Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Regulatory Guidelines for Complementary Medicines (ARGCM)

Part V: Policy Documents and Guidelines

Version 4.2, August 2011

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

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

Version history

Version	Description of change	Author	Effective date
V4.0	The ARGCM was amended to take into account the TGA restructure of July 2010. Some editorial changes were made, such as corrections of typographic errors.	Office of Complementary Medicines	March 2011
V4.1	Version 4.0 was transferred into the new TGA template. The content remained the same, but page numbers changed. This version was also labelled 'Version 4.0'	Office of Parliamentary and Strategic Support	May 2011
V4.2	A version history table was added. The version was labelled as 'Version 4.2'. Changes were also made to capitalisation of titles.	Office of Parliamentary and Strategic Support	August 2011

Contents

1. Overview

The purpose of this Part of the Guidelines is to provide details of the Therapeutic Goods Administration (TGA) policy guidelines relevant to complementary medicines.

The regulatory requirements for the Registration of complementary medicines are discussed in Part I of the Guidelines, the regulatory requirements for Listed complementary medicines in Part II and the regulatory requirements for the Evaluation of complementary medicine substances in Part III.

Detailed guidance on policy in specific areas is provided in the following sections:

- Section 2 – Levels and kinds of evidence to support indications and claims
- Section 3 – Minimising the risk of Transmissible Spongiform Encephalopathies (TSEs)
- Section 4 – Quantified by Input
- Section 5 – European Union (EU) Guidelines referenced in the ARGCM
- Section 6 – Section 7 declarations
- Section 7 – Confidentiality

2. Levels and kinds of evidence to support indications and claims

The *Guidelines for Levels and Kinds of Evidence to Support Indications and Claims* have been developed to assist sponsors in determining the appropriate evidence to support indications and claims made in relation to Listable medicines. In particular, they relate to non-Registerable Medicines, including Complementary Medicines, sunscreens and other Listable Medicines.

An electronic copy of the guidelines is located at <http://www.tga.gov.au/industry/cm-evidence-claims.htm>.

3. Minimising the risk of Transmissible Spongiform Encephalopathies (TSEs)

The document *Supplementary Requirements for Therapeutic Goods for Minimising the Risk of Transmitting Transmissible Spongiform Encephalopathies (TSEs)* (effective December 2004) provides guidance on the management of TSE risks associated with putatively 'low-risk' ingredients that are currently included in Category C of the European Medicines Agency (EMEA) *Guideline Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* (EMEA/410/01 Rev 2, October 2003).

The EMEA Guideline represents the main Therapeutic Good Adminstration (TGA) strategy for managing Transmissible Spongiform Encephalopathy (TSE) risks associated with all other materials of animal origin.

The TGA guidance document outlines a self-assessment process whereby sponsors of therapeutic goods containing Category C ingredients can collate information necessary to certify compliance with the TGA requirements to minimise TSE transmission risks.

For Registered medicines, self-certification should be provided at the time of submission of a new registration application, or an application for variation of an existing Australian Register of Therapeutic Goods (ARTG entry) for a product that contains a Category C ingredient.

For Listed medicines containing Category C ingredients, sponsors must complete the necessary fields in the Electronic Listing Facility (ELF) (such as country of origin, animal, animal part etc.).

All sponsors must hold evidence to support compliance with the TGA's guidance document. This evidence may be called upon at any time as part of a TGA review program.

Since scientific knowledge about TSE transmission and risk materials is evolving, it is intended that the document will be amended from time to time. Changes to the policy will be made as relevant new information about TSE risk management comes to light.

An electronic copy of the guidelines is located at >http://www.tga.gov.au/industry/tse-supplementary-requirements.htm>.

For more information on the requirements for products containing ingredients of higher risk (Categories A and B), see the *Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* (EMEA/410/01 Rev 2, October 2003).

4. Quantified by Input

4.1. Background

The document *Guidance on the Use of the Term 'Quantified by Input' for Complementary Medicines* was developed to provide guidance on the appropriate criteria for permitting quantification by input as an alternative to performing an assay for the content of an active ingredient(s) in a complementary medicine during batch release testing.

The issue of use of the term 'Quantified by Input' on certificates of analysis has been raised by the Therapeutic Goods Administration's (TGA's) Office of Manufacturing Quality (OMQ) and referred to the Office of Complementary Medicines (OCM) for consideration. In addition, complementary medicine manufacturers have sought clarification over the requirement to assay certain ingredients in complementary medicines. These matters raise questions as to what are the circumstances under which the practice of 'quantified by input' is appropriate and what terminology should be used on certificates of analysis where this practice has been applied.

