Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

# Australian Regulatory Guidelines for Complementary Medicines (ARGCM)

## Part III: Evaluation of Complementary Medicine Substances

Version 4.2, August 2011

TGA Health Safety Regulation



# About the Therapeutic Goods Administration (TGA)

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

# Version history

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

# Contents

# 1. Overview

The purpose of Part III of the *Australian Regulatory Guidelines for Complementary Medicines* (ARGCM) is to provide guidance to sponsors submitting applications for the evaluation of complementary medicine substances. This part covers new complementary medicine substances, "switch" substances[1] and excipients used in Listed and Registered complementary medicines. The regulatory requirements for Registered medicines are discussed in Part I. The regulatory requirements for Listed medicines are discussed in Part II.

The primary reason for the evaluation of new complementary medicine substances and switch substances is to determine whether the substances are of sufficiently low risk to allow their inclusion in Listed medicines. It should be noted that, once it is approved for use in Listed medicines, the substance may be used by any sponsor.

The parameters considered when evaluating a complementary medicine substance are *quality* and *safety*. Quality aspects are evaluated for the purpose of characterising the substance and establishing a compositional guideline for it. The safety evaluation determines whether the substance, once characterised, is of sufficiently low risk to allow its inclusion in Listed medicines.

Complementary medicine substances are not evaluated for efficacy. However, the evaluation process may include consideration of the potential indications for products containing the substance. Potential indications are considered only to determine the likely amount and duration of exposure to the substance. For example, when evaluating a substance that may be indicated for long-term use, the Therapeutic Goods Administration (TGA) will need to consider whether safety studies submitted are of sufficient duration. Clinical and other efficacy data, while not evaluated from an efficacy perspective, often include information on adverse events that is useful in the safety evaluation.

This section provides an overview of the guidelines for the evaluation of new complementary medicine substances. Detailed guidance is provided in the following sections:

- Section 2 – Eligibility for evaluation as a complementary medicine substance
- Section 3 – Evaluation process
- Section 4 – Quality
- Section 5 – Safety.

## 1.1. Eligibility for evaluation as a complementary medicine substance

Before submitting an application for evaluation of a complementary medicine substance, it is first necessary to establish that the substance is, in fact, a complementary medicine substance.

Essentially, if the substance is a designated active ingredient that has an established identity and tradition of use, it is a complementary medicine substance. The Office of Complementary Medicines

[1] "Switch" substances are complementary medicine substances that, as active ingredients, are currently included in Registered complementary medicines but, subject to an application for evaluation as a substance for use in Listed medicines, their status may be "switched" to Listable. For example, this may be a substance for which the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) restriction has been removed, or one that is currently approved for use as an excipient only.

(OCM) also evaluates excipients that are used in complementary medicines and substances referred to the OCM by other regulatory areas in the TGA.

Once it has been established that a substance is a complementary medicine substance, the next step is to determine whether the substance is likely to meet the criteria for inclusion in Listed medicines. Substances that are subject to the conditions of a Schedule (or applicable Appendix) to the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) are not permitted in Listed medicines.

Eligibility for evaluation as a complementary substance is discussed in detail in Section 2.

## 1.2. The evaluation process

Applications for the evaluation of complementary medicine substances should be sent to the TGA, together with accompanying data and payment. Following lodgement, subject to the payment of the appropriate fees, applications pass through the following phases: pre-assessment, evaluation and peer review, Advisory Committee on Complementary Medicine (ACCM) consideration, and, if acceptable, approval and 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 data addressing a number of key parameters have been provided.

Applications that have been accepted in the pre-assessment phase are progressed to the evaluation phase, where the data are evaluated and a report is generated. Evaluation reports are reviewed within the OCM to ensure consistency in evaluation.

The ACCM considers the evaluation report and, among other things, makes recommendations to the TGA on the suitability of the substance for inclusion in complementary medicines.

Subject to a positive recommendation by ACCM, the TGA will make a decision on whether or not to approve the substance for use in complementary medicines. For a substance that is an active ingredient to be included in Listed complementary medicines, it will need also to be included in Schedule 4 to the Therapeutic Goods Regulations 1990 (the Regulations).

The evaluation process, including lodgement, pre-assessment, evaluation, ACCM consideration, implementation, and fees for substance applications, is discussed in detail in Section 3.

## 1.3. Quality

Information on the quality of a complementary medicine substance is required to characterise the substance for the purpose of developing a compositional guideline.

Information that should be provided includes the substance name, composition, structure and general properties; manufacturing details, including process and controls; substance characteristics, including impurities and incidental constituents; specifications and details of analytical test methods, with method validation data; stability data; and a proposed compositional guideline.

Where a substance is the subject of a monograph in a TGA recognised pharmacopoeia, a separate compositional guideline is usually not required.

Information on the quality of a substance is discussed in detail in Section 4. As there is a wide range in the compositional complexity of complementary medicine substances, Section 4 has been divided into two major subsections: simple and complex substances. The headings and numbering system used in the two major subsections follow the Common Technical Document (CTD) format. Data provided in applications for evaluation of complementary medicine substances do not need to be presented in this format, although for ease of evaluation, it is encouraged.

## 1.4. Safety

Applications for the evaluation of complementary medicine substances must include data that support the safety of the substance. Where a sponsor seeks to have a substance approved for use in Listed medicines, they need to prove that the substance is of "low risk".

Safety may be established by detailed reference to the published literature, the submission of original study data, or a combination of both. Where there is sufficient evidence based on human experience to support safety, conventional studies involving animal and *in vitro* studies are not necessary (see Section 5.2).

Section 5 of this part provides detailed guidance on safety requirements, including information on history and patterns of use, biological activity, toxicology, clinical trials, adverse reactions and animal origin considerations. Section 5 also provides details of the data requirements for evaluation of the safety of new oral and topical excipients.

## 1.5. Naming of new substances and terminology

TGA has developed and maintains lists of Australian approved terminology, *TGA Approved Terminology for Medicines*, to ensure accuracy and consistency in the information available to consumers and compiled in the Australian Register of Therapeutic Goods (ARTG). All ingredients, constituents, container types, dosage forms, routes of administration and units of expression or proportion must be declared, together with their Australian Approved Names (AANs).

When submitting an application for evaluation of a complementary medicine substance that does not currently have an AAN, sponsors will need to submit a proposal for a new AAN with their application.

ARGCM Part IV, provides information on AANs and guidance on applying for a new ingredient name.

# 2. Eligibility

This section details the criteria used to determine the eligibility of a substance for evaluation as a complementary medicine substance. The Office of Complementary Medicines (OCM) evaluates complementary medicines. In addition, the OCM evaluates excipients used in complementary medicines and substances referred to the OCM by other regulatory areas in the Therapeutic Goods Administration (TGA).

Complementary substances that are active ingredients are evaluated to determine whether the substances are of sufficiently low risk to allow their inclusion in Listed complementary medicines. Excipients used in complementary medicines may be included in Registered or Listed medicines.

## 2.1. Substances that may be included in Listed medicines

The TGA maintains a list of *Substances that may be used as active ingredients in Listed medicines in Australia*. Note that some of the substances in the list may be subject to restrictions, and that the list is subject to change. Please contact the OCM if you need assistance in determining the current status of an ingredient.

Note that the inclusion of a substance in the document entitled the *TGA Approved Terminology for Medicines* does not mean that the substance has been approved for use in Listed medicines, or that the substance has been previously included in a medicine in the Australian Register of Therapeutic Goods (ARTG). The *TGA Approved Terminology for Medicines* is the source of the Australian Approved Name (AAN) for a substance. Herbal substances are named by identifying the herb species, the plant part(s) and the preparation. It might be necessary to combine an AAN for each of these pieces of information to make the complete AAN for the herbal substance.

## 2.2. Active ingredients for inclusion in Listed medicines

The first step that a sponsor should undertake is to establish whether the proposed substance is a complementary medicine.

Complementary medicines are therapeutic goods consisting wholly or principally of one or more designated active ingredients, each of which has a clearly established identity and a traditional use.

Designated active ingredients are those ingredients or classes of ingredients as described in Schedule 14 to the Therapeutic Goods Regulations 1990 (the Regulations).

The following list details the designated active ingredients included in Schedule 14 (as of 3rd June 2010) for clarity, some of the ingredient classes have been paraphrased:

- amino acids;
- charcoal;
- choline salts;
- essential oils;

- plant or herbal materials or synthetically produced substitutes for materials of that kind including:
  - plant fibres;
  - enzymes;
  - algae;
  - fungi;
  - cellulose and derivatives of cellulose;
  - chlorophyll;
- homoeopathic medicines;
- micro-organisms, whole or extracted (excluding vaccines);
- minerals including mineral salts and naturally occurring minerals;
- mucopolysaccharides;
- non-human animal materials or synthetically produced substitutes for materials of that kind including:
  - dried material;
  - bone and cartilage;
  - fats and oils;
  - other extracts and concentrates;
  - lipids including essential fatty acids or phospholipids
- substances produced by or obtained from bees including:
  - royal jelly;
  - bee pollen;
  - propolis;
- sugars, polysaccharides and carbohydrates; and
- vitamins and provitamins.

For an up-to-date list of designated active ingredients, see Schedule 14 of the current consolidated version of the Regulations.

Traditional use means use that is well-documented, or otherwise established, according to the accumulated experience of many traditional healthcare practitioners over an extended period and accords with well-established procedures of preparation, application and dosage.

Once it has been established that a substance is a complementary medicine, the next step is to determine whether or not the substance is likely to meet the criteria for inclusion in Listed medicines.

Substances that are subject to the conditions of a Schedule (or applicable Appendix) to the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) are not permitted in Listed medicines. If the substance is subject to conditions in the SUSMP, or contains a constituent that is subject to the conditions of a Schedule (or applicable Appendix) to the SUSMP, then it will not be accepted for evaluation as a potential Listable substance. The Listable status of herbal ingredients is discussed in more detail below.

Some substances are subject to the conditions of a Schedule (or applicable Appendix) to the SUSMP only when the quantity in the formulated product exceeds certain limits. If the quantity of the substance, when included in the formulated product, would be below the SUSMP limits, then the substance can still be evaluated as a potential Listable substance. If the substance is one that has not previously been considered for scheduling, but may meet the criteria for inclusion in a Schedule

to the SUSMP[2] then it is recommended that the sponsor first seek advice about this from the OCM. If the substance is included in a Schedule to the SUSMP, but the sponsor believes that it should not be, the sponsor should firstly make a submission to the Secretary of the Department of Health and Ageing (DoHA) for reconsideration of its Schedule[3].

## 2.3. Assessing the status of herbal ingredients

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

- the ingredient is currently eligible for inclusion in a Listed medicine without further evaluation;
- the ingredient (or one or more of its constituents) is subject to restrictions such that products containing the ingredient would need to be Registered before supply in Australia; and
- the ingredient is eligible for evaluation as a new complementary substance, to determine whether it is of sufficiently low risk to be included in Listed medicines.

### 2.3.1. Determining Listable status

Where a herbal ingredient:

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

then the ingredient is generally eligible to be included in Listed medicines without the need for further evaluation.

### 2.3.2. Definition of a herbal substance

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

Regulation 2 states:

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

Sponsors who are uncertain if their herbal ingredient meets the legal definition, may wish to supply to the OCM for a determination, details of the manufacturing process (preferably in the form of a

[2] Refer to the *Guidelines for Classification of Medicines and Poisons* included in the document entitled *Guidelines for the Advisory Committee on Medicines Scheduling (ACMS)*.
[3] The Secretary of the Department of Health and Aging (DoHA) makes decisions about the scheduling of substances. The SUSMP incorporates the decisions of the DoHA Secretary about these substances.

flow diagram) outlining the various processing steps, solvents used and extraction ratios. Where more than one solvent is used in an extraction step, the concentration of each should be provided.

### 2.3.3. Schedule 4 to the Regulations

Schedule 4 to the Regulations outlines those goods eligible for inclusion in the part of the ARTG for Listed medicines. In the case of herbal ingredients, Part 4 of Schedule 4 incorporates a list of herbal substances that are not eligible for inclusion in Listed medicines or whose inclusion may be subject to certain restrictions. Herbal substances that are not included in Part 4 of Schedule 4 may be included in Listed medicines, provided that the herbal substance is already present in medicines included in the ARTG for supply in Australia. Herbal substances that are not present in medicines included in the ARTG for supply in Australia are not currently eligible for inclusion in Listed medicines (see Section 2.4 *Herbal Ingredients that Are Not Currently Listable*).

## 2.4. Herbal ingredients that are not currently Listable

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

Ingredients (whether directly or because of one or more constituents) that are subject to the conditions of a Schedule (or applicable Appendix) to the SUSMP are not eligible for evaluation as complementary medicine substances for use in Listed medicines. Sponsors wishing to supply complementary medicines containing ingredients scheduled as poisons will need to seek product Registration. Part I of this document provides guidance on the Registration of complementary medicines. Alternatively, sponsors may wish to make a submission to the Secretary of the Department of Health and Aging for reconsideration of the scheduling status of the ingredient or constituent.

## 2.5. Assessing the status of non-herbal ingredients

Non-herbal complementary medicines include vitamins, minerals, amino acids, homoeopathic medicines and substances of animal origin. Non-herbal complementary medicines that may be used as active ingredients in Listed medicines are included in Parts 1, 2, 3 and 5 of Schedule 4 to the Regulations. If your substance is not already included in Schedule 4, it is not currently eligible for inclusion in Listed medicines. However, it may be eligible for evaluation to determine whether it is of sufficiently low risk to allow its inclusion in Listed medicines, provided that it is not subject to the conditions of a Schedule (or applicable Appendix) to the SUSMP.

## 2.6. Excipient ingredients

In addition to evaluating active complementary substances, the OCM is also responsible for the evaluation of new excipient substances that are, or are to be, included in complementary medicines. New excipient ingredients that are, or are to be included, in Listed medicines that are not

[4] Herbal ingredients subject to a schedule in the SUSMP may be evaluated for eligibility as a Listable substance following a successful application to the Secretary of DoHA to "down-schedule" or amend the scheduling conditions for the substance. Sponsors wishing to submit concurrent OCM / DoHA applications should contact the OCM for further guidance, before submitting applications of this type.

complementary medicines (e.g. sunscreens) are evaluated by the Office of Medicine Authorisation (OMA).

### 2.6.1. Oral excipients

The requirements for approval to use a new oral excipient are the same as those for approval of a new complementary medicine substance. These requirements are stipulated in Sections 2, 3, 4 and 5 of this Part of the Guidelines.

### 2.6.2. Topical excipients

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

- the sponsor is able to identify the excipient as a substance included in the Cosmetic, Toiletry, and Fragrance Association's *International Cosmetic Ingredient Dictionary* (page number and reference should be quoted); and
- the sponsor certifies that the excipient does not appear in the European Economic Community (EEC) Directive 76/768 *List of Substances Which Must Not Form Part of the Composition of Cosmetic Products*;
- the sponsor provides documentary evidence that the excipient has been approved by the appropriate regulatory agency in Sweden, Canada, USA, UK or The Netherlands; or (less desirably);
- the sponsor certifies that there have been market-place sales of comparable products containing the excipient in one of those five countries for at least two years; and
- the sponsor provides an assurance that the prescribed safety data will be provided to the TGA within six months of the product being placed in the ARTG.

Such excipients are allocated a "provisional" status until such time as they are evaluated by the TGA. The safety data that must be submitted within six months for new topical excipients that meet the aforementioned criteria are:

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

Additional data on acute dermal toxicity and absorption following dermal application would also provide valuable information on the profile of the substance.

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

New topical excipients that do not meet the aforementioned criteria must be evaluated before their inclusion in Listed complementary medicines.

## 2.7. Substances referred to the Office of Complementary Medicines for evaluation

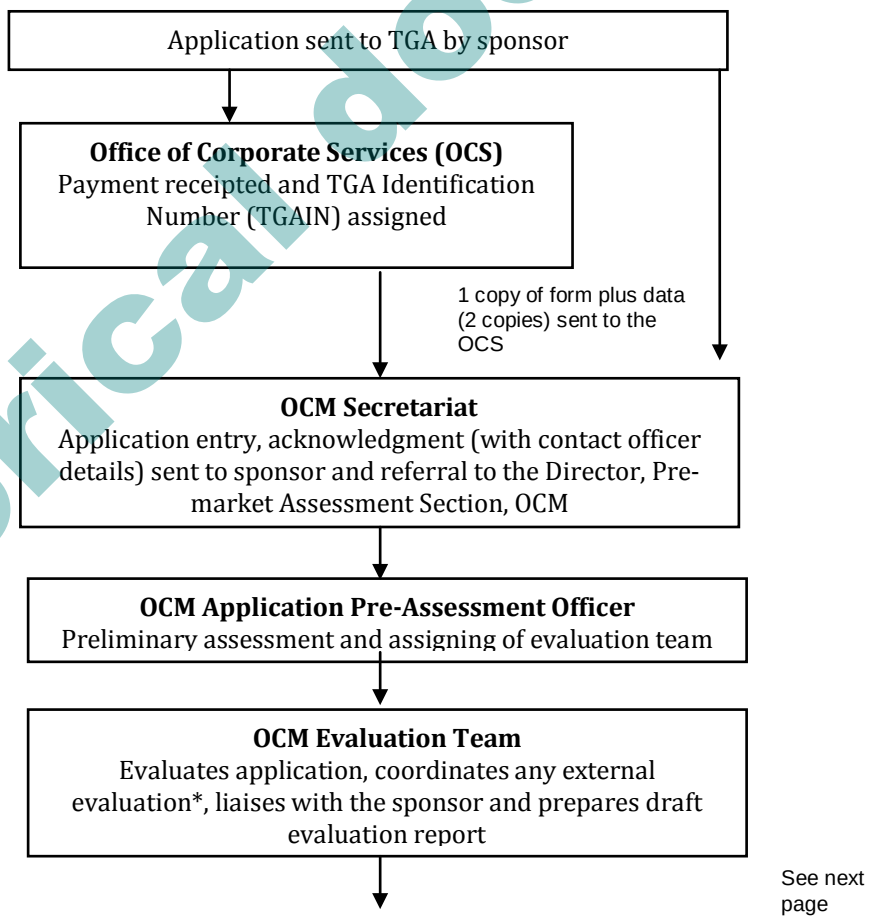
Substances that are not complementary medicines may be referred to the OCM for evaluation if it is considered by the TGA that that is an appropriate route of evaluation. If you believe that it is appropriate for the OCM to evaluate your substance, you will need to submit a justification with your application. It is suggested that you first seek the advice of the OCM about this.

# 3. Evaluation process

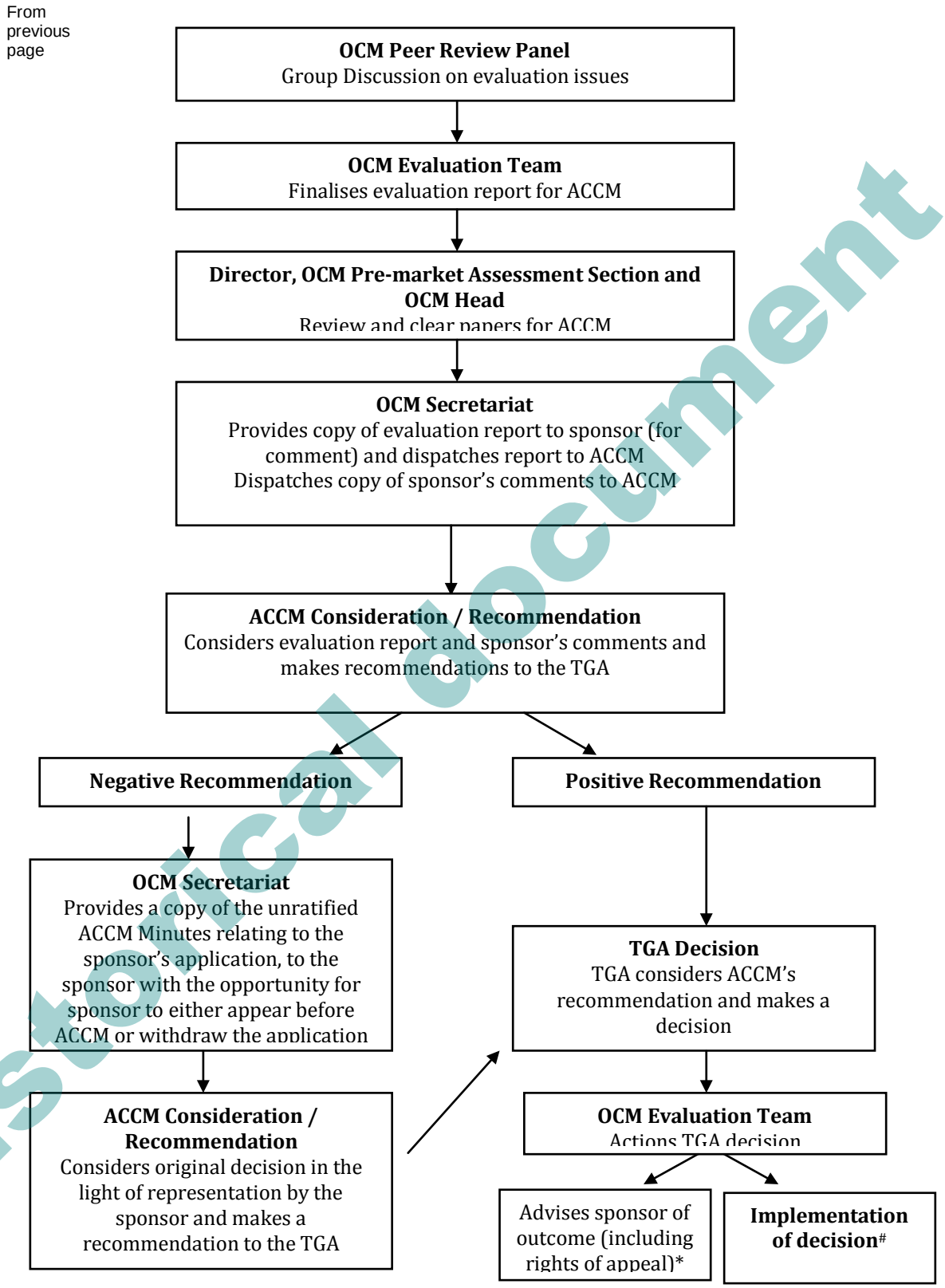
This section details the evaluation process for a complementary medicine substance application and includes: a flow chart, lodgement details, the pre-market process and the fee structure.

