



Australian Government

Department of Health and Ageing
Therapeutic Goods Administration

Australian regulatory guideline for over-the-counter medicines

Appendix 2: Guidelines on quality aspects of OTC applications

Version 1.2, July 2021

TGA Health Safety
Regulation



About the Therapeutic Goods Administration (TGA)

- The TGA is part of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- 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 <www.tga.gov.au>.

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Version history

Version	Description of change	Author	Effective date
V1.0	Update of ARGOM Chapters <ul style="list-style-type: none"> • 4 Quality • 4A Manufacture • 4B Formulation • 4C Starting material specification • 4D Finished product specification • 4E Stability testing • 4F Microbiological testing Re-formatting of the above chapters as Appendix 2 – Guideline on quality aspects of OTC applications.	MAG – OTCME	October 2012
V1.1	Update to 6.6 Colourings in medicines for topical and oral use	MAG GSU	May 2014
V1.2	Addition of footnotes to information about intermediate products	COMB	July 2021

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Introduction

The *Therapeutic Goods Act 1989*¹ (the Act) requires that applications for a product registration be evaluated “*having regard to whether the **quality**, safety and efficacy of the goods for the purposes for which they are to be used have been satisfactorily established*”.

All applications for over-the-counter (OTC) medicine registration must be supported by evidence to substantiate the quality of the product. This part of the guidance document describes the information regarding the quality of the product should be submitted for OTC medicine applications. It is divided into eleven sections as follows:

1. [Application format and content](#)
2. [Active substance](#)
3. [Description and composition of the medicines \(finished product\)](#)
4. [Development pharmaceuticals and formulation](#)
5. [Manufacture of the medicines](#)
6. [Control of excipients](#)
7. [Control of finished product](#)
8. [Finished product container](#)
9. [Stability of the finished products](#)
10. [Microbiological testing](#)
11. [Checklist for submission of stability data](#)

¹ <https://www.tga.gov.au/legislation-legislative-instruments>

1. Application format and content

The preferred format for OTC product registration applications is the Common Technical Document (CTD). A detailed description of the CTD format can be found on the Therapeutic Goods Administration (TGA) web site².

For many OTC product registration applications, not all parts of the CTD will be relevant. In these cases, the absence of the specific information should be identified in the application, for example by means of a statement such as 'not applicable' against the relevant heading in the Table of Contents.

The CTD document, International Conference on Harmonisation (ICH) *M4Q Common Technical Document for the Registration of Pharmaceuticals for Human Use – Quality* (CPMP/ICH/2887/99 Rev 1)³, provides guidance in preparing the quality section (Module 3) of the application and the critical summary (Module 2.3, *Quality Overall Summary*).

Further guidance on specific quality matters, such as assay validation and design of stability studies can also be found in the relevant European Union (EU) guidelines that have been adopted by the TGA (some with TGA annotations)⁴.

2. Active substance

The term 'active substance' has been used in this chapter when referring to the raw material (i.e. before it is mixed with the other ingredients in the finished product formulation). The term 'active ingredient' is used to refer to the therapeutically active component in the finished product formulation after manufacture, in line with the definition of 'active ingredient' in the *Therapeutic Goods Order No. 69 (TGO 69) - General requirements for labels for medicines*⁵ and *Therapeutic Goods Order No. 78 (TGO 78) - Standard for Tablets and Capsules*⁶.

The term 'active pharmaceutical ingredient' (or 'API') is commonly used as a synonym for 'active substance'. However, as defined in the *Therapeutic Goods (Manufacturing Principles) Determination No. 1 of 2009*⁷, 'active pharmaceutical ingredient' can refer either to a single substance or a mixture of substances (that become an active ingredient in the finished product). Therefore, to avoid confusion, its use will be minimised in this document.

2.1 Manufacturer of active substance(s)

Details regarding the active substance manufacturer, manufacturing process and process validation, are not generally required to be submitted to the TGA for OTC product registration applications. However, these details may be required where the active

² <https://www.tga.gov.au/publication/common-technical-document-ctd>

³ <http://www.tga.gov.au/industry/pm-argpm-ctd.htm#eumod2>

⁴ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

⁵ <http://www.tga.gov.au/industry/legislation-tgo.htm>

⁶ <http://www.tga.gov.au/industry/legislation-tgo.htm>

⁷ <http://www.tga.gov.au/industry/legislation-manuf.htm>

substance is a new chemical entity (NCE). Other additional data requirements for NCEs are detailed in the *ARGOM Appendix 4 Guidelines on OTC application for new substances*⁸.

For OTC medicines, it is the responsibility of the sponsor to ensure that the active substance is manufactured to a standard consistent with the principles of the Code⁹ of Good Manufacturing Practice (GMP)¹⁰ (or in the case of overseas manufacturers, with an appropriate standard of GMP comparable to that required for Australian manufacturers¹¹). Evidence of licensing or approval of the manufacturer of the active substance does not need to be submitted to the TGA, except where it is an intermediate product (e.g. premixes).¹²

Where the active substance is a component of an intermediate product that is purchased already manufactured, the manufacture of the intermediate product is considered a significant step in the manufacture of the medicines. Under these circumstances, evidence of licensing or approval of the manufacturer of the intermediate product will be required (irrespective of whether it is a proprietary ingredient). For further information refer to '[Section 5 Manufacture of the medicine](#)'.

2.2 Control of active substance [active pharmaceutical ingredient (API) specifications]

Applications to register OTC products should include information concerning the specifications applying to the active substance(s).

This information should include:

- a critical summary and justification for the acceptance testing specifications applied by the finished product manufacturer; and
- test methods and validation data, where required (see '[Section 2.2.1 Pharmacopoeial active substances](#)' and '[Section 2.2.2 Non-pharmacopoeial active substances](#)').

In all cases, the specifications must characterise the active substance and ensure that all batches are of suitable and consistent quality for use in the manufacture of the finished product.

2.2.1 Pharmacopoeial active substances

A pharmacopoeial active substance is an active substance that is the subject of a monograph in at least one of the default standard pharmacopoeias (see '[Section 7 Control of finished product](#)' on default standards).

Where an active substance is the subject of a monograph in the default standard mandated or adopted for the product the active substance must comply with the requirements of that monograph, as interpreted in accordance with the General Notices of that standard.

⁸ <http://www.tga.gov.au/industry/otc-argom-app4.htm>

⁹ The 'Code' is defined in the Therapeutic Goods (Manufacturing Principles) Determination No. 1 of 2009 (see <http://www.tga.gov.au/industry/legislation-manuf.htm>).

¹⁰ <http://www.tga.gov.au/industry/manuf-medicines-cgmp.htm>

¹¹ <http://www.tga.gov.au/industry/manuf-overseas-medicines-gmp-clearance.htm>

¹² For more information on proprietary ingredient mixtures that contain an active ingredient see [Streamlining proprietary ingredient categories](#).

Compliance with the requirements of a monograph is most clearly demonstrated by including all of the tests and limits from the relevant monograph in the acceptance specifications; however, it may also be possible to use a monograph from an alternative default standard pharmacopoeia where this will ensure compliance with the monograph in the default standard for the product.

Where the default standard mandated or adopted for the product does not include a monograph for an active substance, but that active substance is the subject of a monograph in one or more of the other default standard pharmacopoeias, the active substance should comply with the requirements of one of these monographs.

If the active substance is the subject of a Certificate of Suitability (CEP) issued by the European Directorate for the Quality of Medicines (EDQM)¹³, the sponsor is encouraged to provide a copy of the CEP together with a letter of access.

Where all of the tests, limits and test methods are those of a monograph from a default standard pharmacopoeia and none of the compendial tests has been deleted, it is usually sufficient to state that this is the case and no additional justification is required. However, the acceptance specifications for the substance must be updated as necessary in order to be consistent with the new editions of the substance monograph in the current edition of the relevant pharmacopoeia.

It is generally not acceptable to:

- adopt only some of the tests from a pharmacopoeial monograph
- selectively combine some tests and/or limits from the relevant British Pharmacopoeia (BP)/ European Pharmacopoeia (Ph. Eur.) monograph with some tests and/or limits from the United States Pharmacopoeia (USP) monograph (without having ensured full compliance with either one or the other monograph).

Where a sponsor applies pharmacopoeial limits but wishes to use different test methods, for example using High Performance Liquid Chromatography (HPLC) for assay rather than titration or Infra Red (IR) for identification rather than a colourimetric test, this should be stated and full details of the test methods should be provided (especially in respect of related substances tests). This will permit the TGA to assess whether the in-house and compendial methods are equivalent and/or whether the modified specifications ensure the overall quality of the substance. Validation data to support the test method may be requested in certain cases.

In some cases, it may be necessary to include tests and limits in the active substance specifications that are not included in the relevant pharmacopoeial monograph. For example:

- tests and limits for residual solvents may be needed (see [Section 2.2.4 Solvent/Sterilant residues](#)’).
- tests and limits may be needed for new impurities associated with new methods of active substance manufacture, as discussed in the monograph *Substances for Pharmaceutical Use*¹⁴ (Ph. Eur. monograph 2034) and *USP General Notices Chapter 5 Monograph Components*¹⁵).

¹³ <http://www.edqm.eu/en/Certificates-of-Suitability-97.html>

¹⁴ <http://www.edqm.eu/en/European-Pharmacopoeia-1401.html>

¹⁵ <http://www.uspnf.com/uspnf/login>

- control of additional properties (e.g. physical characteristics, functionality-related characteristics, microbial contamination) may be necessary in association with individual finished product manufacturing processes or formulations.

Usually, the need for any such additional tests will have been investigated as part of selection and characterisation of the active substance during development of the product.

Where a default standard monograph exists but a sponsor wishes to substitute an in-house set of tests and limits, for example replacing a test and limits for density with refractive index, full details should be provided for evaluation (see '[Section 2.2.2 Non-Pharmacopoeial active substances](#)'). The sponsor should justify the use of non-pharmacopoeial specifications. In particular, it must be clear that the in-house tests and limits will ensure compliance with the requirements of the default standard.

2.2.2 Non-pharmacopoeial active substances

A non-pharmacopoeial active substance is an active substance that is not the subject of a monograph in any of the default standard pharmacopoeias (see '[Section 7 Control of finished product](#)' on default standards)

The critical summary should include a list of the tests, limits and test methods [e.g. *assay (non aqueous titrimetry): 99.0 101.0%*].

In proposing tests and limits, sponsors should consider the relevant European Union active substance guidelines adopted by the TGA¹⁶ as well as general pharmacopoeial monographs such as the BP/Ph. Eur. monograph *Substances for Pharmaceutical Use*.

Specifications for active substances should include tests and limits for:

- appearance/description
- identification
- content/assay
- impurities such as residual solvents, sulfated ash, heavy metals and related substances (synthetic impurities and degradants)
- other parameters which are relevant to the individual substance, such as water content/loss on drying, the presence or proportion of isomers, optical rotation, melting point and the clarity, colour and pH of solutions.

Control of additional properties such as particle size distribution or microbial contamination may be necessary in association with individual finished product manufacturing processes or formulations.

The specifications applied should be justified in respect of their ability to ensure the quality and consistency of the substance.

Full details of the test methods should be provided for evaluation. Validation data may be required in support of certain test methods (consult '[Section 7.9 Analytical procedures and validation](#)' for further information).

¹⁶ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm#qualityactive>

2.2.2.1. Related substances

For a NCE, the related substances specifications should be based on the approach detailed in the ICH document *Impurities Testing Guideline: Impurities in new drug substances* (CPMP/ICH/2737/99)¹⁷.

Note: Other additional data requirements for NCEs are detailed in the *ARGOM Appendix 1 Guidelines on efficacy and safety aspects of OTC applications*¹⁸

For other active substances, the following limits can generally be applied without a detailed justification:

- Individual identified impurities: not more than 0.5 %
- Individual unidentified impurities: not more than 0.1 %
- Total impurities: not more than 1.0 %

2.2.3 Specifications for intermediate products

Where the active substance is purchased already manufactured as part of an ingredient blend or premix,¹⁹ the finished product manufacturer's acceptance specifications for this material must be provided.

For an ingredient blend containing the active substance, the specifications should, as a minimum, normally include tests for:

- identification of the active
- content of the active
- impurity tests
- any other tests relevant to manufacture or quality of the finished product, for example particle size distribution/sieve analysis where the blend is to be used in direct compression or in suspensions.

Omission of some of these tests may be justifiable if the relevant quality parameter is assured by other means such as impurity testing of the individual components, or testing of subsequent intermediate or final product (or is shown to be irrelevant to the particular blend).

The sponsor should also state whether the components of the blend or premix are of pharmacopoeial grade and comply with any relevant default standards.

2.2.4 Solvent/Sterilant residues

Where organic solvents or sterilants are used in manufacture, it is the sponsor's responsibility to ensure that residues are appropriately controlled. Compliance with a specific default standard does not necessarily assure appropriate control of solvent residues.

