



Australian Government
Department of Health and Ageing
Therapeutic Goods Administration



Consultation Paper

Microbiological Standards for Medicines in the Australia New Zealand Therapeutic Products Authority (ANZTPA)

Call for Comment – July 2006

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How to comment on this Consultation Paper

Submissions may be sent by post and/or e-mail and, where possible, should be structured to address the specific questions posed in the consultation paper. In addition, stakeholders are encouraged to provide other comments that will assist in the deliberations of the Committee.

Content of submissions

Your submission should include:

- your name and full contact details including: address, telephone number, and if applicable, facsimile and e-mail address
- the particular point being addressed (eg, Proposal 2)
- information and data concerning the impact of proposed changes on affected parties
- relevant evidence and/or examples to support the views expressed
- in the case of organisations, the level at which the submission was authorised.

Confidentiality of submissions

If you wish any information contained in the submission to be treated as confidential, please clearly identify the information and outline the reason it is confidential.

Address for submissions

Electronic submissions should be e-mailed to <standards@anztpa.org>.

Hardcopy submissions should be addressed to either of the addresses below:

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Questions relating to submissions

Any questions relating to submissions should be directed to the Project Officer by e-mail at <standards@anztpa.org>.

Deadline for submissions

The deadline for receipt of submissions is close of business, 15 September 2006.

Executive Summary

The proposed commencement of the Australia New Zealand Therapeutic Products Authority (ANZTPA) provides an opportunity for the adoption of internationally harmonised standards to apply to therapeutic products in both Australia and New Zealand. Accordingly, wherever possible, the Authority will seek to use internationally recognised standards in place of Australian or New Zealand specific ones.

The British Pharmacopoeia (BP), European Pharmacopoeia (Ph Eur) and United States Pharmacopoeia-National Formulary (USP-NF) have been nominated as appropriate standards to generally apply to the medicines that will be regulated by the ANZTPA. These pharmacopoeial standards are referred to as the default standards.

The three pharmacopoeias include internationally recognised and harmonised requirements for the Test for Sterility and the Bacterial Endotoxin Test. These tests are already recognised and accepted by New Zealand's Medsafe and Australia's Therapeutic Goods Administration and it is proposed that this continues. There has also been recent international consensus on the microbial attributes for particular types of non-sterile medicines, and it is proposed that the ANZTPA adopt these requirements.

However, there are also areas of inconsistency and/or conflicts between the three pharmacopoeias, in particular:

- how the preservative efficacy of sterile, and non-sterile, multidose medicines can be assured, and
- how the microbial attributes of non-sterile oral complementary medicines containing material of natural origin, can be assured.

The purpose of this consultation paper is to seek stakeholder input into the microbiological standards that should apply to medicines regulated by the ANZTPA, when it commences operation, when there are inconsistencies and/or conflicts between pharmacopoeias.

Proposals for the microbiological standard for medicines are stated below. The standard would take the form of a Managing Director's Order.

PROPOSAL 1 – Preservative efficacy

All sterile and non-sterile multidose medicines should comply with the requirements detailed in "Efficacy of Antimicrobial Preservation" (Appendix XVI C and Supplementary Chapter 1 J of the BP, inclusive of 5.1.3 of the Ph Eur), and not Chapter <51> Antimicrobial Effectiveness Test of the USP-NF, except that:

- Compliance with Chapter <51> Antimicrobial Effectiveness Test of the USP-NF and its acceptance criteria would be allowed for types of multidose medicines specified in the standard (currently, only liquid antacids would be specified).

Exemptions from the standard would be considered by the ANZTPA on a case-by-case basis for individual multidose medicines, such as where the risk of adverse reaction is demonstrated to outweigh the benefit of a preservation system that complies with the acceptance criteria of the Ph Eur/BP.

PROPOSAL 2 – Microbial attributes for non-sterile medicines

Non-sterile medicines that are included within the scope of the ‘harmonised’ pharmacopoeial text (as indicated in Table 1) should comply with the BP, Ph Eur or the USP-NF ‘harmonised’ text on Microbial Attributes (ie methods and acceptance criteria).

Complementary medicine oral dosage forms containing material of natural origin, except herbal medicinal products to which boiling water is added before use, should comply with the requirements detailed in Appendix XVI D of the BP / 5.1.4 of the Ph Eur. These ‘non-harmonised’ (“Special Ph Eur provision”) acceptance criteria apply to oral dosage forms containing raw material of natural origin for which antimicrobial pretreatment is not feasible, and therefore the ANZTPA will accept a total aerobic microbial count (TAMC) of the raw material exceeding 10^3 colony forming units (CFU) per g or mL (ie the ANZTPA will accept a TAMC of up to 10^4 CFU per g or mL for finished product). The various USP-NF acceptance criteria in specific and generic monographs will not be accepted by the ANZTPA for these medicines.

Herbal medicinal products to which boiling water is added before use should comply with limits specified in the standard (a TAMC of not more than 10^5 CFU per g amongst which there should be not more than 100 yeasts and mould, not more than 100 Bile-tolerant Gram negative bacteria, no *E. coli* in 1g and no salmonellae in 10g). These limits replicate the current *TGAL Guidelines* for this type of medicine. The requirements detailed in Appendix XVI D of the BP / 5.1.4 of the Ph Eur (‘non-harmonised’ Special Ph Eur provision), and in various USP-NF monographs, will not be accepted by the ANZTPA for these medicines.

Proposal 2 is tabulated in Table 1.

PROPOSAL 3 – Sterility testing and Bacterial endotoxin testing

Medicines that are required to be sterile shall comply with the requirements of the BP, Ph Eur or the USP-NF ‘harmonised’ text on Test for Sterility and the Bacterial Endotoxin Test (where applicable). The ‘harmonised’ text has been accepted by the TGA since the USP-NF published it in early 2005.

This proposal is included for completeness, as it is equivalent to the default standard that will apply to sterile medicines. These issues would not be included in a Managing Director’s Order.

Table 1: Proposed Microbial Acceptance Criteria Pertaining to Non-Sterile Medicine Dosage Forms

| ANZTPA NON-STERILE MEDICINE | APPLICABLE MICROBIAL ATTRIBUTES |
|--|--|
| <i>Prescription medicines</i> | |
| <i>Over-the-Counter (OTC) medicines</i> | BP, Ph Eur, USP-NF ‘harmonised’ acceptance criteria (refer Table 5) |
| <i>Complementary medicines not intended for oral use</i> | |
| <p><i>Complementary medicines oral dosage forms:</i></p> <ul style="list-style-type: none"> • <i>Not containing material of natural origin (includes simulated natural raw materials that are synthetically produced)</i> • <i>Containing raw material of natural origin (for which antimicrobial pretreatment is not feasible)</i> • <i>Herbal medicinal products to which boiling water is added before use eg. dried herbs used for preparation of herbal teas</i> | <p>BP, Ph Eur, USP-NF ‘harmonised’ acceptance criteria (refer Table 5)</p> <p>Special Ph Eur/BP provision, ‘non-harmonised’ requirement for oral dosage forms, ie</p> <p>TAMC $\leq 10^4$ CFU/g/mL</p> <p>TYMC $\leq 10^2$ CFU/g/mL</p> <p>Bile-tolerant Gram negative bacteria $\leq 10^2$ CFU/g/mL</p> <p><i>E. coli</i> absent 1g/mL</p> <p><i>Salmonella</i> absent 10 g/mL</p> <p><i>St. aureus</i> absent 1 g/mL</p> <p>TAMC $\leq 10^5$ CFU/g/mL</p> <p>TYMC $\leq 10^2$ CFU/g/mL</p> <p>Bile-tolerant Gram negative bacteria $\leq 10^2$ CFU/g/mL</p> <p><i>E. coli</i> absent 1g/mL</p> <p><i>Salmonella</i> absent 10 g/mL</p> |
| <i>Substances for pharmaceutical use</i> | BP, Ph Eur, USP-NF ‘harmonised’ acceptance criteria (refer Table 5) |

