Australian Government
Department of Health
Therapeutic Goods Administration

Guidance 17: Microbial quality of prescription and over-the-counter medicines

Previously ARGPM Appendices 16 & 17: Preservative efficacy testing and Microbial quality of medicines

Version 1.0, July 2013

TGA Health Safety Regulation

Check the TGA website for up-to-date guidance

The most up-to-date information about prescription medicine registration in Australia is on the TGA website <http://www.tga.gov.au>. Now that guidance is presented in a series of web pages, updates are likely to be more common than in the past. If you subscribe to the TGA guidelines email alert service, you will be emailed every time the TGA web guidance is updated.

TGA web pages are dated, and can be printed.

A PDF format is being provided during the transition between the former version of the ARGPM (Australian Regulatory Guidelines for Prescription Medicines) and the new web format. Please note that information in the PDF should not be relied upon to be up-to-date.

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication	Office of Medicines Authorisation	1/07/2013

Contents

Introduction

This guidance is to assist sponsors and manufacturers of prescription and over-the-counter medicines (excluding complementary medicines) to comply with Therapeutic Goods Order No. 77 - Microbiological standards for medicines (TGO 77).

17.1 What is Therapeutic Goods Order No. 77 Microbiological standards for medicines?

TGO 77 specifies the minimum microbiological quality requirements (including preservative efficacy requirements) that a medicine should comply with throughout its shelf life, unless it is exempt (see 'Exemptions from TGO 77', below).

Exemptions from TGO 77

Sponsors may request an exemption from all or part of TGO 77 (under Clause 5(2)(b)) for a particular medicine if there is a clear reason why the medicine is not able to comply.

Note

TGO 77 came into effect on 1 January 2010. The *TGA laboratories' guidelines for assessing the results of microbiological tests on non-sterile pharmaceuticals for human use* that were in use before 2010 were revoked on 1 January 2010.

Related information and guidance

The Guidance on Therapeutic Goods Order No. 77 Microbiological standards for medicines provides a plain-English interpretation of TGO 77 and should be read in conjunction with TGO 77 and this guidance.

17.2 Microbial requirements for dosage forms to be supplied sterile

Dosage forms to be supplied sterile include, but are not restricted to, those that are:

- administered by injection
- intended for ophthalmic use
- intended for irrigation use
- intended for intraurethral use

- intended for use as an implant
- intended for use on open wounds or severely damaged skin (e.g. burns)
- intended for otic use postsurgery (other otic preparations are also often supplied sterile)
- liquid inhalants that are intended for nebulisation
- peritoneal dialysis solutions.

17.2.1 Microbial quality criteria

Sterile dosage forms should comply with the harmonised pharmacopoeial Test for Sterility and, where applicable, the Bacterial Endotoxins Test.

For sponsors applying to enter a medicine on the ARTG

Include a specification for sterility, and where applicable for bacterial endotoxins, in the release and expiry specifications for a sterile medicine.

17.2.1.1 Sterility

A sterile medicine should comply with the harmonised Test for Sterility in the current edition of a default standard, as specified in Clause 7 of TGO 77.

Relevant sections in default standards are:

- Appendix XVI A, 'Test for sterility', of the British Pharmacopoeia (BP)
- Chapter 2.6.1, 'Sterility', of the European Pharmacopoeia (Ph. Eur.)
- Chapter 71,'Sterility tests', of the United States Pharmacopeia–National Formulary (USP–NF).

Related information and guidance

- TGA guidelines for sterility testing of therapeutic goods

17.2.1.2 Bacterial endotoxins

Where applicable, a sterile medicine should comply with the harmonised requirements of the Bacterial Endotoxins Test of a default standard. This requirement is specified in Clause 7 of TGO 77.

- Guidance on bacterial endotoxin limits can be found in relevant pharmacopoeial monographs or in the following chapters of the default standards:
- Appendix XIV C, 'Test for bacterial endotoxins (LAL Test)', of the BP
- Chapter 2.6.14, 'Bacterial endotoxins', of the Ph. Eur.
- Chapter 85, 'Bacterial endotoxins test', of the USP-NF.

17.2.2 Batch release testing

Each batch of a sterile medicine is to be tested for sterility before release, unless the TGA has approved parametric release of the medicine.

If a test for bacterial endotoxins is required for a sterile medicine, then this test is to be performed before the release of each batch.

17.2.3 Test methods

Tests for sterility and bacterial endotoxins should be carried out according to the default standards, unless a suitable alternative method has been reviewed and approved by the TGA.

17.2.3.1 Sterility

The default standards and TGO 77 permit the use of a suitable alternative method of analysis to the pharmacopoeial Test for Sterility (e.g. a rapid microbiological test method). Any alternative test method needs to be reviewed and approved by the TGA before it is implemented.