The limits applying to solvent/sterilant residues are detailed in the following default standards and TGA-adopted documents:

¹⁷ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

¹⁸ <http://www.tga.gov.au/industry/otc-argom-app1.htm>

¹⁹ For more information on proprietary ingredient mixtures that contain an active ingredient see [Streamlining proprietary ingredient categories](#).

- BP Supplementary Chapter IV D *Residual Solvents*, which incorporates Ph. Eur. *Section 5.04 Residual Solvents*, and is applied via the BP general monograph *Substances for Pharmaceutical Use* (Ph. Eur. 2034)
- Ph. Eur. Section 5.04 *Residual Solvents*, which is applied via the general monograph *Substances for Pharmaceutical Use* (Ph. Eur. 2034)
- USP <467> *Residual Solvents*
- *Note For Guidance On Impurities: Residual Solvents* (CPMP/ICH/283/95)²⁰.
- Annex 1: Specifications for Class 1 and Class 2 Residual Solvents in active substances
Annex 2: Residues of solvents used in the manufacture of finished products (CPMP/QWP/450/03)²¹.
- *Note for Guidance on Limitations to the Use of Ethylene Oxide in the Manufacture of Medicinal Products* (CPMP/ICH/159/01)²², with TGA annotation prohibiting use in decontamination of herbal products.

2.3 Stability of the active substance

Details of stability studies conducted on the active substance are not generally required for registration applications for OTC products. However, such details are required where the active substance is a NCE. Inclusion of such information with an application may provide a useful guide to the problems which may be encountered during stability studies on finished products.

3. Description and composition of the medicine (finished product)

The application should include a brief description of the finished product and its composition, as specified under CTD²³ module 3.2.P.1. In particular, the application should include:

- a visual description
- table(s) of the ingredients and quantities, including overages (if any)
- details of the function of the ingredients in the product (e.g. disintegrant, antimicrobial preservative)

Sponsors should use Australian Approved Name (AAN)²⁴ terminology. For those ingredients without an AAN, an *Application form for proposing a chemical name*, available from the TGA website²⁵, should be completed and either included with the application or submitted separately to the TGA (to the attention of the “The Secretariat, Australian

²⁰ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm#qualityactive>

²¹ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm#qualityactive>

²² <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm#qualitymedicinal>

²³ <http://www.tga.gov.au/industry/pm-argpm-ctd.htm>

²⁴ <http://www.tga.gov.au/industry/medicines-approved-terminology.htm>

²⁵ <http://www.tga.gov.au/industry/medicines-approved-terminology.htm#forms>

Approved Names Committee'). The Australian Register of Therapeutic Goods (ARTG) entry can only be finalised using AANs.

Any processing solvents should be included in the electronic application form under the category 'starting materials not present in the final product'; however this information will not be included on the ARTG record for the product.

Note 1: Where the form has been submitted separately, it is recommended that the application letter include a statement alerting the evaluator to this fact.

Note 2: Other data requirements for new substances are detailed in *ARGOM Appendix 4 Guidelines on OTC application for new substances*²⁶.

3.1 Colouring ingredients permitted in medicines for oral use

The colours allowed by the TGA in medicines for oral use are included in the TGA document *Colours permitted in medicines for topical and oral use*²⁷, available on the TGA website. This restriction does not apply to dermal products or medicated lipsticks.

3.2 Proprietary ingredients

The term 'proprietary ingredient' means a formulated ingredient obtained from another manufacturer for which the formulation details are not known to the sponsor (flavouring and fragrance ingredients, for instance, are often sourced as proprietary ingredients).

If a proprietary ingredient is included in the product the sponsor should ensure that either:

- the formulation details have already been disclosed to the TGA (in which case the reference number of the ingredient should be stated in the application form)
- the manufacturer of the proprietary ingredient has been requested to provide the TGA with details of the formulation on a *Notification of a proprietary ingredient form*²⁸, available from the TGA website.

If the label contains a negative disclosure (e.g. 'sugar free' or 'alcohol free'), the sponsor should check with the manufacturer or supplier that the substance is not contained in any proprietary ingredient included in the formulation. The sponsor should also check with the manufacturer or supplier whether the proprietary ingredient contains any ingredients that must be disclosed on the label, as listed in the First Schedule of the TGO 69²⁹.

For details of requirements relating to the control of proprietary ingredients see [Section 6 Control of excipients](#)'.

²⁶ <http://www.tga.gov.au/industry/otc-argom-app4.htm>

²⁷ <http://www.tga.gov.au/industry/medicines-colourings.htm>

²⁸ <http://www.tga.gov.au/industry/medicines-forms-proprietary-ingredient.htm>

²⁹ <http://www.tga.gov.au/industry/legislation-tgo.htm>

3.3 Ingredients of human or animal origin

Any materials of human or animal origin used as ingredients, excipients or during manufacture (e.g. fermentation medium) need to be assessed for viral and prion safety, including the risk of transmissible spongiform encephalopathies (TSEs) from ruminant-derived materials.

Therefore, when an electronic application is submitted to the TGA the sponsor must state whether each ingredient is of animal origin and if this is the case provide details regarding the material.

Guidance on the requirements for minimising the risk of TSEs in therapeutic goods³⁰ is available on the TGA website. This guidance classifies materials of animal origin into three categories (A, B and C) depending on the animal species and tissues that they are derived from.

Ruminant-derived raw materials that are classified as Category A (high infectivity) and Category B (lower infectivity) tissues or fluids will be subject to full TGA viral and prion safety evaluation.

Category C materials are those currently classified as having no detectable infectivity, as described in the TGA guidelines. These materials may be eligible for self-assessment. The TGA website contains a questionnaire³¹ designed to help sponsors collect the data needed in order to self-certify therapeutic goods against the TGA requirements.

As part of the electronic application process sponsors are required to agree to the following statutory declaration:

'Any Category C ruminant ingredients included in this product have been 'self-assessed' in accordance with the TGA's 'Supplementary requirements for therapeutic goods for minimising the risk of transmitting transmissible spongiform encephalopathies (TSEs)³², and comply with those requirements'.

4. Development pharmaceuticals and formulation

Information which is relevant to the subheadings specified in the CTD³³ under module 3.2.P.2 should be included in this section. For example, explanations for the choice of excipients, the use of a modified release dosage form, or justifications for overages. For most OTC medicines this section will be brief.

³⁰ <http://www.tga.gov.au/industry/tse-approach.htm>

³¹ <http://www.tga.gov.au/industry/tse-sponsor-questionnaire.htm>

³² <http://www.tga.gov.au/industry/tse-supplementary-requirements.htm>

³³ <http://www.tga.gov.au/industry/pm-argpm-ctd.htm>

4.1 Overages and ranges

Details should be provided of any overage or range that is applied during manufacture, including a justification for the overage or range and supporting validation data where appropriate.

Any assay limits which are unusually wide as a consequence of the proposed overage should also be addressed. Refer to '[Section 7 Control of finished product](#)', for examples of some commonly applied assay limits. Overages are not to be included in the formulation details section of the electronic application form.

Justifications for 'stability' overages would generally include comment on:

- the intrinsic stability of the active substance, and any studies performed to investigate and/or control its stability in the product
- any implications for safety or efficacy of the product, as a consequence of the wide range of the ingredient's content over the shelf life of the product
- any implications for safety of the product resulting from the presence of any degradants.

For some substances the weight used in a batch may vary according to its moisture content or according to its potency. Variation of the quantity of active substance, to adjust for potency, may affect the proportions of excipients present in the finished product relative to the nominal formula. In some situations, the manufacturer may opt to compensate for the fluctuations in the weight of raw material by adjusting the amount of a nominated excipient in order to maintain a target weight for the batch. In this case, the following information should be provided regarding the proposed range in quantity:

- estimated potency and/or water content
- a formula showing how the amount of adjustment will be calculated.
- an indication of which other excipients will be varied correspondingly, if any, and within what limits

Validation data may be necessary to support a wide range. Such validation data can be generated using 'side batches' (small scale batches or modified portions of production batches) with the formulation or properties (e.g. pH) at the extremes of the proposed range. Validation data may include:

- compliance with the finished product specifications
- stability data
- in some circumstances, comparative dissolution profiles may also be appropriate.

4.2 Modified/sustained release products

Where a product has modified or unusual medicinal release characteristics (e.g. sustained release or enteric coated) or an unusual method of manufacture, the 'Development pharmaceuticals' section of the application must include a detailed discussion of product development, and the relationship with the finished product specifications where relevant (e.g. the reasons for choosing a particular dissolution test method and limit). For further

guidance see *ARGOM Appendix 1 Guidelines on efficacy and safety aspects of OTC applications: Section 10 Modified Release Products*³⁴.

4.3 Reformulation of existing products

Where a reformulated product is to replace an existing product the changes should be identified. A statement of the reasons for the reformulation should be provided. The application must also include a table comparing the old and new formulations. Where a sponsor wishes to reformulate a product, the impact on the specifications and stability of the reformulated product must be addressed. Stability data generated on the reformulated product are required to support such applications, unless otherwise justified (refer to [‘Section 9 Stability of the finished product’](#)).

5. Manufacture of the medicine

5.1 Status of manufacturer(s)

5.1.1 Medicine

Where Australian manufacturers are nominated in an application, each manufacturer must be licensed by the TGA to perform manufacturing of the type proposed. The manufacturer’s licence carries details of the types of manufacture permitted under the licence.

Where a product is imported, each nominated overseas manufacturer is required to comply with the equivalent standard of GMP as would be required of an Australian manufacturer. GMP clearance of overseas manufacturers by the TGA is required.

The TGA website contains information regarding the manufacture of therapeutic goods³⁵; and details of the information required to establish the standard of an overseas manufacturer and the procedure for GMP clearance³⁶.

5.1.2 Excipients

For excipients in OTC medicines, evidence of licensing or approval of the excipient manufacturer is not required. Information regarding requirements for control of excipients is included in [‘Section 6 Control of excipients’](#).

5.1.3 Intermediate products

Intermediate products are partly processed materials which must undergo further manufacturing steps before they become final medicines. Where an intermediate product is purchased already manufactured and its manufacture is considered a significant step in the manufacture of the medicine [e.g. a tablet granulation, an active pre-mix³⁷ (see also

³⁴ <http://www.tga.gov.au/industry/otc-argom-app1.htm>

³⁵ <http://www.tga.gov.au/industry/manuf-gmp-tg.htm>

³⁶ <http://www.tga.gov.au/industry/manuf-overseas.htm>

³⁷ For more information on proprietary ingredient mixtures that contain an active ingredient see Streamlining proprietary ingredient categories.

‘[Section 2.1 Manufacturer of active substance\(s\)](#)’), or a vehicle for a topical product], evidence of licensing or approval of the manufacturer will be required (irrespective of whether it is a proprietary ingredient).

Where the manufacture of an ingredient that is a mixture is not considered a significant step in medicine manufacture, GMP evidence is not required (e.g. most colours, printing inks, flavours and fragrances, and proprietary ingredients whose sole purpose is as a source of the preservative system for the medicine).

5.2 Manufacturing information

The following information must be provided:

- The steps of manufacture undertaken at each manufacturing site. A manufacturing site must be nominated for each of the following steps; the manufacture of the dosage form, packaging and labelling, chemical and physical testing, microbial testing, release for supply and, for sterile products, sterilisation.
- A brief outline of the method of manufacture. This should preferably include a flow diagram or chart showing steps in the manufacturing process, including filling, packaging and in-process controls. Sponsors and manufacturers must ensure that all steps in manufacture comply with the Code³⁸ of GMP (or in the case of overseas manufacturers, with an acceptable standard of GMP comparable to that required for Australian manufacturers).
- Details or an assurance regarding the validation of the manufacturing process. The extent of information required depends on the nature of the product (see ‘[Section 5.2.1 Manufacturing process validation](#)’).

5.2.1 Manufacturing process validation

The manufacturing process must be validated in accordance with the requirements of GMP. The document *Note for Guidance on Process Validation* (CPMP/QWP/848/96)³⁹ contains useful additional information.

The manufacture of the following ‘higher risk’ OTC products requires particular attention to manufacturing process validation:

- Microdose products (solid oral dosage forms where the active ingredient is present in an amount of less than 2mg or 2% w/w of the dosage form).
- Sterile products.
- Products with a sustained release characteristic (not including enteric coated products).
- Metered dose inhalers.
- Novel dosage forms.
- Nasal corticosteroids

³⁸ The ‘Code’ is defined in the *Therapeutic Goods (Manufacturing Principles) Determination No. 1 of 2009* (see <http://www.tga.gov.au/industry/legislation-manuf.htm>). Links to the Code of GMP can be found at <http://www.tga.gov.au/industry/manuf-medicines-cgmp.htm>

³⁹ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm#qualitymedicinal>

Note: 'higher risk' in this context means that there are likely to be critical parts of the manufacturing process for which inadequate control could have adverse consequences for the safety and/or efficacy of the finished product [see also *Annex II to Note for Guidance on Process Validation (CPMP/QWP/848/96)*⁴⁰ and *EMA/CVMP/598/99 Non Standard Processes (CPMP/QWP/2054/03)*⁴¹ available on the TGA website].

