R12/90100

Standard Operating Procedure (SOP)
Guidelines for evaluators - new listable substances

Date of last update: 9 May 2012 - automatically updates on opening.

Principle

One of the major functions of the Pre-Market Assessment Section of the Office of Complementary Medicines (OCM) is to evaluate the suitability of new substances for use as active or excipient ingredients in therapeutic goods.

It is desirable that evaluators adopt a consistent evaluation style so that we move towards a more uniform presentation of evaluation reports of good scientific and editorial quality.

Scope

This Standard Operating Procedure (SOP) deals with the evaluation of new complementary medicine substances for use in listable therapeutic goods, whether as active or excipient ingredients. It relates to new substance evaluations initiated following a sponsor's application or following an internal TGA decision. Many of the principles outlined are applicable to other evaluations, such as the evaluation of the efficacy or safety of registered medicines or to a safety review of an existing listable substance or to the evaluation of a new complementary medicine substance for use in registrable goods. However in these cases additional procedures need to be followed and these are outlined in other Standard Operating Procedures. Other relevant SOPs are:

- New substance evaluations (SOP- new substance evaluations.doc)
- Pre assessment unit (SOP- Substance Application Pre-assessment.doc)
- Amending Regulations (SOP - Amending schedule 4.doc)
- Australian Approved Names (TO BE DEVELOPED)
- CMEC briefing papers (SOP - CMEC briefing papers.doc)
- Registration applications (SOP - Registration applications.doc)

Use of this SOP

This SOP is intended for use within the OCM by OCM staff. The Manager, Pre-Market Assessment Section, OCM is responsible for amending this SOP.

SOP approved:

.....
Manager,
Pre-Market Assessment Section
OCM
Date:

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1. OVERVIEW

1.1 Objective of evaluations

An evaluation report is just that - an evaluation, not a summary. The report must include a detailed analysis of all relevant available information but must then draw all these analysed findings into a coherent argument. The aim of evaluation reports for new listable substances is to argue a case as to why (or why not) a substance should be permitted to be used in listable goods. The report should also provide a rationale for any dose restrictions, label warning statements or other restrictions you believe are justified on safety grounds.

The report format presented later in this SOP provides a framework that has been tested and found to assist evaluators in developing a coherent argument, and to assist CMEC members in finding their way around a report. The suggested report presentation aligns with the draft *Risk assessment framework for evaluations of new substances for use in listable complementary medicines.*

All experimental data, and the methods by which they were obtained, should be subject to a critical and independent scientific assessment. Interpret the data without any personal bias and recognise any kind of bias in the presentation and interpretation of data provided by the sponsor.

1.2 Relevant regulatory requirements

Because new substance evaluations generally result, ultimately, in new listed medicines entering the market, an evaluator should have a good understanding of the regulatory system for listed medicines, and of the types of products likely to incorporate the substance. By having this understanding you will know the likely context of use of the substance and be aware of other requirements that will impact on the safety of the substance.

You should be aware that regulatory and policy requirements change frequently. You should therefore use on-line resources rather than paper versions of the relevant legislative documents. You should also be aware that you may need to check at the beginning of an evaluation whether there are any relevant changes likely to come into effect during the time of the evaluation.

Relevant legislative requirements are contained in:

Therapeutic Goods Act 1989 ('the Act') and the Therapeutic Goods Regulations. Both these documents are available on the TGA intranet. The Act contains the general provisions relating to all therapeutic goods while the Regulations tend to be more specific in nature. Schedule 4 of the Regulations defines listable therapeutic goods. Schedule 10 establishes the goods that can be evaluated by the OCM, and Schedule 14 defines complementary medicine substances. There are also a lot of useful definitions of terms used in the Regulations, in their preamble.

- *Standard for the Uniform Scheduling of Drugs and Poisons* (SUSDP) – schedules 2 (pharmacy only), 3 (pharmacist only) and 4 (medical, dental or veterinary practitioners only) restrict the groups who can supply particular medicines and in some cases provide

additional dose or labelling restrictions. For example, iron, zinc and selenium compounds have a daily dose or dosage unit restriction; vitamin A has a labelling requirement and a daily dose restriction. Schedules 5 and 6 relate mostly to household chemicals but include some essential oils as well as camphor. Many of these substances have volume and closure restrictions.

Listable goods cannot contain a substance that is included in any of the schedules to the SUSDP.

- Various Therapeutic Goods Orders, especially TGO 48 – *General requirements for labels for drug products*, which will restrict how sponsors can use information on labels (e.g. how Australian Approved Names are to be used). TGO 22 contains requirements for child resistant closures, relevant for iron compounds. Most TGOs are available via the TGA intranet. Note that TGO 48 is under review at present and an amended labelling order is due in late 2001.

- Therapeutic Goods Advertising Code – defines conditions that cannot be referred to in advertising. The Advertising Code and the related *Guidelines on levels and kinds of evidence to support claims* document are available on the TGA internet site.

- Customs (Prohibited Imports) Regulations – schedules 4 and 8. Listable medicines may not contain substances included in these Regulations unless the sponsor holds a valid import permit. Some herbal substances are included in these schedules (e.g. *Passiflora incarnata* by virtue of containing harmine, sassafras oil as it is a source of safrole). The C(PI) Regulations are available via the ScalePlus website (http:\\www.scaleplus.law.gov.au).

1.3 Making decisions regarding an application and communicating these to a sponsor

Although the Act and Regulations contain a number of provisions giving the TGA power to obtain information from a sponsor in relation to an application to list or register a product, there are no such powers relating to substances. The TGA does have the regulatory power to charge fees for the evaluation of new substances.

Despite there being no formal power to request information, the process to be followed in seeking additional information from a sponsor when conducting a new substance evaluation is very similar. The TGA Legal Unit recommends the 'fact→evidence→reasons' approach. Using this approach, an evaluator would identify the need for certain types and standards of information to be available in order to evaluate the safety of a new substance (the facts), would clearly identify the material already provided by the sponsor in the application (the evidence) and would then state why the existing material does not meet the required standard and therefore why the sponsor is being asked to supply further information (the reasons).

Sponsors must be given adequate time to respond to a request for information (usually 2-3 months is offered) and must be provided with an opportunity to state their reasons for not providing this information (i.e. they must be provided with the opportunity for a 'hearing').

1.4 Choosing literature for evaluation and evaluating search strategies

All applications should outline the search strategy used to obtain the supporting material presented to OCM and should provide full text copies of relevant papers. Abstracts of papers are rarely suitable for use in evaluations. For the majority of applications it will be necessary to carry out some form of checking of the validity of the search strategy, to ensure that papers with adverse findings in relation to the substance have been included. Unless an evaluator is very familiar with the literature on a particular subject and is aware that a thorough literature search has been conducted, the TGA library staff should be asked to evaluate the search strategy. As part of this process, the librarians may identify important papers that have not been supplied; copies of these should be obtained. If only a few papers are required it may be more cost effective to ask the TGA library to obtain copies. If a large number of papers are required the sponsor should be asked to provide these. However it is important to be aware that, in asking the sponsor to provide more information, additional evaluation fees may be payable. Therefore additional material should not be requested unless it is considered to be critical for the evaluation to proceed.