## 3.1. Flow chart

The following flow chart illustrates the stages through which an application for the evaluation of a new substance progresses within the Therapeutic Goods Administration (TGA). More detailed information is provided in subsections 3.2 and 3.3. There are currently no statutory time frames for the evaluation of complementary medicine substances. The completeness of the original application and the quality of the data submitted will influence the length of time for evaluation. To date, applications for new substances evaluated through the Office of Complementary Medicines (OCM) / Advisory Committee on Complementary Medicines (ACCM) route have taken approximately 8 months from the receipt of the application to review by the ACCM.




*External evaluation in this context means external to the OCM, e.g. TGA Office of Laboratory and Scientific Services.






*Guidance on appeal mechanisms in relation to decisions made by the TGA is included in ARGCM Part IV– Review of Decisions.
# Before the new substance can be used in Listed medicines, a change to the Therapeutic Goods Regulations 1990 (the Regulations) is required. This may be facilitated via a gazette notice, or Amendment Regulations may be required. Refer to Section 3.3.4 – Implementation, for details. Sponsors will be notified of the intended date of gazettal.

## 3.2. Lodgement

Applications for the evaluation of complementary medicine substances should use the application form entitled *Application for Evaluation of a New Complementary Medicine Substance*.

One copy of the application form, together with the fee, should be sent to the Office of Corporate Services (OCS). A second copy of the application form together with accompanying data should be sent to the OCM.

The OCS will send a receipt to the sponsor and advise the sponsor of the TGAIN that has been allocated to the application. The OCS will forward the application together with receipt details and the TGA Identification Number (TGAIN) to the OCM.

## 3.3. Pre-market

Applications for evaluation of substances pass through the following phases:

- pre-assessment;
- evaluation and peer review;
- ACCM consideration; and
- Implementation.

### 3.3.1. Pre-assessment

The pre-assessment process involves a brief review of the application data to determine if the application is acceptable for evaluation by the OCM. The pre-assessment process does not initiate or replace the formal evaluation of the application.

The pre-assessment review of the eligibility of individual applications is made soon after their receipt by the OCM, and the outcome is communicated to the sponsor as rapidly as possible.

In general, the pre-assessment process aims to differentiate applications that are impractical, unworkable or, for whatever reason, unacceptable, from those which the OCM can begin evaluating. The acceptability of applications is determined on a case-by-case basis. The "clock" on the application stops if the OCM seeks, from the sponsor, supplemental information to support the application.

#### 3.3.1.1. Payments and refunds

The OCM's Pre-Market Assessment Section (PREMAS)will generally not consider an application for which a TGAIN has not been assigned. An application will not be assigned a TGAIN until the application portion of the fee has been received by the OCS. The application portion of the total fee is not refundable.

Sponsors are expected to self-determine the page-count of their application before lodgement with the TGA, and pay the appropriate fee.

During the pre-assessment process, a page-count will be undertaken to determine the definitive evaluation fee for the application (which might differ from the application and evaluation fees received by the TGA). If the sponsor has paid more than the required evaluation fee, a refund will be arranged. Where less than the required fee has been paid, the sponsor must make up the

shortfall before the application can be accepted for evaluation. Outstanding evaluation fees will remain an impediment to the acceptance of the application for evaluation, no matter if the sponsor has dealt with any or all informational deficiencies highlighted during pre-assessment.

The OCS is responsible for collecting fees; the OCM does not request or collect fees. This is because, under the *Therapeutic Goods Act 1989* (the Act), appropriate delegation must be held to formally request payment for applications.

However, the OCM is obligated to alert sponsors to the effect of outstanding evaluation fees on the processing of their application; specifically, that applications will not be considered for evaluation while evaluation fees remain outstanding and, as a result, the application may ultimately lapse.

Refund of evaluation fees paid by the sponsor will be considered only if the OCM has not invested significant resources in the processing of the evaluation. Refund of evaluation fees may be considered where an application has been rejected, or withdrawn, at the pre-assessment stage. In this circumstance, the sponsor will be refunded the fees received by the TGA, less a portion for administrative costs for the pre-assessment process. A refund will not be approved where the application has received a significant pre-assessment review of the original application and / or supplementary data, which, in the opinion of the PREMAS Director, constitutes an evaluation of the application. The OCM cannot offer a refund directly to the sponsor; rather, refunds must be requested in writing from the OCS, which holds the delegation to pass monies from the Commonwealth.

#### 3.3.1.2. Data considered during the pre-assessment process

The following application data are considered during the pre-assessment process:

- substance name, characterisation, compositional guidelines, manufacturing processes, stability and analytical methodology; and
- substance toxicological data, and data on history of use, clinical trials and adverse reactions.

#### 3.3.1.3. Application rejection or lapse

Where the pre-assessment process determines the need for additional information and / or assurances, the sponsor will be asked to provide such information. If the information sought is not supplied, the application may be rejected.

The OCM may reject an application where:

- fees are outstanding;
- the application is presented in an unacceptable format, including where it contains contradictory, ambiguous or unclear wording, or untranslated (non-English) text; there is gross insufficiency of information; or unrealistic or unachievable application aims;
- the sponsor fails to reasonably respond to any or all requests for additional information to support the application during the pre-assessment or evaluation phases; and / or
- the application is profoundly deficient.

In these cases, the sponsor will be informed that the application has been rejected and the reasons for it. If an application is rejected and a new application for the same substance by the same sponsor is subsequently made, then the sponsor may request a reduction in fees (see Regulation 45 of the Therapeutic Goods Regulations 1990 (the Regulations) for further details). Where such an application is made, the sponsor should indicate which data have previously been provided and which data are new.

The OCM may deem an application lapsed at the pre-assessment stage if any portion of the evaluation fees remains outstanding for 8 weeks or more following receipt of the application, and the sponsor has been officially notified of the shortfall by the OCM.

Any application, irrespective of its merits, presentation and standard, will not be processed by the OCM if the substance proposed cannot, for whatever reason, be used in Listed medicines (e.g. the substance is subject to the conditions of a Schedule (or applicable Appendix) to the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP).

In addition, if the substance proposed for review as a complementary medicine substance does not meet the definition of a complementary medicine substance in, the OCM is, by legislation, not permitted to review the application further. In this instance, the application may be transferred to another Office of the TGA as appropriate, or the sponsor may wish to withdraw the application. Recognising the expertise in the OCM for assessing substances, these other branches may refer the substance to the OCM for evaluation, which in turn may refer the matter to the ACCM for review. However, it is these other Offices, not the OCM, that retain the legislative responsibility for progressing the application. Where a sponsor believes that it is appropriate for the OCM to evaluate a substance, they will need to submit a justification (refer to Section 2.7 – *Substances Referred to the OCM for Evaluation*).

#### 3.3.1.4. Application acceptance

The application is accepted where it is of such merit and standard as to allow the immediate start of evaluation by the OCM, provided the correct fee has been paid.

#### 3.3.1.5. Application acceptance pending

Where additional application data or clarification of information are required, a contact officer for the application is assigned, whose responsibility it is to provide the sponsor with oral and written notice on deficiencies in the application and to seek the provision of additional data, information and / or clarification. No further resources will be committed to the processing of the application until deficiencies in the application are remedied.

### 3.3.2. Evaluation and peer review

Applications that have been accepted during the pre-assessment process are progressed to the evaluation phase. An evaluation team is allocated, each with a team leader and the appropriate expertise to evaluate the safety and quality aspects of the application. An evaluation report is drafted for review by the peer review panel.

The peer review panel comprises the collective expertise of the OCM. The panel considers the evaluation report prepared, and provides comment and suggestions. The purpose of peer review is to ensure consistency in evaluation of substances by the OCM. Following peer review, the evaluation team deals with issues identified in the peer review and prepares the final evaluation report and the briefing paper for ACCM.

At any time during the evaluation process, sponsors may be asked for further information to clarify issues or address deficiencies.

Final reports and briefing papers are cleared by the OCM senior officers. Once cleared, a copy of the report is provided to the sponsor for comment, and the papers are provided to the ACCM Secretariat for inclusion on the next available ACCM agenda.

### 3.3.3. Advisory Committee on Complementary Medicines consideration

The ACCM is constituted under the Regulations to provide advice to the TGA on complementary medicines. ACCM meetings are held four times per year.

Evaluation reports prepared by the OCM, together with any comment provided by sponsors, are presented to ACCM members for their consideration and recommendation to the TGA. In relation to active complementary medicine substances, ACCM may recommend that a substance is or is not acceptable for use in Listed medicines, may recommend that a substance is acceptable subject to certain conditions, or may seek further information before making a recommendation.

Sponsors are advised of the ACCM recommendations in relation to their substance applications as soon as practicable after the ACCM meeting at which the evaluation report was considered. ACCM recommendations are also posted on the TGA website following the ACCM meeting.

Based on the recommendations of ACCM, the TGA will make a decision about a substance. If the decision is to reject an application, the sponsor will be advised of this as soon as practicable. Depending on the basis for rejection, a sponsor may wish to consider the option of Registration for a product containing the substance (Refer to Part I of these Guidelines).

Where applications for new substances for use in Listed 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 non-recommended substance 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[5]);
- 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 Committee's 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; and
  - 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;
- after the sponsor has left the meeting the ACCM 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 Committee's 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

[5] Guidance on appeal mechanisms in relation to decisions made by the TGA is included in ARGCM Part IV – *Review of Decisions*.

or inappropriately weighted the information contained in the application(s). It is not considered appropriate to introduce new information not previously evaluated by the ACCM.

If the decision is to approve a substance for use in Listed medicines, and the substance is an active ingredient, regulatory changes will be initiated as required.

### 3.3.4. Implementation

Subject to a positive ACCM recommendation / TGA decision in relation to a substance application, changes to the Regulations must be made before the new substance can be used in Listed medicines.

Schedule 4 to the Regulations details Listable therapeutic goods. In order to include a new substance in Schedule 4 to the Regulations, an amendment to the Regulations needs to be made.

In most instances, this can be achieved via the publication of a gazettal notice under the provisions of Chapter 2, Section 9A(5) of the Act. However, if a substance is already mentioned in Schedule 4 to the Regulations, gazettal cannot be used. In this instance, Amendment Regulations need to be drafted and approved.

Amendment Regulations require:

- approval by the TGA Executive;
- approval by the Minister responsible for the Department of Health and Ageing (or the Parliamentary Secretary);
- drafting by the Office of Legislative Drafting and Publishing, based on instructions prepared by the OCM in conjunction with the TGA's Office of Legal Services (OLS), and drafting of explanatory memoranda by the OCM;
- final approval by the Minister;
- endorsement by the Government's Executive Council; and
- royal assent from the Governor-General.

Where the proposed Amendment Regulations may have a regulatory impact, consultation with stakeholders must be included in the above process.

Gazettal is more expeditious than the Amendment Regulations process. The process involves the drafting of a gazette notice by the OCM in conjunction with the OLS, endorsement by the TGA Executive, the signature of the TGA's National Manager and publication in the *Commonwealth of Australia Gazette*. The Regulations are subsequently amended to reflect the gazetted information.

Once a substance has been included in Schedule 4 to the Regulations via Amendment Regulations or gazettal, it may be included in Listed medicines.

## 3.4. Fee structure

Evaluation fees are based on the total page count of clinical and / or toxicological data.

Fees are subject to change, and sponsors should refer to the latest version of the document entitled *Summary of Fees and Charges* for the current fees for complementary medicine substances.

Table 1 details the types of data included in applications for evaluation of complementary medicine substances and indicates whether the data are included in the page count for the purpose of calculating the evaluation fees.

**Table 1. Types of data included in page count**

| Type of data applicable? | Evaluation fee |
|---|---|
| Clinical / efficacy data (including Clinical Study Reports) | **Yes** |
| Published papers and published reviews | **Yes** |
| Copies of pages from reference texts[6] | **No** |
| MEDLINE search and abstracts | **Yes** |
| Summaries of studies | **Yes** |
| Summary tables | **No** |
| Expert reports | **No** |
| Overviews / summaries (if accompanied with data) | **No** |
| Bioavailability / bioequivalence study | **Yes** |
| Meta-analysis reports | **Yes** |
| Animal Studies | **Yes** |
| Pharmacology | **Yes** |
| Pharmacokinetics | **Yes** |
| Pharmacodynamics | **Yes** |
| Case reports and adverse reaction reports | **Yes** |
| Chemistry and quality control | **No** |



[6] A definition of reference texts from which pages are not counted for the purpose of calculating evaluation fees will be included. Essentially, the TGA exempts monographs from acceptable pharmacopoeias (e.g. British Pharmacopoeia (BP), European Pharmacopoeia (Ph Eur), United States Pharmacopoeia (USP), *Martindale*), toxicology and pharmacology texts, and other references such as the *Handbook of Pharmaceutical Excipients* from inclusion in the page count for the purpose of determining applicable fees. However, reports from symposia published in book form are not considered to be reference texts.

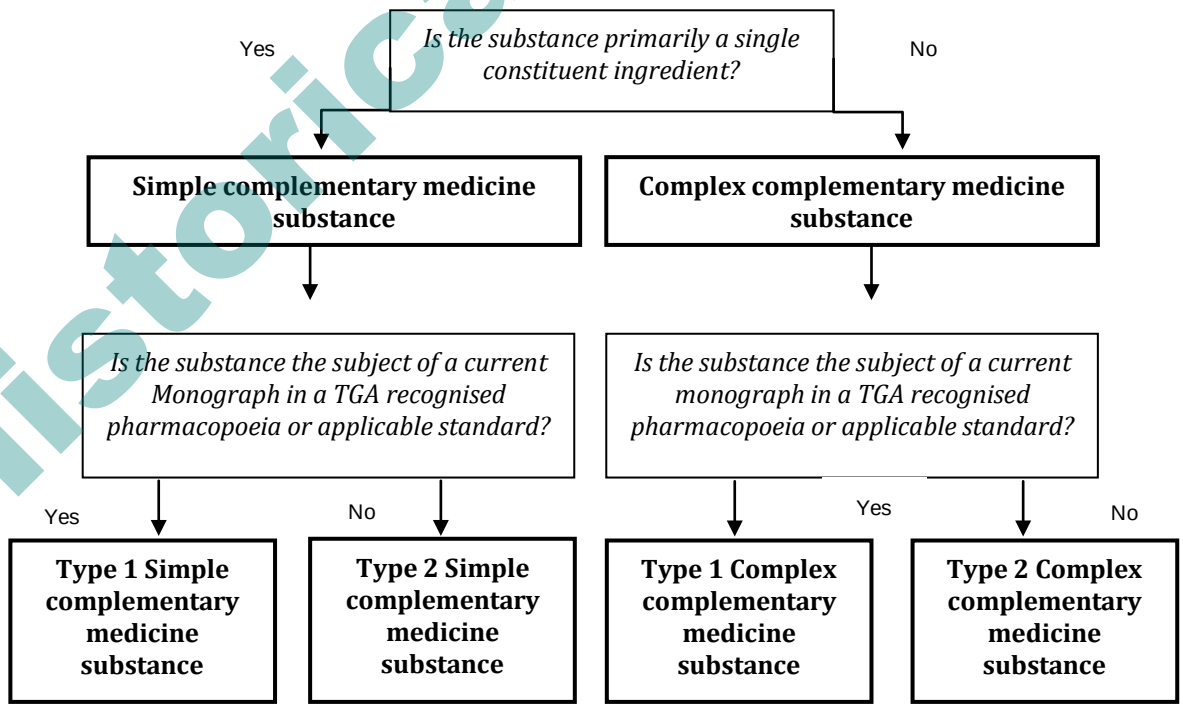
# 4. Quality

This section has the following subsections:



The section provides guidance on the information required to characterise complementary medicine substances for the purpose of developing compositional guidelines. As there is a wide range in the compositional complexity of complementary medicine substances, these guidelines have been divided into two major subsections: simple complementary medicine substances and complex complementary medicine substances.

Simple complementary medicine substances are primarily single-constituent ingredients that can be readily characterised (e.g. methionine). Complex complementary medicine substances have a number of constituents (e.g. herbal extracts). Both simple and complex complementary medicine substances are classified according to whether there is (Type 1) or is not (Type 2) an existing Therapeutic Goods Administration (TGA)-recognised standard, as charted below.



This section is generally applicable to active complementary medicine substances and excipients used in complementary medicines. Where a quality parameter is not relevant for an excipient, this will be explicitly stated.

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

Data provided in applications for evaluation of complementary medicine substances do not need to be presented in CTD format but, for ease of evaluation, it is encouraged.

## 4.1. Simple complementary medicine substances

These guidelines apply to those substances for use in complementary medicines that are substantially single-constituent ingredients. They may be obtained from natural sources, by extraction or other means, or may be produced by chemical or biochemical synthesis. Such substances fall within one of the following two categories:

Type 1 - The substance is the subject of a current monograph in the British Pharmacopoeia (BP), the European Pharmacopoeia (PH Eur) and the United States Pharmacopeia (USP) or other suitable monograph or standard (see note).

Type 2 - The substance is not the subject of a current monograph in a TGA-recognised pharmacopoeia or other applicable standard.

Note: The BP, the PH Eur,the 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[7]. Note that the BP, PH Eur and 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.

If the substance is the subject of a food standard, then the TGA will consider the suitability of this standard as a means of controlling the quality of the substance. A monograph or standard would be considered suitable if the information contained therein is consistent with the information that would be provided in a Type 2 submission.

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

### 4.1.1. Type 1 Simple complementary medicine substances

The following information should be provided for substances where a pharmacopoeial monograph or other standard is applicable.

#### 4.1.1.1. General information

**Description (Composition)**

Any information not included in the monograph/ standard description should be mentioned.

**Nomenclature**

Provide the name of the substance. If an Australian Approved Name (AAN) has not been allocated for the substance, provide the proposed name. Refer to (Section 1.5 – *Naming of New Substances and Terminology* for further information).

**Structure**

Provide the chemical structure (graphic), molecular formula, molecular weight and Chemical Abstracts Service Registry (CAS) number for the substance, unless this is provided in the relevant monograph or standard.

**General properties**

Provide any physico-chemical information relevant to the characterisation of the substance or that may be required for the manufacture, performance or stability of its intended final dosage form that is not covered by the relevant monograph or standard (e.g. solubility or particle size).

#### 4.1.1.2. Manufacture

Note: On commercially sensitive aspects of the manufacturing process: Where a manufacturer is unwilling to supply manufacturing details to the Australian sponsor, then the option exists for the information to be supplied directly to the TGA. In that case, any matters arising from the review of this data will be pursued with the manufacturer. The sponsor will be notified that matters have been raised, but no details will be provided without the manufacturer's authorisation. Please note that the Australian sponsor will need to provide written authorisation to the TGA before the TGA can communicate with the manufacturer.

**Manufacturer(s)**

Provide the manufacturer's name and address, and addresses of all sites involved in the manufacture / testing of the substance. This information is not mandatory, but it may assist the TGA in the evaluation process.

**Manufacturing process and process controls**

Sponsors should be aware of the manufacturing process and consider whether the process used is adequately controlled by the monograph or standard, including the requirements of relevant general BP, PH Eur and USP monographs. The provision of this information is not mandatory.

**Control of materials**

Not applicable.

**Controls of critical steps and intermediates**

Not applicable.

**Manufacturing process development**

Sponsors should consider whether there have there been any significant changes made to the manufacturing process of the substance used in producing non-clinical, clinical, scale-up, pilot and production-scale batches, as this may affect the composition of the substance. The provision of this information is not mandatory.

### 4.1.1.3. Characterisation

**Identity, elucidation of structures and other characteristics**

This is not applicable unless the substance is derived from, or contains, genetically modified organisms (GMOs) or genetically modified (GM) products. Additional information about the requirements for GMOs and GM products is given in ARGCM Part IV – *Genetically Modified Organisms*.

**Impurities and incidental constituents**

Information concerning impurities that are not dealt with in the monograph or standard should be provided. While this information is not mandatory, sponsors should be aware that the manufacturing process for the substance may differ from the process for the substance upon which the monograph is based and, consequently, different impurities may be present. Further guidance in relation to impurities and incidental constituents in general, is provided in *Impurities and Incidental Constituents* (Section 4.5).