TAMC: Total aerobic microbial count

TYMC: Total yeast and mould count

CFU/g/mL: Colony Forming Units per g or per mL

1 Introduction

- 1.1** In early 2005 the Therapeutic Products Interim Ministerial Council established the Joint Interim Expert Advisory Committee on Standards (the Committee), a group of Australian and New Zealand experts, to make recommendations on standards for the new Australia New Zealand Therapeutic Products Authority (ANZTPA, the Authority). Further information on the Joint Interim Expert Advisory Committee on Standards and its work can be found at < <http://www.anztpa.org/committees/jieacs.htm>>. The Committee called for comment on the consultation document *Pharmacopoeial standards for medicines in the Australia New Zealand therapeutic products agency* in September 2005, at < <http://www.anztpa.org/consult/pharmacopoeia.htm>>.
- 1.2** The Committee, taking into account responses from stakeholders, has recommended that the default standards for medicines regulated by the Authority should be monographs of the British Pharmacopoeia (BP), the European Pharmacopoeia (Ph Eur) and the United States Pharmacopoeia-National Formulary (USP-NF), as equally acceptable standards. The role of the default standards is to define the standards with which medicines must comply in the absence of a standard authorised by the ANZTPA. (See Part 2 of the draft Medicines Rule, available at <<http://www.anztpa.org/consult/consdocs1.htm#medrule>>).
- 1.3** The Committee, taking into account responses from stakeholders, also recommended that where the ANZTPA intended to generally depart from the requirements of a default standard, the processes for formalising such a position in a standard should be followed. A Managing Director's Order (similar to the Therapeutic Goods Orders currently in place in Australia) will define the standard that is to be applied to a medicine. An Order will constitute a legal requirement, unlike the advisory status of guidelines currently used by the TGA.
- 1.4** Where the BP and/or Ph Eur and/or USP-NF contain a monograph that specifies a test method or acceptance criteria for a particular attribute of a medicine, then inconsistency or conflict of pharmacopoeial requirements is possible. The consultation document on default standards (see 1.1) highlighted two specific microbiological examples where such conflict occurs – preservative efficacy and microbial attributes of non-sterile medicines. Where this inconsistency or conflict is considered to have significant implications for quality, safety or efficacy of the medicine, the inconsistency or conflict could be resolved by either specific or general requirements.
- 1.5** The purpose of this consultation paper is to seek stakeholder input into the microbiological standards that should apply to medicines in Australia and New Zealand when the ANZTPA commences operation. The principal issues to be considered are how the preservative efficacy of sterile and non-sterile multidose medicines, and the microbial attributes of non-sterile medicines, can be assured. This consultation paper is distributed on behalf of the Committee.

- 1.6 This paper presents proposals on microbiological standards. Comment is invited and welcome. Negative comment or objections to the proposals in this paper should be supported by an appropriate level of scientific justification and/or cogent reasons for the Committee's consideration. To facilitate review of your comments by the Committee, please specify the relevant paragraph number in your comments.
- 1.7 It is intended that the proposals, as amended by the Committee in response to stakeholder input, will be formalised as a draft Managing Director's Order. Further stakeholder consultation would be undertaken on the draft Order (see Consultation phase three of the Stakeholder consultation programme 2006/07, at <http://www.anztpa.org/consult/programme0607.htm>).
- 1.8 The various types of non-sterile medicines that will be regulated by the ANZTPA are summarised in Table 1.

2 Pharmacopoeias

2.1 *Status of BP/ Ph Eur*

- 2.1.1 By virtue of European law, the BP is obliged to include the requirements and monographs of the Ph Eur. The BP adopts and publishes both the 'harmonised' and 'non-harmonised' texts of the Ph Eur. Further discussion in this consultation document assumes that topics elaborated by the Ph Eur and the BP are essentially the same. In addition to the Ph Eur texts, the BP contains monographs for a wide range of formulated products.

2.2 *Status of USP-NF*

- 2.2.1 The USP-NF contains official monographs for substances, including excipients, and products. These monographs are regarded as official standards in the USA by virtue of their being referenced as official compendia in the adulteration and misbranding provisions of the USA's Federal Food, Drug and Cosmetic Act.
- 2.2.2 Non-mandatory monographs for products regulated as dietary supplements in the USA are included in the USP-NF. Dietary supplements are generally regulated as foods, rather than drugs (ie medicines), by the USA's FDA.

2.3 *Pharmacopoeial harmonisation of microbiological aspects*

- 2.3.1 The Japanese Pharmacopoeia (JP), the Ph Eur and USP-NF have been engaged in a process of pharmacopoeial harmonisation under the International Committee for Harmonisation (ICH) for a number of years. Under the ICH Q6A process, the Pharmacopoeial Discussion Group (PDG) has recently 'harmonised' test methods and acceptance criteria for microbial contamination of medicines, other than herbal drugs and herbal preparations. The process of harmonisation proceeds through

multiple, non-synchronised stages in the Ph Eur and USP-NF. ‘Harmonised’ text for microbial attributes (4.2.1 of this consultation paper) refers to text appearing in edition 5.6 of Ph Eur (June 2006) and the Second Supplement of the USP 29-NF 24. The text in the Ph Eur marked as “Special Ph Eur provision for...”, which is applicable to oral dosage forms containing raw materials of natural origin and to herbal medicines prepared either with or without boiling water, is ‘non-harmonised’.

- 2.3.2 The PDG has achieved harmonisation between the Ph Eur (and hence BP), JP and USP-NF for the Test for Sterility and the Bacterial Endotoxin Test for sterile pharmaceuticals. The ‘harmonised’ texts for these tests have been published. These tests are acceptable to Australia’s Therapeutic Goods Administration (TGA) and New Zealand’s Medsafe when conducted and interpreted according to the general ‘harmonised’ texts for sterile medicines. ***It is proposed that the ANZTPA will follow the default standards (ie the BP, Ph Eur or USP-NF) in relation to the Test for Sterility and the Bacterial Endotoxin Test.***
- 2.3.3 Harmonisation of the requirements for preservative efficacy has been under discussion for many years. The requirements published in the latest editions of the BP/Ph Eur and USP-NF reflect the results of the harmonisation efforts. Essentially the test methodologies and product categories are the same. Major differences between the BP/Ph Eur and the USP-NF now lie in the sampling times and acceptance criteria and it is unlikely that any further changes will occur in the near future. The differences for the major product categories are detailed in Tables 2, 3 and 4.
- 2.3.4 In this document, where ‘harmonised’ is used in quote marks, this refers to matters that have been through the ICH-PDG process and been signed off through all stages. Where the word harmonised is used in its general English meaning it is used without quote marks. Where ‘non-harmonised’ is used in quote marks, this refers to the Special Ph Eur provision.

3 Discussion - Preservative Efficacy

3.1 ***General***

- 3.1.1 During the consultation process on the default standards for the ANZTPA, the requirements of preservative efficacy testing were identified as an example of where there is inconsistency or conflict occurring in the requirements of different pharmacopoeias that could have significant implications for quality, safety or efficacy.
- 3.1.2 Preservatives are included in pharmaceutical preparations intended for use on more than one occasion to prevent or inhibit the growth of micro-organisms which may pose a risk of infection to the user or may lead to product degradation. The matter of the selection of the appropriate preservative system for a particular formulation is outside of the scope of this consultation paper.

- 3.1.3 The pharmacopoeias that will set the default standards for the ANZTPA have effectively harmonised the methodology and most product categories to be used in preservative efficacy testing, as described in Efficacy of Antimicrobial Preservation of the BP (Appendix XVI C and Supplementary Chapter 1 J), 5.1.3 of the Ph Eur and in Chapter <51> Antimicrobial Effectiveness Test in the USP-NF.
- 3.1.4 However, the PDG could not agree to harmonise the sampling times and acceptance criteria. Major differences currently exist between the Ph Eur/BP and the USP-NF in the sampling times and acceptance criteria and it is unlikely that harmonisation will occur in the near future. The differences for the major product categories are detailed in Tables 2, 3 and 4.
- 3.1.5 More detailed information on the proposed preservative efficacy standard can be found in Appendix A (pages 18 to 21) which considers the TGA experience (A1), BP preservative efficacy testing (A2), pharmacopoeial harmonisation (A3), comparison of acceptance criteria (A4), injections and ophthalmic products (A5), antacids (A6) and literature reports (A7).

3.2 Requirement for Ph Eur/BP sampling times and acceptance criteria

- 3.2.1 The sampling times and acceptance criteria of the USP-NF are not considered to be sufficiently stringent particularly for the high risk parenteral and ophthalmic products. There is evidence to suggest that ophthalmic products which satisfied the requirements of the USP-NF test have been implicated in in-use contamination. Hence, regulatory authorities in the European Union are reluctant to accept anything less than compliance with the most stringent Ph Eur/BP criteria (Criteria A), particularly for parenterals and ophthalmics. The TGA has always taken a more lenient approach than the European Union, frequently accepting compliance with the less stringent Ph Eur/BP criteria (Criteria B) provided the manufacturer has submitted adequate justification. This more lenient approach is feasible because of the TGA's strict policies regarding multiple dose injections and its requirement for justification of the open shelf period for both multidose injections and ophthalmic preparations. ***It is proposed that the ANZTPA will require medicines to comply with the sampling times and acceptance criteria of the Ph Eur/BP, and not the USP-NF, for the efficacy of antimicrobial preservation, unless otherwise approved.***
- 3.2.2 Since the methodology for the preservative efficacy tests of the BP/Ph Eur and USP-NF are essentially the same, it is possible for North American manufacturers to modify their sampling criteria to satisfy the requirements of their non-USA markets, ie for export to the European Union and Australia. It is possible that many preserved products which have been tested and meet the USP-NF acceptance criteria might also satisfy the Ph Eur/BP acceptance criteria.