At times the OCM initiates evaluations of new complementary medicine substances itself, i.e. an evaluation is conducted without being triggered by a formal application. In this case it is necessary for the evaluator to carry out a literature search. This is best done in conjunction with the TGA Library. Evaluators should decide what they want from a database search and then discuss their requirements with a librarian. The librarian will carry out the searching and, generally, provide the evaluator with a list of titles retrieved and, in some cases, abstracts of the papers.

2. EVALUATING SINGLE STUDIES

Most evaluation reports in the complementary medicine area will be based on published papers, which usually do not include all the details desirable for evaluation. Many of the studies on which these published papers are based will not have been done under conditions of Good Laboratory Practice (GLP) or Quality Assurance (QA). And sometimes we may have to consider/include information based on traditional use. Whatever the data source, the evaluation report should be well structured and clearly written. When finalised, it will go to the Complementary Medicines Evaluation Committee (CMEC) and members will have to make important decisions based on the data and assessment you have presented.

The following points are put forward as a general guide to evaluating a single study.

- What was the object of the study? The study's hypothesis should be outlined at the beginning of the evaluation. If no hypothesis is presented in the study, this should be stated.

- Was the design of the study likely to produce results that will meet the objective? e.g. were the right things measured (sometimes parameters are measured that have no clinical significance)?

- 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 you can draw from the study regarding the use of the substance in listable goods.

- Was the study conducted for a sufficient period of time to produce results?

- What was the age and health status of the participants and how does this impact on the conclusions of the study? For example, hypercholesterolaemics may respond differently to a lipid-lowering drug than normolipidaemics. 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.

- Clearly identify what was tested. e.g. Was it the actual substance you are evaluating, or some related substance evaluated some time earlier for a different reason? If it is a herbal substance, was it extracted and prepared in the same manner as the substance under review?

- 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 compound containing it, or a formulation? For example, if you are evaluating the safety of chromium, were the doses expressed quantitatively in terms of elemental chromium, a chromium salt, or the formulation?

- If a multi-ingredient formulation was tested, does this affect the conclusions you are able to draw from the study? Remember that excipients can affect absorption, efficacy, toxicity etc.

- If the study was an oral one, do you know (from pharmacokinetic data) the extent of oral absorption of the substance, its distribution and potential for accumulation in the body, its metabolic fate and the route and extent of its excretion? What are the target organs?

- Was there a sex-related effect? If this is relevant, was it investigated?

- Was the investigation conducted under conditions of Good Laboratory Practice?

- If discounting experimental results, give clear reasons for doing so.

- Do not use statements like 'It was concluded that . . . ' You are the evaluator, it is what you conclude that is important.

- Remember that the overall purpose of a new substance evaluation is, in almost all cases, to assess safety and quality, not efficacy.

3. WORKING AS PART OF AN EVALUATION TEAM

Evaluations are often conducted by a team of evaluators. This has the advantage of allowing evaluators to concentrate on their area of scientific expertise, of reducing the number of weeks required to conduct an evaluation and of allowing 'cross-fertilisation' of ideas. However there are times when it is preferable for one evaluator to conduct the entire evaluation, such as when the size of the application is small or the subject matter is very specialised.

When the application pre-assessment unit conducts a preliminary assessment of an application, an evaluation team will be assigned and a team leader selected. The responsibilities of team members are:

- To critically evaluate the scientific data provided in the application.
- To prepare a draft written report on their areas of responsibility.
- To develop or refine a compositional guideline for the substance.
- To develop an appropriate approved name or names (in the case of salts and derivatives of a substance under review) (see separate SOP - *Australian Approved Names*).
- To present and discuss their report at the Peer Review Panel.
- To prepare a final report on their area of responsibility.
- To undertake other tasks as requested by the team leader.

The team leader has the following additional responsibilities:

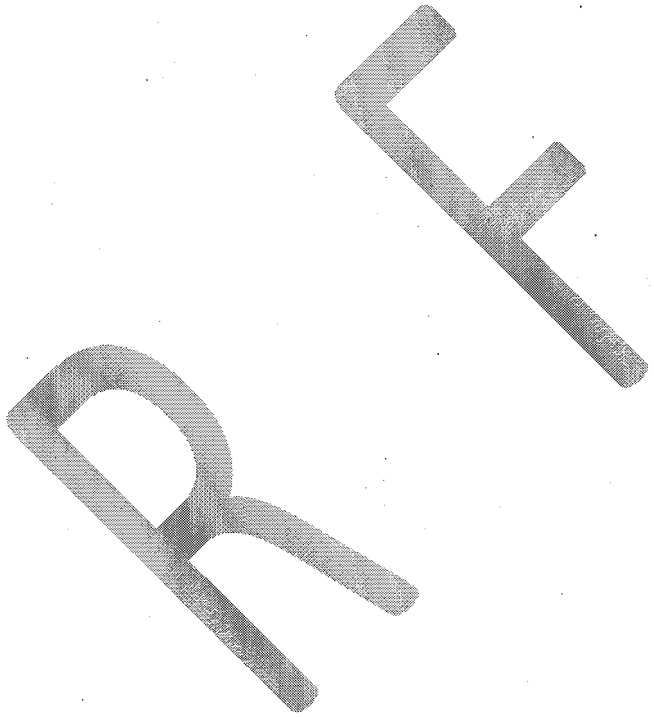
- Preparation of letters to the sponsor, whether signed by themself or the Manager, and other sponsor liaison where necessary.
- Ensuring all team members have a clear understanding of their area of responsibility.
- Preparation of final evaluation paper based on contribution from individual team members.
- Writing the CMEC briefing paper (see separate SOP - *CMEC briefing papers*)
- Follow-up action resulting from CMEC consideration.

It is vital that team members have a clear understanding of the application areas they are to work on and that they meet the timelines established by the team. It is also very important that all members adhere to the editing style described later in this SOP. When the team leader comes to assemble all members' contributions into the one overall evaluation document, different word processing styles, or use of old versions of Word on home computers, can disrupt the document formatting. At worst, the team leader may face hours of reformatting. At the least, the outcome will be reports that look untidy and are less easy for CMEC members to read.

4. FORMAT AND CONTENT OF EVALUATION REPORTS

A suggested format for the presentation of evaluation report for new listable substances, or for a safety review of an existing substance, is as follows. While there will be some variation with different applications, consistency in report presentation is desirable, particularly to assist CMEC members to locate information. A template document is currently being developed that will be laid out in the established OCM/CMEC style.

There is a template evaluation report document for new substances under the launchpad, new documents button. From there, go to the 'section' sheet. This template sets out all editing requirements.



4.1 Title page

Item x.y.z
CMEC(Meeting no.)
Date (month year of meeting)

The above is in normal type aligned at top right for all evaluation reports going to CMEC.

