Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

Australian Guidelines for Complementary Medicines (ARGCM)

Part II: Listed Complementary Medicines

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 help sponsors seeking to include complementary medicines on the Australian Register of Therapeutic Goods (ARTG) as Listed medicines. The regulatory requirements for the Registration of complementary medicines are discussed in Part I of the Guidelines, and for complementary medicine substances in Part III.

This first section provides an overview of the requirements for including complementary medicines as Listed goods. Detailed guidance is provided in the following sections:

- Section 2. – Eligibility for including Listed complementary medicines on the ARTG
- Section 3. – The Listing Process
- Section 4. – The Electronic Listing Facility – Version 3 (ELF 3)
- Section 5. – Quality
- Section 6. – Safety and efficacy
- Section 7. – Labelling and presentation
- Section 8. – Post market review
- Section 9. – Product changes
- Section 10. – Other requirements.

1.1 Background

The *Therapeutic Goods Act 1989* (the Act) requires that therapeutic goods that are imported or manufactured for supply in Australia be included in the ARTG, unless they are specifically exempted from this requirement by Schedule 5 of the Therapeutic Goods Regulations 1990 (the Regulations). It is an offence under the Act to import, export, manufacture or supply non-exempt goods that have not been entered in the ARTG.

Medicines may be either 'Listed' or 'Registered' in the ARTG, depending on their ingredients or the intended purpose of their use. Schedules 3 and 4 of the Regulations outline those goods that must be Listed or Registered.

Medicinal products submitted for inclusion in the ARTG for Listed goods are made eligible on the basis of an application made via the Electronic Listing Facility – Version 3 (ELF 3). Sponsors of Listed medicines provide certain product information and a formal declaration that all the requirements, as set out in subsection 26A(2) of the Act, have been met. Section 2 of this part of the Guidelines is designed to help sponsors determine whether their medicinal products are eligible for Listing and whether or not they comply with all the Listing requirements.

2. Eligibility for including Listed complementary medicines on the ARTG

This section details the criteria used to determine the eligibility of a product for inclusion in the Australian Register of Therapeutic Goods (ARTG) as a Listed complementary medicine.

This section is divided into the following subsections:

2.1 General criteria for Listed complementary medicines

To be eligible as a Listed complementary medicine in the ARTG for supply in Australia, the product must contain only ingredients that may been approved for use in Listed complementary medicines and that make only general and/or medium level indications[1] as defined in the *Guidelines for Levels and Kinds of Evidence to Support Indications and Claims.*

Substances that have been approved for use in Listed complementary medicines are discussed further in Subsection 2.2. Guidance in determining the acceptability of indications and the evidence that must be held by a sponsor to support those indications are discussed in Subsection 6.2.2.

Schedule 4 of the Therapeutic Goods Regulations 1990 (the Regulations) outlines those therapeutic goods that must be included in the part of the ARTG for Listed goods. The following provides further guidance on the interpretation of Schedule 4 of the Regulations and Parts of the *Therapeutic Goods Act 1989* (the Act) in relation to the general criteria for Listed complementary medicines.

To be suitable for Listing in the ARTG for supply in Australia, medicinal products:

- with the exception of homoeopathic products[2], must be:
  - preparations containing as their active ingredients only permitted vitamins, minerals, amino acids, herbal substances, or 'other substances' specified in Schedule 4 of the Regulations; OR
  - medicated throat lozenges where the medication consists only of volatile oils and their constituents alone or in combination with ascorbic acid or its salts; OR
  - medicated space sprays where the medication consists only of volatile oils and their constituents; OR

[1] Indication(s), in relation to therapeutic goods, means the specific use(s) of the goods. Indications are for the purpose of market entry to record the therapeutic use of the product on the ARTG. Claims, in contrast, represent advertising statements about the product and need to be seen in the broader advertising context. The link between indications and claims is through Section 22(5) of the Act, which requires that sponsors may make only claims that are consistent with the indications for the product recorded on the ARTG.

[2] Specific guidance in relation to homoeopathic preparations is included in ARGCM Part IV.

  - sunscreen preparations for application to the skin with a sun-protection factor (SPF) of 4 or more when tested by the method of the Australian Standard for Sunscreens (currently AS / NZS 2604:1998); OR
  - uncompounded British Pharmacopoeia (BP) medicinal substances packed for retail sale; OR
  - 'medicine kits' consisting solely of medicines if Part 3-2 of the Act applies to any of the individual therapeutic goods contained in the kit;
- must contain only permitted excipient ingredients;
- must be labelled and advertised only for those indications accepted in relation to the inclusion of the goods in the ARTG, and must NOT be indicated for the treatment of a serious form of a disease, condition, ailment or defect specified in Part 1 or 2 of Appendix 6 to the Therapeutic Goods Advertising Code (TGAC);
- must conform to every standard (if any) applicable to the medicine;
- must be labelled in compliance with the general requirements for labels for medicines (currently Therapeutic Goods Order No. 69 (TGO 69) as amended by TGO 69C) as current and in force;
- must comply with the labelling requirements of AS / NZS 2604:1998 if the product is claiming to be a sunscreen with a sun-protection factor of 4 or more;
- must meet the requirements for acceptable presentation (see Subsection 7.2 to this part of the Guidelines for further information about unacceptable presentation);
- must meet the requirement that, if any steps in manufacture of the medicine are undertaken in Australia, each one must be carried out by a person who is the holder of a licence to carry out that step in manufacture;
- must meet the requirement that, if any steps in manufacture of the product occur in another country, evidence must be supplied to demonstrate that the manufacturing and quality-control procedures used are acceptable;
- must comply with any quality and safety criteria prescribed in the Regulations;
- must NOT be a type of product that needs to be sterile, such as eye drops;
- must NOT contain an ingredient or a component of an ingredient such that the product is subject to the conditions of a Schedule (or applicable Appendix) to the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP);
- must NOT contain substances that are prohibited imports for the purposes of the *Customs Act 1901* (see subsection 4.1.7.1(g) of this part for further information); and
- must have evidence, held by the sponsor of the product, to support any claim that the sponsor makes relating to the medicine.

Medicinal products submitted for Listing must satisfy all the above requirements. Products that are not exempt goods[3] and that are not eligible for Listing, must be Registered in the ARTG.

[3] Some medicines do not need to be included in the ARTG (see Section 18 of the Act); some medicines and persons are exempt from the manufacturing requirements of Part 4 of the Act (see Section 34 of the Act).

2.2 Ingredients approved for use in Listed complementary medicines

With the exception of herbal ingredients, Schedule 4 of the Regulations includes lists of ingredients that may be included in Listed medicines. In the case of herbal ingredients, any herbal ingredient that is currently included in a therapeutic good included in the ARTG may be used in Listed medicines, unless it is subject to the conditions of a Schedule (or applicable Appendix) to the SUSMP, or included in Schedule 4 or otherwise restricted by Part 5 (Division 2) of Schedule 4 of the Regulations.

2.2.1 Approved active ingredients

The majority of substances that can be included in Listed medicines are those that were included in therapeutic goods supplied in Australia before the Act came into operation in 1991, but note that substances permitted for use in Listed medicines are subject to ongoing review.

The Therapeutic Goods Administration (TGA) maintains a list of approved active ingredients that may be included in Listed medicines. This is available from the TGA website at: <http://www.tga.gov.au/industry/cm-listed-substances.htm>. To be consistent with their use in low-risk medicines, some ingredients in the list are subject to conditions. These include advisory or warning statements on product labels, limits on plant parts and / or preparations, quantitative limits, or component-related restrictions. It should also be noted that the list is subject to ongoing change. Contact the TGA if you need help in determining the current status of an ingredient.

Sponsors should also note that the inclusion of a substance in the document entitled *TGA Approved Terminology for Medicines* does not mean that the substance has been approved for use in Listed medicines, or that the substance has previously been included in a medicine in the ARTG. The *TGA Approved Terminology for Medicines* is the source of the Australian Approved Name (AAN) and, should a substance be approved for use in Listed medicines, it must be identified by its AAN. Herbal substances are generally named by identifying the herb species, the plant part(s) and the preparation, using approved terminology.

If a sponsor applies, via the Electronic Listing Facility (ELF), to list on the ARTG a medicine that contains a substance ineligible for use in Listed medicines or a substance that does not fully meet certain restrictions or legislative requirements relating to it, the ELF system will 'fail validation' and prevent the sponsor from submitting the application to the TGA (refer to Section 4 of this part of the Guidelines for information on ELF Version 3 [ELF 3]).

2.3 Assessing the status of herbal ingredients for use in Listed medicines

This subsection offers guidance on how to assess the status of a particular herbal ingredient, with a view to determining whether:

- the herbal ingredient is currently eligible for inclusion in a Listed medicine without further evaluation; OR
- the herbal ingredient (or one or more of its components) is subject to restrictions such that products containing it would need to be Registered before supply in Australia; **OR**
- the ingredient, if not eligible for inclusion in a Listed medicine, is eligible for evaluation as a new complementary substance.

2.3.1 Determining Status as a Listed Substance

Where a herbal ingredient:

- meets the current definition of *herbal substance*, as given in Regulation 2 of the Regulations;
- is included in a medicine included in the ARTG for supply in Australia as an active ingredient[4]; and
- is not subject to the conditions of a Schedule (or applicable Appendix) to the SUSMP, or the restrictions outlined in Schedule 4 of the Regulations,

then the ingredient is generally considered eligible for inclusion in Listed medicines without the need for further evaluation.

2.3.2 Definition of a herbal substance

Regulation 2 (Interpretation) defines a *herbal substance* for the purposes of Schedule 4 to the Regulations. This effectively means that only those herbal ingredients that comply with this definition are currently permitted to be included in Listed medicines.

Regulation 2 states:

> ***Herbal substance*** *means all or part of a plant or substance (other than a pure chemical or a substance of bacterial origin):*
>
> *a) that is obtained only by drying, crushing, distilling, extracting, expressing, comminuting, mixing with an inert diluent substance or another herbal substance or mixing with water, ethanol, glycerol or aqueous ethanol; and*
>
> *b) that is not subjected to any other treatment or process other than a treatment or process that is necessary for its presentation in a pharmaceutical form.*

Isolated components derived from plants, or synthesised to mimic a naturally occurring substance, are not considered acceptable as a herbal substance ingredient for use in Listed medicines. However, the isolated component may be eligible for use as a complementary medicine ingredient (see ARGCM Part I).

Sponsors who are uncertain whether or not a particular herbal ingredient meets the legal definition of a herbal substance, may wish to supply details of the manufacturing process (preferably in the form of a flow diagram) outlining the various processing steps, solvents used and extraction ratios, to the TGA for a determination. Where more than one solvent is used in an extraction step, the concentration of each solvent should be provided.

2.3.3 Schedule 4 to the Regulations

Schedule 4 to the Regulations outlines those goods eligible for inclusion in the part of the ARTG for Listed medicines. In the case of herbal ingredients, Part 4 of Schedule 4, incorporates a list of herbal substances that are not eligible for inclusion in Listed medicines or may only be included subject to certain restrictions. Herbal substances that are not included in Part 4 of Schedule 4 may be included in Listed medicines provided that the herbal substance is already present in medicines included in the ARTG for supply in Australia. Herbal substances that are not present in medicines included in the ARTG for supply in Australia are not currently eligible for inclusion in Listed medicines (see below).

As explained in Subsection 2.2.1, inclusion of a substance, including a herbal substance, in the *TGA Approved Terminology for Medicines* does not necessarily mean that the substance is Listable. To assist sponsors, those herbal substances suitable for inclusion in Listed medicines are identified by the addition of an 'L' code against such items in the Herbal Substances Section of the *TGA Approved Terminology for Medicines* list. Note that the *TGA Approved Terminology for Medicines* information is updated from time to time.

[4] For information on whether a herbal ingredient is currently included in a medicine included on the ARTG, contact the TGA.

2.3.4 Herbal ingredients that are not permitted for use in Listed medicines

Herbal ingredients that are not currently Listable may be eligible for evaluation as complementary medicine substances, provided that they are not subject to the conditions of a Schedule (or applicable Appendix) to the SUSMP, either directly or because of a scheduled component in the ingredient, or are otherwise restricted or subject to the provisions in Schedule 4 of the Regulations (see Subsection 2.3.3 above).

Ingredients (either directly or because of one or more components) that are subject to the conditions of a Schedule (or relevant Appendix, e.g. Appendix C and / or G) to the SUSMP are not eligible for evaluation as complementary medicine substances for use in Listed medicines.

Sponsors wishing to supply complementary medicines containing scheduled poisons, or otherwise restricted ingredients, will need to seek product Registration. Refer to Part I of the Guidelines for information on the Registration of complementary medicines.

Alternatively, sponsors may wish to make a submission to the Advisory Committee on Medicines Scheduling (ACMS) for reconsideration of the scheduling status of the ingredient or constituent.

2.4 Assessing the status of non-herbal substances

Non-herbal complementary substances include vitamins, minerals, amino acids, homoeopathic medicines and substances of animal origin. Non-herbal complementary substances that may be used as active ingredients in Listed medicines are included in Parts 1, 2, 3 and 5 of Schedule 4 to the Regulations. If a substance is not already included in Schedule 4, it is not currently eligible for inclusion in Listed medicines.

However, the substance, provided that it (or a component) is not subject to the conditions of a Schedule (or applicable Appendix) to the SUSMP, may be eligible for evaluation to determine if it is of sufficiently low risk to allow its inclusion in Listed medicines.

2.5 Assessing the status of excipient ingredients

Excipient ingredients are those substances in a product that do not contribute to its therapeutic effect. They include, for example, ingredients such as fillers, binding agents, flavours, fragrances and printing inks. Disclosure of excipients must not be such as to imply that the excipient has therapeutic activity. For example, it would not be acceptable to make a partial disclosure of the form, 'contains vitamin C' when the product contains a sub-therapeutic dose of ascorbyl palmitate as antioxidant.

The OCM is responsible for the evaluation of new excipient ingredients, including colours, to be included in complementary medicines. New excipient ingredients that are to be included in Listed medicines that are not complementary medicines (e.g. sunscreens) are evaluated by Office of Medicines Authorisation. A list of approved Listable excipient ingredients is available at <http://www.tga.gov.au/industry/cm-ingredients.htm>.

The following two subsections provide further information to help assess the status of an excipient with regards to its approval for use in Listed medicines.

2.5.1 Excipients other than topical excipients

The requirements for approval to use a new oral excipient, or an excipient other than for topical application, are the same as those required for approval of a new complementary medicine substance. These requirements are stipulated in ARGCM Part III. In general, the evaluation criteria for new excipients are common across all areas of the TGA.

2.5.2 Topical excipients

New topical excipients are a special class of excipients that may be included in topical Listed complementary medicines without prior evaluation provided that the following criteria are met:

- the sponsor is able to identify the excipient as a substance included in the Cosmetic, Toiletry, and Fragrance Association's *International Cosmetic Ingredient Dictionary* (page number and text extract should be given);
- the sponsor provides assurance that the excipient does not appear in Annex II to the European Economic Community (EEC) Directive 76/768 *List of substances which must not form part of the composition of cosmetic products;*
- the sponsor provides assurance that the excipient has been approved by the appropriate regulatory agency in Sweden, Canada, USA, UK or The Netherlands, or (less desirably) assurance that there have been market-place sales of comparable products containing the excipient in one of those five countries for at least two years; and
- the sponsor provides an assurance that the prescribed safety data will be provided to the TGA within six months of the issue of the certificate of Listing the product in the ARTG.

Such excipients are allocated 'provisional name'[5] status until such time as the excipient is evaluated by the TGA. Where a new topical excipient is included in a topical Listed complementary medicine, safety data must be provided to the OCM within six months of the date of inclusion of the product in the ARTG. Failure to submit the prescribed data within that time may result in cancellation of the product from the ARTG and its recall. The safety data that must be submitted for new topical excipients include:

- acute oral toxicity: LD_{50}-animal or alternative method;
- irritation study: skin and eye; animal or alternative method; and
- sensitisation study: skin; animal or alternative method.

The data will be evaluated by the TGA and, if cleared, the excipient will be given an AAN and can thereafter be used in other topical complementary medicines (subject to any conditions or limitations) without the need for further evaluation. If there are concerns about the safety of the excipient, or if the data provided by the sponsor are incomplete or otherwise unacceptable, the product may be removed from the Register and / or recalled.

The following additional studies may be requested in individual cases where concerns become evident at the time of evaluation:

- eye irritation study;
- *in vitro* mutagenicity (Ames) test; and/or
- *in vitro* percutaneous absorption test.

Alternatively, all of the above information can be submitted before Listing, together with the *Application for an Evaluation of a New Complementary Medicine Substance* form.

If the substance is cleared, it will be given an AAN and its use will thereafter be permitted in other topical complementary medicines (subject to any conditions or limitations) without the need for further evaluation. The sponsor will be advised of the AAN and will then be able to submit an application to List / Register the product.

5 Details for naming substances that do not have an approved name, including 'provisional names' (PRVs) are included in ARGCM Part IV, Naming of New Substances and Terminology.

Alternative sources of data on the safety of the excipient will be considered. For instance, if the excipient has been cleared by the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) or by the US Cosmetic Ingredient Review (CIR) group, the review document may be sufficient in itself. Copies of CIR reviews are available at <http://www.cir-safety.org>. Copies of NICNAS reviews may be available from the supplier of the excipient.