### 4.1.1.4. Control of the substance

**Compositional guideline**

This is not applicable unless approval is sought to vary the requirements of the monograph or standard. In that case, a copy of the proposed compositional guideline should be presented.

**Analytical procedures**

This is not applicable where the procedures described in the monograph or standard are employed. If this is not the case, details of the test methods should be provided.

**Validation of analytical procedures**

This is not applicable where the procedures described in the monograph or standard are employed. If this is not the case, validation data for analytical test methods should be provided.

**Batch analyses**

Certificates of analysis for at least two recent, commercial-scale production batches should be provided to demonstrate routine compliance with the monograph or compositional guideline. 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. If available, 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 help the TGA to determine whether the substance intended for supply is the same as that on which safety data have been provided.

For Registered and Listed products, ingredients may be quantified by input in some situations (see ARGCM Part V– *Quantified by Input* for details).

**Justification of compositional guideline**

This is not applicable where a monograph or standard is used.

#### 4.1.1.5. Reference standards or materials

This is not applicable unless in-house reference materials are used. In that case, information on how the reference material has been characterised is required.

#### 4.1.1.6. Container closure system

Not applicable.

#### 4.1.1.7. Stability

**Stability summary and conclusions**

Not applicable.

**Post-approval stability protocol and stability commitment**

Not applicable.

**Stability data**

The monograph or standards are applicable throughout the storage period of the substance. Compliance of material stored for the manufacturer's assigned storage / retest period with the monograph or standard should be demonstrated. Guidance in relation to stability testing is provided in *Stability Testing* (Section 4.3).

#### 4.1.1.8. Compositional guideline

A compositional guideline is a summary of descriptions, tests and limits that define the composition and characteristics of the substance. Where the pharmacopoeial monograph or standard sufficiently characterises the substance, a separate compositional guideline is not required (see note below). Further guidance in relation to compositional guidelines is provided in the section entitled "*Compositional Guidelines* (Section 4.4).

Note on differences between compositional guidelines and monograph specifications: It should be noted that a monograph or standard is designed to provide a means of controlling the quality of a substance. It is not designed to characterise the material to the extent required for entry in the Australian Register of Therapeutic Goods (ARTG). The compositional guideline should allow for characterisation as well as quality control of the substance. To achieve this, it may be necessary to include in the compositional guideline a statement concerning the manufacturing process or the origin of starting materials.

### 4.1.2. Type 2 Simple complementary medicine substances

The following information should be provided for substances where a pharmacopoeial monograph or other standard is not applicable.

Note: where relevant, the complementary medicine substance must comply with the general monographs of the BP, PH Eur or USP.

#### 4.1.2.1. General information

**Description (composition)**

For example: Calcium citrate is the salt formed between two molecules of citric acid and three of calcium. The substance is a tetrahydrate.

**Nomenclature**

Give the name of the substance. If an AAN has not been allocated for the substance, state the proposed name. Refer to *Naming of New Substances* (Appendix 1) for further information.

**Structure**

Provide the chemical structure (graphic), molecular formula, molecular weight and Chemical Abstracts Service (CAS) Registry Number for the substance.

**General properties**

Information should be provided about the physico-chemical properties relevant to the characterisation of the substance or that may be required for the manufacture, performance or stability of its intended final dosage form; for example, physical description, melting point, particle size, solubility or polymorphism.

#### 4.1.2.2. Manufacture

Note: On commercially sensitive aspects of the manufacturing process: Where a manufacturer is unwilling to supply manufacturing details to the Australian sponsor, then the option exists for the information to be supplied directly to the TGA. In that case, any matters arising from the review of this data will be pursued with the manufacturer. The sponsor will be notified that matters have been raised but no details will be provided without the manufacturer's authorisation. Please note that the Australian sponsor will need to provide written authorisation to the TGA before the TGA can communicate with the manufacturer.

**Manufacturer(s)**

Provide the manufacturer's name and address and addresses of all sites involved in the manufacture / testing of the substance. This information is not mandatory, but it may assist the TGA in the evaluation process.

**Manufacturing process and process controls**

Provide a flow chart of the synthesis / production process that identifies the starting materials, catalysts and solvents used, yield ranges and operating conditions for all of the steps.

Provide a sequential, procedural narrative of the manufacturing process, including a detailed description covering, for example, the quantities of raw materials, solvents, catalysts and reagents that reflect a representative batch scale for commercial manufacture; critical steps and process controls; equipment; and operating conditions (e.g. temperature, pressure, pH and time).

Any reprocessing steps should be identified, and evidence should be provided that they have no significant effect on the final quality of the substance.

**Control of materials**

Quality and control of the starting materials, solvents, reagents and catalysts used in the manufacture should be provided. These are usually given in the form of specifications for these materials or a reference to an acceptable standard (e.g. Ethanol BP).

**Controls of critical steps and intermediates**

Provide information on the control of critical steps and intermediates, specifically:

> **critical steps** – details of the tests and acceptance criteria performed at critical steps of the manufacturing process to ensure the process is controlled; and
>
> **intermediates** – information on the quality and control of any intermediates isolated during the process.

**Manufacturing process development**

Information should be provided about any significant changes made to the manufacturing process of the substance used in producing non-clinical, clinical, scale-up, pilot and production scale batches.

### 4.1.2.3. Characterisation

**Identity, elucidation of structures and other characteristics**

Data should be provided confirming the chemical structure of the substance produced by the nominated procedures. This should include potential isomerism. Correlation with literature reports is acceptable. The sponsor should state if the substance is derived from or contains GMOs or GM products. Additional information about the requirements for GMOs and GM products is provided in ARGCM Part IV – *Genetically Modified Organisms*

**Impurities and incidental constituents**

Information should be provided about impurities – solvents / catalyst residues / synthesis or process impurities / degradation products. This includes characterisation and typical levels in regular production batches. A summary should be provided of any degradation studies carried out to identify impurities arising from exposure to stress conditions (e.g. heat, light, pH or moisture). Further guidance in relation to impurities and contaminants in general, is provided in *Impurities and Incidental Constituents* (Section 4.5).

### 4.1.2.4. Control of the active substance

**Compositional guideline**

Provide a compositional guideline following pharmacopoeial format. Guidance in relation to this is provided in *Compositional Guidelines* (Section 4.4).

**Analytical procedures**

Details of the test methods should be provided.

**Validation of analytical procedures**

Validation data for test methods should be provided. Validation data are not required for methods described in a TGA-recognised text such as a pharmacopoeia (e.g. Heavy metals BP).

**Batch analyses**

Certificates of analysis should be provided for at least two recent commercial-scale production batches to demonstrate routine compliance with the compositional guideline.

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. If available, 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 help TGA to determine if the substance intended for supply is the same as that on which safety data have been provided. For Registered and Listed products, ingredients may be quantified by input in some situations – see Parts I and II for details.

**Justification of compositional guideline**

A justification for the compositional guideline should be provided. The justification should refer to development data, pharmacopoeial standards, test data for the active substance used in toxicology and clinical studies, and results from stability studies, as appropriate, and they should take into account expected analytical and manufacturing variability.

### 4.1.2.5. Reference standards or materials

Information should be provided about the reference standards used in the tests; for example, for identification, assay and impurities. Information should be provided about how these reference substances were established and, where applicable, how their potencies were assigned.

### 4.1.2.6. Container closure system

A description of the general characteristics of the container closure system should be provided where this might influence the stability of the substance.

### 4.1.2.7. Stability

**Stability summary and conclusions**

Details of the recommended storage conditions for commercial batches should be provided.

**Post-approval stability protocol and stability commitment**

This should be provided where extended data are not available at the time of application.

**Stability data**

Stability data to support the nominated shelf life / retest period should be provided for at least two commercial-scale batches produced by the nominated process and stored in typical packaging for a nominated period under defined conditions. If data on commercial-scale batches are not available, stability data should be provided for pilot-scale batches manufactured using the same process as intended for commercial-scale batches.

Stability data monitored at a series of time points using stability-indicating methods should be provided. Compliance with all compositional guideline requirements that may be susceptible to change during storage should be demonstrated. Guidance in relation to stability testing is provided in *Stability Testing* (Section 4.3).

#### 4.1.2.8. Compositional guideline

A summary of descriptions, tests and limits that define the composition and characteristics of the substance should be provided. Further guidance is provided in *Compositional Guidelines* (Section 4.4).

Note: On differences between compositional guidelines and monograph specifications: It should be noted that a monograph or standard is designed to provide a means of controlling the quality of a substance. It is not designed to characterise the material to the extent required for entry in the ARTG. The compositional guideline for herbal substances should allow for characterisation as well as quality control of the substance. To achieve this, it may be necessary to include in the compositional guideline a statement concerning the manufacturing process or the origin of starting materials.

## 4.2. Complex complementary medicine substances

These guidelines apply to those substances for use in complementary medicines that are complex materials, generally of herbal or other origin (including complex substances of animal origin). Complex herbal ingredients may be "herbal substances" as defined in Regulation 2 of the *Therapeutic Goods Regulations 1990* (the Regulations) or complex ingredients derived from herbal substances. Further specific guidance on quality aspects for herbal substances is included in ARGCM Part IV.

Such substances fall within one of the following two categories:

Type 1 - The substance is the subject of a current monograph in the BP, PH Eur and USP or other suitable monograph or standard (see note).

Type 2 - The substance is not the subject of a current monograph in a TGA-recognised pharmacopoeia or other applicable standard.

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 and USP specifications are expiry specifications. The requirements of applicable general monographs of the BP, PH Eur and USP must also be met, except where a justification for not doing so is authorised by the TGA. Examples of these general monographs are those entitled "Herbal Drugs", "Herbal Drug Preparations" and "Extracts". The TGA will consider the suitability of other national or international pharmacopoeial monographs or standards on a case-by-case basis. Note that the most recent edition of any cited pharmacopoeial monograph or standard should be used, or a justification for not doing so included.

If the substance is the subject of a food standard, then the TGA will consider the suitability of this standard as a means of controlling the quality of the substance. A monograph or standard would be considered suitable if the information contained therein is consistent with the information that would be provided in a Type 2 submission.

### 4.2.1. Type 1 Complex complementary medicine substances

The following information should be provided for substances where a pharmacopoeial monograph or other standard is applicable.

#### 4.2.1.1. General information

**Description (Composition)**

Any information not included in the monograph / standard description should be mentioned.

**Nomenclature**

State the name of the substance. If an AAN has not been allocated for the substance, state 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 should be provided. Refer to ARGCM Part IV – *Naming of New Substances* for further information. For traditional Chinese medicines, include the Chinese name (in Pin Yin and Chinese characters).

**Structure**

The chemical structure (graphic), molecular formula, molecular weight and CAS Registry Number should be provided for any nominated characterised constituents, unless these are provided in a relevant monograph or standard.

**General properties**

Provide any physico-chemical information relevant to the characterisation of the substance or that may be required for the manufacture, performance or stability of its intended final dosage form that is not covered by the relevant monograph or standard (e.g. solubility or particle size).

#### 4.2.1.2. Manufacture

Note: On commercially sensitive aspects of the manufacturing process: Where a manufacturer is unwilling to supply manufacturing details to the Australian sponsor then the option exists for the information to be supplied directly to the TGA. In that case, any matters arising from the review of this data will be pursued with the manufacturer. The sponsor will be notified that matters have been raised but no details will be provided without the manufacturer's authorisation. Please note that the Australian sponsor will need to provide written authorisation to the TGA before the TGA can communicate with the manufacturer.

**Manufacturer(s)**

Provide the manufacturer's name and address and addresses of all sites involved in the manufacture / testing of the substance. This information is not mandatory, but it may assist the TGA in the evaluation process.

**Manufacturing process and process controls**

Sponsors should be aware of the manufacturing process and consider whether the process used is adequately controlled by the monograph or standard, including the requirements of general BP, PH Eur or USP monographs. The provision of this information is not mandatory.

**Control of materials**

Materials should be adequately controlled. For herbal substances, information should be provided on the site of collection, time of harvesting and stage of growth, drying and storage conditions and how these can influence the quality of the substance.

**Controls of critical steps and intermediates**

Not applicable.

**Manufacturing process development**

Sponsors should consider whether there have been any significant changes made to the manufacturing process of the substance used in producing non-clinical, clinical, scale-up, pilot and production-scale batches, as this may affect the composition of the substance. The provision of this information is not mandatory.

### 4.2.1.3. Characterisation

**Identity, elucidation of structures and other characteristics**

This is not applicable for constituents detailed in the monograph. However, if additional constituents are nominated in the application, these should be characterised. The sponsor should state if the substance is derived from or contains GMOs or GM products. The requirements for GMOs and GM products are included in ARGCM Part IV – *Genetically Modified Organisms*

**Impurities and incidental constituents**

Information concerning impurities that are not covered in the monograph or standard should be provided. While this information is not mandatory, sponsors should be aware that the manufacturing process for the substance may differ from the process for the substance upon which the monograph is based and, consequently, different impurities may be present.

Further guidance in relation to impurities and incidental constituents in general, is provided in *Impurities and Incidental Constituents* (Section 4.5).

### 4.2.1.4. Control of the active substance

**Compositional guideline**

This is not applicable unless approval is sought to vary the requirements of the monograph or standard. In that case, a copy of the proposed compositional guidelines should be presented.

**Analytical procedures**

This section is not applicable where the procedures described in the monograph or standard are employed. If that is not the case, details of the additional test methods should be provided.

**Validation of analytical procedures**

This is not applicable where the procedures described in the monograph or standard are employed. If this is not the case, validation data for analytical test methods should be provided.

**Batch analyses**

Certificates of analysis should be provided for at least two recent, commercial-scale production batches, to demonstrate routine compliance with the compositional guideline 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.

If available, 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 help the TGA to determine if the substance intended for supply is the same as that on which safety data have been provided. For Registered and Listed products, ingredients may be quantified by input in some situations – see Parts I and II for details.

**Justification of compositional guideline**

This is not applicable where a monograph or standard is used.

#### 4.2.1.5. Reference standards or materials

This is not applicable unless in-house reference materials are used. In that case, information is required on how the reference material has been characterised.

#### 4.2.1.6. Container closure system

Not applicable.

#### 4.2.1.7. Stability

**Stability summary and conclusions**

Not applicable.

**Post-approval stability protocol and stability commitment**

Not applicable.

**Stability data**

The monograph or standards are applicable throughout the storage period of the substance. Compliance of material stored for the manufacturer's assigned storage / retest period with the monograph or standard should be demonstrated. Guidance in relation to stability testing is provided in *Stability Testing* (Section 4.3).

#### 4.2.1.8. Compositional guideline

A compositional guideline is a summary of descriptions, tests and limits that define the composition and relevant characteristics of the substance. Where the pharmacopoeial monograph or standard sufficiently characterises the substance, a separate compositional guideline is not required (see note below). Further guidance in relation to compositional guidelines is provided in *Compositional Guidelines* (Section 4.4).

Note: On differences between compositional guidelines and monograph specifications: It should be noted that a monograph or standard is designed to provide a means of controlling the quality of a substance. It is not designed to characterise the material to the extent required for entry in the ARTG. The compositional guideline should allow for characterisation as well as quality control of the substance. To achieve that, it may be necessary to include in the compositional guideline a statement concerning the manufacturing process or the origin of starting materials.

### 4.2.2. Type 2 complex complementary medicine substances

The following information should be provided for substances where a pharmacopoeial monograph or other standard is not applicable.

Note: Where relevant, the complementary medicine substance must comply with the general monographs.

#### 4.2.2.1. General information

**Description (composition)**

Qualitative and quantitative particulars of the substance should be provided.

- For unprocessed substances, including chopped or powdered herbs, equivalent amounts of therapeutically active constituents (if known and where relevant) or marker compounds should be provided. Active constituents are not applicable for excipient ingredient status.
- For processed substances – herbal extracts, for example – the physical state of the substance should be provided. For herbal extracts, extraction steps, extraction ratios and any solvent used, equivalent amounts of therapeutically active constituents (if known and where relevant) or marker compounds obtained by the extraction process should be provided. Where more than one solvent is used in an extraction step, the concentration of each solvent should be provided. The equivalent dry or fresh weight of the starting material from which the extract was prepared should also be provided.
- Where applicable, information on the use of added materials – carriers and diluents, for example – should be provided.

**Nomenclature**

Give the name of the substance. If an AAN has not been allocated for the substance, state 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 should be provided. Refer to ARGCM Part IV – *Naming of New Substances* for further information. For traditional Chinese medicine substances, include the Chinese name (in Pin Yin and Chinese characters).

**Structure**

The chemical structure (graphic), molecular formula, molecular weight and CAS Registry Number for any characterised constituents, including marker compounds, should be provided.

### General properties

Information should be provided about the physico-chemical properties relevant to the characterisation of the substance (e.g. appearance, colour, texture, gross section, odour, taste, fraction characteristic) or that may be important for the manufacture, performance or stability of its intended final dosage form.

### 4.2.2.2. Manufacture

Note: On commercially sensitive aspects of the manufacturing process: Where a manufacturer is unwilling to supply manufacturing details to the Australian sponsor then the option exists for the information to be supplied directly to the TGA. In that case, any matters arising from the review of this data will be pursued with the manufacturer. The sponsor will be notified that matters have been raised but no details will be provided without the manufacturer's authorisation. Please note that the Australian sponsor will need to provide written authorisation to the TGA before the TGA can communicate with the manufacturer.

### Manufacturer(s)

Provide the manufacturer's name and address and addresses of all sites involved in the manufacture / testing of the substance. This information is not mandatory, but it may assist the TGA in the evaluation process.

### Manufacturing process and process controls

A flow chart of the process should be provided, which identifies the starting materials, reagents and solvents used, yield ranges and operating conditions for all of the steps. Any standardisation procedures should be described; for example, use of diluents, addition of batches of higher/lower content of characterised constituents.

Provide a sequential, procedural narrative of the manufacturing process, including a detailed description covering, for example, the quantities of raw materials, solvents, catalysts and reagents that reflect a representative batch scale for commercial manufacture; critical steps and process controls; equipment; and operating conditions (e.g. temperature, pressure, pH and time).

Any reprocessing steps should be identified, and evidence should be provided that they have no significant effect on the final quality of the substance.

### Control of materials

Information on quality and control of the starting materials, solvents and reagents used in the manufacture should be provided. For herbal substances, information on the site of collection, time of harvesting and stage of growth, preliminary treatment at the spot of collection, and drying and storage conditions should be provided.

### Control of critical steps and intermediates

Provide information on the control of critical steps and intermediates, specifically:

**critical steps** details of the tests and acceptance criteria (with justification including experimental data) performed at critical steps of the manufacturing process to ensure the process is controlled; and

**intermediates** information on the quality and control of any intermediates isolated during the process.

**Manufacturing process development**

Information should be provided about any significant changes made to the manufacturing process and / or manufacturing site of the herbal substance used in producing non-clinical, clinical, scale-up, pilot and production-scale batches.

### 4.2.2.3. Characterisation

**Identity, elucidation of structures and other characteristics**

Macroscopic and microscopic features of the plant that distinguish it from adulterants or substitutes should be provided. Information on botanical variation should be provided where this is relevant to the quality of a substance. Data should be provided to confirm the chemical structure of characterised constituents in the substance produced by the nominated procedures.

Chromatographic or spectrophotometric fingerprints, if relevant, should be provided. Guidance in relation to profile chromatograms is provided in *Profile Chromatograms* (Section 4.7). Information on any known toxic constituents should be provided (literature reports may be used to support this component of a submission). The sponsor should state if the substance is derived from or contains GMOs or GM products. Additional information about the requirements for GMOs and GM products is included in the ARGCM Part IV – *Genetically Modified Organisms*

**Impurities and incidental constituents**

Information about impurities / solvents / process impurities / degradation products should be provided, as well as characterisation and typical levels in regular production batches. A summary should be provided of any degradation studies carried out to identify impurities arising from exposure to stress conditions (e.g. heat, light, pH or moisture).

Where relevant, comments should be provided on the presence of pesticides, fumigants, toxic metals, microbial toxins, radionuclides, microbial contamination, likely contaminants / adulterants, and foreign matter.

Further guidance in relation to impurities and contaminants in general, is provided in *Impurities and Incidental Constituents* (Section 4.5).

### 4.2.2.4. Control of the substance[8]

**Compositional guideline**

Provide a compositional guideline for the substance, including constituents with known therapeutic activity (where relevant) or markers[9], following pharmacopoeial format. Active constituents are not applicable for excipient ingredients. Guidance in relation to compositional guidelines is provided in *Compositional Guidelines* (Section 4.4).

**Analytical procedures**

Give details of the test methods.

[8] For active complementary medicines, if, according to the state of scientific knowledge, the constituent(s) responsible for the therapeutic activity is (are) not known, the substance itself is considered to be the active ingredient.

[9] Markers are chemically defined constituents of a herbal substance that are of interest for control purposes, independent of whether or not they have any therapeutic activities. Markers may serve to quantify the amount of a herbal substance in a herbal medicinal product if they have been quantitatively determined in the herbal substance or herbal preparation.

**Validation of analytical procedures**

Validation data for test methods should be provided. Validation data are not required for methods described in a TGA-recognised text such as a pharmacopoeia (e.g. Heavy metals BP).