Evaluation of a new listable substance OR
Safety review of a listable substance

[Name of substance]
[TGAIN XXXXX]
[Sponsor]

Office of Complementary Medicines, TGA

Evaluator/s:
[names and organisations of all evaluators]

Abbreviations:

Insert common abbreviations here. May do this on a separate page if there are a lot

Attachments:
Number all attachments here, for example:
1. Flowchart of manufacturing procedures
2. Extract from the Pharmacopoeia of the People's Republic of China

The title page is where you should insert footers for the whole document. The footer has 'CMEC-in-Confidence' centred, regular type, 10 point size, and page number aligned right. There is no need to insert the word 'Page' before the page number.

The report should then be presented in the following order:

- Summary and assessment
- Conclusion
- Summary of clinical trials (tabulated)
- Table of Contents;

followed by the body of the report with the following headings:

- Introduction
- Characterisation of the substance
- History and patterns of previous human use
- Biological activity
- Toxicology
- Clinical trials
- Adverse reactions that have arisen from its use
- References.

Although the main body of the report (from 'Introduction' onwards) needs to be written before the Summary & Assessment and Conclusion, the latter sections are best put at the beginning of the document, particularly in larger evaluations, for ease of reading and comprehension by CMEC members.

4.2 Summary and Assessment

This section should commence with a brief statement of the purpose of the evaluation paper – e.g. 'to assess the suitability of [substance name] for use as an active/excipient ingredient in listable therapeutic goods'.

This section includes a concise overview of the studies provided in the application, together with a critical assessment of what this information means in terms of whether the substance should be approved for use in listable goods. Because it deals with the main issues concerning the application, the Summary and Assessment is the most important part of the evaluation report. It is not a re-presentation of the results, but an evaluation of the results.

The focus of the Summary and Assessment is on a streamlined argument that will support the conclusion you will soon reach. However the argument presented should not be so streamlined that inconsistencies between studies, or areas of uncertainty, are omitted.

Not all areas of discussion that are present in the body of the report have to be covered in the assessment if they do not require discussion, but all important findings from the detailed evaluation should be presented. Where data from specific studies are referred to, the studies must be clearly identified so the reader can then turn to that study, but detailed referencing is not generally required in the Summary & Assessment.

For ease of reading by CMEC members, the Summary and Assessment should be presented under the six headings that have been identified in the risk assessment framework for new complementary medicine substances:

- Characterisation of the substance
- History and patterns of previous human use
- Biological activity
- Toxicology
- Clinical trials
- Adverse reactions that have arisen from its use.

The usual length of the Summary and Assessment section is 2 to 3 pages, but may vary depending on the evaluation. It would be unusual for this section to be shorter than 2 pages.

In very detailed evaluations it may be appropriate to separate the Summary and assessment section into two - Summary; and Assessment. In this case, the Summary section would include a concise summary or overview of the information/studies provided in the application; i.e. the data. It would not include assessment of the information. The Assessment is then the critical evaluation of the total data in relation to the application.

The Summary & Assessment, and indeed the entire evaluation report, should be based on the application on hand. It should not draw on, or refer to, other related products or substances that are still under review, or contain any commercial-in-confidence material that was not submitted by the sponsor of the application. The reason for this is because evaluation reports are sent to sponsors at the same time they are sent to CMEC and therefore must not contain any confidential material about other products or sponsors. Comparisons with other products or substances, or reference to any other confidential matters, should be placed in the accompanying briefing paper, which is not sent to sponsors.

4.3 Conclusion

This should usually not exceed half a page in length. For some straightforward applications, one or two sentences may be adequate. Make it quite clear whether you, as evaluator, consider the new substance to be of sufficient quality and safety as to be suitable for use in listable therapeutic goods. You should identify any labelling requirements or other restrictions you believe are necessary. Other restrictions you may suggest include restrictions on route of administration, dosage form, maximum daily dose or dose size, container or pack size or type, closure type or contraindications. The conclusion may be used to reinforce, briefly, the main assessment issues. It is *your* advice to CMEC, which the Committee may or may not accept, so be sure that your conclusions are based on firm scientific evidence.

4.4 Summary of clinical trials

This section is a tabulated presentation of the key features of all clinical trials of the substance that is the subject of the evaluation paper. In some cases there may be no clinical trials to summarise, in which case this section of the report would be omitted.

The purpose of this section is to give CMEC members a quick overview of the range of monitored human exposure there has been to the substance. For example it will indicate the duration of exposure, the type of exposure (e.g. oral, topical) and the group of people exposed, the type of trial (e.g. controlled, randomised) and the key outcomes in terms of safety and efficacy. The table is generally not a critical review of the trial evidence, but the tabular presentation does allow the reader to make a quick and reasonably accurate summation of whether or not available clinical evidence tells us anything about the safety of the substance.

The summary table can be prepared while writing the section on clinical trials. However by placing it within the Summary & Assessment/Conclusion sections, it allows CMEC members to easily locate it. This author finds that the preparation of the summary table is a very useful first step in reviewing trials as, once the trials are tabulated, the study weaknesses often become immediately apparent. The established format for the summary of clinical trials is presented over the page. When a number of trials are available, it is generally best to present the best designed studies first (e.g. the randomised, placebo-controlled, double blind studies) and to then work down towards the weakest study types (perhaps summaries of case reports). Where possible, studies should also be presented in descending duration of exposure within trial type (e.g. put the 6 month trial before the 10 day trial). By doing this, CMEC members see first of all the strongest type of evidence available to support the safety of the substance.

4.5 Table of contents

Tables of Contents should be generated using the automatic table of contents facility provided in Word. The table is generated from the heading styles established in the report. The template document has pre-established headings and table of contents styles.

The Table of Contents begins on a separate page from the Conclusion. The Table of Contents refers to the body of the report, not the Summary/Assessment/Conclusion discussed above. Include headings of all levels in the Table of Contents if possible. Make headings as concise as possible. (For example, don't use whole study/paper titles for headings.) In some cases, it may be necessary to shorten a section title within the Table of Contents to keep the title and the page number on the same line. Bold text should not be used.

It is most important that the headings are well thought out and organise the available data in the most logical way. For example, for animal toxicology studies you could use an order of presentation that put the smallest animals first and worked up to the largest; and put short-term, repeat-dose studies and clinical trials before longer-term studies/trials. Sometimes it may be more appropriate to put studies in chronological order.

Table 1 Summary of clinical trials of [insert name of the substance under review]

Study design (Reference)	Subject details	Treatment details (dose and route)	Endpoints	Key outcomes	ADRs
6 month Randomised, placebo controlled, double blind Cunningham et al 2001	N=376 Aged 47-70 Hypercholesterolemic	100 mg/day TID Oral Plus 400 mg/day treatment Y	Serum total cholesterol	Total cholesterol reduced by 15% compared to baseline ($P<0.01$) and by 12% compared to placebo ($P<0.05$)	Gastrointestinal distress (50/176 verum group) Mouth ulcers (1/176)
3 month Randomised, placebo controlled, double blind Newman-Martin et al 2001	N=115 Aged 65-75 yrs No pre-existing medical conditions	150 mg/day BID Oral	Serum total cholesterol	NSD between verum and placebo groups or between baseline levels and levels at completion of trial	1 death in verum group from aortic aneurysum

4.5 Main body of report

Again, this should start on a new page. The main body of the report is where all the information is presented. The information should be presented under the main risk assessment headings identified above (ie Characterisation of the substance, History and patterns of previous human use, Biological activity, Toxicology, Clinical trials, Adverse reactions that have arisen from its use), following a brief introduction. Within these major headings, a number of sub-headings can be used, depending on the nature of the evaluation.