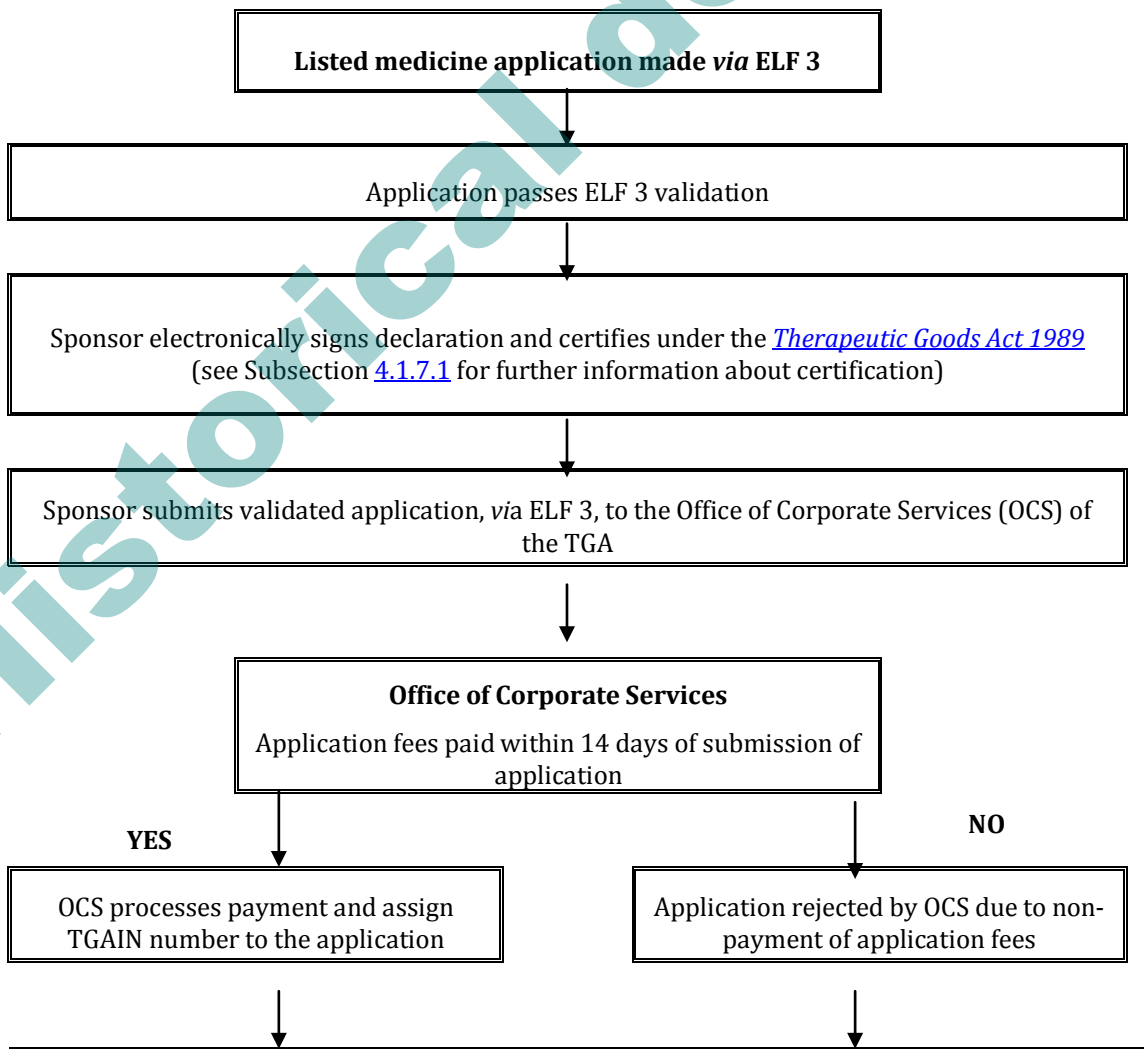
3. The Listing process

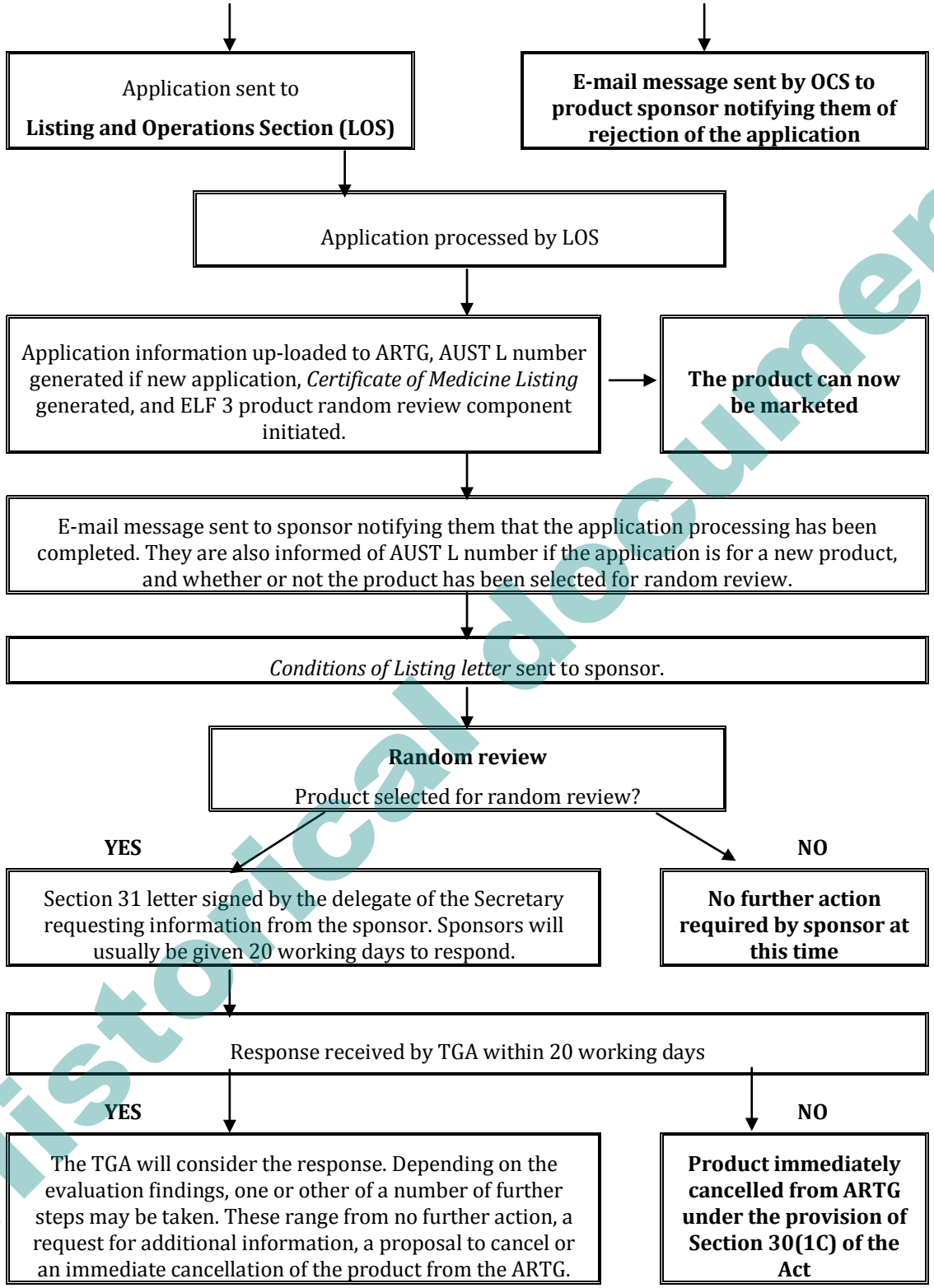
This section details the process Listed medicine applications follow when submitted to the Therapeutic Goods Administration (TGA) for inclusion on the Australian Register of Therapeutic Goods (ARTG). Listed medicine applications are submitted via the Electronic Listing Facility – Version 3 (ELF 3).

This section is divided into the following subsections:

3.1 Flow chart

The following flow chart illustrates the process for Listing a medicine in the ARTG:





3.2 Listed medicine application lodgement and validation via ELF 3

Applications to List medicines on the ARTG are done using ELF 3. Before an application can be submitted to the TGA to List a medicine on the ARTG, it must pass ELF 3 validation. Section 4 to these Guidelines provides further details on the ELF 3 system.

3.3 Payment processing

Once an application has been submitted to the OCS within the TGA, the sponsor has a maximum of 14 days to pay the fees required. If payment is not made within 14 days, then the application will be rejected by the OCS. Should an application be rejected, an e-mail message will be sent to the sponsor notifying them that the application has been rejected. Should the sponsor wish to re-submit the application after it has been rejected they will need to draft a new application, validate and submit it.

The OCS aims to process applications within two working days of receiving payment from the sponsor.

3.4 Listing and operations section processing

Once the OCS completes payment processing, the application is released into the Listing part of the TGA's eBusiness Services (eBS) system. Once the application has written to the ARTG and an AUST L number has been assigned, the Listing and Operations Section (LOS) complete the Listing process. Processing of the application by the LOS results in the following:

- a Certificate of Medicine Listing is generated;
- a Conditions of Listing letter is generated and sent to the Sponsor;
- the automated ELF 3 random review process is initiated; and
- an E-mail message is sent to the sponsor informing them that the product has successfully Listed on the ARTG, giving them the product AUST L number and telling them whether or not the product has been selected for random review.

The LOS aims to process applications within two working days of receiving the application from the O CS.

The product details will not be viewable on the web copy of the ARTG until the day after the information has written to the ARTG.

3.5 Random post market review process

An integral component of the ELF 3 Listing process is the desk-based review of a random sample of products. ELF 3 randomly selects a pre-determined number of applications for review. The random reviews are designed to allow the TGA to review certain product information and confirm that the certifications made by the sponsor at the time of Listing, under the Act, are correct.

Further information about certifications made under the Act is located in Subsection 4.1.7.1 of these guidelines.

When a product is randomly selected for review, the Listing Compliance Section (LCS) of the Office of Complementary Medicines (OCM) will issue the sponsor with a notice under Section 31 of the Act, signed by a delegate to the Secretary of the Department of Health and Ageing, outlining the information required for the review.

Information sought may range from aspects relating to the presentation and advertising material associated with the product, such as product labels, to information about the manufacture of the goods. The sponsor may also be asked to supply information about the evidence held in support of the therapeutic indications and claims relating to the product.

Further information regarding reviews undertaken by the LCS is located in Section 8 to these guidelines.

3.6 Fee structure

Since 1998–99, the TGA has operated on a full-cost-recovery basis. The fees and charges imposed on sponsors of Listed complementary medicines must cover all activities that fall within the scope of the Act. This includes regulation of the industry, the TGA's public health responsibilities, responsibilities to consumers for information on products and TGA's support for the industry generally (i.e. facilitation of exports and international harmonisation of standards).

The TGA collects its revenue primarily through annual charges, evaluation and assessment fees and licence fees. Each year the TGA meets with representatives of the four major industries to discuss and agree on the TGA's schedule of fees and charges for the forthcoming financial year.

For further information about fees and charges for Listed complementary medicines, refer to the following address on the TGA website: <http://www.tga.gov.au/about/fees.htm>.

3.6.1 New Listed medicine application

Fees must be paid within 14 days of an application being submitted to the TGA, otherwise it will be rejected. Fees are non-refundable or transferable. Details of the current fees and charges are available from the following address on the TGA website: <http://www.tga.gov.au/about/fees.htm>.

3.6.2 Product variation

The current fee to make a change that constitutes a 'variation' to a currently Listed product can be determined from the fees and charges information available from the following address on the TGA website: <http://www.tga.gov.au/about/fees.htm>.

In addition, the types of changes which attract fees are identified in the document *Guidance on Product Changes in ELF 3*.

4. The Electronic Listing Facility – Version 3 (ELF 3)

The Electronic Listing Facility – Version 3 (ELF 3) is a component of the Therapeutic Goods Administration's (TGA's) eBusiness Services System (eBS). The eBS project was undertaken as a way of improving the way in which regulatory information is managed. eBS established a framework where information is recorded once, and is readily accessible, shared across the organisation, and can be reported on flexibly. eBS has established a base for electronic commerce and electronic lodgement of data packages in support of applications for entry of products onto the Australian Register of Therapeutic Goods (ARTG), and has enabled clients to access appropriate legal information online.

The ELF 3 system went live on 15 September 2003 and provides sponsors and their appointed agents with an electronic environment for the submission of Listed medicine applications for entry on the ARTG. The ELF 3 system also provides users with the ability to view and update current ARTG medicine Listings.

The section is divided into the following subsection:

4.1 Overview of the ELF system

4.1.1 Introduction

The TGA ELF 3 system provides a web-browser-based electronic lodgement and validation facility for sponsors to enter new Listed medicines onto the ARTG and to update information about existing Listings. ELF 3 allows users to:

- create draft applications from scratch, from an existing draft application or from an existing ARTG entry;
- change certain information for multiple current Listings;
- submit completed applications to the TGA for processing;
- view previously submitted applications;
- view the details of medicines already Listed on the ARTG;
- view restricted Proprietary Ingredients;
- view the label checklist; and
- view the latest news relating to ELF 3.

ELF 3 uses a web front-end that interfaces with the TGA's Lotus Notes databases.

4.1.2 Gaining access to ELF 3

Before being able to access ELF 3, a sponsor must first be a recognised client of the TGA and apply for access to eBS. Each client of the TGA is issued with a unique 'client identification number'.

To obtain a client identification number, sponsors must complete a Client Details Form and submit it to the TGA. A Client Details Form is available from the eBS web page, in the 'eBS Access Forms' Section.

Once sponsors have obtained their client identification number, they can apply for access to eBS. This involves completing an E-Business form and returning it to the TGA. The TGA will establish access for the sponsor to become the 'E-Business Administrator' for their company. Once this is established, sponsors can then apply for and set up user accounts for themselves and other personnel in their company.

The E-Business form is available from the ebs website.

Sponsors needing further information about either obtaining a client identification number or gaining access to eBS, should contact the TGA by telephoning 1800 010 642 or sending an e-mail message to ebs@tga.gov.au.

4.1.3 ELF 3 User Guide

To assist users of ELF 3, a User Guide has been produced and is available electronically at the following address on the TGA website: <http://www.tga.gov.au/about/ebs-elf-userguide.htm>. It is also provided as Attachment 1 to this document.

The ELF 3 User Guide is a training document for the ELF 3 system. It outlines the eBS and ELF 3 systems, and provides users with instructions for creating and submitting Listed medicine applications.

4.1.4 Security of operations

Security for eBS is handled at an organisation level. Each user will be allocated a User Name and Password. Once logged on, the user will be able to see all their current applications.

Access to ELF 3 allows for two types of user:

- drafter – users who are drafters can carry out all functions relating to applications, excluding their final submission; and
- submitter – users who are submitters can carry out all the same functions as a drafter and also submit completed, validated applications.

4.1.5 Accessing the ELF 3 system

ELF 3 is accessed using an Internet browser. The eBS home page is located on the TGA website at the following address: <http://www.ebs.tga.gov.au>. Everyone will be able to access the TGA eBS login page. Secure login is required to access the TGA eBS system beyond this point.

4.1.6 Validation system within ELF 3

Once an application has been completed, to either List a new medicine or update information on an existing Listed medicine, the application must pass ELF 3 validation before it can be submitted to the TGA. To initiate the validation component of ELF 3, the 'validate' button located at either the top or bottom of the main application form must be pressed.

The validation engine will compare the information in the application against the rules and restrictions surrounding Listed medicines.

Once the validation engine has completed its check of the application against the Listing rules, a validation report is generated. If the validation has been successful, the status of the application will change from 'draft' to 'passed validation'.

If the validation fails, the validation report will provide a message outlining why this has happened. The user will need to make the changes specified before reapplying for validation. Only applications that have the status of 'passed validation' can be submitted to the TGA.

Users should be aware that the ELF 3 system is designed to convert non-submitted applications that have the status of 'passed validation' to 'draft' status if there are any amendments or additions to Listing rules in the validation engine before the application is submitted. This means that those applications that may have passed validation and subsequently changed to draft, will be required to undergo re-validation before being submitted to the TGA.

Users should also be aware that successful validation of an application does not mean that the product has been approved by the TGA nor does it mean that the product is eligible for Listing. The ELF system is a tool designed to allow sponsors to electronically submit an application for Listed medicines to the TGA. It does not check the application against every requirement for Listing.

4.1.7 Sponsor certifications under Section 26A of the Act

As indicated above, at the time of submitting a Listed medicine application to the TGA, the sponsor certifies that the goods that are the subject of the application meet the requirements of Section 26A of the *Therapeutic Goods Act 1989* (the Act). In certifying under 26A(2)(a)-(k) of the Act, the sponsor makes a legally binding statement that:

- the medicine is eligible for Listing;
- the medicine is safe for the purposes for which it is to be used;
- the medicine presentation is not unacceptable, and the medicine conforms to every standard (if any) applicable to the medicine and to every requirement (if any) relating to advertising applicable under the Regulations;
- for medicines manufactured in Australia, each step in the manufacture has been carried out by a person who is the holder of a licence, granted under the Act, to carry out that step;
- the medicine complies with all prescribed quality or safety criteria;
- the medicine does not contain substances that are prohibited imports for the purposes of the *Customs Act 1901*;
- all the manufacturers of the medicine are nominated as manufacturers in the application;
- they have, with manufacturers of the medicine who are manufacturers of the prescribed kind, written agreements containing such matters as are prescribed;
- they hold information or evidence to support any claim that the they make relating to the medicine; and
- the information included in or with the application is correct.

If a step in the manufacturer of the product is carried out outside Australia, Section 26A(3) of the Act requires the sponsor to seek pre-clearance by the TGA that the manufacturer is of an acceptable standard. For information on obtaining pre-clearance for an overseas manufacturer, refer to the *Guidelines on the GMP Clearance of Overseas Manufacturers*. Information on the role of the Office of Manufacturing quality (OMQ) of the TGA can be found at the following address: <http://www.tga.gov.au/about/tga-structure-omq.htm>.