**Batch analyses**

Certificates of analysis should be provided for at least two recent, commercial-scale production batches, to demonstrate routine compliance with the compositional guideline. 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. If available, 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 help the TGA to determine whether the substance intended for supply is the same as that on which safety data have been provided. For Registered and Listed products, ingredients may be quantified by input in some situations – see Parts I and II for details.

**Justification of compositional guideline**

A justification for the compositional guideline should be provided. The justifications should refer to development data, pharmacopoeial standards, test data for the active substance used in toxicology and clinical studies, and results from stability studies, as appropriate, and they should take into account expected analytical and manufacturing variability.

### 4.2.2.5. Reference standards or materials

Information should be provided about the reference standards used in the tests for, for example, identification, assay and impurities. Information about how these reference substances were established and, where applicable, how their potencies were assigned should also be given.

### 4.2.2.6. Container closure system

A description should be provided of the commercial packaging, where this can influence the stability of the substance.

### 4.2.2.7. Stability

**Stability summary and conclusions**

Details should be provided of the recommended storage conditions for commercial batches.

**Post-approval stability protocol and stability commitment**

This should be provided where extended data are not available at the time of application.

**Stability data**

Stability data to support the nominated shelf life / retest period should be provided for at least two commercial-scale batches, produced by the nominated process and stored in typical packaging for a nominated period under defined conditions.

If data on commercial-scale batches are not available, stability data should be provided for pilot-scale batches manufactured using the same process as intended for commercial-scale batches.

Stability data monitored at a series of time points using stability-indicating methods should be provided. Compliance with all parameters that may be susceptible to change during storage should be demonstrated. Guidance in relation to stability testing is provided in *Stability Testing* (Section 4.3).

#### 4.2.2.8. Compositional guideline

A summary of descriptions, tests and limits that define the composition and relevant characteristics of the substance should be provided. Further guidance in relation to compositional guidelines is provided in *Compositional Guidelines* (Section 4.4).

Note: On differences between compositional guidelines and monograph specifications: It should be noted that a monograph or standard is designed to provide a means of controlling the quality of a substance. It is not designed to characterise the material to the extent required for entry in the ARTG. The compositional guideline for substances should allow for characterisation as well as quality control of the substance. To achieve that, it may be necessary to include in the compositional guideline a statement concerning the manufacturing process or the origin of starting materials.

## 4.3. Stability testing

This section provides guidance on the design, conduct and reporting of stability studies for complementary medicine substances. The objective of a stability study is to determine the interval during which a substance retains appropriate standards when stored under defined conditions, to support the development of the raw-material compositional guideline for the substance. The generality of these stability testing guidelines reflects the wide range of complementary medicine substances and the TGA's preparedness to be flexible in this context.

While sponsors may choose the format for the presentation of stability data, the following headings may be helpful:

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

### 4.3.1. Critical summary of the stability studies

Sponsors should undertake a critical analysis of the stability studies conducted. The following format is suggested to facilitate evaluation:

- Provide 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;
- Provide a statement as to whether all or some of the batches tested were identical (or essentially the same; for example, identical extraction process used for a herbal ingredient) in terms of composition of the substance intended for supply. If this was not so, the differences should be justified;
- Provide a statement as to whether or not the manufacturing process used for the batches tested is the same as that to be used to manufacture the substance intended for use in products to be sold or supplied in Australia. If the process is not the same, the differences should be justified;

- Give brief details of the results observed for each of the test parameters included in the studies. Separate comments must be provided for each test parameter:
  - a heading including the parameter / test name, limits, and test technique (e.g. *Content of Cholecalciferol, HPLC, 97-103%*); and
  - an assessment and interpretation of the trends observed in the results of testing (numerical description preferred), including discussion of the variability in the results, and any anomalous results. If excessive variability in the results prevents assessment of the trends, this should be stated.
- State for which of the test methods used in the studies, validation data have been generated. Note that all assay methods should be validated and stability-indicating. Any change in test methods while the studies are in progress should be justified on the basis that the methods are equivalent.

### 4.3.2. Stability data guidance

Stability data should be provided for a new complementary medicine substance. Ideally, the data package should include stability data that have been generated under the following storage intervals and conditions:

- 12 months storage at the proposed maximum storage temperature; **OR**
- 6 months storage at both the proposed maximum storage temperature and at least 10 degrees higher; **AND**
- at least 3 months storage elevated humidity, if the substance is susceptible to the effects of moisture.

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/QWP/122/02 Rev 1).

Stability information should be generated on at least 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, they should be provided for pilot-scale batches manufactured using the same process as intended for commercial-scale batches.

As far as practicable, pilot batches should reflect the manufacture of full production batches using the same type of manufacturing equipment and the same manufacturing process. Pilot batches should be of sufficient size to adequately reflect the physical conditions encountered in the manufacture of production batches. The use of laboratory-scale batches is generally inappropriate.

Conditions of storage likely to be encountered in Australia should be a consideration in designing the stability study. Storage conditions should be clearly defined; for example, “store below 25°C”.

The use of uncontrolled temperature conditions in stability studies is undesirable. Terms such as “room temperature” and “normal warehouse conditions” are discouraged, as these allow the product to be exposed to a wide range of conditions and make shelf-life assessment difficult.

The cycling effect of night and day conditions can be useful where the substance or a significant constituent in the substance may be sensitive to light and temperature changes. This should be considered in the design of stability studies for these types of substances.

Where a substance is suspected to be sensitive to moisture, its stability should be determined under conditions of high humidity at the recommended temperature (refer to Section 4.3.3.6 *High-humidity studies*).

Changes in the moisture content can be important for some substances. The extent of loss can be assessed by accurate weighing of the substance over time or by testing "loss on drying".

For guidance on interpreting data on stability refer to the EMEA document *Note for Guidance on Evaluation of Stability Data* (CPMP/ICH/420/02).

### 4.3.3. Appropriate tests

#### 4.3.3.1. General

The purpose of stability tests is to provide evidence on how the quality and safety of a substance varies with time. Stability tests should be of sufficient detail to provide confidence in the safety and quality of a substance.

Stability tests should include the relevant tests that form part of the substance compositional guideline (e.g. assay test) and additional tests that will:

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

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

- The tests need to be stability-indicating, i.e. able to determine that a substance meets the compositional guideline, and the subtle changes as a substance moves from "within specification" to "out of specification". Nevertheless, the limits should reflect the usual range associated with the original substance;
- Tests should measure the degradation of those constituents that are characteristic of the substance; for example, active or marker constituents where they can be identified. Likewise, constituents that degrade should be chosen, as there is little point choosing a constituent that does not change in the substance over time when in fact the quality of the substance deteriorates over time. The appropriate tests in this regard are the most difficult to determine and it is possible that "stress testing" could elicit 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 which may lead to safety concerns (e.g. microbiological growth) or a reduction in the quality (e.g. colour change);
- Tests that involve taste and smell are not regarded as amenable to objective validation but can demonstrate gross changes in a substance; and
- 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 if the detection method is suitably specific, reproducible and quantitative. Section 4.7, *Profile Chromatograms*, provides guidance. If changes are made to the assay or other test method during a stability study, data comparing the two methods should be generated to validate the change.

#### 4.3.3.2. 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 of all analytical methods used in the stability studies, together with validation data that demonstrate accuracy and precision, and

specificity – that is, 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 substance remains within the limits of the compositional guideline; the study design and assay parameters should be such as to allow observation of any trends over time.

It should be noted that loss of a constituent in a substance might be due to factors other than degradation, such as volatilisation etc.

#### 4.3.3.3. Degradation products

Determination of trends in the formation of major degradation products of the substance 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.

#### 4.3.3.4. Physical properties

In addition to assay for content of active or marker constituents in the substance, it is also necessary to monitor the physical properties of the substance during storage. The physical tests will vary with the substance, but possible physical tests to consider include moisture content, appearance, colour, pH and oxidation (peroxide value).

#### 4.3.3.5. Microbial content testing

Where relevant, stability studies should include tests for microbial content. Further processing should not be used as a basis for omitting microbial testing, as the growth of certain micro-organisms may produce toxins (e.g. aflatoxins by fungi) that are not destroyed by further processing even though the micro-organism itself may be destroyed.

#### 4.3.3.6. High-humidity studies

Data should be generated to establish the effect of high humidity on the substance, unless it is unaffected by the presence of moisture. For example, if the substance is already in an aqueous solution and elevated-temperature stability studies have demonstrated minimal change over time, high-humidity studies are not required.

High-humidity studies typically involve the substance being stored at 25°C and 80% relative humidity (RH) or 30°C and 75% RH for 3 months.

Stability data generated using the substance stored at 40°C and 75% RH may also be useful (particularly in the absence of data generated at 25°C / 80% RH or 30°C / 75% RH). However, sponsors should note that, where rapid change in key stability parameters is observed for this storage condition, interpretation of the results might be difficult.

#### 4.3.3.7. Presentation of results

Results obtained at the start of the study and at nominated time intervals during its progress should be presented in tabular format. This allows any trends to be detected and will enhance the predictive value of the study. Data that do not include initial results (i.e. at the start of the study) are of limited value.

Where possible, quantitative results should be quoted, rather than making a statement that the substance complies with a particular compositional guideline requirement. Assay results obtained during the study should be recorded either as absolute values or as percentages of the original content.

The results obtained should be discussed, and explanations given where necessary (e.g. anomalous or unusual results, change in assay method, change in appearance).

## 4.4. Compositional guidelines

Applications for the evaluation of a new complementary medicine substance should include a draft compositional guideline for the proposed substance. This is, in essence, a physicochemical definition of the substance.

If the substance is already defined in a monograph of the BP, Ph Eur or USP a separate compositional guideline is not required. The TGA expects that the substance will meet all requirements of that monograph. More often, however, there are no current pharmacopoeial references for complementary medicine substances.

Compositional data should be given in sufficient detail to allow characterisation of the substance. This should be provided before the application evaluation process is commenced. Applications lodged with the Office of Complementary Medicines (OCM) without relevant compositional and other data may not be accepted.

The origin of the data submitted in the draft compositional guideline may be from any source that is appropriate and authoritative. If the proposed substance is the subject of a pharmacopoeial monograph, and the TGA accepts the monograph as the standard, then the TGA will expect that monograph to apply to the proposed substance, unless otherwise justified in the application.

For example, while there may not be a relevant monograph in the BP, Ph Eur and USP there may be one in the Commission E Monographs, or the People's Republic of China Pharmacopoeia (PRCP). If these monographs do not sufficiently characterise the substance, additional parameters may be required. There may also be acceptable data in the published scientific literature or developed using proprietary methods.

The draft compositional guideline submitted in an application will be reviewed as part of the evaluation process. Modifications may be proposed by the TGA. Further, the Advisory Committee on Complementary Medicines (ACCM) may recommend to the TGA that additional modifications be made following the Committee's consideration of the evaluation report.

This will usually be followed by consultation on the draft compositional guideline with stakeholders. Any requests for significant alteration to draft compositional guidelines during stakeholder consultation may necessitate a new substance safety evaluation.

The process of developing a compositional guideline occurs separately from the gazettal[10] process for a newly approved complementary medicine substance. As soon as a new Listable substance is gazetted, it may be used in Listed therapeutic goods. However, the compositional guideline in draft form will usually undergo stakeholder consultation after gazettal. Once the compositional guideline is finalised, it will be included on the TGA website.

It is expected that products sold or supplied using the newly approved substance should comply with the compositional guideline, even in draft form, as this is the substance upon which the safety evaluation was based. While compliance with the compositional guideline is not a direct legal

[10] It is not always possible to provide legislative underpinning for the use of complementary medicine substances in Listed medicines via the gazettal process. In some instances, a change to the *Therapeutic Goods Regulations 1990* is required. Refer to Part III Section 3, *The Evaluation Process*, for information about this.

requirement, using a substance that does not comply with the compositional guideline may result in the TGA questioning the safety of the substance and any products containing it. Products may be cancelled from the Register if the safety of the substance or product is not known.

Many complementary medicine substances have yet to be defined or characterised in a monograph that is acceptable to the TGA. Therefore, compositional guidelines that substantially characterise these substances should be proposed. In general, compositional guidelines proposed should:

- substantially define the nature or character of a substance;
- allow the substance to be distinguished from adulterants, substitutes or counterfeit versions;
- be specific for components of safety and / or therapeutic significance;
- take into account the biological, chemical and physical variations that may reasonably occur between batches of the substance; and
- be capable of objective validation.

The major components of a substance should be determined, as well as any minor but significant ones.

Note: On differences between compositional guidelines and monograph specifications: It should be noted that a monograph or standard is designed to provide a means of controlling the quality of a substance. It is not designed to characterise the material to the extent required for entry in the ARTG. The compositional guideline for herbal substances should allow for characterisation as well as quality control of the substance.

### 4.4.1. Simple / Complex complementary medicine substances

#### 4.4.1.1. Simple complementary medicine substances

This could include stipulating the macro components such as nitrogen content or sodium content. For liquid formulations, solvent content or solid residue could be important. Simple additional tests that could assist in characterisation might include colour, texture, smell, taste (if appropriate) and pH. Specific tests should be used where there is a need to determine a component in a substance that is significant; for example, the sodium content in a sodium salt of a substance.

#### 4.4.1.2. Complex complementary medicine substances

For a complex substance, this could include stipulating the macro components such as nitrogen or sodium content. For complex liquid formulations, solvent content or solid residue could be important. Simple additional tests that could assist in characterisation might include colour, texture, smell, taste (if appropriate) 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; for example, the sodium content in a sodium salt of a substance, gas chromatographic (GC) analysis of key components in an oil.

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

### 4.4.2. Distinguishing characteristics

The characteristics that will distinguish the substance from substitutes, adulterants or counterfeit products should be determined. This enables the "genuine article" to be distinguished from other products, to ensure quality.

Distinguishing characteristics include particular isomers or homologues that should or should not be present in the substance, and adulterants that are indicative of contamination or substitution.

#### 4.4.2.1. Simple complementary medicine substances

The substance may, for example, be a potassium salt, with the potential for the less-expensive sodium salt to be substituted. As a result, the compositional guideline should address this by including a potassium and sodium limit.

#### 4.4.2.2. Complex complementary medicine substances

The root of a plant, for example, may contain an active component, whereas the stems and leaves do not. As there is the potential for adulteration with the leaves or stems, there should be a focus on those components that would be indicative of the presence of the stem or leaves and that would or should not be present in the root material.

Substances may yield distinctive "profile" or "fingerprint" chromatograms that provide a useful distinguishing characteristic. These chromatograms may, for example, be generated by thin-layer chromatography (TLC), high-performance liquid chromatography (HPLC) or GC.

Chromatograms should be accompanied by complete details of the extraction steps and procedures (including detectors or detection systems) involved in their production. The information should be of sufficient detail to allow an independent authority to generate the same profile chromatogram. Guidance in relation to profile chromatograms is provided in Section 4.7, *Profile Chromatograms*.

Other methods such as deoxyribonucleic acid (DNA) profiles for identity testing of herbal materials, are encouraged, but the methodology used must be validated.

### 4.4.3. Constituents of safety and / or therapeutic significance

Those components that are critical to the safety and / or therapeutic effect of the substance must be identified, including constituents whose presence should be maximised and those that should be minimised.

Sponsors should give special attention to the presence of isomers, metabolites, co-extractives and degradation products. For example, processing may result in the production of a compound of toxicological significance or, alternatively, may reduce the amount of a key component of therapeutic significance. Incorporate limits for these components in the compositional guideline.

### 4.4.4. Biological, chemical and physical Variations

#### 4.4.4.1. Simple complementary medicine substances

Simple substances may be subject to some variation. This variation should be included in the compositional guideline, and the need for it justified (e.g. the moisture content may vary slightly

over a year because of variable humidity in storage). Limits should reflect such variations. Any variations over 10 per cent should be justified on the basis that the substance at one end of the range is as safe as, and of comparable quality to, the substance at the other end of the range.

#### 4.4.4.2. Complex complementary medicine substances

Complex complementary medicine substances may be subject to "natural variation" depending upon many factors, such as:

- genetic variation;
- environmental factors, such as climate, soil type, altitude and other growing conditions;
- maturity and time of harvesting;
- part of the plant used;
- post-harvest treatment and storage conditions; and / or
- processing treatments.

This variation should be included in the compositional guideline and the need for the variation justified. For example, the constituents in certain plants may vary seasonally and batches may contain, at certain times of the year, less of a certain constituent. Limits should reflect the reasonable variation of a constituent. Variations should nevertheless be justified.

As for simple substances, sponsors should also consider what may happen to a constituent or the substance during storage. While a reasonable variation is appropriate, any variations over 10% should be justified on the basis that the substance at one end of the range is as safe as, and of comparable quality to, the substance at the other end of the range.

### 4.4.5. Objective validation

Any methods or procedures used to measure compliance with particular limits should be reproducible by an independent authority. Consider using methods similar to those given in pharmacopoeias for similar substances (e.g. for measuring pH). Validate any methods to ensure that there is sufficient accuracy, precision and specificity.

All details of "in house" methods should be provided. This is particularly important, as it allows the TGA to conduct an independent verification of the method and its suitability.

The compositional guideline should include requirements relating to solvent residues, pesticide residues, heavy metals or any other impurities and incidental constituents. As a starting point, use the limits and methods stipulated in the BP, or justify the use of other pharmacopoeias or monographs where there is no BP monograph. Variations from these methods and limits should be justified on the basis that they are no less stringent than the requirements in the BP or that the substance is no less safe or of lesser quality than would be attained by compliance with the BP requirements.

In addition, any specific limits for incidental components in the substance should be stated; for example, aflatoxins in certain plant parts, and dioxins and polychlorinated biphenyls in fish oils.

## 4.4.6. Preparation of draft compositional guidelines

### 4.4.6.1. Format

The preferred format for draft compositional guidelines is given in Appendix 1, Example Format for Draft Compositional Analysis for Complementary Medicine Substances.

### 4.4.6.2. Detail required

The detail should be the minimum amount of descriptive information to characterise the proposed substance. Sponsors may wish to include additional information, if such is applicable to the proposed substance.

The TGA acknowledges the diversity of data that may be used to define complementary medicine substances and understands that there may be situations where the guidelines do not meet all needs. If insufficient information is available to meet the requirements stated below or there is a belief that such a requirement is not applicable or inappropriate in the definition of the substance, a sufficiently detailed justification of the omission should be provided in the application.

This justification should be on the basis that the omission of the compositional guideline requirement is immaterial or is irrelevant to the safety or quality of the substance. The validity of any justifications will be considered in the application pre-assessment process. It should be noted, however, that any omissions would be reviewed to determine whether the omission is indicative of limited knowledge and / or uncertainty of the composition of the substance.

### 4.4.6.3. Methods

Indicate the method of analysis used to establish the corresponding limit in the "method" column of the guideline, i.e. HPLC, GC or TLC. If the method and limits are based on a pharmacopoeia or published reference, provide all details in the relevant section.

Note that if any proprietary analytical methods are referred to in the draft compositional guidelines, a brief description should be given in draft and complete details in the application. Where a method is a company method, then a brief description of the method should be provided; for example, "company method involving acetone extraction and analysis by HPLC with ultraviolet (UV) detection". Where a published method has been cited, or a company method has been developed, the application should include complete details and full text copies of the literature. This will enable the TGA to readily verify the validity of the method.

Unless written approval is provided in the application, specific details of proprietary methodology will not be distributed to stakeholders during the compositional guideline consultation process. However, general information about the proprietary methods should still be included in the draft compositional guideline.

### 4.4.6.4. Justification

The omission of specific compositional requirements should be justified. This justification should be on the basis that the omission of the compositional guideline requirement is immaterial or is irrelevant to the safety or quality of the substance. A statement that a requirement is irrelevant is not sufficient. The justification should state clearly why this is so. For example, the production of a substance may not involve the use of solvents. In this case, a justification along the following lines would be acceptable: "The production of this substance does not require the use of solvents. On that basis, the compositional guideline requirement for solvent residues has been omitted".

An omission of a compositional guideline requirement that is based upon a particular source or processing requirement may not be acceptable because the compositional guideline does not limit the source of a substance. For example, justifying the absence of limits for agricultural and veterinary chemicals on the basis that the source is certified "organic" would not be acceptable. This is because the source may vary and other sources may not be "organic".

#### 4.4.6.5. Subjective statements

Avoid subjective statements or ill-defined terms in the compositional guideline. For example, the term "clean" is open to wide interpretation and its use adds little value.

## 4.5. Impurities and incidental constituents

This section provides guidance to sponsors on potential impurities and incidental constituents in complementary medicine substances. Impurities and incidental constituents are those constituents that may be present in a substance as a by-product of the production, processing or storage of a substance, and are immaterial to the nature of the substance.

The production, processing and storage of substances may result in the presence of impurities and incidental constituents; for example, micro-organisms, microbial toxins, radionuclides, metals and non-metals, pesticide residues, degradation products, general contaminants, solvent residues and manufacturing by-products. These constituents may be potentially hazardous to human health and their presence therefore needs to be minimised. Sponsors should describe the procedures adopted to achieve this.

### 4.5.1. Principles

The principles relating to the presence of impurities and incidental constituents are:

- the presence of impurities and incidental constituents in raw materials and finished products must not represent an unacceptable risk to public health and safety; and
- because they offer no therapeutic advantage, the presence of impurities and incidental constituents in raw materials and finished products should be minimised, consistent with legal and appropriate production, processing and storage practices.