- 3.2.3 There has been discussion in the literature about the lack of case reports or outbreaks of illness that can be linked to in-use contamination of long-established preserved products that were preserved according to the USP-NF criteria (but not the more stringent BP requirements). However, it is unlikely that contamination of a multidose medicine during use by a patient would be considered as a potential cause of illness unless there was a high level of suspicion from the community and/or healthcare professions. Hence, tests that might have implicated the multidose medicine may not have been carried out.

3.3 **Liquid Antacids**

- 3.3.1 The USP-NF includes a separate category for antacid preparations, with a lower initial inoculum than used for other product types. The BP/Ph Eur acknowledge that aqueous antacid products are difficult to preserve and indicate that it is a matter for agreement between the manufacturer and the Competent Authority (ie the ANZTPA) to agree on alternative criteria. A recent recommendation from the Australian Medicines Evaluation Committee (MEC) has indicated that liquid antacid products in Australia can comply with the USP-NF acceptance criteria. ***It is proposed that the ANZTPA will allow the USP-NF test and acceptance criteria for antimicrobial effectiveness to be used for liquid antacid preparations.*** This proposal would be specified in the standard and requests for exemptions for individual liquid antacids would not be required.

3.4 **Case-by-case exemptions**

- 3.4.1 Preservatives, and combinations of preservatives, have the potential to induce toxicity or hypersensitivity in users, particularly when the medicine is used frequently or over an extended period. Different preservatives, or lower concentrations of preservatives, may provide adequate and reasonable preservation even though the medicine might not fully comply with the optimal Ph Eur/BP criteria, ie Criteria A. To address this scenario, Criteria B of the Ph Eur/BP were published to be used at the discretion of the Competent Authority (ie the ANZTPA) where Criteria A could not be attained because of, for example, increased risk of adverse reactions. There are also products currently on the market in Australia that do not fully comply with the BP/Ph Eur Criteria B, however, alternative criteria have been agreed upon between the sponsor and the TGA for these products. Adopting the requirements of the BP/Ph Eur for preservative efficacy should not result in products with long histories of safety being recalled from the Australian or New Zealand market, provided the claims of safe use can be substantiated. ***It is proposed that the ANZTPA will consider, on a case-by-case basis, an exemption from the standard to allow medicines to not fully comply with the Ph Eur/BP acceptance criteria where the risk of adverse reaction is demonstrated to outweigh the benefit of a preservation system that does comply with the acceptance criteria of the BP / Ph Eur.*** A request for exemption from the standard for an individual medicine would be required.

4 Discussion – Microbial Attributes

4.1 **General**

4.1.1 During the consultation process on the default standards for the ANZTPA, the requirements of microbial attributes were identified as an example of where there is inconsistency or conflict occurring in the requirements of different pharmacopoeias that could have significant implications for quality, safety or efficacy.

4.1.2 The *TGAL Guidelines for Assessing the Results of Microbiological Tests on Non-Sterile Pharmaceuticals for Human Use*, November 1994 (*TGAL Guidelines*) are used by the TGA for the purposes of assessing results of microbiological testing for all non-sterile medicines in Australia. Specific test methods have not been mandated by the TGA. Emphasis is given to ensuring that microbial limits test methods are validated as suitable for recovery of indicator organisms, as well as those organisms that would be considered objectionable in specific dosage forms and individual medicines.

4.2 **'Harmonised' criteria for non-sterile medicines**

4.2.1 In November 2005, the Pharmacopoeial Discussion Group (PDG) finalised three general chapters:

- *Microbial Enumeration Methods.*
- *Tests for Specified Microorganisms.*
- *Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use.* (A non-mandatory information chapter.)

4.2.2 The Ph Eur has announced the publication of the three new 'harmonised' microbial attributes texts in Supplement 5.6 (June 2006), with implementation by 1 January 2007. The Ph Eur's expert group will review individual monographs by December 2006, with revised texts to be published by June 2008 with implementation by January 2009. By 2010, the Ph Eur will delete the current texts, leaving only the revised 'harmonised' text. As mentioned above, publication in the BP will follow publication in the Ph Eur.

4.2.3 The USP-NF published the 'harmonised' microbial attributes text in the Second Supplement of USP 29 – NF 24 as Chapters <61>, <62> and <1111>. These chapters become official on 1 August 2007.

- 4.2.4 An important consideration for the ANZTPA is the scope of the ‘harmonised’ texts. The scope of the ‘harmonised’ texts to be adopted in the Ph Eur, BP and the USP-NF exclude herbal drugs and herbal drug preparations on the grounds that these products are regulated differently in different countries and consensus would have been difficult to achieve. It is not known if or how the USP-NF will apply the ‘harmonised’ acceptance criteria established for non-sterile pharmaceutical preparations to dietary supplements that do not solely contain botanical material.
- 4.2.5 Under ANZTPA’s regulation of complementary medicines, the ‘harmonised’ acceptance criteria of the Ph Eur and USP-NF will technically apply to all complementary medicines, with the exception of oral dosage forms that contain material of natural origin (animal, vegetal or mineral).
- 4.2.6 Tables 1 and 5 present limits on microbial attributes to apply to non-sterile medicines and substances for pharmaceutical use. The Ph Eur/BP definition of “substances for pharmaceutical use” encompasses “any [pharmacopoeial] organic or inorganic substances that are used as active substances or excipients for the production of medicinal products for human or veterinary use”. ***It is proposed that the ANZTPA will accept the Ph Eur, BP or the USP-NF ‘harmonised’ text on Microbial Attributes (ie methods and acceptance criteria) as equally acceptable and applicable to the medicines and substances for pharmaceutical use included under the scope of the ‘harmonised’ pharmacopoeial text.***
- 4.2.7 Table 5 is a comparison of the ‘harmonised’ criteria for non-sterile medicines with the current acceptance criteria of the BP 2005 (Ph Eur 5th Edition) and the *TGAL Guidelines*. For completeness, the ‘non-harmonised’ Special Ph Eur provision criteria are also included towards the end of this table.
- 4.2.8 It is recognised that for some complementary medicine oral dosage forms containing material of natural origin (animal, vegetal or mineral), decontamination processes may cause unwanted changes affecting safety, efficacy or stability of the raw material. Such natural products, for which antimicrobial pre-treatment is not feasible, can default automatically to compliance with the ‘non-harmonised’ Special Ph Eur provision as specified in Table 1. Exemption from the standard for an individual medicine would not be required.
- 4.2.9 It is also recognised that some other herbal materials for oral dosage forms that cannot withstand decontamination processes, will not be able to comply with the ‘non-harmonised’ Special Ph Eur provision. ***It is proposed that the ANZTPA will consider, on a case-by-case basis, the exemption from the ‘non-harmonised’ text of complementary medicine oral dosage forms containing material of herbal origin.*** A request for exemption from the standard for an individual medicine would be required.

- 4.2.10 More detailed information on the proposed microbiological standard can be found in Appendix B (pages 22 to 26) which considers TGA experience (B1), dosage forms included in the ‘harmonised’ test (B2), comment on interpretative statements in the ‘harmonised’ texts (B3), topical products (B4), and differences between current Australian requirements and proposed requirements (B5).

4.3 **Criteria for Herbal Medicinal Products**

- 4.3.1 Herbal drugs and herbal preparations were excluded from the scope of international harmonisation (see 4.2.4). The excluded medicines consist of a complex range of substances that are defined by the BP and/or Ph Eur as follows:

Herbal drugs are mainly whole, fragmented or cut, plants, parts of plants, algae, fungi, lichen in an unprocessed state, usually in dried form but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal drugs. Herbal drugs are precisely defined by the botanical scientific name according to the binominal system (genus, species, variety and author).

Herbal drug preparations are obtained by subjecting herbal drugs to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal drugs, tinctures, extracts, essential oils, expressed juices and processed exudates.

Herbal teas consist exclusively of one or more herbal drugs intended for oral aqueous preparations by means of decoction, infusion or maceration. The preparation is prepared immediately before use. The recommendation on microbial quality takes into account the prescribed preparation method (use of boiling or non-boiling water).

- 4.3.2 There are no internationally ‘harmonised’ microbiological acceptance criteria for herbal medicinal products. There are different and inconsistent pharmacopoeial requirements in the Ph Eur and the USP-NF, which also differ from the *TGAL Guidelines*. (More detailed information can be found in Appendix B, paragraphs B6, B7 and B8.) It is essential that the microbial acceptance criteria required by the ANZTPA for these products ensure consumer safety, are not onerous to industry and can be effectively managed from a regulatory perspective.

