Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian regulatory guidelines for prescription medicines

Appendix 17: Microbial quality of medicines

June 2004

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The TGA is a division 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.

Appendix 17: Microbial quality of medicines

Sterile dosage forms

Sterile medicinal products are to comply with the requirements of the test for sterility as specified in the gazetted edition of the British Pharmacopoeia (BP).

Compliance with the test for sterility as specified in the equivalent European Pharmacopoeia (Ph Eur) is an acceptable alternative as the requirements for this test are equivalent to those in the BP.

In addition, sponsors should refer to the Therapeutic Goods Administration (TGA) *Guidelines for Sterility Testing of Therapeutic Goods*[1]. This document provides guidance for sterility testing of sterile therapeutic medicinal products and medical devices supplied in Australia for human use and incorporates the BP/Ph Eur requirements, as well as the additional requirements prescribed in *Therapeutic Goods Order No 63*[2] for medical devices.

Compliance with the test for sterility specified in the United States Pharmacopoeia (USP) is not acceptable. The following USP test conditions are not acceptable: the reduced test incubation period permitted for product sterilised by moist heat; the prolonged growth promotion and validation test incubation periods; and the very loosely defined test interpretation.

Non-sterile dosage forms

Non-sterile pharmaceuticals should not contain excessive quantities of microbes, and pharmacopoeias suggest suitable test methods and limits. The *limit tests* do not require the product to be sterile but instead prescribe the nature and amount of contamination that is tolerable.

[1] http://www.tga.gov.au/industry/manuf-sterility-testing-guidelines.htm
[2] http://www.comlaw.gov.au/Details/F2007B00464

Policy and procedures

1. It is recommended that all non-sterile pharmaceutical dosage forms should have limits for microbial content in expiry specifications.
2. If a sponsor claims that a non-sterile product cannot or need not have limits for microbial content in its expiry specifications, the TGA may still test the product for microbial content.
3. It is not a requirement that every batch of a product be tested for microbial content at release. Instead, for each product, manufacturers should aim to develop confidence that manufacturing procedures do not permit contamination by excessive numbers of microbes or by pathogenic microbes. This is achieved by testing routine production batches to establish a product history. It would normally be expected that the first 5 or 10 batches of a new product are tested at release. If satisfactory, testing could then be reduced to once every 6 to 12 months or on selected batches (for example, every 10th batch).
4. If the product is one that cannot easily be tested for microbial content (for example, a metered dose inhaler), the final *bulk* product can be tested and must comply. The test methods and limits which apply in this case are the same as if the product were tested in its final form.
5. *Active raw materials* do not need to include microbial specifications when there are suitable limits on the finished product.

USP and BP/Ph Eur methods and limits

The USP has a subchapter entitled *Microbial Limits Test*. The relevant BP section is entitled *Tests for Microbial Contamination*, and essentially adopts the tests and limits of the Ph Eur with some addition and rearrangement. TGA's requirements differ somewhat from those of the BP/Ph Eur and USP as summarised in Table 1 below.

Table 1: TGA Assessment of BP/Ph Eur and USP Microbial Specifications

TGA ASSESSMENT OF BP/Ph Eur & USP MICROBIAL SPECIFICATIONS		
BP/Ph Eur & USP	*Oral Products*	*Topicals*
Test Methods	Acceptable	Acceptable but need to add a medium which will permit growth of *all* pseudomonads* and incubate at a suitable temperature (30-35°C)
Limits	Not tight enough	Acceptable but need to add a requirements for the absence of *all* pseudomonads

*Pseudomonads include organisms previously identified as belonging to the genus *Pseudomonas* but because of advances in molecular identification of microorganisms have been reclassified into a number of other genuses including: *Brevundimonas, Burkholderia, Sphingomonas, Stenotrophomonas, Xanthomonas*

Methods and limits acceptable in Australia

Acceptable *test methods* are those of the BP/Ph Eur and USP except that, for topicals, there should be an additional non-selective medium and incubation temperature (30-35°C) suitable for the detection of *all* pseudomonads rather than just *Pseudomonas aeruginosa*. No pseudomonads should be present. Other methods are acceptable provided they have been validated.