For the above products, the following information should be provided:

- The type of validation (for these products, prospective validation would usually be expected).
- The critical steps in manufacture and acceptance criteria for these steps.
- A summary of the manufacturer's process validation report including the manufacturer's analysis and conclusions.
- For microdose products, the full validation report should be provided.
- For sterile products, the expected validation information is outlined in module 3.2.P.3.5 of the CTD.

Note: Batches should normally be full production scale. However, pilot scale validation data [normally at least 1/10th of the proposed production scale, as defined in *Note for Guidance on Process Validation (CPMP/QWP/848/96)*⁴²] may be acceptable if the sponsor can demonstrate that pilot scale data will be predictive of production scale.

For other OTC products it will be sufficient to provide a written assurance that the manufacturing process has been validated on two or three production scale batches according to the requirements of the Code of GMP, or that the process will be validated as detailed below.

Where a manufacturing process has not been fully validated on production scale batches at the time of approval of a new medicine, the sponsor should provide a written assurance that the manufacturing process will be validated, consistent with the requirements of the Code of GMP, for the first two or three production scale batches, and also provide an assurance that the manufacturer's validation reports on these batches will be made available, if requested for review by the TGA, within three months of release of the batches. The performance of this validation will be made a condition of registration of the medicine.

5.3 Batch to batch variations in quantities of certain excipients

In accordance with the principles of GMP and with the goal of minimising batch to batch variation in stability (and bioavailability), all batches should be manufactured to the nominal formula without variation. To this end, thorough product development studies and process validation studies should be undertaken.

However, it is recognised that it may sometimes be necessary to vary the quantities of certain excipients from batch to batch in order to achieve acceptable results during the manufacturing process.

⁴⁰ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

⁴¹ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm#qualitymedicinal>

⁴² <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

Changes to the nominal amounts of certain excipients that are in conformity with the table below will not be regarded as changing the product's registered details and need not be referred to the TGA. It is expected that appropriate validation studies will be performed and that the results will be available on request or during the course of GMP inspections.

Table 5.1 Nominal amounts of certain excipients.

#	Excipient type	Acceptable range
1	pH adjusting ingredients	qs*
2	Volume adjusting fluids	qs
3	Quantity of ingredients whose function is to contribute to viscosity	± 10%
4	Colour in tablet coating (but not in body of tablet)	qs
5	Solvent in granulating fluid	qs
6	Granulating fluid (fixed composition)	± 10%
7	Disintegrant (even if the excipient serves more than one role in the formulation)	to +25%
8	Coating solution	qs**
9	Talc and water soluble lubricants and glidants	-25% to +100%
10	Water insoluble lubricants and glidants except talc (e.g. magnesium stearate, stearic acid)	± 25%
11	Filler (bulking agent) in hard gelatin capsules	± 10%

**Definition of 'qs': As much as is needed to bring the quantity up to its target measurement or specification.*

***Does not apply to modified release products – approval is required for any variation from the registered formulation.*

Prior approval of the TGA is required if a batch or batches are manufactured outside the ranges specified in the above table or the ranges approved by the TGA for the product. Where there is a repeated need for variation outside the allowed ranges an application to change the formulation should be submitted.

6. Control of excipients

The information concerning the specifications applying to the excipients should include:

- a critical summary and justification for the acceptance testing specifications applied by the finished product manufacturer
- test methods and validation data, where required (see [‘Section 6.1 Pharmacopoeial excipients’](#) and [‘Section 6.2 Non-pharmacopoeial excipients’](#)).

In all cases, the specifications must characterise the excipients and ensure that all batches are of suitable and consistent quality for use in the manufacture of the medicine.

Where all of the tests, limits and test methods are of a default standard monograph (and none of the compendial tests has been deleted) it is generally sufficient to state this.

Where non-pharmacopoeial specifications are applied, a description of the tests, test methods and limits should be provided [e.g. assay (non aqueous titrimetry: 99.0 101.0%)]. The specifications applied should be justified in respect of their ability to assure the quality and consistency of the ingredients used. Similarly, where a pharmacopoeial monograph is used as the specification any deviation from the pharmacopoeial tests, test methods or limits should be justified.

6.1 Pharmacopoeial excipients

A pharmacopoeial excipient is an excipient that is the subject of a monograph in at least one of the default standard pharmacopoeias (see [‘Section 7 Control of finished product’](#) for further details on default standards).

Where an excipient is the subject of a monograph in the default standard mandated or adopted for the product, the raw material must comply with the requirements of that monograph, as interpreted in accordance with the *General Notices* of that standard.

Compliance with the requirements of a monograph is most clearly demonstrated by including all of the tests and limits from the relevant monograph in the acceptance specifications; however, it may also be possible to use a monograph from an alternative default standard pharmacopoeia where this will ensure compliance with the monograph in the default standard for the product.

Where the default standard mandated or adopted for the product does not include a monograph for the excipient, but the excipient is the subject of a monograph in one or more of the other default standard pharmacopoeias, the excipient should comply with the requirements of one of these monographs.

Where all of the tests, limits and test methods are of a monograph from a default standard pharmacopoeia it would be sufficient to state that this is the case. However, it is generally **not** acceptable to:

- adopt only some of the tests from a pharmacopoeial monograph
- selectively combine some tests and/or limits from the relevant BP monograph with some tests and/or limits from the USP monograph (without having ensured full compliance with either one or the other monograph).

Where a sponsor applies pharmacopoeial limits but wishes to use different test methods, for example using HPLC for assay rather than titration or IR for identification rather than a colourimetric test, this should be stated and full details of the test methods should be provided. This will permit the TGA to assess whether the in-house and compendial methods are equivalent and/or whether the modified specifications ensure the overall quality of the substance.

Where the use of a particular grade of an excipient is known to be critical to achieve acceptable finished product attributes, control of additional properties (e.g. physical and functional characteristics such as viscosity, powder fineness, moisture content, or sterility) may be necessary for individual manufacturing processes or formulations.

Where a pharmacopoeial monograph exists but a sponsor wishes to substitute in-house specifications, for example replacing a test and limits for density with refractive index, full details of the limits and test methods should be provided for evaluation. Validation data may be required in support of certain test methods (see '[Section 6.2 Non-pharmacopoeial excipients](#)'), and the sponsor should justify the use of non-pharmacopoeial specifications.

6.2 Non-pharmacopoeial excipients

A non-pharmacopoeial excipient is an excipient that is not the subject of a monograph in any of the default standard pharmacopoeias (consult '[Section 7 Control of finished product](#)' for further details on default standards).

Where there is no pharmacopoeial monograph, full details of the limits and test methods should be provided for evaluation. In some cases, validation data may be required to support test methods [for guidance on the types of analytical methods required to be validated see *Note for guidance on validation of analytical procedures: text and methodology* (CPMP/ICH/381/95)⁴³].

Specifications for excipients should include tests and limits, unless otherwise justified for:

- appearance/description
- identification
- content/assay
- impurities (e.g. water, residual solvents, loss on drying, sulfated ash, heavy metals, synthetic impurities and degradants).

In some cases the assay and/or impurities test(s) may be replaced or supplemented by physicochemical tests such as clarity, colour and/or pH of solutions, or melting point. Requirements for microbial contamination and particle size distribution may also be relevant in relation to use in some finished product formulations.

Excipients which are intrinsically mixtures (e.g. synthetic polymers or fatty acid esters of glycerol where mono, di, and triacyl glycerol species are present and where a range of different fatty acid residues is also present for example surfactants) should include relevant additional tests which control the composition of the mixture such as:

- acid value
- iodine value
- saponification value
- viscosity
- density; and/or
- refractive index.

⁴³ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm#analytical>

6.3 Solvent/Sterilant residues

Refer to 'Section 2 Active substances: [2.2.4 Solvent/Sterilant residues](#)'.

6.4 Proprietary ingredients

Where a proprietary ingredient is used in medicine manufacture or an intermediate product is purchased already manufactured, details of the medicine manufacturer's acceptance specifications for this material must be provided.

The specifications applied to the material should be appropriate for the nature of the ingredient, its function in the medicine and its proportion in the medicine. For example, for proprietary ingredients that are fragrances, flavours or colourings (which are normally minor components present at no more than 2% in the product formulation), some relevant requirements are detailed under the relevant headings, below.

6.5 Perfumes (fragrances) and flavours

For a perfume or flavour that is a proprietary ingredient, or otherwise supplied as a complex mixture, the specifications should include, unless otherwise justified, tests for:

- description (odour, colour, general appearance)
- any relevant general tests that contribute to identification (and control of composition), such as refractive index or density
- identification by prominent peaks in a gas chromatography (GC) or HPLC trace, or major spots in a thin layer chromatogram.

Where there is an applicable default standard monograph for any constituent, the constituent must conform to the specifications in that monograph. In the case of artificial flavourings, where there is no applicable default standard monograph, the excipient would be expected to comply with any relevant monograph in the internationally accepted purity criteria in food use (FAO/WHO)⁴⁴.

6.6 Colourings in medicines for topical and oral use

The guidance *Colourings used in medicines for topical and oral use*⁴⁵ details the specifications that apply.

⁴⁴ <http://www.fao.org/ag/agn/jecfa-flav/search.html?lang=en>

⁴⁵ <http://www.tga.gov.au/industry/medicines-colourings.htm>

7. Control of finished product

This section of the application should include the following information:

- A critical summary (for applications in CTD format⁴⁶, the summary included in module 2.3.P.5 does not need to be duplicated).
- A copy of the release specifications applied by the medicine manufacturer.
- A copy of the expiry specifications (stability specifications are not generally suitable as expiry specifications – see '[Section 7.1 Finished product specifications](#)').
- A justification for the specifications (consult '[Section 7.8 Justification of specifications](#)').
- Test methods and validation data, where required (consult '[Section 7.9 Analytical procedures and validation](#)').

The critical summary should include a brief description of the tests, limits and test methods at batch release and expiry [e.g. *assay (capillary GC): 95.0 105.0%*] together with a brief assessment of their suitability. For dissolution tests, brief details of the apparatus, medium and limit should be provided [e.g. *dissolution (paddle at 50 rpm, 900 mL of water, Q=80% at 30 minutes)*]. Where analytical test methods in the finished product specifications differ from those used for stability testing this must be stated. Where the expiry specifications differ from the batch release specifications, this should be clearly stated.

It is also recommended that the application include analytical batch data for the finished product for a minimum of two pilot or production scale batches of the product. This should preferably be in the form of Certificates of Analysis generated by the medicine manufacturer's laboratories.

7.1 Finished product specifications

The finished product specifications are a set of tests and limits that are applied to the product in order to ensure that every batch is of satisfactory and consistent quality throughout its shelf life. The specifications must monitor all parameters where variation would be likely to affect the safety or efficacy of the product; and must ensure compliance with any applicable default standard(s) or Therapeutic Goods Order(s).

Usually, tighter limits are applied at batch release to critical parameters to allow for analytical error during batch release testing and to allow for possible changes to the product during storage (e.g. decomposition of the active). Where different tests and limits are applied at batch release and expiry, this must be clearly indicated in the application.

The expiry specifications indicate the limits that the product is required to comply with if it was to be tested during the approved shelf life. The stability specifications (tests and limits applied in the stability studies) are not necessarily suitable as expiry specifications, as they often do not include all of the tests and limits that the product is expected to comply with over the shelf-life.

Note: The expiry specifications should include all of the tests that are included in the batch release specifications (or contain an annotation referring to these additional

⁴⁶ <http://www.tga.gov.au/industry/pm-argpm-ctd.htm>

requirements); however, the inclusion of certain tests and limits in the expiry specifications, such as an identification test, does not imply a requirement for any actual testing additional to that specified in the release and stability specifications.

See further discussion of release and expiry specifications in '[Section 7.8 Justification of specifications](#)'.

7.2 Medicines subject to individual pharmacopoeial product monographs

Where the product is the subject of an individual product monograph in only one of the BP, the Ph. Eur., or the United States Pharmacopoeia-National Formulary (USP/NF) (the default standard pharmacopoeias) then the requirements of that monograph, the general monograph for the dosage form if the relevant pharmacopoeia includes one, and any additional requirements referred to in the general notices of the relevant pharmacopoeia (such as appendices and general chapters) constitute a default standard for that product. The expiry specifications must include all of the tests and limits required by that default standard, however, an alternative validated test method may be substituted if it is demonstrated, for the product, that it is equivalent or superior to the test method used by the standard.

