Australian Regulatory Guidelines for Complementary Medicines (ARGCM)
Part I: Registration of Complementary Medicines

Version 4.2, August 2011
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

<table>
<thead>
<tr>
<th>Version</th>
<th>Description of change</th>
<th>Author</th>
<th>Effective date</th>
</tr>
</thead>
<tbody>
<tr>
<td>V4.0</td>
<td>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.</td>
<td>Office of Complementary Medicines</td>
<td>March 2011</td>
</tr>
<tr>
<td>V4.1</td>
<td>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'</td>
<td>Office of Parliamentary and Strategic Support</td>
<td>May 2011</td>
</tr>
<tr>
<td>V4.2</td>
<td>A version history table was added. The version was labelled as 'Version 4.2'. Changes were also made to capitalisation of titles.</td>
<td>Office of Parliamentary and Strategic Support</td>
<td>August 2011</td>
</tr>
</tbody>
</table>
## Contents

1.0 Overview 7

1.1 Registration and scheduling __________________________ 8
1.2 Eligibility for registration as a complementary medicine __ 8
1.3 Route of evaluation and the registration process __________ 9
1.4 Quality _____________________________________________ 9
1.5 Efficacy and safety ________________________________ 9
1.6 Labelling and presentation ____________________________ 10
1.7 Product Information and Consumer Medicine Information __ 10
1.8 Product changes__________________________________ 10
1.9 Post market review__________________________________ 10

2.0 Eligibility for Registration 11

2.1 Manufacture ________________________________________ 11

3.0 Route of evaluation 13

3.1 Schedule 10 requirements ____________________________ 13
3.2 Justifying an alternative evaluation route ______________ 14

4.0 The Registration process 15

4.1 Introduction ________________________________________ 15
4.2 Lodgement __________________________________________ 18
4.3 Pre-assessment of registration applications _____________ 18
4.4 Evaluation __________________________________________ 19
4.5 Advisory Committee for Complementary Medicines (ACCM) __ 19
4.6 Finalising registration following ACCM consideration ______ 20
4.7 Exemptions under therapeutic goods legislation__________ 20

5.0 Administrative information 22

5.1 Application format__________________________________ 22
5.2 Confidentiality____________________________________ 22
5.3 Overseas status_____________________________________ 23
5.4 Reference to confidential manufacturer information ______23

6.0 Quality 24

6.1 Active ingredient – complementary medicine substance ____24
6.2 Finished product______________________________29

7.0 Efficacy and safety 48

7.1 Introduction ________________________________48
7.2 Registration and scheduling ____________________48
7.3 TGA guidelines relevant to efficacy and safety ______49
7.4 Points to consider in preparing an application for registration49
7.5 Efficacy____________________________________53
7.6 Safety____________________________________57
7.7 Benefits and risks – conclusion________________58
7.8 Clinical trials of complementary medicines__________58

8.0 Labelling and presentation 60

8.1 Labelling_____________________________________60
8.2 Unacceptable presentation________________________63
8.3 Ingredient names on labels ______________________64

9.0 Product Information 66

10.0 Consumer Medicine Information 69

10.1 Required headings and content of CMI __________69

11.0 Changes to Registered complementary medicines 72

11.1 About this guidance______________________________72
11.2 Forms________________________________________72
11.3 How much will It cost?__________________________73
11.4 Does the change make the goods “separate and distinct”? __73
11.5 What else do I need to send? _____________________73
11.6 Will the TGA look at other aspects of the product that are not being changed? ____________________________73
11.7 The same changes for many products? ______________74
11.8 What if the proposed change is not in the Changes Table? __74
11.9 How will the TGA acknowledge my notification or my application for approval? ___________________________74
11.10 Groups Order – summary ___________________________75
11.11 Changes Tables codes ___________________________75
11.12 Changes Tables ___________________________79

12.0 Post market review 87
12.1 The sampling program ___________________________87
12.2 Good Manufacturing Practice (GMP) audits ___________87
12.3 Grandfathered products ___________________________87
12.4 The Regulatory Compliance Unit ____________________87
12.5 Problem reporting and recall ________________________88
12.6 Adverse Drug Reaction (ADR) reports _______________88
12.7 Listing Compliance Section __________________________89

Part I Appendix 1 91

Stability of the finished product 91

A1.1 General principles ________________________________91
A1.2 Appropriate tests ________________________________92
A1.4 Prediction of shelf life from accelerated stability data____95
1.0 Overview

This Part provides guidance to applicants submitting applications for the Registration of complementary medicines. The regulatory requirements for Listed medicines are discussed in Part II of these guidelines, and those for the evaluation of complementary medicine substances are discussed in Part III.

The evaluation of an application for Registration of a complementary medicine will include:
1. an assessment of the safety, quality and efficacy of the product; and
2. an assessment of the safety and quality of any new substances that are in the product.

This section gives an overview of the guidelines for the Registration of new complementary medicines. The following sections provide detailed guidance:

- Section 2 – Eligibility for Registration
- Section 3 – Route of evaluation
- Section 4 – The Registration process
- Section 5 – Administrative information
- Section 6 – Quality
- Section 7 – Efficacy and safety
- Section 8 – Labelling and presentation
- Section 9 – Product Information
- Section 10 – Consumer Medicine Information
- Section 11 – Changes to Registered complementary medicines
- Section 12 – Post market review

Sponsors of complementary medicines may apply for Registration of products, containing otherwise Listable substances, that are for indications other than those permitted for Listed Medicines.

In addition, complementary medicines must be Registered if they:
- contain an ingredient or component that is subject to the conditions of a Schedule (or relevant appendix) to the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP); and/or
- contain an ingredient or component that has been identified as not suitable for use in Listed medicines (see Schedule 4, Part 4, Division 1 of the Therapeutic Goods Regulations 1990 [the Regulations]).

The “Registrable Disease List” is a list of diseases/disorders/conditions about which indications/claims may be made only after an evaluation of evidence by the Therapeutic Goods Administration (TGA), prior to approval of the product and its inclusion on the Australian Register of Therapeutic Goods (ARTG).

The Registrable Disease List, which applies to medicines but not devices, is contained in the TGA document Guidelines for Levels and Kinds of Evidence to Support Indications and Claims.
Applicants should review the Guidelines for Levels and Kinds of Evidence to Support Indications and Claims to determine the evidence needed to support indications for complementary medicines for medium and high level claims.

1.1 Registration and scheduling

Registration of a complementary medicine does not necessarily mean that the product will be a general sales item.

If not already scheduled, products are classified in one of the SUSMP’s schedules at the time of their Registration by the TGA. The TGA may seek advice on the appropriate schedule for a product from one or more of the TGA advisory committees.

A Registrable complementary medicine may be:

- a general sales medicine (unscheduled, i.e. not subject to the conditions of a schedule or appendix of the SUSMP);

or may be included in one of the following schedules:

- over-the-counter (OTC) medicines (Pharmacy Medicine – Schedule 2 or Pharmacist Medicine – Schedule 3 of the SUSMP);

- Prescription Medicine (Schedule 4 of the SUSMP).

Applicants should review the Principles of Scheduling in the SUSMP and in the National Coordinating Committee on Therapeutic Goods (NCCTG) Scheduling Policy Framework for Medicines and Chemicals. Medicines are not scheduled solely on the basis of toxicity. As stated in the SUSMP:

Although toxicity is one of the factors considered, and is itself a complex of factors; the decision to include a substance in a particular Schedule also takes into account many other criteria such as the purpose of use, potential for abuse, safety in use and the need for the substance.

Complementary medicine products, which are approved for Registrable indications, may be scheduled.

It is important that applicants consider possible scheduling outcomes before submitting an application, as the data requirements differ for OTC and prescription medicines.

The TGA intends to assess products with similar indications using a “level playing field” for the quality of data provided in support of the indications.

1.2 Eligibility for registration as a complementary medicine

Before submitting an application for Registration of a complementary medicine, it is first necessary to establish that the product contains substances that are, in fact, complementary medicine substances.

Essentially, if the substance is a designated active ingredient, as defined in Schedule 14 of the Regulations, that has an established identity and tradition of use, it is a complementary medicine substance. The Office of Complementary Medicines (OCM) also evaluates excipients that are used in complementary medicines and substances referred to the OCM by other regulatory areas in the TGA.

Eligibility for Registration as a complementary medicine is discussed in detail in Section 2.
1.3 Route of evaluation and the registration process

Applications for the Registration of complementary medicines are made via the Over-the-Counter Medicines Electronic Lodgement System (OPAL) and the dossier is sent to the OCM. After the appropriate fees are paid, applications pass through four or five phases: pre-assessment, evaluation and peer review, possible consideration by the Advisory Committee on Complementary Medicines (ACCM), decision and, if acceptable, implementation.

Pre-assessment involves a brief review of the application data to determine whether the application is eligible for evaluation by the OCM. The pre-assessment process also determines whether the appropriate fees have been paid and whether key data have been provided. Applications passing pre-assessment move to the evaluation phase. The submitted data are evaluated and a report of the findings is prepared. Evaluation reports are reviewed within the OCM to ensure consistency in evaluation. Comment may be sought from the ACCM which may make a recommendation to the Delegate of the Secretary of the Department of Health and Ageing. The Delegate assesses the evaluation report and any ACCM recommendations before deciding on the application. The evaluation process, including electronic lodgement, pre-assessment, evaluation, ACCM consideration, implementation and fees for substance applications, is discussed in detail in Section 4.

1.4 Quality

Information is required on the product and its active ingredients and excipients. The data are evaluated to determine the quality of the product, including the identity, impurities and stability of the ingredients. The assessment also takes into account information about the manufacturing processes and levels of good manufacturing practice (GMP), where appropriate. Details of quality-control measures are required to demonstrate that the product will be produced to a consistent quality. Stability data for the product are required to determine a shelf life over which the product’s quality is maintained.

The headings in Section 5 follow the Common Technical Document (CTD) format. Data provided in applications for Registration of complementary medicines do not have to be in the CTD format, but this is encouraged.

1.5 Efficacy and safety

Applications for the Registration of complementary medicines must include data that demonstrate the safety and efficacy of the product. Section 7 of this Part gives detailed guidance on safety and efficacy requirements, including information on history and patterns of use, biological activity, toxicology, clinical trials, adverse reactions and animal origins.

1.5.1 Efficacy

The sponsor must provide evidence to support the product’s efficacy before the product can be entered into the ARTG. The TGA conducts a detailed review of this evidence which may include consideration by ACCM. The TGA’s assessment of the sponsor’s efficacy data includes a detailed evaluation of the proposed indication(s) and any claims that the sponsor intends to make in the product labelling to determine whether the data supplied adequately support the requested indication(s)/claim(s).

1.5.2 Safety

Safety may be established by detailed reference to the published literature and/or the submission of original study data. Where there is sufficient evidence based on human experience to support safety, conventional studies involving animal and in vitro studies are not necessary.
1.6 Labelling and presentation

Applications to Register a complementary medicine must include details of the labelling and presentation of the product. Section 8 details the requirements for labels and product presentation.

Labelling must comply with the legislation and with the current Therapeutic Goods Labelling Order. The TGA has developed and maintains lists of Australian Approved Terminology for Medicines to ensure accuracy and consistency, and this terminology must be used on all labels.

1.7 Product Information and Consumer Medicine Information

Medicines that contain a Schedule 3 or Schedule 4 substance must have a Product Information (PI) document and a Consumer Medicine Information (CMI) document. The PI contains technical information intended for healthcare practitioners. The CMI contains general information about the medicine, is intended for the patient and is to be written in plain English. No promotional material may be included in the PI or CMI.

1.8 Product changes

Unlike changes to Listed complementary medicines, changes to many aspects of a Registered complementary medicine require prior approval (Notification). Section 11 sets out those that may be changed without prior approval and those for which approval is required.

1.9 Post market review

The OCM works closely with other areas of the TGA to maintain a strong Post Market surveillance program that aims to ensure that medicines supplied in Australia meet acceptable quality standards and are safe and effective.
2.0 Eligibility for Registration

By default, if a therapeutic good is not Listable or exempt it is Registrable. Therapeutic goods required to be Listed and exempt therapeutic goods are specified in Schedules 4 and 5 to the Therapeutic Goods Regulations 1990 (the Regulations).

A product may be Registered if:

- an application is made for Registration in accordance with the Therapeutic Goods Act 1989 (the Act);
- the sponsor has paid the evaluation fee required under the Act;
- the sponsor has complied with any requirements made by the Secretary under the Act;
- the quality, safety and efficacy of the product for the purposes for which it is to be used have been satisfactorily established;
- the presentation of the product is acceptable;
- the product conforms to any standard applicable to it, and any requirements of the Act or Regulations relating to advertising;
- an acceptable standard of good manufacturing practice (GMP) has been used in the manufacture of the product (if the product has been manufactured outside Australia);
- the product has been manufactured in accordance with the Act (if the product has been manufactured in Australia); and
- no other matters require resolution.

2.1 Manufacture

In making a decision about the acceptability of manufacture of the goods, the Therapeutic Goods Administration (TGA) will take into account:

- whether the sponsor has provided:
  - a European Commission (EC)/European Free Trade Area (EFTA) attestation of conformity for the product (if a step in the manufacture of the product has been carried out in an EC or EFTA member country);
  - a non-EC or non-EFTA attestation of conformity for the product (if a step in the manufacture of the product has been carried out in a country declared by the Minister under the Act to be covered by a non-EC/EFTA mutual recognition agreement [MRA]);
  - an acceptable form of evidence from the relevant overseas authority establishing that the manufacture of the product is of an acceptable standard (in any other case).
- if inspection of the product’s manufacturing procedures is considered necessary, whether the sponsor has agreed to provide funds for the TGA to carry out the inspection and evidence that the manufacturer has agreed to such an inspection; and
- whether the sponsor has complied with any requirements made under the Act in relation to the manufacture or preparation of the product.
If a product is exempt from the operation of the Act or a person is exempt from the operation of that Part in relation to the manufacture of the product, it is not necessary that the manufacture of the product complies with that Part of the Act.

In determining the acceptability of the manufacture of a product, the TGA may consider any information provided by a health authority of any country that is a party to the Mutual Recognition Agreement between Australia and the EC/EFTA. The TGA may take into account the general standards of manufacturing practice of a particular manufacturer and the specific standards of manufacture or control adopted by the manufacturer for the product. See information for overseas manufacturers for further guidance on overseas manufacturers.

If a product is Registered, the product will be included in the Australian Register of Therapeutic Goods and the sponsor will be provided with a certificate of Registration. The Registration of therapeutic goods begins on the day specified in the certificate of Registration.
3.0 Route of evaluation

Applications for the Registration of complementary medicines will be assessed by the most appropriate section within the Therapeutic Goods Administration (TGA). Schedule 10 of the Therapeutic Goods Regulations 1990 (the Regulations) stipulates these arrangements. Applications for therapeutic devices will be assessed by the TGA’s Office of Devices Authorisation.

3.1 Schedule 10 requirements

The Office of Medicines Authorisation (OMA) of the TGA will evaluate the following therapeutic goods:

therapeutic goods that contain a substance mentioned in schedule 4, 8 or 9 of the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) or a substance meeting the criteria for mention in any of those schedules;

- a medical gas;
- a vaccine;
- an allergen, except an allergen for skin patch testing on unbroken skin;
- a biotechnology medicine;
- an immunoglobulin;
- a radio contrast agent, except barium sulphate preparation for radiological use;
- a radiopharmaceutical;
- a dialysis solution;
- an irrigation solution;
- a special dosage form, such as a transdermal system or osmotic pump;
- an injectable medicine dosage form;
- a blood product, unless coated on a therapeutic device;
- therapeutic goods referred within the TGA for evaluation by the OMA;
- an excipient in the therapeutic goods listed above;
- a therapeutic device that depends on the release of a substance for some or all of its action.

The following therapeutic goods may be evaluated by the Office of Complementary Medicines (OCM) if the goods do not meet the criteria of the SUSMP:

- a complementary medicine (see Eligibility for Registration);
- an excipient in a complementary medicine;
- therapeutic goods referred for evaluation to the OCM.

The following therapeutic goods may be evaluated by the Over-the-Counter (OTC) Medicines Evaluation Section (MES) if the goods do not meet the criteria of the SUSMP:

- an antiseptic;
• a sunscreen preparation;
• all other therapeutic goods, except therapeutic devices, not listed above as assessable by the OCM or the OMA;
• an excipient in therapeutic goods mentioned as being assessable by the OTC MES;
• therapeutic goods referred for evaluation to the OTC MES.

Where the TGA considers that the expertise of other sections may be relevant to an evaluation, it may refer the evaluation to those areas. However, where the OMA refers an evaluation to the OCM, the referring section will retain statutory control of the application.

3.2 Justifying an alternative evaluation route

A sponsor may request and ‘justify’ the evaluation route for their application. The justification should state the reason the sponsor believes that the product would be more appropriately evaluated by another evaluation area than that specified in Schedule 10 of the Regulations. The justification should be provided before any application for Registration is made.

The justification should explain clearly and logically why the TGA area prescribed in the Regulations is not the most appropriate one to evaluate the application, and demonstrate that it would be more efficient and more effective for another area to do the evaluation.

Factors that may be taken into account are:
• the safety/risk of the product or substances in the product, including any current, proposed or likely scheduling requirements;
• whether the product contains a substances that has a closely related chemical structure and similar therapeutic action to other substances that have previously been assessed by the alternative section;
• the nature of the condition to be treated by the product;
• the overall presentation of the product and the therapeutic claims/indications made in relation to the product;
• the route of administration of the product;
4.0 The Registration process

This section provides an overview of the processes involved in the Registration of complementary medicines.

4.1 Introduction

4.1.1 Objective

An evaluation of an application for a new Registered complementary medicine is a critical review of whether or not the proposed product meets Therapeutic Goods Administration (TGA) requirements for quality, safety and efficacy. Most, but not all evaluations for new Registered complementary medicines are referred to the Advisory Committee on Complementary Medicines (ACCM), but it is possible for a product to be Registered without referral to ACCM.

It is possible to gain provisional approval of a substance for use in Registered complementary medicines before the substance is included in a product.

4.1.2 Relevant regulatory requirements

A number of important regulatory requirements relate to applications for Registration of complementary medicines, including the following:

The **Therapeutic Goods Act 1989** (the Act) contains the general provisions relating to all therapeutic goods. The Act establishes the ACCM and the authority of the TGA to seek information from sponsors, impose standards, approve Registration applications and cancel the Registration of existing goods. The Act also defines the circumstances in which sponsors may appeal decisions made by the TGA, including decisions not to accept a product for Registration and decisions to require a sponsor to provide additional information.

The **Therapeutic Goods Regulations 1990** (the Regulations) are more specific than the Act. Schedule 10 of the Regulations defines which goods are to be evaluated by the Office of Complementary Medicines (OCM). Schedule 14 identifies the active ingredients that can be used in complementary medicines.

The **Standard for the Uniform Scheduling of Medicines and Poisons** (SUSMP) is a Commonwealth document that is enacted through state and territory legislation. Substances are classified into a number of schedules and appendices. Inclusion of a substance in one of these schedules means that it cannot be used in Listed medicines and therefore that a medicine containing it must be Registered.

**Therapeutic Goods Orders** (TGOs) are TGA documents that have legislative force. Of particular relevance for Registered complementary medicines are **TGO 69 – General requirements for labels for medicines**, **TGO 80 – Child-resistant packaging requirements for medicines** and **TGO 77 – Microbiological standards for medicines**.

The **British Pharmacopoeia** (BP), **European Pharmacopoeia** (PH Eur) and **United States Pharmacopoeia-National Formulary** (USP) are the official default standards for regulatory purposes in Australia. They establish a number of general standards for medicines and specific standards for some active ingredients and finished products. The three standards have regulatory force in Australia, unless there is a specific TGO that overrides their requirements.