4.3.3 Table 6 summarises the current recommendations of the BP 2005 (Ph Eur 5th Edition), USP 29 (2006) and the *TGAL Guidelines* (1994), with regard to microbiological acceptance criteria for herbal medicinal products (that are not the subject of individual USP monographs). ***It is proposed that the ANZTPA will require herbal drugs and herbal drug preparations to which boiling water is not added, to comply with the ‘non-harmonised’ Special Ph Eur provision regarding oral dosage forms. The ANZTPA will not accept compliance with specific or generic acceptance criteria of the USP-NF, and will not accept compliance with the current TGAL Guidelines for this type of medicine.***

4.4 ***Herbal Medicinal Products with Boiling Water Added Before Use***

4.4.1 The TGA’s longstanding position has been that, with regard to microbial quality, herbal medicinal products sold for pharmaceutical purposes should be regulated in the same manner as other conventional pharmaceuticals. There appears to be no rationale for the claim that, as herbal medicinal products are of natural origin, a significantly higher microbial load is acceptable. However, in relation to herbal medicinal products to which boiling water is added before use (ie herbal teas), the higher natural bioburden of such medicines, industry benchmarking and risk assessment have been previously considered by the TGA. In 1994 the TGA agreed that there was a case for increasing the allowable total count for this type of oral dosage form to 10⁵ CFU/g. Laboratory studies performed to justify the more stringent limit for herbal teas indicated that where the aerobic bioburden exceeded 10⁵ CFU/g, the prevalence of organisms with the potential to constitute a risk to the user increased.

4.4.2 The Ph Eur/BP recommendations for herbal medicinal products to which boiling water is added before use are considered by the TGA to be too loose to ensure consumer safety. To date, the Ph Eur/BP has not presented any evidence to demonstrate that the high levels of microorganisms permitted by the BP/Ph Eur do not pose a risk to the consumer, or that excessive external contamination of product during growing, harvesting, drying, storage etc cannot be effectively controlled.

4.4.3 Both the USP recommendations and *TGAL Guidelines* are more stringent than the BP/Ph Eur recommendations. The differences between the USP-NF and the *TGAL Guidelines* are detailed in Appendix B, paragraph B9.

4.4.4 Technical arguments to support the TGA’s position with regard to microbial limits specifications for herbal medicinal products to which boiling water is added before use have been widely publicised in the past. ***It is proposed that the ANZTPA will require herbal preparations to which boiling water is added before use to comply with ANZTPA specific requirements (previously published in the TGAL Guidelines) and will not accept compliance with the BP, Ph Eur or USP-NF recommendation for this type of medicine.***

5 Microbiological Standards Proposals for the ANZTPA

The proposals for the microbiological standards for the ANZTPA are as follows. Stakeholders are invited to respond to these proposals.

PROPOSAL 1 – Preservative efficacy

All sterile and non-sterile multidose medicines should comply with the requirements detailed in “Efficacy of Antimicrobial Preservation” (Appendix XVI C and Supplementary Chapter 1 J of the BP, inclusive of 5.1.3 of the Ph Eur), and not Chapter <51> Antimicrobial Effectiveness Test of the USP-NF, except that:

- Compliance with Chapter <51> Antimicrobial Effectiveness Test of the USP-NF and its acceptance criteria would be allowed for types of multidose medicines specified in the standard (currently, only liquid antacids would be specified).

Exemptions from the standard would be considered by the ANZTPA on a case-by-case basis for individual multidose medicines, such as, where the risk of adverse reaction is demonstrated to outweigh the benefit of a preservation system that complies with the acceptance criteria of the Ph Eur/BP.

PROPOSAL 2 – Microbial attributes for non-sterile medicines

Non-sterile medicines that are included within the scope of the ‘harmonised’ pharmacopoeial text (as indicated in Table 1) should comply with the BP, Ph Eur or the USP-NF ‘harmonised’ text on Microbial Attributes (ie methods and acceptance criteria).

Complementary medicine oral dosage forms containing material of natural origin, except herbal medicinal products to which boiling water is added before use, should comply with the requirements detailed in Appendix XVI D of the BP / 5.1.4 of the Ph Eur. These ‘non-harmonised’ (“Special Ph Eur provision”) acceptance criteria apply to oral dosage forms containing raw material of natural origin for which antimicrobial pretreatment is not feasible, and therefore the ANZTPA will accept a total aerobic microbial count (TAMC) of the raw material exceeding 10^3 colony forming units (CFU) per g or mL (ie the ANZTPA will accept a TAMC of up to 10^4 CFU per g or mL). The various USP-NF acceptance criteria in specific and generic monographs will not be accepted by the ANZTPA for these medicines.

Herbal medicinal products to which boiling water is added before use should comply with limits specified in the standard (a TAMC of not more than 10^5 CFU per g amongst which there should be not more than 100 yeasts and mould, not more than 100 Bile-tolerant Gram negative bacteria, no *E. coli* in 1g and no salmonellae in 10g). These limits replicate the current *TGAL Guidelines* for this type of medicine. The requirements detailed in Appendix XVI D of the BP / 5.1.4 of the Ph Eur (‘non-harmonised’ Special Ph Eur provision), and in various USP-NF monographs, will not be accepted by the ANZTPA for these medicines.

Proposal 2 is tabulated in Table 1.

PROPOSAL 3 – Sterility testing and Bacterial endotoxin testing

Medicines that are required to be sterile shall comply with the requirements of the BP, Ph Eur or the USP-NF 'harmonised' text on Test for Sterility and the Bacterial Endotoxin Test (where applicable). The 'harmonised' text has been accepted since the USP-NF published it in early 2005.

This proposal is included for completeness, as it is equivalent to the default standard that will apply to sterile medicines. These issues would not be included in a Managing Director's Order.

Appendix A - Preservative Efficacy

A1 Since 1999 multidose pharmaceutical dosage forms supplied in Australia have been required to comply with the preservative efficacy requirements specified in the BP (Resolution of 15th meeting of the Therapeutic Goods committee (TGC) of 1999).¹ Prior to 1999, multidose dosage forms were required, as a minimum, to comply with the requirements of Chapter <51> Antimicrobial Effectiveness Test of the USP-NF. However, the TGA always encouraged compliance, where possible, with the more stringent requirements of the BP/Ph Eur, in accordance with a Resolution of the TGC from 1985.² The TGC agreed that the TGA could handle the issue of compliance of products already on the market administratively, on a case-by-case basis.

Concerns have been expressed that long-marketed multidose products that have only been tested according to the USP-NF may have to be removed from the Australian and New Zealand market because they cannot comply with the preservative efficacy acceptance criteria of the Ph Eur/BP. These concerns are not associated with any reported incidents related to microbial contamination or infection. It may well be the case that preserved products, which have been tested and meet the USP acceptance criteria, would also satisfy the BP/Ph Eur acceptance criteria. The TGA Laboratories Branch compared the preservative efficacy of multidose contact lens care preparations when tested according to both the BP/Ph Eur and the USP-NF preservative efficacy monographs. The results demonstrated that if a product was able to meet the USP-NF acceptance criteria, it usually also met the BP/Ph Eur Criteria. Conversely, if a product was not able to meet the BP/Ph Eur criteria, it was not able to meet the USP-NF criteria. These observations should not be extrapolated automatically to other products containing different active and excipient ingredients.

A2 When the BP (and later the Ph Eur) first published requirements for preservative efficacy, only one set of acceptance criteria were included. In 1993, a second, less stringent, set of criteria were introduced. The original criteria (Criteria A) were the recommended efficacy to be attained with the less stringent set (Criteria B) to be used where Criteria A could not be attained because of, for example, increased risk of adverse reactions.

Supplementary Chapter 1 J of the BP recognises that not all the target criteria may be reached for some product formulations, for example antacids, and alternative criteria can be agreed upon between the manufacturer and the Competent Authority (ie the ANZTPA).

A3 Harmonisation of the requirements for preservative efficacy has been under discussion for many years. The requirements published in the latest editions of the Ph Eur/BP and USP-NF reflect the results of the harmonisation efforts. Essentially the test methodologies and product categories are the same in these pharmacopoeias. Major differences between the Ph Eur/BP and the USP-NF still exist in the sampling times

1 Microbiological update. *TGA News*, 40 (March 2003). Available at <http://www.tga.gov.au/docs/html/tganews/news40/gen.htm#micro> (accessed March 2006)

2 Preservative efficacy in multidose pharmaceutical preparations. *TGA News*, 29 (May 1999). Available at <http://www.tga.gov.au/docs/html/tganews/news29/lab.htm#preserv> (accessed March 2006).

and acceptance criteria and it is unlikely that any further changes will occur in the near future.³ The Ph Eur (and consequently the BP) would not reduce its acceptance criteria and the USP-NF would not enhance its acceptance criteria. Harmonisation of these aspects is not currently on the PDG agenda.

The major reason for the inability to harmonise the pharmacopoeial sampling requirements and acceptance criteria is the difference in how compliance is interpreted, as summarised by Dr Scott Sutton (current Vice Chairman, USP Committee of Experts, Microbiology and Sterility Assurance).⁴ In the USP-NF, the Antimicrobial Effectiveness Test is elaborated at Chapter <51>, which means that it is a mandatory referee test with which all preserved products must comply. Failure to comply would require the product to be removed from the market by the US FDA. Many long-marketed products with no evidence of contamination issues would then be subject to recall from the US market. In contrast, compliance with the test described in the BP Appendix XVI C and the Ph Eur Chapter 5.1.3 is not mandatory in the European Union. This is explained in Supplementary Chapter 1 J of the BP.