The body of the report consists of a presentation of the studies/information you are evaluating. Details should be sufficient to allow the reader to assess the study/information for himself/herself. Refer to the section titled 'Evaluating single studies' for further detail on the matters that should be considered when evaluating a report (e.g. number of animals used and controls, dosage and dosage form, length of dosing, parameters monitored, whether pathology/histopathology performed for toxicity studies etc). Each study, data report or scientific statement presented should be identified clearly and referenced (i.e. author/s and year of publication).

4.6 Introduction

This section should identify the substance under review and the sponsor of the application. The Introduction should also outline the literature search strategy used, noting whether it is the sponsor's strategy, the TGA's strategy or a combination of both.

4.7 Characterisation of substance

The aim of this section is to clearly define the compositional characteristics of the substance. It will describe the composition, manufacturing process, purity, stability, methods for determining identity, other relevant chemical data and, where appropriate, botanical details.

The Australian Approved Name for the substance should be stated. Common names and accepted synonyms should also be stated. TGA Approved Terminology (e.g. for route of administration) should be used wherever possible. When conducting literature and database searches, bear in mind that there may be a number of different spellings for any given synonym and therefore that different information may be retrieved when different spelling combinations are used.

For chemical substances, manufacturing processes may introduce decomposition products or reaction by-products that can have safety implications. This may have been the cause of toxicity associated with tryptophan, when a new manufacturing process is likely to have allowed the formation of related compounds that were more toxic than tryptophan itself and lead to an outbreak of EMS. Decomposition products present at greater than 0.5% of the substance should be identified and quantified, preferably by a chromatographic technique. Different isomeric forms should be identified. Any solvents or catalysts used during production should be identified.

For biological materials the original organism must be clearly identified using a Latin binomial (eg *Lactobacillus acidophilus*). For listable complementary medicine substances,

biological material will encompass microorganisms (but not vaccines), non-human animal tissue (e.g. chicken meat, fish oils, shark cartilage), and bee products. For animal material, both the name of the species and the part of the animal body used must be stated. For animal material from cattle, sheep, mule deer and goats, certain body parts cannot be used, in order to minimise the risk of transmission of bovine spongiform encephalitis. These parts are identified within schedule 4 of the Regulations. For some other bovine, ovine and caprine material it will be necessary to check with the Immunology Section of TGA to determine whether or not their preclearance is required before the substance can be used in a listable medicine. Biological materials may be subject to microbial spoilage and rancidity if inadequately dried. The application should contain results of microbial analyses to determine freedom from a range of pathogens.

For bacteria, strain as well as species and genera should be identified, as particular strains within a given species can vary greatly in safety. For example, there are some strains of *Clostridium butyricum* that are used, apparently with low risk, in Japanese medicines, whereas there are other strains of this bacterium that cause human botulism. The application should describe the techniques used to identify the strain and to ensure its purity from batch to batch, and the original source of the strain (e.g. human intestines, soil). Particular attention should be paid to techniques to ensure freedom from pathogens. The fermentation substrate (e.g. broth type, carbohydrate source) should be identified and if significant substrate residues remain in the culture these should be quantified (e.g., 'contains 10% residual fructose'). The fermentation process should be described in detail by the sponsor but it may be appropriate to place this material in an attachment to the report if the evaluator considers the process raises no specific issues. Bacterial nomenclature is a rapidly evolving science and it may be necessary to seek advice from the Biological Names Committee of TGA regarding the current, internationally accepted nomenclature for bacteria. Immunobiology Section pre-clearance or advice may be necessary in the case of bacterial substrate that may contain animal material, such as brain heart agar.

For herbal substances, the original organism or plant must be clearly identified using a Latin binomial (for genus and species) as well as the family, class or order name. Sometimes, a sponsor may wish to have a safety evaluation conducted for all plant parts and all preparation methods that are allowed for herbal substances within the Regulations. At other times, a sponsor may apply to restrict the herbal substance to a particular plant part (e.g. the essential oil distilled from the leaf) or route of administration (topical use only). For herbal substances, the plant parts that are being considered (e.g. the root, leaves etc) must be identified as this may have major significance when considering studies presented. Botanical nomenclature is a rapidly evolving science and it may be necessary to seek advice from the Herbal Ingredients Names Committee of TGA regarding the current, internationally accepted nomenclature for various plants.

The extraction process for herbal substances should be clearly outlined as the nature of the extraction process used will determine the components of the herb likely to be present in any extracts of it. Where appropriate, it should also identify the degree of alteration applied to the original herbal material. Particular care should be paid, when dealing with extracts from plant material, as to whether or not the substance that is the subject of the evaluation is a herbal substance, as defined in the Regulations (see section 1.2 of this paper). Detailed information on determining the status of herbal ingredients is available in the following document: (HYPERLINK HERE TO CMEC WP PAPER WHEN AVAILABLE).

Under European Agency for the Evaluation of Medicinal Products (EMEA) guidelines, herbal substances used as active ingredients 'can be considered as sufficiently identical if the specification is the same and no relevant differences in the manufacturing process exists. The identity of specification and manufacturing process is particularly important in those cases where bibliographic data on highly purified extracts are presented or where a new method of preparation of an extract is used. In the case of 'classical' herbal drug preparation such as tinctures and extracts described in pharmacopoeias and used for a long time, a 'comprehensive' specification will not be available from published literature in most cases. For these preparations the starting material, extraction solvent and the drug/extract ratio must be identical.'

Evaluation of the manufacturing process for all classes of ingredients should highlight potential for introduction of impurities, including microbiological contamination. In some cases environmental contamination may be an issue, such as the occurrence under certain circumstances of algal toxins in green lipped mussel. Microbiological contamination (particularly bacterial) is most likely to be an issue for biological substances.

The British Pharmacopoeia 1999 (section 5.4) contains limits for residual solvent levels in therapeutic goods and ingredients of therapeutic goods. The European Pharmacopoeia contains limits for pesticides in therapeutic goods.