For sponsors applying to enter a medicine on the ARTG

Include information and data to demonstrate:

- the alternative test method:
  - is equivalent to, or more stringent than, the pharmacopoeial Test for Sterility
  - is suitable for the reliable recovery of low numbers of a wide range of microorganisms from the medicine to be tested
- the accuracy, precision, specificity, limit of detection and robustness of the alternative test method in comparison with the pharmacopoeial Test for Sterility.

17.2.3.2 Bacterial endotoxins

For sponsors applying to enter a medicine on the ARTG

Include information and data to demonstrate that any alternative test method for bacterial endotoxins is equivalent to, or more stringent than, the pharmacopoeial test method.

Note

Any alternative bacterial endotoxin test method needs to be reviewed and approved by the TGA before it is implemented.

17.3 Microbial requirements for medicines supplied in nonsterile dosage forms

A nonsterile medicine should not contain excessive numbers of microorganisms. It should be free from contamination with specified microorganisms and free from contamination with other microorganisms that might be objectionable in the dosage form.

For sponsors applying to enter a medicine on the ARTG

Include suitable microbial quality acceptance criteria (limits for microbial content) in the release and expiry specifications for a nonsterile medicine.

Include justification for a claim that microbial quality acceptance criteria need not be included in the drug product specifications.

If the dosage form cannot be tested easily for microbial quality (e.g. a metered-dose inhaler), the final bulk product can be tested. The bulk product should comply with the microbial quality acceptance criteria that apply to the finished dosage form.

Note

The TGA may test a medicine for microbial quality irrespective of whether the drug product specifications include microbial quality acceptance criteria.

17.3.1 Microbial quality criteria

The microbial quality acceptance criteria for a nonsterile medicine should comply, at a minimum, with the harmonised pharmacopoeial acceptance criteria for microbiological quality of nonsterile dosage forms (as specified in Clause 9(1) of TGO 77).

The microbial quality criteria are summarised in Table 1 and are specified in the default standards:

- Appendix XVI D, 'Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use', of the BP
- Chapter 5.1.4, 'Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use', of the Ph. Eur
- Chapter 1111, 'Microbiological examination of non-sterile products: acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use', of the USP-NF.

Note

The microbial quality acceptance criteria in TGO 77 (and in the default standards) should not be regarded as comprehensive.

They are the minimal requirements to be met throughout the shelf life of a nonsterile medicine.

Demonstrating the absence of only the specified microorganisms might not be sufficient to ensure the microbial quality of a nonsterile medicine.

Table 1 Microbial quality acceptance criteria for nonsterile medicinal dosage forms

Route of administration	Acceptance criteria (CFU per gram or per millilitre, unless otherwise specified)
Route of administration	Acceptance criteria (CFU per gram or per millilitre, unless otherwise specified)
Nonaqueous preparations for oral use	TAMC $\leq 10^3$ TYMC $\leq 10^2$ *Escherichia coli* absent in 1 g or 1 mL
Aqueous preparations for oral use	TAMC $\leq 10^2$ TYMC $\leq 10^1$ *Escherichia coli* absent in 1 g or 1 mL
Rectal use	TAMC $\leq 10^3$ TYMC $\leq 10^2$
Oromucosal, gingival, cutaneous, nasal or auricular use	TAMC $\leq 10^2$ TYMC $\leq 10^1$ *Staphylococcus aureus* absent in 1 g or 1 mL *Pseudomonas aeruginosa* absent in 1 g or 1 mL
Vaginal use	TAMC $\leq 10^2$ TYMC $\leq 10^1$ *Staphylococcus aureus* absent in 1 g or 1 mL *Pseudomonas aeruginosa* absent in 1 g or 1 mL *Candida albicans* absent in 1 g or 1 mL
Transdermal patches (including adhesive layer and backing)	TAMC $\leq 10^2$ CFU/patch TYMC $\leq 10^1$ CFU/patch *Staphylococcus aureus* absent per patch *Pseudomonas aeruginosa* absent per patch

Route of administration	Acceptance criteria (CFU per gram or per millilitre, unless otherwise specified)
Inhalation use (e.g. liquid preparations for nebulisation, to be manufactured sterile)	TAMC ≤10^2 TYMC ≤10^1 *Staphylococcus aureus* absent in 1 g or 1 mL *Pseudomonas aeruginosa* absent in 1 g or 1 mL BT gram-negative bacteria absent in 1 g or 1 mL
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 (see 'Medicines that contain material of natural origin')	TAMC ≤10^4 TYMC ≤10^2 BT gram-negative bacteria ≤10^2 *Escherichia coli* absent in 1 g or 1 mL *Staphylococcus aureus* absent in 1 g or 1 mL *Salmonella* absent in 10 g or 10 mL
Substances for pharmaceutical use	TAMC ≤10^3 CFU TYMC ≤10^2 CFU

BP = British Pharmacopoeia, BT = bile tolerant, CFU = colony forming unit, Ph. Eur. = European Pharmacopoeia, TAMC = total aerobic microbial count, TYMC = total yeast and mould count

17.3.2 Objectionable microorganisms

In addition to being free from contamination with specified microorganisms, a nonsterile medicine should also be free from contamination with other microorganisms that might be objectionable in the dosage form.