- A4** Since the preservative efficacy tests of the BP/Ph Eur and USP-NF are essentially the same with respect to methodology, it is possible for North American manufacturers exporting product to the European Union and Australia to set up the test according to the USP-NF method. Manufacturers can then modify the USP-NF procedure by incorporating the additional sampling times required by the Ph Eur/BP (ie at 6 and 24 hours for parenteral and ophthalmic preparations or at 2 and 7 days for topical products) and interpreting the log₁₀ reductions at those specific times according to the Ph Eur/BP acceptance criteria.

The USP-NF's first sampling time for parenteral products is at 7 days and for topical products at 14 days. This yields information of little value relative to the actual period and frequency of use. Furthermore, the log₁₀ reduction performance criteria of the USP-NF are less stringent than those of the Ph Eur/BP. For example, the USP-NF requirement is for a 1-log₁₀ reduction in bacteria at 7 days for parenteral products versus a 2-log₁₀ reduction at 6 hours, 3-log₁₀ reduction at 24 hours and no recovery at 7 days as required by the Ph Eur/BP. Regarding the USP-NF requirements for testing of ophthalmic products, it is difficult to correlate, from a safety point of view, the relevance of an initial sampling time of 7 days for a product that is used daily or even more frequently.

A 1-log₁₀ or greater reduction in microorganisms is likely to occur due to the death of challenge microorganisms under the test conditions in the absence of any antimicrobial preservative whatsoever over a period of 7 days. Also, the variability inherent in counting viable organisms is generally recognised as being in the range of +/- 0.5-log₁₀. Therefore, the USP-NF test is an insensitive measure of the activity and efficacy of any preservative in a formulated product.

Adopting the acceptance criteria of the Ph Eur/BP for preservative efficacy should not result in products with long histories of safe use being recalled from the market or

3 Sutton, Scott V. W, Porter, David, (2002), "Development of the antimicrobial effectiveness test as USP Chapter <51>," *PDA Journal of Pharmaceutical Science and Technology*, **56**(6), 300-311.

4 See footnote 3.

requiring re-evaluation by the ANZTPA provided the claims of safe use can be substantiated.

Australia's TGA and New Zealand's Medsafe are aware of literature reports of adverse effects associated with the use of preserved products.

The potential for adverse effects due to preservatives is recognised by the non-mandatory status of the preservative efficacy acceptance criteria in the Ph Eur/BP. The Ph Eur/BP approach is considered to provide more flexibility for sterile and non-sterile medicines, with less risk to user safety than would adoption of the USP-NF requirements for antimicrobial effectiveness testing.

- A5** Regulatory Authorities in the European Union are reluctant to accept anything less than compliance with the Ph Eur/BP Criteria A, particularly for parenterals and ophthalmics.⁵ The Eye-Care Industries European Economic Interest Grouping have approached the European Directorate for the Quality of Medicines with a proposal to separate the criteria for ophthalmics and parenterals to allow compliance with Criteria B for ophthalmics, in view of the recognised limited availability of suitable preservatives capable of meeting Criteria A.⁶ The TGA has always taken a more lenient approach, frequently accepting compliance with Criteria B for parenterals and ophthalmics, provided the manufacturer has submitted an adequate justification. This more lenient approach is taken because of the TGA's strict policies regarding multiple dose injections (derived from Australian Drug Evaluation Committee (ADEC) resolutions⁷) and its requirement for justification of the open shelf period for both multidose injections and ophthalmic preparations.
- A6** The USP-NF category for antacid preparations specifies an initial inoculum that is lower than that used in the general antimicrobial effectiveness test (between 1×10^3 CFU/mL and 1×10^4 CFU/mL of product). The acceptance criteria are no increase in bacteria, yeast and moulds at 14 days and 28 days. The Australian Medicines Evaluation Committee (MEC) has recently resolved that liquid antacid products in Australia can comply with the USP-NF acceptance criteria. The Ph Eur/BP acknowledge that aqueous antacid products are difficult to preserve and indicate that alternative criteria to be met are a matter for agreement between the manufacturer and the Competent Authority (ie the ANZTPA).
- A7** The literature includes discussion concerning the absence of reports linking contamination to adverse events in long-marketed USP preserved products.^{8,9} The wisdom of this assumption has been questioned, highlighting the fact that it may not be

5 Matthews B .R., Skinner F. S., (2006), "Aspects of the preservative requirements for multiple dose eye care products.", *European Journal of Parenteral & Pharmaceutical Sciences*, **11**(1), 23-28.

6 Matthews B.R, Personal communication to TGA staff.

7 Communicable Diseases Network Australia, the National Public Health Partnership and the Australian Health Ministers' Advisory Council (2004). *Infection control guidelines for the prevention of transmission of infectious diseases in the health care setting*. Available at

[http://www.health.gov.au/internet/wcms/publishing.nsf/content/icg-guidelines-index.htm/\\$FILE/part1.pdf](http://www.health.gov.au/internet/wcms/publishing.nsf/content/icg-guidelines-index.htm/$FILE/part1.pdf) (accessed March 2006)

8 See footnote 3.

9 Fels P, Gay M, Kabay A, Urban S, (1987), *Pharm Ind*, **49**(6), 631-637, cited in Matthews, B. R., (1993), "Preservative efficacy testing," *Reg Affairs J.*, 455-461.

possible to link contaminated product to adverse events.¹⁰ On the contrary, there is evidence in the literature to suggest that ophthalmic products which satisfied the requirements of the USP-NF Antimicrobial Effectiveness Test have been implicated in in-use contamination.^{11 12}

10 Spooner D.F. (1989), *J Appl Cosmetol* **7**, 93-101.

11 Matthews, B. R., (1993), "Preservative efficacy testing," *Reg Affairs J.*, 455-461.

12 Spooner, D. F., Davison, A. L., (1993), "The validity of the criteria for pharmacopoeial antimicrobial preservative efficacy tests", *Pharm J.*, **251**, 602-605.

Appendix B – Microbial Attributes

- B1** The *TGAL Guidelines*¹³ are used by the TGA for the purposes of assessing results of microbiological testing for all non-sterile medicines in Australia. The Australian TGC gave approval in principle at their November 1997 meeting for the retention of the *TGAL Guidelines*.¹⁴ This approval was for the purpose of reporting results of microbiological testing on non-sterile medicines, pending the outcome of the international harmonisation discussions.
- B2** The ‘harmonised’ pharmacopoeial chapter that includes acceptance criteria for non-sterile pharmaceutical preparations includes an expanded list of non-sterile dosage forms, compared with the BP 2005. Significant changes are:
- differentiation of aqueous preparations intended for oral use, from non-aqueous preparations intended for oral use, with different acceptance criteria applied to these two dosage forms;
 - inclusion of acceptance criteria for total yeast and mould count for all non-sterile dosage forms; and
 - reduction of the maximum allowable count to enable a claim of compliance for a product from 5×10^x CFU to 2×10^x CFU. For example, acceptance criteria of 10^2 CFU per g is capped at 200 CFU per g, rather than 500 CFU per g.
- B3** The ‘harmonised’ pharmacopoeial chapter that includes acceptance criteria for non-sterile pharmaceutical preparations contains specific statements on interpretation. These statements were included to enable consensus to be achieved in relation to general acceptance criteria for the range of non-sterile dosage forms, and to allow for other testing conditions and limits to be applied by manufacturers and regulatory authorities if necessary. These statements are:

The list [referring to the list of specified microorganisms eg. for cutaneous preparations, an absence of *Ps. aeruginosa* and *St. aureus*] is not necessarily exhaustive and for a given preparation it may be necessary to test for other microorganisms depending on the nature of the starting materials and the manufacturing process.

Where warranted, a risk-based assessment of the relevant factors is conducted by personnel with specialised training in microbiology and the interpretation of microbiological data.