The **Therapeutic Goods Advertising Code** (TGAC) establishes the general requirements for advertising claims for therapeutic goods. Medicine labels are considered to form part of advertising. The TGAC defines the diseases/disorders/conditions that cannot be referred to in advertisements for non-prescription medicines.
4.1.3 Relevant guidelines

The Guidelines for levels and kinds of evidence to support indications and claims offer advice on the level (general, medium and high) of an indication or claim and the evidence required to support it. Registered medicines can carry claims of any level, provided the TGA has evaluated the evidence to support the indication and approved the indication for the Registered medicine.

The Australian Regulatory Guidelines for Prescription Medicines (ARGPM), are intended for evaluation of prescription medicines by the OMA. If a Registered complementary medicine is to be supplied with a prescription from a medical practitioner, the Australian Regulatory Guidelines for Complementary Medicines (ARGCM) apply. However, where relevant, reference may be made to the ARGPM for guidance.

The Australian Regulatory Guidelines for OTC Medicines (ARGOM) apply to the Registration of over-the-counter (OTC) medicines for evaluation by the TGA’s OTC Medicines Evaluation Section. If a Registered complementary medicine is to be supplied as an OTC medicine, the ARGCM guidelines apply. However, where relevant, reference may be made to the ARGOM for guidance.

The website of the European Medicines Agency (EMA) contains detailed information about medicine evaluation, including guidelines on the evaluation of herbal medicines.

Sponsors should be aware that the TGA has adopted a number of EMEA guidance documents covering a range of therapeutic classes, and should check those documents to be aware of any guidelines that may be relevant to their product.

All EMEA/European Union guidelines referenced to in the ARGCM are available in portable document format (pdf) from the TGA web page European Union Guidelines Adopted in Australia.

While the above sources give general guidance, sponsors should also note the policy and general guidance for specific product categories and substances in Parts IV and V of the ARGCM.

4.1.4 Evaluation fees

Evaluation fees are payable for all Registration evaluations. The fee payable depends on the number of pages of clinical and toxicological data supplied. Information on current fees can be found on the TGA website: http://www.tga.gov.au/about/fees.htm.
Figure 1: Registration process flow chart

Application received via the Over-the-counter Medicines Electronic Lodgement System (OPAL). Invoice raised for application fee and evaluation fee (based on clinical/toxicological page count). Fees paid. Data package sent to the OCM.

Application Acceptance Phase

- Acknowledgment letter is sent to the applicant.
- OCM conducts pre-assessment screen.

- Application not accepted or referred to another area. Sponsor is advised.
- Application is accepted.
- Application pending acceptance. Sponsor advised of deficiencies.

Evaluation Phase

Evaluation commences – quality, safety and efficacy data critically evaluated against regulatory requirements. Further information may be sought from the sponsor.

- Evaluation reports are reviewed within OCM and the need for consideration by the ACCM is assessed.

Expert Committee Phase

- ACCM briefing paper prepared by OCM. Sponsor is given a copy for comment.
- Application is not referred to ACCM for consideration.
- The ACMS may be consulted about the scheduling of
- ACCM considers the report and makes a recommendation to the TGA.
- ACCM may consult with other TGA advisory committees for some
- ACCM recommends application not be approved.
- ACCM recommends approval (certain additional qualifications may be recommended).

Decision Phase

- The delegate takes into consideration the recommendations of the ACCM and/or other areas of the TGA and makes a decision on the application.*

- Application is not approved. Sponsor is notified of the decision. Sponsor may appeal the decision under section 60 of the Act.
- Application is approved. Sponsor is notified of decision to enter the product onto the ARTG.
- Application is approved in principle, depending on certain conditions. OCM liaises with the sponsor. Further assessment steps may be necessary. When conditions are fulfilled.

*Decisions to accept or reject an application are made by persons with the authority to make such decisions by delegation of
Figure 1 outlines processing of an application for Registration of a new complementary medicine. The following sections detail the requirements of each of the stages outlined in the flow chart.

### 4.2 Lodgement

The key responsibilities of the TGA are to:
- acknowledge receipt of the application;
- check that fees are allocated correctly; and
- enter the application into the TGA tracking system.

Applications for new Registered complementary medicines are lodged electronically using the online application system currently used for registered OTC medicines. Most potential sponsors of a new registered complementary medicine would be familiar with this system – the OTC Medicines Electronic Lodgement system (OPAL).

Accordingly, the paper-based application form for a new Registered complementary medicine has been removed from the TGA website and replaced with a link to the eBS portal. The submission of the data dossier remains the same - the applicant is still required to submit a hard copy of the dossier to the OCM.

### 4.3 Pre-assessment of registration applications

The key responsibilities of the TGA are as follow:
- The TGA will verify that the application is eligible for evaluation by the OCM. If the medicine is not a complementary medicine, it may be referred to another area of the TGA;
- The TGA will count the pages of clinical and toxicological data. Generally, evaluation will not proceed if insufficient fees have been paid;
- The administration will determine whether or not the level of evidence provided to support the proposed indications or claims matches the level of the claim, as set out in the Guidelines for levels and kinds of evidence to support indications and claims. If not, the sponsor will be advised in writing and asked whether they wish to amend the indications in line with the available evidence, supply further evidence of the appropriate level or withdraw the application;
- The TGA will identify any areas in which the application is obviously deficient. If any significant deficiencies are noted, the sponsor will be contacted in writing in accordance with the Act, and information to remedy these deficiencies will be sought;
- The administration will decide whether or not external clinical evaluation should be sought.

There are three possible outcomes of the pre-assessment process:
- The TGA may reject the application if there are profound deficiencies, if no fees have been paid, if the medicine is not a complementary medicine or if the medicine is required to be in the part of the Register for Listed goods;
- The TGA may grant conditional acceptance where additional fees or additional significant information is sought and the evaluation cannot proceed until the fees are paid or the information is supplied. This situation also applies where advice is being sought from the sponsor about whether or not they wish to amend the product indications to reflect the level of evidence available. When the additional fees are paid or the information is received, the application is referred back to the pre-assessment stage for a decision on whether it can then proceed to evaluation;
• The TGA may accept the application where there are no obvious deficiencies, or only minor
deficiencies that are not considered significant enough to prevent evaluation, and all fees are
paid. The application then proceeds to the evaluation stage.

4.4 Evaluation

In the evaluation stage, the quality, safety and efficacy of the product are critically evaluated and an
evaluation report is produced.

Details of how the TGA evaluates quality, safety and efficacy, and the related issues of labelling and
product information, are found in later sections of these guidelines.

4.5 Advisory Committee for Complementary Medicines (ACCM)

The ACCM is constituted under Regulation 39 of the Regulations. Evaluation reports on most
Registration applications for complementary medicines are presented to the ACCM for
consideration and recommendation to the TGA. Sponsors have the opportunity to provide written
comment on the evaluation report prepared by the OCM. Sponsors will be sent a copy of the
evaluation report and must respond within the given time frame (usually five working days). Written comments may be submitted to correct any factual errors or omissions in the report.
Comments must be no longer than three pages and submitted in sufficient time to allow the ACCM
to consider sponsor comments when it considers the evaluation report.

Where applications for Registered complementary medicines are not recommended by the ACCM
for approval by the TGA, sponsors are offered an opportunity to appear before the ACCM for the
purposes of conveying their views on the Committee’s recommendations, and any views or
interpretations of the evaluated information which may have differed to those of the ACCM.

The process for appearance before the ACCM in this situation is outlined below:

• the sponsor of the application not recommended for approval will be sent a copy of the
unratified Minutes soon after the ACCM meeting and offered an opportunity to make a
presentation on the Committee’s recommendation. (Sponsors are also offered, at the same time.
The opportunity to withdraw the application prior to the Delegate’s consideration of the ACCM
recommendation. Sponsors choosing neither of these options retain their appeal rights with
regard to the Delegate’s decision);

• sponsors who notify the Secretariat of their intention to appear before the ACCM will be
allocated a time at a forthcoming meeting based on available time in the agenda (not necessarily
at the subsequent meeting);

• sponsors will have up to 20 minutes to address the ACCM:
  – the form of the presentation is at the discretion of the sponsor but it should not introduce
    new data;
  – copies of the presentation, or an outline, should be provided in advance of the meeting
    where practicable;
  – presentations can include material prepared by, or presented by, an expert(s) invited by the
    sponsor.

• Members of the ACCM may then ask questions of the sponsor;

1 Guidance on appeal mechanisms in relation to decisions made by the TGA is included in ARGCM Part IV – Review of
Decisions.
After the sponsor has left the meeting, the Committee will consider its position with regard to the original recommendation(s) and this will be communicated to the sponsor in writing by the Secretariat.

The opportunity to appear before the ACCM is at the discretion of the ACCM Chair and dependent on the available time in the agenda for any given meeting. The opportunity should only be taken up in cases where the sponsor genuinely believes that the ACCM may have misinterpreted or inappropriately weighted the information contained in the application(s). It is not considered appropriate to introduce new information not previously considered by the ACCM.

### 4.6 Finalising registration following ACCM consideration

Recommendations from the ACCM and any other recommendations or information from the TGA will be taken into consideration by the appointed delegate of the Secretary of the Department of Health and Ageing. The delegate will make a decision on the application.

A letter will be sent, formally advising the sponsor of the outcome of the application. If there are any conditions placed on the Registration of the new complementary medicine, the sponsor will be notified of them and they will be discussed with the sponsor.

The Australian Register of Therapeutic Goods (ARTG) entry on the provisional record will be amended, if necessary, and the letter and its attachments will be sent to the sponsor. The sponsor will then advise the TGA of any necessary corrections to the provisional record and return the letter and its attachments to the ARTG entry officer, who will then issue a final certificate of Registration.

If the sponsor does not agree with a decision by the Delegate, there are appeal provisions provided in the Act.

### 4.7 Exemptions under therapeutic goods legislation

Sponsors are able to apply for exemptions from some of the requirements set out in the therapeutic goods legislation. 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 consent, under section 14 and 14A of the Act, to supply goods that do not comply with the relevant standard. The Act states that 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.

A common request received by the OCM is for exemption, under Regulation 6A, in order to include a restricted representation in the labelling of a product.

Under the Act (also mentioned in the Therapeutic Goods Advertising Code (TGAC)), advertisements for therapeutic goods may refer to “restricted representations” provided that prior approval is obtained for such a reference.

Approval is processed by the TGA’s Advertising Section following a recommendation from the TGA or one of its advisory committees (such as ACCM). Approvals for restricted representations must be gazetted or published on the TGA website in order to take effect.

Under the Act, permission can also be obtained for the use of a “prohibited representation” (see Appendix 6 of the TGAC) on the label of the goods or in information included in the package of the goods, provided the representation is necessary for the appropriate use of the product. For non-prescription complementary medicines, this sort of exemption is only likely to be granted if the goods are required to carry a warning relating to a disease included in the list of prohibited
representations (e.g. “This product should not be used by those with bipolar depression” or “This product is not suitable for use in the treatment of cancer”).

Exemptions from advertising requirements are not processed until the ACCM has made a recommendation about the indication.

If the sponsor also wishes to advertise the restricted representation, the sponsor must make a submission under the Act to the Director of the TGA’s Advertising Section. In making the decision to grant the exemption, the Delegate must take into consideration any recommendations from the Therapeutic Goods Advertising Code Council (TGACC) and any advice from ACCM or other advisory committees. To assist with the processing of the request, it is advisable for the sponsor, when making a submission under the Act, to also send a copy to the TGACC.
5.0 Administrative information

This section covers administrative information and gives guidance on the format for applications to Register new complementary medicines. Although the format is not mandatory, it is in the best interests of the sponsor to present the application as recommended and provide the requested information to expedite acceptance and evaluation.

5.1 Application format

All documents, including references, must be in English and legible. If original documentation is in another language, it should be translated to English by a certified translator and both the English version and the original document should be provided. Non-English documents without certified translations will not be considered in support of an application.

All pages submitted with the application should be provided in bound folders (e.g. ring binders) and every page should be numbered consecutively. An index of the complete application package should be included at the front of the package. The following numbers of copies for each section should be provided to allow concurrent evaluation of the application by different evaluators and thereby expedite the evaluation process.

- Administrative information 2 copies
- Quality 2 copies
- Safety and efficacy 2 copies

5.2 Confidentiality

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

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

The TGA will not comply with demands for undertakings of confidentiality that seek to limit the lawful use or release of information by the TGA. The TGA and the Advisory Committee on Complementary Medicines (ACCM) have a duty to evaluate therapeutic goods using all information available to them to ensure public safety. To carry out this function successfully, it is necessary that those involved in the evaluation of Registration applications have access to:

- all departmental records of prior applications;
- the accumulated knowledge and experience gained from the evaluation of previous applications.
This does **not** mean that data that are submitted in an application by one company can be referenced in an application for a similar medicine by a different company. Such sharing of data is only allowed when the TGA has received authorisation from both companies. This also applies to joint applications for an identical medicine by two different companies.

It is important that confidentiality statements accompanying applications are consistent with the powers and duties of the Secretary under the [Therapeutic Goods Act](https://www.gov.au/glossary/term/therapeutic-goods-act) 1989 (the Act).

Examples of acceptable confidentiality statements are as follows.

*All and any information contained in this document is to be regarded as a trade secret because the document contains unpublished details and results of private research proprietary to [name of company or sponsor], the disclosure of which to its competitors could be disadvantageous.*

and/or

*All and any information contained in this document is to be regarded as commercial or financial information that is privileged or confidential in that it contains valuable data or information which is used in the business of [name of company or sponsor] and is of a type customarily used in confidence, or regarded as privileged, and has not been disclosed to any member of the public by [name of company or sponsor].*

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

### 5.3 Overseas status

If the product is supplied in other countries, the country, approval date (or date and length of time of supply), and the regulatory status (e.g. approved or not approved dietary supplement) should be stated. Provision of documentation detailing the annual sales volume and estimates of the size of the exposure population is not mandatory, but this is considered to be supporting data and will assist the assessment of the application.

If an application to approve the product has been made to a regulatory authority in any other country, this should be stated as well as the outcome of that application (e.g. approval, withdrawal, rejection).

### 5.4 Reference to confidential manufacturer information

Where the manufacturer of an active ingredient or the manufacturer of the finished product is unwilling to release to the sponsor the detailed information required in an application to Register a complementary medicine, this information can be submitted directly to the TGA. In such a case, the manufacturer would include their own confidentiality statement with their data, which would not be released to the sponsor of the product. The sponsor would refer to the manufacturer’s submitted data in their application package, but any discourse between the TGA and the manufacturer regarding the manufacturer’s data would not involve the sponsor.

Where reference is made to confidential manufacturing information that has been submitted directly to the TGA, the sponsor must include written permission from the manufacturer to reference this material. The TGA cannot consider confidential information from a company in support of another company’s application unless authorised to do so.
6.0 Quality

This section provides guidance on the quality issues that should be addressed in applications for the Registration of complementary medicines, and is divided into two subsections:

6.1  Active Ingredient
6.2  Finished Product

Some complementary medicines are comprised of relatively simple ingredients (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 pharmaceutical medicines. However, complementary medicines that contain complex ingredients that are difficult to characterise and/or certain combinations of multiple active ingredients require special consideration. Within each section in this chapter, guidance will be given for products containing relatively simple complementary medicine ingredients, followed by guidance for other complementary medicines that contain certain combinations of multiple active ingredients that are difficult to characterise or that contain compositionally complex ingredients. Specific guidance is also included for prescription complementary medicines where the requirements differ.

In addition to the requirements as detailed in the specific sections, the quality section of the sponsor's application should include an overview of the quality aspects of the application. This overview should include a product development summary as described below, together with critical summaries of the starting material specifications, the finished product specifications and the stability studies.

The headings used in this section follow the format of the International Conference on Harmonisation (ICH) guideline M4: Common Technical Document (CTD). This section 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 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).

6.1  Active ingredient – complementary medicine substance

This section outlines the information on the active ingredient to be submitted in an application to register a complementary medicine. The types of information and level of detail depend on the active ingredient and on the risk associated with the finished product. For example, more data may be required to fully characterise a complex herbal extract than a single chemically synthesised active ingredient.

Similarly, where the finished product will be a prescription only medicine for a high-level indication, more data and increased control of the active ingredient may be required to ensure consistent efficacy of the finished product. In all cases, the application information must be sufficient to:

- adequately characterise the active ingredient;
- determine the time during which the product meets appropriate standards when stored under defined conditions;
- demonstrate that the active ingredient will be of appropriate and consistent quality.

2 There is a wide range in the compositional complexity of complementary medicine ingredients. Simple complementary medicine substances are primarily single-constituent ingredients that can be readily characterised (methionine). Complex complementary medicine substances (e.g. herbal extracts) have a number of constituents.
Note: 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 ARGCM Part IV, Ingredients of Animal or Human Origin.

6.1.1 Manufacture of the active ingredient

Commercially sensitive aspects of the manufacturing process. Where a manufacturer is unwilling to supply manufacturing details to the Australian sponsor, the option exists for the information to be supplied directly to the Therapeutic Goods Administration (TGA). In this case, any matters arising from the review of these data will be pursued with the manufacturer. The sponsor will be notified that matters have been raised but no details will be provided unless the manufacturer authorises this. Please note that the Australian sponsor will need to provide written authorisation to the TGA before the TGA can communicate directly with the manufacturer.

6.1.1.1 Licensing and control

For most complementary medicines, licensing or evidence of good manufacturing practice (GMP) is not required for the manufacturer of the active ingredient, who 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 TGA. In such a case, it is the responsibility of the manufacturer of the finished product to ensure that the quality of the active substance is acceptable. However, provision of the active ingredient manufacturer’s name and address (while not mandatory) will assist the TGA in the evaluation process. Details of the TGA’s requirements for manufacturers are specified in the PIC/S Guide for Good Manufacturing Practice for Medicinal Products - 15 January 2009.3

Complex substances

Where the active ingredient is difficult to characterise quantitatively, as is the case with some complex herbal extracts, it may be difficult to adequately control the 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.

Prescription complementary medicines

Active ingredients in prescription only medicines, including prescription complementary medicines, are more closely scrutinised and controlled. The active ingredient is specifically linked to the efficacy data that are submitted for the finished product, and the production of a consistently efficacious medicine depends on the production of a consistent quality of the active ingredient.

For this reason, the manufacturer of the active ingredient is included in the ARTG entry for prescription only medicines. This means that changes to the method of manufacture and/or a change in manufacturer require prior approval from the TGA (refer to Section 11, Changes to Registered Complementary Medicines).

6.1.2 Compositional information

The purpose of the compositional information is to provide detailed characterisation of the substance. For simple complementary medicinal substances, this is usually straightforward and may be 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 data.

---

For Registered complementary medicines, the compositional information is treated as commercial-in-confidence (refer to ARGCM Part V, Confidentiality).

The submitted data for the active ingredient in an application to Register a complementary medicine are comparable to those required in an application for a new Listable substance. For this reason, sponsors should refer to ARGCM Part III, Evaluation of Complementary Medicine Substances for guidance on the type and detail of information to be included.

In addition to the requirements outlined in ARGCM Part III, information on solubility (in water and other relevant solvents, such as dissolution media), particle size and polymorphic form (which are specific to Registered complementary medicines) should be provided, where relevant.

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

### 6.1.3 Control of active substance – specifications

**Note:** The British Pharmacopoeia (BP), European Pharmacopoeia (PH Eur), United States Pharmacopeia-National Formulary (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 this is the minimum standard that must be applied in its entirety; otherwise, a justification is required. Note that the BP, PH Eur or USP specifications are expiry specifications. The requirements of applicable general monographs of the BP, PH Eur or 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 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 physico-chemical testing) where variation would be likely to affect the quality or safety of the product.

Typically, the manufacturer of the active ingredient 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 Registered 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 applied by the finished product manufacturer before the ingredient is used in the finished product. For some complex substances, or where the finished product will be a prescription only medicine, the specifications applied to the active ingredient by the ingredient manufacturer may be more closely scrutinised.