For further information about sponsor obligations under the Act, refer to Section 10 of this part of the Guidelines.

4.1.7.1 Explanation of certifications under 26A(2)

This subsection provides further explanation of certifications made under Section 26A(2) of the Act.

(a) The medicine is eligible for Listing.

Schedule 4 of the Therapeutic Goods Regulations 1990 (the Regulations) defines those therapeutic goods that must be included in the part of the ARTG for Listed goods. To be eligible for Listing, the medicine must meet the requirements as stipulated in this Schedule. For example, Listed medicines must contain as their therapeutically active ingredients only those ingredients included in Parts 2, 3 and 5 of Schedule 4.

They must not contain herbal substances mentioned in Division 1 Part 4, but can contain herbal substances mentioned in Division 2 Part 4, provided their inclusion is consistent with the qualification mentioned in column 2 of that item.

The use of ingredients that have not been 'approved' for use in Listed medicines constitutes an incorrect certification against 26A(2)(a) of the Act and provides grounds for the product to be immediately cancelled from the ARTG under the provisions of Section 30(1)(e) of the Act.

(b) The medicine is safe for the purposes for which it is to be used.
For a medicine to be considered safe for the purposes for which it is to be used, it must comprise only 'approved' Listable substances, have indications that are appropriate for individuals to accurately self-diagnose and manage, and be manufactured by appropriately licensed manufacturers. The label must also include all mandatory warning statements.

An incorrect certification against 26A(2)(b) could result in a proposal to cancel the medicine from the ARTG under the provision of Section 30(2)(ba) of the Act.

(c) The presentation of the medicine is not unacceptable.
For further information about the unacceptable presentation of Listed medicines refer to Subsection 7.2 of these guidelines. An incorrect certification against 26A(2)(c) could result in a proposal to cancel of the medicine from the ARTG under the provision of Section 30(2)(ba) of the Act.

(d) The medicine conforms to every standard (if any) applicable to the medicine and to every requirement (if any) relating to advertising applicable under the Regulations.
There are two main elements to this certification: conformance to standards and conformance to advertising requirements applicable under the Regulations.

On the matter of certifying that the product conforms to every applicable standard (if any), note that Chapter 1 Section 3 of the Act includes the following definition of a standard:

> *Standard*, in relation to therapeutic goods, means a standard that:
>
> a. is specified in an order under Section 10 that is applicable to the goods; or
>
> b. if no such order is applicable to the goods but the goods are the subject of a monograph in…the default Standards, the BP, the PH Eur and the USP…is constituted by the statements in that monograph.

This means that, for goods subject to a monograph in the British Pharmacopeia (BP), European Pharmacopoeia (PH Eur) and the United States Pharmacopoeia (USP), the monographs constitute the standards unless another standard for the same goods has been issued as a Therapeutic Goods Order (TGO) – such as TGO 69 – *General requirements for labels for medicines*, and TGO 78 – *General standard for tablets and capsules*.

In certifying that the goods conform to every requirement (if any) relating to advertising applicable under the Regulations, sponsors should ensure that product advertising, which includes the product label, complies with the advertising requirements as outlined in Part 2 Divisions 3 and 4 Regulations 6-9 inclusive.

Sponsors should be aware that the Secretary of the Department of Health and Ageing, or their delegate, may immediately cancel the medicine from the ARTG if there is a serious breach, involving the medicine, of the requirements relating to advertising applicable under the Regulations. In addition, an incorrect certification against 26A(2)(d) could also result in a proposal to cancel of the medicine from the ARTG under the provision of Section 30(2)(ba) of the Act.

(e) If the medicine has been manufactured in Australia, each step in the manufacture has been carried out by a person who is the holder of a Section 38 licence to carry out that step.

The Act defines the requirements under which Australian manufacturers of Listed medicines must operate. That is, unless the manufacturer(s) or the medicines are exempted by Schedules 7 or 8 of the Regulations, the manufacturer(s) must be licensed by the TGA for the step(s) in manufacture that they carry out.

Manufacture, as defined in the Act means:

a. to produce the goods; or

b. to engage in any part of the process of producing the goods or of bringing the goods to their final state, including engaging in the processing, assembling, packaging, labelling, storage, sterilising, testing or releasing for supply of the goods or of any component or ingredient of the goods as part of that process.

The use of an unlicensed Australian manufacturer for the manufacture of Listed medicines constitutes an incorrect certification against 26A(2)(e) of the Act and grounds for immediate cancellation of the medicine from the ARTG under Section 30 (1)(e) of the Act.

(f) The medicine complies with all prescribed quality or safety criteria.

There are currently no prescribed quality or safety criteria in the Regulations. (This provision allows flexibility to provide for unforeseen circumstances that may affect quality and safety.)

(g) The medicine does not contain substances that are prohibited imports for the purposes of the *Customs Act 1901*.

Listed medicines must not contain substances that breach the legislative requirements of the *Customs Act 1901*. For further information about substances that are prohibited imports, as well as information about the personal importation of unapproved therapeutic goods, see <http://www.tga.gov.au/industry/import-export.htm>.

The use of a substance in Listed medicines that is a prohibited import for the purposes of the *Customs Act 1901* constitutes an incorrect certification against 26A(2)(g) of the Act and grounds for immediate cancellation of the medicine from the ARTG under the provisions of Section 30 (1)(e) of the Act.

(h) All the manufacturers of the medicine are nominated as manufacturers in the application.

Sponsors must ensure that all the manufacturers of the medicine are included on the product ARTG entry. Failure to keep the product records up-to-date, or to use a manufacturer who is not nominated as a manufacturer on the product ARTG entry, constitutes an incorrect certification against 26A(2)(h) of the Act and could result in the product being removed from the ARTG under the provisions of Section 30 (2)(ba) of the Act.

(i) The sponsor has, with manufacturers of the medicine who are manufacturers of the prescribed kind, written agreements containing such matters as are prescribed.

There are currently no matters prescribed regarding what must be included in written agreements between sponsors and manufacturers.

(j) The sponsor holds information or evidence to support any claim that they make about the medicine.

Sponsors certify that they hold evidence to support any claim or indication made about the medicine. To help sponsors determine the appropriate evidence to support indications and claims made in relation to Listed medicines, the TGA, in consultation with industry, has prepared a document entitled *Guidelines for Levels and Kinds of Evidence to Support Claims for Therapeutic Goods*.

Should the TGA undertake a review of the evidence held by a sponsor to support any indications and find that the evidence does not support the indication, then this would constitute an incorrect certification against 26A(2)(j) of the Act and could result in the product being cancelled from the ARTG under the provisions of Section 30(2)(ba) of the Act.

(k) The information included in or with the application is correct.

Sponsors must ensure that the information contained in or with the application is correct. Should the TGA find evidence that the information in or with the application is incorrect, then this would constitute an incorrect certification against 26A(2)(k) of the Act and could result in the product being cancelled from the ARTG under the provisions of Section 30(2)(ba) of the Act.

5. Quality

This section provides guidance on the quality standards that must be met for Listed complementary medicines. The section is divided into the following subsections:

5.1. Active ingredient

5.2. Finished product.

Some complementary medicines are comprised of relatively simple ingredients[6] (e.g. amino acids, mineral salts, vitamins) and, unless the medicine contains multiple active ingredients, the quality parameters applying to such products are essentially the same as for other medicines. However, special considerations must be given to those complementary medicines that contain complex ingredients that are difficult to characterise and / or certain combinations of multiple active ingredients. Within each part in this section, guidance will first be given for products containing relatively simple complementary medicine ingredients followed by guidance for other complementary medicines that contain either certain combinations of multiple active ingredients that are difficult to characterise or compositionally complex ingredients.

The headings used in this section follow the format of the International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use) (ICH) guideline M4Q: *Common Technical Document for the Registrations of Pharmaceuticals for Human Use – Quality*. It incorporates information contained in the European Medicines Agency (EMEA) *Note for Guidance on Quality of Herbal Medicinal Products* (CPMP/QWP/2819/00, 26/7/2001) and in the EMEA *Note for Guidance on Specifications: Test Procedures for Herbal Drugs, Herbal Drug Preparations and Herbal Medicinal Products* (CPMP/QWP/2820/00, 26/7/2001).

5.1 Active ingredient – complementary medicine substance

This section outlines the information that should be available on the active ingredient(s) used in a Listed complementary medicine. The types and level of detail of information depend on the nature of the active ingredient. For example, more data may be required to fully characterise a complex herbal extract than to describe a single, chemically synthesised active ingredient.

The information should be sufficient to:

- adequately characterise the active ingredient; and
- demonstrate that the active ingredient used in the complementary medicine will be of appropriate and consistent quality.

Note that there are additional restrictions and requirements for ingredients that are of animal or human origin, or that are genetically modified organisms or genetically modified products. Information on the requirements for these types of ingredients is included in Subsection 6.1.2 – *Ingredients of Animal or Human Origin*.

6 There is a wide range in the compositional complexity of complementary medicine ingredients. Simple complementary medicine substances (e.g. methionine) are primarily single-constituent ingredients that can be readily characterised. Complex complementary medicine substances (e.g. herbal extracts) have a number of components.

5.1.1 Manufacture of the active ingredient

5.1.1.1 Licensing and control

For most complementary medicines, licensing or evidence of good manufacturing practice (GMP) is not currently required for the manufacturer of the active ingredient, and the manufacturer of the active ingredient will not form part of the product entry in the Australian Register of Therapeutic Goods (ARTG). This means that the active ingredient can be sourced from any suitable manufacturer without prior approval of the Therapeutic Goods Administration (TGA). In this case, it is the responsibility of the manufacturer of the finished product to ensure that the quality of the active substance is acceptable.

Complex substances

Where the active ingredient is difficult to characterise quantitatively, such as some complex herbal extracts, it may be difficult to adequately control the active ingredient through quantitative specifications. In this case, a combination of specifications and the detailed method of manufacture may be required to adequately characterise the substance.

5.1.2 Compositional information

The purpose of the compositional information is to provide detailed characterisation of the substance. For simple complementary substances, this is generally straightforward and may be only a simple extension of the specifications. For complex complementary medicines, the compositional information is generally more detailed and contains a significant amount of additional qualitative and quantitative information.

The compositional information about active ingredients should be available through the sponsor. ARGCM Part III – Evaluation of Complementary Medicine Substances can be referred to for guidance on the type and detail of information that should be available on the active ingredient in a Listed complementary medicine.

For additional guidance on herbal ingredients, see ARGCM Part IV – General Guidance, Herbal Ingredients – Quality.

5.1.3 Control of active substance – specifications

Note: The British Pharmacopeia (BP), European Pharmacopoeia (PH Eur) and United States Pharmacopoeia (USP) and Therapeutic Goods Orders (TGOs) are the official standards for regulatory purposes in Australia. Where a substance is covered by a monograph in the BP, PH Eur or USP then this is the minimum standard that must be applied in its entirety, otherwise a justification is required. Note that the BP specifications are expiry specifications. The requirements of applicable general monographs of the BP, PH Eur and USP must also be met except where a justification for not doing so is authorised by the TGA. [7] Examples of these general monographs are those entitled Herbal Drugs, Herbal Drug Preparations and Extracts. The TGA will consider the suitability of other national or international pharmacopoeial monographs or standards on a case-by-case basis. Note that the most recent edition of any cited pharmacopoeial monograph or standard should be used, or a justification for not doing so included.

[7] Sponsors attempting to justify non-compliance with prescribed standards (e.g. BP, Ph Eur, USP or TGOs) should apply to the TGA in writing, seeking an exemption under Section 14 of the *Therapeutic Goods Act 1989*. Section 14 Exemption requests should explain why the standard(s) cannot be met and detail what alternative(s) are proposed and why. The delegate of the Secretary will review the request and sponsors will be advised in writing of the delegate's decision.

The active ingredient acceptance specifications are a set of tests and limits that are applied to the complementary medicine substance in order to ensure that every batch is of satisfactory and consistent quality.

The specifications should monitor all parameters (generally by physicochemical testing) where variation would be likely to affect the quality or safety of the product.

Typically, the manufacturer of the active ingredients will apply specifications to the substance at the time of its manufacture. The finished product manufacturer is also expected to ensure that the active ingredient complies with agreed specifications at the time of manufacture. The two sets of specifications are not necessarily identical.

For most complementary medicines, the manufacturer of the active ingredient will not be controlled to the same extent as the finished-product manufacturer, and therefore the focus will be on the specifications that are applied by the finished-product manufacturer before use in the finished product. For some complex substances, the specifications applied to the active ingredient by the active-ingredient manufacturer may need to be more detailed.

5.1.3.1 Limits and tests

If there is a BP monograph for the active substance, it must be used unless otherwise justified. However, it is generally acceptable to adopt the tests, limits and test methods of a PH Eur or USP monograph as the specification for an ingredient, if justified. Where there is a TGA-recognised monograph or standard for the substance, and if no modifications or additions have been made to the tests and limits of that monograph or standard, then reference to that document is sufficient for this section of the application submission. Note that the most recent edition of any pharmacopoeial standard or monograph should be used or a justification for not doing so should be available. The requirements of applicable general monographs of the BP must also be met except where a justification for not doing so is authorised by the TGA. Examples of these general monographs are those entitled *Herbal Drugs*, *Herbal Drug Preparations* and *Extracts*.

In some cases, the compendial requirements may not in themselves be sufficient to adequately control the quality and consistency of an ingredient, and sponsors may apply additional tests. However, it is generally not acceptable to:

- adopt only some of the tests from a pharmacopoeial monograph; **OR**
- selectively combine some tests and / or limits from the BP monograph with some tests and / or limits from the USP monograph (without having ensured full compliance with either one or the other monograph); **OR**
- adopt an earlier edition of the pharmacopoeial monograph or standard when there is a more recent edition which has been adopted by the TGA.

Where non-pharmacopoeial specifications are applied, a tabulated summary of the tests, test methods and limits should be available if required by the TGA (e.g. *assay (non-aqueous titrimetry): 99.0-101.0 per cent*). The specifications applied should be justified in respect of their ability to assure the quality and consistency of the ingredients used. Similarly, where a pharmacopoeial monograph is used as the specification, any modification to the pharmacopoeial requirements should be justified.

The development of the specifications for the active ingredient should be guided by the compositional information (see ARGCM Part III). The minimum tests and limits included in specifications for an active ingredient include:

- appearance / description;
- identification;

- content / assay; and
- impurities (e.g. residual solvents, heavy metals, synthetic impurities and degradants).

Additional tests and limits may be appropriate and will depend on the nature of the active ingredient. For example, tests for the presence or the proportion of isomers, optical rotation, particle size distribution, and the clarity, colour and pH of solutions may also be relevant.

The potential for microbiological contamination should also be considered. While the TGA applies limits for certain micro-organisms in finished products, it is advisable to implement appropriate controls at the raw material stage. In addition to considering the organisms to which TGA applies limits, sponsors should consider whether the adoption of limits for additional microorganisms is appropriate.

Complex complementary medicine substances

Specifications for a complex complementary medicine substance will vary depending upon the substance. The specifications might include controls on the macro components such as nitrogen content or sodium content. For complex liquid substances, solvent content or viscosity might be important. Additional simple tests that could assist in characterisation might include colour, texture, smell, and pH. More complex or specific tests should be used where there is a need to determine a component in a substance that is significant (e.g. sodium content in a sodium salt of a substance or gas chromatographic (GC) characterisation of key components in an oil).

Of particular importance are the significant yet minor components of a substance (e.g. content of a specific alkaloid). These minor components are often pivotal to the nature and / or safety of the substance, and their identification and analysis in the substance requires the attention of the sponsor. A good starting point may be to use monographs for similar substances as a model and adapt them to the substance in question.

Substances that are intrinsic mixtures (e.g. synthetic polymers or fatty acid esters of glycerol) may require additional tests to control the composition of the mixture. Such tests may include acid value, iodine value, saponification value, viscosity, density and refractive index.

For additional guidance on herbal ingredients, see ARGCM Part IV – General Guidance, Herbal Ingredients – Quality.

5.1.3.2 Impurities and incidental constituents

One of the key purposes of raw-material specifications in the area of complementary medicines is to determine whether or not the active raw material is free of contaminants that may have safety implications. Therefore, incidental constituents and impurities need to be considered and tests and limits included in the active-ingredient specifications.

For further guidance on this issue refer to ARGCM Part III – Impurities and Incidental Constituents.

Limits and tests should also be included in accordance with the requirements outlined in *ARGCM Part III – Guidance on Limits and Tests for Incidental Metals and Non-metals in Therapeutic Goods.*

5.1.3.3 Analytical procedures and validation

Details should be available on all analytical methods used in the specifications, together with validation data that demonstrate that the method is suitable for the material in question. These data should cover, for example, accuracy, precision, specificity (e.g. freedom from interference by degradation products and other likely impurities) and linearity. Validation data are not required for methods described in the BP.

Guidance on validating analytical test methods can be found in Analytical procedure validation for complementary medicines.

5.1.3.4 Batch certificates of analysis

Certificates of analysis should be available for at least two recent commercial-scale production batches to demonstrate routine compliance with the specification or monograph. If data on commercial-scale batches are not available, certificates of analysis for pilot-scale batches manufactured using the same process as intended for commercial-scale batches should be available.

5.1.3.5 Justification of specification

If a sponsor proposes to use an alternative monograph / standard when there is a BP, Ph Eur and USP standards, then justification for doing so may be requested.

If there is no BP, PH Eur and USP monograph for the active ingredient, then a justification for using alternative specifications may be sought. The justification should cover the central function of the active-ingredient specifications, which is to ensure that the substance used in the finished product is of consistent high quality. Specifically, identification, assay, control of impurities and other critical factors in the quality of the active ingredient should be dealt with.