To ensure compliance with batch release specifications, it is best practice to assay all batches of all finished products for the content of active ingredient(s). However, the TGA realises that this may be difficult with some complementary medicines. In recognition of this, the guidance document sets out the conditions under which manufacturers may not be required to perform an assay on an active ingredient (or a component in the active ingredient) in complementary medicine products.

4.2. Scope

This guidance does not extend to medicines other than complementary medicines; nor is it applicable to other medicines containing a complementary medicine component.

4.3. Implementation

To allow sufficient time for manufacturers to change their recording systems, the implementation of the principles outlined in the guidance document will be phased in over a two-year period, which began on 1 January 2004. An additional one-year phase-in period will be allowed for the development of justifications for not assaying active ingredients in finished products.

Note: Manufacturers who wish to quantify an active ingredient(s) in a finished product using 'quantified by input' are expected, as of 1 January 2004, to begin the development of a justification for not assaying the ingredient(s) in the finished product. They should not wait until the end of the phase-in period (1 January 2007) before developing a justification for not performing an assay. Consistent with the principles and guidance in this document and irrespective of the phase-in period, some active ingredient testing must be performed on each batch of the finished product where a quantitative claim is made on the label. That is, there must be sufficient testing to provide assurance that the product is of intended quality.

The TGA acknowledges that justification, validation and implementation of an alternative procedure may take some time. Provided a manufacturer can demonstrate progress in developing a justification for using 'quantified by input' to an OMQ auditor, or in a response to request from the TGA as part of its post-market surveillance program, then this would be considered an acceptable interim measure for not performing an assay.

This approach would be particularly applicable for manufacturers with an extensive product range. Documentation should be available showing a schedule for introducing 'quantified by input', together with progress against the schedule.

In justifying the use of 'quantified by input' and for not undertaking an assay, the issue of what is a reasonable attempt at performing an assay is difficult to judge with objectivity. It may often be a subjective judgment as to whether the justification for not assaying is sufficient. Such cases will be resolved through discussion between the manufacturer and the TGA.

An electronic copy of the guidelines is located at <http://www.tga.gov.au/newsroom/consult-cm-qbi-091008.htm>.

5. European Union (EU) Guidelines referenced in the ARGCM

References to European Union (EU) guidelines are provided to assist sponsors when compiling their applications. However, it remains a sponsor's responsibility to ensure that all relevant legislation and guidelines are taken into account in the preparation of their application.

The guidelines referenced below are available on the Therapeutic Goods Administration (TGA) website <http://www.tga.gov.au/industry/pm-euguidelines-adopted.htm>, or the European Medicines Agency (EMEA) website http://www.ema.europa.eu/, or in Volumes 3A, 3B or 3C of *The Rules Governing Medicinal Products in the EU – EudraLex*, available on the website of the European Commission <EudraLex - Volume 3 Scientific guidelines for medicinal products for human use. - Pharmaceuticals - Enterprise and Industry>.

Where documents have been published in more than one format (i.e. by The Committee for Medicinal Products for Human Use (CHMP) and in the *EudraLex*), the most recently published 'version' has been referenced.

Although it is intended that this section will be updated regularly, applicants are advised to consult the TGA website for the latest versions or additions to the guidelines listed below.

5.1. Application guidelines

Guideline name	Guideline identifier	Referenced in the ARGCM	
		Part	Section
Common Technical Document (CTD) for the Registration of Pharmaceuticals for Human Use – Quality (International Conference on Harmonisation (ICH) Topic M4Q)	http://www.tga.gov.au/industry/pm-ctd.htm	I	6
		II	5
		III	4

5.2. Quality guidelines

5.2.1. General guidelines

Guideline name	Guideline identifier	Referenced in the ARGCM	
		Part	Section
Analytical Procedure Validation for Complementary Medicines	http://www.tga.gov.au/industry/cm-analytical-procedure.htm	I	6.1.3.3
		I	6.2.7.8
		I	6.2.10.2
		I App 3	A1.2.4
		II	5.1.3.3
		II	5.2.7.7
		II	5.2.10.2
		IV	19.5
*Note for Guidance on the Investigation of Bioavailability and Bioequivalence** *Contains an Australian specific notation	CPMP/EWP/QWP/1401/98	I	7.5.1.3
Note for Guidance on Evaluation of Stability Data (ICH Topic Q1E)	CPMP/ICH/420/02	I	6.2.10.2
		II	5.2.10.2
		III	4.3.2
Note for Guidance on Specifications: Test Procedures for Herbal Drugs, Herbal Drug Preparations and Herbal Medicinal Products	CPMP/QWP/2820/00	I	6
		II	5
		III	4
		IV	19