#### 6.1.3.1 Limits and tests

If there is a BP, PH Eur or USP monograph for the active substance, it must be used unless otherwise 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, 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. The requirements of the BP, PH Eur and USP or applicable general monographs 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 pharmacopoeial 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;
- selectively combine some tests and/or limits from the relevant BP monograph with some from the USP monograph (without having ensured full compliance with either);
- adopt an earlier edition of the pharmacopoeial monograph or standard when there is a more recent edition that has been adopted by the TGA.

Where non-pharmacopoeial specifications are applied, a tabulated summary of the tests, test methods and limits should be provided (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 (Section 6.1.2 above). The minimum tests and limits included in specifications for an active ingredient include:

- appearance/description;
- identification;
- content/assay;
- 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, microbial contamination, particle size distribution, and the clarity, colour and pH of solutions may also be relevant.

**Complex complementary medicine substances**

Specifications for a complex complementary medicine substance will vary according to the substance. The specifications might include controls on the macro components, such as nitrogen content or sodium content. For complex liquid formulations, solvent content or viscosity might be important. Additional simple tests that could assist in characterisation could 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, such as sodium content in a sodium salt of a substance or gas chromatograph characterisation of key components in an oil.

Significant minor components of a substance (e.g. content of a specific alkaloid) are particularly important. These components are often pivotal to the nature and/or safety of the substance, and their identification and analysis 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 such aspects of the mixture as:

- acid value;
- iodine value;
• saponification value;
• viscosity;
• density;
• refractive index.

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

6.1.3.2 Impurities and incidental constituents

One of the key purposes of raw material specifications for complementary medicines is to determine whether 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 matter, 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.

6.1.3.3 Analytical procedures and validation

Details should be provided of all analytical methods used in the specifications, together with validation data that demonstrate the suitability of the method for the material in question. The information should cover 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 a TGA-recognised monograph or standard.

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

6.1.3.4 Batch certificates of analysis

Certificates of analysis should be provided 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 should be provided for pilot-scale batches manufactured using the same process as intended for commercial-scale batches.

Certificates of analysis should also be provided for any batches of material used in toxicity tests and clinical trials reported in support of the application. This will assist the TGA in determining whether the substance intended for supply is the same as that on which safety data have been provided. If certificates of analysis are not available, justification as to why they have not been supplied must be provided.

Prescription complementary medicines

For prescription only complementary medicines, it is important that batch analysis data for the active ingredient are included for batches that were used in clinical trials reported in support of the application.

6.1.3.5 Justification of specification

If a sponsor proposes to use an alternative monograph or standard when a BP, PH Eur or USP standard exists, justification for doing so will be required. 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 sections 14 and 14A of the Act. Such requests should explain why the standard(s) cannot be met and detail what alternative(s) are proposed and why.

If there is no relevant monograph or standard for the active ingredient, a justification for the proposed specifications should be provided. The justification should address the central function of the active ingredient specifications, which is to ensure the use of a consistently high-quality substance in the finished product. Specifically, identification, assay, control of impurities and other critical factors in the quality of the active ingredient should be addressed.
6.1.4 Stability

Stability data should be provided for new complementary medicine active ingredients to assist in identifying any particular degradants that may be formed and that should be monitored as part of the overall stability program. The relevant parts of ARGCM Part III, Stability Testing, provide guidance on stability testing of complementary medicine substances.

6.2 Finished product

6.2.1 Description and composition of the product

A description of the finished product that includes the following information should be provided:

- table of the ingredients in the product and their purpose in the formulation (e.g. active, disintegrant, antimicrobial preservative);
- description of the dosage form, including any special character (e.g. modified release);
- type of container and closure for the product, including the materials.

The table of ingredients should provide greater detail than simply the product formulation. It should include overages (additional amounts of ingredients, over the amounts nominated in the product’s formulation, added during manufacture) if any. The table should also include a reference to the quality standard for each of the ingredients (e.g. pharmacopoeial monograph reference or manufacturer's specifications number).

6.2.2 Product development

Information on the development of the finished product should be provided, including a discussion of the studies that led to the proposed dosage form, formulation, method of manufacture and container.

Where a medicine has modified release characteristics or an unusual method of manufacture, the product development summary should include a detailed discussion of the development of those characteristics 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, the developmental work that led to the proposed overage should also be discussed.

6.2.3 Formulation

Components of a formulation are divided into active ingredients and excipient ingredients. Some, called "proprietary ingredients", may be incorporated in the form of proprietary or confidential formulations. Proprietary ingredients are discussed in detail in ARGCM Part IV.

6.2.3.1 Active ingredients

Active ingredients in complementary medicines are those substances that have a therapeutic role in the formulation. The therapeutic role may be to treat, prevent, cure or alleviate a disease, ailment, defect or injury or alleviate a symptom of a disease, ailment, defect or injury, or influence, inhibit or modify a physiological process. Substances included in the formulation as active ingredients must make a contribution to the proposed indications for the medicine.

6.2.3.2 Excipient ingredients

Excipient ingredients are substances used to aid 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 appropriately controlled by specifications.
Sponsors should ensure that the intended use of an excipient is appropriate and that it is used in appropriate amounts to achieve its technical purpose. Sponsors should also ensure that the excipient is approved for use.

6.2.3.3 Proprietary ingredients

A proprietary ingredient is a formulation containing two or more ingredients obtained from another manufacturer, the formulation details of which are not necessarily known to the sponsor. Proprietary ingredients include, for example, fragrances, flavours, colouring ingredients, transdermal patch adhesives, and printing inks. A single ingredient is not normally accepted as a proprietary ingredient formulation.

Information on proprietary ingredients is included in ARGCM Part IV.

Before a proprietary ingredient 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 in the application form), or that the manufacturer of the ingredient has been asked to provide details of the formulation to the TGA on a Notification of a Proprietary Ingredient form.

Sponsors should be aware that there is no evaluation of the proprietary ingredient formulation in terms of safety or efficacy. However, the individual ingredients contained in the proprietary ingredient are assessed for safety. Colouring ingredients to be used in oral products must be approved for ingestion. A list of colourings permitted in medicines for oral use is provided in on the TGA website at http://www.tga.gov.au/industry/cm-colourings-oral-use.htm.

Where the proprietary ingredient is a pre-mix that includes one or more active ingredients, the proprietary ingredient 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 about a substance (e.g. "sugar free" or "alcohol free"), sponsors should also ensure that the substance is not contained in any proprietary ingredient included in the formulation.

6.2.3.4 Colouring ingredients

Colours permitted in medicines for oral use are contained in the document Colourings Permitted in Medicines for Oral Use. Colourings other than those contained in Colourings Permitted in Medicines for Oral Use may be permitted in topical products.

6.2.3.5 Modified release products

Modified release products are dosage forms that have been developed 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 also include products that have been developed for exceptionally fast release of the active ingredient(s).

Applications for a modified release complementary medicine should include a justification for the modified release formulation based on physiological, clinical and/or bioavailability data. In vitro and animal studies can be used as supporting data. Modified release dosage forms may be appropriate when:

- the active ingredient is rapidly absorbed and eliminated (e.g. half-life of less than six-eight hours), with a correspondingly rapid loss of clinical effect;
- absorption is not confined to a limited region of the gastrointestinal tract;
- the product is intended for use over a period long enough to warrant the use of a sustained release formulation;
- the product is able 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 – Standard for tablets and capsules.
Applications for the Registration of a modified release formulation must be accompanied by evidence to demonstrate that the product meets controlled release claims. The evidence would be expected to include both physico-chemical data (dissolution data) and clinical data (bioavailability data). Dissolution data requirements are discussed in Section 6.2.7.6 and clinical data requirements are covered in Section 7.

6.2.3.6 Herbal substances and ingredients derived from herbal substances

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

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

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 manufacturing. Table 1 lists the changes to the nominal amounts of certain excipients that may be made in the manufacture of immediate release non-prescription Registered complementary medicines.
Table 1. Changes to the nominal amounts of certain excipients may be made as set out below.

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

* Does not apply to modified release products – approval is required for any variation from the Registered formulation

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 its composition.

Where the composition varies, fluctuations in the quantity of active raw material may affect the proportions of excipients present in the finished product relative to the nominal formula.

In some situations, the manufacturer may choose to compensate for the fluctuations in the weight of active raw material added by adjusting the amount of a nominated excipient in order to maintain a target weight for the batch.

This should be clearly identified in the application, and it will be taken into account during the evaluation. Batch-to-batch approval is not normally required. The formulation given in the application should have an annotation indicating that the actual weight of active raw material will vary according to its estimated amount, and a formula should be provided showing how the amount of adjustment will be calculated. There should be an indication of which other excipients, if any, will be varied correspondingly, and the limits of the variation.

The reasons for proposed ranges in the quantities of any ingredients should be discussed in the product development summary. Validation data should be provided for the extremes of proposed ranges. Where the product is a tablet or capsule, the validation data should include dissolution or disintegration data, using the test method in the proposed finished product specifications.
6.2.3.8 Overages

If an overage (an additional amount of an ingredient added during manufacture and greater than the amount nominated in the product’s formulation) is used during manufacture, details of the overage used should be included.

The application’s product development summary should include a justification for the proposed overage. Any assay limits that are unusually wide as a consequence of the proposed overage should also be discussed. 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 stated in the formulation details section of the application form.

6.2.4 Manufacture of the finished product

6.2.4.1 Licensing and control

Where Australian manufacturers are nominated in an application, 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 is expected to demonstrate the same acceptable standard of GMP that would be required of an Australian manufacturer. Pre-clearance of overseas manufacturers is mandatory for Registered complementary medicines. Details of the TGA’s requirements for Australian manufacturers are specified in the PICS Guide for Good Manufacturing Practice for Medicinal Products (15 January 2009).

The information required to establish the standard of an overseas manufacturer is found on documents that are available from the TGA website: http://www.tga.gov.au/industry/manuf-overseas-medicines-gmp-clearance.htm.

Where the manufacture of a proprietary ingredient is considered a significant step in the manufacture of the finished product (e.g. a tablet granulation, an 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).

6.2.4.2 Batch formulation

A batch formula should be provided in table format. It should include 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).

6.2.4.3 Description of manufacturing process and process controls

Details of the manufacturing process for the finished product should be provided 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 that are used, even if they are evaporated from the product during manufacture;
- polishing agents that do not appear in the formulation.

6.2.4.4 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 provided (such as manufacturing acceptance criteria for a tablet granulation or in-process controls for pH during mixing of a syrup).

6.2.5 Control of excipients – specifications

All ingredients in Registered complementary medicines, including excipient ingredients, should have suitable specifications. Where there is a TGA-recognised monograph or standard\(^6\) for the substance, and if no modifications or additions have been made to the tests and limits of that monograph or standard, reference to that document is sufficient.

If there is no relevant monograph or standard for the active ingredient, full details of the specifications for each excipient are required.

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 ARGCM Part IV, Ingredients of Animal or Human Origin and Section 15 Genetically Modified Organisms.

6.2.5.1 Proprietary ingredients

The specifications applied to proprietary ingredients should be appropriate for the nature of the ingredient, and for its function and proportion in the finished product.

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

See also Section 6.2.3.3.

6.2.5.2 Colouring ingredients

The specifications that should be applied to colouring agents allowed in complementary medicines for ingestion are detailed in the document Colourings Permitted in Medicines for Oral Use. The specifications for colourings used in topical products should be comparable to the specifications detailed for colourings permitted in medicines for oral use.

6.2.6 Control of active ingredient – 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 or USP this is the minimum standard that must be applied in its entirety; otherwise, a justification is required. Note that the BP, PH Eur or USP specifications are expiry specifications. The requirements of applicable general monographs of the BP, PH Eur or USP must also be met, except where a justification for not doing so is authorised by the TGA. Examples of BP 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.

---

\(^6\) Where there is a BP, PH Eur or USP monograph, this must be followed. If a sponsor proposes to use an alternative monograph or standard when there is a BP, PH Eur or USP standard, they should apply to the TGA in writing, seeking an exemption under section 14 of the Act. Section 14 exemptions 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.
Typically, the manufacturer of the active ingredient will apply specifications for the substance at the time of its manufacture. The finished product manufacturer is also expected to ensure that the active ingredient complies with specifications before using the substance in the finished product.

This section refers to the specifications used by the manufacturer of the finished product to ensure its quality prior to its use.

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

Where there is no BP, PH Eur or USP monograph, it is generally acceptable to adopt the tests, limits and test methods of another recognised monograph as the specification for an ingredient. Where there is a TGA-recognised monograph (BP, PH Eur or USP) or standard for the substance, and if no modifications or additions have been made to the tests and limits of that monograph or standard, reference to that document is sufficient for this section of the application submission.

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 for 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 need not be provided here if they have already been provided under Section 6.1.3, Control of Active Substance – Specifications.

For further guidance on the types of tests and appropriate limits for complementary medicine substances, refer to Section 6.1.3, Control of Active Substance – Specifications.

6.2.7 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 or USP this is the minimum standard that must be applied in its entirety; otherwise, a justification is required. Note that the BP, PH EUR or USP specifications are expiry specifications. The requirements of applicable general monographs of the BP, PH EUR or USP must also be met, except where a justification for not doing so is authorised by the TGA. Examples of BP 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 physico-chemical testing) where variation 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; those against which the product is tested to ensure satisfactory quality throughout its shelf life are referred to as the “expiry” specifications.

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

6.2.7.1 Data requirements

A table of the tests, test methods and limits should be provided (e.g. assay (gas chromatograph): 95.0 – 105.0 per cent). See ARGCM Part IV, Product Specifications for a template for product specifications. For
dissolution tests, brief details of the apparatus, medium and limit should be provided (e.g. dissolution (paddle at 50 rpm, 900 mL of water, Q = 80 per cent at 30 minutes). The summary list should give details of both the batch release and the expiry specifications. 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 stated for clarity. The specification code number and date should be stated.

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

The batch release limits must be chosen in order to guarantee that all batches will comply with the expiry specifications throughout the product’s shelf life. As a minimum, the expiry specifications should include all of the tests in the batch release specifications.

The specifications must include the requirements listed in any relevant Therapeutic Goods Order (e.g. TGO 78) and in any relevant BP, PH Eur or USP general monograph.

Typically, the release and expiry specifications will include an identification test for the active ingredients and an acceptable range of assay for them (usually the limits given in TGO 78). The specifications will also include limits for tests required under other TGOs (e.g. disintegration or dissolution in the case of tablets, capsules and pills), or in the BP, PH Eur or USP. Other common specifications include weight per tablet/capsule/pill, loss on drying, impurities and microbiological specifications (see below).

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 currently promulgated BP, PH Eur or USP edition: the use of earlier editions of the BP, EP or USP would require a justification. If the sponsor considers that the BP, PH Eur or USP test methods are unsatisfactory for the product, the sponsor may propose another method that has been validated.

### 6.2.7.2 Quantified by Input

Sponsors should refer to the TGA guidance document [Quantified by Input](#).

### 6.2.7.3 Impurity Requirements for Non-pharmacopoeial Products

The specifications for finished products for which there is neither a BP, PH Eur or USP monograph for a closely related finished product, should include tests and limits for impurities related to the active ingredient.

For impurity limits, the results of stability studies should be taken into account and reference should be made to information on toxicity. Specifically, the amount and types of impurities that were detected in the stability studies should be consistent with the expiry specifications and the proposed shelf life. Consideration also needs to be given to the materials examined in the toxicity studies so that the product is consistent with the submitted safety data.

Unless otherwise agreed for a particular product, limits on impurities in finished products apply to impurities from all sources except water.

In general, the following limits on impurities will not need to be supported by a detailed justification:

- individual impurities - NMT 1 per cent
- total impurities - NMT 3 per cent

Where the active ingredient is a chemical entity, guidance on the amount and type of information needed on degradation products of the active ingredient can be found in the EMEA Impurities Testing Guideline: Impurities in New Drug Products (ICH Topic Q3A(R))(CPMP/ICH/2738/99).

For products that have more than one active ingredient, the limits on impurities associated with one active ingredient would usually be determined separately from the limits for impurities associated with...
the others. In such cases, the limit on an impurity should usually be expressed relative to the content of the relevant active ingredient.

During the testing of finished products, the TGA Laboratories will consider a sample to have failed if it contains a level of impurities greater than the above general limits, unless:

- the product is closely related to a product that is subject to a BP, PH Eur or USP monograph allowing a greater content than nominated above;
- a higher level has been agreed during the process of evaluation for Registration; or
- the sponsor can justify the level that has been found in the terms outlined above.

6.2.7.4 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, the basis for this decision should be discussed in the application under Section 6.2.7.9, Justification of Finished Product Specifications.

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

6.2.7.5 Microbiological requirements

Sterile products

The official requirements for sterility tests in Australia are those specified in the current gazetted edition of the BP, PH Eur or USP. This is the minimum standard with which manufacturers must comply. The sterility tests published in editions of the BP, PH Eur or USP prior to 1998 are not acceptable. The TGA Guidelines for Sterility Testing of Therapeutic Goods provide guidance for sterility testing of sterile therapeutic goods supplied in Australia for human use. These guidelines, however, are not mandatory for industry.

Generally, products that are required to be sterile (e.g. for ophthalmic use) will require extremely stringent microbiological specifications together with detailed information on manufacturing steps that ensure sterility.

Non-sterile products

TGO 77 – Microbiological standards for medicines 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 their absence can be justified in the application by establishing 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 that the manufacturing processes do not permit contamination by excessive numbers of microorganisms, by testing a number of routine production batches to establish a product history, testing could be reduced to once every six to twelve months or on a selected basis (e.g. every tenth batch).

Products with 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, both the batch release and expiry specifications should include physico-chemical tests and limits for content of preservatives. Given that the effectiveness
of many preservatives is pH dependent, the specifications for such products should usually include requirements for pH that will ensure preservative efficacy. The expiry limits for the preservative should be supported by preservative efficacy testing that is performed during stability testing.

6.2.7.6 Tablets and capsules

If the product is in tablet or capsule form, sponsors should ensure that it complies with the relevant TGO, BP, PH Eur or USP monograph, noting that the requirements of TGOs take precedence over those of the BP, PH Eur or USP. The finished product specifications must include details of any required test (e.g., disintegration), referencing the test limits and test method defined in the TGO or monograph.

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 includes a test, the USP dissolution test should be included in the finished product specifications. If there are no pharmacopoeial monographs for the product or a related product that include 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 after Registration.

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 in which dissolution testing is appropriate.

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. It does not necessarily mean that every batch must be tested at release.

Modified release products must include dissolution testing in the finished product specification. If sponsors wish to employ a non-pharmacopoeial dissolution test, the proposed dissolution requirements will need to be evaluated by the TGA in terms of the dissolution apparatus, the rotational speed, the dissolution medium, the sampling time and limit (USP “Q” value preferred) and the dissolution profile of the product. A justification for the proposed test and limit should be included.

6.2.7.7 Products containing herbal substances and ingredients derived from herbal substances

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

6.2.7.8 Analytical procedures & validation

Validation data are not required for methods described in a TGA-recognised monograph or standard.

Details should be provided of 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 degradation products and other likely impurities), and linearity.

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

6.2.7.9 Justification of finished product specifications

The suitability of the tests, limits and test methods proposed for the finished product should be discussed with 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 included.

The limits applied at batch release should be discussed in terms of their ability to ensure that the product will remain within the expiry specification throughout its 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 comment.

The reasons for proposed ranges in the quantities of any ingredients should be discussed in the application. Validation data should be provided in support of any unusually wide ranges.

6.2.8 Batch certificates of analysis

The sponsor must provide at least three 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 such a case, the sponsor should identify any differences between the trial process and the manufacturing process and undertake to provide certificates of analysis for at least two production batches after Registration has been achieved. ARGCM Part IV contains more guidance on certificates of analysis.