5.2 Finished product

5.2.1 Description and composition of the product

A description of the finished Listed product should be available. It should include the following:

- a table of the ingredients in the product and their purpose in the formulation (e.g. active, disintegrant, antimicrobial preservative). This table should provide greater detail than just the product formulation. It should include overages (see Subsection 5.2.3.8), if any, and a reference to the quality standard for each of the ingredients (e.g. compendial monograph reference or manufacturer's specifications number);
- a description of the dosage form including any special character (e.g. modified release); and
- the type of container and closure for the product, including the materials used.

5.2.2 Product development

Information on the development of the finished product should be available.

This is particularly important for non-conventional dosage forms. For example, where a medicine has modified release characteristics or an unusual method of manufacture, the product development summary should include a discussion of the development of that characteristic or method, and any relationship with the finished product specifications.

For example, for an enteric-coated tablet, dissolution and formulation studies performed during development should be discussed and related to the dissolution test in the finished product specifications.

If any overages are proposed, information about the developmental work that led to the proposed overage should be available.

5.2.3 Formulation

This subsection provides guidance on the formulation of complementary medicines. Components of a formulation are divided into active ingredients and excipient ingredients. Some of these ingredients may be incorporated in the form of proprietary or confidential formulations, called 'proprietary ingredients' (PIs). PIs are discussed in detail in ARGCM Part IV.

5.2.3.1 Active ingredients

Active ingredients in Listed complementary medicines are those substances that have a therapeutic role in the formulation. Substances that are included in the formulation as active ingredients must make a contribution to the proposed indications for the medicine. Where a claim links the presence of an ingredient to the product indication, that ingredient must contribute to that indication. Where claims of synergy are made, there must be evidence to support the synergistic effect. The evidence may be scientific and / or traditional.

5.2.3.2 Excipient ingredients

Excipient ingredients are substances used to assist in the manufacture of therapeutically active substances into dosage forms suitable for administration to consumers. Each excipient ingredient included in a formulation must have a justifiable excipient role and should be controlled by specifications.

Sponsors should ensure that the intended use of an excipient is appropriate and that it is used in amounts sufficient to achieve its technical purpose. Sponsors should also ensure that the excipients are approved for use.

5.2.3.3 Proprietary ingredients

The term 'proprietary ingredient' (PI) means a formulation containing two or more ingredients obtained from another manufacturer for which the formulation details are not necessarily known to the sponsor and includes, for example, fragrances, flavours, colouring ingredients, trans-dermal patch adhesives and printing inks. An unformulated ingredient is not usually accepted as a PI formulation.

Information on PIs is given in ARGCM Part IV.

Before a PI is included in a product, the sponsor should ensure that:

- formulation details have already been disclosed to the TGA (in which case sponsors should state the ingredient's ARTG number at the time of application); **OR**
- sponsors have asked the manufacturer of the PI to provide the TGA with details of the formulation on a Notification of a Proprietary Ingredient form. Sponsors should also note that there is a list of PIs that have been used in Listed medicines but that are not usable in the Electronic Listing Facility – Version 3 (ELF 3) until information about proprietary ingredient purpose and quantities of restricted ingredients have been supplied to the TGA. This list is located on the TGA website at <http://www.tga.gov.au/industry/ebs.htm>.

Sponsors should be aware that there is no evaluation of the PI formulation in terms of safety or efficacy. However, the individual ingredients of the PI are assessed for safety. If the PIs are colours and are to be used in an oral product, the colour must be one that is approved for ingestion (see below).

Where the PI is a pre-mix that includes one or more active ingredients, the PI is handled differently and the active ingredients must be disclosed in labelling and other product information (refer to ARGCM Part IV for details).

If the label contains a negative disclosure (e.g. 'sugar free' or 'alcohol free'), sponsors should also check that the substance is not contained in any PI included in the formulation.\

Before the implementation of ELF 3, it was possible for sponsors to use a PI for different purposes. For example, a PI containing ascorbic acid may have been added to act as an antioxidant for the product (purpose as an excipient mix) or added to the product for use as a source of ascorbic acid for which therapeutic claims were made (purpose as an active pre-mix). With the implementation of ELF 3, PIs have been assigned one purpose and may only be used for that purpose. As such, those PIs that have previously been used in products for different purposes can no longer able to be used in this dual way.

The TGA sought clarification from PI suppliers and, based on their advice, designated a single purpose to all PIs available in ELF 3. Therefore, should a sponsor wish to use a PI for a purpose other than that currently assigned by the PI supplier, the sponsor will need to arrange for the PI supplier to submit a new PI application to the TGA designating the new purpose. The TGA will assign a unique ARTG PI number to the PI for its new purpose.

5.2.3.4 Colouring ingredients

The document *Colourings used in Medicines for Oral Use* is available on the TGA website. Colourings other than those listed there may be permitted in topical products.

5.2.3.5 Modified-release products

Modified-release products are dosage forms that have been formulated to release the active ingredient(s) at a different rate or to release the active ingredient(s) in a different region of the body compared to a conventional counterpart. They include products that have been developed for exceptionally rapid release of the active ingredients.

Data held on a modified-release Listed complementary medicine should include a justification for the modified-release formulation based on physiological, clinical and / or bioavailability data. *In vitro* and animal studies may be used as supporting data. Examples of when modified-release dosage forms may be appropriate include:

- the active ingredient is absorbed and eliminated rapidly (e.g. it has a half-life of less than 6 to 8 hours) and has a correspondingly rapid loss of effectiveness;
- the site of absorption is not restricted to a particular part of the gastrointestinal tract;
- the product is intended for use in conditions of sufficient duration to warrant the use of a sustained-release formulation; or
- the product has to provide therapeutically effective doses of the active ingredient throughout the dosage interval.

Information about different types of modified-release tablets and capsules is given in Therapeutic Goods Order No. 78 (TGO 78) *General Standard for Tablets and Capsules* (refer to Clause 5 (Interpretation)).

Modified-release formulations should be supported by evidence to demonstrate that the product meets controlled-release claims. Dissolution data requirements are discussed in Subsection 5.2.7.5.

5.2.3.6 Herbal substances and ingredients derived from herbal substances

For additional guidance on herbal ingredients, see ARGCM Part IV – General Guidance - Herbal Ingredients – Quality.

5.2.3.7 Batch-to-batch variations in the amount of ingredients

The reasons for a proposed range or ranges in the quantities of any ingredients should be available.

Variations in content of some active ingredients

For some active ingredients, such as herbal substances, the weight of the active raw material used in a batch of the formulated product may vary according to the content of a standardised component. Details of the actual weight of active raw material used for each batch of finished product must be held.

Routine variations in excipients

It is recognised that it may be necessary to vary the quantities of certain excipients from batch to batch in order to achieve acceptable results during the manufacturing process. Consistent with the requirements for non-prescription medicines, the following changes to the nominal amounts of certain excipients may be made. Note that this applies to only immediate release complementary medicines (See Table 1.)

Table 1. Changes permitted to the nominal amounts of certain excipients

Excipient type	Acceptable range around the nominal formulation[8]
pH-adjusting ingredients	qs*
Volume-adjusting fluids	qs
Quantity of ingredients whose function is to contribute to viscosity	+/- 10 %
Colour in tablet coating (but not in body of tablet)	qs
Solvent in granulating fluid	qs
Granulating fluid (fixed composition)	+/- 10 %
Disintegrant (even if the excipient serves more than one role in the formulation)	up to +25 %
Coating solution	qs
Talc and water-soluble lubricants and glidants	-25 % to +100 %
Water-insoluble lubricants and glidants, except talc (e.g. magnesium stearate, stearic acid)	+/- 25 %
Filler (bulking agent) in hard gelatin capsules	+/- 10 %
Polishing agents	qs
Carriers and potency adjusting ingredients for materials of biological and herbal origin	+/- 10 %
Filler (bulking agent) in tablets and soft gelatin capsules to account for the changes in the item above	+/- 10 %

*qs – *quantum satis* or 'as required'

8 Unless excipients are subject to other restrictions (e.g. those identified as 'restricted ingredients' in ELF 3).

5.2.3.8 Overages of active ingredients

Overages may be used during manufacture. An overage is where the amount of an ingredient added during manufacture is greater than that nominated on the product label. Details of the overage used must be available.

Overages may be used to ensure compliance with end-of-shelf-life specifications. Losses of active ingredient may occur during the manufacturing process or during storage, as a result of the instability of the substance. For regulatory compliance purposes, TGO 78 includes expiry limits for a range of vitamins.

Manufacturers should ensure that batch release assay values (where performed) reflect any overages used in the product.

Justification for the proposed overage must be available. An exemption is required where use of an overage leads to specifications that are broader than that allowed by the BP / TGO 78.[9]

The use of an overage to compensate for poor analytical methodology or poor stability performance is not usually considered sufficient justification.

Overages are not to be included in the formulation details section of ELF 3.

5.2.4 Manufacture of the finished product

5.2.4.1 Licensing and control

Where Australian manufacturers are used in making the product, each manufacturer must be licensed to perform manufacturing of the type proposed. The manufacturer's licence carries details of the types of manufacture permitted under the licence.

Where a product is imported, each nominated overseas manufacturer must demonstrate an acceptable standard of GMP as would be required of an Australian manufacturer. Pre-clearance of overseas manufacturers is mandatory for Listed complementary medicines (see Subsection 4.1.7).

Details of the TGA's requirements for manufacturers are specified in the PIC/S Guide to Good Manufacturing Practice for Medicinal Products, PE 009-8. The information needed to establish the standard of an overseas manufacturer is given in the document entitled Guidance on the GMP Clearance of Overseas Medicine Manufacturers.

Where the manufacture of a proprietary ingredient is considered a significant step in the manufacture of the finished product (e.g. a tablet granulation, a tablet coating, an active / excipient pre-mix, or a vehicle for a topical product), evidence of licensing or approval of the manufacturer may be required. GMP evidence is not required where a proprietary ingredient is not considered a significant step in finished product manufacture (e.g. most colours, printing inks, flavours and fragrances, and proprietary ingredients whose sole purpose is as a source of the preservative system for the finished product).

9 Sponsors attempting to justify non-compliance with prescribed standards (e.g. BP, PH Eur, USP or TGOs) should apply to the TGA in writing, seeking an exemption under Section 14 of the Act. Section 14 Exemption requests should explain why the standard(s) cannot be met and detail what alternative(s) are proposed and why. The delegate of the Secretary will review the request and sponsors will be advised in writing of the delegate's decision.

5.2.4.2 Batch formulation

A batch formula should be available that includes all of the components that will be used in the manufacture of the finished product and their amounts on a per batch basis (including any overages).

5.2.4.3 Description of manufacturing process and process controls

Details of the manufacturing process for the finished product should be available for each manufacturing site. Typically, these steps may include the manufacture of the dosage form, packaging and labelling, chemical and physical testing, microbiological testing and release for sale. The manufacturing details should include information about solvents used, even if they are evaporated from the product during manufacture.

5.2.4.4 Control of critical steps and intermediates

Tests and acceptance criteria that are applied to critical steps or intermediates in the manufacture of the finished product should be documented; for example, manufacturing acceptance criteria for a tablet granulation or in-process controls for pH during mixing of a syrup.

5.2.5 Control of excipients - specifications

All ingredients, including excipient ingredients, should have suitable specifications. Where there is a TGA-recognised monograph or standard for the substance, and no modifications or additions have been made to the tests and limits of that monograph or standard, then reference to that document is sufficient.

If a sponsor proposes to use an alternative monograph / standard when there is a BP, PH Eur, USP standards, then justification for doing so may be sought.

If there is no relevant monograph / standard for the excipient, then full details of the specifications for each excipient should be held.

Note that there are additional restrictions and requirements for ingredients that are of animal or human origin or that are genetically modified organisms or genetically modified products. Information on the requirements for these types of ingredients is in Subsection 6.1.2.

5.2.5.1 Proprietary ingredients

The specifications applied to PIs should be appropriate to the type of ingredient, and its function and proportion in the finished product.

For an ingredient blend that contains the active substance, it may be appropriate to have tests for the identification and content of the active ingredient, and impurity tests.

See also Subsection 5.2.3.3.

5.2.5.2 Colouring ingredients

Colourings used in Medicines for Oral Use contains a list of approved colouring agents. In the absence of a BP, PH Eur, USP Monographs, colours shall conform either to the specifications in the FAO / WHO Compendium of Food Additive Specifications (as published by the Joint Food and Agriculture Organization (FAO) / World Health Organization (WHO) Expert Committee on Food Additives (JECFA) on its website), or to those defined in the European Commission Directive 95/45/EC (on specific purity criteria concerning colour for use in foodstuffs – as amended from time to time).

The specifications for colourings used in topical products should be comparable with those in *Colourings used in Medicines for Oral Use*.

5.2.6 Control of active ingredient - specifications

Note: The BP, PH Eur and USP and TGOs are the official standards for regulatory purposes in Australia. Where a substance is covered by a monograph in the BP, PH Eur and USP, then this is the minimum standard that must be applied in its entirety, otherwise a justification is required. Note that the BP, PH Eur and USP specifications are expiry specifications. The requirements of applicable general monographs of the BP must also be met except where a justification for not doing so is authorised by the TGA. Examples of these general monographs are those entitled *Herbal Drugs*, *Herbal Drug Preparations* and *Extracts*. The TGA will consider the suitability of other national or international pharmacopoeial monographs or standards on a case-by-case basis. Note that the most recent edition of any cited pharmacopoeial monograph or standard should be used or a justification for not doing so included.

Typically, the manufacturer of the active ingredient raw material will apply specifications to the substance at the time of its manufacture. The finished-product manufacturer is also expected to ensure the active ingredient complies with specifications before using the substance in the finished product.

This subsection refers to the active-ingredient specifications that should be used by the manufacturer of the finished product to ensure its quality before its use.

The specifications for the active ingredient that are applied by the manufacturer of the finished product should be available. If there are any differences between the active-ingredient specifications used by the active-ingredient manufacturer and the finished-product manufacturer, these should be justified.

If there is a BP, PH Eur and USP monograph for the active substance, it should be used. However, if justified, it is acceptable to adopt the tests, limits and test methods of a PH Eur or USP monograph as the specification for an ingredient. Where there is a TGA-recognised monograph or standard for the substance, and if no modifications or additions have been made to the tests and limits of that monograph or standard, then reference to that document is sufficient for this section of the application submission. Note that the most recent edition of any pharmacopoeial standard or monograph should be used, or a justification for not doing so provided.

Where non-pharmacopoeial specifications are applied, a tabulated summary of the tests, test methods and limits should be provided.

The specifications applied should be justified in terms of their ability to assure the quality and consistency of the ingredients used. Similarly, where a pharmacopoeial monograph is used as the specification, any modification to the pharmacopoeial requirements should be justified. Details of test methods and method validation data should be provided for all non-pharmacopoeial methods (justifications, method details and validation data are not needed if they have already been provided under Subsection 5.1.3 *Control of Active Substance – Specifications).*

5.2.7 Control of the finished product – specifications

Note: The BP, PH Eur, USP, and TGOs are the official standards for regulatory purposes in Australia. Where a substance is covered by a monograph in the BP, PH Eur and USP, then this is the minimum standard that must be applied in its entirety, otherwise a justification is required. Note that the BP, PH Eur and USP specifications are expiry specifications. The requirements of applicable general monographs of the BP, PH Eur and USP must also be met except where a justification for not doing so is authorised by the TGA. Examples of these general monographs are those entitled *Herbal Drugs*, *Herbal Drug Preparations* and *Extracts*. The TGA will consider the suitability of other national or international pharmacopoeial monographs or standards on a case-by-case basis.

Note that the most recent edition of any cited pharmacopoeial monograph or standard should be used, or a justification for not doing so included.

The finished-product specifications are a set of tests and limits that are applied to the finished medicinal product in order to ensure that every batch is of satisfactory and consistent quality at release and throughout its shelf life. The specifications should monitor all parameters (generally by physicochemical testing) in which variations would be likely to affect the safety or efficacy of the product.

The specifications against which a finished product is tested before release for sale are referred to as the 'batch release specifications' in this document. The specifications against which a finished product is tested to ensure satisfactory quality throughout its shelf life are referred to as the 'expiry specifications'.

Products tested by the TGA are tested for compliance with the limits in the expiry specifications.

5.2.7.1 Data requirements

A table of the tests, test methods and limits should be held (e.g. assay (GC): 95.0-105.0 per cent). *ARGCM Part IV, Product Specifications* provides a template for product specifications. For dissolution tests, brief details of the apparatus, medium and limit should be available (e.g. dissolution (paddle at 50 rpm, 900 mL of water, Q=80 per cent at 30 minutes)). A summary list that gives details of both the batch release and expiry specifications should be available. Where the expiry specifications differ from the batch release specifications, this should be noted. It is unusual for batch release specifications and expiry specifications to be identical. If this is the case, it should be specifically noted. The specification code number and date should also be available.

Tighter limits are usually applied to critical parameters at batch release, to allow for possible changes to the product during storage (e.g. decomposition of the active ingredient).

The batch release limits must be chosen so as to guarantee that all batches will comply with the expiry specifications throughout the product's shelf life. At a minimum, the expiry specifications should include all of the tests that are included in the batch release specifications.

The specifications must include the requirements listed in any TGO and in the BP, PH Eur or USP general monograph applicable.

If there is no BP, PH Eur or USP monograph specific to the product, the specifications must include all of the requirements in the BP general monographs (for dosage forms). Sponsors should also check the BP, PH Eur and the USP for monographs for similar products to determine appropriate tests and limits to include in the specifications.

