



**Australian Government**  
**Department of Health and Ageing**  
**Therapeutic Goods Administration**



## **Consultation Paper**

# **Pharmacopoeial Standards for Medicines in the Australia New Zealand Therapeutic Products Agency**

**Call for Comment**

***1 September 2005***

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## ***How to comment on this Consultation Paper***

Submissions may be sent by post and/or email 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 email address.
- The particular point being addressed (eg, Option 2.2).
- 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 why it is confidential.

### ***Address for submissions***

Electronic submissions should be emailed to <standards@jtaproject.com>.

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

The Project Officer  
Pharmacopoeial Standards Subcommittee  
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### ***Questions relating to submissions***

Any questions relating to submissions should be directed to the Project Officer, by email at <standards@jtaproject.com>.

### ***Deadline for submissions***

The deadline for receipt of submissions is close of business, 14 October 2005.

# 1 Introduction

- 1.1 In early 2005 the Therapeutic Products Interim Ministerial Council established the Joint Interim Expert Advisory Committee on Standards (the Committee) as a group of Australian and New Zealand experts to make recommendations on standards for the new Agency. Further information on the Committee and its work can be found at <http://www.anztpa.org/committees/jieacs.htm>. This consultation paper has been distributed on behalf of the Committee.
- 1.2 The purpose of this consultation paper is to seek stakeholder input into the arrangements that should apply, in both Australia and New Zealand, with respect to the default standard(s) for medicines for the new Australia New Zealand Therapeutic Products Agency (the Agency), which is to commence operations in July 2006. The principal issue to be considered is whether or not the legislative arrangements for the Agency should nominate a single pharmacopoeia (and if so, which one) or multiple pharmacopoeias to be used as the default standard(s).
- 1.3 In order to assure the safety and efficacy of medicines, ingredients and the finished product must be manufactured to an acceptable quality standard. The role of the default standard(s) is to define the minimum quality standard with which medicines must comply.
- 1.4 The issue of default standard(s) is being considered in this paper because the current situations in Australia and New Zealand differ in some respects for various types of medicines.
- 1.5 Currently in Australia, there is one default standard, the British Pharmacopoeia (BP). This publication includes all of the requirements of the European Pharmacopoeia (EP). Currently in New Zealand, there is no specifically mandated standard (except for medicines intended for use in the eye, where the test for sterility must be that of the BP/EP or United States Pharmacopoeia (USP-NF)).
- 1.6 It is important to note that a manufacturer can adopt alternative approaches to that specified in a default standard to assure the quality of their products. Where supported by compliance with the code of Good Manufacturing Practice, such approaches are acceptable. However, in the event of a challenge from the Agency, the manufacturer must be able to demonstrate that the ingredient or medicine meets the requirements of the applicable official standard.
- 1.7 This consultation paper makes reference to aspects of the proposed regulatory scheme that have still to be finalised. These gaps, however, should have no significant influence on the ability of stakeholders to provide comment. Further information on the new Agency can be obtained from the Fact Sheets at <http://www.anztpa.org/azguide.htm#f>.

- 1.8 This paper presents a number of Options for consideration, together with some of the Issues which have been considered in devising the Options. Alternative suggestions will be welcome although it would be helpful to the Committee if these suggestions could be supported by appropriate discussion and reasons.

## 2 Background

### 2.1 *General comments on standards*

- 2.1.1 The fundamental purpose of a pharmacopoeial standard is to control the quality of ingredients and of finished products and so to contribute to the efficacy of and safety in the use of medicines. Pharmacopoeial monographs control many parameters, including purity, potency (amount of active ingredient present) and performance characteristics of the medicine. Quality control is achieved by defining tolerances, performance measures and testing procedures that are consistent with modern manufacturing and analytical capabilities.
- 2.1.2 In the new Agency, quality standards, including pharmacopoeial standards, will apply to Class I and Class II medicines.