6.2.9 Container

A description of the container and closure system should be provided, including the materials used. The suitability of the container should be discussed in terms of its compatibility with the product and its performance in protecting the product physically and also in protecting it from moisture and light.

In the case of “standard” package types, it may be sufficient to simply describe the packaging. Many sponsors provide diagrams of the packaging material, identifying bottle or box dimensions, and this is helpful. If the packaging material is unusual, very detailed information should be provided on its composition, as well as an assessment of the potential for undesirable material to be leached from the packaging into the medicine.

6.2.9.1 Child resistant closures

TGO No. 80 – Child-Resistant Packaging requirements for medicines (TGO 80) covers standards for child-resistant packaging for 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 whilst 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 reasonably cause consumers to believe the packaging is child-resistant, then the provisions of TGO 78 relating to performance standards apply. Presentations considered to imply packaging is child-resistant 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 preventing access by children.

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 in December 2000.

The Code of Practice is currently under review by an expert Subcommittee of the Therapeutic Goods Committee (TGC) to ensure that it reflects current packaging technologies and stakeholder needs. Sponsors are encouraged to continue to comply with the Code of Practice on a voluntary basis while it is under review.

6.2.9.3 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 XIII – Uniformity of weight (mass) of delivered doses from multi-dose containers. This is to ensure that the device consistently delivers an accurate dose for oral dosage forms such as granules, powders and liquids.

6.2.10 Finished product stability

All applications to Register a complementary medicine must include stability data for the proposed finished product. The stability data 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 the product’s shelf life. The stability data will form the basis for setting a shelf life and recommended storage conditions for the product.

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

- study design;
- test methods;
- commentary on the results obtained in the studies for individual parameters (including any trends);
- conclusions and summary of claims.

The maximum permitted shelf life is five years.

Explanatory notes that discuss the principles of stability studies in more depth are in Appendix 1 Stability of the Finished Product. Stability data for active ingredients are covered in Section 6.1.4.

6.2.10.1 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 more challenges than the same procedures 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 about stability testing for these substances.

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

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

6.2.10.2 Stability submission requirements

Table 2 summarises the stability data and analysis that is expected to support an application to Register a complementary medicine.
### Table 2. Summary of stability information for the finished product

| Critical summary          | • Provide for each stability study  
|                          | • State the formulation, production and packaging of the product placed on stability testing and whether 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\(^7\)  
|                          | • Justify any deviations from the stability guidelines and address any deficiencies  
| Tests                    | • State and justify the parameters tested during the stability study (preferably tabulated)  
| 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  

\(^7\) Where the data from the stability study shows 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 undertake a critical analysis of the stability studies conducted. The following format is suggested to facilitate evaluation by the TGA.

- Complete 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.

- State whether all or some of the batches tested were identical (e.g. formulation, manufacture, extraction process of a herbal ingredient) to the product intended for supply. If not, the differences should be identified and justified.

- Summarise 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.

- Critically analyse the results, with particular attention to degradation products, trends and indications that the product may fail to comply with the expiry specifications. 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.

- State which test methods are identical to the expiry specifications and provide validation data for test methods for which no validation data have been supplied previously. 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 are 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 in these aspects to the product intended for market should be included. Any differences between the stability and production batches should be stated and justified. Stability data for formulations that are different to that proposed for marketing are not usually considered acceptable to support Registration of a complementary medicine.

A requested shelf life will not normally be approved for the purposes of Registration if there are no data on the actual formulation to be Registered.

Stability information should be generated on a minimum of two commercial-scale (production) batches of the substance. 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, data should be provided for pilot-scale batches manufactured using the same process as intended for commercial-scale batches.

---

8 Where the data from the stability study shows 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.
Where the product is Registered in several strengths, stability data should be generated on two batches of each strength. If the different strengths are a direct scale, at least one batch of each of the highest and lowest strengths should be tested.

**Storage conditions**

The storage conditions used in the stability study should be the same as the recommended storage conditions for the finished product. The storage conditions should be clearly defined using the categories specified in the TGO for Labelling of Therapeutic Goods ([TGO 69](#)), or as revised from time to time:

- Store below −18ºC (Deep freeze);
- Store below −5ºC (Freeze);
- Store below 8ºC (Refrigerate);
- Store at 2ºC to 8ºC (Refrigerate. Do not freeze);
- Store below 25ºC;
- Store below 30ºC.

The TGA will accept for evaluation 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/122/02, rev.1](#)). However, the shelf life assigned to the product on the basis of such data will 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 because they allow the batches to be exposed to a wide range of temperature and humidity conditions and makes the assessment of the stability data difficult.

**Tests**

The parameters tested in stability studies should include relevant physico-chemical 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 that are not appropriate to include in the stability study, such as for the identity of the active ingredients and any other parameters that are usually only tested 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 the quality and the efficacy of the product.

**Methods**

A list of tests used in the stability studies indicating the test method used in each case should be provided. Where a test method is included in a pharmacopoeial monograph for the product, the pharmacopoeial reference (e.g. BP, PH Eur or USP) should be given. It should be noted, however, that many BP assays do not indicate stability. Where a test method is not included in a pharmacopoeial monograph, a full copy of that method should be attached.
The test methods should be stability indicating and validated. They 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, this should be stated and validation data for the new tests should be included.

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 stated. If the change is significant, data should be provided to either demonstrate equivalency with the previous test method, or to allow the evaluator to assess the stability results from the two methods.

Guidance on validation data can be found in Finished product (medicine) analytical procedure validation for complementary medicines.

Data requirements

Both individual and summary data should be provided in well-organised tables. The submission of raw stability data is not accepted as an alternative to tabulated results.

The application should include sufficient stability data to justify a shelf life of at least twelve months. This requires studies in which satisfactory results have been obtained under the following durations and conditions of storage:

- twelve months storage at the recommended storage temperature or six months storage at the recommended storage temperature and six months storage at 10°C or more higher than the recommended storage temperature; and

- at least three months storage at elevated humidity if the container is potentially moisture permeable (e.g. blister packaging).

This is the minimum amount of stability data that should be included in an application to Register a complementary medicine. Stability data for longer periods could support a longer shelf life if the results are acceptable.

6.2.10.3 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, 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 25°C and 80 per cent relative humidity (RH) or 30°C and 75 per cent RH for three months are normally sufficient to establish the adequacy of the packaging to protect the product from moisture for a period of up to two years.

9 The ICH guideline – Note for Guidance on Stability Data Package for Registration Applications in Climatic Zones III and IV (CPMP/ICH/421/02) has been adopted by the TGA with an Australian specific annotation. Sponsors should refer to the ICH guideline and the TGA annotation to determine the Australian specific requirements for stability studies (e.g. study conditions such as temperature, relative humidity and length of time).
Data showing stability for a period of six months are normally sufficient to support a shelf life in excess of two years.

**Suspensions or solutions of poorly soluble ingredients**

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

**Microbial content testing**

All non-sterile dosage forms should include limits for microbial content in the expiry specifications unless, departure from this requirement is justified. Where this exemption does not apply, microbial content testing should be carried out at the end (and preferably at the beginning) of shelf life during stability studies to demonstrate that the product remains within product specifications until expiry. See also Section 6.2.7.5, Microbiological Requirements.

**Preservative efficacy**

Products that are intended for multi-dose use should be adequately preserved for the duration of the claimed shelf life. This applies to both non-sterile products (e.g. aqueous creams, oral liquids) and sterile products (e.g. eye preparations). It is necessary to prevent microbial proliferation in, or microbial contamination of, such products during their normal conditions of storage and use.

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 specific to the formulation and the container. If the requested 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 in accordance 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.

For sterile products (e.g. eye preparations) that are intended for multiple use, the effectiveness of the preservative over the open shelf-life period (e.g. four weeks for eye preparations) must also be demonstrated. Such testing should involve repeated microbial challenges over the open shelf-life period, as this most closely mimics the in-use situation. Alternatively, microbial content testing may be carried out on partially used containers that have been used by patients for the full open shelf life.

Modifications of a pharmacopoeial preservative efficacy test (preferably the PH Eur/BP 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.
6.2.10.4 Post-registration requirements

Sponsors of therapeutic goods are required to carry out an ongoing stability testing program on each product (refer to the [PIC/S Guide for Good Manufacturing Practice for Medicinal Products – 15 January 2009](#)).

Where a shelf life has been allocated on the basis of:
- accelerated testing;
- data generated on a related formulation;
- data generated on the same formulation in a different container; or
- data generated on batches other than production batches,

it is a requirement to provide an assurance that full stability testing will begin on at least the first two production batches and continue for the full period of the product’s shelf life (at the recommended storage condition) and that any adverse trends will be reported to the TGA.

Data may be requested for review at any time or followed up by the TGA’s auditors during GMP audits of the manufacturer. If it is found that the required testing has not been carried out or that adverse trends have not been reported to the TGA, appropriate action may be taken, which may include cancellation of the product’s Registration.

6.2.10.5 Stability protocol for self-assessable shelf life extension

A product’s shelf life may be extended on the basis of stability testing conducted according to a protocol specifically approved for this purpose. For a stability protocol to be considered for the purpose of self-assessable shelf life extensions, it is normally necessary for at least twelve months data, generated at the maximum recommended storage temperature, to be available on at least two production batches of the proposed formulation, 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 may submit the data for evaluation by the TGA.

The protocol should be a stand-alone document, which includes:
- a statement of the intended purpose (e.g. “This protocol is intended for notification of shelf life increases of up to x years following self-assessment of stability data”);
- a statement of the criteria for notifying a shelf-life increase (e.g. “Full-term stability data will be generated using two production batches stored at y °C. All analytical results obtained will comply with the protocol acceptance criteria; otherwise, the TGA will be notified immediately”);
- 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 (validation data should be included if it has not already been supplied to the TGA) (refer to Appendix 1, Section A1.2 Appropriate Tests and Section A1.4 Prediction of Shelf Life from Accelerated Stability Data);
• 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.

6.2.10.6 Shelf life extensions according to an approved protocol

Provided that a protocol for self-assessable shelf life extensions has been approved by the TGA for a particular product, the shelf life extension for that product may be implemented following notification to the TGA, provided that:

• all results up to the end of the notified shelf life fall within the acceptance criteria as specified in the approved stability protocol;

• no other changes to the information previously provided to the TGA about this product (other than as specified in the notification) have been made, or are currently proposed to be made;

• a stability testing protocol has been approved for the product and a copy of the approval letter is attached to the notification;

• at least two full production batches of the Australian formulation product packed in the approved container have been used in the studies;

• the shelf life is not longer than the time for which stability data meeting the approved protocol are available, and in any case is not longer than five years.

6.2.10.7 Prospective extensions of shelf life for individual batches

Under certain circumstances, the TGA may approve a limited extension of shelf life for individual batches approaching their expiry date in the absence of the stability data. The prerequisites are as follows:

• the existing shelf life should be at least two years;

• stability data should be available to the TGA which validate the existing shelf life;

• a recent (less than two months old), dated certificate of analysis should be supplied for the batch, showing compliance with specifications, together with the results obtained at batch release;

• the sponsor should provide an assurance that it has commenced or intends to commence a stability study to validate a permanent extension of the shelf life, unless it is intended as a purely one-off event to ensure continued supply.

Prospective extensions of more than six months, or to a shelf life of more than five years, are not normally acceptable.
7.0 Efficacy and safety

This section is divided into the following subsections:

7.1. Introduction
7.2. Registration and Scheduling
7.3. TGA Guidelines Relevant to Efficacy and Safety
7.4. Points to Consider in Preparing an Application for Registration
7.5. Efficacy
7.6. Safety
7.7. Benefits and Risks – Conclusion
7.8. Clinical Trials of Complementary Medicines

7.1 Introduction

Sponsors of complementary medicines may apply for Registration of products containing otherwise listable substances that are for indications outside those allowed for listable products.

The Therapeutic Goods Administration (TGA) has compiled a list (the Registrable Diseases List) of diseases/disorders/conditions about which indications/claims may be made only after an evaluation of evidence by the TGA before approval of the product and inclusion on the Australian Register of Therapeutic Goods (ARTG). The list applies to medicines but not devices.

The list is contained in the TGA document Guidelines for Levels and Kinds of Evidence to Support Indications and Claims. Applicants should review this document to determine the definitions and levels of evidence needed for medium and high level claims.

7.2 Registration and scheduling

Registration of a complementary medicine does not necessarily mean that the product will be a general sales medicine (ie. not subject to the conditions of a Schedule (or applicable Appendix) to the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP).

The classification of products in one of the SUSMP’s Schedules is done at the time of Registration of the product by the TGA. The TGA may seek advice on the appropriate schedule for a product from one or more of the TGA Advisory Committees.

A Registrable complementary medicine may be included in one of the following Schedules:
- General sales medicine (unscheduled);
- Over-the-Counter (OTC) medicine (Pharmacy Medicine – Schedule 2 or Pharmacist Medicine – Schedule 3);
- Prescription medicine (Schedule 4).

Applicants should review the Principles of Scheduling found in the SUSMP and in the National Coordinating Committee on Therapeutic Goods (NCCTG) Scheduling Policy Framework for Medicines and Chemicals. From these documents it can be seen that medicines are not scheduled solely on the basis of toxicity. As stated in the SUSMP:
Although toxicity is one of the factors considered, and is itself a complex of factors, the decision to include a substance in a particular Schedule also takes into account many other criteria such as the purpose of use, potential for abuse, safety in use and the need for the substance.

Products with similar indications are likely to have similar schedules. Complementary medicines, which are approved for Registrable indications, may be considered for inclusion in a Schedule to the SUSMP.

It is important that applicants consider possible scheduling outcomes before submitting an application, as the data requirements differ for OTC and prescription products. If applicants are unsure of the schedule of their product or how it may change they should seek advice from the Office of Complementary Medicines.

7.3 TGA guidelines relevant to efficacy and safety

It is the general intention of the TGA that products with similar indications will be assessed using a “level playing field” for the quality of data provided in support of the indication. It may be important for sponsors to look at the guidelines applying to registered pharmaceutical products for the same indications.

Guidelines on levels and kinds of evidence to support claims on therapeutic goods offers advice on the level (general, medium and high) of an indication or claim and the evidence required to support it. Registered medicines can carry claims of any level, provided the TGA has evaluated the evidence to support the indication and approved the indication for the Registered medicine.

The Australian Regulatory Guidelines for Prescription Medicines (ARGPM), are intended for evaluation of prescription medicines by the Office of Medicines Authorisation (OMA). If a Registered complementary medicine is to be supplied with a prescription from a medical practitioner, the Australian Regulatory Guidelines for Complementary Medicines (ARGCM; these guidelines) apply. However, where relevant, reference may be made to the ARGPM for guidance.

The Australian Regulatory Guidelines for OTC Medicines (ARGOM) applies to the Registration of OTC medicines by the OTC Medicines Evaluation Section. If a Registered complementary medicine is to be supplied as an OTC medicine, then the ARGCM applies. However, where relevant, reference may be made to the ARGOM for guidance.

The website of the European Medicines Agency (EMA) contains detailed information about medicine evaluation, including guidelines on the evaluation of herbal medicines.

Applicants should be aware that the TGA has adopted a number of guidance documents produced by the EMA. These cover a range of therapeutic classes. Applicants should check these documents to be aware of any guidelines that may be relevant to their product.

All EMA-European Union guidelines referenced in the ARGCM are available in portable document format (pdf) from the TGA web page – European Union Guidelines Adopted in Australia.

The United States Food and Drug Administration (FDA) has produced a large number of guidelines covering a wide range of therapeutic classes. Applicants should check the FDA website to be aware of any guidelines that may be relevant to their products.

The TGA guideline Literature Based Submissions – Points to Consider provides advice on how to undertake literature-based submissions for products being evaluated by the OMA, and may be helpful to sponsors making such submissions.

7.4 Points to consider in preparing an application for registration

The following is presented to assist applicants in compiling the best possible data package and submission for Registration of a complementary medicine. Not all sections may be relevant to all applications, but sponsors are advised to consider the applicability of these comments to each application.
7.4.1 Quality of data

It is likely that many submissions to demonstrate efficacy and safety will be bibliographic, or literature based (i.e. they will consist solely of published papers). In these cases it is important that applicants are able to comment on the quality of the data submitted and place it in context to the body of data which exists. Applicants not familiar with literature searching should read the TGA guideline Points to Consider - Literature Based Submissions, Section 7.4.1.1 details the areas that should be addressed in an application.

Sponsors are also encouraged to submit applications based on clinical trials conducted on the product for Registration.

Applications based on the literature or on clinical trials should include:

- an index of contents;
- an overview referenced to the submission by page number;
- an expert report referenced to the submission by page number;
- full copies (not abstracts) of all relevant reports and clinical trials.

The Expert Report

However the application is based, an expert report should be included and cross-referenced by page number to the submission. The expert, who may be employed by the sponsor, should be a person with appropriate qualifications and experience.

The expert report should include a critical appraisal of the quality of the data generated from each trial and the relevance of the results to the efficacy and safety of the product.

Where more than one indication is claimed, each indication should be separately justified in relation to the data included in the submission.

Where more than one active ingredient is included in the product, each active ingredient and the product as a whole should be justified in terms of their inherent efficacy and safety. The justification should include a consideration of the pharmacodynamics and pharmacokinetics of each active ingredient in relation to the product as a whole. See also Section 7.5.3, Well Documented Ingredients.

For adverse events, the expert report should provide an assessment of overall incidence, seriousness, causality of effects, dose–response relationship, special population subgroups such as the elderly and patients with renal or hepatic impairment, and an indication of reversibility or otherwise.

Guidance on the content and format of an expert report may be found in the International Conference on Harmonisation (ICH) guidance document Structure and Content of Clinical Study Reports, which is published by the EMEA as Note for Guidance on Structure and Content of Clinical Study Reports (ICH Topic E3) CPMP/ICH/137/95.

In addition, Module 1.4 of the TGA’s Common Technical Document (CTD) Module 1 – Administrative Information and Prescribing Information for Australia, contains a pro-forma for supplying information about the expert.

7.4.1.1 Searching the literature on complementary medicines

In compiling a literature-based submission it is not appropriate to simply collect and submit a few favourable published papers. The sponsor must demonstrate that:

- the relevant literature has been methodically scrutinised;
- the range of papers selected for submission is justified;
- issues raised in the literature in relation to the application have been addressed.

This brief guide is intended to aid sponsors with the literature search methodology that underpins these three requirements.
There is no fixed search strategy that can be applied in all cases, since, to be successful, each application requires flexibility and responsiveness to the strands of inquiry revealed in the literature.

It is important that, whatever the methodology used, there is a clear explanation and justification included in the application.

The essential elements of a systematic search of the literature are information sources, search terms, and search strategy.

As with other aspects of a submission, reporting on the methodology of how a submission is prepared is a key factor in enabling the TGA evaluation to assess the quality of the data submitted. The completeness of the search conducted by the applicant is a measure of the quality of the search.

Applicants not familiar with literature searching should read the TGA guidance document Literature-Based Submissions - Points to Consider.

The information provided in the literature search report should include the search strategy and comment on the selection of papers included in the submission.

The search strategy should include the names of the databases searched, and the logic, terms and commands used in the search. It is also important that the period (years) covered by the search is also included.

It is not mandatory to include the search output in the application, but sponsors should comment on why they have selected the papers submitted. Particular attention should be paid to explaining both why some papers are included and others are excluded.