Where the product is subject to a monograph in the BP, PH Eur or USP, the expiry specifications must include all of the tests and limits in that monograph. It is a legal requirement for finished products that have a monograph in the BP, PH Eur or USP to comply with the requirements of that monograph. Note that this refers to the current editions of each pharmacopoeia and that the use of earlier editions would require a justification. If the sponsor considers that the BP, PH Eur or USP test methods are unsatisfactory for the product, they may propose another method that has been validated.

5.2.7.2 Quantified by input

Sponsors should refer to the guidance document *Quantified by Input*.

5.2.7.3 Residual solvents

In addition to controlling residual solvents in the active ingredient, it is necessary to consider the total amount of residual solvents that may be present in the finished product. This includes solvent residues that are present in the active ingredient and all excipients, and solvent residues resulting from the manufacture of the finished product.

Depending on the amounts and types of solvent residues from each of these sources, it may be appropriate to include a test and limits for residual solvents in the finished-product specifications.

If the control of residual solvents in the finished-product specifications is deemed to be unnecessary, then the basis for this decision should be justified and available to the TGA.

Tests and limits in the specifications, or justification for not including them, should be based on the BP Appendix *Residual Solvents.*

5.2.7.4 Microbiological requirements

Sterile Products

Medicines required to be sterile cannot be included on the ARTG as Listed medicines.

Non-Sterile Products

The *Therapeutic Goods Order No. 77 – Microbiological Standards for Medicines* (TGO 77) sets out the microbial limits that apply to non-sterile dosage forms.

All non-sterile dosage forms should include limits for microbial content in the finished product batch release and expiry specifications. Microbial specifications for solid oral or dry powder products may not be necessary if it can be demonstrated during product development that the product is at a very low risk of contamination and microbial growth is not supported.

It is not a requirement that every batch of a product be tested at batch release. Once it has been demonstrated, by testing a number of routine production batches to establish a product history, that the manufacturing processes do not permit contamination by excessive numbers of microorganisms, testing could be reduced to once every 6 to 12 months or some other selected basis (e.g. every tenth batch).

Products with a significant water content (e.g. creams, gels and oral liquids) are likely to support microbial growth. Such products should include tests and limits for microbial content in both the batch release and expiry specifications.

For products containing an antimicrobial preservative(s), expiry specifications should include tests to ensure the efficacy of preservatives. Given that the effectiveness of many preservatives is pH dependent, the specifications for such products should usually include the pH range within which preservative efficacy will be ensured. The expiry limits for the preservative should be supported by preservative efficacy testing that is performed during stability testing.

5.2.7.5 Tablets and capsules

If the product is in tablet or capsule form, sponsors should ensure that it complies with the applicable TGO or general monographs of the BP, PH Eur and USP. Where this is the case, the finished-product specifications must include details of any test required (e.g. disintegration), referencing the test limits and test method defined in the Order or monograph.

Dissolution may be an indicator for bioavailability and is considered an important part of quality control for solid, oral-dosage forms. Sponsors of all tablet products, and capsules where feasible, are encouraged to employ dissolution testing. Disintegration testing is not required where dissolution testing has been performed. TGO 78 provides guidance on situations where dissolution testing is appropriate. Further information on dissolution requirements for specific dosage forms can be found in USP Chapter <724> *Drug Release* and Chapter <2040> *Disintegration and Dissolution of Dietary Supplements*.

If there is a BP monograph for the product, but it does not include a dissolution test, and there is also a USP monograph for the product that does include a dissolution test, sponsors are encouraged to include the USP dissolution test in the finished-product specifications.

If there are no pharmacopoeial monographs for the product, or a related product, that includes a dissolution test, the development of a dissolution test at the time of product development is encouraged. Once developed, dissolution testing is a valuable tool in validating changes to the product post-Listing.

The results of dissolution testing from stability studies should be used in setting the dissolution limits for expiry. Note that the inclusion of a dissolution test in the finished product specifications means that the product must meet the limits throughout its shelf life, but it does not necessarily mean that every batch must be tested at release.

Modified release products should include dissolution testing data in the finished product specification. If sponsors wish to employ a non-pharmacopoeial dissolution test, a justification for the proposed test and limit should be available.

5.2.7.6 Products containing herbal substances and ingredients derived from herbal substances

For additional guidance on herbal ingredients, see *ARGCM Part IV – General Guidance, Herbal Ingredients – Quality*.

5.2.7.7 Analytical procedures and validation

Complete validation data are not required for methods described in a TGA recognised monograph or standard. However, data must be available to show there is no excipient interference and the equipment used must be suitable for the purpose.

Details should be available for all analytical methods used in the specifications, together with validation data that demonstrate (among other things) accuracy, precision, specificity (e.g. freedom from interference by excipients, degradation products and other likely impurities), and linearity.

Guidance on validating analytical test methods can be found in Analytical procedure validation for complementary medicines.

5.2.7.8 Justification of finished product specifications

The suitability of the tests, limits and test methods for the finished product should include reference to the results of the method validation studies and the ability of the specifications to guarantee the quality and consistency of the finished product. A detailed commentary or justification for any unusual features in the finished-product specifications should be detailed.

The limits applied at batch release should be available and justified in terms of their ability to ensure that the product will remain within the expiry specification throughout the product shelf

life. For example, if the batch release and expiry limits for assay are identical, the implication is that there will be no loss of the active ingredient throughout the shelf life. Any changes or unusual variability in the results obtained in the stability studies require justification in this respect.

The reasons for proposed range(s) in the quantities of any ingredients should be justified. Validation data should be provided in support of any unusually wide range(s).

5.2.8 Batch certificates of analysis

The sponsor must have available at least two certificates of analysis for the final product, to demonstrate compliance with batch release specifications. These certificates should relate to one or more production batches of the medicine or to trial batches if production batches have not been manufactured. In this case, the sponsor should identify any differences between the batch and proposed production manufacturing processes, and undertake to provide certificates of analysis for at least two production batches after Registration has been achieved. ARGCM Part IV includes a guideline on certificates of analysis.

5.2.9 Container

A description of the container and closure system should be available, including the materials used. The suitability of the container should be justified in terms of its compatibility with the product and its capacity to protect the product from mechanical damage, moisture and light.

In the case of commonly used types of pharmaceutical package, it may be sufficient to simply describe the packaging. If the packaging material is unusual, then detailed information should be provided on the composition of the material, together with an assessment of the potential for undesirable material to be leached from the packaging into the medicine.

5.2.9.1 Child-resistant closures

The TGO 80 – *Child-Resistant Packaging Requirements for Medicines* (TGO 80) was gazetted on 1 September 2010.

This order broadens the scope of application of standards for child-resistant packaging from medicines containing only certain specified substances, as given in *Therapeutic Goods Order No. 80 Child-Resistant Packaging Requirements for Medicines* (TGO 80). The application now covers medicines and other therapeutic goods containing any of the substances specified in the First Schedule to the Order, as well as other therapeutic goods which imply, through their presentation, that the packaging is child-resistant.

This means that, while the use of child-resistant packaging is not mandatory unless the goods contains a substance specified in the First Schedule, if the goods are presented in a way that could cause consumers reasonably to believe the packaging is child-resistant, then the provisions of this Order relating to performance standards (paragraphs 3 and 4) apply. Presentations considered to indicate child-resistant packaging include closures with the push-down and turn graphics, typically used on child-resistant caps, and label statements referring to the closure as being child-safe or designed to prevent access by children.

5.2.9.1 Tamper-evident packaging

In addition, sponsors should meet the requirements of the *Code of Practice for the Tamper-Evident Packaging (TEP) of Therapeutic Goods*. This code of practice is based on the *Guideline for the Tamper-Evident Packaging of Medicines, Complementary Healthcare Products and Medical Devices (Edition 1)*, which was developed by the therapeutic goods industry associations in cooperation with the TGA, State and Territory Health Departments and consumers, and was released in December 2000.

The document *Code of Practice for the Tamper-Evident Packaging (TEP) of Therapeutic Goods* (Edition 1, June 2003) should be used as a standard for therapeutic goods in Australia.[10]

5.2.9.3 Dose measuring device

Where the packaging includes or refers to a dose measuring device, the device should be shown to comply with the test and limits of the BP Appendix XIIL – *Uniformity of Weight (Mass) of Delivered Doses from Multi-dose Containers*. This is to ensure that the device consistently delivers an accurate amount of oral dosage forms such as granules, powders and liquids.

5.2.10 Finished product stability

The stability data for a Listed medicine held by a sponsor must be sufficient to demonstrate, or indicate with a high probability, that the product intended for market will remain safe, of consistent quality and efficacious throughout its shelf life. The stability data or justification will form the basis for setting a shelf life and recommended storage conditions for the product.

For Listed medicines it may be possible to justify the setting of a shelf life based on stability data for a similar product (see Subsection 5.2.10.7).

While sponsors may choose the format for the presentation of stability data they hold, the following headings are recommended:

- Study design;
- Test methods;
- Commentary on the results obtained in the studies for individual parameters (including any trends); and
- Conclusions and summary of claims.

The maximum shelf life permitted is five years and applies to the product in its final container.

Explanatory notes that discuss the principles of stability studies in more depth are in ARGCM Part 1, Appendix 1. Additional guidance for sponsors is also provided in *Questions & Answers on the Stability Testing of Listed Complementary Medicines*.

5.2.10.1 Products Containing Complex Active Ingredients

It is recognised that the development and implementation of a stability protocol for products containing complex herbal-based ingredients can present greater challenges than those for products containing simple chemical ingredients.

The generality of these stability testing guidelines reflects the wide range of complementary medicine substances and the TGA's preparedness to be flexible in relation to stability testing for these substances.

Additional guidance on stability testing of products containing complex herbal-based substances can be found in ARGCM Part 1, Appendix 1 *Stability of the Finished Product* and ARGCM Part IV, Herbal Ingredients – Quality.

10 Sponsors attempting to justify non-compliance with prescribed standards (e.g. BP, PH Eur, USP or TGOs) should apply to the TGA in writing, seeking an exemption under Section 14 of the Act. Section 14 exemption requests should explain why the standard(s) cannot be met and detail what alternative(s) are proposed and why. The delegate of the Secretary will review the request, and sponsors will be advised in writing of the delegate's decision.

In general, where the guidelines discussed in this subsection cannot be followed because of technical problems related to the nature of the active ingredients, this should be fully justified. The sponsor should consider the purpose of the specific guideline and how else it might be achieved. The justification should clearly explain the technical problem and any proposed alternative. Justifications for not following these stability guidelines will be considered on a case-by-case basis.

5.2.10.2 Stability testing requirements

Table 2 summarises the data and analysis that are expected to be provided to support the stated shelf life of a complementary medicine. Each of the requirements is discussed following the table.

Table 2. Summary of stability information to be held for the finished product

Critical summary	• Provided for each stability study • State the formulation, production and packaging of the product placed on stability and if it is identical to that proposed for marketing • State the conditions under which the stability data were collected • Summarise the stability results • Critically analyse the stability results[11] • Justify any deviations from the stability guidelines and address any deficiencies
Tests	• State and justify (preferably in tabulated form) the parameters tested during the stability study
Methods	• State which test methods are identical to those in the finished product expiry specifications • Give details of the test methods and validation data for test methods that are NOT identical to those in the finished product expiry specifications • Include data to demonstrate equivalent performance for test methods that were changed during the course of the stability study
Tabulated data	• Tabulated individual and summary data for batches at every test station

11 Where the data from the stability study show little or no change over time (indicating minimal degradation), with little or no variability, it may be apparent that the substance or product will remain well within acceptable criteria during the shelf life. Under these circumstances, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission is available.

Critical summary

Sponsors should have undertaken a critical analysis of the stability studies conducted. The following format is suggested, to facilitate review by the TGA.

- A table giving batch numbers, size and scale (pilot, commercial-scale), storage conditions (temperature, humidity, lighting conditions), and storage duration. If the storage conditions were not controlled, this should be stated;
- A statement whether all or some of the batches tested were identical (e.g. formulation, manufacture, extraction process of a herbal ingredient etc.) to the product intended for supply. If not, the differences should be identified and justified;
- Summary of the results observed for each of the test parameters at each set of storage conditions in the studies. Separate comments must be provided for each test parameter;
- Critical analysis of the results, with particular attention to degradation products, trends and indications that the product may fail to comply with the expiry specifications.[12] For guidance on interpreting data on stability see the EMEA document *Note for Guidance on Evaluation of Stability Data* (CPMP/ICH/420/02);
- Any deficiencies should be addressed and justified and any deviations from the stability protocol or these guidelines should be justified; and
- State which test methods are identical to the expiry specifications, and provide validation data for test methods that have not been previously validated. Any change in test methods while the studies are in progress should be justified on the basis that the two methods are equivalent.

Batch Types

It is expected that the batches used in the stability study will be identical to the product intended for marketing. This includes formulation, container and other packaging, method of manufacture and equipment. A statement confirming that the stability batches are identical to the product intended for market with regard to these aspects should be included. If there are any differences between the stability and production batches, then these should be justified.

A shelf life cannot be allocated if there is no scientific justification for one.

Stability information should be generated on a minimum of two commercial-scale (production) batches of the product. All manufacturing processes should have been carried out on these batches (e.g. filtration, packaging and sterilisation). If data on production batches are not available, they should be available for pilot-scale batches manufactured using the same process as intended for commercial-scale batches.

Where the product is Listed in several strengths, stability data should be generated on two batches of each strength, unless otherwise justified. If the different strengths are a direct scale, at least one batch of each of the highest and lowest strengths should be tested.

12 Where the data from the stability study show little or no change over time (indicating minimal degradation), with little or no variability, it may be apparent that the substance or product will remain well within acceptable criteria during the shelf life. Under these circumstances, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission is available.

Storage Conditions

The storage conditions used in the stability study should be the same as the storage conditions recommended for the finished product. The storage conditions should be clearly defined and be in terms of the categories specified in the TGO for labelling of therapeutic goods (TGO 69, or as revised from time to time).

The TGA will accept stability data generated using storage conditions as outlined in the EMEA document *Guideline on Stability Testing: Stability Testing of Existing Active Substances and Related Finished Products* (CPMP/QWP/122/02, rev 1). However, the shelf life which is assigned to the product on the basis of such data should be determined according to the general principles outlined in this chapter.

The use of uncontrolled storage conditions during stability studies is undesirable. Terms such as 'room temperature' or 'warehouse conditions' are discouraged as they allow the batches to be exposed to a wide range of temperature and humidity conditions, which makes the assessment of the stability data difficult.

Tests

The parameters tested in stability studies should include relevant physicochemical and microbiological parameters such that the quality of the product can be fully assessed during storage. It is expected that the key parameters included in the expiry specifications will be tested during stability testing.

There may be some tests in the expiry specifications which it is not appropriate to include in the stability study, such as identity of the active ingredients and any other parameters that are usually tested only at batch release. It may also be the case that additional tests that are not in the expiry specifications should be included in the stability studies, such as additional tests for degradation or loss of water for liquid preparations.

It is expected that a test for the presence of degradation products, and / or change in the profile chromatogram of the active ingredient, will be included in stability testing to identify changes in the active ingredient during storage. This is a critical issue since it relates to both quality and efficacy of the product.

Methods

A list of tests used in the stability studies, indicating the method used in each case, should be available. Where a test method is included in a pharmacopoeial monograph, the pharmacopoeial reference (e.g. BP) should be given. It should be noted, however, that many pharmacopoeial assays do not include stability. Where a test method is not included in a pharmacopoeial monograph, a full copy of that method should be available.

The test methods should be stability indicating and validated. The test methods may be identical to those that were developed and validated for use in the expiry specifications. If additional tests or alternative test methods are used in the stability studies, then this should be stated and validation data for the new tests should be available.

Since stability studies are conducted over long periods, it is not uncommon for test methods to be updated or changed during the studies. If a test method is changed during the course of the stability study, this should be noted.

If the change is significant, then data should be provided to either demonstrate equivalence with the previous test method, or allow assessment of the stability from the two methods.

Guidance on validation data can be found in ARGCM Part I, Appendix 1 *Finished Product Stability* and guidance on validating analytical test methods can be found in Analytical procedure validation for complementary medicines.

Justification requirements

Both individual and summary data should be available in well-organised tables. Raw stability data are not acceptable.

Unless otherwise scientifically justified, stability data should be sufficient to justify a shelf life of at least 12 months. This requires studies in which satisfactory results have been obtained under the following duration and conditions of storage:

- 12 months storage at the recommended storage temperature or 6 months storage at the recommended storage temperature and 6 months storage at 10 degrees Celsius (ºC) or more higher than the recommended storage temperature; and
- at least 3 months storage at elevated humidity if the container is potentially moisture permeable (e.g. blister packaging).

This is the minimum amount of stability data required to justify shelf life. Stability data for longer periods could support a longer shelf life if the results are acceptable.

5.2.10.3 Additional stability tests for different product dosage forms and presentations

The following are additional tests that must be included in stability studies for specific product types. There may be other product types for which these tests are relevant, and sponsors should consider this possibility when developing a stability protocol.

Potentially water-permeable containers

Where the container or closure for a solid dosage form product is potentially water permeable, then stability data are required to demonstrate that the container adequately protects the product from moisture.

This includes containers made from polyvinyl chloride (PVC), with or without a polyvinylidene chloride (PVDC) coating, or low-density polyethylene (LDPE); but does not include bottles made from glass or high-density polyethylene (HDPE).

Satisfactory stability results when the product is stored at 25ºC and 80 per cent relative humidity (RH) or 30ºC and 75 per cent RH for 3 months are normally sufficient to establish the adequacy of the packaging to protect the product from moisture for a period of up to 2 years. Data showing stability for a period of 6 months are normally sufficient to support a shelf life of over 2 years.