In considering these principles, it should be recognised that the presence of impurities and incidental constituents is a function of production, processing and storage practices. Reliance upon finished product, testing alone is not seen as the most practical or comprehensive means of managing their presence. On that basis, the sponsor's focus should include managing the production, processing and storage practices so as to minimise the presence of impurities and incidental constituents.

The legal standards for therapeutic goods in Australia cite the requirements in the relevant monographs, and the limits in this text are the legally binding limits with which manufacturers must comply. Sponsors should be aware that the presence of impurities and incidental constituents needs to be considered even where a substance complies with a relevant monograph.

While it is the legal standard, the monographs do not include a comprehensive list of all impurities and incidental constituents, and sponsors should give consideration to the management of risks associated with impurities and incidental constituents in general. The following are some practical guidelines on how these risks can be managed.

### 4.5.2. General approach

The approach for impurities and incidental constituents takes into account that the exposure to some of these constituents from medicines is not the only route of exposure. For example, diet and the environment may also be significant sources of exposure and, consequently, influence the exposure that would be considered acceptable for medicines. Given the potentially large range of impurities and incidental constituents, the varying and changing exposures to these constituents over time, and the wide variation in exposures likely to be found in the general community, it is difficult to develop a "list" of limits for each constituent in all raw materials or finished products.

A practical approach is to minimise the presence of impurities and incidental constituents in medicines consistent with those levels that would be associated with the legal and appropriate production, processing and storage practices (e.g. Hazard analysis critical control points (HACCP) principles or code of good manufacturing practice (GMP)). This approach recognises the presence of some impurities and incidental constituents as unavoidable, but seeks to minimise their presence in medicines and, consequently, their significance in public health and safety.

Given that sponsors are often in the best position to identify the specific risks that may or may not apply to their raw materials and finished products, applications should consider the risks for relevant impurities and incidental constituents that have been identified and how they may be managed to minimise risk.

### 4.5.3. Specific impurities and incidental constituents

In developing compositional guideline requirements for the impurities and incidental constituents in a substance, the following three questions need to be answered:

- What specific impurities and incidental constituents need to be considered?
- What tests should be used?
- What limits should be specified?

#### 4.5.3.1. What specific impurities and incidental constituents need to be considered?

Sponsors should consider each type of likely impurity and incidental constituent, and determine whether it is relevant to the substance in question. They should include consideration of the following:

- microbiological limits;
- microbial toxins, e.g. aflatoxins, ochratoxins;
- radionuclides;
- radiolytic residues;
- metals and non-metals, e.g. lead, arsenic, selenium;
- agricultural and veterinary chemicals, e.g. pesticides, fungicides;
- general contaminants, e.g. dioxins, polychlorinated biphenyls;
- solvent residues; and
- manufacturing by-products, e.g. reagents, catalysts, co-extractives, degradation products.

Justification for omitting a test or requirement should be based upon sound reasoning as to why it is unnecessary; for example, "The plant which is extracted grows only in the Amazon rain forest and is totally removed from any source of radionuclide contamination. A compositional guideline requirement for radionuclides is therefore unnecessary".

Further, it is generally not an acceptable justification to state that there is no evidence that an impurity is present, without providing data showing what testing has been performed to support this.

#### 4.5.3.2. What tests should be used?

Having determined the specific incidental constituents that should be considered for the substance, the next step is to decide what method or tests should be used to determine them. The advice of an analyst may be appropriate, as there are standard tests that can be used to determine many incidental constituents.

Any test that is applied should be validated and reproducible by an independent authority. It is not advisable to apply to a particular substance a test that has never been used to analyse that substance.

As a starting point, it is suggested that tests or methods used in pharmacopoeial references be used (e.g. limit tests in the default standards). This creates consistency and simplifies the process. Other useful references include the methods used by the US Environmental Protection Agency (US EPA) and the US Food and Drug Administration (US FDA). Other references and non-pharmacopoeial methods could also be considered. If a non-pharmacopoeial method is proposed, then complete details of the method should be documented.

#### 4.5.3.3. What limits should be specified?

The two key considerations in developing the limits are the need to ensure that the presence of incidental constituents does not represent an unacceptable risk to public health and safety, and that their presence is minimised consistent with legal and appropriate production, processing and storage practices (e.g. principles of HACCP or GMP).

As a starting point, it is suggested that the limits used in pharmacopoeial references be used. Other limits could be proposed, but if a non-pharmacopoeial limit is proposed, then complete details of the reasoning for this should be documented.

**Microbiological limits**

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

**Microbial toxins**

The potential for microbial toxin contamination should be fully considered. Where necessary, suitable validated methods should be used, and the acceptance criteria should be justified on the basis that the limits are as low as practicable.

**Radionuclides**

The potential for contamination with radionuclides should be considered, particularly where substances might be sourced from contaminated areas.

### Metals and non-metals

Metals and non-metals should be considered. As a minimum, the heavy metals test in the BP should be considered. Specific limits for metals such as lead, mercury, arsenic and cadmium should also be applied.

### Agricultural and veterinary chemicals

The potential for residues of pesticides, fumigants etc. should be fully considered. Where necessary, validated methods should be used, and the acceptance criteria should be justified. The method, acceptance criteria and guidance on the methodology (BP Appendix XI L – *Pesticide Residues*) should be applied, unless otherwise justified.

### General contaminants

Depending upon the substance, specific contaminants, for example dioxins and polychlorinated biphenyls, may be present, and the range of their concentrations and should be given. Some examples of appropriate limits would include "not detected in a sample, i.e. <0.001 mg/kg" or "less than 0.01 mg/kg based upon the limit that is used for an equivalent food". The limits applicable to food may not be appropriate for complementary medicine substances and sponsors may justify the use of other limits.

### Residual solvents

The BP contains a supplementary chapter entitled *Residual Solvents* that includes information about solvent residues and their permissible limits. Note that the BP (and the other default standards) are the legal standard for medicines in Australia and any instance non-compliance must be formally justified with regard to product safety and quality.

### Manufacturing by-products

Sponsors should also give consideration to the presence of manufacturing by-products, such as catalyst residues, synthesis or process impurities, and degradation products. The likely presence of these substances needs to be determined, and typical levels in regular production batches should be documented, particularly where they are of significance to safety or quality. Particular attention should be given to the presence of isomers, metabolites, co-extractives and degradation products.

### Irradiation and radiolytic products

Substances may be sterilised using ionising radiation. This may produce new constituents in the substance – referred to as radiolytic products – or affect certain constituents in the substance (e.g. vitamins). Sponsors should consider what radiolytic products may be formed in their substances, what constituents of the substance may be affected, monitor levels of these products or constituents and, if necessary, establish and document limits. Sponsors should also establish and maintain documentation about substances that have been irradiated, so that they are in a position to provide definitive information to consumers should it be requested.

### Decontaminating treatments

If a decontaminating treatment has been used, it must be demonstrated that the quality of the substance has not been adversely affected and that no harmful residues remain. The BP prohibits the use of ethylene oxide to decontaminate herbal substances. In relation to other pharmaceutical raw materials and finished products, it is recommended that ethylene oxide be used only when essential and where alternative processes and / or decontamination agents cannot be used.

Where ethylene oxide is used, the residual ethylene oxide must not exceed 1 part per million (ppm, the current limit of detection) and residual ethylene chlorhydrin must not exceed 50 ppm. Any amounts above these limits must be justified.

**Further guidance**

For further guidance, an example of the consideration of an incidental constituent and an example of an incidental constituent compositional guideline requirement is provided in Appendix 2, *Impurities and Incidental Constituents*.

# 4.6. Guidance on limits and tests for incidental metals and non-metals in therapeutic goods

This section provides guidance to sponsors in developing limits and selecting appropriate tests for incidental metals and non-metals in therapeutic goods. For the purposes of this guidance, incidental metals and non-metals are those elements that may be potentially hazardous and yet whose presence in therapeutic goods is unavoidable. Some examples are lead, mercury, arsenic, cadmium and iodine.

Some of these substances are sometimes referred to as "heavy metals", but the guidance provided could be applied to any incidental metal or non-metal.

## 4.6.1. Limits for incidental metals and non-metals

As with all therapeutic goods, the levels of incidental metals and non-metals:

- should not represent an unacceptable risk to public health and safety; and
- should be minimised and consistent with legal requirements and appropriate production, processing and storage practices (e.g. principles of HACCP or GMP).

The legal standards for therapeutic goods in Australia cite the requirements in the default standards and the limits given in that text are legally binding limits with which manufacturers must comply. Sponsors should be aware that the presence of incidental metals and non-metals needs to be considered even where a substance complies with a BP monograph.

While the default standards are the legal standards, they do not contain a list of limits for all incidental metals and non-metals. Therefore, sponsors need to give consideration to determining appropriate limits for their products or starting materials.

In the first instance, sponsors should ensure that the *Standard for the Uniform Scheduling of Medicines and Poisons* (SUSMP) does not stipulate a particular limit for a metal or non-metal constituent in a substance. Lead, for example, is included in a Schedule to the SUSMP and a substance containing more than 10 mg/kg lead would be subject to the conditions of the SUSMP.

Substances that are subject to the conditions of a Schedule (or applicable Appendix) to the SUSMP are not permitted in Listed medicines. If a substance is subject to the conditions of a Schedule (or applicable Appendix) to the SUSMP, or contains a metal or non-metal that is subject to the conditions of a Schedule (or applicable Appendix) to the SUSMP, then it will not be accepted for evaluation as a potential Listable substance.

If the SUSMP requirements are not applicable, then sponsors can use an approach similar to that used in the default standards for pesticide residues to determine a limit for metal or non-metal constituents. This approach involves assuming that the amount of a residue from the daily dose of a therapeutic good should not exceed 1 per cent of the acceptable daily intake (ADI) of that residue. The equation for calculating the upper limit is:

$$\text{Limit} = \frac{\text{ADI} \times M}{\text{MDD} \times 100}$$

where

ADI = the acceptable daily intake in mg/kg bodyweight per day for the metal or non-metal, as specified by a source such as the Food and Agriculture Organization – World Health Organization (FAO–WHO), US EPA, US FDA or Food Standards Australia New Zealand (FSANZ).

M = body weight in kilograms (e.g. 60 kg)

MDD = daily dose of the formulation/substance in kilograms.

If a raw material is intended for the preparation of extracts, tinctures or other pharmaceutical forms the preparation method of which modifies the content of metals and non-metals in the finished product, the limits are calculated using the following equation:

$$\text{Limit} = \frac{\text{ADI} \times M \times E}{\text{MDD} \times 100}$$

where E = the extraction factor of the method of preparation, determined experimentally.

**Sample calculation for lead**

1. Lead has an ADI of 0.0036 mg/kg bodyweight.[11]
2. A 200 mg tablet is to be taken up to three times a day. The maximum daily dose is therefore 0.0006 kg.

A calculated limit for lead is therefore:

$$\text{Limit} = \frac{0.0036 \times 60}{0.0006 \times 100} = 3.6 \text{ mg/kg}$$

This calculated limit could then be considered in the context of the typical levels found in the formulation.

Having determined limits on the basis of a consideration of the ADI, sponsors can then consider the typical levels of incidental metals and non-metals in their therapeutic goods or starting materials.

If typical levels are well below the limits calculated from the expressions above, then the sponsor should consider whether a lower limit should be proposed. Before considering a\ lower limit, the sponsor should ensure that batch or source variation would not result in the proposed lower limit being exceeded. If the sponsor is confident that typical levels will be below the proposed lower level, then the sponsor should consider proposing the lower level as a means of minimising the presence of incidental metals and non-metals.

This combined "safety" followed by "minimisation" assessment ensures that limits are developed that are consistent with protecting public health and safety but are also established at levels that are as low as reasonably achievable.

If typical levels are above the limits calculated from the expressions above, then the sponsor should determine the reason for this. There are materials that contain elevated levels of incidental metals and non-metals; seaweed, for example, contains high levels of iodine. Nevertheless, the sponsor should be in a position to justify that the levels of the incidental metal or non-metal are typical and

[11] 22nd Australian Total Diet Survey, FSANZ

are not associated with contamination of the substance or indicative of poor quality. If this can be established, then the sponsor should proceed to propose limits that are indicative of typical levels in the substance and that take into account any batch or source variation, even though the exposure associated with these limits may exceed 1 per cent of the ADI. Limits that would result in exposure greater than the ADI for a metal or non-metal are unlikely to be accepted.

### 4.6.2. Tests for incidental metals and non-metals

Having established limits for relevant incidental metals or non-metals, sponsors should consider the most appropriate means of determining compliance with these limits. For most metals and non-metals, there are various methods of analysis. These vary in complexity, accuracy, and specificity and, ultimately, cost.

The TGA considers that the limit tests in the default standards are a useful starting point for sponsors, provided they are suitable for the substance being analysed. However, other methods such as those used by the US EPA are also acceptable. Where the sponsor develops an "in house" method, then it should be validated.

In implementing GMP and when conducting tests during formulation development or routine quality control, sponsors should be aware that a result is only as good as the original sampling. Given the low levels of incidental metals and non-metals that may be present, sponsors should ensure that any sampling takes into account:

- the need to avoid potential contamination of the sample; and
- that the original sample may not be homogeneous and that therefore more than one sample from a batch may be required.

Sponsors should consider adopting tests where the limit of reporting (quantitation) is at least 10 per cent of the limit proposed for the incidental metal or non-metal in the substance or therapeutic good. This may not always be possible where a very low limit is proposed. However, results that are well below the proposed limits provide greater confidence that the limits proposed will not be exceeded.

## 4.7. Profile chromatograms

A profile chromatogram or, as it is more commonly known, a "fingerprint" chromatogram, is a chromatographic profile of a botanical raw material or other substance that can be compared with that of a reference sample or standard. Ideally, the profile will be unique to the substance and assist in assessing the identity, quality and batch-to-batch consistency. Profile chromatograms may also be generated for finished products, but the presence of excipients or other active ingredients may make this impractical.

### 4.7.1. Principles

A profile chromatogram may be useful for quality assessment where:

- the components of a substance are unknown; and
- the active constituent is unknown, but useful marker compounds in the substance have been identified and are representative quality indicators for the substance.

A well-constructed profile chromatogram can be used for routine quality control as a reproducible and objective measure of a substance's batch-to-batch variability. A profile chromatogram can also be a useful tool for indicating the stability of a substance, where the technique and conditions have been chosen to ensure that stability-indicating components are determined.

On its own, a profile chromatogram is not suitable where a constituent of toxicological or therapeutic activity has been identified in a substance.

In these cases, specific methods to determine the amount of the toxicologically or therapeutically active constituent are required. The profile chromatogram would nevertheless still be useful for profiling the other constituents in the substance.

The profile chromatogram should aim to reflect the possible variation that may occur for a substance, so sponsors should ensure that profile chromatograms represent, as far as practicable, as wide a range as possible of a substance's variability. This may involve an investigation of the profiles of substances from different sources, and, for botanicals, possibly different seasons.

This is most relevant if there are concerns that the safety or quality could be compromised by the source of the substance. Where the literature indicates potential substitution or adulteration is possible, then the conditions and techniques used to develop the profile chromatogram should also enable the detection of adulterants and differentiation from substitutes.

In developing a profile chromatogram, sponsors need to give consideration to substances that are not determined as part of the profile. For example, a profile chromatogram may be generated for the flavonoids in a substance and yet the majority of the substance is comprised of other components, such as starches or sugars. If known and where practicable, a profile chromatogram should therefore be accompanied by information about the other constituents in the substance that are not profiled. Justification for not profiling these other constituents should be provided on the basis that these other constituents have no effect on the quality of the substance.

### 4.7.2. Profile development

No single technique can be recommended for developing a profile chromatogram. Sponsors should first undertake a rigorous literature search to ensure that profile chromatogram conditions have not already been developed by other researchers. Sponsors can assess the most appropriate technique to use by considering the nature of the major or significant constituents of the substance; for example, volatile oils in a substance would be better determined by GC than HPLC, whereas TLC may be more appropriate than HPLC for determining sugars in a substance.

In developing a profile chromatogram, sponsors may need to experiment with the different chromatographic techniques by using different solvents (including extraction solvents) or elution conditions, different stationary phases, and different detection or derivatisation techniques. The techniques and conditions used to develop a profile chromatogram should be optimised to produce the maximum amount of information. In addition, sponsors may wish to combine techniques to obtain more detailed profiles of a substance. In general, techniques and procedures should be:

- objective and reproducible;
- tailored to suit the characteristics of the components that are the target of the determination;
- selective enough to separate the components that, as far as is known, are characteristic of the substance;
- sufficiently general to profile as many components as possible (more information is better than less);
- robust enough to ensure that labile or unstable components are identified, particularly where a substance's stability is concerned; and
- optimised to produce high-quality profile chromatograms (texts are available that provide assistance on optimising chromatographic separations).

It is anticipated that the chromatographic profile of a substance will form part of a compositional guideline for the substance. Sponsors should therefore be aware that a representative profile chromatogram and the techniques and conditions for developing these chromatograms would be publicly available. This is to ensure that substances used in complementary medicines are of suitable quality.

### 4.7.3. Profile chromatogram interpretation

The interpretation of profile chromatograms involves:

- developing profile chromatogram specifications from chromatograms of material of acceptable quality;
- comparing and contrasting the size, shape and distribution of relevant peaks or spots in sample and in standard or reference chromatograms; and
- assessing these differences and similarities against the profile chromatogram specifications to determine compliance with the specification.

Before any sample of a substance can be assessed against standard material, the specifications with which future samples will need to comply must be determined. For profile chromatograms, this approach involves determining the key or indicative peaks / spots and then developing tolerances that can then be used for assessing samples of the substance.

To develop these tolerances it may be necessary to examine profile chromatograms of:

- degraded or poor quality material containing the substance, as this will provide an indication of the peak or spot changes associated with a sub-standard substance; and / or
- the substance "spiked" with known adulterants or substitutes, as this will provide an indication of the specificity of the method.

The key or indicative peaks / spots are those that are associated with the degradation of the substance and / or the presence of adulterants or substitutes. In selecting these, sponsors should not focus unduly on one type of constituent (e.g. flavonoids). Sponsors should work from the general to the specific, rather than focusing on specific constituents at the outset.

The size, shape and distribution of the responses can be used to determine profile chromatogram specifications. Sponsors may also wish to consider the ratios of certain responses and not just the individual responses for constituents. Ratios can sometimes represent better indicators of quality because they allow controls to be determined for more than one constituent and may be particularly useful where more than one substance is therapeutically active.

The allowable extent of variations in profile chromatograms will need to be determined on a case-by-case basis. This is because slight variations can be of importance, particularly if the variation is associated with the presence of one or more toxic substances. Conversely, gross changes may sometimes be of limited significance.

As a starting point, sponsors should consider specifications that limit:

- any changes in component responses that are greater than +/-10 per cent, where the responses are associated with constituents of known therapeutic activity; and
- any changes in component responses that are greater than +/-20 per cent, where the responses are associated with constituents that are unknown or are not linked to therapeutic activity.

Sponsors can adopt wider specification limits where these can be justified. Large variations in profile chromatogram specifications should not be used as a means of legitimising substandard

material. Specifications should be sufficiently broad to allow for normal variations in the constituents of the substance.

Once profile chromatogram specifications have been developed, they can then be used to assess routine samples of the substance. It is preferable to analyse authentic reference material at the same time as the sample, to minimise changes in profile due to variation in analytical conditions.

The analyst should note any similarities and differences between the chromatograms obtained from the sample and the reference sample, particularly for any components identified in the specifications. Similarities are as important as differences and should be recorded, particularly where the sponsor is aware that a peak or spot is associated with a constituent of therapeutic or toxicological significance. Differences in responses that exceed the +/- 10 per cent or +/- 20 per cent criteria discussed earlier should be explored and the use of such samples in a finished product must be justified.

# 5. Safety

The subsections in this section are:



## 5.1. Introduction

The primary objective of regulating complementary medicines is the protection of public health and safety. The safety of complementary medicine substances for use in Listed medicines is established through an evaluation process that aims to ensure that any substance approved for use in Listed products is of "low risk". Once established as being of low risk, many complementary medicine substances need no further controls on their use in Listed complementary medicines. However, where risks or potential risks are identified in association with the use or uses of a particular substance – in its use by particular population subgroups such as children or pregnant women, for example – certain restrictions and / or controls may be imposed to manage the risk and the substance may still be eligible, with restrictions, for use in Listed medicines. Such options include the use of label advisory information, restrictions on dosage, route of administration, plant part or plant preparation, and / or restriction of the form in which the substance can be presented.

The inherent safety, or otherwise, of potentially Listable substances that may be used in complementary medicines is established through an evaluation process undertaken by the Therapeutic Goods Administration (TGA). The Office of Complementary Medicines (OCM) staff prepare a comprehensive evaluation report on the safety of the substance, based on the data and information available. This is normally supplied by a sponsor who is requesting evaluation of the substance. In evaluating safety, it is important to distinguish the situation where risk has been evaluated from that in which there are insufficient data to identify risk. Care needs to be taken to avoid mistaking the absence of reliable evidence of risk for reliable evidence of the absence of risk. Advisory Committee on Complementary Medicines (ACCM) sometimes recommends against the use of substances in Listed medicines, not because of direct evidence of their hazard, but because of insufficient evidence to provide assurance of safety.