5.2.2. Active substance guidelines

Guideline name	Guideline identifier	Referenced in the ARGCM	
		Part	Section
Note for Guidance on Stability Data Package for Registration in Climatic Zones III and IV (ICH Topic Q1 F) – Adopted by the TGA with annotation	CPMP/ICH/421/02	I	6.2.10.2
Note for Guidance on Impurities: Testing Impurities in New Drug Substances (ICH Topic Q3A(R))	CPMP/ICH/2737/99	I	6.2.7.3
Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products	CPMP/QWP/122/02, rev 1	I	6.2.10.2
		II	5.2.10.2
		III	4.3.2

5.2.3. Medicinal product guidelines

Guideline name	Guideline identifier	Referenced in the ARGCM	
		Part	Section
Note for Guidance on Impurities in New Drug Products (Revision 2) (ICH Topic Q3B(R))	CPMP/ICH/2738/99	I	6.2.7.3
Note for Guidance on Quality of Herbal Medicinal Products	CPMP/QWP/2819/00	I	6
		II	5
		III	4

5.3. Biotechnology guidelines

5.3.1. Active substance and medicinal product guidelines

Guideline name	Guideline identifier	Referenced in the ARGCM	
		Part	Section
Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products* *Contains an Australian specific notation	EMEA/410/01 Rev 2	IV	20.1
		V	3

5.4. Clinical guidelines

5.4.1. General efficacy guidelines

Guideline name	Guideline identifier	Referenced in the ARGCM	
		Part	Section
*Note for Guidance on Good Clinical Practice** (ICH Topic E6) *Annotated with TGA comments	CPMP/ICH/135/95	I	7.8
Note for Guidance on Structure and Content of Clinical Study Reports (ICH Topic E3)	CPMP/ICH/137/95	I	7.4.1
		I	7.5.2

5.5. Nonclinical guidelines

5.5.1. Pharmacology guidelines

Guideline name	Guideline identifier	Referenced in the ARGCM	
		Part	Section
Note for Guidance on Safety Pharmacology Studies for Human Pharmaceuticals (ICH Topic S7A)	CPMP/ICH/539/00	III	5.3

5.5.2. Pharmacokinetics guidelines

Guideline name	Guideline Identifier	Referenced in the ARGCM	
		Part	Section
Repeated Dose Tissue Distribution Studies (ICH Topic S3B)	pp. 21 - 24 of Rules 1998 (3B) - 3BS3a	III	5.4.2
The Assessment of Systemic Exposure in Toxicity Studies (ICH Topic S3A)	pp. 89 - 101 of Rules 1998 (3B) - 3BS10a	III	5.4.2

5.5.3. Toxicology guidelines

Guideline name	Guideline identifier	Referenced in the ARGCM	
		Part	Section
Genotoxicity: Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals (ICH Topic S2A)	pp. 51-62 of *EudraLex* 1998, Volume 3B – 3BS6a	III	5.4.3
Note for Guidance on Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals (ICH Topic S2B)	CPMP/ICH/174/95	III	5.4.3
Note for Guidance on Dose Selection for Carcinogenicity Studies of Pharmaceuticals (ICH Topic S1C)	CPMP/ICH/383/95	III	5.4.4
Note for Guidance on Carcinogenicity: Testing for Carcinogenicity of Pharmaceuticals (ICH Topic S1B)	CPMP/ICH/299/95	III	5.4.4
Guideline on Repeated Dose Toxicity	CPMP/SWP/1042/99 Rev 1	III	5.4.4
Detection of Toxicity to Reproduction for Medicinal Products including Toxicity to Male Fertility	pp. 25-44 of EudraLex 1998, volume 3B – 3BS4a	III	5.4.5

6. Section 7 declarations

6.1. Background

Section 7 declarations are made under the *Therapeutic Goods Act 1989* (the Act) to provide greater clarity for consumers, the food and medicines industries and regulators in determining whether a product is a food or a therapeutic good.