Suspensions or solutions of poorly soluble ingredients

The effects of cycles of low and high temperatures, such as might be experienced over night and day, could have a significant effect on products that are suspensions or are solutions of low-solubility ingredients. In these cases, the investigation of the effects of cyclic temperature changes should be investigated and reported with the stability data.

Microbial content testing

All dosage forms of Listed medicines should include limits for microbial content in the expiry specifications, unless departure from this requirement is justified. Where justified, microbial content testing should be carried out at the end (and preferably also at the beginning) of the shelf life during stability studies to demonstrate that the product remains within product specifications until expiry. See also Subsection 5.2.7.4 – *Microbiological Requirements*.

Preservative efficacy

Products that are intended for multi-dose use should be adequately preserved for the duration of the claimed shelf life. Microbial proliferation in, or microbial contamination of, such products during their normal conditions of storage and use, must be prevented.

During product development, preservative efficacy testing should be performed at the beginning and end of the claimed shelf life, to demonstrate that the antimicrobial activity of the product as such or, if necessary, with the addition of preservatives, has not been impaired by storage. Data must be available which are specific to the formulation and the container. If the shelf life is based on data generated under accelerated conditions, preservative efficacy tests should be performed on samples that have been stored at the higher temperature.

For all multi-dose products, tests that accord with the BP / PH Eur *Efficacy of Antimicrobial Preservatives in Pharmaceutical Products* are mandatory. Chemical assays of the level of preservative are not accepted as substitutes for biological tests.

Modifications of a pharmacopoeial preservative efficacy test (preferably the BP / PH Eur test) that include a rechallenge with reduced numbers of organisms could be used.

Dissolution rate

For solid dosage forms that include a dissolution test in the specifications, the behaviour of the dissolution rate over time should be investigated during the stability study. Dissolution profiles, generated by sampling at more than one time, may provide useful additional information about possible changes to the dissolution characteristics of the formulation during storage.

5.2.10.4 Post Listing requirements

Sponsors of therapeutic goods are required to carry out an ongoing stability testing program refer to the PIC/S Guide to Good Manufacturing Practice for Medicinal Products, PE 009-8.

Where a shelf life has been allocated on the basis of:

- accelerated testing; **OR**
- data generated on a related formulation; **OR**
- data generated on the same formulation in a different container; **OR**
- data generated on batches other than production batches;
- then full stability testing should commence on at least the first two production batches and continue for the full period of the product's shelf life (at the recommended storage conditions).

The TGA may ask for review data at any time. If it is found that the testing required has not been done, or justification for not doing so has not been provided, or that adverse trends have not been reflected in the shelf life, appropriate action may be taken. This may include cancellation of the product from the ARTG.

5.2.10.5 Stability protocol for self-assessable shelf life extension

A product's shelf life may be extended on the basis of sponsor-held stability data that were obtained using a protocol suitable for assessing shelf life extensions, or can otherwise be scientifically justified. It is normally necessary to have at least 12-months data, generated at the maximum recommended storage temperature, available on at least two production batches of the proposed formulation, and in the container proposed for marketing or one that is less protective.

To provide a suitable margin of safety, the limits for results of critical test parameters should normally be a little tighter than the expiry limits. Where some results are outside these limits, the sponsor must be able to justify the wider limits.

The protocol should be available and include:

- a statement of the intended purpose (e.g. 'This protocol is intended for justification of shelf life increases of up to X years following self assessment of stability data.');
- the precise formulation of the product (if overages are included, this should be stated and a justification provided);
- the immediate container specifications;
- the storage conditions to be included on the label;
- the finished product expiry specifications and the protocol acceptance criteria (including acceptable limits for results of each test);
- a statement of the proposed tests and validated test methods should be available (refer to *ARGCM Part III - Appropriate Tests* and *ARGCM Part I Appendix 1 - Prediction of Shelf Life from Accelerated Stability Data*); and
- a matrix indicating the time stations at which each of the tests will be conducted, as well as the storage conditions to be used in the study.

5.2.10.6 Prospective extensions of shelf life for individual batches

A limited extension of shelf life for individual batches approaching their expiry date in the absence of the stability data may be justifiable under certain circumstances, namely:

- when stability data are available that validate the existing shelf life;
- a recent (less than 2 months old), dated certificate of analysis is available for the batch, showing compliance with specifications, together with the results obtained at batch release; and
- the sponsor can provide an assurance that a stability study to validate a permanent extension of the shelf life has commenced or will commence, unless the permission sought is purely intended as a one-off requirement to ensure continued supply.

Extensions of more than 6 months are not normally acceptable using this approach.

5.2.10.7 Deviations from the requirements for determining the shelf life of listed medicines

The TGA recognises the technical difficulties that may be associated with stability testing of complex multi-ingredient complementary medicines. Accordingly, the shelf life of a Listed medicine may be determined by reference to stability studies performed on similar products.

A sponsor using this option must hold evidence to justify the applicability of the data from other products. In using data from other products, stability data for the other product must be obtained using a protocol consistent with the principles elaborated in Subsection 5.2.10.

If, at the time of Listing the product on the ARTG, complete stability data are not available, the sponsor may make a judgment on an interim or abbreviated shelf life. The judgment must supportable by evidence and may be used until the results of stability testing are available.

It may not be possible to check the stability of all active ingredients in a multi-ingredient complementary medicine. In such cases, appropriate studies which force degradation (e.g. with heat) may then be used as stability indicators for the product. With adequate experience of product formulations and their stability, it may be possible to group ingredients and to selectively monitor for a smaller number of ingredients. Ideally, all those with a label claim should be monitored.

Stability of minerals

Stability studies on mineral ingredients may not be required, if such can be justified. However, organo salts of minerals, such as selenomethionine and chromium picolinate, are not as stable as inorganic salts and should be treated as labile ingredients.

Where the efficacy is believed to be associated with an element in a particular oxidation state (e.g. ferrous salts), evidence should be held to show that the element remains in this oxidation state during the shelf life of the product.

Where the efficacy is due to the other chemical characteristics of a mineral compound (e.g. calcium carbonate for use in antacids), sponsors should hold evidence to demonstrate the stability of the mineral compound throughout the shelf life of the product.

Stability of herbal ingredients

In the case of non-standardised herbal products where there is no identified active ingredient(s), it will be acceptable to monitor physical changes (e.g. appearance and disintegration time), as well as changes to the overall chromatographic profile of the product (see *ARGCM Part III - Profile Chromatograms* and ARGCM Part 1 Appendix 1 *Stability of the Finished Product*). The sponsor must decide on the significance to the quality, safety or efficacy of the product of any changes in the chromatographic profile. Generally, a 'change' to a herbal component would be one greater than 10 per cent. However, in some cases, such as epoxides in essential oils, this value will be too high. Sponsors are responsible for determining the content of their finished product specification. The specifications may be based on, but not limited to, those given in official standards (e.g. BP, PH Eur, USP and TGOs).

In the case of Listed products containing herbal ingredients that make a label claim for a standardised component, it is necessary to monitor the component throughout the stability trial. A change of more than 10 per cent in the standard component should not be tolerated. In addition, the chromatographic profile and any other tests should be monitored (as per non-standardised herbal products above).

Chromatographic procedures must be fully validated to cover the possibility that any changes in chromatographic results are not due to system variations. However, changes in, for example, equipment performance and high-performance liquid chromatography (HPLC) column characteristics can still occur and, for this reason, it would be advisable to store a sample of the product under conditions that will minimise degradation (e.g. in a refrigerator), and use this as a reference at the different time stations during the trial. Where thin-layer chromatography (TLC) is used, it may be possible to collect and store a digital image of the chromatographic plate at the start of the trial and use this as a reference throughout the remainder of the trial. The TLC procedure should be fully validated to ensure consistency between time stations.

In undertaking these studies, a minimum of two production batches should be used. Pilot-scale batches can be substituted as an interim measure. Full-term data at the nominated storage temperature should be collected. Accelerated stability testing is acceptable.

6. Safety and efficacy

The subsections in this section are:

6.1 Safety

6.1.1 Introduction

Listed medicines are low-risk medicines. They may contain only ingredients that have been assessed by the Therapeutic Goods Administration (TGA) to be of low risk, they must be manufactured by licensed manufacturers in accordance with the principles of good manufacturing practice (GMP) and they may carry indications only for health maintenance and health enhancement or certain indications for non-serious, self-limiting conditions. Listed medicines may not refer to serious forms of disease, disorders or conditions and, generally, must not indicate that they are for treatment, cure, management or prevention of disease, disorders or conditions. Details for assessing the suitability of ingredients for use in Listed medicines are described in *ARGCM Part III – Safety*.

Once established as being of low risk, most Listed complementary medicine need no further controls on their use. However, where risks or potential risks are found to be associated with the use or uses of a particular complementary medicine substance (for example, in its use by particular population subgroups, such as children or pregnant women, or in its interactions with other medicines), certain restrictions and / or controls may be imposed to manage the risk, to ensure that the use of the substance and product is consistent with low risk. Such options include: the use of label advisory information; restrictions on dosage, route of administration, plant part or plant preparation; and / or restriction of the form in which the substance can be presented.

Sponsors should ensure that they are fully aware of any condition or restriction affecting the use of ingredients in their products so that the product fully complies with all legislative requirements applicable in Australia.

6.1.2 Ingredients of animal and human origin

There are a number of ingredients derived from either animal or human materials that are approved for use in Listed medicines. These ingredients present a safety risk to consumers, as they might contain certain viruses and / or agents capable of transmitting Transmissible Spongiform Encephalopathies (TSEs).

To minimise the potential risks posed by these ingredients, sponsors of Listed medicines may be required to seek pre-clearance from the TGA before their use.

Detailed information about the clearance of products containing ingredients of animal or human origin is included in ARGCM Part IV – Ingredients of Animal and Human Origin.

6.1.3 Pre-clearance application for animal-derived ingredients

When entering information into the Electronic Listing Facility Version 3 (ELF 3) about ingredients derived from animals or humans, sponsors will be required to give the animal species, country of origin, animal part and animal preparation. Depending on the information entered, sponsors may be required to enter a Therapeutic Goods Administration Laboratories (TGAL) pre-clearance number.

A form has been developed to assist users of ELF 3 seeking pre-clearance for animal-derived ingredients. The form, which explains what the TGA is looking for and what supporting documents need to be provided, is available at <http://www.tga.gov.au/industry/cm-forms-animal-derived-ingredients.htm>.

6.2 Efficacy

This section provides guidance to sponsors about the requirement for sponsors of Listed complementary medicines to hold appropriate evidence to substantiate all indications and claims made about their products.

This subsection is divided into the following further subsections:

6.2.1 Introduction

Consistent with their low risk, Listed complementary medicines may carry only certain indications and claims for the symptomatic relief of conditions (other than serious disease, disorders, or conditions), health maintenance, health enhancement and risk reduction in the context of healthy individuals (see Table 3)(Refer to section 2.1 and subsection 6.1.1 for further information on acceptable indications).

Table 3.

Summary of indications and claims permitted for Listed complementary medicines
Health maintenance in the context of healthy individuals
Health enhancement in the context of healthy individuals
Nutritional support
Symptomatic relief of non-serious diseases, disorders and conditions
May aid or assist in the management of non-serious diseases, disorders and conditions
Reduction in the risk of a particular non-serious disease, disorder, condition, symptom or ailment

The *Therapeutic Goods Act 1989* (the Act) requires that, at the time of Listing, sponsors must certify that they hold the evidence to support indications and claims made in relation to Listable goods. The indications / claims on Listed medicines are not subject to pre-market evaluation at the time of Listing. The evidence held by sponsors must be sufficient to substantiate that the indications and claims are true, valid and not misleading.

6.2.2 Guidelines for levels and kinds of evidence to support indications and claims

In order to facilitate compliance with the requirement to hold appropriate evidence to support particular indications, the TGA and the then Complementary Medicines Evaluation Committee (the precursor to the Advisory Committee on Complementary Medicines) developed guidelines to assist sponsors in determining the appropriate evidence to support indications and claims made in

relation to Listed medicines (*Guidelines for Levels and Kinds of Evidence to Support Indications and Claims*. In particular, the Levels of Evidence Guidelines relate to Listable complementary medicines, sunscreens and other Listable medicines.

Indications and claims can be based on evidence of traditional use of a substance or product, and / or on scientific evidence. Indications / claims and evidence are categorised as being 'general', 'medium' or 'high' level.

Listed medicines may contain only general or medium-level indications (see Table 4). Should a sponsor wish to make a high-level claim for their product, then the product will be required to undergo full evaluation for Registration by the TGA for quality, safety and efficacy. For further information about the requirements for product Registration refer to Part I of the ARGCM.

The three principles relating to indications and claims about therapeutic goods are:

1. before claiming an intended use or indication, sponsors must hold adequate evidence to support all claims they make about a product;
2. claims must be true, valid, and not misleading; and
3. claims should not lead to unsafe or inappropriate use of a product.

There are two types of evidence that may be used to support claims. These are:

- evidence based on traditional use of a substance or product; and
- scientific evidence.

Indications using evidence based on traditional use must clearly this within the claim to differentiate them from indications based on scientific evidence.

As an example of the type of evidence that must be held by a sponsor at the time of Listing a medicine on the ARTG, Table 4 outlines the minimum level of scientific evidence required for medium and general level indications. High-level evidence may also be used to support medium and general-level claims.

Table 4. Levels of scientific evidence required to support indications and claims for Listed medicines

Level	Type of evidence
Medium	Evidence obtained from well-designed, controlled trials without randomisation. In the case of a homoeopathic preparation, evidence from well-designed, controlled homoeopathic proving; **OR** Evidence obtained from well-designed analytical studies, preferably from more than one centre or research group, and including epidemiological cohort and case-control studies; **OR** Evidence obtained from multiple time series with or without intervention, including within-country and between-country population studies. **NOTE**: In practice, the sources of most medium-level evidence will be peer-reviewed published papers and evidence-based reference texts. However, other evidence that meets the requirements, including independently reviewed unpublished evidence, may also be acceptable. Websites evaluating peer-reviewed published evidence may be a source of suitable evidence.
General	Descriptive studies, case series or reports of relevant expert committees. Texts, such as TGA-approved pharmacopoeias or monographs, or other evidence-based reference texts, may be included in this level.

Supporting evidence: Evidence derived from non-human data, such as *in vitro* studies and animal studies, and non-clinical studies such as biochemical, nutritional and microbiological studies, does not stand alone and may be used only as supporting evidence.

Sponsors may wish to look at the Oxford University Centre for Evidence-Based Medicine website for further explanation of the terminology used to decide the types of scientific evidence.

6.2.3 Post-Market Requirements – Efficacy

At the time of Listing, sponsors of Listed medicines certify under Section 26A(2) of the Act that they hold information or evidence to support any claim that they make about the medicine. As such, this evidence can be sought for review by the TGA at any time following medicine Listing.

The Listing Compliance Section of the Office of Complementary Medicines may include reviews of efficacy information held by sponsors as part of its random and targeted post market monitoring activities, as well as in response to either product safety concerns or as a result of a complaint about a product.

If claim about a Listed medicine is made at the time of listing, the goods are subject to the conditions set out in Section 28(6) of the Act as follows:

- that when the sponsor listed the medicine they had information or evidence that supported the claim and that the information or evidence complied with the requirements of any regulations that stipulate the amount, standard or type of information or evidence required;
- that the sponsor must retain the information or evidence at all times while the goods remain listed; and
- that the sponsor must give the information or evidence to the TGA is the TGA asks for it.

7. Labelling and presentation

This section provides guidance to sponsors about the legislative requirements for labelling Listed complementary medicines, together with other guidance to help ensure the presentation of their Listed medicines is acceptable.

Product labels are not to be submitted to the Therapeutic Goods Administration (TGA) at the time of Listing. There are no provisions for product labels to be included with applications submitted *via* the Electronic Listing Facility Version 3 (ELF 3). The Listing Compliance Section within the Office of Complementary Medicines (OCM) includes reviews of product labels as part of both its random and targeted reviews. For further information about the random and targeted reviews undertaken, sponsors are referred to Section 9 of this part of the Guidelines.

This section is divided into the following subsections:

7.1 Labelling

This section provides general guidance to sponsors about the labelling requirements of Listed complementary medicines.

A product's 'label' includes the label attached to the container (e.g. bottle, tube or blister pack), the primary pack (e.g. carton) and any printed information supplied with the container or primary pack (e.g. package insert). A 'label' is defined in the *Therapeutic Goods Act 1989* (the Act) as follows:

Label, in relation to therapeutic goods, means a display of printed information:

a. on or attached to the goods; or
b. on or attached to a container or primary pack in which the goods are supplied; or
c. supplied with such a container or pack.

The Therapeutic Goods Order No. 69 – General requirements for labels for medicines (TGO 69) defines a 'label' as follows:

> ***'label'** means a display of printed information upon, or securely affixed to, the container and any primary pack containing the goods*

Labelling is expected to comply with the requirements of:

- TGO 69 and TGO 69C – TGA labelling orders;
- the *Therapeutic Goods Regulations 1990* (the Regulations) – relating to restricted or prohibited representations;
- the *Therapeutic Goods Advertising Code*;
- the *Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP)* labelling requirements; and
- any labelling requirements specified in the *Required Advisory Statements for Medicine Labels* (RASML).

TGO 69 stipulates a number of labelling requirements, including but not limited to:

- the use of the English language and metric units on labels;
- the use of Australian Approved Names (AANs);
- the excipients that must be declared on labels;
- the requirements for print size, statement of active ingredients, batch numbers, expiry dates, name and address of sponsor, dosage form, directions for use;
- definitions of terms such as 'container' and 'main label';
- some exemptions for small containers and for individually wrapped goods;
- some particular labelling requirements for homoeopathic medicines; and
- the expression of quantities of ingredients in labels, with particular requirements for herbal medicines.