Where the product is the subject of individual product monographs in more than one of the default standard pharmacopoeias, then the expiry specifications must include all of the tests and limits required by one of the default standards (including requirements in general monographs, appendices, and general chapters where these are relevant). Sponsors should note that the *Therapeutic Goods Order (TGO) 78 Standard for tablets and capsules*⁴⁷ currently requires tablets and capsules that are the subject of an individual product monograph in the BP to comply with that monograph, even when there is also a relevant USP monograph. This requirement is currently under review. It is not acceptable to combine the requirements of two or more default standards without ensuring full compliance with at least one default standard. The sponsor should nominate in the application the default standard that they intend to adopt.

It may also be necessary to include tests and limits to control critical parameters specific to the product that are not covered in the default standard monograph. For example, a test and limits for preservative content is generally required for products containing preservatives (see '[Section 9.6.6 Preservative efficacy](#)').

The specifications must also ensure compliance with any relevant Therapeutic Goods Orders, for example, the TGO 77 *Microbiological standards for medicines*⁴⁸ and TGO 78 *Standard for tablets and capsules*⁴⁹.

7.3 Medicines not subject to individual pharmacopoeial product monographs

If there is no individual monograph for the product, any relevant BP, Ph. Eur. or USP/NF general monograph for the dosage form will still constitute a default standard. The specifications for such products must include all of the requirements in at least one of

⁴⁷ <http://www.tga.gov.au/industry/legislation-tgo.htm>

⁴⁸ <http://www.tga.gov.au/industry/legislation-tgo.htm>

⁴⁹ <http://www.tga.gov.au/industry/legislation-tgo.htm>

these default standards. Sponsors should note that the general notices of the relevant pharmacopoeia may also require the product to comply with the requirements of any applicable appendices or general chapters.

The specifications must also ensure compliance with any relevant Therapeutic Goods Orders, as discussed above for products subject to individual pharmacopoeial monographs.

If there are individual monographs for similar products these should be consulted when determining appropriate tests and limits to include in the specifications. For example, for an oral tablet for which there is currently no pharmacopoeial monograph it may be useful to consult published monograph(s) for other oral dosage form(s) containing one or more of the same active ingredients (alone or in combination with different active ingredients).

7.4 Related substances

The finished product specifications should include tests and limits for substances related to the active substance (synthetic impurities and degradants).

For a product that is subject to the requirements of an individual default standard monograph which includes requirements for related substances, it will generally be adequate to include these requirements in the specifications. However, active substances from different suppliers may have different impurity profiles that are not addressed by the pharmacopoeial test procedure. Similarly, the excipients in a finished product can vary among manufacturers and may have the potential to cause the formation of impurities that are not addressed by the pharmacopoeial procedure. Manufacturers are expected to take these factors into account when verifying the pharmacopoeial tests and limits for use with the proposed product⁵⁰.

For the same reasons, the absence of tests and limits for related substances should be justified even if the product is subject to the requirements of an individual default standard monograph that includes no requirements for control of related substances.

For products that are not subject to the requirements of an individual default standard monograph or Therapeutic Goods Order, the following guidelines apply.

- For products containing new active ingredients, degradation products should be reported, identified and/or qualified if they are present at levels above those described in the EU document *Note for guidance on impurities in new medicinal products* ICHQ3B(R) (CPMP/ICH/2738/99)⁵¹.
- For well established OTC medicines, when not subject to pharmacopoeial limits, the following expiry limits on impurities can generally be applied without a detailed justification:
 - Individual impurities: not more than 1% (relative to the active)
 - Total impurities: not more than 3% (relative to the active)
- For other products, such as those recently down-scheduled from S4, requirements for control of degradation products will be assessed on a case-by-case basis.

The results of stability studies should be taken into account when setting impurity limits. There may be some products for which lower limits on impurities are appropriate. Unless

⁵⁰ See also USP <1226> Verification of Compendial Procedures

⁵¹ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm#qualitymedicinal>

otherwise agreed to for a particular product, limits on impurities in finished products apply to impurities from all sources.

For products that have more than one active ingredient, the limits on impurities associated with one active are usually determined separately from the limits for impurities associated with the other active(s). In such cases, the limit on an impurity should usually be expressed relative to the content of the relevant active ingredient.

Additional guidance can be obtained from the relevant appendices and general chapters of the BP, Ph. Eur. and USP/NF.

7.5 Tablets and capsules

Tablets and capsules must comply with either the TGO 78 *Standard for tablets and capsules*⁵². Sponsors should also consult *Guidance on Therapeutic Goods Order No.78 Standards for tablets and capsules*⁵³ for further clarification on the requirements for tablets and capsules. It does not form part of TGO 78 and is intended only to assist sponsors to achieve compliance with TGO 78.

7.5.1 Dissolution and disintegration testing

Where the TGO 78 requires compliance with a 'suitable' dissolution test, or where a dissolution test is considered appropriate for other reasons, for example modified release products, it is expected that the dissolution test method has been validated to assure product quality and performance. Any relevant dissolution test methods described in the BP and USP should be considered during the development of the dissolution method. The dissolution method and supporting validation data should be submitted for evaluation, including details of the apparatus, rotational speed, dissolution medium and limit.

Under TGO 78, tablets or capsules that are not required to comply with a dissolution test are required to comply with the relevant test for disintegration in the BP general monographs for Tablets or Capsules. Under these circumstances, the BP disintegration test and limits should be included in the expiry specifications, regardless of whether a dissolution test is also proposed.

For modified release products, the conditions under which the active substance is released, and the timing of release, are normally critical parameters for product performance. Therefore, modified release products will be expected to include appropriate dissolution testing in the finished product specification.

7.5.2 Subdivision of tablets

Where the directions for use permit the subdivision of tablets (e.g. ½ tablet doses) the efficacy of the break-mark(s) must be assessed during the development of the product, in respect of uniformity of mass of the subdivided parts, in order to ensure that the consumer will receive the intended dose. Test results should be submitted to demonstrate that this is the case. For products that are subject to the BP or Ph. Eur. as the default standard the sponsor must submit the results of testing according to the test detailed in the BP general monograph for *Tablets - Subdivision of tablets*.

⁵² <http://www.tga.gov.au/industry/legislation-tgo.htm>

⁵³ <http://www.tga.gov.au/industry/legislation-tgo-78-guide.htm>

7.6 Microbiological requirements

The TGO 77 *Microbiological Standards for Medicines*⁵⁴ specifies the minimum microbiological requirements with which a medicine must comply throughout its shelf life.

The guidance document *Guidance on Therapeutic Goods Order No. 77 Microbiological Standards for Medicines*⁵⁵ provides a plain English explanation of the various requirements of TGO 77 and their application. It does not form part of TGO 77 and is intended only to assist sponsors to achieve compliance with TGO 77.

For further information regarding microbiological requirements consult '[Section 9.6.5 Microbial content testing](#)' and '[Section 9.6.6 Preservative efficacy](#)', as well as '[Section 10 Microbiological testing](#)'.

7.7 Solvent/Sterilant residues

Solvent residues must be appropriately controlled in the finished product, in accordance with the *Residual Solvents* requirements of the relevant default standard and the corresponding ICH guidance documents; which are listed in '[Section 2 Active substances: 2.2.4 Solvent/Sterilant residues](#)'.

In particular, sponsors should ensure that no 'Class 1' solvents have been used in the manufacture of the medicine.

The limits applying to solvent/sterilant residues are also discussed in '[Section 2 Active substances, 2.2.4 Solvent/Sterilant residues](#)' and '[Section 6 Control of excipients](#)'.

7.8 Justification of specifications

The justification for the finished product specifications should take into account the results from stability studies as well as tests and limits in relevant monographs. Where relevant, the justification may address relevant clinical or toxicological data. The tests and limits should also be considered in terms of the supporting validation data. A detailed justification for any unusual features in the finished product specifications should be included.

7.8.1 Release specifications

The limits applied at batch release should be justified in terms of their ability to ensure that the product will comply with the expiry specification throughout the product shelf life. Any changes or unusual variability in the results obtained in the stability studies should be taken into account. Usually, tighter limits are applied at batch release to critical parameters to allow for analytical error during batch release testing and to allow for possible changes to the product during storage (e.g. decomposition of the active).

The TGA expects that all of the tests included in the finished product release specifications will be performed on all batches at release, except where a reduced schedule of tests has been approved by the TGA.

⁵⁴ <http://www.tga.gov.au/industry/legislation-tgo.htm>

⁵⁵ <http://www.tga.gov.au/industry/legislation-tgo-77-guide.htm>

A reduced schedule of tests at batch release (periodic, rotational or skip testing) is the testing of certain parameters at a predetermined interval or on pre-selected batches, rather than testing of every batch. An example of a reduced schedule of tests is testing every fifth batch of a tablet formulation for friability conditional on the first three production batches found to be satisfactory in this respect. Any proposal for a reduced schedule of tests at batch release must be detailed in the application and justified. The extent of justification required will depend on the type of product and parameter proposed for reduced testing. Details of the reduced schedule of tests must be included on the finished product release specifications.

7.8.2 Expiry specifications

Any expiry limits which are less stringent than those commonly applied to the relevant dosage form should be justified in detail.

Note: TGO 78⁵⁶ allow wider limits for content of some active ingredients.

Some commonly applied expiry limits are:

Table 7.1 Content of active ingredients in the absence of an individual default standard

Dosage Form	Content
In tablets and capsules:	92.5 - 107.5% of stated content as required by TGO 78
In most other products, e.g. topical products and oral liquids:	90.0 - 110.0% of stated content

Table 7.2 Content of preservative(s) and antioxidant(s) present as excipients

Limit	
Upper limit :	120% of stated content
Lower limit for preservative:	The lowest concentration for which effectiveness has been demonstrated by preservative efficacy testing in stability studies
Lower limit for antioxidants:	The lowest concentration for which absence of significant oxidation of the product has been demonstrated in stability studies

For medicines that may reasonably be expected to contain significant quantities of ethylene oxide or ethylene chlorohydrin the limits are as described in the *Note for Guidance on Limitations to the Use of Ethylene Oxide in the Manufacture of Medicinal Products* (CPMP/ICH/159/01)⁵⁷:

⁵⁶ <http://www.tga.gov.au/industry/legislation-tgo.htm>

⁵⁷ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

-
- Ethylene oxide: not more than 1 microgram per gram
 - Ethylene chlorohydrins: not more than 50 micrograms per gram

Where the default standard has stricter specific requirements, these take precedence.

7.9 Analytical procedures and validation

Details must be provided for all analytical methods that are used in the finished product specifications and the stability studies, together with validation data where appropriate (e.g. for assay of active ingredient, preservatives, and related substances). Where the test methods used in the stability studies differ from those of the finished product specifications this should be clearly stated and justified. Where a test method is included in a relevant pharmacopoeial monograph, the pharmacopoeial reference must be given. Where a test method is not included in a pharmacopoeial monograph, a full copy of that test method must be provided.

Supporting validation data is required for all critical assay methods, including assay methods that are described in a relevant pharmacopoeial monograph. The sponsor cannot assume that a test method described in a pharmacopoeial monograph is suitable for all formulations to which the monograph applies.

Applications will not be accepted for evaluation where:

- the analytical methods used are not stated
- the results of validation testing are not given or where the issue of validation is not addressed.

The validation data for critical assays should be in accordance with the ICH guideline *Note for Guidance on Validation of Analytical Procedures: Text and Methodology Rev 1* (CPMP/ICH/381/95)⁵⁸. For some of the most common categories of tests, the performance parameters for which validation data are normally expected are summarised in the following table.

⁵⁸ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

Table 7.3 Performance parameters for validation data.

Performance Parameter	Identification test	Quantitative test for Impurities	Limit test for Impurities	Assay
Accuracy	-	+	-/+	+
Precision	-	+	-	+
Specificity	+	+	+	+
Detection Limit	-	-/+	+	-
Quantitation Limit	-	+	-	-
Linearity / Range	-	+	-	+
Robustness	see note below			

+ Performance Parameter is normally evaluated

- Performance Parameter is not normally evaluated

-/+ Performance Parameter may be required in some cases

Note: Where robustness testing has not been performed as part of method validation, the suitability requirements that are applied in the test method should be comprehensive enough to control any potential lack of robustness that may be present.

Additional sources of information on method validation include the following (much of the guidance on validation of compendial procedures also applies to validation generally):

- BP Supplementary Chapter SC III F. Validation of Analytical Procedures
- USP chapters <1225> *Validation of Compendial Procedures*

Sources of information on requirements for establishing the suitability of compendial procedures for analysis of the proposed formulation include the following:

- information under the subheading *Published Methods* in BP Supplementary chapter SC III D. Monograph Development, stating what users can and cannot expect from published methods
- USP chapter <1226> *Verification of Compendial Procedures*

A copy of the validation report should be provided. The report should include (or be accompanied by) a summary clearly stating the results obtained for each parameter assessed, as well as the acceptance criteria and a conclusion as to whether the results were acceptable. Where a chromatographic procedure is used, the report should also include (or be accompanied by) a selection of relevant chromatograms associated with the validation of specificity. For example, reference chromatograms, sample chromatograms, placebo chromatograms, and chromatograms of known degradants and/or chromatograms obtained in forced degradation studies should be provided.

