered in moisture-permeable containers, and especially for those that are potentially sensitive to moisture
- investigate the possibility of leaching of substances from the container/closure system into the medicine
- store liquid medicines in an inverted orientation.

For biological medicines

- Did not include temperature excursions or temperature cycling in the stability study when these temperature excursions will be inevitable under the intended conditions of transport.
- Included only pilot-scale batches in the stability study and not batches made by the commercial process.

14.5.3 Analytical methodology/testing issues

- Did not fully describe test methods and sample sizes.
- Did not provide validation of analytical methods.
- Used an HPLC assay procedure to detect impurities without validating the procedure for this purpose.

Note

HPLC assay procedures used to measure the active ingredient are often unsuitable for separation and detection of impurities because they use too short a run time; however, such a procedure would be acceptable if it is validated for impurity detection.

Longer run times do not in themselves ensure good separation.

14.5.4 Data reporting and evaluation issues

- Provided Qualitative expression of results ('passes test' or similar) when a quantitative figure was available.
- Did not include quantitative or semi-quantitative determinations of the content of degradation products, or provided only total content rather than values for individual impurities.
- Did not comment on or conduct additional tests when there is a lack of mass balance between the formation of degradation products and the loss of the active substance. For example:
  - Failure to investigate whether the assay procedures are sufficiently specific, whether the active substance is volatile, or whether the active substance is adsorbed onto the container wall.
- Did not conduct additional tests to investigate the significance of obvious alterations in the characteristics of the medicine. For example, a distinct change in the colour of the medicine may require additional investigation for degradation.
- Did not include information on the physical characteristics of the medicine during storage, such as dissolution characteristics, homogeneity and particle size.
- Did not provide results from intermediate time points to help assess trends in the parameters measured.
- Did not provide results for individual dosage units where these are available (e.g. dissolution profiles).

- Attempts to extrapolate data obtained in the trial beyond reasonable limits.
- Did not take into account the worst-case scenario in predicting a shelf life from regression analysis of the data.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication Guidance 14: Stability testing for prescription medicines – previously ARGPM 14: Stability testing	Office of Medicines Authorisation	01/07/2013
V1.1	Shortened title and modified headings Replacement of section 14.4: modification of specific requirements for biological medicines Added hyperlinks to EU guidelines	Scientific Evaluation Branch; Laboratories Branch; Regulatory Guidance Team	March 2017

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