There are also labelling requirements established under the SUSMP. If a medicine contains a scheduled substance, then there are additional labelling requirements established under poisons legislation. As there are slight variations from State to State in the way in which they have adopted requirements identified under the SUSMP, sponsors should contact for advice the Health Department in the State or Territory where their product will be supplied.

While general guidance is provided in these guidelines, sponsors should also note the policy guidelines for specific product categories and substances in **ARGCM Part V**.

A label checklist is included on the home page of the ELF 3 system. Sponsors should be completely satisfied that their product label complies with all of the requirements of this checklist and that the label text is expressed clearly, accurately and concisely.

7.1.1 Statement of ingredients

TGO 69 requires that labels contain the name and quantity of all active ingredients, the name and quantity of any preservative in a topical product and the names of certain excipients specified in the Order (refer to TGO 69 for details).

If sponsors wish to include in a label details of other ingredients, the following considerations apply:

- There is no objection to a quantitative statement of all ingredients in the product (actives and excipients) or a quantitative statement of the actives and a qualitative statement of the excipients;
- The selective disclosure of individual excipients will not generally be accepted since this might be interpreted as implying that the excipient has a therapeutic activity. Labels that disclose only some excipients must be accompanied by a justification for doing so that addresses this issue;
- There is no objection to the disclosure of excipients known to cause adverse effects in some individuals (in many cases this is required by TGO 69) or to a statement that the product does not contain an excipient known to cause adverse effects in some individuals (e.g. gluten); and
- Selective disclosure of excipients that do not need to be disclosed under TGO 69 will need to be justified, e.g. flavours, colours. The selective disclosure of individual excipients will not be accepted if this could imply that the excipient may have a therapeutic activity, but is acceptable where it does not, e.g. cosmetic components in a sunscreen.

7.1.2 Directions for use and dosage

Directions for use must clearly identify the dose for each target population for which the product is intended (e.g. *'adults: two tablets twice daily; children 6 to 12 years: one tablet twice daily'*). If the product is not intended for use in children, the label should specify that the dose is an *adult* dose (e.g. "*adult dose: 10 mL*').

Where the labelling gives doses for only children over a specified age, the label should include a statement such as *'Do not give to children under 12 years'* or '*Not recommended for children under 12 years'*.

TGO 69 requires that labels state the product's dose and frequency of administration. Non-specific directions such as 'as required' are generally considered inappropriate.

Labelling should recommend use of metric measuring devices to accurately measure doses. Where the recommended doses cannot be measured using a readily available metric measuring device, a suitable measuring device should be provided in the pack (refer to Subsection 5.2.9.3 – Dose Measuring Device).

For solid or semi-solid dose forms such as powders or gels, if the labelled dose corresponds to the quantity contained in one or more *level* 5 mL medicinal measuring spoons, a dosage stated that way would be acceptable (e.g. *'Adult dose: one level 5 mL medicinal measuring spoonful…').*

References to culinary 'spoonful' (e.g. teaspoon, dessertspoon, tablespoon etc.) will not be accepted under any circumstances.

Sponsors should note that some indications require mandatory warning statements on the label, even though the dosage instructions state that the product is for use in adults. For example, products with the indication 'relief of the symptoms of colds' require two warnings to be included on the label, in addition to directions for use:

- 'If symptoms persist consult your healthcare practitioner' (or words to that effect); and
- 'Adults only' **OR** 'Not to be used in children under two years of age without medical advice' (or words to that effect).

7.1.3 Distinctiveness of labels

To reduce the possibility of confusion among consumers, the name and presentation of new products should be such that they are clearly distinguishable from existing products.

7.1.4 Reference to other products

Reference in labelling to a sponsor's other products may be permitted, provided that the other products are included in the Australian Register of Therapeutic Goods (ARTG) or specifically exempt or excluded from the requirement to be included in the ARTG.

7.1.5 Logos and symbols

Non-corporate logos or symbols on labels should be appropriate for the claimed therapeutic use of the product in the population group for which it is intended (e.g. an illustration of an infant would be inappropriate for a product with a dose range starting at 2 years).

7.1.6 Sugars in medicinal products

Inclusion of a statement that the product contains no sugar is acceptable provided sucrose, glucose, fructose and other sugars with a cariogenic potential or the potential to affect diabetics are not included in the formulation.

If the formulation includes a proprietary ingredient (PI), sponsors must check with the manufacturer of the ingredient that it does not contain such a sugar. In addition, the formulation of

the active ingredient(s) (in addition to excipients) should be carefully examined to ensure that carriers etc. do not contain sugars with a cariogenic potential.

7.1.7 Negative disclosure statements

A product label may include a statement that the product does not contain a substance known to cause adverse effects in some individuals (e.g. 'gluten free', 'alcohol free') provided the statement is true.

If the label includes a negative disclosure statement, sponsors should ensure that the substance is not contained in any ingredient in the product formulation.

For products containing PIs, sponsors must check with the manufacturer of the ingredient to ensure the integrity of the negative disclosure statement.

7.1.8 Language on labels

The information on the labels should be written in clear and easily understood English.

Text in languages other than English may be included on labels, provided that all mandatory information required to appear on the label is in English. A certified declaration may be required, during a post market review of the product, to confirm that the meaning in the other language text is the same as that given in the English text.

7.1.9 Internet addresses

Sponsors who wish to include Internet addresses on labelling should only do so provided they can ensure that the information about the product included on the website (including any direct links from that website) is consistent with the information included on the ARTG for that product.

Websites promoting use or supply of therapeutic products, although they do not require approval, have always been considered to fall within the definition of advertising and so must comply with all aspects of the Therapeutic Goods Advertising Code (TGAC). Thus, it could be argued that any labelling reviewed as part of post market surveillance that includes a website address could result in that website being reviewed for compliance to the TGAC.

7.2 Unacceptable presentation

Products are ineligible for Listing in the ARTG if 'the presentation of the goods is unacceptable'. An explanation of what constitutes 'unacceptable presentation' may be found in the Act. For the purposes of the Act, the presentation of therapeutic goods is unacceptable if it could mislead or confuse as to the content or proper use of the goods. Without limiting the previous words in this subsection, the presentation of therapeutic goods is unacceptable:

- if it states or suggests that the goods have ingredients, components or characteristics that they do not have; **OR**
- if a name applied to the goods is the same as the name applied to other therapeutic goods that are supplied in Australia where those other goods contain additional or different therapeutically active ingredients; **OR**
- if the label of the goods does not declare the presence of a therapeutically active ingredient; **OR**
- if a form of presentation of the goods may lead to unsafe use of the goods or suggests a purpose that is not in accordance with conditions applicable to the supply of the goods in Australia; **OR**
- in certain prescribed cases. Currently, Regulation 3A prescribes that any labelling, packaging or presentation of therapeutic goods (including novelty dosage forms in the shapes of animals, robots, cartoon characters or other similar objects) that is likely to result in those goods being mistaken for, or confused with, confectionery or toys is unacceptable.

It is important to note that, before a decision can be made about presentation, all aspects of the product must be considered; name, indications, directions for use, packaging, dosage form, pictorials etc.

Selected examples (not an exhaustive list) of unacceptable presentation are given below:

- The same name is proposed for a reformulated product, without labelling that adequately informs the consumer that it has different active ingredients from the product previously supplied under that name;

As a general guideline, label flashes such as 'New Formulation' or 'Now with / without…' should not be used to describe any product, presentation or therapeutic indication / claim which has been available and generally promoted in Australia for more than 12 months.

- The appropriate dosage for all age-groups in the likely target population is not stated (e.g. adults, children 6-12 years etc., as appropriate);
- Warning or cautionary statements needed for proper usage of the product are omitted;
- Claims are made that a formulation is 'hypo-allergenic' or 'non-irritant', unless the sponsor holds confirmatory evidence from clinical tests that can be produced on request;
- Claims are made that a product is 'free from artificial colours' if not completely accurate. In this context, sponsors need to take careful account of substances such as sugars and colouring agents that may be present in PIs;
- Therapeutically active ingredients are present in the formulation but not declared as such on the label (and / or misleadingly declared as 'excipients' in the application);
- Statements are made attributing a therapeutic role to ingredients not declared as active ingredients;
- Statements or pictures suggest that the product has uses or actions different from, or in addition to, the approved indications for use;
- Presentation of a product is in a form likely to result in its being confused with food or confectionery (e.g. in confectionery-like novelty shapes and packaging); and
- Product names are used that are likely to be misleading as to the composition of the formulation.

7.3 Ingredient names on labels

The TGA has developed and maintains lists of Australian Approved Terminology for medicines, to ensure accuracy and consistency in the information compiled in ARTG. These lists are published in the *TGA Approved Terminology for Medicines*. The lists outline the terminology names for ingredients (active and excipient), containers, dosage forms, routes of administration and units of expression and proportion.

Australian Approved Terminology has been developed by the TGA because there is currently no single internationally agreed list or primary reference available that comprehensively covers all substances or terms used, or likely to be used, in therapeutic goods in Australia.

Australian approved terminology should be used for all information on the labels.
Complete details relating to the terminology for medicines is provided in the *TGA Approved Terminology for Medicines* on the TGA website.

Sponsors and other users of the *TGA Approved Terminology for Medicines* should note the following:

- Inclusion of a substance in the *TGA Approved Terminology for Medicines* does not mean that the substance has been approved for use in Listed medicines, or that the substance has been previously included in a medicine in the ARTG. The *TGA Approved Terminology for Medicines* is the source of the Australian Approved Name (AAN);
- Herbal substances are generally named by identifying the herb species, the plant part(s) and the preparation, using approved terminology (AANs);
- The citation of an authority or reference for a name in the list does not imply that the standard specified by that authority is applicable to the substance used in a particular medicine; and
- The lists of substances included in the *TGA Approved Terminology for Medicines* are not lists of ingredients found in products currently included in the ARTG.

If there is no AAN for an ingredient, then the ingredient is more than likely not currently available for use in Listed medicines. Therefore, the substance must be evaluated and approved for use in Listed medicines, or the product must undergo evaluation for Registration (see *ARGCM Part IV, Naming of New Substances and Terminology* for details).

Sponsors wishing to have the product evaluated for Registration on the ARTG are referred to Part I of the Guidelines, *Registration of Complementary Medicines*. Sponsors who wish to have substances evaluated for use in Listed medicines are referred to Part III of the Guidelines, *Evaluation of Complementary Medicine Substances.*

8. Post market review

This section provides information to sponsors concerning the activities of the Listing Compliance Section of the Office of Complementary Medicines (OCM). The section undertakes random and targeted reviews of Listed complementary medicines supplied in Australia.

The section is divided into the following subsections:

8.1 Background

The regulation of complementary medicines in Australia allows for early market access for low-risk complementary medicines through the Therapeutic Goods Administration's (TGA's) Listed medicine system. In facilitating early market access, there is reliance on a comprehensive risk-based system for the post market monitoring of Listed complementary medicines.

The objectives of the post market program in the TGA for complementary medicines are to:

- provide assurance of the safety of complementary medicines through a risk-based program of post market monitoring and surveillance;
- provide consumer confidence in the safety and quality of complementary medicines; and
- ensure industry compliance with regulatory standards and guidelines for complementary medicines.

The measures required to meet the objectives include:

- targeted and random desk-based audits of Listed medicines;
- monitoring of suspected adverse reactions;
- targeted and random laboratory testing of medicines and ingredients;
- targeted and random surveillance in the market place;
- an effective, responsive and timely recalls procedure;
- audit of Good Manufacturing Practice (GMP);
- an effective co-regulatory approach to control advertising; and

- These measures provide timely identification and appropriate regulatory responses to problems associated with the formulation, manufacture, labelling and advertising of medicines.

8.2 Listing Compliance Section of the Office of Complementary Medicines

The Listing Compliance Section (LCS) operates in the following functional areas:

- monitoring of medicines Listed on the ARTG through the Electronic Listing Facility Version 3 (ELF 3);
- investigation of medicines where a potential problem has been identified;
- safety and efficacy reviews;
- regulatory action; and
- administration and business processes.

8.2.1 Post-market monitoring of ELF 3

Following Listing of medicines on the ARTG, a proportion of them will undergo a random or targeted, desk-based post market review. Reviews are performed at one or other of three levels. The information required for review at each level will include, **but not be restricted** to:

- Level 1 Review

Information available on ELF 3 to be reviewed:

  - claims and indications;
  - ingredients;
  - current GMP certification for nominated manufacturers; and
  - sponsor self-certification and Office of Scientific Evaluation (OSE) pre-clearance documentation for ingredients of animal origin.

The following information may need to be supplied by the sponsor, under the provisions of Section 31(2) of the *Therapeutic Goods Act 1989* (the Act), within the time period stated in the Section 31 letter:

  - a summary of the types of evidence that support the indications claimed for the medicine (bibliography);
  - the claimed shelf life of the medicine;
  - specifications for the final medicine; and
  - a draft label.

Furthermore, the sponsor may be asked to supply the following information within a nominated period after the release for sale of a batch of the medicine:

  - certificates of analysis for the final product; and
  - the final label.

- Level 2 Review

Following the Level 1 review of medicines on the ARTG, a proportion of these medicines will undergo further, targeted review. The following information may need to be supplied by the sponsor:

  - selected manufacturing batch records;
  - planned stability program or existing stability data; and
  - promotion and advertising material.

- Level 3 Review

Following the Level 2 review of medicines on the ARTG, a proportion of these medicines will be required to undergo further, targeted review. The following information may need to be supplied by the sponsor:

  - samples of the medicine for testing; and
  - evidence held to support efficacy (including copies of all reference papers).

It should be noted that targeted reviews undertaken by the LCS may not necessarily follow the cascading steps outlined above. That is, a Level 3 targeted review may be initiated for a product without a Level 1 or 2 review having been made.

8.3 Medicine investigation

The LCS investigates the quality and safety, as well as the efficacy, of individual batches of medicines following adverse events and complaints about specific medicines. Problem reports and complaints about complementary medicines come to the LCS from a number of areas within the TGA, as well as directly from consumers and industry.

8.4 Specific safety and efficacy reviews

Further to the medicine investigation and the ELF 3 monitoring described above, the LCS carries out specific safety and efficacy reviews for:

- substances;
- individual medicines; and
- medicine groups.

8.5 Regulatory action

The LCS carries out the regulatory actions needed to implement ELF 3 monitoring, medicine investigation and safety / efficacy reviews. Typically, these actions include:

- Section 28 notices (additional conditions);
- Section 30 notices (cancellations and proposals to cancel);
- Section 30EA (recalls);
- Section 31 notices (submit information); and
- changes to the Therapeutic Goods Regulations 1990.

8.6 Laboratory testing program

The laboratory testing program complements the desk-based audit of Listed medicines and evaluation of Registered medicines, as well as other post market regulatory activities. However, laboratory testing is both resource and time-intensive and there is therefore a limit to the number and range of analyses that can be conducted. This necessitates a testing program that targets medicines likely to carry higher risk. The testing program involves the selection of both random and targeted samples for analysis. Further, testing includes samples at both market entry (i.e. at time of Listing / Registration) and at any time during a product's shelf life, especially following a problem report. A risk-based approach guides all aspects of the laboratory program.

The sampling program is directed by considerations such as:

- the variability inherent in the manufacturing and quality control procedures;
- advice from the GMP auditors following audits of individual manufacturers to determine compliance with the Code of Good Manufacturing Practice;
- investigation of complaints from consumers and practitioners about medicine performance;
- conduct of surveys to follow up literature reports of problems in other countries;
- repeat testing of medicines with a history of poor compliance with standards; and
- development and / or availability of improved methods of analysis.

Laboratory testing is carried out to determine:

- a quantitative and qualitative characterisation of ingredients (including active and excipient ingredients);
- ingredient release profiles;
- levels of impurities and degradation products;
- the presence of heavy metals, residues, and contaminants, including microbiological contaminants; and
- adulteration by prescription and / or other restricted substances.

8.7 Good Manufacturing Practice (GMP) audits

Manufacturers of therapeutic goods in Australia are subject to regular inspections by the TGA's Office of Manufacturing Quality. Details of requirements for manufacture are specified in the *PIC/S Guide for Good Manufacturing Practice for Medicinal Products*.

8.8 The Regulatory Compliance Unit

The TGA's Regulatory Compliance Unit investigates breaches of the therapeutic goods legislation and coordinates prosecutions.

8.9 Problem reporting and recall

8.9.1 Recalls

Recalls of therapeutic goods are coordinated by the TGA's Recalls Section. Information can be obtained at <http://www.tga.gov.au/safety/problem.htm>.

8.9.2 Adverse reaction reporting

The Act requires sponsors of medicines Registered or Listed in Australia to report adverse reactions about which they become aware:

Notification of adverse effects etc. of goods

1. As soon as a person in relation to whom therapeutic goods are Registered or Listed becomes aware of information of a kind mentioned in subsection (2) relating to the goods, the person must give the information to the Secretary* in writing.

   Maximum penalty: 400 penalty units.

2. The information with which subsection (1) is concerned is information of the following kinds:

   a. information that contradicts information already furnished by the person under this Act;
   b. information that indicates that the use of the goods in accordance with the recommendations for their use may have an unintended harmful effect;
   c. information that indicates that the goods, when used in accordance with the recommendations for their use, may not be as effective as the application for Registration or Listing of the goods or information already furnished by the person under this Act suggests; and
   d. information that indicates that the quality, safety or efficacy of the goods is unacceptable.

* See Section 10.1.3 to these Guidelines for further information regarding reporting methods.

A pharmacovigilance guideline for prescription medicines in Australia was introduced by the TGA on 1 July 2002. The pharmacovigilance requirements for other Registered and Listed medicines are currently under review.

Until such time as pharmacovigilance requirements specific to complementary medicines are published, sponsors should make reference to the *Australian Pharmacovigilance Guideline*.