### 2.2 *The European Pharmacopoeia (EP)*

- 2.2.1 The EP contains specific monographs for pharmaceutical ingredients, general monographs for medicinal dosage forms and general chapters dealing with test methodologies and the interpretation of tests. Apart from a few selected biological and radiochemical products, the EP does not contain monographs for formulated preparations.
- 2.2.2 The EP is the responsibility of the European Directorate for the Quality of Medicines which is a division of the Council of Europe. The EP is published in print and electronic forms with three supplements per year. Changes and updates to the EP proceed through independent expert committees comprised of industry, academic and government stakeholders. The Therapeutic Goods Administration (TGA) has observer status at the EP Commission and on a number of EP expert committees, which gives an opportunity to comment and influence EP activity at an early stage.

### 2.3 *The British Pharmacopoeia (BP)*

- 2.3.1 By virtue of European law, the BP is obliged to include the requirements and monographs of the EP. In addition to the requirements of the EP, the BP also contains monographs for formulated products.

2.3.2 The body responsible for maintaining and publishing the BP is the BP Commission, which is a unit of the UK Medicines and Healthcare products Regulatory Agency. Changes and updates to the BP proceed through independent expert committees comprised of industry, academic and government stakeholders. It is published annually in print and electronic forms.

## **2.4 *The United States Pharmacopoeia – National Formulary (USP-NF)***

2.4.1 The full title for the USP is the USP-NF. The abbreviation NF represents the National Formulary which has been included with the USP since 1975. The NF primarily includes monographs on excipients. The USP-NF contains monographs for substances 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. Monographs (non-official) for products regulated as dietary supplements in the USA are also included in the USP-NF.

2.4.2 As well as monographs, the USP-NF also contains general chapters on tests and assays and general information relating to manufacturing and pharmacy practices, eg, packaging, labelling, compounding and good manufacturing practices for bulk pharmaceutical excipients.

2.4.3 The USP-NF is owned, maintained and published by the United States Pharmacopoeia Convention Inc., a not-for-profit organisation independent of the US government.

2.4.4 The USP-NF is supported by groups of experts from industry, academia and government who are responsible for monograph development. It is published annually, along with two supplements, in print and electronic form.

## **2.5 *Pharmacopoeial harmonisation***

2.5.1 The Japanese Pharmacopoeia, the EP and USP-NF have been engaged in a process of pharmacopoeial harmonisation for a number of years. The overall process is slow. However, a number of monographs for excipients and for general methods have been harmonised.

## **2.6 *Current situation in Australia***

2.6.1 The *Therapeutic Goods Act 1989* allows for the making of Therapeutic Goods Orders (TGOs) to define the standards with which medicines must comply. Where a specific TGO does not exist, then the *Therapeutic Goods Act 1989* requires that a medicine comply with relevant monographs of the BP.

- 2.6.2 In addition to compliance with these official standards, the TGA and sponsors may negotiate specifications during evaluation of a medicine to be registered for supply in Australia. Similarly, medicines listed in the Australian Register of Therapeutic Goods (ARTG) may be subject to specific conditions relating to compliance with particular standards. These additional requirements are binding on the sponsor.
- 2.6.3 Sponsors may apply to the TGA for an exemption from official standards where this can be justified. Such exemptions are granted where there is no compromise to the quality, safety or efficacy of the medicine.
- 2.6.4 Manufacturers of listed and registered medicines are required to have specifications for each ingredient and medicine. In the absence of an official standard in a TGO or in the BP, in-house specifications developed by the manufacturer are used for regulatory compliance purposes where appropriate. These in-house specifications are often based on pharmacopoeial principles.
- 2.6.5 Successive editions of the BP are adopted in Australia on the recommendation of the Therapeutic Goods Committee (TGC), an independent statutory committee appointed by the Minister for Health and Ageing. Stakeholder consultation is used to inform the recommendation of the TGC. Because of this consultation process, there is usually a delay between the adoption of the BP in the United Kingdom and adoption of the BP in Australia. For example, the 2004 edition of the BP became official in the United Kingdom on 1 December 2004 and official in Australia on 1 July 2005.

