Australian Government
Department of Health
Therapeutic Goods Administration

Microbiological quality of prescription and over-the-counter medicines

Complying with Therapeutic Goods (Microbiological standards for medicines) (TGO 100) Order 2018

Version 2.0, October 2019

TGA Health Safety Regulation

Contents

Introduction

This guidance will assist sponsors and manufacturers of prescription and over-the-counter medicines (excluding complementary medicines) to comply with Therapeutic Goods (Microbiological standards for medicines) (TGO 100) Order 2018.

17.1 What is Therapeutic Goods (Microbiological standards for medicines) (TGO 100) Order 2018?

TGO 100 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 'General exemptions from TGO 100'). TGO 100 does not cover the requirements for microorganism components used in a medicine.

General exemptions from TGO 100

Medicines may be exempt from meeting the requirements set out in TGO 100 if they meet specific conditions (under Clause 7).

TGO 100 came into effect on 8 December 2018.

TGOs 77 and 98 that were in use before December 2018 were repealed on 1 October and 8 December 2018, respectively.

Related information

The default standards:

- British Pharmacopoeia (BP)
- European Pharmacopoeia (EP)
- United States Pharmacopeia-National Formulary (USP-NF)

are adopted as in force from time to time as permitted under subsection 10(4) of the *Therapeutic Goods Act 1989* (the Act).

17.2 Sterile dosage form microbiological quality requirements

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 Microbiological quality criteria for sterile dosage forms

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

Specifications to include for sterile dosage forms

When applying to enter a sterile dosage form medicine on the ARTG, include a specification for sterility, and where applicable for bacterial endotoxins, in the release and expiry specifications.

17.2.1.1 Sterility testing of sterile medicines

A sterile medicine should comply with the harmonised pharmacopoeial Test for Sterility in the current edition of a default standard, as specified in Clause 9 of TGO 100.

Relevant sections in default standards are:

- Appendix XVI A of the BP, 'Test for sterility'
- Chapter 2.6.1 of the EP, 'Sterility'
- Chapter 71 of the USP–NF, 'Sterility tests'.

Related information and guidance

TGA guidelines for sterility testing of therapeutic goods

17.2.1.2 Bacterial endotoxin testing of sterile medicines

Where applicable, a sterile medicine should comply with the harmonised requirements of the Bacterial Endotoxins Test in the current edition of a default standard, as specified in Clause 9 of TGO 100.

Guidance on bacterial endotoxin limits can be found in relevant pharmacopoeial monographs or in the following chapters of the default standards:

- Appendix XIV C of the BP, 'Test for bacterial endotoxins (LAL Test)'
- Chapter 2.6.14 of the EP, 'Bacterial endotoxins'
- Chapter 85 of the USP-NF, 'Bacterial endotoxins test'.

17.2.2 Batch release testing of sterile medicines

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 for sterile medicines

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 Alternative methods for testing sterility

The default standards and TGO 100 permit the use of a suitable, alternative method of analysis to the pharmacopoeial Test for Sterility (for example, a rapid microbiological test method).

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

Information required if alternative methods for sterility testing are used

When applying to enter a medicine on the ARTG, include information and data to demonstrate:

- the alternative test method:
  - is not inferior to 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 Alternative methods for bacterial endotoxins test

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

Information required if alternative methods for bacterial endotoxin testing are used

When applying to enter a medicine on the ARTG, include information and data to demonstrate that the alternative test method:

- is not inferior to the pharmacopoeial Bacterial Endotoxins Test method.

17.3 Nonsterile dosage form microbiological quality requirements

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.

Specifications required for nonsterile dosage forms

When applying to enter a nonsterile dosage form medicine on the ARTG:

- Include suitable microbiological quality acceptance criteria (limits for microbial content) in the release and expiry specifications for a nonsterile medicine.
- Include justification for a claim that microbiological quality acceptance criteria need not be included in the drug product specifications.
- If microbiological quality cannot easily be tested for in the dosage form (for example, a metered-dose inhaler), the final bulk product can be tested. The bulk product should comply with the microbiological quality acceptance criteria that apply to the finished dosage form.

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

17.3.1 Microbiological quality criteria for nonsterile medicines

The microbiological 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 11(1) of TGO 100).

The microbiological quality criteria are summarised in Table 1 Microbiological quality acceptance criteria for nonsterile medicinal dosage forms and are specified in the default standards:

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

The microbiological quality acceptance criteria in TGO 100 (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 microbiological quality of a nonsterile medicine.