Note: The inclusion of this summary is recommended in order to facilitate evaluation of the data; however, for applications in CTD format where an appropriate summary is included in module 2.3.P.5, this does not need to be duplicated.

7.9.1 Stability indicating assays

Active ingredient assays should be demonstrated to be capable of reliably quantifying a decrease in the amount of the active ingredient due to degradation (i.e. a stability indicating assay). Pharmacopoeial methods are not necessarily stability indicating.

7.9.1.1 Well-known degradants

When the identity of all degradants is well known, sensitivity to degradation may be established by demonstrating that the known degradants do not interfere with the analysis. It may be appropriate to analyse known degradants as pure substances and also when mixed with excipients, sample extract and/or reference solution.

The potential for interference from excipient degradants should also be considered (refer to [Section 7.9.1.2 Forced degradation studies](#)).

7.9.1.2 Forced degradation studies

When the identity of the degradants is not clear or when the sponsor does not have access to authentic specimens of the degradants, forced degradation studies should be undertaken. Commonly used forcing degradation conditions include treatment with some or all of the following (as appropriate to the product):

- an aqueous solution of a mineral acid
- an aqueous solution of sodium hydroxide
- an aqueous solution of a strong oxidising solution such as hydrogen peroxide
- heating the product
- exposing the product to direct sunlight (or another source of ultraviolet light) for a prolonged period.

Interference by excipient degradants can also be assessed by subjecting placebo blends to the forcing conditions.

The following information should be provided for evaluation:

- tabulated recovery data for the non-degraded product and following treatment under the different degradation conditions.
- copies of relevant chromatograms (in the case of chromatographic assays), comparing the impurity profiles.
- results of peak purity analysis (for HPLC assays), if an appropriate detector and software are available.
- if the product contains more than one active, the sponsor should address whether degradants from one active can interfere with assay of the other active.

The primary purpose of forced degradation studies is to validate the assay method rather than to establish the stability of the finished product. In order to demonstrate that the assay method is sensitive to degradation, some degradation of the active ingredient must be shown. If degradation has not occurred under the conditions used, the study may be repeated using more forcing degradation conditions. Where degradation of the relevant active ingredient is intrinsically difficult to achieve, a justification should be provided for not submitting the usual data.

It is valuable to demonstrate that a decrease in the active ingredient content is accompanied by a corresponding increase in impurity content (sometimes referred to as 'mass balance'). Where the assay methods for the active and related substances differ it may be necessary to investigate both assays within the forced degradation study, in order to demonstrate that the degradation products can be detected using the related substance assay.

8. Finished product container

Details of the container type and material(s) must be provided; as well as details of specifications applied to the container components.

For plastic and rubber packaging components, evidence should be provided that the components comply with the relevant BP/Ph. Eur. and/or USP/NF requirements for polymeric materials used in packaging of medicines, or are approved for use with foodstuffs.

The sponsor should ensure that the container closure system complies with the requirements of the TGO 80 *Child-Resistant Packaging Requirements for Medicines*⁵⁹, where applicable. Where the TGO 80 applies to the product, the sponsor should provide details of the container closure system and an assurance that it complies with the TGO 80.

Although the *Code of Practice for the Tamper-Evident Packaging (TEP) of Therapeutic Goods* (Ed 1 June 2003)⁶⁰ is currently under review, voluntary compliance is recommended by the TGA.

8.1 Measuring devices or other dose delivery devices

Some measuring devices or dose delivering devices may require a separate listing on the ARTG, sponsors should refer to the *Australian Regulatory Guideline for Medical Devices* (ARGMD)⁶¹ for further guidance.

All submissions should include details of any measuring device or other dose delivery device that is intended to be supplied with an OTC medicine. The submission should include a copy of the specifications for the measuring device. If the design, composition and performance of the device is not clearly described in the submitted specifications, it may be necessary to submit drawings or a sample of the measuring device for evaluation.

Calibrations on measuring devices should be exclusively in metric units and allow all the doses shown on the labels to be measured accurately.

The ability of the device to deliver the correct dose accurately and reproducibly must be ensured. In particular, the BP/Ph. Eur. Appendix XII C. *Consistency of Formulated Preparations* includes a test and requirement for *Uniformity of Weight (Mass) of Delivered Doses from Multidose Containers* (Ph. Eur. monograph 2.9.27). Where this requirement applies, it is sufficient that the sponsor provide an assurance that the proposed measuring device complies with the requirements of this test.

⁵⁹ <http://www.tga.gov.au/industry/legislation-tgo.htm>

⁶⁰ <http://www.tga.gov.au/industry/packaging-tamper-evident-cop.htm>

⁶¹ <http://www.tga.gov.au/industry/devices-argmd.htm>

Note: Sponsors intending to supply measuring devices with the product should also consult the current versions of the Australian Standards AS 2224.2 and AS 2224.1 for plastic and glass medicine measures, respectively. These Australian Standards provide guidance on materials, design, dimensions, construction, markings and performance attributes of medicine devices. These Standards are not mandatory requirements in this context; however, if the device does comply with all or part of the relevant Standard, it will facilitate the evaluation if this is stated.

9. Stability of the finished product

Full details of stability testing conducted on the product together with associated validation must be included in the submission. The design of stability studies should be consistent with the relevant CPMP/ICH guidelines⁶² and associated TGA annotations (see '[Section 9.3 Stability study design](#)').

At the time of submission, the data package should include sufficient stability data to justify a shelf life of at least 12 months.

9.1 General principles

The objective of a stability study is to determine the time during which a pharmaceutical product meets appropriate standards when stored under defined conditions. The product must be shown to remain, or be likely to remain, within its expiry specifications throughout the proposed shelf life when stored under the proposed storage conditions.

The requirement to remain within the expiry specifications applies to all batches, including those which may be released at the low end of the release limits. Therefore, the difference between release and expiry specifications must take into account the results of stability testing.

9.1.1 Formulation

The formulation (and the manufacturing process used to manufacture the formulation) used in the stability studies should be the same as that proposed for registration. Stability data on related formulations may be submitted as supporting evidence provided the differences between the formulation employed in the stability trial, and that proposed for registration are clearly stated and the relevance justified. A shelf-life will not normally be allocated for the purposes of registration if there are no data on the formulation to be registered.

9.1.2 Container

The stability of the finished product should be assessed in the container closure system proposed for registration. If the product is to be registered in more than one container closure system, stability data should normally be provided for each presentation unless a bracketing/matrixing approach can be adequately justified. Stability data in other types of container are of limited value, unless comparative studies are provided that clearly demonstrate the equivalence or superiority of the container closure system intended for registration over the system used in the stability trials.

⁶² <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

9.2 Data requirements

- A critical summary of the stability studies (see further details below).
- Full details and results of stability studies on the ‘primary batches’ (these studies should be designed in accordance with the relevant ICH guidelines).
Note: ‘primary batches’ are those described under ‘[Section 9.4 Minimum data requirements](#)’.
- Test methods and validation data, where required.

9.2.1 Critical summary of the stability studies

Where appropriate summary/s has/have already been provided under Module 2 and/or Module 3.2.P.8.1 in a CTD⁶³-formatted dossier, this does not need to be duplicated). The critical summary should include all of the following (for each of the submitted studies):

- A clear statement as to whether all (or some) of the batches tested were identical with the product intended for marketing in terms of formulation, container, method of manufacture and manufacturing equipment (if not, the differences should be justified and full details provided).
- Details of test methods and supporting validation data. If the stability study test methods are identical to those in the routine quality control specification it is sufficient to state this. Any change in test methods while the studies are in progress should be justified and validated.
- A table giving batch numbers, batch types (pilot or production), batch size or scale, storage conditions (temperature, humidity, lighting conditions, and storage upright or inverted for liquids), and storage durations. The controls applied to the storage conditions should be stated. For details of requirements for minimum number of batches, minimum study duration and storage conditions, see ‘[Section 9.4 Minimum data requirements](#)’ and ‘[Section 9.5 Storage conditions](#)’.
- Brief details and a critical analysis of the results observed for each of the test parameters included in the studies. Separate comments should be provided for each test parameter, including the following:
 - a heading (parameter/test name, limits, and test technique) for example *Content of salicylic acid (HPLC - NMT 0.3%)*.
 - an assessment and interpretation of the trends observed in the results of testing (numerical description is preferred). The variability in the results and any anomalous results should be considered. If the results show excessive variability that prevents the assessment of the trends, this should be stated. It may be appropriate to discuss the results of any investigations into the loss of the active ingredient.
- The basis for selecting the proposed shelf life and storage condition should be discussed.

9.2.2 Critical summary of the stability studies for extension of shelf life

Where a sponsor applies to extend the shelf life of a registered product, the critical summary should address the above points and also state whether stability studies for the

⁶³ <http://www.tga.gov.au/industry/pm-argpm-ctd.htm>

product have previously been evaluated by the TGA. If this is the case, the summary should:

- provide details of the date of the approval letter as well as file and reference numbers, if known
- state whether the stability data provided are a continuation of studies previously evaluated by the TGA (i.e. an extension of a study using the same batches, storage conditions and test methods).

9.3 Stability study design

The design of stability studies should be consistent with the following EMEA/CPMP/ICH documents (and any subsequent editions adopted by the TGA), taking into consideration the relevant TGA annotations and the following guidance, where appropriate. These documents and accompanying TGA annotation(s) can be found on the TGA website⁶⁴ as updated from time to time:

- *Stability Testing Guidelines: Stability Testing of New Drug substances and Products (Revision 2)* [CPMP/ICH/2736/99 Revision 2 (Q1A)]
- *Guideline on Stability Testing: Stability Testing of Existing Active substances and Related Finished Products* (CPMP/QWP/122/02 Rev 1)
- *Note for Guidance on Evaluation of Stability Data* (CPMP/ICH/420/02)
- TGA annotated *Note for Guidance on Stability Data Package for Registration in Climatic Zones III and IV*-(CPMP/ICH/421/02)
- *Note for Guidance on Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Medicinal Products* (CPMP/ICH/4104/00)
- *Note for Guidance on In-use Stability Testing of Human Medicinal Products* (CPMP/QWP/2934/99)
- *Photostability Testing of New Drug substances and Medicinal Products* (pp. 157-166 of Rules 1998 (3A) – 3AQ18a)

The stability data will be evaluated in accordance with all relevant CPMP/CHMP/ICH guidelines, therefore sponsors should also consult any other TGA adopted CPMP/CHMP/ICH guidelines⁶⁵ which are of relevance to the sponsor's product.

The following sections are intended to assist applicants in applying the CHMP/ICH guidelines and in understanding how these guidelines are interpreted.



Transition period

There will be no requirement to justify submission of stability studies that were designed to meet the requirements of the previous ARGOM and were commenced prior to or within 12 months of the implementation of the current ARGOM. After this period a justification will be required. The sponsor should

⁶⁴ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

⁶⁵ <http://www.tga.gov.au/industry/pm-euguidelines-adopted.htm>

clearly state whether the stability studies were designed in accordance with the requirements.

9.4 Minimum data requirements

The *Guideline on Stability Testing: Stability Testing of Existing Drug Substances and Related Finished Products* (CPMP/QWP/122/02 Rev 1)⁶⁶ distinguishes between two different types of product for which different minimum requirements are imposed for the dataset submitted with the application. These requirements can be briefly summarised as follows (sponsors must consult the guidelines for full details):

- **‘Option a’:** For conventional dosage forms such as immediate release solid dosage forms and solutions, when the active ingredient(s) are known to be stable, it is acceptable to provide a minimum of six months of long term, intermediate (if applicable) and accelerated stability data on a minimum of two batches of at least pilot scale.

Note: *Stability Testing Guidelines: Stability Testing of New Drug Substances and Products (Revision 2)* [CPMP/ICH/2736/99 (Q1A)]⁶⁷ defines a pilot scale batch as one manufactured by a procedure fully representative of and simulating that to be applied to a full production scale batch. For solid oral dosage forms, a pilot scale is generally at least one tenth of a full production scale batch or 100,000 tablets or capsules, whichever is the larger.

- **‘Option b’:** For products which are likely to be unstable, or for which stability failure would be critical, data for three batches are required in the submission. Two of the three batches should be of at least pilot scale (the third batch may be smaller). The data must include at least 12 months of long term results, in addition to six months of accelerated data (and six months of intermediate data, if applicable).

Stability studies should be conducted on each individual strength and container size of the finished product unless bracketing or matrixing is applied [see *Note for Guidance on Bracketing and Matrixing Designs for Stability Testing of Drug Substances and Medicinal Products* (CPMP/ICH/4104/00)⁶⁸].