¹³ TGA Laboratories' guidelines for assessing the results of microbiological tests on non-sterile pharmaceuticals for human use (1994). Available at

<http://www.tga.gov.au/docs/pdf/unsteril.pdf> (accessed March 2006)

¹⁴ Microbial limits for non-sterile pharmaceuticals. *TGA News*, 26 (April 1998). Available at <http://www.tga.gov.au/docs/html/tganews/news26/lab.htm#micro> (accessed March 2006)

- B4** The European Pharmacopoeia Group of Experts No.1 agreed that preparations intended for topical use should be free from contamination with pseudomonads, rather than just *Ps. aeruginosa*, since it is established that some pseudomonads, other than *Ps. aeruginosa*, may serve as opportunistic pathogens of the compromised host under certain conditions. The technical arguments provided by the TGA on this matter have been widely publicised in the past and may be reviewed in the paper published by Shelley Tang.¹⁵

The position that topical products should be free from contamination with pseudomonads is consistent with the approach of the USA's FDA, which has acknowledged the importance of pseudomonads as potential opportunistic pathogens in products intended for topical or nasal use. The current USA FDA *Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories* states that "... topical preparations contaminated with gram negative organisms are a probable moderate to serious health hazard" and "it is widely recognised that *Pseudomonas cepacia* [now known as *Burkholderia cepacia*] is objectionable if found in a topical product or nasal solution in high numbers" and recognises that the test methods of the current USP-NF may not be adequate for detection of this organism.¹⁶

- B5** As can be seen from Table 5, the main differences between the 'harmonised' acceptance criteria for non-sterile pharmaceutical preparations and the *TGAL Guidelines*, other than for herbal medicinal products, are:
- A significant expansion of the various categories of non-sterile dosage forms.
 - Inclusion of acceptance criteria for non-sterile substances for pharmaceutical use.
 - With regard to finished dosage forms intended for topical use:
 - Antiseptic and corticosteroid preparations intended for topical use are not recognised as a specific topical dosage form. The harmonised acceptance criteria for oromucosal, gingival, cutaneous, nasal and auricular use dosage forms would be applied to these preparations.
 - Inclusion of acceptance criteria for total yeast and mould count.
 - A requirement for absence of *Ps. aeruginosa* rather than a requirement for absence of pseudomonads. A statement was specifically included in the 'harmonised' chapter to allow for other testing conditions and limits to be applied by manufacturers and regulatory agencies where considered necessary (see B3 above).

¹⁵ Tang, S., (1998), "Microbial Limits Reviewed: The Basis for Unique Australian Regulatory Requirements for Microbial Quality of Non-Sterile Pharmaceuticals," *PDA Journal of Pharmaceutical Science & Technology* 52(6): 3, May-June, 100-109.

¹⁶ US FDA *Guide to Inspections of Microbiological Pharmaceutical Quality Control Laboratories*.
<www.fda.gov/ora/inspect_ref/igs/micro.html> (accessed March 2006)

- With regard to finished oral dosage forms:
 - Differentiation of aqueous preparations intended for oral use, from non-aqueous preparations intended for oral use, with different acceptance criteria applied to these two dosage forms.
 - Acceptance criteria for non-aqueous preparations intended for oral use are similar to the limits recommended by the *TGAL Guidelines* with the exception that the harmonised acceptance criteria do not include a limit for enterobacteria or a requirement for absence of salmonellae. Given that these dosage forms are at low risk of microbial contamination and that synthetic chemical preparations are unlikely to be contaminated with salmonellae, the absence of a limit for enterobacteria or a requirement for absence of salmonellae is not considered to be significant.
 - Acceptance criteria for aqueous preparations intended for oral use are more stringent than the limits recommended by the *TGAL Guidelines* even though the harmonised acceptance criteria do not include a limit for enterobacteria or a requirement for absence of salmonellae. Given that the harmonised acceptance criteria include a TAMC limit of $\leq 10^2$ CFU per g/mL and that synthetic chemical preparations are unlikely to be contaminated with salmonellae, the absence of a limit for enterobacteria or a requirement for absence of salmonellae is not considered to be significant.
 - The Ph Eur/BP will retain as a ‘non-harmonised’ requirement, a special provision for oral dosage forms that contain raw material of natural (animal, vegetal or mineral) origin for which antimicrobial pre-treatment is not feasible and for which the Competent Authority accepts a TAMC of the raw material exceeding 10^3 CFU per g/mL. The acceptance criteria for this dosage form are similar to those of the *TGAL Guidelines* with the exception that the Ph Eur/BP acceptance criteria additionally require an absence of *St. aureus* in 1 g/mL.
 - The Ph Eur/BP will also retain two ‘non-harmonised’ special provision requirements for herbal medicinal products consisting solely of one or more herbal drugs (whole, reduced or powdered). One requirement will be applicable to herbal medicinal products to which boiling water is added before use, with the other requirement applicable to herbal medicinal products to which boiling water is not added before use. The acceptance criteria for these two dosage forms are significantly less stringent than those of the corresponding *TGAL Guidelines*.
- B6** Appendix XVI D of the BP 2005, and 5.1.4 in the Ph Eur 5th Edition, include two generic, non-mandatory, microbiological acceptance criteria for finished herbal medicinal products that consist solely of one or more herbal drugs (whole, reduced or powdered), depending on whether or not boiling water is added to the product before use. These acceptance criteria specify different bacterial and fungal count limits as well as requirements for absence of *E. coli* and *Salmonella*.
- B7** The USP-NF includes seven, generic, “guidance”, microbiological acceptance criteria for dietary supplements that contain botanical material for use where an individual USP-NF monograph does not specify microbiological acceptance criteria. These

generic acceptance criteria cover the categories of dried or powdered botanicals, powdered botanical extracts, tinctures, fluid extracts, infusions/decoctions, nutritional supplements with botanicals and botanicals to be treated with boiling water before use. These seven acceptance criteria include five different bacterial and fungal count limits and different requirements for absence of *E. coli* and *Salmonella*. The USP-NF states:

When objectionable organisms are not specified in the individual monograph, it is the manufacturer's responsibility to determine which microorganisms in their products are objectionable.

Where microbiological acceptance criteria are specified in individual USP-NF monographs, these acceptance criteria are not always consistent and can vary significantly for similar dosage forms of different botanical material. From an industry perspective, this creates the potential for market inequity - why should the acceptance criteria for red clover tablets be more stringent than the acceptance criteria for valerian tablets? From a regulatory perspective, it creates a cumbersome system within which to operate.

- B8** The *TGAL Guidelines* include two, generic, recommendations for microbiological acceptance criteria that are applicable to finished herbal medicinal products. The generic acceptance criteria are for oral dosage forms that contain material of natural origin and for herbal teas (where boiling water is added to the dried herb(s) before use). Herbal medicinal products to which boiling water is not added before use are considered in the same category as oral dosage forms that contain material of natural origin. This category is not just restricted to products that contain material of botanical origin, but also includes products, for example, that contain material of animal origin. While the acceptance criteria for the two categories specify different total aerobic bacterial count limits, the criteria for fungal count, enterobacterial count and for absence of *E. coli* and *Salmonella* are the same. As can be seen from Table 6, the *TGAL Guidelines* for herbal medicinal products to which boiling water may, or may not be added before use, are more stringent than the limits recommended by the Ph Eur/BP and the USP-NF. Laboratory studies performed to justify the more stringent limit for herbal teas indicated that where the aerobic bioburden exceeded 10⁵ CFU/g, the prevalence of organisms with the potential to constitute a risk to the user increased.¹⁷
- B9** The *TGAL Guidelines* differ from the generic USP-NF recommendations for herbal medicinal products to which boiling water is added before use in relation to slightly more stringent criteria for fungal count and requirements for enterobacteria count and absence of salmonellae. The USP-NF recommendation with regard to *E. coli* however, is significantly more stringent than the corresponding *TGAL Guidelines* recommendation. As a consequence, revalidation of product specific *E. coli* test methods would be required if the USP-NF was mandated as a standard for products currently supplied in Australia rather than the limits of the *TGAL Guidelines*, unless existing methods were validated with a 10g sample.

¹⁷ Tang, S., (1994), "Microbiological quality of herbal teas" *TGAL Information Bulletin* 6(1): September 1994.

The *TGAL Guidelines* recommended limit for enterobacteria count is $\leq 10^2$ CFU/g, which is 1- \log_{10} lower than that recommended by the USP-NF. Technical arguments to support this lower limit are based on the demonstrated importance of testing for enterobacteria as an indicator for product quality in relation to the potential for contamination with pathogens such as *E. coli* and salmonellae; the higher the levels of enterobacteria present, the higher the potential for contamination of the product with enteric pathogens.

The *TGAL Guidelines* recommended limit for fungal count is $\leq 10^2$ CFU/g, which is also 1- \log_{10} lower than that recommended by the USP-NF. Technical arguments to support this lower limit are based primarily on the potential for possible contamination of product with mycotoxins.

Further justification regarding the position proposed for the ANZTPA may be reviewed in the paper published by Tang.