7.4.1.2 Information sources

Various types of print and electronic sources may be considered for inclusion in a literature search. The minimum would be:

1. Pharmacopoeias, which may be national, international or country specific. Entries should be provided in English, where possible, but this does not preclude the submission of texts in other languages;

2. The current editions of Merck Index and Martindale;

3. A monograph from HSDB (Hazardous Substances Databank), RTECS (Register of Toxic Effects of Chemical Substances), Poisindex or similar toxicology database;

4. A bibliographic search of ToxNet, Medline and Embase;

5. Current and/or classical references in the specific field under review (e.g. herbal or homoeopathic pharmacopoeias or standard works on the materia medica of traditional medicines);

6. Standard reproductive toxicity texts (e.g. Shepherd’s Catalog of Teratogenic Agents).

Details of the sources highlighted above are listed in the references below. However, there are many other sources that may need to be considered for a particular submission.

A comprehensive search would normally include multiple and significant biomedical, pharmaceutical, food science, botanical, toxicological and alternative medicine databases. Among the major databases of peer-reviewed literature are MEDLINE, EMBASE, TOXLINE, BIOSIS (Biological Abstracts), CHEMICAL ABSTRACTS, FSTA (Food Science and Technology Abstracts), IBIDS (International Bibliographic Information on Dietary Supplements), NAPRALERT, AMED (Allied and Alternative Medicine), MANTIS, CAB ABSTRACTS, SCISEARCH (Science Citation Index).

Some of the above are free, and the others are available on subscription in various electronic formats.

Depending on the nature of the substance in the application, specialist sources may have to be used. For example, if a product is of marine origin, the literature search may include databases of aquatic literature and pertinent standard references in marine science.
If the source used is “in-house”, as some databases are, or is the result of individual research, such as an unpublished thesis or personal bibliography, it is important that its nature is fully described in order to establish its currency, authority and comprehensiveness.

The Internet is merely a platform for information. Any Internet search engine will pick up references, but these are only of value in an application in the light of their integrity, authority and scientific validity. Significant databases are available free on the Internet, and searches of specific sites can be valuable starting points. A few examples are given in the references below.

### 7.4.1.3 Search terms

As many relevant terms as possible for the substance should be identified and used in the literature search. Terms should include generic and trade names, traditional names, botanical terminology and Chemical Abstracts Service (CAS) registry numbers (see references below).

In the case of botanicals or substances that may have multiple constituents, terms for the constituents should also be searched (e.g. in the case of ginger, terms such as zingerols, zingiberenes, as well as zingiber and ginger).

Where different terms are used, there should be clear evidence of identity. For example, shosaikoto (Japanese) is *xiaochaihu tang* (Chinese Pin Yin), but is also called *Minor bupleurum decoction* in the Chinese literature. Similarly, there should be evidence of chemical identity (e.g. CAS registry numbers are consistent across different records).

In addition to nomenclature, terms for particular aspects of the search should be considered, such as:

1. constituents, analysis, composition;
2. toxicity, carcinogenicity, mutagenicity;
3. teratogenicity, pregnancy, lactation;
4. safety, adverse reactions, adverse events, interactions, poisoning, overdose;
5. pharmacokinetics, pharmacodynamics, pharmacology, metabolism, bioavailability.

This list is indicative rather than complete or prescriptive.

### 7.4.1.4 Search strategy

The selecting and combining of terms is fundamentally important in electronic database searches, as is an understanding of the nature of each database. It is outside the scope of these guidelines to address all the complex technical requirements of electronic information retrieval, but some advice is provided in the TGA’s guidance document *Literature - Based Submissions – Points to Consider*.

Searches should not be limited to English, but when foreign language papers are provided they should be accompanied by certified translations.

When submitting an application, the report on the literature search should include a detailed description of the methodology, including the complete strategy used for any database searches, an appraisal of the results and the rationale for the selection of papers.

### 7.4.1.5 Quality of individual publications

In selecting papers to be included in an application, the sponsor should assess:

- the quality of the paper;
- the design of the study reported in the paper;
- the clinical significance of the results.

The quality of the paper can be judged by assessing its scientific impartiality, the completeness of the reporting, the clarity and logic of the argument, and the validity of any conclusions drawn from the study.
The credibility of the journal in which the paper appears (whether subject to peer review or not), duplication of publication (same data in multiple publications) and subsequent comment on the paper (letters, articles or editorials about the paper) may also aid an assessment of the quality of the paper.

Published reports of clinical trials should only be considered as pivotal where:

- the trials are conducted using the same active ingredients, dosage regimen, dose form and route of administration as the product proposed for Registration;
- the trials are reported in sufficient detail to allow an independent assessment of the results (including methods and a statistical analysis of the results) in relation to the efficacy and safety of the product proposed for Registration.

Abstracts that do not contain sufficient detail to allow an independent assessment may be used as supportive data but will not be accepted as pivotal data.

Well-conducted published reviews (either from journals or textbooks) may serve as pivotal material for well-documented ingredients, but only as supporting material for less well documented ingredients.

The quality of an individual paper is also affected by where it fits in the hierarchy of evidence. Papers will need to be discussed individually and collectively in to rank their evidence.

The generally accepted approach, shown below, is that set out by the National Health and Medical Research Council (NHMRC). Data from randomised, double-blind controlled studies is given greater weight than data from non-randomised, uncontrolled or open studies.

<table>
<thead>
<tr>
<th>Level of evidence</th>
<th>Type of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Evidence obtained from a systematic review of all relevant randomised controlled trials (RCTs).</td>
</tr>
<tr>
<td>II</td>
<td>Evidence from at least one properly designed RCT.</td>
</tr>
<tr>
<td>III-1</td>
<td>Evidence obtained from well-designed pseudo-RCTs (alternate allocation or some other method).</td>
</tr>
<tr>
<td>III-2</td>
<td>Evidence obtained from comparative studies (including systematic review of such studies) with concurrent controls and allocation not randomised, cohort studies, case-control studies, or interrupted time series with a control group.</td>
</tr>
<tr>
<td>III-3</td>
<td>Evidence obtained from comparative studies with historical control, two or more single-arm studies, or interrupted time series without a parallel control group.</td>
</tr>
<tr>
<td>IV</td>
<td>Evidence obtained from case-series, either post-test or pre-test/post-test.</td>
</tr>
</tbody>
</table>

Source: NHMRC 1999

### 7.5 Efficacy

The efficacy section of the application should consist of the following sections subsections:

- an overview;
- study reports and/or publications.

---

17 It is particularly important that there are sufficient details describing the ingredients in the published report to ensure that the trials have been conducted using the ingredients proposed for Registration.
7.5.1 Overview

The overview should present a critical assessment of the clinical data pertinent to the efficacy of the medicine in the intended population. This section should include all the relevant data, both positive and negative, and should explain how the data support the proposed indications and claims. The overview should contain the following subsections:

- pharmacodynamics;
- pharmacokinetics;
- clinical studies.

7.5.1.1 Pharmacodynamics

The pharmacodynamics section should include information on the mechanism of action, if known. It should also include information to justify the proposed dose and dose interval, and any information that may be relevant to formulation differences in the submitted studies and to possible interactions with other medicinal products or substances.

7.5.1.2 Pharmacokinetics

Pharmacokinetics describes the action of the body on the medicine, and includes the absorption, distribution, metabolism and elimination of the medicine. The pharmacokinetics of a medicine may be affected by the formulation of the medicine, by the age, sex and race of the person taking it, and by disease, particularly renal and hepatic impairment, in the person. The need to maintain medicine levels within specified levels in the bloodstream may be important in certain disease states and therefore the bioavailability of some complementary medicines may be very important. Other factors include smoking, concomitant medicines and diet.

Applicants should be aware of the relationship between pharmacokinetics, formulations and batch-to-batch consistency in the manufacturing process. In those diseases in which these may be crucial to efficacy, it is expected that details of pharmacokinetics will be included in the application.

In clinical publications it is often difficult to establish details of the formulations used, particularly with complementary medicines. However, in submissions for indications of treatment of serious diseases where this is considered clinically important, applicants are encouraged to make every attempt to retrieve this information.

7.5.1.3 Bioavailability

Bioavailability describes the proportion of administered medicine reaching the systemic circulation; the formal definition is the rate at and extent to which the active substance is absorbed from a pharmaceutical form and becomes available at the site of action.

In most medicines the active substance is intended to have a systemic effect, so a more practical definition is the extent to and rate at which a substance or its active component is delivered from a pharmaceutical form and becomes available in the general circulation.

Bioavailability is 100 per cent following an intravenous (IV) injection, but medicines are usually given orally and the proportion of medicine reaching the systemic circulation varies with different formulations and dosage forms, and from patient to patient. The “absolute bioavailability” of a given dosage form is the comparison of the dosage form with intravenous administration (e.g. tablet versus IV) and “relative bioavailability” is the comparison with another non-intravenous route (e.g. tablet versus oral solution).

The main parameters measured in bioavailability studies are the maximal blood concentration ($C_{\text{max}}$) and the area under the blood medicine concentration-time curve (AUC) which reflects the total amount of medicine that reaches the systemic sampling site. The time to maximal blood concentration ($T_{\text{max}}$) and the half-life of the product (time for the $C_{\text{max}}$ to fall to half the $C_{\text{max}}$) are also often calculated.
Bioavailability is important because to exert a therapeutic effect the active ingredient of a medicine must be delivered to its site of action in an effective concentration for the required time period to initiate and maintain the action of the medicine.

Bioavailability data for a given formulation provides an estimate of the relative fraction of the orally administered dose that is absorbed into the systemic circulation when compared to the bioavailability data for a solution, suspension or intravenous dosage form.

Bioavailability is therefore a test of the performance of the dosage form, and bioavailability studies are a way to document the product quality. They should be reliable and reproducible.

Bioavailability studies are also important in comparing different formulations and dosage forms, which may be considered equivalent (bioequivalent) if there is no significant difference in the bioavailability of the different products when they are administered under similar conditions.

Differing results seen in different published papers may be due to the differing bioavailability of various formulations of the active substance.

Sponsors planning to market a dosage form different from that described in the published papers presented in their submission may need to conduct a bioavailability study. It may be to prove that the active ingredient is delivered into the systemic circulation or to demonstrate bioequivalence to the formulation used in the published papers. If a bioavailability study is not conducted in these circumstances, a justification for not doing it should be provided.

In order to conduct bioavailability studies, it is essential that the active ingredient of the medicine is known and that there is a method for testing the level of active ingredient in the systemic circulation. The test method (assay) must be accurate, precise, selective for the active ingredient, sensitive (able to test to the level present in circulation) and reproducible.

Additional information on bioavailability may be found in the following guidelines:

- **Note for Guidance on the Investigation of Bioavailability and Bioequivalence. CPMP/EWP/QWP/1401/98 (EMEA 2001);**
- **Guidance for Industry– Bioavailability and Bioequivalence Studies for Orally Administered Drug Products – General Considerations (Revision 1), FDA, March 2003.**

For some complementary medicines, the active ingredient may not be known or there may not be a validated assay for it. In such cases it may not be possible to undertake bioavailability studies. If this is the case, the applicant will have to provide a justification for not providing bioavailability data, detailing the efforts made to identify the active ingredient and/or to develop an appropriate assay.

If bioavailability is considered crucial for the effectiveness of the medicine and the active ingredient is not known or cannot be assayed, the need for specific clinical studies of efficacy to demonstrate the effectiveness of the medicine should be considered.

### 7.5.1.4 Clinical studies

The clinical studies section should include an overview of clinical studies relevant to the proposed indications. The sponsor should differentiate those studies considered pivotal to the submission from those considered to be supportive. One suggested approach is to classify the studies according to the hierarchy of evidence in **Section 7.4.1.5.** However, other approaches may be relevant (e.g. those studies with identical formulation, those with unknown formulations). Whatever approach is used, the randomised controlled trials should be identified.

The following issues should be considered and discussed:

- any differences between the studied population and the population that would be expected to receive the product after marketing;
- implications of the study designs, including selection of patients, duration of studies and choice of endpoints measured;
- validation of any scales used in the studies;
- statistical methods and other matters that could affect the interpretation of the study results;
- similarities and differences in results among different studies, or in different patient subpopulations, and their effect on the interpretation of the efficacy data;
- any observed relationships between efficacy, dose and dosage regimen for each indication, both in the overall population and in any patient subgroups;
- where the product is intended for long-term use, the relevance of efficacy results obtained in short-term studies (likelihood of long-term efficacy, establishment of long-term dosage, possibility of development of tolerance);
- the clinical relevance of the magnitude of the observed effects;
- where surrogate markers are used in the clinical studies, the nature and magnitude of the expected clinical benefit and the basis of these expectations;
- where the studied patient population is special in some way, the applicability of the trial result to the general population.

In addition, if clinical data for the population likely to take the medicine are inadequate, justification should be given for extrapolating efficacy from those populations studied to others, or to the general population.

### 7.5.2 Study reports and/or publications

If a clinical trial has been conducted by the sponsor of the product then a study report should be provided. The study report should be written to comply with the following guideline: CPMP/ICH/137/95 ICH Topic E3 – Structure and Content of Clinical Study Reports. As stated in the guideline, the structure and format required is intended to assist sponsors in the development of a report that is complete, free from ambiguity, well organised and easy to review. It is therefore important that all the headings in the guideline are used. If no information is available for a particular heading, an explanation for the lack of information should be provided. Appendices 3 and 4, containing case record forms and individual patient data listings, are not required.

If the sponsor's study has been published, the published paper should also be included. It is important that the sponsor ensures that the data in the study report and the publication are consistent. Any differences should be explained in detail.

### 7.5.3 Well-documented ingredients

Where an active ingredient has been well known for many years and is well described in standard textbooks/guidelines, it is possible to use these as the basis of the efficacy and safety information.

These standard texts would usually cover substances that have been used in medicines, foods and/or cosmetics in Australia or overseas for many years (such as vitamins and minerals).

The following are examples of the reference texts that are usually acceptable as sources of information on the safety, efficacy and dosage regimen of ingredients:

- Martindale: The Complete Drug Reference, Sweetman SC (ed), Pharmaceutical Press, United Kingdom;
- Handbook of Non-Prescription Drugs, American Society of Health System Pharmacists, United States;
- Remington’s Pharmaceutical Sciences, Gennaro AR (ed), Mack Publishing Company, United States;
- Handbook of Pharmaceutical Excipients, Kibbe AH (ed), American Society of Health System Pharmacists, United States;
Note that indications and dosage must be the same as described in these textbooks. Any use outside the documented indications and/or dosages, or any new route of administration, will require evidence of efficacy and safety, unless otherwise justified.

Note also that anecdotal or limited clinical reports of efficacy alone (e.g. in Martindale, “xxx has also been used in ...”) are not considered evidence of efficacy and safety.

Applications for products with well-documented ingredients should include details of the relevant texts (photocopies of the relevant pages are preferred) with particular references to the accepted indications and dosage of the active ingredients.

7.6 Safety

The safety section should include the following:

- overview of safety;
- any studies that address specific safety issues;
- any studies not submitted in the efficacy section that have been referred to in the overview;
- post-marketing data.

There is no need to submit duplicate copies of studies submitted in the efficacy section. However, the location of the studies in the application should be clearly identified.

7.6.1 Overview of safety

The overview of safety provides a concise critical assessment of the safety data, noting how the results may support and justify any restrictions placed on the product.

The safety profile of the medicine should be described on the basis of an analysis of all the clinical studies included in the submission. The data should be outlined in a detailed, clear and objective manner. Tabulations of adverse events are often helpful.

There should be a brief discussion of common and expected adverse events (both serious and non-serious). Any conclusions about a causal relationship between the product and the event, or lack of it, should be provided.

The following issues should be considered:

- adverse effects that are expected because of the mechanism of action;
- any likely adverse effects expected because of animal data or product quality information (manufacturing processes);
- the nature of the patient population and the extent of exposure;
- any limitations of the safety data derived from the clinical trials (e.g. inclusion/exclusion criteria, trial subject demographics);
- relationship of adverse events to dose, dose regimen and treatment duration;
- similarities and differences in results among studies, and their effect on the interpretation of the safety data;
- any differences in the rates of adverse events in population subgroups, such as those defined by demographic factors, gender, age, race, weight, concomitant illness or concomitant therapy;\(^{18}\)

\(^{18}\) Because of greater awareness of the potential for interactions between concomitantly administered medicines, there has been an international focus on interaction studies rather than on \textit{ad hoc} observational studies. Guidance on points to consider...
• long-term safety;
• any methods to prevent, mitigate or manage adverse events;
• overdose reactions, potential for dependence, rebound phenomena and abuse, or the lack of data on these aspects.

7.6.2 Post marketing data

The sponsor should include all data on the worldwide marketing experience, including all relevant Post Marketing data available to the applicant. This may include published and unpublished data.

Any new or different safety issues identified following marketing should be highlighted and any regulatory action relating to safety taken by an overseas regulatory agency should be detailed.

Details of the number of people estimated to have been exposed should be provided and categorised, as appropriate, by indication, dosage, route of administration, treatment duration and geographical location.

The data should be presented as a tabulation of the adverse events that have been reported, including any serious adverse events and any potentially serious interactions with other medicines.

7.7 Benefits and risks – conclusion

The evaluation of high-level claims (i.e. for the use of medicines for serious illnesses) requires an assessment of the balance between the benefits of a medicine and the risks of its use. There is no simple measure for this: the acceptable level of risk varies with the nature of the benefit, the risk from taking the medicine and the risk of the untreated disease.

Generally, the more serious and life threatening the untreated disease and the greater the benefit, the higher is the level of risk that the TGA is prepared to accept. The benefit–risk balance is also affected by the availability of alternative treatments, the risk profile of those therapies, and the risks of foregoing treatment where this is a medically acceptable option.

Sponsors should understand that the decision to approve a product as a Registrable medicine is a complex one, and is based on the need for the medicine and its benefit–risk ratio.

7.8 Clinical trials of complementary medicines

There is no requirement for complementary medicines, or any other medicine, to be trialled in Australia before an application for Registration is submitted. However, if Australian trials have been completed before application, the TGA expects to see the results of the trials included in the application.

Application under the TGA's Clinical Trial Exemption (CTX) scheme, or notification under the Clinical Trial Notification (CTN) scheme, is required for clinical investigational use of:
• any medicine or device not entered in the ARTG, including any new formulation of an existing product or any new route of administration;
• a marketed medicine or device beyond the conditions of its marketing approval, including new indications extending the use of the product to a new patient group and the extension of doses or duration of treatments outside the approved range.

Before beginning clinical trials in Australia, all parties involved in the planning, design, conduct and monitoring of clinical trials should be aware of the relevant guidelines for such trials. These include:

• the requirements of the TGA, as outlined in *Access to Unapproved Therapeutic Goods – Clinical Trials in Australia*;

• The *National Statement on Ethical Conduct in Research Involving Humans* (NHMRC 2007);

• the current *World Medical Association Declaration of Helsinki*;

• the International Conference on Harmonisation’s *Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95)* or ISO 14155 Clinical Investigation of Medical Devices, whichever is applicable;

• any requirements of Australian laws.
8.0 Labelling and presentation

This section is divided into the following subsections:

8.1. Labelling
8.2. Unacceptable Presentation
8.3. Ingredient Names on Labels

8.1 Labelling

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). Labelling 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.

Labelling is expected to comply with the requirements of:

- Therapeutic Goods Order No. 69 – General requirements for labels for medicines (TGO 69);
- the Therapeutic Goods Regulations 1990 (the Regulations) – relating to restricted or prohibited representations;
- the Therapeutic Goods Advertising Code (TGAC);
- the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP) labelling requirements;
- 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 in 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;
- the expression of quantities of ingredients in labels, with particular requirements for herbal medicines.
There are also labelling requirements established under the SUSMP and RASML. If a medicine contains a scheduled substance, there are additional labelling requirements established under poisons legislation.

Because states and territories vary in the ways they have adopted SUSMP requirements, sponsors should contact the health department, in the state or territory where their product will be supplied, for advice.

While general guidance is provided in this section, sponsors should also note the policy guidance for specific product categories and substances in Parts IV and V of these guidelines.