## **2.7 Current situation in New Zealand**

- 2.7.1 The *Medicines Act 1981* does not specifically mandate standards (except in a few very limited cases, where the BP, USP and other publications are referenced). Medsafe generally follows the technical guidance provided by the BP, EP and USP, which Medsafe regards as essentially equivalent and equally acceptable standards.
- 2.7.2 Medsafe may negotiate a specification with a sponsor at the time of pre-market review of a medicine, using the above publications as the basis for discussion. A manufacturer's in-house specification will be considered where appropriate.
- 2.7.3 Successive editions of the EP, BP and USP-NF are automatically adopted in New Zealand. Current NZ legislation requires that a reference to the EP, BP or USP-NF in a licence, consent or approval is taken to refer to the edition of the publication in force at that time, including amendments.

## **2.8 *Moving towards the new Agency***

- 2.8.1 For prescription and over-the-counter (OTC) medicines, both Medsafe and the TGA currently conduct a detailed pre-market review to assess the suitability of the quality standards applied by the sponsor to the ingredients and to the finished medicine. Australian legislation requires compliance to be assessed against TGOs and the BP. New Zealand does not have mandatory standards and the EP, BP, and USP-NF may be used as a basis for quality control.
- 2.8.2 Under the proposed Rules of the new Agency, prescription and OTC medicines will continue to be subject to pre-market review. These types of medicines will be termed Class II medicines.
- 2.8.3 In New Zealand, most vitamin and herbal products are not regulated as medicines and are subject to dietary supplement regulations administered by the New Zealand Food Safety Authority.
- 2.8.4 Currently in Australia, most vitamin and herbal products are regulated as lower risk medicines by the TGA and are required to comply with TGOs and the BP. The quality standards applied by manufacturers of lower risk medicines are not subject to review prior to inclusion as listed goods in the ARTG. Instead, the sponsor of a lower risk medicine is required to certify that the medicine complies with the official standards. This certification may be assessed as part of post-market surveillance by the TGA. In the absence of a pre-market review it is important to have suitable standards in place to provide consumers and the TGA with confidence in the medicine's quality.
- 2.8.5 It has been agreed that the new Agency will regulate complementary medicines, such as those currently regulated as dietary supplements in New Zealand and as listed medicines in Australia. This group of medicines will be termed Class I medicines.
- 2.8.6 In the event of concerns relating to quality or regulatory compliance, both Medsafe and the TGA use the specifications agreed at the time of a medicine's approval as the basis for further actions. This will continue to be the case under the new Agency.

## **3 Possible options for the new Agency**

- 3.1 There are two primary options for the Agency for pharmacopoeial standards: either a single pharmacopoeia or multiple pharmacopoeias.

### ***OPTION 1 – A single pharmacopoeia as the standard***

- Option 1.1 The British Pharmacopoeia (noting that this includes the requirements of the European Pharmacopoeia), or

- Option 1.2 The United States Pharmacopoeia-National Formulary, or
- Option 1.3 The European Pharmacopoeia (noting that this contains few monographs for finished products).

### ***OPTION 2 – Multiple pharmacopoeias as the standards***

- Option 2.1 The British Pharmacopoeia and the United States Pharmacopoeia-National Formulary as equally acceptable standards, or
  - Option 2.2 The British Pharmacopoeia as the standard, and where there is no applicable BP monograph then the USP-NF is to be used, or
  - Option 2.3 The United States Pharmacopoeia-National Formulary as the standard, and where there is no applicable USP-NF monograph then the BP is to be used,
  - Option 2.4 The European Pharmacopoeia as the standard, and where there is no applicable EP monograph then either the BP or the USP-NF may be used, or
  - Option 2.5 The European Pharmacopoeia as the standard, and where there is no applicable EP monograph then the BP or the USP-NF or another national pharmacopoeia may be used.
- 3.2** Under the Agency, it is proposed that Managing Director’s Orders (similar to TGOs in Australia) will be developed to cover quality matters that are not addressed by the default standard(s). Such Orders would be developed and implemented following industry and stakeholder consultation and on the recommendation of an independent expert advisory committee. A separate consultation has already been undertaken on the requirements for medicine labelling, which will be issued as a Managing Director’s Order when finalised. General or specific technical requirements could be promulgated as Managing Director’s Orders (see 4.12).
- 3.3** Under the Agency, it is proposed that manufacturers will be required to update their specifications as each edition of a default pharmacopoeia comes into effect in Europe, the UK and/or the USA. It is anticipated that the Agency will require the current edition of the pharmacopoeia in the region of origin to be in force in Australia and New Zealand. This will avoid delays in implementation as new standards are promulgated. The proposal constitutes a change to the current Australian practice outlined in 2.6.5.
- 3.4** Under the Agency, it is proposed that, irrespective of the default standard(s), a medicine will be required to comply with any additional standards required by the Agency at the time that the medicine is approved for supply in Australia and New Zealand.