Table 2: Preservative Efficacy Acceptance Criteria for Parenteral and Ophthalmic Preparations

| TEST ORGANISMS | PHARMACOPOEIA | SAMPLING TIME/LOG REDUCTIONS | | | | |
|---|-----------------------|------------------------------|----------|--------|---------|---------|
| | | 6 hours | 24 hours | 7 days | 14 days | 28 days |
| Vegetative Bacteria <i>(Ps. aeruginosa, St. aureus, USP also E. coli)</i> | Ph Eur/BP Criteria A | 2 | 3 | - | - | NR |
| | Ph Eur/BP Criteria B* | - | 1 | 3 | - | NI |
| | USP† | | | 1 | 3 | NI |
| Yeasts & Moulds <i>(C. albicans, A. niger)</i> | Ph Eur/BP Criteria A | - | - | 2 | - | NI |
| | Ph Eur/BP Criteria B* | - | - | - | 1 | NI |
| | USP† | - | - | NI | NI | NI |

Notes: * “The A criteria express the recommended efficacy to be achieved. In justified cases where the A criteria cannot be attained, for example for reasons of an increased risk of adverse reactions, the B criteria must be satisfied.” (Cited from Ph Eur/BP)

† USP includes otic products and sterile nasal products in this category

NI: No increase

NR: No recovery

Table 3: Preservative Efficacy Acceptance Criteria for Topical Products

| TEST ORGANISMS | PHARMACOPOEIA | SAMPLING TIME/LOG REDUCTIONS | | | |
|---|-----------------------|------------------------------|--------|---------|---------|
| | | 2 days | 7 days | 14 days | 28 days |
| Vegetative Bacteria <i>(Ps. aeruginosa, St. aureus, USP also E. coli)</i> | Ph Eur/BP Criteria A | 2 | 3 | - | NI |
| | Ph Eur/BP Criteria B* | - | - | 3 | NI |
| | USP | - | - | 2 | NI |
| Yeasts & Moulds <i>(C. albicans, A. niger)</i> | Ph Eur/BP Criteria A | - | - | 2 | NI |
| | Ph Eur/BP Criteria B* | - | - | 1 | NI |
| | USP | - | - | NI | NI |

Notes: * “The A criteria express the recommended efficacy to be achieved. In justified cases where the A criteria cannot be attained, for example for reasons of an increased risk of adverse reactions, the B criteria must be satisfied.” (Cited from Ph Eur/BP).

NI: No increase

Table 4: Preservative Efficacy Acceptance Criteria for Oral Products

| TEST ORGANISMS | PHARMACOPOEIA | SAMPLING TIME/LOG REDUCTIONS | |
|---|----------------------|------------------------------|---------|
| | | 14 days | 28 days |
| Vegetative Bacteria (<i>Ps. aeruginosa</i> , <i>St. aureus</i> , USP also <i>E. coli</i>) | Ph Eur/BP Criteria A | 3 | NI |
| | USP | 1 | NI |
| Yeasts & Moulds (<i>C. albicans</i> , <i>A. niger</i>) | Ph Eur/BP Criteria A | 1 | NI |
| | USP | NI | NI |

Notes: USP has another category for *antacid preparations*. The initial inoculum is lower (between 1×10^3 CFU/mL and 1×10^4 CFU/mL of product) and the criteria are no increase in bacteria, yeast and moulds at 14 days and 28 days.

NI: No increase

Table 5: Acceptance Criteria for Microbiological Quality of Non-Sterile Dosage Forms

| NON-STERILE DOSAGE FORM | ACCEPTANCE CRITERIA FOR MICROBIOLOGICAL QUALITY | | |
|--|--|--|---|
| | 'HARMONISED' PH EUR, USP-NF, JP PHARMACOPOEIAL TEXT | BP 2005/PH EUR 5 TH EDITION | TGAL GUIDELINES (NOVEMBER 1994) |
| <i>Rectal use:</i> | TAMC $\leq 10^3$ CFU/g/mL TYMC $\leq 10^2$ CFU/g/mL | Category 3A: TVAC $\leq 10^3$ CFU/g/mL TYMC $\leq 10^2$ CFU/g/mL <i>E. coli</i> absent 1g/mL | Not identified as a specific dosage form |
| <i>Oromucosal, gingival, cutaneous, nasal or auricular use:</i> | TAMC $\leq 10^2$ CFU/g/mL TYMC $\leq 10^1$ CFU/g/mL <i>St. aureus</i> absent 1g/mL <i>Ps. aeruginosa</i> absent 1g/mL Note: Antiseptic and corticosteroid preparations intended for topical use included in this category. | Category 2: TVAC (aerobic bacteria plus fungi) $\leq 10^2$ CFU/g/mL Enterobacteria and certain other Gram negative bacteria $\leq 10^1$ CFU/g/mL <i>St. aureus</i> absent 1g/mL <i>Ps. aeruginosa</i> absent 1g/mL | Topical preparations other than antiseptics and corticosteroids: TAMC $\leq 10^2$ CFU/g/mL Pseudomonads absent <i>St. aureus</i> absent |
| <i>Vaginal use:</i> | TAMC $\leq 10^2$ CFU/g/mL TYMC $\leq 10^1$ CFU/g/mL <i>St. aureus</i> absent 1g/mL <i>Ps. aeruginosa</i> absent 1g/mL <i>C. albicans</i> absent 1 g/mL | Not identified as a specific dosage form | Not identified as a specific dosage form |
| <i>Transdermal patches*:</i> * Includes adhesive layer and backing. | TAMC $\leq 10^2$ CFU/patch TYMC $\leq 10^1$ CFU/patch <i>St. aureus</i> absent per patch <i>Ps. aeruginosa</i> absent per patch | Category 2: TVAC (aerobic bacteria plus fungi) $\leq 10^2$ CFU/patch Enterobacteria and certain other Gram negative bacteria absent per patch <i>St. aureus</i> absent per patch <i>Ps. aeruginosa</i> absent per patch | Not identified as a specific dosage form |
| <i>Inhalation use*:</i> | TAMC $\leq 10^2$ CFU/g/mL | Category 2: TVAC (aerobic bacteria | Not identified as a specific dosage form |

| NON-STERILE DOSAGE FORM | ACCEPTANCE CRITERIA FOR MICROBIOLOGICAL QUALITY | | |
|--|--|--|---|
| | 'HARMONISED' PH EUR, USP-NF, JP PHARMACOPOEIAL TEXT | BP 2005/PH EUR 5 TH EDITION | TGAL GUIDELINES (NOVEMBER 1994) |
| * Liquid preparations for nebulisation to be manufactured sterile. | TYMC $\leq 10^1$ CFU/g/mL <i>St. aureus</i> absent 1g/mL <i>Ps. aeruginosa</i> absent 1g/mL BT gram-negative bacteria absent 1 g/mL | plus fungi) $\leq 10^2$ CFU/g/mL Enterobacteria and certain other Gram negative bacteria $\leq 10^1$ CFU/g/mL <i>St. aureus</i> absent 1g/mL <i>Ps. aeruginosa</i> absent 1g/mL | |
| <i>Non-aqueous preparations for oral use:</i> | TAMC $\leq 10^3$ CFU/g/mL TYMC $\leq 10^2$ CFU/g/mL <i>E. coli</i> absent 1g/mL | Category 3A: TVAC $\leq 10^3$ CFU/g/mL TYMC $\leq 10^2$ CFU/g/mL <i>E. coli</i> absent 1g/mL | Oral preparations (other than those containing raw material of vegetable or animal origin): TAMC $\leq 10^3$ CFU/g/mL TYMC $\leq 10^2$ CFU/g/mL Enterobacteria $\leq 10^2$ CFU/g/mL <i>E coli</i> absent 1g/mL Salmonellae absent 10 g/mL |
| <i>Aqueous preparations for oral use:</i> | TAMC $\leq 10^2$ CFU/g/mL TYMC $\leq 10^1$ CFU/g/mL <i>E. coli</i> absent 1g/mL | Category 3A: TVAC $\leq 10^3$ CFU/g/mL TYMC $\leq 10^2$ CFU/g/mL <i>E. coli</i> absent 1g/mL | Oral preparations other than those containing raw material of vegetable or animal origin: TAMC $\leq 10^3$ CFU/g/mL TYMC $\leq 10^2$ CFU/g/mL Enterobacteria $\leq 10^2$ CFU/g/mL <i>E coli</i> absent 1g/mL Salmonellae absent 10 g/mL |
| <i>Non-sterile substances for pharmaceutical use:</i> | TAMC $\leq 10^3$ CFU/g/mL TYMC $\leq 10^2$ CFU/g/mL | Not identified as a specific category | Not identified as a specific category |