The pharmacovigilance guideline advises that sponsors are expected to validate and follow-up all serious reactions reported by them to the TGA.

Notification of adverse effects etc. of goods

In order to meet the expedited reporting time frames, sponsors may submit an initial report containing at least the minimum data required (see Section 2.3 and Annex 1) and submit a follow-up report containing more detailed information. All clinical information that becomes available to the sponsor as a result of follow-up activities should be provided.

Serious adverse reaction

This includes an adverse reaction that falls into one or more of the following categories:

- Fatal;
- Life-threatening;
- Results in persistent or significant disability / incapacity; and/or
- Results in or prolongs hospitalisation.

This also includes congenital anomalies / birth defects and serious adverse clinical consequences associated with use outside the terms of the approved Product

Information (PI) (including, for example, prescribed doses higher than those recommended), overdoses or abuse. Medical judgment should be exercised in deciding whether a reaction is serious in other situations. Important adverse reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the patient should be considered as serious.

Spontaneous report or spontaneous notification

A communication to a company, regulatory authority or other organisation that describes an adverse reaction in a patient given one or more medicines and which does not derive from a study.

Unexpected adverse reaction

This is an adverse reaction that is not specifically included as a suspected adverse effect in the approved Product Information (PI). This includes any adverse reaction whose nature, severity or outcome is inconsistent with the information in the PI. It also includes class-related reactions which are mentioned in the PI but which are not specifically described as occurring with this product and adverse reactions which are included in the approved PI but are described as not having an established causal relationship to the product.

Further enquiries about the reporting of adverse drug reactions should be directed to the TGA's Office of Product Review by email to <adr.reports@tga.gov.au> or by phone on 1800 044 114.

9. Product changes

Following the inclusion of a product as a Listed medicine in the Australian Register of Therapeutic Goods (ARTG), sponsors may wish to change details previously advised to the Therapeutic Goods Administration (TGA). Factors such as product stability, changes in manufacturer and developing marketing strategies may require amendment of product details entered at the time of the product's inclusion in the ARTG. This guidance has been developed to provide assistance to sponsors so that they are able to determine if a change to their ARTG entry for a particular product is needed and the regulatory impact that making certain changes to currently Listed products may have.

This guidance applies only to medicines Listed in the ARTG for supply in Australia. It does not apply to Registered medicines or medicines Listed in the ARTG for export only.

All changes that need to be made to existing Listed complementary medicines are to be undertaken via the Electronic Listing Facility Version 3 (ELF 3) system. See Section 4 to this Guideline for further information about ELF 3.

When a change to the product record is made, upon validation ELF 3 recognises the type of change made according to the categories described in the Changes Tables (see *Guidance on Product Changes in ELF 3*). These changes have been determined by the legislative requirements of the *Therapeutic Goods Act 1989* (the Act), the *Therapeutic Goods Regulations 1990* (the Regulations) and the Therapeutic Goods (Groups) Order No. 1 of 2001 (the Groups Order).

When several changes are made to a product, the ELF 3 system applies hierarchical logic to the application. For example, if a change that is considered a Grouping change is made at the same time as a change that is considered a Variation change, then the ELF 3 system will assign the type of change as a Grouping, with the appropriate fee needing to be paid. The hierarchy used is, in descending order, New, Grouping, Variation and ARTG.

This section is divided into the following subsections:

9.1 About this guidance

While this guidance gives summary information about the legislation, sponsors are strongly advised to refer to the Act and the Regulations for complete information on the implications for the product.

9.2 Notes for sponsors

9.2.1 Identifying 'missing' information in your ARTG product record

Sponsors of medicines Listed via previous versions of ELF, or submitted in hard copy, should note that the data model for the new ARTG is substantially different to the previous ARTG mainframe database. In addition, ELF 3 requires more information to be entered than was required with earlier versions of ELF.

Sponsors should therefore be aware that the most accurate way of determining whether further information is required, or whether mandatory information is missing against their ARTG product record, is to 'clone' their products into ELF 3 and undertake a re-validation and re-certification. Sponsors should not rely on the ARTG 'print view' to identify missing information.

9.2.2 Adding indications for 'grandfathered' products

It was not mandatory for the sponsors of Listed medicines that were 'grandfathered', to include the product indications at the time the medicines were first Listed on the ARTG.

For grandfathered products Listed without indications, the TGA has inserted the following statement into the ARTG record:

> 'This product accepted for Registration / Listing as "currently supplied" at the time of commencement of the Act. Indications held in ARTG paper records'.

Sponsors of grandfathered Listed products should be aware that updating the product indications field on the ARTG (i.e. adding an indication whether there wasn't one previously) will result in a 'grouping' change and attract a fee.

9.2.3 Single event changes

The ELF 3 system has been designed to allow sponsors to make the same changes to multiple current Listings under certain circumstances using the "Change Multiple Listings" form in ELF 3. These changes are limited to:

- product names;
- common manufacturing steps; and
- manufacturers.

Sponsors should refer to the *ELF 3 User Guide* (Appendix 1) for further information about the steps to follow to make changes in ELF 3.

Sponsors should be aware that, while they are able to make the same changes to multiple products for the changes described above, those changes that result in a separate and distinct good (under the Act), whether covered by the Groups Order or not, will attract a fee for each product.

For example, if a sponsor undertakes a product name change to several current Listings (which is covered by the Groups Order), they will be required to pay a separate grouping fee for each product, to initiate the change.

Allowing more than one product to be changed for the one fee constitutes a fee waiver (for all but the first product). While there are provisions in the Regulations to allow evaluation fee waivers and reductions for Registered medicines (in certain circumstances), the Regulations do not allow for application fee waivers or reductions for Listed medicines.

9.3 Does the change make the goods 'separate and distinct'

The Act outlines those criteria which make medicines that are Listed goods (other than export only medicines) *separate and distinct* from the present goods. These criteria include:

- different active ingredients; **OR**
- different quantities of active ingredients; **OR**
- different dosage form; **OR**
- different name; **OR**
- different indications; **OR**
- different excipients; **OR**
- different directions for use where a restricted ingredient is included and the restriction is based on the recommended dose; **OR**
- different quantities or concentrations of excipients, where the excipients are restricted ingredients.

For further information, refer to the document *Guidance on Product Changes in ELF 3*, which can be downloaded from <http://www.tga.gov.au/about/ebs-elf-product-changes.htm>.

The following definition of restricted ingredient has been included in the Regulations:

A substance is a ***restricted ingredient*** if:

a. it is an ingredient in a relevant medicine; and

b. for that medicine to be eligible for Listing, the permissible quantity or concentration of the ingredient in the medicine is restricted by operation of any of the following:

i. Schedule 4;
ii. The Poisons Standard;
iii. A condition imposed under Section 28 of the Act;
iv. A standard under Section 10 of the Act; or
v. Any other provision in the Act or the Regulations that deals with the eligibility of medicines for Listing.

A ***relevant medicine*** means a medicine that is Listed and that is not an export only medicine.

Where the Groups Order applies, the 'new' goods, although technically *separate and distinct* from the present goods, may be 'grouped' in the same ARTG entry as the existing goods. If the 'new' goods are separate and distinct and the Groups Order does **not** apply, sponsors need to submit a new application to List the goods.

9.4 Groups Order – summary

The Groups Order specifies the circumstances in which separate and distinct therapeutic goods can be 'grouped' in the same ARTG entry (i.e. under the same AUST L number).

Listed medicines for supply in Australia may be 'Grouped' in the following circumstances:

9.4.1 Name change

Goods may be grouped when the only difference between the new goods and the existing goods is the proprietary name and when the new goods are to be Listed in place of the existing goods.

9.4.2 Different export name

Goods may be grouped when the only difference between the new goods and the existing goods is the export name.

9.4.3 Different indications

Goods may be grouped when the indications are changed and the new goods are to be Listed in place of the existing goods.

9.4.4 Different directions for use

Goods may be grouped when the directions for use are changed where the medicine includes a restricted ingredient based on single or daily dose and the new goods are to be Listed in place of the existing goods.

9.4.5 Different quantity of excipient that is a restricted ingredient

Goods may be grouped when there is a change to the quantity or concentration of a restricted ingredient that is not an active ingredient and the new goods are to be Listed in place of the existing goods. See subsection 9.3 above for the definition of a restricted ingredient.

9.4.6 Removal or addition of a fragrance, flavour, printing ink or colour

Goods may be grouped when the formulation is changed by the addition or removal of a fragrance, flavour, printing ink or colouring agent and when the new goods are to be Listed in place of the existing goods.

9.4.7 Different composition of proprietary excipient

Goods may be grouped when the dosage form of the new medicine is the same as the dosage form of the existing medicine, the new medicine is to replace the existing medicine and the only difference between the existing medicine and the new medicine is a substance included in a proprietary excipient.

The following definition has been included in the Groups Order:

> *Proprietary excipient,* in relation to Listed medicines, for the purposes of subsection 16(1A) of the Act, means a fragrance, flavouring, colouring, printing ink, film coating material, empty capsule shell, preservative premix or other excipient premix, which does not contain any active ingredients, supplied to a licensed manufacturer for further use in a medicine, and the formulation of which is confidential from the sponsor.

9.5 Types of changes

The types of changes types are:

- New;
- group / grouping;
- vary / variation; and
- correction of ARTG Record.

Definitions for these terms follow.

9.5.1 New:

Requires a new product application when compared with the currently Listed product. The intended change creates a separate and distinct good, therefore a unique AUST L number will be issued. An application fee is payable.

9.5.2 Group / Grouping:

A change that is permitted under the Groups Order. Grouping is appropriate only when the goods are intended to replace the currently supplied goods. The current AUST L is maintained. An application fee is payable.

9.5.3 Vary / Variation:

A minor change to a product's details. The current AUST L number is maintained. An application fee is payable.

9.5.4 Correction of ARTG Record:

A minor change to a product's details. The current AUST L number is maintained. No application fee is payable.

9.6 Terminology used to describe the changes

The terms used to describe changes are:

- change;
- update addition;
- update deletion;
- addition; and
- deletion;

Definitions of these terms are given below.

9.6.1 Change:

Field has a value but the value has changed.

This generally applies to changes made to the product ARTG record as a result of sponsor-initiated changes related to the product (e.g. change of manufacturer or changes to indications).

9.6.2 Update addition:

Generally applies when information is entered to a mandatory field in ELF 3 when the field was previously empty.

Update addition changes are generally due to system changes (e.g. the data model changes between the new and old ARTG, and the different versions of ELF). They also provide for changes to the rules, such as the addition of mandatory warning statements (to be added as a result of a safety review). Update addition changes generally do not attract a fee.

9.6.3 Update deletion:

Deletion of information from a non-mandatory field.

9.6.4 Addition:

Addition of information to the product records e.g. addition of an ingredient or export name.

9.6.5 Deletion:

Removal of information from the product record – opposite to addition.

9.7 Changes tables

A separate document entitled *Guidance on Product Changes in ELF 3*, contains tables that include details of the types of changes, ELF references and whether or not fees are payable for the change.

This additional guidance document has been prepared for the reference of sponsors, but should not be considered an exhaustive list and will be updated by the TGA from time to time.

10 Other requirements

This section has the following subsections:

10.1 Conditions of Listing

This subsection provides guidance to sponsors about statutory and additional conditions of Listing that apply to Listed complementary medicines. Sponsors should see also Subsection 4.1.7 *Sponsor Certifications under Section 26A of the Act*.

10.1.1 Section 28 of the Therapeutic Goods Act 1989

Section 28 of the *Therapeutic Goods Act 1989* (the Act) provides legislative powers for the Secretary to impose conditions on Listed therapeutic goods. These conditions may relate to:

- the manufacture of the goods; **OR**
- the custody, use, supply, disposal or destruction of the goods; **OR**
- the keeping of records relating to the goods; **OR**
- matters dealt with in, or matters additional to matters dealt with in, standards applicable to the goods; **OR**
- such other matters relating to the goods as the Secretary thinks appropriate (e.g. testing, labelling and adverse reactions).

Conditions may be imposed at the time the medicine is Listed, or at any time after. In addition, existing conditions may be varied or removed. Failure to comply with a condition of Listing may result in the cancellation of the Listed medicine. If a therapeutic good is Listed in relation to a person, it is illegal for that person to engage in conduct that breaches a condition of the Listing for that therapeutic good.

Sponsors are advised in writing of any conditions of Listing and may appeal against the imposition of any of them. There is, however, a time limit for an appeal and this interval, together with details of the process for an appeal, is advised in the letter from the Therapeutic Goods Administration (TGA) imposing the conditions.

The imposition or variation of a condition will take effect:

- on the day on which the notice is given, if the notice states that the action is necessary to prevent imminent risk of death, serious illness or serious injury; **OR**
- in any other case, on the day specified in the notice, which will be a day not earlier than 28 days after the notice is given.

10.1.2 Statutory conditions of Listing

There are a number of statutory conditions of Listing that automatically apply from the day the medicine is Listed on the Australian Register of Therapeutic Goods (ARTG).

As these are statutory conditions of Listing included in the Act their imposition cannot be challenged by sponsors.

Listed therapeutic goods are subject to the following statutory conditions:

The person in relation to whom the goods are Listed will:

- allow an authorised person:
  - to enter, at any reasonable time, premises at which the person deals with the goods; and
  - while on those premises, to inspect those premises and therapeutic goods at those premises and to take samples of goods of that kind.
- if requested to do so by an authorised person, produce to the person such documents relating to the goods as the person requires and allow the person to copy the documents.

Listed medicines are subject to a condition that the person in relation to whom the medicine is Listed will deliver a reasonable number of samples of the medicine if asked to do so by the TGA. The request will specify a time by which the samples are to be provided. This will not be less than 10 working days after the request.

If a claim is made by a sponsor in relation to a product and the claim is included in the ARTG, then the Listing of the product is subject to the following conditions:

- a condition that the sponsor of the goods had, at the time when the claim was made, information or evidence that supported the claim and complied with the requirements (if any) of the Therapeutic Goods Regulations 1990 (the Regulations);
- a condition that the sponsor retains the information or evidence at all times while the goods remain Listed; and
- a condition that, at any time while the goods remain Listed, the sponsor will, if asked to do so by the TGA, give the information or evidence to the Secretary.

10.1.3 Additional conditions of Listing

There are a number of 'Additional Conditions of Listing' imposed by the delegate of the Secretary at the time complementary medicines are Listed on the ARTG. They include the following:

- The sponsor shall keep records relating to the Listed medicine as are necessary to: (a) Expedite recall if necessary of any batch of the Listed medicine; (b) Identify the manufacturer(s) of each batch of the Listed medicine. Where any part of or step in manufacture in Australia of the Listed medicine is sub-contracted to a third party who is not the sponsor, copies of relevant good manufacturing practice (GMP) agreements in relation to such manufacture shall be kept;
- The sponsor shall retain records of the distribution of the Listed medicine for a period of five years and shall provide the records or copies of the records to the Head, Office of Complementary Medicines (OCM). Therapeutic Goods Administration (TGA), upon request;
- The sponsor of the Listed medicine must not, by any means, intentionally or recklessly advertise the medicine for an indication other than those accepted in relation to the inclusion of the medicine in the ARTG;
- All reports of adverse reactions or similar experiences associated with the use or administration of the Listed medicine shall be notified to the Head, Office of Medicines Safety Monitoring (OMSM), TGA, as soon as practicable after the sponsor of the goods detects those reports. Sponsors of Listed medicines must retain records of such reports for a period of not less than 18 months from the day the Head, OMSM is notified of the report or reports;
- The sponsor shall not supply the Listed medicine after the expiry date of the goods; and
- Where a Listed medicine is distributed overseas as well as in Australia, product recall or any other regulatory action taken in relation to the medicine outside Australia which has or may

have relevance to the quality, safety or efficacy of the goods distributed in Australia, must be notified to the Director, OCM, TGA immediately the action or information is known to the sponsor.

As the above conditions of Listing are imposed by a delegate of the Secretary, sponsors receive a signed letter notifying of the additional conditions and their rights to appeal.

10.1.4 Substances with conditions of Listing surrounding their use

There is a small number of substances that have conditions of Listing imposed when used in Listed complementary medicines. For example, the following condition of Listing is imposed on medicines containing 100 micrograms (mcg) or more of folic acid:

- Where the medicine is a conventional release folic acid supplement preparation, in tablet form, of strength of 100 micrograms or more per dosage unit, the additional conditions are as follows:
  - Where the medicine contains folic acid as a single active ingredient, the dissolution characteristics for folic acid in this medicine must comply with the dissolution requirements in the United States Pharmacopoeia (USP) monograph for folic acid tablets;
  - Where the medicine contains multiple active ingredients, the dissolution characteristics for folic acid in this medicine must comply with the dissolution requirements in the USP monograph for nutritional supplements, as amended by its first supplement;
  - The dissolution characteristics for this medicine must comply with the dissolution requirements of the relevant USP monograph over the shelf life of the product when stored under the conditions included on the product label; and
  - It is the responsibility of manufacturers to develop and validate the analytical methods for the determination of folic acid that should be used in conjunction with the USP dissolution criteria.

10.2 Endangered species

Part IV of the ARGCM – *General Guidance*, details sponsor responsibilities regarding the use of ingredients that may be regulated under the *Environment Protection and Biodiversity Conservation Act 1999* as either native species and / or identified under the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES).

Further information about ingredients that may be subject to regulation under the *Environment Protection and Biodiversity Conservation Act 1999* is available from the Commonwealth Department of Sustainability, Environment, Water, Population and Communities as follows:

Department of Sustainability, Environment, Water, Population and Communities

Phone: (02) 6274 1111

Fax: (02) 6274 1666

Website: <http://www.environment.gov.au>

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
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