The criteria used to assess the safety of a complementary medicine substance described in this chapter recognise the need for a level of evaluation commensurate with the level of risk, and acknowledge that the conventional safety data package available for prescription and over-the-counter (OTC) medicines is rarely, if ever, available for assessing a complementary medicine substance. Nevertheless, though conventional toxicity data are not available, there are other data for complementary medicine substances that can be used to support the safety evaluation. These data are described in the sections that follow.

Some of the substances that are intended for use in complementary medicines within the therapeutic goods regulatory domain in Australia are available for supply in other countries under significantly less-stringent regulatory controls. In some countries, the products that contain complementary medicine substances are regulated as foods, food ingredients, food additives or dietary supplements. As foods generally do not need to undergo pre-market evaluation, post-market vigilance within food regulatory domains may not be as rigorous as in therapeutic domains, and rarely includes a formal system for adverse-reaction reporting. While substances and products regulated under less-rigorous controls may not provide a high degree of assurance of their safety in use, particularly if there is limited control on composition and adverse-reaction reporting, information about such use may nevertheless be helpful in supporting safety. Where results from epidemiological studies of food or dietary supplements are of sufficient power, or other adequate post-market safety studies are available, these data may be sufficient to establish safety.

### 5.1.1. The risk-assessment framework

The risk-assessment framework used for the safety evaluation of a new substance acknowledges that there may be information from well-established medicinal, food or other uses of the substance, or products containing the substance, that can be used to support or establish safety. By "well-established" use, it is meant that a sufficient number of people were treated or otherwise exposed to the substance or to products containing the substance (or substances justified as essentially similar to the substance) over a period sufficient to support the safety of the substance for its intended purpose. Many substances have been used for periods up to and exceeding hundreds of years. The long-term use of some substances may have created a comprehensive body of experience recorded in the published literature. It can be expected that a substance or product containing it that has a long history of use will have useful bibliographic data and information published in official pharmacopoeias and scientific texts.[12]

Safety may be established by detailed reference to the published literature, the submission of original study data, or a combination of both. Where there is sufficient evidence based on human experience to support safety, conventional studies involving animal and *in vitro* studies are not necessary. Where such human experience is deficient, or it is suspected that there are effects that are difficult or impossible to detect with confidence in population or clinical studies, the safety assessment will need to be supported by other studies unless otherwise justified.

These could include studies of properties such as single and repeat-dose toxicity, immunotoxicity, toxicity to reproduction, genotoxicity and carcinogenicity studies as appropriate.

Safety may be established by detailed reference to published literature, the submission of original study data, or a combination of both. The documentation submitted by a sponsor should cover all aspects of safety assessment and must include a review of the literature, taking into account pre- and post-marketing studies and, where possible, epidemiological studies, in particular of comparative epidemiological studies that involve exposure to the substance. All evidence, both favourable and unfavourable, should be documented.

While it is in the nature of complementary medicine substances that the data package may be incomplete, particular attention must be paid to any missing information. Justification must be provided to demonstrate why an acceptable level of safety can be supported, even though some studies are lacking. Post-marketing experience with other products containing the same or a similar substance is of particular importance and should be emphasised by sponsors.

In supporting safety, the greater the consistency of the evidence from different studies, the greater the strength of the evidence. Sponsors should ensure that the data submitted are relevant to the particular substance and reflect the totality (balance and range) of the evidence available. A well-

[12] The inclusion of a substance in official pharmacopoeias or reference texts may contribute to the substantiation of the substance as a complementary medicine.

constructed (systematic) literature search should be undertaken to help ensure that the general body of evidence relevant to evaluating safety is taken into account (see Section 5.1.2, *Choosing Literature for Evaluation and Evaluating Search Strategies*). The balance and range of evidence may also be reflected in an authoritative review. This would normally be peer-reviewed and published. In instances where there is a large search output, it may not be appropriate to include all of the papers in the submission. In these cases, there should be justification for the inclusion / exclusion of papers; for example on the basis of the quality of the study.

### 5.1.2. Choosing literature for evaluation and evaluating search strategies

All applications should include an outline of the search strategy used to obtain the data to support safety. Copies of full papers, in English, must be submitted in the application. Where there are papers in other languages, certified translations should be provided. Foreign-language reports should be included in a systematic survey of the literature and, if not included in the application, reasons given for non-inclusion. Abstracts of papers are rarely suitable for use for evaluation. A suggested approach to searching the literature on complementary medicines is included in *Searching the Literature on Complementary Medicines*, Section 5.9. As part of the TGA's evaluation process, TGA library staff will evaluate the adequacy of the search strategy submitted in the application. The librarians may identify important papers that have not been supplied, and ask the sponsor to provide copies of these. Requests for such additional information may attract additional evaluation fees. Sponsors may justify why particular papers identified in this way are not pertinent to the evaluation.

Ideally, the studies relied on by a sponsor to support safety should be largely consistent with the surrounding body of evidence. Wide variation in outcomes of studies, and inconsistent or conflicting results of studies, will raise serious questions about the adequacy of a sponsor's substantiation.

Where there are inconsistencies in the evidence, it is important to examine if there is a plausible explanation for them. In some instances, for example, the differences in results might be attributable to differences in dosage, dosage form, route and schedule of administration, the population tested, or other aspects of study methodology. If several studies of different quality have been considered, greater weight should be given to the higher quality work. A summary of the types of data used to assess the safety of a complementary medicine substance and the objectives of those data are shown in Table 2 (below).

**Table 2. Types of data collected to support the safety evaluation of complementary medicine substances for use in Listed medicines, and their objectives.**

| Data | Objective |
|---|---|
| History, mode and patterns of previous human use | To determine the conditions, if any, under which the substance has been used by humans in the past |
| Biological activity | To describe the role of the substance in human metabolism |
| Toxicology | To describe what is known about and, where possible, quantify potential risk associated with the use of the substance |
| Clinical trials | To report the results of use of the substance by humans under clinical trial conditions to identify risks from the experience of use in humans |
| Adverse reactions | To determine the nature, severity and frequency of adverse reactions where there has been a history of use of the substance |

Details of general data requirements for assessing safety and the suitability of studies for inclusion in an application are included in Appendix 3. All studies should be in accordance with an acceptable code of Good Laboratory Practice (GLP) and, in the case of clinical studies, of Good Clinical Practice (GCP). The report should include certification of compliance in the conduct of each study.

## 5.2. History and patterns of previous human use

The objective of this section is to detail the information requirements to support the safety evaluation of the substance, based on previous human exposure to the substance. To establish safety, sufficient numbers of people must have been treated or otherwise exposed to the substance or to products containing the substance (or to a substance justified as essentially identical to the substance). Where there is sufficient evidence based on human experience to support safety, other conventional safety studies involving animals and *in vitro* studies will not be necessary. However, where data documenting human exposure to the substance are deficient, or there are suspicions of effects that are difficult or impossible to detect with population or clinical studies, the safety evaluation (unless otherwise justified) will need to be supported by other studies (e.g. by single and repeat-dose toxicity, immunotoxicity, reproduction, genotoxicity and carcinogenicity studies).

If a sponsor is relying, in part or all, on evidence of traditional use to demonstrate safety, the application must clearly indicate whether the substance under review is compositionally the same as that used traditionally.

For example, traditional use may involve specific preparation practices that remove toxins or may restrict use to certain plant parts (e.g. stems, leaves). The application must indicate how the substance was used traditionally, including dosage, dosage form and route, and schedule of administration. The population and culture in which this tradition occurred should be identified.

An examination of the substance's availability in other countries, the length of time it has been available, and the regulatory conditions controlling its availability should be presented. If the use of a substance is permitted in food in Australia, the applicable reference in the *Australia New Zealand Food Standards Code* should be given.

Where substances have been evaluated by other recognised regulatory authorities or evaluation agencies (e.g. the Joint Food and Agriculture Organization (FAO) / World Health Organization (WHO) Expert Committee on Food Additives) the reports from those evaluations should be discussed. It is important to highlight the purpose of the other agency's evaluation, which may have been for a more-restricted purpose than that proposed. An evaluation of safety for cosmetic use (topical), for example, is unlikely to have considered safety for oral use. Similarly, an evaluation of a food additive is unlikely to have considered dermal toxicity and possibly not inhalational toxicity. In contrast, a review of industrial safety will have considered exposure in amounts far greater than would occur through use in therapeutic goods. These reports may also have recommended particular restrictions on the substance; if so, they should be described and their relevance to therapeutic usage drawn out.

The application should point out circumstances where a particular substance has been withdrawn from sale in any other country, for whatever reason, or where an overseas evaluation of the safety of the substance before supply has shown that it is not suitable for use.

Where substances have been approved by the US Food and Drug Administration (US FDA) as being of "Generally Recognised As Safe" (GRAS) status, or recommended for approval by the (US) Flavour and Extract Manufacturers Association (FEMA), the need for further evaluation of the substance for use in Listable goods in Australia will be reduced. Again, it is important to consider if the evaluation done by these agencies is directly relevant to the use proposed in Australia. It is also essential that the sponsor provides a copy of this GRAS approval, to verify GRAS status and to identify the approved conditions of use.

Similarly, where a substance has been an ingredient of a Registered good, or is permitted as an excipient in a therapeutic good, such history of use will be considered, but it is essential to demonstrate that the proposed substance is the same as that used in those goods. Information on the number of doses supplied and the period over which they were supplied is particularly valuable.

Where possible, information on population exposure data should be included in the application. Where data are not available on the particular substance, data derived from related substances (such as the precursor of the substance under evaluation) may be useful as supporting evidence. For some nutrients and food types, the National Nutrition Survey will contain useful estimates of consumption.

A substance used in therapeutic goods may present a different risk profile to that resulting from its use in food. For example, when isolated from the food matrix, a substance may no longer be protected from oxidation that leads to degradation products not encountered when the substance is consumed in food.

Other components in the food matrix, such as fibre, may affect the rate of absorption or otherwise interact with the substance when it is present in food. There may be no such effect when the substance is delivered in a therapeutic formulation. These matrix effects may be significant in terms of safety for some substances and may require limits on the proposed unit or daily dosage.

Modern extraction methods or other processes may produce, in some cases, substances that have a considerably different compositional profile from those produced using traditional methodology. Here it will therefore be insufficient to rely entirely on evidence of traditional use to support the safety-in-use of these substances. Ginger extracts are an example of this; highly concentrated extracts have caused bleeding in some cases, while no such problem has been reported with

traditional extracts. In some instances, the extraction of a substance from its natural matrix may make it more prone to oxidation to a toxic product.

### 5.2.1. Exposure

To assess the safety of a substance for use in complementary medicines, it is necessary to estimate the overall exposure to the substance. The exposure evaluation determines the amount of the substance that populations may be exposed to from all sources, including the diet, water and the environment. Determination of the exposure to a substance provides information that will allow the effect of the use to be assessed.

Key considerations in assessing the exposure include determining the following:

- the possible sources of the complementary medicine substance to which the population will be exposed; for example, will the population be exposed to this substance only from complementary medicines or from additional sources such as food?
- the amount of exposure from these other sources and / or from the use in complementary medicines. For example, is the exposure from complementary medicines likely to be the major source of exposure or is it an additional exposure that would be less than that from other sources such as food? To determine this, exposure from each of the other sources and the complementary medicine source should be researched and compiled.
- the form of the exposure to the complementary medicine substance as opposed to other forms. For example, is the complementary medicine substance the same substance as exposed to from other sources or is it in a different form (e.g. different cation, chemically or physically modified in some way)? If the substance is different then how is it different and what is the significance of this difference?
- the nature of the exposure to the complementary medicine substance and other sources. For example, is the exposure from complementary medicines a short-term exposure (for a specific purpose) whereas the exposure from other sources is longer term?
- the route of exposure to the complementary medicine substance and other sources of it. For example, is the route of administration for the complementary medicine substance the same as from other sources (e.g. oral as distinct from topical)?

Information on each of these will assist in determining the risk or relative risk that the complementary medicine substance represents. Sponsors should therefore consider providing information on each of the above criteria.

### 5.2.2. Human poisoning

For some substances, there will be literature reports of human poisoning; generally accidental poisoning of young children and suicide attempts in adults. Reports of poisonings should be provided and commented on, with particular reference paid to the doses consumed, the specific form of the substance (e.g. sodium selenate, selenomethionine etc.) and the circumstances of the poisoning (e.g. inadequate closures on bottles or chronic toxicity via the diet). The symptoms of the poisoning should be described and any biochemical parameters reported.

## 5.3. Biological activity

Appropriate studies, including human exposure and animal and *in vitro* studies using appropriate modes and routes of administration, should provide information on absorption, tissue distribution and storage, bioaccumulation, biotransformation and the mode and extent of excretion or elimination of the parent substance and its degradation products.

For detailed information regarding safety pharmacology studies, sponsors should consult the European Medicines Agency (EMEA) document: *Note for Guidance on Safety Pharmacology Studies for Human Pharmaceuticals (ICH Topic S7A)* (CPMP/ICH/539/00).

## 5.4. Toxicology

Toxicological data for new complementary medicine substances should be included in the application under the following sub-headings (which follow the Common Technical Document (CTD) format (Module 4 – *Non-clinical Study Reports*)). Where data are not available for each of the headings, this should be clearly stated. This provides evidence that information has been sought in these areas and that they have not been overlooked.

- Single-Dose Toxicity (in order by species, by route);
- Repeat-Dose Toxicity (in order by species, by route, by duration);
- Genotoxicity;
- Carcinogenicity;
- Reproductive and Developmental Toxicity (including range-finding studies);
- Local Tolerance; and
- Other Toxicity Studies (if available) (e.g. Immunotoxicity, Metabolites).

### 5.4.1. Single-dose toxicity in animals

While acute-toxicity studies may not necessarily reflect risks associated with the levels of prolonged exposure found with therapeutic goods, studies of acute, systemic toxicity do provide insights into bioavailability, potency comparisons with other known toxic agents and an indication of which target organs might be affected. They may also offer insight into likely acute-poisoning effects; for example, in a suicide attempt or if the substance is accidentally swallowed by a child (e.g. an essential oil for aromatherapy). There are some substances, such as eucalyptus and tea tree oil, which appear, on a gram per kilogram (g / kg) body weight basis, to be more toxic to humans than to test animals.

Acute-oral-toxicity studies should be performed on at least one mammalian species and in both sexes to assess possible sex-related differences in response. The rat is the preferred species for acute-toxicity studies, but studies in higher mammals should also be considered. Studies using other species are important for revealing possible species differences in response. Since the ultimate goal is trans-species extrapolation to man, knowledge of such differences may be crucial. A number of dose levels should be included in order to reveal the spectrum of toxicity and the maximum tolerated dose level.

The inclusion of the results of $LD_{50}$ testing for each species and route of administration is not mandatory. However when included, all animals should be observed at regular intervals for the clinical signs exhibited, particularly before death, with the focus on progression, severity and duration. Necropsy findings should be available for both decedents and survivors, and organs showing macroscopic changes should be examined histopathologically.

### 5.4.2. Repeat-dose toxicity in animals

Repeat-dose studies (sub-chronic and chronic toxicity) allow the substance or its metabolites to accumulate in the body. They provide greater confidence in making predictions about how the substance may affect humans. The recommended length of the repeat-dose study is usually related to the duration of use of the substance. Nevertheless, sub-chronic studies of at least 90 days duration are essential to determine the effects of repeated exposure and as a preliminary dose-ranging study for chronic studies.

The aim of long-term, repeat-dose toxicity studies on animals is to identify the organs and / or systems to which the substance is toxic, and the threshold doses for toxic effects. Therefore, sub-chronic studies should demonstrate a range of activity from the "no observable adverse effect level" (NOAEL) through to a level that is clearly toxic. Evidence of the stability of the substance in the form administered, and of the actual dose rates achieved, should be provided.

Observations of growth, behaviour, food consumption, clinical abnormalities and mortality should be recorded throughout the study. All animals dying during the test should be examined for macroscopic and microscopic changes. At the conclusion of the dosing period, surviving animals (other than those allocated to recovery experiments) should be killed and data recorded on organ weights, gross morphology and histopathology. Haematology, and blood biochemistry, urinalysis and other biochemical studies should be made, at least at termination and, where sampling would not compromise the study, at earlier intervals. Organs identified as systemic targets in acute-toxicity tests should be carefully scrutinised.

Where statistical methods are used to support the evaluation of the responses, the validity of the method and the power of the test to establish a substance-related effect should be considered. A statement of the smallest difference that would achieve statistical significance under the conditions of the test would aid considerably in the interpretation of the results.

Sometimes sub-chronic toxicity studies may include a recovery period to provide information on the reversibility of the observed changes. If this is the case, the observed recovery profile should be discussed.

Long-term studies are particularly important for two reasons:

- they simulate the effects of lifetime exposure, and may reveal toxic effects that appear later than those that are apparent from sub-chronic studies
- they permit a comprehensive assessment of a substance's oncogenic potential.

Chronic-toxicity studies normally involve long-term, continuous daily exposure to graded amounts of the test material in the diet. The use of a rodent and a non-rodent species is desirable to provide data on interspecies variation. The rat, mouse and dog are the species whose toxicological response profiles are best known. The results of dog studies as short as six months are generally acceptable.

Chronic-toxicity studies should normally include one control and three test groups. The highest exposure level should induce a recognisable response. For materials of low intrinsic toxicity, where a response may be difficult to achieve, the highest level should be the maximum that is practicably achievable. At least one exposure level should result in no observable adverse effects (the NOAEL). Survival rates in all groups should be sufficiently high to enable a meaningful statistical analysis of the data.

The interpretation of chronic-toxicity studies may be greatly influenced by toxicokinetic considerations, particularly when species differences are apparent.

Wherever possible, plasma levels of the test substance (and / or its metabolites) should be measured at steady state.

Subheadings could include "Oral route" or "Dermal administration" (ordered by species). Studies are usually sorted by route of administration before they are ordered by duration, starting with the shorter studies and moving to the longer. For prescription medicines where duration of human use of the medicine is expected to be more than 30 days, animal studies of at least 6 months duration are recommended.

For further information, sponsors should refer for guidance to the International Conference on Harmonisation (ICH) documents: *The Assessment of Systemic Exposure in Toxicity Studies* (ICH Topic S3A) (pp. 89-101 of EudraLex 1998, Volume 3B – 3BS10a), and *Repeated Dose Tissue Distribution Studies* (ICH Topic S3B) (pp. 21-24 of EudraLex 1998, Volume 3B – 3BS3a).

### 5.4.3. Genotoxicity

Mutagenicity studies are conducted to determine the potential for a substance to contribute to genetic damage in humans. A basic package of genotoxicity studies will generally comprise:

- a test designed to demonstrate the induction of point mutations (base-pair substitution and frame shift) in a microbial assay (e.g. *Salmonella* microsome test) with and without the use of appropriate metabolic activation systems
- a test designed to demonstrate the production of chromosome damage in an *in vitro* mammalian-cell assay (e.g. chromosomal aberration assay in Chinese hamster ovary cells) with and without the use of appropriate metabolic activation systems.

If a positive result is returned in either of these two tests, results of the following two tests should be provided:

- a test designed to demonstrate the production of cytogenetic damage (e.g. micronuclei) in the bone marrow or other proliferative cells of intact animals
- a test designed to demonstrate genotoxic damage involving other than cytogenetic damage (e.g. Unscheduled DNA Synthesis (UDS) or $P^{32}$ post-labelling adduct formation) and preferably a suspect or known target tissue for the substance.

Supplementary tests (e.g. sister chromatid exchange, micronucleus test) should also be used to provide clarification of unexpected or equivocal results in the basic test portfolio, or to provide additional evidence. *In vivo* germ-cell tests using laboratory animals (e.g. mouse specific locus tests, heritable translocation assay) could be essential for the evaluation of a suspected mammalian mutagen.

If there are many data then they should be presented under subheadings. Subheadings could be "*In vitro*" and "*In vivo*", both with further subheadings such as "Gene mutations", "Chromosomal effects", "Unscheduled DNA synthesis" etc. as appropriate.

The documents *Genotoxicity: Specific Aspects of Regulatory Genotoxicity Tests for Pharmaceuticals* (ICH Topic S2A) (pp. 51-62 of EudraLex 1998, Volume 3B – 3BS6a) and *Note for Guidance on Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals* (ICH Topic S2B) (CPMP/ICH/174/95) provide details of a standard battery of tests.

### 5.4.4. Carcinogenicity

Recognising that humans may respond quite differently to test animals, and that animal toxicity studies are a guide only, the ACCM has indicated that it will not generally reject an application simply because there are no data available on the carcinogenicity of a substance. An extract from this guidance follows:

*There was considerable discussion about the significance of the lack of specific carcinogenicity studies, particularly if the substance were to be taken on a long-term basis. Carcinogenicity studies are also lacking for many over-the-counter, non-complementary medicines, although the majority of these medicines are intended for short-term use. Members noted that well-designed animal carcinogenicity studies are very expensive to conduct and that this cost is likely to be an impediment in the case of non-patentable substances such as most complementary medicine substances.*

*Given that it may not be economically feasible for full carcinogenicity studies of complementary medicine substances, members then considered the type of data that could be used instead in an assessment of carcinogenic potential. While in vitro mutagenicity studies have, individually, a low predictive value in terms of human carcinogenicity, any unusual results arising from a number of different mutagenicity studies could indicate the need for further investigation. Substances that are hormonally active or show signs of other forms of toxicity could also raise concerns. In addition, acute and chronic toxicity studies may identify issues of concern in relation to carcinogenicity. Finally, for most complementary medicines, there is a history of human exposure through the diet or traditional medicine use that can provide information on carcinogenic potential.*

The toxicity profile of a substance and the indication and duration of the intended use may influence the need for carcinogenicity studies (see EMEA document: *Guideline on Repeated Dose Toxicity* (CPMP/SWP/300/95).