For example, pseudomonad-type bacteria[1] are considered to be objectionable in aqueous dosage forms that are intended for inhalant, cutaneous, nasal, auricular, oromucosal, gingival or vaginal use and in transdermal patches.

These dosage forms are expected to be free from contamination with these types of bacteria.

Drug product specifications for these dosage forms should include an absence of pseudomonads in 1 g or 1 mL, or per patch.

Evaluation of the significance of, and risk from, other objectionable microorganisms should consider:

- the formulation of the medicine

[1] Pseudomonads include bacteria that were previously identified as belonging to the genus *Pseudomonas*. Advances in molecular identification have resulted in the reclassification of some of these bacteria to other genera, including *Burkholderia, Ralstonia, Stenotrophomonas, Sphingomonas* and *Brevundimonas*.

- its route of administration
- its method of application
- the population for which the medicine is intended, including:
  - the possibility of underlying illness in the user of the medicine
  - the possible concurrent use of immunosuppressive agents or corticosteroids.

For sponsors applying to enter a medicine on the ARTG

Confirm that the risk to the user from contamination of a medicine with objectionable microorganisms has been assessed.

Confirm that this risk assessment is available for review if required by the TGA.

Related information and guidance

Annex 20, 'Quality risk management', of the Pharmaceutical Inspection Co-operation Scheme (PIC/S) Guide to good manufacturing practice 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.

17.3.3 Starting materials

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 for microbial quality.

Nonmandatory recommendations about microbial quality acceptance criteria for nonsterile 'substances for pharmaceutical use' (i.e. starting materials) are found in:

- Appendix XVI D, 'Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use', of the BP
- Chapter 5.1.4, 'Microbiological quality of non-sterile pharmaceutical preparations and substances for pharmaceutical use', of the Ph. Eur
- Chapter 1111, 'Microbiological examination of non-sterile products: acceptance criteria for pharmaceutical preparations and substances for pharmaceutical use', of the USP-NF.

Process waters

The Ph. Eur. and the BP include monographs for Water for Injections, Highly Purified Water and Purified Water that include specific requirements for microbiological monitoring and microbial quality.

The Committee for Proprietary Medicinal Products (CPMP) guideline Note for guidance on quality of water for pharmaceutical use (CPMP/QWP/158/01 Revision) provides guidance on the use of these different grades of process water in the manufacture of drug substances and medicinal dosage forms.

For sponsors applying to enter a parenteral medicine on the ARTG

Ensure compliance with TGO 89 Standard for Water for Injections for parenteral medicines.

17.3.4 Medicines that contain material of natural origin

A medicine that might be classified as being 'of natural origin' is an oral dosage form that contains a raw material(s) of natural origin (animal, vegetal or mineral) where the raw material has not been fully processed.

A nonsterile medicine that is intended for oral use and that contains natural ingredients is to comply with Clause 9(1) of TGO 77 (i.e. the internationally harmonised pharmacopoeial microbial quality acceptance criteria for this type of dosage form).

Appendix XVI.D of the BP and Chapter 5.1.4 of the Ph. Eur. 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 10^3 CFU per g or per mL'.

Chapter 1111 of the USP-NF does not include these special provision criteria.

If an aqueous or nonaqueous oral dosage form that contains material of natural origin cannot meet the microbial quality acceptance criteria in Table 1:

- apply to the TGA for approval to use the special provision criteria of the BP and Ph. Eur. instead.

17.3.5 Batch release testing

There is no requirement for every batch of a nonsterile medicine to be tested for microbial quality before release. Periodic testing or 'skip-lot' testing can be performed, if justified.

The frequency of testing should be based on:

- the bioburden history of the medicine (determined by testing a series of consecutive routine production batches)
- the manufacturing process for the medicine
- the controls that are inherent in good manufacturing practice.

It is generally expected that the first 5-10 batches of a new medicine should be tested for microbial quality before release.

If test results for these batches are satisfactory, testing could be performed periodically, rather than on every batch (e.g. every 10th batch, or once every 6-12 months).

17.3.6 Test methods

17.3.6.1 Referee testing

TGO 77 specifies the microbiological test methods that are to be used for referee testing of a medicine (i.e. where a sponsor contests the test results obtained by an official testing laboratory for a medicine).

Referee testing is to be performed in accordance with the harmonised pharmacopoeial Tests for Microbial Contamination, as described in the default standards.

17.3.6.2 Quality control testing

TGO 77 does not specify the microbiological test methods to be used for routine quality control testing of a nonsterile medicine.