8.1.1 Labels in applications

Sponsors should include drafts of all product labelling in applications. Artwork ready for printing or examples of the printed labels are preferred. If only the draft label text is submitted, the size, colour and positioning of the text on the label should be made clear. This information is necessary to assess compliance with the various legislative requirements for labelling. Where draft labelling is submitted, copies of the final printed labels must also be provided to the TGA once the product has been registered.

Where the only difference in labelling between pack sizes is the pack size and the sponsor gives an assurance to that effect, only one set of labels need be provided with the application. An assurance that the text size is also identical must also be included. If the text size is different for the alternative pack size label, or if the presentation of the information is different, the label for the alternate pack sizes should also be submitted.

8.1.2 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 (refer to TGO 69 for more details).

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

- There is no objection to a quantitative statement of all ingredients in the product (active ingredients and excipients) or a quantitative statement of the active ingredients and a qualitative statement of the excipients;
- The selective disclosure of individual excipients will not normally 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).

8.1.3 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 only includes doses for 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 Section 6.2.9.3 – 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 5mL medicinal measuring spoons, a dosage stated that way would be acceptable (e.g. "Adult dose: one level 5mL 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 to be included 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).

8.1.4 Comparisons

Comparisons with a competing commercial medicine product are normally not permitted. There may be some circumstances in which this type of comparison is appropriate, for example where a product has been substantially reformulated to improve efficacy. In such cases, a justification for the comparison should be provided.

Statements comparing a product with other treatments or generic medicine substances are discouraged. Where such a statement is made, the application must include evidence to support the claim.

8.1.5 Endorsements

Labels must not contain or imply endorsement of the product except as permitted by the TGAC (Clause 4.4).

The sponsor should remove an endorsement from the labelling (by way of a notification application to the TGA) once the endorsement is no longer applicable.

8.1.6 Distinctiveness of labels

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

8.1.7 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.

8.1.8 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 an age dose range starting at two years).

8.1.9 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, the sponsor 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 and other such ingredients do not contain sugars with a cariogenic potential.
8.1.10 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 proprietary ingredient(s), sponsors must check with the manufacturer of the ingredient to ensure the integrity of the negative disclosure statement.

8.1.11 Warning statements and contraindications
In addition to the warning statements required by the SUSMP and RASML, labels should also include details of significant contraindications and drug interactions, additional warning statements where necessary, and details of the maximum daily dose to be administered.

Where a product may interact with food or other drug products to produce a significant adverse reaction, specific warnings may be required on the label or on package inserts.

8.1.12 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 of the other language text is identical to, or in words to the effect of, that of the English text.

8.1.13 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 in and of themselves have always been considered to fall within the definition of an advertisement and so must comply with all aspects of the TGAC, although they do not require approval. However, arguably any labelling reviewed as part of post market surveillance that includes a website could result in that website being reviewed for compliance to the TGAC.

8.2 Unacceptable presentation
Products are ineligible for inclusion on the ARTG if “the presentation of the goods is unacceptable”. An explanation of what constitutes “unacceptable presentation” may be found in the Therapeutic Goods Act 1989 (the Act). For the purposes of the Act, the presentation of therapeutic goods is unacceptable if it is capable of being misleading or confusing as to the content or proper use of the goods. In addition, 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;
- 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;
- if the label of the goods does not declare the presence of a therapeutically active ingredient;
- 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.
Some examples of unacceptable presentation are given below (note that these are examples only and are not intended as an exhaustive list):

- 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 for more than twelve months in Australia.

- The appropriate dosage for all age groups in the likely target population is not stated (e.g. adults, children six–twelve years etc, as appropriate);

- Warning or cautionary statements necessary for proper usage of the product are omitted;

- Claims are made that a product provides a transdermal delivery system for active ingredients when that characteristic of the formulation has not been established to be true;

- Claims are made that a formulation is “hypo-allergenic” or “non-irritant”, unless the sponsor holds evidence of confirmatory clinical tests that can be produced on request;

- Claims are made that a product is “suitable for diabetics” or “free from artificial colours” if not completely accurate. In this regard, applicants need to take careful account of substances such as sugars and colouring agents that may be present in proprietary ingredients;

- Therapeutically active ingredients are present in the formulation but not declared as such on the label (and/or are 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 a confectionary (e.g. in confectionary-like novelty shapes and packaging);

- Product names that are likely to be misleading as to the composition of the formulation.

### 8.3 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 the ARTG. These lists are published in the TGA Approved Terminology for Medicines, and outline the terminology 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 which comprehensively covers all substances or terms used, or likely to be used, in therapeutic goods in Australia.

**Australian Approved Terminology must be used for all relevant information on the labels.** Complete details of the terminology for medicines are provided in TGA Approved Terminology for Medicines.

Applicants and other users of the list should note the following:
• Inclusion of a substance in *TGA Approved Terminology for Medicines* does not mean that the substance has been approved or that the substance has been previously included in a medicine in the ARTG;

• TGA Approved Terminology for Medicines is the source of AANs;

• Herbal substances are generally named by identifying the herb species, the plant part(s) and the preparation. It may be necessary to combine the AANs for these pieces of information to make the complete AAN for the herbal substance;

• 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;

• The lists of substances included in *TGA Approved Terminology for Medicines* is not a list of ingredients found in products currently included in the ARTG.

If there is no AAN for an ingredient, an application for an AAN for the substance must be submitted in conjunction with the application to Register the medicine product. Information on how to apply for an AAN is in ARGCM Part IV, *Naming of New Substances and Terminology.*
9.0 Product Information

All applications to Register new Schedule 3 medicines and medicines that will only be supplied with a prescription from a medical doctor must be accompanied by a draft Product Information (PI) document, which will be evaluated as part of the application. A PI is not required for other Registered medicines; however, it is strongly recommended for medicines that are almost exclusively supplied on the advice of a healthcare practitioner.

The PI document contains technical information intended for prescribers and pharmacists. Although the PI may be enclosed in the product packaging, this is not encouraged as the information is written in a form meant for healthcare professionals.

The PI should not be confused with package inserts such as the Consumer Medicine Information (CMI) or other package inserts, which are an extension of the labelling (see Section 8, Labelling and Presentation).

The PI is meant to present a scientific, objective account of the product's usefulness and limitations, as shown by the data supporting the application, for the benefit of professionals recommending or prescribing the product. It must not include promotional material.

Once a PI has been approved for a Registered medicine, no changes can be made to it without prior TGA approval (refer Section 11, Changes to Registered Complementary Medicines), except for safety-related changes in accordance with publications or notices from the TGA or the Advisory Committee on the Safety of Medicines (ACSOM).

The PI submitted with an application should contain information under the following headings.

Medicine Product Name

- the proposed name of the product.

Active ingredients

- the names of all of the active ingredients, using Australian Approved Names (AANs);
- if an AAN has not been allocated for the substance, the proposed name;
- for herbal substances, the species name (Latin binomial), plant part and preparation (e.g. Hypericum perforatum herb top extract dry) and any herbal component names;
- for traditional Chinese medicines, the Chinese name (see ARGCM Part IV, Naming of New Substances and Terminology for further information);
- any physical characteristics of the active ingredient that may affect the medicine (e.g. particle size or solubility);
- where the active ingredient is a chemical entity, the chemical structure and the Chemical Abstracts Service (CAS) registry number.

Product description

- the formulation, including excipients, using AANs;
- the dosage form, using Australian Approved Terminology;
- any special characteristics of the product (e.g. slow release).
Pharmacology

- the pharmacology, including pharmacokinetics and pharmacological actions, especially in humans.

Clinical Trials

- a summary of the data that were submitted in the application in support of efficacy.

Indications

- the therapeutic indications of the product, including the outcome of the treatment (i.e. treatment, cure, adjunct therapy).

Contraindications

- those conditions for which, or under which, the product should not be used (in the rare case where the medicine should never be given, additional information outlining the reasons should be provided).

Precautions

- precautions or actions that must be taken to avoid or minimise anticipated risks.

Under this heading, statements must appear under bold subheadings of Use in pregnancy, Use in lactation, Use in special populations (e.g. children or the elderly) and Interactions with other drugs, and may be included under headings of Carcinogenic potential and Mutagenic potential where information could be relevant to the prescriber.

Under the Use in pregnancy subheading, a proposed or approved Australian Pregnancy Categorisation should be included as a minimum. Any additional information must be consistent with this categorisation.

Under the Interactions with other drugs subheading, include known clinically relevant interactions and other potentially serious interactions based on the pharmacology of the drug. It is useful to group interactions according to outcome (e.g. potentiation or reduction of effect) and to explain the mechanism of action, where this is known.

Adverse reactions

Give warnings of possible adverse reactions occurring in normal circumstances of use, in particular circumstances, such as renal, hepatic or cardiac failure, or in the elderly or children. Quantify these reactions, giving frequency in terms of severity and clinical importance, where known.

Dosage

Where relevant, include information on:

- recommended dosage (dose and interval);
- dosage adjustment in renal or liver insufficiency, dialysis, concomitant disease;
- maximum tolerated daily dose and maximum dose for an entire course of therapy;
- advice to healthcare professionals about monitoring patients taking the medicine;
other pertinent information, such as relationship to meals and compatibility with other drugs and fluids.

**Overdosage**

Include information on the symptoms, signs and recommended treatment of overdosage or poisoning.

**Presentation**

Include information on:

- the medicine, including dosage form, strength of each active ingredient, and quantity of doses per container;
- identifying details of the medicine (e.g. colour, shape, identifying markings);
- container type (e.g. blister strip in carton or plastic bottle with child-resistant closure);
- schedule details from the Standard for the Uniform Scheduling of Medicines and Poisons where relevant;
- name and address of the sponsor.
10.0 Consumer Medicine Information

The Regulations require that sponsors supply a Consumer Medicine Information (CMI) document with the following classes of medicines:

- medicines containing ingredients that are listed in Schedule 3 to the Standard for the Uniform Scheduling of Medicines and Poisons
- medicines that are supplied only with a prescription from a medical doctor.

The CMI may be provided in the primary pack (i.e. as a package insert) or in electronic form via pharmacy computers. All applications to register a medicine containing a Schedule 3 ingredient or a prescription medicine must include a draft CMI. Note that it is an offence for the sponsor to supply these products without a CMI.

The CMI must be consistent with the information that is in the Product Information (PI) and it must not include promotional material. The CMI must be in English and written in language that will be readily understood by patients. Sponsors are encouraged to follow the useability guidelines Writing About Medicines for People: Useability Guidelines for Consumer Medicine Information.

10.1 Required headings and content of CMI

The requirements for the contents of the CMI are specified in Schedule 12 (prescription medicines) and Schedule 13 (medicines containing Schedule 3 ingredients) to the Regulations. The subheadings in the CMI must be the headings specified in the relevant schedule.

Identification

- the name of the medicinal product, which is the name given to the product by the sponsor, including or followed by the non-proprietary names of the active ingredients and the dosage form or strength, or both, of the product;
- a statement of the active ingredients (expressed quantitatively) and excipients (expressed qualitatively), using their common names, in the case of each presentation of the product;
- the pharmaceutical form and the contents by weight, volume or number of doses of the product, in the case of each presentation of the product, together with its identifying Australian Register of Therapeutic Goods number.

What the product is used for and how it works

- the therapeutic indications, unless a competent authority determines that dissemination of such information may have serious disadvantages for the patient.
• the pharmaco-therapeutic group, or type of activity, if there is a term that is easily comprehensible for the patient; if not, a simple description of what the medicinal product is for and how it works, in one or two sentences.

Advice before using the medicinal product

A list of factors that are useful to consider before taking the medicinal product, including, if appropriate:
• contraindications, including consideration of whether the patient has experienced previous allergic reactions;
• precautions for use, taking into account the particular condition of certain categories of users, such as the elderly, children, infants, pregnant or breastfeeding women, people with specific pathological conditions;
• potential effects of the product on the ability to drive vehicles or to operate machinery;
• interactions with other medicinal products or other forms of interaction (e.g. with alcohol, tobacco, foodstuffs) that may affect the action of the product;
• special warnings, such as effects on sensitivity to sun exposure.

How to use the medicinal product properly

The necessary and usual instructions for proper use of the medicinal product, in particular:
• the dosage, together with an indication that this may not always apply and may be modified by the prescriber;
• the method and, if necessary, route of administration;
• the frequency of administration, specifying, if necessary, the appropriate time at which the medicinal product should or must be used.

In addition, depending upon the nature of the product:
• the duration of treatment, if the duration should be limited;
• the expected effect of using the product;
• what to do if one or more doses have not been taken at the right time;
• the way the treatment should be stopped, if stopping the treatment may lead to withdrawal symptoms or other adverse effects.

Further information

• for example, habit-forming potential and whether a doctor’s prescription is required.

Unwanted effects

• a description of the undesirable effects that can occur during normal use of the product and, if necessary, the action to be taken if such effects are experienced;
• an express invitation to the patient to communicate any undesirable effect, especially if it is not mentioned in the CMI document, to his or her doctor or pharmacist.
In case of overdose

- the action to be undertaken in the case of overdose (e.g. symptoms and emergency procedures).

Storage conditions

- an indication of the appropriate storage conditions;
- a reference to the expiry date indicated on the label, with a warning against using the product after this date;
- if appropriate, a warning against visible signs of deterioration.

Where to go for further information

- a direction to patients to discuss any concerns with the doctor or pharmacist and, if appropriate, where further information may be obtained.

Sponsor

- the name and address of the Australian sponsor of the product.

Date of information

- the date on which the CMI was last revised.
11.0 Changes to Registered complementary medicines

This section is divided into the following subsections:

11.1. About this Guidance
11.2. Forms
11.3. How Much Will It Cost?
11.4. Does the Change Make the Goods "Separate and Distinct"?
11.5. What Else Do I Need to Send?
11.6. Will the TGA Look at Other Aspects of the Product That Are Not Being Changed?
11.7. The Same Changes for Many Products?
11.8. What if the Proposed Change is Not in the Changes Table?
11.9. How Will the TGA Acknowledge My Notification or My Application for Approval?
11.10. Groups Order – Summary
11.11. Changes Table Codes
11.12. Changes Tables

Following the inclusion of a product as a Registered medicine in the Australian Register of Therapeutic Goods (ARTG), sponsors may wish to change certain details held by the Therapeutic Goods Administration (TGA). Factors such as product stability, manufacturer changes and developing marketing strategies may dictate changes to the product details approved at the time of the product’s inclusion in the ARTG.

It is a condition of registration of therapeutic goods that sponsors notify the TGA of any changes in information that may have been relevant to a decision to Register the goods.

This section sets out the steps that sponsors must take before proceeding with a change. Note that the Therapeutic Goods Act 1989 (the Act) provides for penalties where a change is implemented without the approval of the TGA.

11.1 About this guidance

While this guidance gives summary information about the legislation, sponsors are strongly advised to refer to the legislation itself for complete information on the implications for the product. This document refers only to Registered complementary medicine products.

11.2 Forms

Applications for variation of an existing product should be made on the appropriate forms, which are available from the Complementary Medicines page of the TGA website: http://www.tga.gov.au/industry/cm-forms-registered-variation.htm.
11.3 How much will It cost?

All applications to the Non-Prescription Medicines Branch of the TGA, whether for notification or prior approval, attract an application fee. For applications that require approval, a separate evaluation fee is payable. Information on current fees is available on the TGA website: <http://www.tga.gov.au/about/fees.htm>.

The Therapeutic Goods Regulations 1990 (the Regulations) provide for the waiver or reduction of evaluation fees under certain circumstances. If the change to the product is such that sponsors feel they are eligible for a waiver or reduction of the evaluation fee, sponsors should pay the full fee at the time of application and include a request for waiver/reduction with the application. Reductions or waivers are not granted as a matter of course. Each application is judged on its own merits. If approved, the appropriate amount will be refunded. Processing delays may result if the correct fees are not paid at the time of application.

Refer to Regulation 45 for the criteria applying to the waiver and/or reduction of fees.

11.4 Does the change make the goods “separate and distinct”?

Some changes may render the changed goods separate and distinct from the product originally Registered. The Act lists those criteria which make goods separate and distinct. Where the Therapeutic Goods (Groups) Order (the “Groups Order”) applies, the new product, although technically separate and distinct from the original, may be grouped in the same ARTG entry as the original product. If the new product is separate and distinct and the Groups Order does not apply, sponsors will need to submit a new application for registration of the product.

See Section 11.10 - Groups Order Summary for the requirements of the Groups Order.

11.5 What else do I need to send?

For applications that require approval, and for some applications that require notification, sponsors will need to submit further documentation with the variation form. Some supporting documentation requirements are self-evident. For example, if sponsors wish to change details of the label, they will need to send a copy of the present label and a draft copy of the new label, highlighting the changes.

In other cases, what is required as supporting documentation may not be so evident. If sponsors have consulted the various references and are still unsure, they should contact the staff of the Office of Complementary Medicines (OCM).

In some instances, certain assurances about the change will also need to be made before the application can proceed. Where these are required, details are given below (see Section 11.11 – Changes Tables Codes). Note that it is the sponsor’s responsibility to ensure that the required assurances are given in the application. If they are not given, the change may require prior approval, rather than notification.

11.6 Will the TGA look at other aspects of the product that are not being changed?

Generally, the TGA will only review the requested change at the time of application. However, some changes naturally affect other aspects of the product, which may require further clarification. If a problem is detected that is unrelated to the requested change, it may be followed up separately, but will not normally hold up processing of the application.

Obviously, some flexibility will be necessary, as it will be in the interests of both the TGA and the sponsor to have all outstanding matters resolved before the change is implemented. Sponsors can minimise the
potential for delays by examining the product to ensure that the product complies with the latest requirements, including any supplements or amendments, in:

- the Therapeutic Goods Regulations 1990;
- any cited pharmacopoeia (e.g. the most recent BP, PH Eur or USP);
- the Standard for the Uniform Scheduling of Medicines and Poisons (SUSMP);
- TGA Approved Terminology for Medicines;
- relevant Therapeutic Goods Orders (TGOs), including TGO 69 – General Requirements for Labels for Medicines;
- the Therapeutic Goods Advertising Code.

Sponsors should be aware that sometimes a proposed change might involve additional consequential changes (e.g. removal of a colouring agent may also require change to visual identification). In such cases, each of the relevant changes should be specified in the application.

11.7 The same changes for many products?

If sponsors wish to implement an identical change across a range of similar products, only one application form may need to be completed in certain cases. An example is the notification of a change of the same principal manufacturer (licensed) for a range of Registered products. However, a significant change to several products (e.g. removal of gluten) would require individual applications for each product.

11.8 What if the proposed change is not in the Changes Table?

If sponsors cannot find a description of the proposed change in the Changes Table, they should contact the staff of the OCM. The absence of the proposed change does not imply that sponsors may proceed with the change without notifying the TGA or seeking prior approval of the change.

11.9 How will the TGA acknowledge my notification or my application for approval?

Sponsors will be sent an acknowledgment in response to all submissions for changes that require either notification or prior approval.

For changes requiring notification, sponsors need not wait until they receive the acknowledgment of the notification before implementing the change.

For changes that require prior approval, a letter of approval, signed by the delegate of the Secretary, is sent. It is important that sponsors do not proceed with this type of change until they receive the approval letter. Should the application be refused, a rejection letter containing details of procedures for review of the decision will be sent.
11.10 Groups Order – summary

The Groups Order specifies the circumstances in which separate and distinct therapeutic products can be grouped in the same ARTG entry (ie. under the same AUST R number).

The Act sets out the criteria that make products "separate and distinct". These are:

- a different name;
- different indications;
- different directions for use;
- a different type of container;
- a different dosage form; or
- a different formulation or composition.

When the Groups Order does not apply, the changed product must have a separate ARTG entry and bear a separate AUST R number. If this is the case, sponsors should apply for registration of the changed product as if it were entirely new.

The provisions of the Groups Order (as applied to non-prescription drug products) may be summarised as follows.