This section of the evaluation report will include a draft compositional guideline defining the composition of the substance, for consideration by CMEC at the time of the safety evaluation. The draft guideline must be submitted by the sponsor as part of the evaluation, or developed in-house if a TGA-initiated application is underway. In some cases a pharmacopoeial monograph will be available and should be used in preference to a sponsor-developed one. However for many complementary medicine substances there will be no existing monographs on which to draw. A template has been developed for compositional guidelines for chemical substances. (HYPERLINK HERE)

In terms of stability, some assessment of the substance stability should be made as this will provide a useful guide to the sorts of problems that may be encountered with finished products containing the substance. However the detail required for a new substance evaluation is much simpler than that required for an application to register a new medicine, as the final formulation, packaging material and storage conditions will have a very significant impact on product stability. Some simple measures are valid for use in assessing substance stability, such as colour, odour, clarity, peroxide value (for oily substances), moisture content, microbial count, disintegration time, loss on drying.

4.8 History and patterns of previous human use

The objective of this section is to establish conditions, if any, under which the substance has been used by humans in the past. This section will examine any tradition of use the substance may have (e.g. as a therapeutic good, cosmetic or a food), the purposes for which it was used, the doses used or amounts consumed in the diet (by average consumers and by "high" consumers), the period of use, and the sub-population it has been used by.

If the sponsor is relying, in part or all, on evidence of traditional use to demonstrate safety,

the evaluation report must consider whether the substance under review is 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. rhubarb stems are used, not rhubarb leaves). Thought must also be given as to how the substance was used (e.g. for short periods of time only, or only during late pregnancy to induce labour), and whether its use in non-prescription medicines could compromise safety. The 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. It is relevant here to describe Australian regulatory requirements for related substances, to aid consistency in decision making. For example, if evaluating a new form of vitamin C (e.g. selenium ascorbate), it would be important to point out the existing restrictions on the use of other ascorbates (no dose limits or warning statements, four metal salts listable, not scheduled) and other selenium compounds (listable with dose limits in the SUSDP, warning statements required). For some substances under evaluation there may be existing permission to use them in foods. If this is the case, the relevant requirements in the Food Standards Code should be given.

Where substances have been evaluated by other recognised regulatory or evaluation agencies the reports from those evaluations should be discussed. It is important to highlight the purpose of the other agency's evaluation as the agency may have evaluated for a purpose that is more limited than we would be proposing. For example, an evaluation of safety for cosmetic use 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, these restrictions should be described and their relevance to therapeutic usage drawn out.

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

Where substances have been approved by the US Food and Drug Administration (FDA) as being of GRAS status (Generally Recognised as Safe), or recommended for approval by the (US) Flavor 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 whether 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 grandfathered Registered good or is permitted as an excipient in a therapeutic good, such history of use will be considered. However it is necessary to demonstrate in the evaluation report that the substance under review is the same as that used in grandfathered goods or as an excipient. When assessing safety based on use in grandfathered goods it is particularly important to indicate concentration of the substance per dosage unit and, if possible, the types of uses for the products. This information can be obtained from searching the Australian Register of

Therapeutic Goods (ARTG) and by checking with sponsors of grandfathered goods. It is valuable to obtain information on the number of doses supplied and the period of time over which they were supplied, although it can be difficult to obtain this information from industry.

Reference will be made in this section to any population exposure data that is accessible. Where data are not available on the particular substance, data derived from related substances (such as the precursor from which the substance under evaluation was derived) may be useful as secondary evidence. For some nutrients and food types, the National Nutrition Survey will contain useful consumption estimates.

A substance used in therapeutic goods may present a different risk profile to that resulting from its food use. For example, consumption of β-carotene through the diet is negatively associated with incidence of certain types of cancers. However in contrast, consumption of isolated β-carotene in supplements is positively associated with certain endothelial cell cancers. Food has a satiating factor so intake of particular components may be limited. With capsules, for example, there is no real limit to what people can swallow other than the cost of the product. Other components of foods, such as fibre, may limit the absorption of a substance in a food matrix, but in a therapeutic form there may be no such limit to absorption. Therefore you can get a potential for acute and chronic overconsumption with therapeutic goods that may not be arise with foods. This may be significant in terms of toxicity for some substances and may lead to a recommendation to limit the daily dosage or dosage per unit for the substance.

For herbal substances, modern extraction methods may produce extracts that have a considerably different chemical and safety profile from those extracts produced using traditional techniques. Therefore it is insufficient to rely entirely on evidence of traditional safety for these substances. An example of this is for ginger extracts, where particular highly concentrated extracts have been associated with bleeding in some cases, while traditional extracts do not seem to cause this problem.

4.9 Biological activity

The aim of this section of the report is to describe the potential role the substance will play in human metabolism. This criterion will include a summary of the physiological and/or pharmacological activity of the substance in humans, including its biochemistry.

If the substance occurs naturally in the body (e.g. selenium, glucosamine), discuss its biochemistry and activity under appropriate headings (e.g. absorption, transport, distribution, metabolism, excretion).

For Primary Pharmacology (i.e. desired effect of the active/formulation), subheadings may include: 'Mechanism of action', '*In vitro* activity', '*In vivo* activity' and 'Human studies'.

If there are studies on secondary pharmacology (e.g. adverse physiological effects or functional toxicity at high doses, including effects on hepatic enzyme activity and drug interactions), appropriate headings and sub-headings are required. All studies presented and summarised need to be adequately referenced.

Pharmacokinetics is probably the most difficult section to organise under headings if there is a lot of information, and flexibility is needed from evaluation to evaluation. However, typical sub-headings are 'Methods', which includes a summary of the methods used (e.g. HPLC, radioactive tracer studies) and information on limits of detection, Absorption and plasma kinetics, Distribution, Metabolism, Excretion, Binding to plasma proteins, and Human studies.

4.10 Toxicology, including acute, short and long term toxicity studies, carcinogenicity, genotoxicity, reproductive toxicity, immunotoxicity, neurotoxicity and behavioural effects

The aim of this section of the report is to describe what is known about, and where possible to quantify, potential risk associated with the use of the substance.

This criterion will include the mechanism of action and what is known about its activity, and its relevance to humans. Where human data are not available, information gained from animal and *in vitro* studies may provide useful information. This criterion will also look at data relating to acute, repeat-dose and chronic toxicity, anything known about potential carcinogenic or genotoxic effects, and any known effects relating to reproductive toxicity, such as effects in pregnancy and lactation, effects on fertility, and teratogenicity. Potential immunotoxicity, neurotoxicity and behavioural effects will also be taken into consideration.

For many substances used in complementary medicines, only limited data relating to these risk assessment criteria are available. In practice, animal toxicity studies have been found by experience to be one of the most poorly reported areas of complementary medicine research. Frequently, published papers do not define the reason the study was conducted or the experimental hypothesis. Small numbers of test animals are common. In some studies, the morbidity and mortality rate even among control animals can be so high that the study findings are worthless and the standards of animal care questionable. Remember that humans may respond quite differently to test animals and therefore that animal toxicity studies are only a guide. CMEC has recently indicated (meeting 27) 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 draft 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 considered 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."

Toxicology data included in submissions should be presented in detail sufficient to allow independent scientific assessment (e.g. individual animal data should be provided). Study details should include the route of administration, dose levels and the number of animals per dose level, the origin of the animals, their sex, weight range and maturity, all parameters measured, the frequency at which observations were made, the duration of each study and the relationship between the time of administration and the onset of the effects observed.