Limits on microbial content for non-sterile products are described in Table 3. Note that there are different limits for products for topical and oral administration, both quantitatively and qualitatively. The guidelines are only abroad indication of the microbial limits that may be applied. The list does not include every combination of number and type of undesirable organism that may make a product unfit for its intended use.

Products containing material of natural origin

Oral products should normally comply with the limits in Category 2a of the TGA guidelines (Table 3). A manufacturer may apply Category 2b limits if the product contains materials of natural origin.

The BP and the Ph Eur include in their requirements *for Microbial Quality of Pharmaceutical Preparations* include a category for oral products containing materials of natural origin (plant, animal or mineral). Table 3 also includes a category for products for oral use containing raw materials of vegetable or animal origin. The BP/Ph Eur further defines these materials as those *for which antimicrobial pretreatment is not feasible and for which the competent authority accepts a microbial contamination of the raw material exceeding 10^3 viable micro-organisms per gram or per millilitre.*

The TGA does not require general microbial limits for raw materials. The only stipulation is that the finished products that contain these raw materials must comply with the TGA Guidelines.

The types of materials which would be classified as being *of natural origin* and which would cause products containing them to be classified Category 3b (BP/Ph Eur) or 2b (Table 3) are raw plant materials or animal material which have not been fully processed.

Topical products

These products should normally comply with the limits in Category 1a of the TGA. Guidelines (Table 3) or Category 1b if they contain antiseptics or corticosteoids.

Transdermal patches

Limits on the microbial content of *transdermal patches* should be the same as those applied to topical products (Category 1a, Table 3) except that the limits apply per patch instead of per gram. The same requirement for the absence of all pseudomonads also applies to transdermal patches.

Haemodialysis solutions

There are no limits specified in the BP/Ph Eur for *haemodialysis solutions*. Concentrated haemodialysis solutions are prepared and stored using materials and methods designed to produce solutions having as low a degree of microbial contamination as possible. In certain circumstances, it may be necessary to use sterile solutions. Because of the large volumes used, haemodialysis solutions are usually prepared by diluting a concentrated solution with water. The Ph Eur/BP requires that the water used for the dilution of haemodialysis solutions contains <100 CFU/mL.

Other products

Requirements for other groups of products are as follows:

Table 2: General requirements

Route of administration or type of product	*Requirement*
Injectable	Should be sterile
Intraurethral route	Should be sterile
Irrigation solutions	Should be sterile
Nasal route	As for topical products
Ophthalmic route	Should be sterile
Otic route	As for topical products*
Peritoneal dialysis solutions	Should be sterile
Pulmonary inhalation route	As for topical products
Rectal route	As for oral products
Vaginal route	As for topical products

* Otic products for post surgical use should be sterile

Table 3: Therapeutic Goods Administration's Guidelines for Assessing the Results of Microbiological Tests on Non-Sterile Pharmaceuticals for Human Use

Category	Type of Preparation	Suggested Limit
1	**Products for Topical Application** (including those for use in body cavities)	
1a	For use on broken* and unbroken skin (other than antiseptics and coricosteroids)	TAMC** not more than 10^2 per mL or per gram amongst which there should be - no pseudomonads - no *Staphylococcus aureus*
1b	Antiseptics and corticosteroids	TAMC not more than 10/mL or per gram amongst which there should be - no pseudomonads - no *Staphylococcus aureus*
2	**Products for Oral Use**	
2a	Products other than those containing raw material of vegetable or animal origin	TAMC not more than 10^3/mL per gram amongst which there should be - not more than 10^2 yeast and mould - not more than 10^2 enterobacteria - no *E coli* in 1mL or 1g - no salmonellae in 10mL or 10g
2b	Products containing raw materials of vegetable or animal origin	TAMC not more than 10^4/mL per gram amongst which there should be - not more than 10^2 yeast and mould - not more than 10^2 enterobacteria - no *E coli* in 1mL or 1g - no salmonellae in 10mL or 10g
2c	Herbal teas	TAMC not more than 10^5/mL per gram amongst which there should be - not more than 10^2 yeast and mould - not more than 10^2 enterobacteria - no *E coli* in 1mL or 1g - no salmonellae in 10mL or 10g

* *broken skin* refers to minor cuts and abrasions; products intended for use on large open wounds or severely damaged skin should be sterile

** Total Aerobic Microbial Count

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Reference/Publication #