The choice of species and strain of animal is important for carcinogenicity studies. A well defined and stable incidence of neoplasms in untreated controls may be crucial to the determination of whether a particular lesion is substance-related. Historical data describing the normal incidence and variation in tumour rates would be useful, but this will not necessarily resolve conflicts in the assessment. For example, if the control group incidence is below the normal range but the test groups produce an incidence within the historical control range, the strength of any dose-related trend will be of major importance in determining the outcome of the test. For prescription medicines, rat studies of two year's duration are recommended for studies of carcinogenic potential.

Further information about carcinogenicity studies is provided in the documents:

- *Note for Guidance on Carcinogenicity: Testing for Carcinogenicity of Pharmaceuticals* (ICH Topic S1B) (CPMP/ICH/299/95);
- *Note for Guidance on Dose Selection for Carcinogenicity Studies of Pharmaceuticals* (CPMP/ICH/383/95), and
- *Note for Guidance on Carcinogenic Potential* (CPMP/SWP/2877/00).

### 5.4.5. Reproductive toxicity

A well-designed, multi-generation reproduction study should provide information on the effects of a substance on all aspects of reproduction, including sexual behaviour, gonadal function, spermatogenic and oestrus cycles, fertility, fecundity, parturition, lactation, pre- and post-natal growth, development and maturation of the offspring. The study may also provide preliminary data on teratogenesis. Developmental studies are intended to provide information on embryotoxicity, teratogenicity, altered growth and the induction of functional deficits (post-natal behaviour). Indications of maternal toxic responses should be reported, to aid in the interpretation of any effects.

Presenting the data under subheadings will aid in their assessment. Typical subheadings would be, if there is information available, "Pharmacokinetics in pregnancy and lactation", "Fertility and general reproductive performance", "Teratology studies", and "Peri- and postnatal studies".

For detailed information about reproductive toxicology, sponsors should refer for guidance to the ICH document: *Detection of Toxicity to Reproduction for Medicinal Products including Toxicity to Male Fertility* (pp. 25-44 of EudraLex 1998, Volume 3B – 3BS4a).

### 5.4.6. Local tolerance in animals

Local tolerance testing should be focused at the potential sites of administration proposed for human use and be conducted using a similar method of administration. Both single and repeat-dose studies should be conducted for each proposed route of administration.

The inclusion of site(s) which may come into contact with a product through accidental exposure is also recommended.

The frequency and duration of administration should closely resemble the proposed therapeutic use of a product. Also, the preparation tested should be the same or closely resemble that proposed for human use, both in terms of dose of the active(s) and excipients.

Usually, only one species should be evaluated for each type of test. Where two or more toxicological end-points are being investigated (e.g. ocular tolerance and skin sensitisation), species appropriate to the test will need to be used.

In cases where a product has not been tested previously, systemic toxicity testing will be required, aside from local tolerance studies. However, should the topical absorption of a product be demonstrated to be negligible (e.g. via measurements of systemic exposure), no systemic toxicity testing will be required.

Investigation of all typical routes of administration, e.g. dermal, ocular, inhalation and parenteral may be useful where the bioavailability is markedly influenced by the route of administration. In general, if the substance may ultimately be used in a range of topical products or in products for inhalation, skin and eye irritation, and skin sensitisation, studies are also relevant.

Phototoxicity and photosensitization testing should be considered for all products presenting such risks when used as intended.

### 5.4.7. Other toxicity studies

Depending upon the proposed use or route of administration of a substance, additional studies may be required. When significant and unique toxicities to certain organs and / or systems are evident, the sponsor should provide further explanation of the mechanism of toxic actions, if necessary by performing additional *in vitro* or *in vivo* studies. When conducting such studies, the most appropriate route of administration is the route through which humans will be exposed. For example, inhalation studies may be required where a substance is likely to come into contact with the airways. These studies would differ according to the likely exposure.

For example, exposure through aromatherapy is unlikely to require specific toxicity studies, whereas exposure via an aerosol delivery system would.

Although it is recognised that toxicity tests usually determine the toxicity of the substance under evaluation, impurities, degradation products and metabolites may sometimes make an overall contribution to safety assessment. Generally speaking, studies using the manufacturing grade of the substance provide an estimate of the potential toxicity of the parent substance as well as the principal metabolites and impurities. However, in certain cases, specific toxicological information on the individual components may be useful. When processing or chemical degradation results in exposure to derivatives of the substance under evaluation, their contribution to the toxicological profile may also warrant consideration.

Intolerance to substances should always be considered a possibility, even though tests for reactions to these substances are not part of the normal data package required for assessment of new substances.

If satisfactory models based on animal studies (to predict intolerance in humans) have not been developed, interpretation from human studies may present difficulties. Where there are grounds to anticipate or suspect intolerance reactions, reasonable studies might include double-blind challenge feeding studies.

The use of a substance may significantly alter nutritional intake and generate a need for nutritional considerations in the interpretation of toxicological profiles. In appropriate cases, therefore, the relationship between toxicity and nutritional status should be assessed.

## 5.5. Clinical trials

The aim of providing data from clinical trials (if available) as part of the safety evaluation is to report the results from use of the substance under controlled conditions that maximise the opportunity to identify adverse reactions and risk (see Part 1, Section 7.5.1.4 – *Clinical Studies* and Part I, Section 7.8 – *Clinical Trials of Complementary Medicines*). Data from clinical trials addressing safety issues should be submitted. Clinical trial data submitted in support of the safety of complementary medicine substances will not be evaluated for efficacy.

## 5.6. Adverse reactions

Adverse reactions are defined by the WHO as "a response to a medicine which is noxious and unintended, and which occurs at doses normally used or tested in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function".

A serious reaction is one that "results in death, requires in-patient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is life-threatening". Birth defects and malignancy are considered by the TGA to be serious reactions.

The aim of this section is to report on the nature, severity and frequency of adverse reactions where there has been a history of use of the substance, to help quantify risks associated with its future use. This part of the application should describe the adverse reactions that have been reported for the substance and the reporting system that was in place in the population exposed to the substance. It is important to carefully document the strengths and limitations of the reporting system to allow a qualified evaluation of the data and how accurately they reflect the incidence and prevalence of adverse reactions and their degree of seriousness.

The number of reported adverse reactions and their degree of seriousness should be commented on against the overall usage of the substance. It is important to highlight in this section any particular characteristics of the user group of certain medicines. For example, herbal medicines based on *Ginkgo biloba* may be used predominantly by elderly people who are likely to already be using other medications and who may have pre-existing medical conditions. This may be the group most strongly represented in adverse reactions.

All reports, published and unpublished, and individual case reports relevant to the proposed substance should be submitted. Reports should include studies that, although not suitable for efficacy assessment due to poor trial design, inadequate analysis or other reason, will provide data about the safety of the substance. Any documented or potential interactions of the substance with food or medicines should also be considered.

When searching for reports of adverse reactions, remember to search under different synonyms for the substance and, if relevant, for closely related substances or components of the substance (e.g. for kava, the search should include, among other things, *Piper methysticum*, kawa, *Piper inebrians*, kavain, dihydrokavain, methysticin etc.).

In considering reports of adverse reactions, it is important to assess the appropriateness of the methodology used to identify and record the reactions. For example, were the adverse reactions monitored only by patient recording or were they sought systematically? If the latter, how robust was the approach in identifying all adverse events, including those occurring some time after exposure to the substance. It is of little value to report, for example, "only one adverse reaction was identified in three clinical trials involving 20 patients" if, in fact, there was little or no chance of adverse reactions being observed during the study.

In all instances, the relevance of the product formulation actually used in the studies to the assessment of the safety of the substance needs to be considered and commented upon. It is recommended that, in addition to a description of the clinical trials reviewed for adverse reactions, that results also be presented in tabular form (see Table 3 for an example). The summary table is a very useful first step in reviewing trials as, when the trials are tabulated, the study weaknesses often become apparent. When a number of trials are available, present the best-designed studies first, then work down to the weakest studies. Where possible, studies should also be presented in descending duration of exposure within the trial type (e.g. put a 6-month trial before a 10-day trial).

Selected individual case reports of adverse reactions, and reports obtained from national medicine safety surveillance authorities, should be summarised separately from data from clinical studies.

In Australia, the TGA operates an Office of Medicines Safety Monitoring which supports the Advisory Committee on the Safety of Medicines (ACSOM). Details about information available on adverse reactions to medicines in Australia can be obtained from <http://www.tga.gov.au/safety/problem-medicine.htm>.

The US FDA has a comprehensive system for tracking, monitoring and analysing adverse event reports involving food, cosmetics and dietary supplements: <http://www.fda.gov/Safety/MedWatch/default.htm>

The US FDA has discontinued its previous adverse reaction reporting system for dietary supplements (Special Nutritional Adverse Event Monitoring System) and, through the Centre for Food Safety and Applied Nutrition, is developing a new comprehensive system for tracking, monitoring and analysing adverse event reports involving food, cosmetics and dietary supplements.

Adverse-reaction reports obtained from national medicine safety surveillance authorities should include a description of all available clinical information and the outcome of the reaction. If there are several such reports, the narratives should be included as an attachment. An example of the format for the tabular presentation of data is given in Table 4.

A summary and conclusion about the safety of the substance, based on the reports of adverse reactions, should be provided.

**Table 3 Example format – Summary of safety aspects of clinical trials of [insert name of the substance under evaluation]**

| Type of study (reference) | Subject details | Treatment details (dose, duration, route) | Adverse reactions and safety indicators | Endpoints | Key outcomes |
|---|---|---|---|---|---|
| Randomised, placebo controlled double blind<br>(Cunningham *et al*. 2001) | 56 patients,<br>mean age 60 years: 7 male; 49 female.<br>Hypercholesterolaemic | 5 mg per day PO for 8 weeks after 6 weeks of dietary stabilisation | No differences between test and placebo for bwt, heart rate, systolic & diastolic bp, ALT, glucose, creatinine<br>Adverse reaction reports: cephalea (1/27), insomnia (1/27), muscle cramps (1/27) | At least two plasma lipid (overnight fast), blood biochemistry measurements & clinical examination at 15-day intervals | Total cholesterol and LDL cholesterol decreased significantly ($p$<0.001) in the (substance) treatment group by 15 per cent 8 weeks after the start of treatment. Difference between groups also significant ($p$<0.001). There were no significant changes in HDL cholesterol, plasma triglycerides, or VLDL cholesterol levels compared with the placebo values. |

**Table 4. Example format – Summary of adverse drug reactions for [insert name of the substance under evaluation]**

| Report reference and date reported | Patient details | Product details | Treatment details | Other medicines | Adverse reaction | Comments (e.g. outcome; laboratory results) | Causality |
|---|---|---|---|---|---|---|---|
| Adverse Drug Reactions Systems (Aust) Report No. 24369 30-6-98 | Male, 34 years | Brand name Ingredients: (active ingredient details) | 480 mg tablets PO 3 times daily for 10 weeks | Aspirin off and on; cod liver oil 275 mg PO twice daily | Psychosis, (psychotic ideation); manic reaction (hypomania) | Recovery after (Brand name) stopped | Probable |
| BfArM 9204235 (Germany) 16-6-92 | Female, 59 years | Brand name Ingredients: (active ingredient details) | 200 mg capsules twice daily PO | Headache; impaired alertness; amnesia, nausea | Serepax 45 mg daily PO | Recovery after all medication stopped | Possible |

PO: (*per os*) oral administration
ALT: alanine aminotransferase
LDL: low-density lipoprotein
HDL: high-density lipoprotein
VLDL: very-low-density lipoprotein

## 5.7. Ingredients of human or animal origin

Ingredients of animal and human origin with potential viral and Transmissible Spongiform Encephalopathy (TSE) risks must be approved before their inclusion in Listed medicines. Information about the clearance of products containing ingredients of animal or human origin is included in ARGCM Part IV – *Ingredients of Human or Animal Origin*.

## 5.8. New topical excipients

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

- the sponsor is able to identify the excipient as a substance included in the Personal Care Products Council Cosmetic, Toiletry and Fragrance Association (CTFA) *International Cosmetic Ingredient Dictionary* (page number and reference should be quoted); **AND**
- the sponsor certifies that the excipient does not appear in the European Economic Community (EEC) Directive 76/768 List of substances which must not form part of the composition of cosmetic products; **AND**
- the sponsor provides documentary evidence that the excipient has been approved by the appropriate regulatory agency in Sweden, Canada, USA, UK or The Netherlands; **OR (LESS DESIRABLY);**
- the sponsor certifies that there have been market-place sales of comparable products containing the excipient in one of those five countries for at least two years; **AND**
- the sponsor provides an assurance that the prescribed data will be provided to the TGA within six months of the product being placed in the Australian Register of Therapeutic Goods (ARTG).

Such excipients are allocated a "provisional" status until such time as they are evaluated by the TGA. Where a new topical excipient is included in a topical Listed complementary medicine, safety data must be provided to the Office of Complementary Medicine (OCM) within six months of the date of inclusion of the product in the ARTG. The safety data that must be submitted for new topical excipients which meet the aforementioned criteria are:

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

Additional data on acute dermal toxicity and absorption following dermal application would provide valuable information on the profile of the substance. New topical excipients that do not meet the aforementioned criteria must be evaluated before their inclusion in Listed complementary medicines.

## 5.9. Searching the literature on complementary medicines

Papers *per se* do not provide the evidence in support of an application. Ideally, the sponsor needs to show that:

- the literature has been methodically scrutinised;
- the range of papers selected for submission is justified; and
- issues raised in the literature with a bearing on the application have been resolved.

This brief guide is intended to help sponsors adopt a literature search methodology that will satisfy these three requirements.

There is no single search strategy that can be applied in all cases; 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, it is clearly explained and justified in the application.

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

***Information sources***

These are the types of print and electronic sources that 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 inclusion of texts in other languages;
2. the current editions of the *Merck Index* and *Martindale*;
3. a monograph from the *Hazardous Substances Databank* (HSDB), the *Register of Toxic Effects of Chemical Substances* (RTECS), *Poisindex* or similar toxicology databases;
4. a bibliographic search of TOXNET and MEDLINE;
5. current and / or classical references in the specific field under review; for example, herbal or homoeopathic pharmacopoeias or standard works on the *materia medica* of traditional medicines; and
6. standard reproductive toxicity texts; for example, *Shepherd's Catalog of Teratogenic Agents*.

Details of the sources highlighted above are listed in the references below, but 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, and SCISEARCH (Science Citation Index).

Some of the above are free. The others are available in various electronic formats by subscription.

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 no more than a platform for information delivery. Any Internet search engine will pick up references but their value to the application depends on their integrity, authority and scientific validity. Significant databases are available free on the web, and searches of specific sites can be valuable starting points. A few examples are given in the references below.

#### 5.9.1.1. Search terms

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

In the case of botanicals, or substances where there may be multiple constituents, terms for the constituents should also be searched; for example, in the case of ginger, terms such as zingerols, zingiberenes should be searched, as well as zingiber and ginger.

Where different terms are used, there should be clear evidence of identity; for example, *shosaikoto* (Japanese) is *xiao chai hu tang* (Chinese Pin Yin), and both are also called "Minor bupleurum decoction" in the Chinese literature. Similarly, there should be evidence of chemical identity; for example, 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; and
5. pharmacokinetics, pharmacodynamics, pharmacology, metabolism, bioavailability.

This list is indicative rather than complete or prescriptive.

#### 5.9.1.2. Search strategy

The selecting and combining of terms is of fundamental importance in searching electronic databases, as is an understanding of the structure of each database. It is outside the scope of these guidelines to address all the complex technical requirements of electronic information retrieval, but some guidance is provided in the TGA document *Literature Based Submissions – Points to Consider.*

Searches should not be limited to English, but every effort should be made to provide relevant, certified translations of papers.

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 (if the entire download is not submitted), and the rationale for the selection of papers.

The following is a description of a systematic search conducted to trace literature about the safety of ginger extracts.

***Parameters of search***

Literature relating to ginger (*Zingiber officinale*) in relation to uses in traditional medicine, pharmacology, toxicology, biochemistry and adverse effects.

The search covered the period 1966 to [date], with time frames varying according to each database.

***Search method***

The first step was to identify the constituents of ginger. Pharmacopoeias, herbal pharmacopoeias and standard herbal texts were consulted for monographs, as were handbooks of Ayurvedic medicine, handbooks of Chinese *materia medica* and Dukes ethnobotanical database. These sources also provided information on established usage and preparation methods.

After checking the information contained in reference books, a list of constituents was drawn up. The CAS Registry on STN was searched for records of CAS numbers and structure diagrams for the following terms: **zingiberene, zingerone, gingerol, shogaol**. This provided a basis for analysing the potential toxicity of individual components.

The terms **ginger, zingiber**, together with the above constituent names, were also used to search RTECS on CD-ROM and the POISINDEX and REPRORISK modules of MICROMEDEX (Internet version).

It was important to consider variant forms of the botanical nomenclature for possible inclusion in the search terms. For example, the Commission E monograph referred to ginger root (*Zingiberis rhizoma*) so a decision had to be made as to whether to use just **zingiber** or retrieving both by using the truncated form **zingiber*** as appropriate on the databases searched. Having established and cross-referenced the list of constituents and CAS registry numbers for consistency, an initial search was done on OVID MEDLINE. The term ginger was found to map to a subject heading Ginger.

The term was entered and combined with the subheadings for adverse effects and toxicity. Few records were retrieved so it was decided to do a broader search.

Searches were conducted using all the identified terms on TOXLINE and TOXNET. This gave a starting point for the toxicology literature. All records were retrieved in full and examined.

A multifile index search was done on the Dialog host system across biomedical, alternative medicine, food science and toxicology databases using the free text terms ginger or **zingiber? or gingerol? or shogaol? or zingiberene? or zingerone?**. The truncation mark on the Dialog system is a question mark. This was used to make sure both singular and plural forms of the terms were retrieved. Some 73 databases were searched.

From the numbers of records retrieved, the following databases were selected for extensive searching: MEDLINE, EMBASE, BIOSIS, SCISEARCH, DERWENT DRUG FILE, FSTA, FOODLINE, AMED. The search terms used were (**ginger or zingiber? or gingerol? or shogaol? or zingiberene? or zingerone?**) and (**adverse or safe? or toxic? or carcinogen? or mutagen?**). The duplicate detection command was used. All remaining titles were downloaded and scrutinised and relevant citations retrieved in full and compared with those already retrieved.

This search revealed possible cardiotonic and central nervous system effects for ginger, and a potential for increasing the bioavailability of other medicines. It was decided that further specific searches needed to be done, particularly on the pharmacokinetics of ginger and its metabolites, and on the effects of ginger or its constituents on platelet aggregation.

The following two searches were then carried out using the same database cluster selected above. The strategies were:

**(ginger or zingiber? or gingerol? or shogaol? or zingiberene? or zingerone?) and (pharmacokinetic? or metabolite? or metabolism or digest? Or pharmacodynamic? or pharmacolog? or pharmacodynamics or blood) (ginger or zingiber? or gingerol? or shogoal? or zingiberene? or zingerone?) and (platelet? or coagulant or thromboxine or thromboxane)**

The evaluator read through all the papers and abstracts retrieved in these searches. Further references were identified in the reading and these were obtained as required.

Note especially that it is important to clearly identify in the report:

1. the print sources by full citation details including chapter pagination, edition, imprint, paragraph, volume as appropriate;
2. the databases by title and host system, e.g. PUBMED on the Internet, OVID MEDLINE etc., including date range searched;
3. the full search strategy, including the logic (And, Or, With, Near) of how terms were combined, not just a list of terms searched; and
4. how papers and monographs were selected for submission with the application.

Information specialists from the TGA's Office of Information Management may assess and comment on these searches as part of the evaluation process.

#### 5.9.1.3. References to information sources

**CAS Registry Numbers**

A CAS Registry Number is a unique numeric identifier that designates a single chemical substance and is a link to information about that substance. Information on CAS numbers and how to access the registry can be found at <http://www.cas.org/expertise/cascontent/registry/index.html>. CAS numbers also appear on other database records e.g. MEDLINE and RTECS.

**HSDB (Hazardous Substances Databank)**

HSDB is a component database of TOXNET (see below). It contains monographs on the toxicity and exposure limits of chemicals.

**Martindale**

*Martindale: the Complete Drug Reference*, London: Pharmaceutical Press. Also available as a database on MICROMEDEX (see Shepherd's Catalog below).

**MEDLINE**

MEDLINE is the major publicly accessible database of biomedical literature. Produced by the US National Library of Medicine, it is available in many formats. The web version is PUBMED at <http://www.ncbi.nlm.nih.gov/entrez/query.fcgi>.

**The Merck Index, edited by S. Budavari *et al*.**

The Merck Index: an Encyclopedia of Chemicals, Drugs, and Biologicals. Rahway, N.J.: Merck & Co. Also available as a CD-ROM.