9.4.1 Requirements for additional stability commitment

In cases where stability data have been provided only at pilot scale, or where full term production batch data have been provided for fewer than three production batches, the CPMP guideline states that a commitment should be made to conduct full term stability studies on production batches of the goods, up to a total of three. **However, for OTC medicine registrations, data for two production batches will generally be sufficient.**

In these cases, it will be made a condition of registration that stability trials are conducted on the first post-registration production batches of the goods, up to a total of two (see also [‘Section 9.8 Post registration requirements’](#)).

⁶⁶ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

⁶⁷ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

⁶⁸ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

9.5 Storage conditions

Selection of storage conditions for the stability studies should be appropriate for the storage conditions that are to be stated on the label of the finished product, and should be consistent with those described in the relevant CPMP/ICH guidelines tabulated in '[Section 9.3 Stability study design](#)' (some departure from the ICH conditions is permissible where the conditions specified in the Australian Labelling Order are inconsistent with the ICH conditions, as detailed in the dot-points below).

Long term studies should be conducted at the maximum temperature stated on the finished product label, unless the guidelines prescribe differently. For example, where the labelled storage condition is 'Store at 2°C to 8°C (Refrigerate. Do not freeze)' the long term storage condition in stability trials should be 5°C±3°C.

The following additional points should be noted:

- For products labelled 'Store below -18°C (Deep Freeze)', the storage conditions - 20°C±5°C detailed in sub-section 2.2.7.5 of the *Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products* (CPMP/QWP/122/02 Rev 1)⁶⁹ are acceptable.
- For products labelled 'Store below 8°C (Refrigerate)', without the caution Do not freeze, stability must be demonstrated both at 5°C±3°C and at -20°C±5°C. This is particularly important for products that may have physical stability issues (e.g. segregation, formation of precipitates, or denaturation of proteins).
- Similarly, for products labelled with the condition 'Store below -5°C (Freeze)', which also allows for storage in a deep freezer, stability must be demonstrated at -20°C±5°C, as well as under controlled conditions at -5°C (ideally, the temperature control for stability trials at -5°C should be within ±3°C, as for refrigerated storage; but, as this is not a standard ICH temperature for stability studies, this will be evaluated on a case-by-case basis).
- Where products are packaged in potentially moisture permeable materials, studies under high or low humidity may be required, as discussed below.

Australia has climatic conditions encompassing ICH zones I-IV, therefore conditions of storage likely to be encountered in Australia should be considered in designing the stability trial. However, as described in the CHMP/ICH stability guidelines, stability data for products stored in impermeable containers may be conducted under any humidity condition.

Containers that are generally considered to be moisture-impermeable include:

- Al/Al blisters,
- HDPE or glass bottles fitted with HDPE or metal closures.

If a sponsor considers that high humidity data are not needed for a solid dosage form that is packed in a particular material, this should be supported by information on the composition, thickness, density and moisture transmissibility of the packaging materials.

⁶⁹ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

9.5.1 High humidity studies

The use of moisture-permeable containers and/or closures for the packaging of pharmaceuticals raises questions concerning the stability of the contents when stored under conditions of high humidity. High relative humidity can affect chemical stability and physical stability (e.g. altered dissolution rate).

Data should be generated to establish the effect of high humidity on solid dosage forms packaged in containers that are likely to be permeable to moisture. Examples of containers that would generally be considered moisture-permeable include:

- Plastic blister packs such as polyvinyl chloride blisters,
- Low density polyethylene bottles,
- Glass or high density polyethylene bottles when fitted with closures made of moisture-permeable polymers.

The *Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products* (CPMP/QWP/122/02 Rev 1)⁷⁰ require 6 months of data at 40°C/75%RH to be provided in applications to register products that are to be stored at 25°C or 30°C. These data, if satisfactory, would also be generally sufficient to establish the adequacy of the packaging to protect the product from moisture. However, some products may be adversely affected by the high temperature used in such studies. The TGA annotation to the *Note for Guidance on Stability Data Package for Registration in Climatic Zones III and IV* (CPMP/ICH/421/02)⁷¹ provides useful guidance in this case. Relevant parts of the annotation are reproduced below.

If a product does not show satisfactory stability for at least 3 months at 40°C/75% RH, there are several acceptable options:

- *argue that, as the container is designed to provide a barrier to water vapour, further investigation of stability under conditions of high humidity is not necessary*
- *demonstrate, by testing at least 3 batches, that the product is stable for 3-6 months at 30°C/75% RH*
- *package the product in a container/closure system that is less permeable to water vapour*
- *label the product 'Store below 25°C'.*

If a product is labelled 'Store below 25°C', the TGA will accept:

- *long term stability testing at 25°C/60% RH in place of 30°C/65% RH*
- *6 months testing at 25°C/80% RH or 30°C/65% RH (at least 3 batches) in place of 40°C/75% RH. Nevertheless, initial testing of the product should be conducted in accordance with the guideline, that is, at 30°C/65% RH and 40°C/75% RH. If stability is inadequate under these conditions (and, if tested, the alternative condition of 30°C/75% RH) the use of more protective packaging should be considered before the option of labelling the product 'Store below 25°C'.*

Generally, if a product shows satisfactory stability for at least 3 months at a high humidity test condition (40°C/75% RH, 30°C/75% RH, 30°C/65% RH or 25°C/80% RH, as appropriate), then the TGA will consider a shelf life of up to 2 years, subject to satisfactory

⁷⁰ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

⁷¹ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

long term stability data. If a product is stable for 6 months under these conditions then a shelf life in excess of 2 years will be considered.

[Any of these four storage conditions would be acceptable for high humidity testing of a product labelled 'Store below 25°C', but only 40°C/75% RH or 30°C/75% RH would be acceptable for a product labelled 'Store below 30°C'.]

These short term high humidity data provide support for stability data accumulated at the maximum recommended storage temperature at lower relative humidity, but do not remove the need for studies for the duration of the shelf life.

9.5.2 Low humidity studies

Aqueous solutions, suspensions and emulsions supplied in permeable plastic containers may lose water by evaporation on storage. Stability studies consistent with those described in section 2.2.7.3 *Finished products packaged in semi-permeable containers in the Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products* (CPMP/QWP/122/02 Rev 1)⁷² should be carried out for products in this category.

9.5.3 Cycling of temperature and humidity

The cycling effect of night and day temperatures and humidity can be important in certain cases, such as creams, suspensions and inhaler products where the active ingredient may be present partly in suspension and partly in solution. Where relevant, the cycling effect of temperatures and humidity should be considered in the design of stability studies.

Temperature cycling study(s) should be designed to mimic the likely conditions of actual marketplace storage, and should take into account product-specific chemical and physical degradation properties. The most common period of cycle is 24 hours, reflecting the normal diurnal rhythm.

Such data may be useful in confirming the stability of the product under conditions of stress. However, it is difficult to derive accurate predictions for the shelf life of a product from this information, and it is not a routine requirement.

9.5.4 In-use data

In-use stability data should be generated where relevant, for example:

- Where chemical and microbiological deterioration occurs once a multidose product container is opened (e.g. for antacids, and sterile preparations such as those intended for ophthalmic use), in-use testing should be performed to justify the proposed storage period and conditions after the container is opened.

Note: For sterile products that are intended for multiple use the preservative efficacy must be demonstrated over the open shelf life period (for eye preparations this is 4 weeks) – see ['Section 9.6.6 Preservative efficacy'](#) further information)

- Where the product must be reconstituted or diluted prior to use (e.g. oral powders for suspension), and is claimed or implied to be stable when stored for a certain period or mixed with other products (e.g. food or beverages), in-use testing should justify the claimed or implied storage period and conditions including diluent.

⁷² <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

The *Note for Guidance on In-use Stability Testing of Human Medicinal Products* (CPMP/QWP/2934/99)⁷³ should be consulted for products requiring in-use stability data. The stability of the in-use form of the product should be established for the period of time and under the conditions for which storage is recommended.

9.6 Appropriate tests

9.6.1 General

The TGA-adopted CPMP/ICH guidelines *Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products* (CPMP/QWP/122/02 Rev 1)⁷⁴ and *Note for Guidance on Stability Testing: Stability Testing of New Drug Substances and Products* (CPMP/ICH/2736/99)⁷⁵ provide guidance in the selection of appropriate tests and limits for stability studies.

All test methods used in stability studies should be appropriately validated, and test method and validation data should be provided, in line with the requirements set out in '[Section 7.9 Analytical procedures and validation](#)'. If test methods and validation data have been included elsewhere in the dossier they do not need to be duplicated in the Stability section.

Where test methods are identical to those in the finished product specifications, this should be explicitly stated. Alternative test methods may be used in stability studies, but they should be fully described and appropriately validated.

Dissolution procedures other than those in finished product specifications are discouraged (except to add extra test points for the generation of dissolution profiles).

Test methods should not be changed during stability studies, as it may be difficult to compare results obtained before and after a change. If a change to a test method is required, the change should be justified and validated. Both procedures should be conducted at several stations to allow the results to be compared, unless another approach can be justified. Changes to dissolution test methodology during stability studies are strongly discouraged.

Where a test gives quantitative results these should be provided instead of indicating 'complies' or 'passes'. However, if 'complies' refers to a limit that is tighter than the specification limit (e.g. to a limit of '< 100' in microbial testing where the specification limit is '< 1000') this may be acceptable provided it is unambiguously indicated in the stability reports.

9.6.2 Assay

For assays it is particularly important that quantitative results are provided, so that any trends over time can be observed. Where multiple assay results are provided at one time-point, it should be clear what these represent (e.g. repeat injections of analytical solution or replicate sampling from a defined number of dosage units).

For tablets and capsules it is vital that an adequate number of individual dose unit results are sampled to minimise the effect of individual dose unit variations. The number sampled

⁷³ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

⁷⁴ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

⁷⁵ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

(and pooled or averaged) should be consistent with that required under TGO 78 *Standard for Tablets and Capsules*⁷⁶.

The active ingredient assay method should be stability indicating (refer to '[Section 7.9 Analytical procedures and validation](#)'). Where a loss of the active ingredient is observed in the stability studies, the fate of the active ingredient may require investigation. It should be noted that loss of the active ingredient may be due to factors other than degradation, such as complexing with excipients, adsorption onto or absorption into the container wall and volatilisation.

In addition to assay of the active ingredient, it may be necessary to assay other components, such as preservatives or antioxidants.

9.6.3 Degradation products

Chromatographic techniques are preferred for the separation and detection of degradation products, but validated alternative methods of quantification may be acceptable. If reference standards for degradants are unavailable, response factors should be taken into account in the calculation of results. If response factors cannot be determined, the method used to calculate the level of the degradant should be justified.

Trends in the formation of degradation products, as well as assay of the active ingredient, will be considered in the evaluation of the stability data and in assigning a shelf life to a product. Therefore, the levels of degradation products should be quantified as far as possible; and the quantitative results provided. Results should be given for total and all individual degradants detected, even where the identity of the degradant is unknown. Where appropriate, relative retention times should be given for unidentified degradation products to aid correlation and interpretation of data.

More information regarding control of degradation products is included in '[Section 7.4 Related substances](#)' and '[Section 7.9.1 Stability indicating assays](#)'.

Synthetic impurities that are not also degradants need not be reported, provided they are adequately controlled in the active substance specification. Retention times of any synthetic impurities should be determined to ensure that they do not interfere with measurement of the degradation products.

9.6.4 Physical properties

It is necessary to monitor the physical properties of the product during storage. The physical tests that are appropriate to include in the stability study will vary with the formulation in question. Some important physical attributes of the major dosage forms are outlined in the following table.

⁷⁶ <http://www.tga.gov.au/industry/legislation-tgo.htm>

Table 9.1 Physical attributes of the major dosage forms.

Dosage form	Physical tests
Tablets and capsules	Dissolution, disintegration (if dissolution is not required), appearance, odour, hardness, friability, moisture content, brittleness (hard gelatin capsules)
Liquid formulations	Appearance, colour, odour, pH, clarity (solutions) and particle size distributions (suspensions), resuspendibility (suspensions), viscosity, moisture content (powders for reconstitution), phase separation (emulsions)
Ointments and creams	Appearance, odour, viscosity, softening range, loss of water, physical and chemical homogeneity, particle size distribution, particle formation, pH, phase separation (emulsions)
Aerosols	Leak test, particulate contamination, valve function and appearance, weight loss. For metered dose aerosols refer to the BP monograph <i>Preparations for Inhalation</i> ⁷⁷ and also to the specific product monographs. Metered dose aerosols and some pump actuated aerosols will also require measurements of active ingredient mass aerodynamic particle size distribution on ageing
Suppositories and pessaries	Appearance, softening temperature (moulded products), dissolution rate (compressed products), disintegration testing
Freeze-dried material (including materials for reconstitution)	Appearance of both freeze dried and reconstituted material, pH, water content, rate of solution
Medicated soap bars	Appearance, odour, weight loss and pH

Loss of moisture by transpiration can be important for some products, such as water based creams in moisture permeable containers. The extent of loss can be assessed by accurate weighing of marked individual packs over time. If severe, it may also be apparent as an increase in the concentration of the active ingredient or other components in the product.