11.10.1 Name change

Products may be grouped when the only difference between the new product and the existing one is the proprietary name, and when the new product is to replace the existing one in use.

11.10.2 Change in the amount of an excipient

Products may be grouped when the formulation of the new product is to be changed by increasing or decreasing the amount of an excipient (but not by adding or deleting an excipient) and when the new product is to replace the existing one in use.

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

Products 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 product is to be Registered in place of the existing one.

11.11 Changes Tables codes

The following codes should be read in conjunction with the Changes Tables below. Assurances should be made in writing, signed and dated by an authorised person, and should accompany the variation form. Note that the exact wording, as given here, should be used. Failure to make the assurances required for notifiable changes may render the change unapprovable.
### 11.11.1 Status codes

<table>
<thead>
<tr>
<th>Status Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEW</td>
<td>New application for registration required.</td>
</tr>
<tr>
<td>A</td>
<td>Prior approval required before proceeding with the change.</td>
</tr>
<tr>
<td>N</td>
<td>Notification to the OCM before proceeding with the change, provided that the required supporting documentation has been supplied.</td>
</tr>
<tr>
<td>O</td>
<td>No prior approval or notification required. Changes with status &quot;O&quot; have been included for completeness and do not imply that this information is required for evaluation of an equivalent new product.</td>
</tr>
<tr>
<td>ASK</td>
<td>Contact the OCM.</td>
</tr>
</tbody>
</table>
Documentation and assurance codes

<table>
<thead>
<tr>
<th>Code</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>E</td>
<td>Evidence to support the change where an ARTG entry is to be corrected.</td>
</tr>
<tr>
<td>G</td>
<td>Good Manufacturing Practice pre-clearance certificate.</td>
</tr>
<tr>
<td>L</td>
<td>A copy of the current label of the goods plus a draft copy of the new label, with the relevant changes highlighted, have been supplied.</td>
</tr>
<tr>
<td>T</td>
<td>The submission is accompanied by written requests to effect the change, from both the existing and the proposed sponsors.</td>
</tr>
<tr>
<td>PI</td>
<td>A copy of the current Product Information (PI) of the product plus a draft copy of the new PI, with the relevant changes highlighted, have been supplied.</td>
</tr>
<tr>
<td>P</td>
<td>The SUSMP schedule (or &quot;N&quot; for unscheduled goods) for the new pack size is stated in the application form.</td>
</tr>
</tbody>
</table>

1. The new product is intended to replace the existing product in use.
2. The only difference between the new product and the existing product is the name.
3. The only differences between the new product and the existing product are related to the indications for use and/or the directions for use.
4. No additional indications have been introduced or directions for use altered (other than change to wording).
5. No aspects of the labelling, PI, CMI, pharmaceutical data or other product details have been changed or are to be changed, other than changes nominated in this application and those made in conformity with the Changes Table.
6. The labelling for the new pack size is unchanged, other than to indicate the new pack size number/volume.
7. The only changes made are those that bring the label into compliance with requirements of the Labelling Order, or Schedule 2 to the Therapeutic Goods Regulations.
8. The change is in compliance with a requirement introduced in the most recent version or amendment of the Standard for the Uniform Scheduling of Medicines and Poisons or Required Advisory Statements for Medicine Labels.
9. The nominated manufacturer is licensed to manufacture products of this type.
10. The container type (as defined in TGA Approved Terminology for Drugs) is unchanged and container material is unchanged.
11. A stability testing protocol has been approved for this product and a copy of the approval letter is attached.
12. All of the following:
   a. neither the existing nor the new material is a modified starch
   b. the changeover has been validated
   c. at least 6 months stability data have been generated at the maximum recommended storage temperature on product manufactured using the new type of starch, or 3 months data at a temperature at least 10°C higher than the maximum recommended storage temperature
<p>| | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
</tr>
</thead>
</table>
| 13. | a. The changeover has been validated and the sponsor is satisfied that the change will not adversely affect the stability of the product.  
 | b. Stability testing will continue for the full term of the product’s shelf life and the TGA will be advised immediately of any batches not meeting specifications. |
| 14. | No new text or graphics have been introduced. |
| 15. | The change of material is one of the following:  
 | a. polystyrene to PVC, polyethylene, polypropylene or glass  
 | b. PVC to polyethylene, polypropylene or glass  
 | c. polyethylene to glass or polypropylene of density ≥ 0.89  
 | d. from one density of polyethylene to a higher density  
 | e. any change between glass, polyethylene of density ≥ 0.95, and polypropylene of density ≥ 0.89. |
| 16. | The new container/closure system has demonstrated equal or better moisture protection in the USP-NF Test for Containers – Permeation (water vapour transmission) to that of the existing container/closure system. |
| 17. | The information on the container label is not less than the information on the primary pack. |
| 18. | The change to the plastic component is one of the following:  
 | a. PVC to PVC/PVDC or to PVC/PCTFE  
 | b. PVC/PVDC to PVC/PCTFE  
 | or the change to the plastic component is to a material with demonstrated lower or equivalent water permeability than the existing material (see for example USP-NF monograph 671 Containers Permeation). |
| 19. | Manufacturing method and specifications, other than visual identification, have not been changed. |
| 20. | Two production batches have been tested according to the approved stability protocol and all results fall within the acceptance criteria, as specified in the approved stability protocol. |
| 21. | The changes are in accordance with the Therapeutic Goods Act 1989. |
### 11.12 Changes Tables

<table>
<thead>
<tr>
<th>Label change (including package insert)</th>
<th>Status</th>
<th>A/D</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPN Proprietary name (if grouping applies)</td>
<td>A</td>
<td>1, 2, L</td>
</tr>
<tr>
<td>PIN Proprietary name (if grouping does not apply)</td>
<td>NEW</td>
<td>-</td>
</tr>
<tr>
<td>GIN New therapeutic indications (if grouping applies)</td>
<td>A</td>
<td>1, 3, L</td>
</tr>
<tr>
<td>PTI New therapeutic indications (if grouping does not apply)</td>
<td>NEW</td>
<td>-</td>
</tr>
<tr>
<td>LIW Therapeutic indications or directions for use – change of wording without altering meaning</td>
<td>A</td>
<td>4, L</td>
</tr>
<tr>
<td>LIS Therapeutic indications – removal of subset of indications from label</td>
<td>N</td>
<td>5, L</td>
</tr>
<tr>
<td>LIR Therapeutic indications – addition of Registered indications to label</td>
<td>A</td>
<td>5, L</td>
</tr>
<tr>
<td>GDU Directions for use – e.g. dosage instructions (if grouping applies) (See also LIW)</td>
<td>A</td>
<td>1, 3, L</td>
</tr>
<tr>
<td>LDU Directions for use (if grouping does not apply)</td>
<td>NEW</td>
<td>-</td>
</tr>
<tr>
<td>PSC Recommended storage conditions – more restrictive</td>
<td>N</td>
<td>5</td>
</tr>
<tr>
<td>PST Recommended storage conditions – less restrictive</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>LSR Addition of more restrictive safety-related statements</td>
<td>N</td>
<td>5, L</td>
</tr>
<tr>
<td>LSF Changes on label (signal headings, warning statements) in compliance with new SUSMP requirements, where the change in scheduling is from S4 to a lower schedule</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>LSU Changes on label (signal headings, warning statements) in compliance with new SUSMP requirements, other than LSF</td>
<td>N</td>
<td>5, 8, L</td>
</tr>
<tr>
<td>LLO Changes to bring a label into compliance with the Labelling Order – other than changes to the proprietary name, indications or directions for use</td>
<td>N</td>
<td>5, 7, L</td>
</tr>
<tr>
<td>LLR Addition of a required representation to a label (Schedule 2 to the Therapeutic Goods Regulations)</td>
<td>N</td>
<td>5, 7, L</td>
</tr>
</tbody>
</table>

* A/D = assurances to be given and supporting documentation required for the given status to apply.
### Label change (including package insert)

<table>
<thead>
<tr>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>5, L</td>
</tr>
<tr>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>N</td>
<td>5, L</td>
</tr>
<tr>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>Ask</td>
<td>-</td>
</tr>
</tbody>
</table>

#### LCF
Colour, font, type size only (no change in label copy)

#### LGR
Introduction of new graphics/icons (other than as specified in change SSP)

#### LFO
Reformatting of pre-existing text (ie. moving of blocks of text and not rewording – see LIW, LRT)

#### LRT
Rereading of pre-existing text without altering meaning (other than indications or directions for use – see LIW)

#### LDT
Deletion or addition of text to the label (e.g. addition or removal of claims such as *clinically proven, fast/rapid action*; general claims regarding the product, its nature, mechanism of action, qualifying statements etc)

#### LOC
Other changes

### Sponsor changes

<table>
<thead>
<tr>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>5, L</td>
</tr>
<tr>
<td>Write to OCM</td>
<td>-</td>
</tr>
<tr>
<td>N</td>
<td>5, T, L</td>
</tr>
</tbody>
</table>

#### SSP
Sponsor name/logo (same sponsor of goods) and/or change to manufacturer/supplier details on label

#### SAD
Sponsor address

#### STR
Transfer goods to another sponsor

### Product detail changes

<table>
<thead>
<tr>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1, 2, L</td>
</tr>
<tr>
<td>NEW</td>
<td>-</td>
</tr>
<tr>
<td>N</td>
<td>5, 6, 10, 13, L, P</td>
</tr>
<tr>
<td>N</td>
<td>5, 6, 10, 13, L, P</td>
</tr>
</tbody>
</table>

#### GPN
Proprietary name (if grouping applies)

#### PIN
Proprietary name (if grouping does not apply)

#### PSZ
Pack size – other than liquids/semi-solids (see PLS) or metered dose aerosols (see PMZ) (see also KBT, KGL, KBL and KOT)

#### PLS
Pack size – liquids/semi-solids

* A/D = assurances to be given and supporting documentation required for the given status to apply.
## Product detail changes

<table>
<thead>
<tr>
<th>Product detail changes</th>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>PMZ Pack size – metered dose aerosols</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>GIN New therapeutic indications (if grouping applies)</td>
<td>A</td>
<td>1, 3, L</td>
</tr>
<tr>
<td>PTI New therapeutic indications (if grouping does not apply)</td>
<td>NEW</td>
<td>-</td>
</tr>
<tr>
<td>PDF Dosage form (as defined in <em>TGA Standard Terminology</em>)</td>
<td>NEW</td>
<td>-</td>
</tr>
<tr>
<td>PVI Visual identification (note that novelty shapes, e.g. animal-shaped tablets, are not acceptable)</td>
<td>N</td>
<td>5, 13, 19</td>
</tr>
<tr>
<td>PSL Shelf life – increase (other than in change PSP)</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>PSR Shelf life – decrease</td>
<td>N</td>
<td>5</td>
</tr>
<tr>
<td>PSP Shelf life – increase (in accordance with an approved stability testing protocol for that product)</td>
<td>N</td>
<td>5, 11, 20</td>
</tr>
<tr>
<td>PPR Approval of a stability testing protocol for a specific product</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>PSC Recommended storage conditions – more restrictive</td>
<td>N</td>
<td>5</td>
</tr>
<tr>
<td>PST Recommended storage conditions – less restrictive</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>PMI Sterility status/technique</td>
<td>A</td>
<td>-</td>
</tr>
</tbody>
</table>

## Formulation changes – active ingredients

<table>
<thead>
<tr>
<th>Formulation changes – active ingredients</th>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAI Addition of active ingredient</td>
<td>NEW</td>
<td>-</td>
</tr>
<tr>
<td>AAD Deletion of active ingredient</td>
<td>NEW</td>
<td>-</td>
</tr>
<tr>
<td>AAA Amount of an active ingredient</td>
<td>NEW</td>
<td>-</td>
</tr>
<tr>
<td>AOV Overage – decrease</td>
<td>N</td>
<td>5</td>
</tr>
<tr>
<td>AOA Overage – increase</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>GPA Change to amount of an excipient ingredient within a proprietary ingredient that contains an active substance (if grouping applies)</td>
<td>A</td>
<td>1</td>
</tr>
</tbody>
</table>

* A/D = assurances to be given and supporting documentation required for the given status to apply.
### Formulation changes – active ingredients

<table>
<thead>
<tr>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>API</td>
<td>Change to a proprietary ingredient that contains an active ingredient, other than as above in change GPA</td>
</tr>
</tbody>
</table>

### Formulation changes – excipient ingredients

<table>
<thead>
<tr>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPI</td>
<td>Removal and/or addition of a fragrance, flavour, printing ink or colouring agent (if grouping applies), other than change ERT</td>
</tr>
<tr>
<td>ERE</td>
<td>Removal or addition of a fragrance, flavour, printing ink or colouring agent (if grouping does not apply)</td>
</tr>
</tbody>
</table>
| ERT | Removal of fragrance, flavour, printing ink and/or colouring agent if the total agent is present at not more than 2% w/w or w/v (if grouping applies)  
Note: This change may result in consequential changes (e.g. deletion from the label of declared ingredients that are no longer relevant; change to visual identification and finished product specifications) that should also be addressed in accordance with the Changes Table. | N | 5 |
<p>| EAD | Addition of excipient other than those above in change GPI | NEW | - |
| EDE | Deletion of excipient other than those above in change GPI | NEW | - |
| GEX | Amount of excipient (if grouping applies) | A | 1 |
| EAM | Amount of excipient (if grouping does not apply) | NEW | - |
| EST | Type of starch | N | 5, 12 |
| EWI | Change to ingredients within a proprietary ingredient that is a flavour, fragrance, printing ink or colour (proprietary ingredient has same name) | N | 5, 13 |
| EWA | Change to ingredients within a proprietary ingredient that is an excipient (other than above in change EWI) | A | - |</p>
<table>
<thead>
<tr>
<th>Quality control changes – finished product specifications</th>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>QFX Specification ranges – more restrictive</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>QFE Specification ranges – less restrictive</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>QFT Addition of an extra test</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>QFU Deletion of an existing test</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>QFA Analytical method – to comply with amendments to a standard (e.g. the BP, PH Eur, USP or a TGO)</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>QFB Analytical method – which has been demonstrated to maintain or improve analytical performance (accuracy, precision and/or specificity)</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>QFC Analytical method – other than as specified above in change QFB</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>QFS Expiry specification ranges following changes to the BP, PH Eur, USP or the General standard for tablets and capsules</td>
<td>O</td>
<td>-</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Quality control changes – starting material specifications</th>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>QSX Range – more restrictive</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>QSE Range – less restrictive</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>QST Addition of an extra test</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>QSU Deletion of an existing test</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>QSA Analytical method – to comply with amendments to a standard (e.g. the BP, PH Eur, USP or a TGO)</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>QSB Analytical method – which has been demonstrated to maintain or improve analytical performance (accuracy, precision and/or specificity)</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>QSC Analytical method – other than as specified above in change QSB</td>
<td>A</td>
<td>-</td>
</tr>
<tr>
<td>QSM Manufacturer of starting material (specifications unchanged)</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>QSS Supplier of starting material</td>
<td>O</td>
<td>-</td>
</tr>
<tr>
<td>Packaging changes</td>
<td>Status</td>
<td>A/D*</td>
</tr>
<tr>
<td>-------------------</td>
<td>--------</td>
<td>------</td>
</tr>
<tr>
<td>KCT</td>
<td>Container type (as defined in <em>TGA Standard Terminology</em>)</td>
<td>NEW</td>
</tr>
<tr>
<td>KBT</td>
<td>Container material – if the container is a bottle, the goods are a solid dosage form (e.g. tablet) and the change is of a type listed in assurance 15</td>
<td>N</td>
</tr>
<tr>
<td>KGL</td>
<td>Container material – clear to coloured glass</td>
<td>O</td>
</tr>
<tr>
<td>KBL</td>
<td>Container material – if the container is a blister pack, the goods are a solid dosage form (e.g. tablet) and the change is of a type listed in assurance 18</td>
<td>N</td>
</tr>
<tr>
<td>KOT</td>
<td>Container material – other than in changes KBT, KGL or KBL</td>
<td>A</td>
</tr>
<tr>
<td>KCL</td>
<td>Closure</td>
<td>N</td>
</tr>
<tr>
<td>KSL</td>
<td>Tamper-resistant seal – addition (including label notice to alert consumers to presence of seal)</td>
<td>O</td>
</tr>
<tr>
<td>KSX</td>
<td>Tamper-resistant seal – removal (including removal of label notice re seal)</td>
<td>O</td>
</tr>
<tr>
<td>KWA</td>
<td>Inert wadding material – addition, substitution or removal where stability is not affected by the action</td>
<td>O</td>
</tr>
<tr>
<td>KDA</td>
<td>Desiccant – inclusion in container</td>
<td>A</td>
</tr>
<tr>
<td>KDX</td>
<td>Desiccant – removal from container</td>
<td>A</td>
</tr>
<tr>
<td>KPP</td>
<td>Specifications of primary pack (other than labelling)</td>
<td>O</td>
</tr>
<tr>
<td>KSP</td>
<td>Introduction of a measuring device (e.g. spoon, cylinder) or applicator (e.g. finger cot)</td>
<td>N</td>
</tr>
<tr>
<td>KMD</td>
<td>Changes to existing measuring device (e.g. spoon, cylinder) or applicator supplied with the goods, or removal of a measuring device or applicator, where other means of accurately measuring or applying the dose are readily available</td>
<td>N</td>
</tr>
<tr>
<td>KPA</td>
<td>Introduction of a primary pack (no new text or graphics)</td>
<td>N</td>
</tr>
<tr>
<td>KPI</td>
<td>Introduction of a package insert</td>
<td>A</td>
</tr>
<tr>
<td>KRI</td>
<td>Removal of a package insert</td>
<td>A</td>
</tr>
</tbody>
</table>

* A/D = assurances to be given and supporting documentation required for the given status to apply.
### Packaging changes

<table>
<thead>
<tr>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Changes to package insert (see Label Change section)</td>
<td></td>
</tr>
</tbody>
</table>

**KPX**  
Removal of a primary pack  
N 5, 17

**KRP**  
Introduction of a refill pack  
A -

**KRR**  
Removal of refill pack  
N -

### Manufacturing changes – finished product

<table>
<thead>
<tr>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>TGA-licensed Australian manufacturer (includes site of manufacture)</td>
<td></td>
</tr>
</tbody>
</table>

**MMA**  
TGA-licensed Australian manufacturer (includes site of manufacture)  
N 5, 9

**MOS**  
Overseas manufacturer (includes site of manufacture), if GMP pre-clearance certificate provided  
N 5, G

**MOP**  
Overseas manufacturer (includes site of manufacture), if GMP pre-clearance not provided  
A -

**MPR**  
Manufacturing process (other than MBS)  
N 13

**MBS**  
Batch size for pressurised inhalation (nasal and oral respiratory) products  
A -

**Consumer Medicine Information (CMI)**

<table>
<thead>
<tr>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Introduction of a CMI for a Schedule 3 product Registered after 4 July 1995 where the CMI complies with Schedule 13 to the Therapeutic Goods Regulations 1990 and is not to be included as</td>
<td></td>
</tr>
</tbody>
</table>

**CPI**  
Introduction of a CMI for a Schedule 3 product Registered after 4 July 1995 where the CMI complies with Schedule 13 to the Therapeutic Goods Regulations 1990 and is not to be included as  
O -
### Consumer Medicine Information (CMI)

<table>
<thead>
<tr>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>a package insert. &lt;br&gt;Note: Change KPI applies where the CMI is to be included as a package insert.</td>
<td>-</td>
</tr>
<tr>
<td>CPO Changes to an existing CMI, where the changes are consistent with all previously approved product details and the CMI is not to be included as a package insert. &lt;br&gt;Note: Refer to the Label Change section for guidance on changes to a CMI where the CMI is to be included as a package insert (package inserts are treated as part of the label).</td>
<td>O</td>
</tr>
</tbody>
</table>

### Product Information (PI)

<table>
<thead>
<tr>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPI Introduction of a PI for an existing product</td>
<td>A</td>
</tr>
<tr>
<td>DRS Addition of more restrictive safety-related statements</td>
<td>N 5, PI</td>
</tr>
<tr>
<td>DOT Changes other than the addition of more restrictive safety-related statements</td>
<td>A</td>
</tr>
</tbody>
</table>

### Other

<table>
<thead>
<tr>
<th>Status</th>
<th>A/D*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTA Correction of ARTG record in accordance with section 9D(3) of the <em>Therapeutic Goods Act 1989</em></td>
<td>N E, 5, 21</td>
</tr>
</tbody>
</table>

* A/D = assurances to be given and supporting documentation required for the given status to apply.
12.0 Post market review

This section is divided into the following subsections:

12.1. The Sampling Program
12.2. Good Manufacturing Practice (GMP) Audits
12.3. Grandfathered Products
12.4. The Surveillance Unit
12.5. Problem Reporting and Recall
12.6. Adverse Drug Reaction (ADR) Reports
12.7. Listing and Compliance Section

Medicines supplied on the Australian market are subject to a number of levels of surveillance by the Therapeutic Goods Administration (TGA).