Routine quality control testing can use the harmonised pharmacopoeial Tests for Microbial Contamination (as described in the default standards), or suitable alternative microbiological test methods, including rapid methods.

The pharmacopoeial test methods were designed to demonstrate that a medicine or substance meets monograph requirements. The methods were not designed 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 the reliable recovery of pseudomonads other than *P. aeruginosa*. For a medicine where pseudomonads are considered to be objectionable in the dosage form, the *P. aeruginosa* test method should be modified to include an additional nonselective culture medium that is incubated at 30-32 °C for at least 48 hours.

17.3.6.3 Alternative test methods

If alternative microbiological test methods are to be used for testing a medicine, sponsors should demonstrate that the alternative methods are at least equivalent to the harmonised pharmacopoeial test methods, and that they are suitable for the recovery of specified microorganisms and other objectionable organisms from the medicine to be tested.

17.4 Preservative efficacy criteria for medicines for multidose use

A multidose-use medicine should be adequately preserved for the duration of its claimed shelf life (see the TGA guidance Stability testing for prescription medicines). This is to prevent microbial proliferation in a nonsterile medicine, and to prevent microbial contamination of a sterile or nonsterile medicine, during the normal conditions of storage and use.

Unless the formulation of a medicine is 'self-preserving', one or more suitable antimicrobial preservatives are included in the formulation.

A medicine (other than a liquid oral antacid medicine) that is intended for use on more than one occasion (multidose use) should comply with the requirements of the current edition of Appendix XVI C of the BP, 'Efficacy of antimicrobial preservation', or Chapter 5.1.3 of the Ph. Eur., 'Efficacy of antimicrobial preservation'. A liquid oral antacid medicine may comply with the requirements of the relevant test in the USP-NF, Chapter 51 'Antimicrobial effectiveness test'. These requirements are specified in Clause 8 of TGO 77.

Note on preservative efficacy testing

A chemical assay of the content of the preservative(s) in the formulation is not accepted as a substitute for an antimicrobial preservative efficacy test. Chemical concentration alone is not sufficient to assess the biological activity of a formulation, because other chemical and physical changes in the formulation can influence the efficacy of the antimicrobial preservative(s).

However, a chemical assay can be used for routine batch testing of a preserved medicine.

17.4.1 Closed shelf life data for multidose medicines

Include real-time antimicrobial preservative efficacy information and data for the medicine formulation:

- in its immediate container for market (see Note)
- from test samples stored in accordance with label storage conditions
- at both the beginning and end of the proposed closed shelf life:
  - from at least two (preferably three) separately manufactured batches tested at the beginning of shelf life
  - from at least one primary stability batch tested at the proposed shelf life.

Note

Testing can be performed in an alternative container if testing in the immediate container for market is not possible. Prior to testing ensure that the medicine has been filled into and stored in the immediate container for market.

For oral powders or granule preparations that are reconstituted before use, demonstrate adequate preservation for the reconstituted preparation over the proposed reconstituted shelf life.

If real-time preservative efficacy data is not available at the end of the proposed closed shelf life, then include:

- data up to and including the last testing point from ongoing stability studies
- an assurance that end-of-shelf-life data will be provided to the TGA when it is available, if the TGA requests it
- an assurance that the TGA will be informed of any preservation problems detected during ongoing stability studies.

Sometimes accelerated ageing studies might be used to support a proposed shelf life. If using accelerated ageing studies, then include test samples for storage at the higher temperature.

17.4.2 Open shelf life data for sterile medicines

In an application for registration, justify the open shelf life for a sterile medicine that is intended for multidose use (e.g. a multidose injectable or ophthalmic preparation). Also, provide **one of** the following information and data to support an open shelf life period:

- results of preservative efficacy tests that involve repeated microbial challenges of the medicine over the open shelf life period (as this most closely mimics the in-use situation). A sponsor can use a modification of a pharmacopoeial preservative efficacy test (preferably the Ph. Eur. or BP preservative efficacy test) that includes rechallenges of the medicine with reduced numbers of challenge organisms (compared with the initial challenge). Guidance can 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.
- results of preservative efficacy tests on the contents of containers of the medicine after simulated in-use
- results of sterility tests on the contents of containers of the medicine after simulated in-use
- results of microbial content tests on the contents of partially used containers of the medicine that have been used by patients for the full duration of the open shelf life (including details of the number of samples tested, the test method used, method validation, and numbers and types of organisms recovered from the partially used containers).

17.4.3 Release and expiry specifications

An antimicrobial preservative efficacy test is not usually included in the release and expiry specifications for a medicine because this testing is normally performed during product development and stability studies. During product development, preservative efficacy should be assessed at the lower limit for preservative content in the end-of-shelf-life specification.

Therapeutic Goods Administration

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