For other dosage forms not included in the above table, the sponsor should define the appropriate tests.

⁷⁷ <http://www.pharmacopoeia.co.uk/>

9.6.5 Microbial content testing

As defined in TGO 77 *Microbiological standards for medicines*⁷⁸ sterile OTC dosage forms must comply with the *Test for sterility* of a default standard. TGO 77 also includes bacterial endotoxin test requirements, but these are not relevant to OTC products.

For non-sterile dosage forms, microbial content testing should be carried out at the end (and preferably at the beginning) of shelf life during stability studies to demonstrate that the product remains within product specifications until expiry; unless the absence of limits for microbial content in the expiry specifications have been justified (see '[Section 10.2 Non-sterile medicines](#)').

9.6.6 Preservative efficacy

Products that are intended for multi-dose use should be adequately preserved for the duration of the claimed shelf life. This applies to both non-sterile products (e.g. aqueous creams, lotions, and oral liquids) and sterile products (e.g. eye preparations). It is necessary to prevent microbial proliferation in, or microbial contamination of, such products during their normal conditions of storage and use.

During product development, preservative efficacy testing should be performed at the beginning and end of the claimed shelf life to demonstrate that the antimicrobial activity of the product as such or, if necessary, with the addition of a preservative(s), has not been impaired by storage. Data must be specific to the formulation and the container. If the requested shelf life is based on data generated under accelerated conditions, preservative efficacy tests should be performed on samples that have been stored at the higher temperature.

The TGO 77 *Microbiological standards for medicines* specify the minimum microbiological requirements with which a medicine must comply throughout its shelf life. In relation to preservative efficacy Clause 8 of TGO 77:

- i. *requires a multidose medicine, other than a liquid oral antacid medicine, to comply with the requirements of Appendix XVI.C of the British Pharmacopoeia or Chapter 5.1.3 of the European Pharmacopoeia.*
- ii. *permits a multidose liquid oral antacid medicine to comply with the requirements of Chapter <51> of the United States Pharmacopoeia-National Formulary.*

Chemical assays of the level of preservative are not accepted as substitutes for biological tests.

Note: Chemical tests and limits for content of preservatives are acceptable for routine quality control, provided the limits have been justified on the basis of preservative efficacy studies over the shelf life. Given that the effectiveness of many preservatives is pH dependent, the specifications for such products should usually also include requirements for pH which will ensure preservative efficacy (the limits should have been justified on the basis of preservative efficacy studies over the shelf life).

For sterile products (e.g. eye preparations), that are intended for multiple use, the preservative efficacy of the product over the open shelf-life period (e.g. 4 weeks for eye preparations) must also be demonstrated. Such testing should involve repeated microbial challenges over the open shelf-life period as this most closely mimics the in-use situation.

⁷⁸ <http://www.tga.gov.au/industry/legislation-tgo.htm>

Alternatively, microbial content testing may be carried out on partially used containers that have been used by patients for the full open shelf life.

Modifications of a pharmacopoeial preservative efficacy test (preferably the Ph. Eur. /BP test) that include a rechallenge with reduced numbers of organisms could be used.

Guidance may also be obtained from the normative part of the international standard *ISO 14730 Ophthalmic optics – Contact lens care products – Antimicrobial preservative efficacy testing and guidance on determining discard dating* which describes a test procedure and performance criteria for preservative efficacy over an open shelf life period of 28 days.

Note: This reference is not being supplied as a standard that must be applied to a product. It is supplied solely to demonstrate the elements of the type of tests that would be required to support an open shelf life period.

9.6.7 Dissolution

Test conditions should be those applied in the finished product specification (refer to [‘Section 7.5 Tablets and capsules’](#)). If different test conditions and/or limits are used, this should be justified, and validation data should be provided.

Dissolution data should be generated on at least six individual units at each test station and should be reported as both mean data and either individual data or ranges.

For certain products, dissolution profiles should be generated showing the percent of nominal content dissolved at a number of time points (at appropriate time intervals). Products for which it is relevant to generate dissolution profiles include:

- modified release products
- certain immediate release products where it has been shown that rapid release of the active ingredient leads to a higher incidence of adverse effects
- in cases where there is uncertainty about the validity of the dissolution test method
- in cases where single-point data suggest there may be a problem with the dissolution rate of the product (especially with aging).

9.6.8 Extractables

The possibility of leaching of substances from container-closure systems into the product should be considered in the design of stability studies and data should be generated for any product where this could occur (e.g. liquid preparations in containers that have component/s made of plastic or rubber materials that are not covered by relevant default standard monographs), and particularly where this may be a hazard, for example:

- ophthalmics supplied in non-glass containers or with plastic or rubber stoppers
- plastic components of liquid products intended for inhalation.

9.7 Prediction of shelf life from stability data

Prediction of shelf life is facilitated if the data include frequent intermediate stations (in line with the CPMP/ICH recommendations), are derived from several batches, consider a range of conditions, are of high precision, include analysis for breakdown products, and consider the physical properties of the formulation.

The *Note for guidance on Evaluation of Stability Data (CPMP/ICH/420/02)*⁷⁹ provides detailed guidance on evaluation of the data from formal stability studies. The guideline presumes that the required amount of 'minimum data' are available, as outlined under '[Section 9.4 Minimum data requirements](#)'.

For products intended for storage in a freezer no extrapolation beyond the period covered by the long term data is permitted (and testing of a single batch at an appropriate elevated temperature should also be conducted to address the effect of short term excursions outside the proposed label storage condition, such as during shipping or handling).

For other products, the assessment should begin with any significant change under accelerated conditions and, if appropriate, at the intermediate condition, and progress through the trends and variability of the long term data. Based on the outcome of this assessment, the guideline describes rules for the amount of extrapolation that can be permitted beyond the period covered by the long term data and Appendix A of the guideline provides a decision tree. In the case of products labelled 'Store below 25°C' or 'store below 30°C' where the accelerated and long-term data show little change or variability, the maximum extrapolation of shelf life is up to twice, but should not be more than 12 months beyond the period covered by long-term data [as per *Note for Guidance on Evaluation of Stability Data (CPMP/ICH/420/02)* section 2.4.1.1 and *Appendix A of Note for Guidance on Evaluation of Stability Data*]. In the case of products labelled 'store below 8°C' the maximum extrapolation of shelf life is up to one and a half times but should not be more than 6 months beyond the period covered by long-term data.

The maximum permitted total shelf life is normally five years.

9.8 Post-registration stability requirements

Sponsors of therapeutic goods are required to carry out an ongoing stability testing program on each product (refer to details contained in the Code of GMP⁸⁰ - Chapter 6 Quality control, or for additional advice contact the TGA).

Where a shelf life has been allocated on the basis of anything less than full-term data on two production batches, it will be made a specific condition of registration of the product that a stability testing program be initiated on the first production batches of the goods (to a total of two), and that any adverse results be immediately reported to the TGA.

Data may be requested for review at any time or followed up by the TGA's auditors during GMP audits of the manufacturer. If it is found that the required testing has not been carried out or that adverse trends have not been reported to the TGA, appropriate action may be taken which may include cancellation of the product's registration.

⁷⁹ <http://www.tga.gov.au/industry/pm-euguidelines-adopted-quality.htm>

⁸⁰ <http://www.tga.gov.au/industry/manuf-medicines-cgmp.htm>

9.9 Product modifications that require stability data

Applications to make certain changes to a product may require supporting stability data. For example:

- Change in composition of a product
- Change of container
- Extension of shelf life.

9.10 Requirements for a proposed stability testing protocol for self assessable shelf life extension

A product's shelf life may be extended on the basis of stability testing conducted according to a protocol that was specifically approved by the TGA for this purpose. For a stability protocol to be considered for the purpose of self assessable shelf life extensions, it is necessary for at least 12 months data, generated at the maximum recommended storage temperature, to be available on at least two production batches of the proposed formulation, in the container proposed for marketing, or one which is less protective.

To provide a suitable margin of safety, the limits for results of critical test parameters should normally be a little tighter than the expiry limits. Where some results are outside these limits, the sponsor may submit the data for evaluation by the TGA.

The protocol should be a stand alone document which includes:

- a statement of the intended purpose (e.g. *'This protocol is intended for notification of shelf life increases of up to x years following self assessment of stability data'*).
- a statement of the criteria for notifying a shelf life increase (e.g. *'full term stability data will be generated using two production batches stored at y°C, all analytical results obtained will comply with the protocol acceptance criteria'*):
 - the precise formulation of the product (if overages are included, this should be stated).
 - the immediate container specifications.
 - the storage conditions to be included on the label.
 - the finished product expiry specifications and the protocol acceptance criteria (including acceptable limits for results of each test).
 - a statement of the proposed tests and validated test methods (validation data should be included, unless referenced to elsewhere in the application).
 - a matrix indicating the time stations at which each of the tests will be conducted as well as the storage conditions to be used in the study.

9.10.1 Shelf life extensions according to an approved protocol

The sponsor may submit an application to the TGA for shelf life extension without submitting additional data for assessment, if a protocol for self assessable shelf life extensions has been approved by the TGA for a particular product, and provided that:

- all results up to the end of the notified shelf life fall within the acceptance criteria as specified in the approved stability protocol.
- no other changes to quality related aspects of the product have been made, or are currently proposed to be made.
- a copy of the approval letter for the stability testing protocol is attached to the notification.
- at least two full production batches of the approved formulated product packed in the approved container have been used in the studies.
- the shelf life is not longer than the time for which stability data meeting the approved protocol are available.
- the shelf life is not longer than 5 years.

9.11 Prospective extensions of shelf life for individual batches

Under certain circumstances, the TGA may approve a limited extension of shelf life for individual batches approaching their expiry date in the absence of the stability data. The prerequisites are:

- the existing shelf life should be at least 2 years;
- stability data are available to the TGA which validate the existing shelf life;
- a recent (less than 2 months old), dated certificate of analysis should be supplied for the batch, showing compliance with specifications, together with the results obtained at batch release; and
- the sponsor should provide an assurance that it has commenced or intends to commence a stability study to validate a permanent extension of the shelf life, unless it is purely intended as a one off required to ensure continued supply.

Prospective extensions of more than 6 months, or to a shelf life of more than 5-years, are not normally acceptable.

10. Microbiological testing

The TGO 77 *Microbiological standards for medicines*⁸¹ specifies the minimum microbiological requirements with which a medicine must comply throughout its shelf life.

The guidance document *Guidance on Therapeutic Goods Order No. 77 Microbiological Standards for Medicines*⁸² provides a plain English explanation of the various requirements

⁸¹ <http://www.tga.gov.au/industry/legislation-tgo.htm>

⁸² <http://www.tga.gov.au/industry/legislation-tgo-77-guide.htm>

of TGO 77 and their application. It does not form part of TGO 77 and is intended only to assist sponsors to achieve compliance with TGO 77.

Note: The TGA Laboratories' guidelines for assessing the results of microbiological tests on non-sterile pharmaceuticals for human use will be revoked on 1 January 2010.

10.1 Sterile medicines

10.1.1 Policy and procedures

- A sterile medicine must comply with the requirements of the harmonised Test for Sterility as specified in the current edition of a default standard, that is Appendix XVI of the *British Pharmacopoeia*, Chapter 2.6.1 of the *European Pharmacopoeia* or Chapter <71> of the *United States Pharmacopoeia-National Formulary*. This requirement is specified in Clause 7 of TGO 77⁸³.
- Each batch of sterile medicine must be tested for sterility prior to batch release unless approval has been obtained from the TGA for parametric release of the medicine.
- The *TGA Guidelines for sterility testing of therapeutic goods*⁸⁴ provides guidance for laboratory staff performing the Test for Sterility in accordance with the harmonised pharmacopoeial requirements. These guidelines are not mandatory.

10.2 Non-sterile medicines

Non-sterile medicines should not contain excessive numbers of microorganisms. Under the requirements of TGO 77⁸⁵, they should be free from contamination with *specified microorganisms* and should be free from contamination with other microorganisms that might be objectionable in the dosage form.

Note: Specified microorganisms are the indicator organisms identified in the default standards and TGO 77, for example *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, *Salmonella*, *Bile tolerant Gram negative bacteria* and *Candida albicans*.

10.2.1 Policy and procedures

1. The release and expiry specifications for a non-sterile medicine should include suitable microbial quality acceptance criteria for the dosage form.
2. The microbial quality acceptance criteria for a non-sterile medicine must comply at a minimum with the harmonised pharmacopoeial acceptance criteria for microbiological quality of non-sterile dosage forms, as specified in the current edition of a default standard, that is:
 - a. Appendix XVI.D of the *British Pharmacopoeia*
 - b. Chapter 5.1.4 of the *European Pharmacopoeia*
 - c. Chapter <1111> of the *United States Pharmacopoeia-National Formulary*.