| NON-STERILE DOSAGE FORM | ACCEPTANCE CRITERIA FOR MICROBIOLOGICAL QUALITY | | |
|--|--|---|---|
| | ‘HARMONISED’ PH EUR, USP-NF, JP PHARMACOPOEIAL TEXT | BP 2005/PH EUR 5 TH EDITION | TGAL GUIDELINES (NOVEMBER 1994) |
| <p><i>Oral dosage forms (Special Ph. Eur. provision):</i></p> <p><i>For oral dosage forms, containing raw material of natural (animal, vegetal, mineral) origin for which antimicrobial pre-treatment is not feasible and for which the competent authority accepts a TAMC of the raw material exceeding 10³ CFU/g/mL</i></p> | <p>‘NON-HARMONISED’ PH EUR TEXT</p> <p>TAMC ≤10⁴ CFU/g/mL TYMC ≤10² CFU/g/mL BT Gram negative bacteria ≤10² CFU/g/mL <i>E. coli</i> absent 1g/mL <i>Salmonella</i> absent 10 g/mL <i>St. aureus</i> absent 1 g/mL</p> | <p>Category 3B:</p> <p>TVAC ≤10⁴ CFU/g/mL TYMC ≤10² CFU/g/mL Enterobacteria and certain other Gram negative bacteria ≤10² CFU/g/mL <i>E. coli</i> absent 1g/mL <i>Salmonella</i> absent 10 g/mL <i>St. aureus</i> absent 1 g/mL</p> | <p>Oral preparations containing raw materials of vegetable or animal origin:</p> <p>TAMC ≤10⁴ CFU/g/mL TYMC ≤10² CFU/g/mL Enterobacteria ≤10² CFU/g/mL <i>E. coli</i> absent 1g/mL <i>Salmonellae</i> absent 10 g/mL</p> |
| <p><i>Special Ph. Eur provision for herbal medicinal products consisting solely of one or more herbal drugs (whole, reduced or powdered):</i></p> <p><i>- herbal medicinal products to which boiling water is added before use</i></p> <p><i>- herbal medicinal products to which boiling water is not added before use</i></p> | <p>‘NON-HARMONISED’ PH EUR TEXT</p> <p>TAMC ≤10⁷ CFU/g/mL TYMC ≤10⁵ CFU/g/mL <i>E. coli</i> ≤10² CFU/g/mL</p> <p>TAMC ≤10⁵ CFU/g/mL TYMC ≤10⁴ CFU/g/mL BT Gram negative bacteria ≤10³ CFU/g/mL <i>E. coli</i> absent 1g/mL <i>Salmonella</i> absent 10 g/mL</p> | <p>Category 4A:</p> <p>TVABC ≤10⁷ CFU/g/mL TYMC ≤10⁵ CFU/g/mL <i>E. coli</i> ≤10² CFU/g/mL</p> <p>Category 4B:</p> <p>TVABC ≤10⁵ CFU/g/mL TYMC ≤10⁴ CFU/g/mL Enterobacteria and certain other Gram negative bacteria ≤10³ CFU/g/mL <i>E. coli</i> absent 1g/mL <i>Salmonella</i> absent 10 g/mL</p> | <p>Herbal teas (assumes preparation with boiling water):</p> <p>TAMC ≤10⁵ CFU/g/mL TYMC ≤10² CFU/g/mL Enterobacteria ≤10² CFU/g/mL <i>E. coli</i> absent 1g/mL <i>Salmonellae</i> absent 10 g/mL</p> <p>Oral preparations containing raw materials of vegetable or animal origin:</p> <p>TAMC ≤10⁴ CFU/g/mL TYMC ≤10² CFU/g/mL Enterobacteria ≤10² CFU/g/mL <i>E. coli</i> absent 1g/mL <i>Salmonellae</i> absent 10 g/mL</p> |

Notes:

TAMC: Total aerobic microbial count TYMC: Total yeast and mould count

TVAC: Total viable aerobic count BT: Bile-tolerant

CFU/g/mL: Colony Forming Units per g or per mL

BP 2005 Category 2: Preparations for topical use, and for use in the respiratory tract except where required to be sterile, and transdermal patches.

BP 2005 Category 3A: Preparations for oral and rectal administration.

BP 2005 Category 3B: Preparations for oral administration containing raw materials of natural (animal, vegetable or mineral) origin for which antimicrobial pre-treatment is not feasible and for which the competent authority accepts microbial contamination of the raw material exceeding 10^3 viable micro-organisms per gram or per millilitre. Herbal medicinal products described in category 4 are excluded.

BP 2005 Category 4A: Herbal medicinal products consisting solely of one or more herbal drugs (whole, reduced or powdered): Herbal medicinal products to which boiling water is added before use.

BP 2005 Category 4B: Herbal medicinal products consisting solely of one or more herbal drugs (whole, reduced or powdered): Herbal medicinal products to which boiling water is not added before use.

Table 6: Acceptance Criteria for Microbiological Quality of Herbal Drugs and Herbal Drug Preparations

| ACCEPTANCE CRITERIA FOR MICROBIOLOGICAL QUALITY OF NON-STERILE MEDICINES THAT CONTAIN BOTANICAL MATERIAL | | | |
|---|--|---|---------------------------------------|
| USP 2006 CATEGORY | USP-NF 29 (2006) ACCEPTANCE CRITERIA | BP 2005/PH EUR 5 TH EDITION ACCEPTANCE CRITERIA | TGAL GUIDELINES (NOVEMBER 1994) |
| <i>Dried or powdered botanicals</i> | TAMC $\leq 10^5$ CFU/g/mL TYMC $\leq 10^3$ CFU/g/mL BT Gram negative bacteria $\leq 10^3$ CFU/g/mL <i>E. coli</i> absent 10g/mL <i>Salmonella</i> absent 10 g/mL | Not identified as a specific category | Not identified as a specific category |
| <i>Powdered botanical extracts</i> | TAMC $\leq 10^4$ CFU/g/mL TYMC $\leq 10^3$ CFU/g/mL <i>E. coli</i> absent 10g/mL <i>Salmonella</i> absent 10 g/mL | Not identified as a specific category | Not identified as a specific category |
| <i>Tinctures</i> | TAMC $\leq 10^4$ CFU/g/mL TYMC $\leq 10^3$ CFU/g/mL | Not identified as a specific category | Not identified as a specific category |
| <i>Fluid extracts</i> | TAMC $\leq 10^4$ CFU/g/mL TYMC $\leq 10^3$ CFU/g/mL | Not identified as a specific category | Not identified as a specific category |
| <i>Infusions/decoctions</i> | TAMC $\leq 10^2$ CFU/g/mL TYMC $\leq 10^1$ CFU/g/mL | Not identified as a specific category | Not identified as a specific category |
| <i>Nutritional supplements with botanicals</i> | TAMC $\leq 10^4$ CFU/g/mL TYMC $\leq 10^3$ CFU/g/mL <i>E. coli</i> absent 10g/mL <i>Salmonella</i> absent 10 g/mL | Not identified as a specific category | Not identified as a specific category |

| ACCEPTANCE CRITERIA FOR MICROBIOLOGICAL QUALITY OF NON-STERILE MEDICINES THAT CONTAIN BOTANICAL MATERIAL | | | |
|---|---|---|--|
| USP 2006 CATEGORY | USP-NF 29 (2006) ACCEPTANCE CRITERIA | BP 2005/PH EUR 5 TH EDITION ACCEPTANCE CRITERIA | TGAL GUIDELINES (NOVEMBER 1994) |
| <i>Botanicals (herbal medicinal products, herbal teas) that are treated with boiling water before use</i> | TAMC $\leq 10^5$ CFU/g/mL TYMC $\leq 10^3$ CFU/g/mL <i>E. coli</i> absent 10g/mL | Category 4A: TVABC $\leq 10^7$ CFU/g/mL TYMC $\leq 10^5$ CFU/g/mL <i>E. coli</i> $\leq 10^2$ CFU/g/mL | Herbal teas: TAMC $\leq 10^5$ CFU/g/mL TYMC $\leq 10^2$ CFU/g/mL Enterobacteria $\leq 10^2$ CFU/g/mL <i>E coli</i> absent 1g/mL Salmonellae absent 10 g/mL |
| <i>Botanicals (herbal medicinal products) that are not treated with boiling water before use</i> | Not identified as a specific category but requirements for <i>dried or powdered botanicals</i> would apply: TAMC $\leq 10^5$ CFU/g/mL TYMC $\leq 10^3$ CFU/g/mL BT Gram negative bacteria $\leq 10^3$ CFU/g/mL <i>E. coli</i> absent 10g/mL <i>Salmonella</i> absent 10 g/mL | Category 4B: TVABC $\leq 10^5$ CFU/g/mL TYMC $\leq 10^4$ CFU/g/mL Enterobacteria and certain other Gram negative bacteria $\leq 10^3$ CFU/g/mL <i>E. coli</i> absent 1g/mL <i>Salmonella</i> absent 10 g/mL | Not identified as a specific category but covered by <i>Oral preparations containing raw materials of vegetable or animal origin:</i> TAMC $\leq 10^4$ CFU/g/mL TYMC $\leq 10^2$ CFU/g/mL Enterobacteria $\leq 10^2$ CFU/g/mL <i>E coli</i> absent 1g/mL Salmonellae absent 10 g/mL |

Notes:

TAMC: Total aerobic microbial count TYMC: Total yeast and mould count

TVABC: Total viable aerobic count BT: Bile-tolerant

CFU/g/mL: Colony Forming Units per g or per mL

BP 2005 Category 4A: Herbal medicinal products consisting solely of one or more herbal drugs (whole, reduced or powdered); Herbal medicinal products to which boiling water is added before use.

BP 2005 Category 4B: Herbal medicinal products consisting solely of one or more herbal drugs (whole, reduced or powdered); Herbal medicinal products to which boiling water is not added before use.