**RTECS (Register of Toxic Effects of Chemical Substances)**

RTECS is a collection of toxicology monographs compiled by the National Institute for Occupational Safety and Health (NIOSH) of the US Department of Health and Human Services and produced by the Canadian Centre for Occupational Health and Safety. A commercial database is available on subscription on CD-ROM, Internet or commercial database hosts. Information at <http://www.ccohs.ca/products/rtecs/>.

**Shepherd's Catalog of Teratogenic Agents Shepherd, Thomas H.**

*Catalog of Teratogenic Agents*. Baltimore, Md.: Johns Hopkins University Press. Also available as a component of the REPRORISK module of MICROMEDEX, a suite of health and pharmacology databases. For information about MICROMEDEX see <http://www.micromedex.com>. MICROMEDEX is supplied in Australia by Health Communications Network.

**TOXLINE**

TOXLINE is a toxicology database that complements MEDLINE and TOXNET. It ceased taking new records in December 2000 but is still a major source of references. It is available as part of TOXNET (below).

**TOXNET**

TOXNET is a suite of toxicology databases produced by the US National Library of Medicine. Available at <http://toxnet.nlm.nih.gov/>.

# Part III Appendix 1 Example format for draft compositional guidelines for complementary medicine substances



**Name of the substance**

This name must refer to the current or proposed Australian Approved Name (AAN) of the substance.

**Character of the substance**

Provide a brief, general description of the substance, its source and how the substance relates to its original source. It is important to include details of any processes that would distinguish the substance from similar yet different substances. For example: Compound X is a salt of citric acid and sodium hydroxide.

**Table 5. Substance specific requirements**

| Requirement | Method(s) | Limits |
|---|---|---|
| **Description**<br>Give a physical description of the substance including such items as physical form, colour, texture, viscosity, crystallinity (if solid) and organoleptic qualities.<br>*e.g. white to straw crystalline solid.*<br>Describe other, more-specific tests such as:<br>– melting point / boiling point<br>– moisture content / loss on drying<br>– solids content<br>– pH of aqueous solution. | Visual or otherwise. Refer to pharmacopoeial methods where possible (attach details of proprietary methods) | Complies |

| Requirement | Method(s) | Limits |
|---|---|---|
| **Identification**<br>Describe qualitative or general tests that distinguish the substance from similar yet different substances.<br>For Example:<br>– limit tests<br>– refractive index<br>– optical rotation<br>– ultraviolet or infra-red spectrum<br>– colour tests for anions or cations. | List methods of identification. Refer to pharmacopoeial methods where possible (attach details of proprietary methods) | Complies |
| **Assay**<br>Describe quantitative or specific tests that determine the presence and amount of a specific substance. More than one substance can be assayed. | State and if necessary describe methods of assay or provide brief details. | Limits for assay(s) taking into account practical but reasonable biological, physical and chemical variation |

**Table 6. Incidental constituents**

| Requirement | Method(s) | Limits |
|---|---|---|
| **Solvent Residues**<br>Specifically address those solvents that are included in the default standards.<br>Address any additional solvents that may be used in the production, preparation, manufacturing or formulation | List methods of assay e.g. BP 2003 Appendix VIII C | Total limit of solvents<br>Solvent specific limits |
| **Incidental metals and non-metals**<br>Specifically address the metals in the *British Pharmacopoeia* (BP) limit test for heavy metals (Appendix VII). Include any limits for specific metals or non-metals e.g. cadmium, arsenic, lead, mercury | List methods of assay e.g. BP 2003 Appendix VIII C | Total limit of heavy metals<br>Metal specific limits |

| Requirement | Method(s) | Limits |
|---|---|---|
| **Microbiology**<br>Consider including limits for those microorganisms in the TGO 77 Microbiological standards for medicines<br>Investigate any additional micro-organisms that may be specific for the substance e.g. for substances derived from chicken consider Salmonella and Camphylobacter limits | List methods | Total and specific microbiological loading |
| **Pesticide residues (including agricultural and veterinary substances)**<br>Specifically address the limits stipulated in the BP2003 Appendix XI L and whether the product would comply with these limits. In addition state any additional residue limits that may be relevant. | List methods of assay e.g. BP 2003 Appendix XI L | e.g. complies with limits in BP2003 |
| **Other organic or inorganic impurities or toxins**<br>Include other substances that may be of safety or therapeutic significance.<br>What specific substances are assayed? E.g. dioxins, PCBs, mycotoxins<br>Give consideration to by-products, co-extracted substances, inactive isomers and degradation products | List methods of assay | Total limit of impurities in substance<br>Impurity specific limits |

# Part III Appendix 2 Impurities and incidental constituents

This appendix provides guidance on the management of impurities and incidental constituents that are not specifically controlled in a legal Therapeutic Goods Administration (TGA) standard. A legal TGA standard means the *Therapeutic Goods Act 1989* (the Act) and Therapeutic Goods Regulations 1990 (the Regulations) and any standards made official through the Act or Regulations, including Therapeutic Goods Orders and the British Pharmacopoeia (BP), the United States Pharmacopeia – National Formulary (USP) and the European Pharmacopeia (PH Eur). For example, the BP gives limits for certain pesticides in Appendix XI L – *Pesticide Residues*, but the list is not comprehensive. If a complementary medicine substance contains a veterinary or agricultural (pesticide) residue that is not specifically restricted in the BP, then the risk associated with that pesticide should be assessed based on the generic approach described in the BP.

## A2.1. Example – An incidental constituent – how its presence might be managed

The goal of the process is to demonstrate that the applicant has actively and consciously considered the presence of the incidental constituent. This is demonstrated by identifying the incidental constituents for the particular goods or materials, and taking reasonable steps to minimise the presence of these in the goods, consistent with legal and accepted production, processing and storage practices.

The example below is for pesticide residues, one of the more difficult incidental constituents to deal with. However, the approach would be similar for all incidental constituents. The approach below represents a comprehensive approach that may not be necessary where adequate justification exists for a shorter or less-involved approach.

## A2.2. Pesticide residues

Pesticide residues may be found in a raw material as a result of treatment or from environmental contamination; that is, the pesticide(s) may be intentionally added or result from inadvertent contamination. Furthermore, the effects of processing and storage may affect these residues and result in a concentration or reduction of residues in finished goods.

Given the wide range of pesticide residues, it is not practical to test raw materials for all pesticide residues, as this would be prohibitively expensive and time-consuming, and methods are limited as to their scope and application. In addition, an approach to minimise or avoid excess residues at the supply stage will obviate costly and time-consuming downstream problems. Furthermore, analytical testing is only as good as the sample that is taken and, for some raw materials, the batches may not be homogenous. In these situations, the analytical result may reflect the residues in the sample but not in the batch.

A more practical and straightforward approach is to take a "know your product" approach which includes:

- identifying the likely pesticide residue risks;
- determining the likelihood and consequences of these risks;
- developing approaches for managing these risks;
- implementing approaches to manage the risks; and
- reviewing these approaches to make sure that they are working.

## A2.3. Identify the risks

Suppliers are useful sources of information about the pesticide residues in their products. The information they provide can identify the chemicals that need to be considered. Usually, only a handful of pesticides are used in the production, processing and storage of a specific raw material, and often these remain unchanged for long periods. By obtaining the data on the specific chemicals from the supplier, the applicant can target any downstream testing and more adequately put together a framework for managing the risks associated with likely pesticide residues. It is a lot easier to manage the risks associated with six pesticides than six hundred pesticides!

For example, a supplier may certify that certain raw materials are "organic". If this is the case, obtain a copy of what this certification entails, as some chemicals are permitted in certain "organic" agricultural production processes. Another approach would be to ask a supplier to deliver product that complies with the limits stipulated in the default standards. Sometimes a supplier is providing product to a number of companies and, as the default standard requirements are well known, it is possible that they may already be certifying the raw material for another customer. In this case, a similar certification for another a new customer may be straightforward. Sometimes certification is provided charged for and sponsors will need to decide whether or not they are prepared to accept the additional cost.

When considering the presence of pesticide residues, some thought needs to be given to those pesticides, typically organochlorines that may be present throughout the environment. Specific questions about these pesticide residues need to be asked to be satisfied that contaminated raw materials are not provided. The limits for organochlorins are given in the default standards.

Occasionally, suppliers can have difficulties in providing the information about the pesticides used, or may refuse to provide the information. In these circumstances, investigate other suppliers, or obtain as much information as possible about the production processes. Where is the source of the raw material? Are pesticides likely to be used? What pests are the raw materials susceptible to? Is there a history of pesticide contamination in the area where the raw materials are sourced? Should we ask suppliers to provide a test batch before ordering in bulk? The answers to these questions can provide information to analysts who can "tailor" the testing (possibly of the test batch) to the likely substances that may be present, and consequently reduce testing costs. If sponsors find that suppliers are unhelpful or refuse to cooperate, then they need to ask themselves whether they are prepared to take the risk – if it is too good to be true then it probably isn't.

While not limiting the range of substances that should be managed or that will be considered, the substances of particular focus will be organochlorines (e.g. DDT, endosulfan), organophosphates (e.g. chlorpyrifos, parathion), and carbamates (e.g. carbaryl, methomyl). In addition, it must also be recognised that the legal standards for therapeutic goods in Australia reference the requirements in the default standards and that the limits in this text are the legally binding limits with which

manufacturers must comply. Depending upon the particular pesticide residues, it may be more cost-effective to batch samples for analysis to get the best value for money.

## A2.4. Determining the likelihood and consequences of these risks

The next step is to determine what residues are likely and at what levels, and their overall significance.

The information gathered from suppliers may provide an indication of the substances that are likely and this may be sufficient to highlight an issue. For example, a chemical may be banned. If this chemical could be found in the raw material, then this could represent a high risk and the need to select a different source.

The details already gathered from suppliers may also include information on the levels in raw materials. For example, a supplier of a raw material from the United States may be able to provide the "tolerance" for a chemical in the raw material and this can be used to determine if the tolerance exceeds the default standard limits.

Recognising the limitations of testing, more information can be obtained by testing batches of a raw material. The purpose of the testing is to obtain an idea of the likely ranges of the pesticide residues. If testing is undertaken, ensure that the sample is as representative as possible. Plan testing to get the best value for money.

Testing of different batches of the raw material over a period may highlight the presence and levels of typical substances that should be managed. If no substances are found after comprehensive historical testing, then this may indicate that the likelihood of pesticide residues is very low.

Once sponsors have information on the residues typically present, it is essential to consider how these residues may behave in further production steps, in order to obtain an indication of what may be the typical residues in the finished goods. This can be undertaken by assuming no losses during processing and by multiplying the residues in the components by their contributions to the finished goods to determine residue levels in the finished goods. However, this process would be valid only where the processing and storage do not result in concentration of the residues.

Literature searches can often provide information on the likely effects of processing on raw materials. In the case of pesticides, information from the US Environmental Protection Agency (EPA) or the Codex Committee on Pesticide Residues can often provide good information about the effects of processing for specific chemicals. Other sources of information include pesticide-manufacturing companies.

Sometimes a pesticide residue may be present in a raw material that is then treated in a way that entirely or substantially removes the residue. For example, some pesticide residues are very volatile and a processing step that involves air drying at 70°C for an hour would substantially remove the residue. This would mean that the significance of the residue in the raw material was minimal. However, it would be wise to confirm this by analysis of a batch that was known to contain the particular pesticide residue.

In reality though, once sponsors have an idea of the pesticides that may be present in the final product, it is often easier to simply test the final product, rather than determine what may happen to these residues during production. There are some circumstances where a particular chemical may be difficult to analyse for or maybe an expensive test. In these situations, an effort at characterising the likely residues in the finished goods could be worthwhile.

## A2.5. Developing approaches for managing these risks

Once sponsors have an idea of the significance of particular pesticide residues, they need to decide what to do about them. For some raw materials, the risks may be too high and alternative suppliers may need to be sought.

Managing some pesticide residues in raw materials may involve a testing regime. Sponsors should develop the standard operating procedures and compositional requirements for these tests. These should be practical and workable procedures that include proper sampling procedures for example, "tailored" testing for specific compounds or use of test kits for compounds. Sponsors should investigate testing contracts and search the market for the best analysis prices.

## A2.6. Implementing approaches to manage the risks

Follow through on plans to manage risks by making sure that the proper procedures are being followed.

## A2.7. Reviewing these approaches to make sure that they are working

Once a plan has been implemented for managing the risks for pesticide residues, it is essential that procedures be reviewed periodically, to detect any changes in the pesticide residues that may be present. Procedures should be reviewed when there are, for example, changes in suppliers, changes in the appearance or other characteristics or compositional requirements of the raw material, and changes in the price for a raw material. These are all circumstances that point to a possible change in source.

## A2.8. Example

**Table 7. An "impurities and incidental and constituents" compositional guideline**

| Impurity | Test | Limits |
|---|---|---|
| **Solvent residues**<br>· residual solvents | BP2003 Appendix VIII L Residual solvents | Complies |
| **Heavy metals and non-metals**<br>· heavy metals<br>· arsenic<br>· lead<br>· mercury | USP24 method <231>*<br>USP24 method <251><br>EPA method 7000A<br>AOAC method 986.15<br>* Equivalent to the method given in BP 2003 Appendix VII | NMT 10 mg/kg<br>NMT 5 mg/kg<br>NMT 0.25 mg/kg<br>NMT 0.5 mg/kg |

| Impurity | Test | Limits |
|---|---|---|
| **Pesticide residues (including agricultural and veterinary substances)**<br>· residues of pesticides<br>· fungicide – chloroquasicol | Method as per BP2003 Appendix XI L<br><br>Company method (extraction with ethyl acetate, cleanup on florisil, GC determination with ECD detection) | Complies<br><br>NMT 1 mg/kg |
| **Other organic or inorganic impurities or toxins**<br>· aflatoxins<br>· triphenylaminopropanol (reaction starting material)<br>· trans-isomer (reaction by-product) | Section 49.2.15 (AOAC Method 993.17) AOAC 16th edition.<br>Applicant's method (extraction with ethanol, GC determination with ECD detection)<br>Applicant's method (extraction with ethanol, GC determination with ECD detection) | Not detected<br>NMT 100 mg/Kg<br>NMT1% |

AOAC 16th edition – Scott, P.M. 1995. Chapter 49, Natural Toxins. pp 49-1 to 49-49. *Official Methods of Analysis*, 16th ed. Association of Official Analytical Chemists International, Gaithersburg, MD.
BP2003 – British Pharmacopoeia (2003)
EPA – United States Environment Protection Agency
USP24 – United States Pharmacopoeia 24th edition
NMT – not more than

# Part III Appendix 3 Safety data requirements and suitability

## A3.1. General data requirements

For many substances, a combination of data based on previous human exposure and animal and *in vitro* studies are used to support safety. In practice, animal and *in vitro* toxicity studies have been found to be one of the most poorly reported areas of complementary medicine research. The following general points should be considered when preparing and compiling data to support safety:

- Data should be substantially complete (as at the time of the application) and be well organised;
- Data should be presented in detail sufficient to allow independent scientific assessment (e.g. original studies should ideally provide individual animal data);
- Where possible, sponsors should supply copies of original reports. Summaries and reprints of published material do not usually contain adequate detail for evaluation. Abstracts on their own are not acceptable;
- Sponsors must submit all information in English. Where published material is not in English, sponsors should supply the original language version and a certified English translation;
- Sponsors should include a complete inventory of available toxicological data. This inventory must indicate any studies that sponsors may have provided with earlier applications or submissions;
- Details of studies planned or in progress should be disclosed, together with their projected completion dates. If the application includes details of interim studies, the final report, and any other interim reports, should be submitted as soon they become available;
- Irrespective of the successful outcome of any application, any additional studies relevant to the safety assessment of the substance should be provided as soon as they become available;
- All studies should be conducted in accordance with an acceptable code of good laboratory practice (GLP) and, in the case of clinical studies, good clinical practice (GCP). The report should include certification of compliance in the conduct of each study; and
- Each study should clearly identify the name and address of the laboratory that did the work, the names of the scientists responsible, the report code number and the dates the studies were performed.

Many sponsors find it helpful to include a summary that concisely deals with every aspect of toxicity studied. Normally, the summary should not extend beyond a few pages. Tables are a good way to condense data. Studies reported in the summary should be cross-referenced with reports in the main submission.

Sponsors should disclose details of any applications to other regulatory agencies – state the outcome of such applications and whether any of the data were rejected, either in the submission

or when notified by the other regulatory agency. Where an application contains data previously rejected by another agency, an explanation as to why the rejection was not considered valid should be submitted. Sponsors must not omit any report that could influence assessment of safety of the substance.

Sponsors must specify the purity and batch number of the material used in each test. It may be appropriate to cross-reference with data in the substance profile. Keynote studies, from which a no observable adverse effect level (NOAEL) is established, should be undertaken with material of a comparable composition to that intended for use (i.e. typical substance rather than highly purified material).

Study details should include:

- the route of administration;
- the dose levels;
- the number of animals or subjects per dose level;
- the animals' or subjects' origin, gender, weight range and maturity or age;
- the frequency at which observations were made;
- the duration of each study;
- the relationship between the time of administration and the onset of the effects observed; and
- all measurements made.

In the summary, sponsors should identify all substance-related biochemical and physical changes observed in the study, with appropriate cross-referencing to the detailed data. Where it is claimed that the manifestations are not toxicologically significant (e.g. minor changes in organ weight), evidence of their reversibility may be required. In anticipation of such a possibility, it may be possible to include sub-groups for subsequent recovery assessment from earlier tests.

Sponsors should include detailed results from individual animals in prolonged toxicity studies. Where they will help review the data, sponsors should include supplementary tables or diagrams (e.g. growth curves, tumour incidence tables). It should be possible to organise tables so that the most appropriate comparisons (e.g. control and treated groups) appear on the same page and results of histopathological observations can be readily evaluated in relation to dose, sex and duration of treatment.

Common problems in toxicity studies include:

- published papers not defining the reason the study was conducted or the experimental hypothesis
- insufficient numbers of test animals
- the morbidity and mortality rate even among control animals can be so high that the study findings are worthless
- the standards of animal care in the studies are questionable.

Due to the importance of toxicological studies to the evaluation of the safety of new complementary medicine substances, the following sub-headings (which follow the Common Technical Document (CTD) format (Module 4)) should be used in an application, whether or not data are available for each of the headings. Where data are not available, this should be clearly stated. This provides evidence that information has been sought in these areas and that they have not been overlooked.

More information on requirements for the content of toxicology studies is included in ARGCM Part III – *Toxicology*.

- Single-Dose Toxicity (in order by species, by route);
- Repeat-Dose Toxicity (in order by species, by route, by duration);
- Genotoxicity;
- Carcinogenicity;
- Reproductive and Developmental Toxicity (including range-finding studies);
- Local Tolerance; and
- Other Toxicity Studies (if available) (e.g. Immunotoxicity, Metabolites).

## A3.2. Evaluating the suitability of single studies for inclusion in applications

Most, but not all, data supporting safety in the complementary medicine area will be based on published papers rather than original studies. Many published papers do not include all the details desirable for safety evaluation. It is important to recognise and deal with the deficiencies in single studies, to ensure that the total data submitted in an application are adequate to establish safety. For example, many of the studies on which these published papers are based may not have been done under conditions of quality assurance (QA) or GLP (e.g. may not have been carried out in accordance with the Organisation for Economic Cooperation and Development (OECD) GLP guidelines – *OECD Principles on Good Laboratory Practice*. ENV/MC/CHEM(98)17; 1998).

In making a judgment to exclude or include a single study in an application, the adequacy of the overall data package is the critical determinant. For example, a certain deficiency in one study may be compensated by inclusion of another study that may itself have other deficiencies. The following points are put forward as a general guide for assessing the limitations of a single study for inclusion in an application:

- What was the object of the study? The study's hypothesis should be outlined;
- Is the substance in the study adequately characterised? If not, or if it differs from that in the application, the relevance of the study should be justified. This is particularly important for substances that are not prepared using traditional methodology;
- Was the design of the study likely to produce results that will meet the objective? For example, were the right parameters measured? Sometimes parameters are measured that have no direct safety significance but may be a surrogate for determining a safety outcome;
- Was the number of animals / humans, and controls, in the study sufficient for a reasonable conclusion to be drawn or for statistical analysis to be conducted?;
- Was statistical analysis done where necessary, and on the most appropriate parameters?
- Was the route of administration appropriate in terms of the application? Note that injection and intraperitoneal routes are not Listable routes and this may alter the conclusions about the use of the substance in Listable goods that can be drawn from the study;
- Was the study conducted for a sufficient time to both produce results and be relevant to the potential schedule of administration?
- What was the age and health status of the participants and how might this influence the conclusions of the study? For example, the responses of hypercholesterolaemics and normolipidaemics to a lipid-lowering drug may differ. If a substance is likely to be used by frail,

aged people, a clinical trial conducted in healthy, young people may be of little relevance in assessing safety for the target group;

- Were the doses employed comparable to those likely to be used in Listable goods and adequate to produce an effect?
- Did the doses used refer to the active ingredient, a substance containing it, or a product? For example, for a mineral, were the doses expressed quantitatively in terms of elemental mineral, a salt, or a product containing the substance?
- If a multi-ingredient formulation was studied, does this affect the conclusions that can be drawn from the study? For example, excipients may affect the rate of absorption; and
- Were gender-related effects investigated?

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TRIM Reference R11/428597