Table 1 Microbiological quality acceptance criteria for nonsterile medicinal dosage forms

Route of administration	Acceptance criteria (CFU per gram or per millilitre, unless otherwise specified)
Non-aqueous preparations for oral use	TAMC ≤10^3 TYMC ≤10^2 *Escherichia coli* absent in 1 g or 1 mL
Aqueous preparations for oral use	TAMC ≤10^2 TYMC ≤10^1 *Escherichia coli* absent in 1 g or 1 mL
Rectal use	TAMC ≤10^3 TYMC ≤10^2
Oromucosal, gingival, cutaneous, nasal or auricular use	TAMC ≤10^2 TYMC ≤10^1 *Staphylococcus aureus* absent in 1 g or 1 mL *Pseudomonas aeruginosa* absent in 1 g or 1 mL
Vaginal use	TAMC ≤10^2 TYMC ≤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 ≤10^2 CFU/patch TYMC ≤10^1 CFU/patch *Staphylococcus aureus* absent per patch *Pseudomonas aeruginosa* absent per patch
Inhalation use (Note: 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

Route of administration	Acceptance criteria (CFU per gram or per millilitre, unless otherwise specified)
EP/BP special provision criteria for oral dosage forms containing raw materials of natural origin (animal, vegetal or mineral) for which antimicrobial pre-treatment is not feasible and for which the competent authority accepts TAMC of the raw material exceeding 10^3 CFU per g or per mL (see 'Material of natural origin in nonsterile medicines')	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

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

17.3.2 Objectionable microorganisms and nonsterile medicines

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 are considered to be objectionable in:

- aqueous dosage forms that are intended for inhalant, cutaneous, nasal, auricular, oromucosal, gingival, rectal or vaginal use
- transdermal patches.

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

Pseudomonad-type bacteria 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*.

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
- 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.

Information required for objectionable microorganisms

When 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 for nonsterile medicines

There are no mandatory microbiological quality acceptance criteria for starting materials, unless an ingredient is the subject of an individual monograph of a default standard that includes requirements for microbiological quality.

Non-mandatory recommendations about microbiological quality acceptance criteria for nonsterile 'substances for pharmaceutical use' (i.e. starting materials) are found in:

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

17.3.4 Material of natural origin in nonsterile medicines

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 11(1) of TGO 100 (the internationally harmonised pharmacopoeial microbiological quality acceptance criteria for this type of dosage form).

Appendix XVI.D of the BP and Chapter 5.1.4 of the EP include special provision criteria 'for oral dosage forms containing raw materials of natural origin (animal, vegetal or mineral) for which:

- antimicrobial pre-treatment is not feasible, and
- 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 non-aqueous oral dosage form that contains material of natural origin cannot meet the microbiological quality acceptance criteria in Table 1 Microbiological quality acceptance criteria for nonsterile medicinal dosage forms, apply to the TGA for approval to use the special provision criteria of the BP and EP instead.

17.3.5 Batch release testing for nonsterile medicines

There is no requirement for every batch of a nonsterile medicine to be tested for microbiological 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 expected that the first 5-10 batches of a new medicine should be tested for microbiological quality before release.

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

17.3.6 Test methods for nonsterile medicines

17.3.6.1 Referee testing for nonsterile medicines

TGO 100 specifies the microbiological test methods that are to be used for referee testing of a medicine (for example, 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 for nonsterile medicines

TGO 100 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 for nonsterile medicines

If alternative microbiological test methods are to be used for testing a medicine, you should demonstrate that the alternative methods:

- are not inferior 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 Multidose use medicine preservative efficacy criteria

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 preservative are to be included in the formulation.

An aqueous-based 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 EP, 'Efficacy of antimicrobial preservation'.

A liquid oral antacid medicine may comply with the requirements of the relevant test in:

- Chapter 51 of the USP-NF, 'Antimicrobial effectiveness testing'.

These requirements are specified in Clause 10 of TGO 100.

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

When applying to enter an aqueous-based multidose medicine on the ARTG, include real-time antimicrobial preservative efficacy information and data for the medicine formulation:

- in its immediate container for market (see Testing in alternative containers below)
- 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.

Testing in alternative containers

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 multidose medicines

When applying to enter a sterile aqueous-based multidose medicine (for example, a multidose injectable or ophthalmic preparation) on the ARTG, include a justification for the open shelf life period and, to support the open shelf life period, provide one of the following information and data:

- 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). You can use a modification of a pharmacopoeial preservative efficacy test (preferably the EP 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 test/s for sterility on the contents of containers of the medicine after simulated in-use
- results of microbiological 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 verification (as applicable), and numbers and types of organisms recovered from the partially used containers).

If the harmonised pharmacopoeial microbiological content test method is used, then the method is validated and only needs to be verified for the product under test.

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, as 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.

Version history

Version	Description of change	Author	Effective date
V1.0	Original publication Previously ARGPM Appendices 16 & 17: Preservative efficacy testing and Microbial quality of medicines.	Office of Medicines Authorisation	01/07/2013
V2.0	Updated name from 'Guidance 17: Microbial quality of prescription and over-the-counter medicines' Updated to be in line with new TGO 100	Laboratories Branch	October 2019

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