Essentially, a Section 7 declaration enables the Secretary to the Department of Health and Ageing to declare that particular goods or classes of goods are or are not therapeutic goods. Goods or classes of goods that are declared to be therapeutic goods *via* a Section 7 declaration must be included on the Australian Register of Therapeutic Goods (ARTG).

A declaration does not necessarily mean that a product, or class of products, is approved for supply in Australia. It is the responsibility of sponsors to make an application to have particular products included on the ARTG if they have not already done so.

A list declarations made under Section 7 of the Act is available at <http://www.tga.gov.au/industry/cm-section7.htm>

6.2. Guidelines for managing a proposal for a Section 7 declaration

A proposal to make a Section 7 declaration under Section 7 is coordinated by the TGA's Office of Complementary Medicines (OCM). As part of this process, the TGA will consider the existing regulatory status of the substances or products that are the subject of the proposal. Action may need to be taken to review the safety of the substance / product before circulation of a proposal (e.g. in instances where a substance is not approved for use in Listed medicines).

Notice that a declaration is under consideration will be published in appropriate newsletters and Internet sites of the TGA and Food Standards Australia New Zealand (FSANZ) and circulated to industry associations and other stakeholder bodies, inviting comment. Advertisements in the press may be used in some circumstances. Circulated material will include a draft declaration, a draft statement of reasons and background information as appropriate. The length of the comment period will depend on the urgency of the proposal, although comment would normally close 30 days after the date of publication of the proposal.

Comments received will be collated and considered by the OCM and, where necessary, referred to the Advisory Committee on Complementary Medicines (ACCM) for advice before publication of the final declaration. Following this process, the Secretary may make a declaration with respect to the proposal, in an amended or unamended form. If comment has resulted in a declaration that differs significantly from the draft, a second round of consultation may be warranted.

7. Confidentiality

7.1. Freedom of Information Act 1982

Sponsors may request that data contained in their application remain confidential and exempt from the provisions of the *Freedom of Information Act 1982* (FOI Act). The Department of Health and Ageing is not the final arbiter of whether or not a document is exempt from disclosure. The Department's practice, consistent with the requirements of the FOI Act, is to consult with the sponsor who submitted the information claimed to be confidential:

- to establish whether release of the information is possible
- to give the sponsor the opportunity to request a review by the Administrative Appeals Tribunal (AAT) of any decision made by the Therapeutic Goods Administration (TGA) to release the sponsor's information under the terms of the FOI Act.

7.1.1. Release of Information

Applications and the information therein that are received by the TGA are treated as commercial-in-confidence. Accordingly, details of an application will be discussed only with the sponsor of the application or the sponsor's appointed agent.

Under certain circumstances, the TGA may be required by law to release information, including confidential information (e.g. under subpoena, to a court of law). However, in such cases, the TGA seeks undertakings from the parties involved or, if these cannot be obtained, confidentiality orders from the court concerned, to protect the information.

The TGA will not comply with demands for undertakings of confidentiality that seek to limit the lawful use or release of information by the TGA. To ensure public safety, the TGA and the Advisory Committee on Complementary Medicines (ACCM) have a duty to evaluate therapeutic goods using all information available to them. Therefore, relevant information may be accessed subject to law.

To carry out this function successfully, persons involved in the evaluation of applications must have access to:

- all Departmental records of previous applications; and
- the accumulated knowledge and experience that has been gained from the evaluation of previous applications.

This does **not** mean that data that are submitted in an application by one company can be referenced in an application for a similar medicine by a different company. This sharing of data is allowed only when an authorisation to do so has been received by the TGA from both companies. This applies also to joint applications for an identical medicine by two different companies.

7.2. Confidentiality statements

It is important that confidentiality statements accompanying applications are consistent with the powers and duties of the Secretary under the *Therapeutic Goods 1989 Act* (the Act), in particular Section 61 of the Act.

The following is an example of an acceptable confidentiality statement:

'All and any information contained in this document is to be regarded as:

- a trade secret as it contains unpublished details and results of private research proprietary to [name of company or sponsor] the disclosure of which to its competitors could be disadvantageous; and / or
- commercial or financial information that is privileged or confidential in that it contains valuable data or information which is used in its business and is of a type customarily used in confidence, or regarded as privileged, and has not been disclosed to any member of the public by [name of company or sponsor].'

This would be accepted only on the basis that the statement is asserted by a company as commercial-in-confidence. When information that is already public knowledge (e.g. information contained in the patent application, appearing in a published article etc.) is submitted under the cover of such a confidentiality statement, the information cannot be claimed to be confidential.

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