12.1 The sampling program

The TGA laboratories undertake a continuous sampling program in all states of Australia. Products are purchased in the marketplace, or obtained from manufacturers or sponsors, and subjected to analysis and regulatory scrutiny. Products are tested against the TGA-approved finished product expiry specifications and any relevant Therapeutic Goods Orders (TGOs) or other legal requirements. Products not meeting the required standards may be subject to corrective action, recall or removal from the Australian Register of Therapeutic Goods (ARTG).

12.2 Good Manufacturing Practice (GMP) audits

Manufacturers of therapeutic goods in Australia are subject to regular inspections by the TGA's Office of Manufacturing Quality (OMQ). Details of requirements for manufacture are specified in the PIC/S Guide for Good Manufacturing Practice for Medicinal Products – 15 January 2009. The evaluation committees may request that particular problems encountered during the evaluation process be followed up with the manufacturer during subsequent GMP audits.

12.3 Grandfathered products

Those products entered in the ARTG under the “grandfather” provisions of the Therapeutic Goods Act 1989 (the Act) may be subject to future evaluation to determine whether they should remain on the ARTG. Sponsors of such products should ensure that they hold evidence to substantiate the quality, safety and efficacy of the products. Sponsors should also ensure that an ongoing stability testing program is in place for each product under their control.

12.4 The Regulatory Compliance Unit

The TGA’s Regulatory Compliance Unit (RCU) investigates breaches of the legislation and coordinates prosecutions. The RCU works closely with all other areas of the TGA.

Investigations may be initiated on the basis of:

- a complaint by the public or a healthcare practitioner;

- referral from another section of the TGA, such as the Office of Laboratories and Scientific Services, the Advertising Unit or the Office of Complementary Medicines;
• referral from another Australian agency, such as the Australian Quarantine and Inspection Service or Australian Customs;

• referral from a related international agency.

12.5 Problem reporting and recall

Recalls of therapeutic goods are coordinated by the Recalls Section of the TGA. A sponsor can initiate the recall of a medicine after receiving reports from such sources as manufacturers, wholesalers, retail and hospital pharmacists, medical practitioners and patients.

A recall action can also be initiated as a result of analysis and testing of samples by the TGA or other Australian Government or state/territory government laboratories, or as a result of advice received from one of the medicine evaluation committees (such as the Advisory Committee on Complementary Medicines), the Advisory Committee on the Safety of Medicines or other bodies. Recall of medicines manufactured overseas might be initiated by reports appearing in United States Food and Drug Administration Enforcement Reports and similar publications of health authorities, or from information received directly from such authorities.

Further information about recall procedures can be found in the Uniform Recall Procedure for Therapeutic Goods 2004 edition.

12.6 Adverse Drug Reaction (ADR) reports

In Australia, reports of suspected adverse reactions to drugs/medicines are sought from health professionals and are also received from consumers. Sponsors of medicines Registered or Listed in Australia are under an obligation to report adverse reactions about which they become aware.

12.6.1 Reporting requirements

The Act requires sponsors of medicines Registered or Listed in ARTG 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;

   d. information that indicates that the quality, safety or efficacy of the goods is unacceptable.
12.6.2 Pharmacovigilance guidelines

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 pharmacovigilance requirements specifically relating to complementary medicines are published, sponsors should refer to the Australian Pharmacovigilance Guideline.

12.6.3 Reporting timeframes

The Australian Pharmacovigilance Guideline advises:

- Sponsors should report serious unexpected and serious expected\textsuperscript{13} reactions occurring in Australia to the TGA in an expedited manner (i.e. immediately and in no case later than 15 calendar days). Any suspected increase in the frequency of serious reactions should also be reported on an expedited basis.
- Sponsors are required to advise the TGA within 72 hours of any:
  - significant safety issue identified by the sponsor as a result of its ongoing review and analysis of all information (including foreign reports of ADRs) that is pertinent to the safety or benefit–risk assessment of the product; or
  - action which has been taken by a foreign regulatory agency, including the basis for such action.

These situations are quite different from the reporting of individual spontaneous ADRs, where the sponsor is allowed up to 15 days to confirm and follow up details before submitting an individual serious ADR report to the TGA.

\textsuperscript{13} Definitions for these terms are included in Annex 1 to the Australian Pharmacovigilance Guideline.

12.6.4 More information

Enquiries about the reporting of adverse drug reactions should be directed to the TGA. See Report a problem with a therapeutic product.

12.7 Listing Compliance Section

The Listing Compliance Section within the OCM monitors complementary medicine products already available for supply on the Australian market.

The objectives of the post-market program are to:
- provide a high level of assurance of the safety of complementary medicines through a risk-based program of post-market monitoring and surveillance;
- provide a high level of consumer confidence in the efficacy, safety and quality of complementary medicines;
- ensure a high level of industry compliance with regulatory standards and guidelines for complementary medicines.

Functions of the LCS are:
- monitoring of complementary medicines Listed on the ARTG through the Electronic Listing Facility Version 3 (ELF 3);
- investigation of medicines for which a potential problem has been identified;
• reviewing evidence supporting indications and claims made for Listed complementary medicines;
• regulatory action; and
• administration and business processes.

These objectives/functions are achieved (in cooperation with other areas of the TGA) by:
• targeted and random desk-based audits of Listed products;
• monitoring of suspected adverse reactions;
• targeted and random laboratory testing of products and ingredients;
• targeted and random surveillance in the marketplace;
• an effective, responsive and timely recalls procedure;
• audits of GMP; and
• an effective co-regulatory approach to control advertising.
Part I Appendix 1

Stability of the finished product

Full details of stability testing conducted on the product, together with associated method validation data, must be included with the application. ARGCM Part I, Stability of the Finished Product sets out the requirements for stability data to support the Registration of a complementary medicine. This appendix provides additional detailed guidance on the design, conduct and reporting of stability studies.

A1.1 General principles

The objective of a stability study is to determine the time during which a product meets appropriate standards when stored under defined conditions. The product must be shown to remain, or to be likely to remain, within its expiry specifications throughout the proposed shelf life when stored under the proposed storage conditions. The difference between release and expiry specifications must take into account the results of stability testing.

A1.1.1 Stability batches

Stability studies must demonstrate the stability of the product intended for marketing. Therefore, the formulation, method of manufacture, container and packaging should be identical to those proposed for marketing. A minimum of two batches should be used in the stability study.

It is recognised that pilot or small-scale production batches may need to be used for stability testing because of the time required for stability studies. It is important to note that there may be apparently small differences between small-scale or pilot batches and full-scale production batches that will have a significant effect on the stability of the product. There is also more chance of variability between pilot batches than between production batches. For these reasons, any differences between the method of manufacture for the study and the method for production should be identified, and three pilot batches should be placed on stability testing instead of two production batches. Stability results for pilot batches are not a substitute for real-time stability testing of the market product; the first two full-scale production batches should be placed on stability testing and the results monitored closely.

There may be some instances where stability data for a slightly different formulation will be considered. One example might be where the only difference is a change during product development to the type of starch, colouring or flavouring. In such a case, a justification for accepting the data for a different formulation should be included. Note that this type of stability data is not a substitute for testing of the market product and will only usually be considered as supporting data. Supporting stability data may be used when there are only short-term stability results for the market product.

Stability testing should be carried out in the container/closure system in which the product will be marketed in Australia. It may, however, be acceptable to provide stability data on the same formulation packaged in different materials, depending on the nature of the materials involved. It may be useful to contact the Office of Complementary Medicines for advice about this.
A1.2 Appropriate tests

The purpose of stability tests is to provide evidence on how the quality and safety of the product varies with time. Stability tests should be detailed enough to give confidence in the safety and quality of the product.

Stability tests should include the relevant tests that form part of the finished product expiry specifications (e.g. assay tests) and include additional tests that will:

- specifically indicate both the presence and increase in concentration of constituents or other substances of toxicological significance;
- indicate changes in the product over time.

Alternative test methods may be used in stability studies but they should be fully described and validated. If a dissolution test is included in the expiry specifications, that same method should be incorporated into the stability testing program.

Where the results for a test included in the expiry specifications are unlikely to change during storage (e.g. identification of the active substance or uniformity of tablet mass), there is no need to include that test in the stability studies.

Generally, the tests for stability will meet the following criteria:

- The tests need to be ‘stability indicating’. This means that they should be able to determine that the product meets the expiry specifications, and to determine the subtle changes that occur as the product moves from ‘within specification’ to ‘out of specification’;
- Tests should measure the degradation of those constituents that are characteristic of the active ingredients (e.g. active or marker constituents where they can be identified). Likewise, constituents that degrade should be chosen, because there is little point in choosing a constituent that does not change in the substance while the quality of the substance deteriorates over time. The appropriate tests for these processes are the most difficult to determine; it is possible that ‘stress testing’ could produce changes in a substance that can then be used as a basis for identifying degradation products;
- Tests should measure those parameters that may increase over time and that may lead to safety concerns (e.g. microbiological growth) or a reduction in quality (e.g. colour change);
- Tests that involve taste and smell are not regarded as capable of objective validation but are capable of demonstrating gross changes to the product;
- Tests should be validated, reproducible and capable of being used by an independent body. Chromatograms may be one means of demonstrating the ‘profile or ‘fingerprint’ of a substance, but this will depend on the substance and whether the detection method is suitably specific, reproducible and quantitative. For guidance on profile chromatograms, refer to ARGCM Part III, Profile Chromatograms;
- If changes are made to the assay or other test methods during a stability study, data should be generated comparing the two methods to validate the change;
- Changes to dissolution test methodology during stability studies are strongly discouraged.

A1.2.1 Assay of active constituents

Active constituents should be assayed using stability-indicating test methods. Analytical test methods should be validated, with the exception of test methods included in a relevant pharmacopoeial monograph. Details should be provided for all analytical methods used in the stability studies together with validation data that demonstrate accuracy, precision and specificity.
(ie. freedom from interference by degradation products and other likely impurities), and show the shape of the calibration curve (linearity is preferred).

It is not sufficient to determine that the ingredient remains within the limits of the expiry specifications; the study design and assay parameters should allow any trends over time to be observed.

Note that loss of a constituent in an ingredient might be due to factors other than degradation, such as volatilisation.

**A1.2.2 Degradation products**

Determination of trends in the formation of major degradation products of an ingredient may provide a better basis for determining its stability than assay results for the active constituents in the substance, and should be considered where safety may be an issue. For example, the formation of 1 per cent of a degradant, which could be significant toxicologically, might not be detected using the assay test alone because of variability in assay results or the precision of the assay method.

**A1.2.3 Physical properties**

In addition to assays for content of active ingredients, it is also necessary to monitor the physical properties of the product during storage.

The physical tests will vary with the formulation in question, but important attributes of the major dosage forms may include the following.

<table>
<thead>
<tr>
<th>Dosage form</th>
<th>Physical tests</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tablets and capsules</td>
<td>Dissolution or disintegration, appearance, odour, hardness, friability, moisture content, brittleness (hard gelatin capsules)</td>
</tr>
<tr>
<td>Liquid formulations</td>
<td>Appearance, colour, odour, pH, clarity (solutions) and particle size distributions (suspensions), resuspendability (suspensions), viscosity, moisture content (powders for reconstitution), phase separation (emulsions)</td>
</tr>
<tr>
<td>Ointments and creams</td>
<td>Appearance, odour, viscosity, softening range, loss of water, physical and chemical homogeneity, particle size distribution, particle formation, pH, phase separation (emulsions)</td>
</tr>
<tr>
<td>Suppositories and pessaries</td>
<td>Appearance, softening temperature (moulded products), dissolution rate (compressed products), disintegration testing</td>
</tr>
<tr>
<td>Freeze-dried material (including materials for reconstitution)</td>
<td>Appearance of both freeze-dried and reconstituted material, pH, water content, rate of solution</td>
</tr>
<tr>
<td>Medicated soap bars</td>
<td>Appearance, odour, weight loss, pH</td>
</tr>
</tbody>
</table>

For other dosage forms not included in the above table, the sponsor should define the appropriate tests.

**A1.2.4 Validation of test methods**

For excipients, specificity is generally demonstrated by performing the assay procedure on an excipient (placebo) blend. Similarly, it is sometimes useful to demonstrate that extraction solvents do not interfere with the analysis by performing the assay procedure in the absence of a sample (or placebo sample).
Where a chromatographic procedure is used, copies of relevant chromatograms should be provided.

Sponsors should demonstrate that the test method is sensitive to degradation of the active ingredient.

When the identity of all usual degradants is well known, specificity may be demonstrated by analysing the known degradants and demonstrating that they do not interfere with the analysis. It may be appropriate to analyse known degradants as pure substances and also when admixed with a sample extract or reference solution.

When the identity of the degradants is not clear or when the sponsor does not have access to authentic specimens of the degradants, forced degradation studies should be undertaken. Commonly used forcing degradation conditions include treatment with:

- an aqueous solution of a mineral acid;
- an aqueous solution of sodium hydroxide;
- an aqueous solution of a strong oxidising solution, such as hydrogen peroxide;
- heat;
- exposure to direct sunlight (or another source of ultraviolet light) for a prolonged period.

Some sponsors also choose to examine whether excipient degradants may interfere with the analysis by subjecting placebo blends to the forcing conditions.

Forced degradation studies are used to validate the test method (and not the finished product). In order to demonstrate that the test method is sensitive to degradation, it is necessary to demonstrate that degradation has occurred.

Tabulated recovery data for the different degradation conditions and for non-degraded product are very useful for demonstrating that significant degradation has occurred for at least one of the degradation conditions.

If degradation has not occurred under the conditions used, sponsors should consider using more forcing degradation conditions.

Where a product contains more than one active ingredient, sponsors should consider whether degradants from one can interfere with the assay of another.

Where degradation of the relevant active ingredient is intrinsically difficult to achieve, sponsors should justify not submitting the usual data.

Where a chromatographic procedure is used, copies of chromatograms relevant to the validation studies should be provided, including reference chromatograms, sample chromatograms, placebo chromatograms, and chromatograms of known degradants and/or chromatograms obtained in forced degradation studies.

Test methods must be validated and should be stability-indicating. Pharmacopoeial methods are not necessarily stability-indicating.
Guidance on validating analytical test methods can be found in *Finished product (medicine) analytical procedure validation for complementary medicines*.

A1.3 Presentation of results

Results obtained at the commencement and at nominated time intervals throughout the study should be provided in tabular format. This will allow any trends to be detected and will improve the predictive value of the study. Data that do not include initial results (ie. at the start of the study) are of limited value.

Where relevant, quantitative results should be given, rather than a statement that the product complies with a particular specification. Assay results obtained during the study should be recorded either as absolute values (such as number of mg of active substance per capsule) or as a percentage of the nominal (labelled) content. If more than one assay result is available, expression of results as a percentage of the values at time zero is useful, but such figures are not sufficient by themselves.

For tablets and capsules, an average content should be obtained by conducting the assay on pooled samples, or by averaging individual dose unit results. This will minimise the effect of individual dose unit variations.

In all cases, the results should be discussed and explanations given where necessary (e.g. anomalous or unusual results, change in assay method, change in appearance).

A1.4 Prediction of shelf life from accelerated stability data

The sponsor must nominate in the application the intended shelf life and storage temperature, as well as any specific conditions such as storage away from light. The stability data must support the proposed shelf life. Therapeutic Goods Order No. 69 – *General Requirements for Labelling of Medicines (TGO 69)* identifies the particular storage temperatures applicable to therapeutic goods.

The stability of a medicinal substance is directly related to the kinetics of the various degradation reactions. However, the relevant physico-chemical equations are strictly applicable only when a single reaction occurs by a single mechanism. Because pharmaceutical products are usually mixtures of substances and may be in the solid state (for example, powders and tablets), these theoretical models do not necessarily hold and cannot be relied upon as predictive tools. The issue of physical stability (e.g. dissolution rate and particle formation) adds a further complication. There is, therefore, no substitute for the shelf life being determined empirically, ultimately over the shelf life.

However, it is acknowledged that the accumulation of stability data is a lengthy procedure and it is sometimes necessary to predict an interim shelf life for a product stored at a defined temperature from stability data obtained at a higher temperature. This ‘accelerated’ stability testing is useful in providing information from which to assess the stability of a new product, but it should ultimately be confirmed with long-term stability studies at the recommended storage temperature for the duration of the nominated shelf life.
In most circumstances, the following general rule-of-thumb is used:

If no trends are noted after storage for a period of \((x)\) months at an elevated temperature (at least 10°C above the maximum storage temperature proposed for the product), an interim shelf life of a maximum of \(2(x)\) months may be permitted, where \(2(x)\) does not exceed three years. For some products, alternative interpretations may be considered, if justified.

An interim shelf life can be assigned during registration, when limited data are available to assess a final shelf life. In this case, the sponsor must undertake to submit ongoing stability data to demonstrate that the interim shelf life is appropriate for the final shelf life.

Alternatively, the sponsor can submit a variation at a later date to obtain an extension to the interim shelf life if ongoing stability data supports this.

Shelf lives of longer than three years should be supported by data on production batches stored at the maximum recommended temperature for the duration of the proposed shelf life. Stability studies involving at least two production batches, stored at the maximum recommended temperature, should be continued for the full period to validate the predicted shelf life.

A1.5 Checklist for submission of stability data

Complying with these guidelines will minimise evaluation time. Sponsors should use the following checklist, which will reduce delays and requests for further information during the evaluation.

- Specify the formulations used in the study and state which batches are identical to those proposed for registration in Australia.
- State whether the batches used in the study were laboratory, pilot or production batches, and the scale.
- Clearly describe the packaging used in the study and state whether it is identical to the pack that will be used in Australia.
- Present stability data on at least two production batches or three pilot batches of the product.
- Specify the temperature, lighting and humidity conditions applied during the study.
- Fully describe all test methods and sample sizes.
- Provide validation of analytical methods (and include copies of relevant chromatograms).
- Provide quantitative results where possible (in preference to “passes test” or similar wording).
- Where possible, include quantitative or semi-quantitative determinations of the content of degradation products.
- Do not use a high-performance liquid chromatography assay procedure to detect impurities without validation for this purpose.
- Comment or conduct additional tests where there is a lack of balance between the formation of degradation products and the loss of the active substance.
- Consider additional tests to investigate the significance of obvious alterations in the characteristics of the product (e.g. a distinct change in the colour of the product may necessitate additional investigation for degradation products).
- Include relevant information on the physical characteristics of the product during storage, such as dissolution characteristics, homogeneity and particle size.
Include stability studies under conditions of high humidity for products that are to be registered in moisture-permeable containers, and especially for those that are potentially labile to moisture.

Provide results from enough time stations to allow assessment of any trends in the data.

Provide results for individual dosage units where these are appropriate (e.g., dissolution profiles).