⁸³ <http://www.tga.gov.au/industry/legislation-tgo.htm>

⁸⁴ <http://www.tga.gov.au/industry/manuf-sterility-testing-guidelines.htm>

⁸⁵ <http://www.tga.gov.au/industry/legislation-tgo.htm>

This requirement is specified in Clause 9(1) of TGO 77⁸⁶. The harmonised pharmacopoeial acceptance criteria for microbiological quality of non-sterile dosage forms are summarised in Table 10.1 of this chapter.

3. In addition to ensuring that a medicine is free from contamination with specified microorganisms the TGA will expect a sponsor to:
 - a. assess the risk of contamination of the medicine with other objectionable microorganisms
 - b. ensure that this risk assessment is available for review should it be required by the TGA.

A single risk assessment may cover a group of products having similar formulations (e.g. the same excipients but a different quantity of the active), dosage forms, manufacturing processes, etc.

4. Where a sponsor claims that a non-sterile medicine cannot, or need not include microbial quality acceptance criteria in the finished product specifications, then the sponsor will be required to provide cogent reasons to the TGA to justify the absence of microbial quality acceptance criteria.

For example, specifications for solid oral or dry powder products may not need to include microbial quality acceptance criteria if it can be justified in the application by establishing during product development that the product is at a very low risk of contamination and microbial growth is not supported.

Products with significant water content (e.g. creams, gels and oral liquids) are likely to support microbial growth. Such products should include tests and limits for microbial content in both the batch release and expiry specifications.

Note: The sponsor should be aware that the TGA might test a medicine for microbial quality irrespective of whether the finished product specifications include microbial quality acceptance criteria.

5. There is no requirement for every batch of non-sterile medicine to be tested for microbial quality prior to release. If justified, periodic testing or 'skip-lot' testing can be performed. The frequency of testing should be determined based on the bioburden history of the medicine, the manufacturing process for the medicine, and the controls that are inherent in GMP. A bioburden history for the medicine can be determined by testing a series of consecutive routine production batches. It is generally expected that the first 5 to 10 batches of a new medicine should be tested for microbial quality prior to release. If test results for these batches are satisfactory, then testing could be performed periodically, rather than on every batch. For example, where justified, microbial quality testing could be performed on selected batches for example every tenth batch, or once every 6 to 12 months.
6. If the medicine is one that cannot be easily tested for microbial quality (e.g. a metered dose inhaler), then the final bulk product can be tested. The bulk product must comply with the microbial quality acceptance criteria that apply to the medicine in its final form.
7. There are no mandatory microbial quality acceptance criteria for starting materials unless an ingredient is the subject of an individual monograph of a default standard that includes requirements regarding microbial quality. The following harmonised chapters of the default standards include a non-mandatory recommendation about

⁸⁶ <http://www.tga.gov.au/industry/legislation-tgo.htm>

suitable microbial quality acceptance criteria for non-sterile 'substances for pharmaceutical use':

- a. Appendix XVI.D of the *British Pharmacopoeia*
- b. Chapter 5.1.4 of the *European Pharmacopoeia*
- c. Chapter <1111> of the *United States Pharmacopoeia-National Formulary*.

10.2.2 Microbial quality acceptance criteria for non-sterile medicines

TGO 77⁸⁷ adopts the harmonised BP, Ph. Eur. and USP-NF microbial quality acceptance criteria for the various non-sterile OTC medicine dosage forms. The acceptance criteria for the various non-sterile dosage forms are summarised table below.

Table 10.1 TGO 77 Microbial quality acceptance criteria for non-sterile OTC medicines.

Non-sterile dosage form	Acceptance criteria
Rectal use	TAMC $\leq 10^3$ CFU in 1 g or 1 mL TYMC $\leq 10^2$ CFU in 1 g or 1 mL
Oromucosal, gingival, cutaneous, nasal or auricular use Note: Antiseptic and corticosteroid preparations intended for topical use are included in this category.	TAMC $\leq 10^2$ CFU in 1 g or 1 mL TYMC $\leq 10^1$ CFU in 1 g or 1 mL <i>Staphylococcus aureus</i> absent in 1 g or 1 mL <i>Pseudomonas aeruginosa</i> absent in 1 g or 1 mL
Vaginal use	TAMC $\leq 10^2$ CFU in 1 g or 1 mL TYMC $\leq 10^1$ CFU in 1 g or 1 mL <i>Staphylococcus aureus</i> absent in 1 g or 1 mL <i>Pseudomonas aeruginosa</i> absent in 1 g or 1 mL <i>Candida albicans</i> absent in 1 g or 1 mL
Transdermal patches* *Includes adhesive layer and backing.	TAMC $\leq 10^2$ CFU/patch TYMC $\leq 10^1$ CFU/patch <i>Staphylococcus aureus</i> absent per patch <i>Pseudomonas aeruginosa</i> absent per patch

⁸⁷ <http://www.tga.gov.au/industry/legislation-tgo.htm>

Non-sterile dosage form	Acceptance criteria
Inhalation use# #Liquid preparations for nebulisation to be manufactured sterile.	TAMC $\leq 10^2$ CFU in 1 g or 1 mL TYMC $\leq 10^1$ CFU in 1 g or 1 mL <i>Staphylococcus aureus</i> absent in 1 g or 1 mL <i>Pseudomonas aeruginosa</i> absent in 1 g or 1 mL BT gram-negative bacteria absent in 1 g or 1 mL
Non-aqueous preparations for oral use	TAMC $\leq 10^3$ CFU in 1 g or 1 mL TYMC $\leq 10^2$ CFU in 1 g or 1 mL <i>Escherichia coli</i> absent in 1 g or 1 mL
Aqueous preparations for oral use	TAMC $\leq 10^2$ CFU in 1 g or 1 mL TYMC $\leq 10^1$ CFU in 1 g or 1 mL <i>Escherichia coli</i> absent in 1 g or 1 mL
Substances for pharmaceutical use	TAMC $\leq 10^3$ CFU in 1 g or 1 mL TYMC $\leq 10^2$ CFU in 1 g or 1 mL
<i>Ph. Eur./BP special provision criteria for oral dosage forms containing raw materials of natural origin (animal, vegetal or mineral) for which antimicrobial pretreatment is not feasible and for which the competent authority accepts TAMC of the raw material exceeding 10³ CFU per g or per mL</i>	TAMC $\leq 10^4$ CFU in 1 g or 1 mL TYMC $\leq 10^2$ CFU in 1 g or 1 mL BT gram-negative bacteria $\leq 10^2$ CFU in 1 g or 1 mL <i>Escherichia coli</i> absent in 1 g or 1 mL <i>Staphylococcus aureus</i> absent in 1 g or 1 mL <i>Salmonella</i> absent in 10g or 10 mL

TAMC: Total aerobic microbial count, TYMC: Total yeast and mould count, BT: Bile tolerant, CFU: Colony forming unit

The microbial quality acceptance criteria in TGO 77⁸⁸ (and in the default standards) should not be regarded as comprehensive microbial quality acceptance criteria, but rather as the minimal requirements to be met throughout the shelf life of a non-sterile medicine. Demonstrating the absence of only the *specified microorganisms* might not be sufficient to ensure the microbial quality of a non-sterile medicine.

In addition to the specified microorganisms mentioned in Table 10.1, the TGA will expect a sponsor to evaluate the significance and risk of other microorganisms in the medicine not specifically mentioned in Table 10.1, to determine whether the other microorganisms are

⁸⁸ <http://www.tga.gov.au/industry/legislation-tgo.htm>

objectionable in the dosage form. The significance of, and risk from these other microorganisms should be evaluated in terms of the formulation of the medicine, its route of administration and method of application, and the population for which the medicine is intended. This latter point should consider the possibility of underlying illness/disease in the user of the medicine and/or the possible use of immunosuppressive agents or corticosteroids by the user. It will not be unusual for a finished product specification to include acceptance criteria for additional microorganisms that are not specified in TGO 77⁸⁹.

Note: Annex 20 'Quality Risk Management' of the Pharmaceutical Inspection Co-operations Scheme (PIC/S) 'Guide to GMP for Medicinal Products' includes information and guidance on the principles and some of the tools of quality risk management, and their application to different aspects of medicine quality.

For example, pseudomonad-type bacteria are considered to be objectionable in aqueous dosage forms intended for inhalant, cutaneous, nasal, auricular, oromucosal, gingival and vaginal use, and in transdermal patches. As such, the TGA will expect these dosage forms to be free from contamination with these types of bacteria.

Note: Pseudomonads include bacteria previously identified as belonging to the genus *Pseudomonas* but because of advances in molecular identification of bacteria they have been reclassified into a number of other genera including *Burkholderia*, *Ralstonia*, *Stenotrophomonas*, *Sphingomonas* and *Brevundimonas*.

10.2.3 Products containing material of natural origin

The types of products that are classified as being 'of natural origin' are oral dosage forms which contain raw materials of natural origin (animal, vegetal or mineral) that have not been fully processed.

Appendix XVI.D of the *British Pharmacopoeia* and Chapter 5.1.4 of the *European Pharmacopoeia* include special provision criteria 'for oral dosage forms containing raw materials of natural origin (animal, vegetal or mineral) for which antimicrobial pretreatment is not feasible and for which the competent authority accepts TAMC of the raw material exceeding 10³ CFU per g or per mL'. Chapter <1111> of the United States Pharmacopoeia-National Formulary does not include the special provision criteria. The special provision criteria of the BP and Ph. Eur. are summarised in Table 10.1.

10.2.4 Microbiological test methods

TGO 77⁹⁰ does not specify the microbiological test methods to be used for routine quality control testing of medicines.

Note: TGO 77 only specifies the microbiological test methods that must be used for referee testing of a medicine that is where a sponsor contests the test results obtained by an official testing laboratory for a medicine. For referee testing TGO 77 requires the testing to be performed in accordance with the harmonised pharmacopoeial Tests for Microbial Contamination, as described in the default standards.

The harmonised pharmacopoeial *Tests for microbial contamination* (as described in the default standards) can be used for routine quality control testing of medicines, as can alternative microbiological test methods, including rapid microbiological test methods.

⁸⁹ <http://www.tga.gov.au/industry/legislation-tgo.htm>

⁹⁰ <http://www.tga.gov.au/industry/legislation-tgo.htm>

Where the pharmacopoeial test methods are to be used to test a medicine it is important to note that these test methods were originally designed to demonstrate that a medicine/substance meets monograph requirements. They were not designed for use as test methods to detect all potential pathogens and therefore should not be regarded as rigorous quality control tests for all dosage forms. For example, the *Pseudomonas aeruginosa* test method is not suitable for reliable recovery of pseudomonads, other than for *Pseudomonas aeruginosa*. For medicines where the presence of pseudomonads is considered objectionable, the *Pseudomonas aeruginosa* test method would need to be modified to include an additional non-selective culture medium incubated at 30°-32°C for 48 hours.

Where alternative microbiological test methods are to be used they should be validated to be at least equivalent to the harmonised pharmacopoeial test methods, and to be suitable for recovery of *specified microorganisms* and other *objectionable organisms* from the medicine to be tested.

11. Checklist for submission of stability data

Use of the following checklist is entirely optional, but may reduce delays and requests for further information during the evaluation. This checklist should **not** be submitted with the application.

Ensure that you:

	have enough stability data to support a shelf life of at least 12 months
	present stability data on at least two batches of each strength of the product (unless bracketing and matrixing are applied – see above)
	specify the formulation(s) used in the study, and state which batches are identical to those proposed for registration in Australia
	provide details of batch numbers and date of manufacture of each batch, as well as the dates on which they were placed on the stability trials
	state whether the batches used in the study were laboratory, pilot or production batches (and specify the size of each batch - e.g. 50 kg or 100,000 tablets)
	clearly describe the packaging used in the study and confirm whether it is identical to the pack that will be used in Australia
	indicate the orientation of the containers (e.g. upright, inverted) in the case of products for which orientation could influence stability
	specify the temperature, lighting and humidity conditions applied during the study, and confirm that these were in line with the relevant ICH requirements (or provide justification for any differences)
	fully describe all test methods (and provide validation data where relevant)
	ensure that all appropriate chemical and physical parameters are monitored, as detailed under 'Appropriate Tests', above
	include stability studies under conditions of high or low humidity where appropriate (see under relevant headings above)
	provide quantitative results where possible
	provide results from sufficient time stations to allow assessment of any trends in the parameters
	for dissolution testing, provide results for individual dosage units (or both mean and range)
	provide explanation/assessment where there are obvious alterations in the characteristics of the product
	provide explanation/assessment where there is a lack of balance between the formation of degradation products and the loss of the active ingredient
	provide an observational or statistical analysis to support any extrapolation (where the long term data do not cover the whole of the proposed shelf life) and ensure that the extrapolation does not exceed the amount permitted under the ICH guidelines
	provide a post-approval stability protocol and commitment (as described above) if the shelf life has not been confirmed with stability data on sufficient production batches covering the whole period.

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