All compound-related biochemical and physical changes observed in the study should be identified in the evaluation paper. Where you consider that the manifestations are not toxicologically significant (e.g. minor changes in organ weight), evidence of their reversibility should be discussed.

Due to the importance of toxicology studies to the evaluation of the safety of new complementary medicine substances, the following sub-headings should be used in this section of the evaluation paper, whether or not data is available for each of these headings. Where data are not available this should be clearly stated. By doing this, it is apparent to the reader of the report that information has been sought in these areas and that these factors have not been overlooked.

If the substance has been investigated in the past by the National Drugs and Poisons Schedule Committee (NDPSC), whether or not it has been included in the SUSDP, the NDPSC Secretariat may hold toxicology information on the substance. It may therefore be possible to access this information. Contact the NDPSC Secretariat for advice.

Acute toxicity and local tolerance in animals

While acute toxicity studies may not necessarily reflect risks associated with the levels of prolonged exposure found with therapeutic goods, acute studies of systemic toxicity do provide insight 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 accidentally swallowed by a child (e.g. an essential oil for aromatherapy). There are some substances, such as eucalyptus and tea tree oil, where humans appear to be more sensitive to their toxic effects on a g/kg body weight basis, than test animals.

Acute oral toxicity studies should be performed in both sexes to assess possible sex-related differences in response. The rat is the preferred rodent for acute toxicity studies. 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 species differences may be crucial.

Acute dermal, inhalation and parenteral studies may be useful where the bioavailability is markedly influenced by the route of administration. Skin and eye irritation studies and skin sensitisation studies are also relevant as the substance may ultimately be used in topical

products or in products for inhalation. Include not only the LD_{50} results for each species and route of administration (where available), but also the clinical signs exhibited before death, if possible, and the necropsy findings, if any.

Repeat-dose, sub-chronic and chronic toxicity in animals
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 prior to commencement of chronic studies. Subchronic studies should demonstrate a range of activity from the 'No Observable Effect Level' (NOEL) through to a clearly toxic level. Evidence of the stability of the compound in the form administered and the actual dose rates achieved should be given. In practice, however, these studies are often absent or deficient for complementary medicine substances.

Observation 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. Analytical tests such as haematology, blood biochemistry, urinalysis and other biochemical tests should be done, 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 compound-related effect should be considered. A statement of the smallest difference which would achieve statistical significance under the conditions of the test would aid considerably in its interpretation.

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 which appear later than those which are apparent from subchronic studies; and
- they permit a comprehensive assessment of a compound'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 inter-species variation. The rat, mouse and dog are the species whose toxicological response profiles are best known. Studies in the dog are generally acceptable when limited to only six months.

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 which is practicably achievable. At least one exposure level should result in no observable effects (the NOEL). 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 compound (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 drugs where duration of human use of the drug is expected to be more than 30 days, animal studies of at least 6 months duration are recommended.

Carcinogenicity
The choice of species and strain of animal is important. A well-defined and stable incidence of neoplasms in untreated controls may be crucial to the determination of whether a particular lesion is compound-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 drugs, rat studies of two year's duration are recommended for studies of carcinogenic potential.

Genotoxicity
Mutagenicity studies are conducted to determine the potential for a compound 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; and

- 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; and

- a test designed to demonstrate genotoxic damage involving other than cytogenetic damage (e.g. UDS or P32 post-labelling adduct formation) and preferably a suspect or known target tissue for the chemical 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 a lot of data, subheadings could be '*In vitro*' and '*In vivo*', both with further subheadings such as 'Gene mutations', 'Chromosomal effects', 'Unscheduled DNA synthesis' etc. as appropriate.

Reproductive toxicity
A well designed multi-generation reproduction study should provide information relevant to 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 (postnatal behaviour). Indications of maternal toxic responses should be reported as an aid to the interpretation of any effects.

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'.

Human poisoning
For some substances evaluated by CMEC, there will be literature reports of human poisoning, generally accidental poisoning of young children and suicide attempts in adults. Reports of poisonings should be evaluated in detail, with particular reference paid to the doses consumed, the chemical form of the substance (e.g. sodium selenate vs selenious acid) 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 identified and any relevant biochemical parameters reported. Information on poisoning should be available on the Poisindex database which is available via the TGA intranet.

4.11 Clinical trials

The aim of this section of the evaluation report is to report the results of use of the substance by humans under clinical trial conditions and identify risks from the experience of use in humans.

Data derived from clinical trials will be critically evaluated to help assess risks associated with use of the substance under controlled clinical conditions. Particular attention should be paid to the design of the trial as this will, to a large extent, drive the outcomes of the study. A flawed study design will lead to results that are of little value. In conducting a safety review it is not necessary to evaluate in detail the efficacy outcome of the study. However it is worth briefly stating the efficacy outcome, reserving the detailed analysis for the matters that are directly relevant to safety.

Clinical trials should also be summarised in Table 1 (see earlier section).

Trials should be assessed individually, with details of methodology, numbers of subjects and description of participants, controls, randomisation, blinding, route of administration, time frame, parameters measured, results, adverse effects (incidence and description), and

statistical criteria. It is particularly important to document the doses taken and the duration of usage as this is useful in assessing whether or not any daily dose limits should be applied, or warning statements developed.

In evaluating clinical studies it is important to briefly consider the clinical significance of the study findings. For example, a study may find that treatment with a medicine results in a statistically significant change in a parameter, but this change may have no clinical significance.

4.12 What, if any, adverse reactions have arisen from its use?

The aim of this section of the report is to determine 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 use.

Adverse reactions are defined by the World Health Organisation as 'a response to a drug 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 which 'results in death, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, or is life-threatening'. Birth defects and malignancy are included by the TGA in the definition of a serious reaction.

This part of the evaluation report should describe the adverse reactions reporting system in place in the population exposed to the substance in the past, and adverse reactions that may have been reported. It is important to carefully document the strengths and limitations of the reporting system to allow a qualified evaluation of the data and its ability to accurately 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 evaluated 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 reaction reports.

Reports of Australian adverse reactions can be obtained from the Adverse Drug Reactions Unit (ADRU). When requesting reports ask for a summary and full text of reports and ask for checks under different synonyms for the substance and, if relevant, for closely related substances (e.g. 'tryptophan', 'L-tryptophan', 'levotryptophan', '5-hydroxy tryptophan'). For Australian reports of adverse reactions, data should be presented in the form of a table, such as the following:

SUMMARY OF ADVERSE DRUG REACTION SYSTEM ENTRIES FOR TRYPTOPHAN

ADRAC Report No. and Date	Sex, Age	Adverse Reaction	Dose and Brand (if known)	Other Medication	Causality
34539 30-6-84	M, 34	Psychosis, (psychotic ideation) Manic Reaction, (hypomania)	1.2 g/day PO brand not stated	[S]Carbidopa 150 mg/day PO	possible
38530 30-6-85	F, 59	Headache, Vision Abnormal, Nausea, Abdominal Pain, (stomach cramp)	Neuromed 1 g/day PO	[O]Mogadon 10 mg/day PO	certain

[S]Other medication suspected of causing the reported adverse reaction
[O]Other medication not suspected of causing the reported adverse reaction

Another major adverse reactions database that should be checked is the World Health Organisation database. This database is only accessible to the ADRU staff and individual, detailed patient reports are not routinely available. Also, this database may not carry reports for the types of complementary medicine substances OCM is likely to evaluate.