- 3.5** Under the Agency, it is proposed that there should be no ‘mixing and matching’ of tests from monographs in different pharmacopoeias unless authorised by the Agency. As a generalisation, and consistent with pharmacopoeial philosophy, the Agency would expect that where a pharmacopoeial standard is applied to a medicine then compliance should be to that standard in its entirety, together with the applicable general standards of that pharmacopoeia and the interpretations applied by that pharmacopoeia.
- 3.6** Under the Agency, and consistent with current Australian and New Zealand practice, it will be expected that, where a choice of pharmacopoeial standards exists and in order to avoid compromise to quality, safety and efficacy, manufacturers will select the monograph that provides for optimum control of the following quality parameters: content or purity of active ingredient; the type and levels of impurities, including chemical, physical, microbiological and viral; the identity of the active ingredient; physical properties of the substance or formulation; performance criteria.

## **4 Some issues to be considered**

- 4.1** A single pharmacopoeial default standard is unequivocal and gives a uniform approach to quality requirements for medicines. In the event of the need to independently verify the quality of a medicine, reliance on a single authoritative standard removes any ambiguity and makes regulatory decision-making transparent. Consumers, practitioners, suppliers, manufacturers and sponsors have certainty as to what is the applicable standard.
- 4.2** Specifying more than one acceptable standard offers flexibility for some manufacturers and could enable them to select the standard they deem to be appropriate to their business needs.
- 4.3** Since the choice of standard is not usually featured in medicine labelling, allowing multiple standards will make it possible for products that meet different quality standards to appear similar to the user.
- 4.4** Manufacturers of pharmaceuticals for the international market may already manufacture and/or supply medicines according to more than one pharmacopoeial standard. The adoption of multiple default standards could broaden the range of medicines available, facilitate the introduction of new medicines, and improve continuity of supply of medicines in the Australian and New Zealand markets.
- 4.5** Pharmacopoeias may differ in their requirements for the content of active ingredient, eg, an assay in the USP-NF may set limits of 90.0–110.0% of the stated amount whereas the BP may set assay limits of 95.0–105.0%. Two medicines containing the same nominal quantity of the same active ingredient, but manufactured to different pharmacopoeial standards, could have different shelf lives. This may offer a sponsor the opportunity for an economic advantage by the selection of the monograph with the wider assay limits.

- 4.6** Differences between pharmacopoeial requirements can be significant for biological products, eg, vaccines. This may have clinical implications for patients if medicines manufactured to different standards were used interchangeably.
- 4.7** Pharmacopoeial monographs for ingredients and finished products are supported by the general tests and interpretations (General Notices) in each pharmacopoeia. Adopting more than one pharmacopoeia as default standards means that the general tests and interpretations of the different pharmacopoeias are also adopted.
- 4.8** Although harmonisation of the EP, BP, USP-NF and Japanese Pharmacopoeia is progressing, albeit slowly, there remain a significant number of differences in general tests and monographs as well as in specific monographs. If a choice of standards is allowed, sponsors and manufacturers have an opportunity to select the requirements that offer the lowest level of control in order to reduce compliance costs.
- 4.9** Manufacturers who supply the American and European markets are required to ensure compliance with both the USP-NF and the EP. However, manufacturers who produce for the American and Australian markets, but not for the European market, are currently required to comply with both BP and USP-NF standards.
- 4.10** If more than one pharmacopoeia is allowed then it would be necessary for manufacturers, sponsors and the Agency to stay abreast of developments in each of the approved pharmacopoeias to ensure continued compliance.
- 4.11** Manufacturers have commented that, in some cases, BP grade materials are more expensive or less readily available than other pharmacopoeial grades.
- 4.12** If multiple pharmacopoeial standards as described under Option 2 (see 3.1) are allowed, an issue for consideration is that of inconsistency between these standards.
- 4.12.1 A likely consequence of allowing multiple standards is that there will be inconsistency, or conflict, between elements of the various standards. This inconsistency could relate to the tests and limits applied to a particular ingredient or it could relate to the general requirements applied to a group of products.
- 4.12.2 If the inconsistency between monographs were to be considered serious enough to have clinical implications, or where one standard allowed significantly lower quality control, then it may be necessary to have Rules or Managing Director's Orders to guide manufacturers and the Agency as to what would be acceptable in the event of conflicting pharmacopoeial requirements.
- 4.12.3 If two or more pharmacopoeias were to be approved as default standards, and where a monograph is present in more than one of these pharmacopoeias, then inconsistency or conflict that is considered to have significant implications for quality, safety or efficacy of the medicine could be resolved by either specific or general requirements. Examples of such requirements could be:

- a. Where the content or potency of the active ingredient is measured in units of activity, rather than by mass or volume, the requirements of the EP or BP are to be applied.

[note: This will ensure that International Units (IUs) are used and will avoid medication errors due to confusion between USP units and IUs which have been standard in Australia for many years. This will also be consistent with the proposed labelling requirements for medicines for Australia and New Zealand which requires IUs to be used where applicable].

- b. For XXX Tablets, the monograph of the YY Pharmacopoeia is to be applied.
- c. For general test XYZ, the requirements of XX Pharmacopoeia are to be applied.
- d. The tests for preservative efficacy should be performed in accordance with the EP or BP.

[note: The preservative efficacy test methodology of the EP, BP and USP-NF are essentially the same. However, the TGA does not accept the interpretation and sampling times of the USP-NF. The TGA experience is that most North American manufacturers set up the test according to the USP-NF method and incorporate the additional sampling times of the EP and BP (i.e., at 6 and 24 hours for parenteral, ophthalmic and ear preparations or at 2 and 7 days for topical products) and interpret the log reductions at specific times according to the EP and BP requirements. The USP-NF first sampling time for parenteral products is at 7 days and at 14 days for topical products which yields results of little value. Furthermore, the log reduction performance criteria of the USP-NF are less stringent than those in the EP and BP. For example, for bacteria, 1-log reduction at 7 days for parenteral products is required in the USP-NF versus 2-log reduction at 6 hours, 3-log reduction at 24 hours and no recovery at 7 days required by the EP and BP.]

- e. Microbial limits testing for non-sterile products should be performed in accordance with the Agency standard.

[note: Methods for microbial limits testing are in the process of being harmonised between the EP, BP, USP-NF and Japanese Pharmacopoeia. At present, the TGA allows methods based on the EP, BP or USP-NF, as long as the method has been validated using the actual product. The pharmacopoeias all contain guidance on method validation, which is accepted by the TGA. However, the TGA does not accept all of the microbial limits and presence/absence tests of the EP, BP or USP-NF. The TGA justified its position that the limits were not sufficiently stringent to Australia's Therapeutic Goods Committee, which endorsed the TGA Guidelines.]

## 5 Summary

In responding to this consultation paper, an indication of your preference on the following specific matters would be appreciated.

- 5.1 Do you favour one of the Options for the default pharmacopoeial standard(s) for the new Agency that has been specified in 3.1? If so, which one? Please provide your reasons with some supporting examples/data if possible.
- 5.2 Do you wish to suggest an Option other than those included in 3.1? If so, please provide your reasons with some supporting examples/data if possible.
- 5.3 If the new Agency were to allow more than one default pharmacopoeial standard, do you consider that requirements are needed to avoid inappropriate or selective use? If so, please specify these requirements and provide your reasons with some supporting examples/data if possible.
- 5.4 Do you wish to comment on any of the Issues raised in this paper? If so, please specify the paragraph number in your comments.
- 5.5 Do you wish to make any other comments that may be helpful to the Committee in considering this issue?