The US FDA operates an adverse reactions reporting system for dietary supplements (The Special Nutritionals Adverse Event Monitoring System - SN/AEMS) (http://vm.cfsan.fda.gov/~dms/aems.html). This database has no assessment of causality and, as it generally involves multicomponent products, is of limited use other than showing overall trends, such as a particular brand of medicines being associated with a number of very similar reactions (e.g. bleeding).

Any documented or potential interactions of the substance with other foods or medicines should be discussed. It will be important to have sufficient data (biological and exposure) to assess the variability in the sensitivity of individuals or sub-populations to adverse reactions. Drug interaction reports are often contained in the published medical literature. The Australian Adverse Drug Reactions database highlights suspected drug interactions, as noted in the example table above.

4.13 Use of expert reports

Sometimes, sponsors supply an expert report on the safety or efficacy of a substance as part of their application. These reports may be thorough and well-written reports. In these cases it is appropriate to include the expert report as an attachment to the evaluation report and to take the approach of critiquing or validating the expert report rather than repeating the evaluation it contains.

For example, the evaluator may select certain key papers cited in the expert report and conduct their own review of these reports to determine whether or not they agree with the expert. The expert's literature search strategy should be examined to make sure they have not omitted important papers, or papers that have been published since the time the expert report was prepared. The evaluator should also confirm that the expert report refers to the same

substance that is the subject of the evaluation; sometimes expert reports are written on closely related substances or products and may not be directly relevant to the application on hand.

4.14 References

All papers referred to in the evaluation must be referenced in full at the end of the report. A standard system for references is suggested, such as:

> Lewis W and Dalakas MC. (1995). Mitochondrial toxicity of antiviral drugs. *Nature Medicine* 1:417–22.
>
> Lewis W, Dalakas C, Jones B, Thompsen Z. (1999). Life is dangerous. *JAMA* 146: 17.

The names of all authors should be included in the full citation contained in the reference section.

Commas and stops associated with authors' names are unnecessary. It is helpful to spell out the journal names in full. Abbreviated journal names can be confusing and more difficult to trace in database searches. However there are some common abbreviated journal names that are acceptable (e.g. JAMA, MJA, BMJ). The page numbers can often be shortened; e.g. 417–9, 2982–91; but 450–551. Put in brackets after the reference, if applicable, 'Abstract only' or 'Cited by so and so' or 'translated from such and such a language'.

Presentation of sponsor's reports in the reference list can be more difficult, as often the reports do not have defined authors. Identify report by title, date, number, where done. Confidential company report'

When citing references within the body of the report, the following format should be used:

> (Lewis & Dalakas 1995; Smith 1959a; Smith 1959b).

4.14 Attachments

At times it will be necessary to attach detailed material that does not form part of the evaluation proper. For example, the sponsor may have submitted a diagrammatic representation of the manufacturing process for a new substance, which may provide useful background for CMEC but not be so relevant that it needs to be placed within the evaluation report. In these cases, the material should be provided as an attachment to the evaluation paper.

Chemical structures should almost always be placed in attachments that do not form part of the electronic evaluation report as experience has shown that their presence can greatly disrupt the formating of the report.

Attachments must be numbered and referred to in the relevant part of the evaluation report. In the above example, under the main section heading 'Characterisation of substance', the evaluator could outline the salient points of the manufacturing process and then refer the reader to the attachment as follows: 'For further details on the manufacturing process, see attachment 1 to this document'.

Each attachment should be clearly identified in the top right hand corner of its first page as follows, for example:

Attachment 1
Item 6.1.1 (where this is the item number of the evaluation paper)
CMEC 20
June 2000

Each attachment should also have its pages numbered in the bottom right hand corner (hand-written is acceptable). Where material in attachments is confidential, which is generally the case, 'CMEC-in-Confidence' should be written in the bottom centre of each page.

Ensure that all attachments are identified in the front page of the evaluation report.

4.15 Examples of evaluation reports

An example of an evaluation report prepared for the amino acid arginine for use as an active ingredient in listable goods, using the above section headings, is found at:
..\CMEC\CMEC MEETINGS\meeting 11-20\meeting 20\Arginine\arginine_evaluation.doc

5 EDITING OF EVALUATION REPORTS

5.1 Introduction

There are three essential references for editorial style: the list of the Standard International (SI) Units for scientific measurements; the Australian Government Publishing Service Style Manual (recommended for use by all Public Servants); and TGA Approved Terminology for Drugs (available on the Symonston server or the TGA intranet site).

Reducing numbers of words and key strokes should always be an aim; and concise, short sentences are easier to read. It is established AGPS style for government documents, and for all documents being published, that there is only one space after full stops. Concise reporting of study data is acceptable (e.g. 'Sprague-Dawley rats (16/sex/group) were dosed . . . .') provided it does not detract from accuracy and completeness.
better than full justification.

5.2 Tables

Tables should be set out as clearly and simply as possible. Use table format rather than tab settings. Tables always require a concise one-line heading above the table. Tables should be numbered according to their placement in the particular major section they are found in. For example, the first table in section 2, characterisation of the substance, would be numbered Table 2.1 and the second table Table 2.2. In addition, it is unnecessary to say words to the effect that 'The results are presented in the following table' when the table heading tells you this anyway.

Tables should not be split between pages unless this is absolutely unavoidable for very large

ones. Columns of numbers in tables should be aligned on decimal points when tabulating values for the same parameter. If values refer to different parameters, central alignment may be preferable. One or two significant figures are generally adequate, especially when assays are not very accurate. Figures for standard deviation are not routinely required but may be relevant in some circumstances. If the standard deviations are worthy of comment, for example, when inter-animal variability is excessive, discuss them in the text.

Tables should be used in addition to, not instead of, evaluation of the data. In other words, what they demonstrate should be explained in the text. However the text following the table should not restate all the data presented in the table. Instead, it should summarise and evaluate the findings and draw conclusions. Abbreviations and/or contractions used in tables should be spelled out as footnotes, if their meanings are not obvious.

5.3 SI Units

The following are commonly used SI (Standard International) Units: L, mL (millilitre), ML (megalitre), M (molar), g, mg, kg, h, s, m, km. (*Not:* l for litre, sec for second, Kg, ml, mls, gm or hr.) Note that the abbreviations do not have full stops after them. The stop used in abbreviations for units of measurement represents a multiplication sign. Days, weeks, months and years are not abbreviated.

A space is left between the number and the unit; e.g. 10 mg. It is desirable to use a 'Hard Space' (ctrl-shift-spacebar) to avoid separation of the number and unit between lines.

If the number starts a sentence, it and the symbol should be spelled out; e.g. 'Ten milligrams', but this can usually be avoided by not starting the sentence with the unit of measurement. Appropriate symbols should be used; e.g. 4 µg not 4 ug or 4 micg.

A space should be left between groups of three digits; e.g. 27 000, but in four-digit numbers the space may be omitted. A comma should not be used as a 'thousands' marker (this denotes a decimal place in Europe).

A zero should be used before the decimal marker with numbers less than one; e.g. 0.55.

5.4 Abbreviations, acronyms and contractions

If a word is reduced in length and the shortened form does not end in the same letter as the whole word, it is called an abbreviation, and is followed by a full stop; e.g. Prof., etc., Aust., Co., Vic., Tas.

'That is' and 'for example' can be abbreviated to i.e. and e.g. respectively. These abbreviations are not followed by a comma; and etc. is not preceded by a comma. They are not reduced to **eg** and **ie** (without a full stop). Too many abbreviations in a document, particularly of words that are not usually abbreviated (e.g. 'approx.'), is untidy, and sometimes confusing.

If a word is reduced in length, but the shortened form still ends with the last letter of the word, it is called a contraction, and the shortened form is not followed by a full stop; e.g. Dr, Ms, Mrs, Pty, Ltd, Qld.

Acronyms do not have full stops between letters. In addition, the word 'the' is generally assumed to be included in the acronym; e.g. ANU, TGA, CMEC; not 'the ANU', 'the TGA', 'the ADEC'. Acronyms should be spelled out the first time they are used, except perhaps for CMEC and TGA.

A list of common abbreviations that are suitable for use in evaluation reports is found at the end of this document.

Latin words that are commonly used in English, and generally in abbreviated form, (for example et al, i.e., op. cit., et al.) it is not necessary to use italics. (See the Australian Government Style Manual for guidance here).

5.5 Spelling

The following are preferred Australian style:

- 's', rather than 'z', spellings; e.g. emphasise, catheterise, sensitisation
- Program, not programme
- Among, not amongst; while, not whilst (The latter versions are archaic!)
- Haematology, not hematology
- Fetus, not foetus
- Oestrous (adjective) and oestrus (noun), not estrous and estrus.

5.6 Numbers

It is the general convention that numbers one to nine are spelled out, and numerals are used from 10 on. The exceptions to this rule, in scientific publications, are units of measurement: all units of measurement are written in figures. The following are correct examples: nine rats; four sheep; three studies; two vials; seven pages; six cardiovascular parameters; 16 guinea pigs; 400 pages; 11 studies; 20 assays; 2 kg; 3 mL; 15 mg/kg; a 4-fold increase; 19 μg/g; 4 times; 20 times. Exceptions are in text within brackets, and for saying 6/10, when figures are best used exclusively.

5.7 Diagrams

At times evaluators may wish to scan or draw in complex diagrams. This generally occurs when describing chemical structures or when illustrating biochemical pathways. In the initial stage of document preparation it is preferable to place these diagrams at the end of the document, or as separate documents, as they consume a lot of memory and can make report re-ordering/repagination difficult to do. If necessary, diagrams can be inserted in the appropriate part of the document during the final editing stage.

5.8 Page breaks

If a new heading/study starts less than a quarter of a page from the page bottom, is it best to carry it over to the next page. Tables should not be split between pages. Use the Word equivalent of 'Block Protect' rather than a series of returns or a hard page break to avoid splitting.

5.9 Line breaks

There is generally no need to split a word at the end of a line by hyphenation, unless it is an extremely long chemical name, for example, and carrying it all over would leave half a line or more blank. In addition, it is desirable not to split a figure and its unit of measurement like 12 mg — in this case, do a 'Hard Space' (control + shift + spacebar) between 12 and the mg, which carries the lot over to the next line.

5.10 Punctuation

Commas are the most misused of punctuation marks. Reading a sentence aloud helps you put commas in the right place, where the natural pauses fall. Generally you use commas after new clauses introduced by the words but, if, which, where or when, but remember to 'close off' the clause with a comma if it does not end the sentence. For example: The hepatic lesions, which were seen in 6/10 rats dosed at 50 mg/kg PO, were about 2 mm in diameter, pale yellow, and had a discrete border.

Only one letter space should be left after full stops, between sentences.

1970s is correct, not 1970's, which implies the possessive.

There is usually no need to put a comma in front of 'respectively' or etc., although some people prefer to do this.

5.11 Consistency

Lack of editorial consistency within a report is probably the most common mistake we all make, and gives the reader the (correct) impression that the document was carelessly prepared. As well as being irritating to the reader, lack of consistency can lead to confusion as to whether or not the writer meant to convey a different meaning in some instances. For example, if you choose to use red blood cells instead of erythrocytes (generally preferred), stick to it throughout the evaluation. Don't, for instance, have a random mixture of erythrocytes, red blood cells, RBCs, RBC's (incorrect anyway) and rbcs.

5.12 Foreign words

Foreign words used in a document in English are generally put in italics. Apart from the commonly used *et al, in vitro* and *in vivo*, use of foreign word/phrases such as *per se*, *viz.*, *idem, loc cit, sic* etc. should be minimised. Use of foreign words and phrases often seems pretentious, especially if there is a ready English equivalent (e.g. as such for *per se),* and not everyone knows what they mean or how to spell them.

5.13 Difficult word usages

Use of 'which' and 'that' is often confused. As a general rule, 'which' is preceded by a comma and introduces new information; e.g. The study, which was carried out under conditions of GLP, investigated levels of TSH in plasma. 'That', on the other hand, is used to introduce a defining clause, and is not preceded by a comma; e.g. The study that investigated levels of TSH in plasma was not carried out under conditions of GLP.

'Aim' is often used incorrectly. We aim at (increas)ing, not aim to (increase).

'Anticipate' does not mean 'expect', but 'to take action in the expectation of". It would be incorrect to refer to 'plasma levels anticipated in clinical use', for example.

As well as. A as well as B takes a singular verb, unlike A and B. It means 'and not only', not 'besides', and implies that A is the more unusual or important in the context.

Use 'compared with', not 'compared to'. And 'compared with' is often used incorrectly, as in 'The mean erythrocyte count in group B was lower compared with group C.' This should read 'The mean erythrocyte count in group B was lower than that of group C.'

Avoid unnecessary words such as 'The erythrocyte count was found to be reduced in ...' when you could say 'The erythrocyte count was reduced in ....'. Phrases such as 'It was observed that' are usually obvious and can be deleted.

'Due to' is not used the same way as 'owing to' or 'because of". 'Due to' is an adjectival phrase and must refer to a noun.
Correct: Jaundice due to intravascular haemolysis was evident in all dosed groups.
Incorrect: Rats were jaundiced due to intravascular haemolysis.
In the first sentence above, due belongs to the noun jaundice. In the second sentence, it does not belong to the noun rats.
In addition, the phrase 'Due to the fact that ... ' is incorrect. Use 'Owing to'.

Scientific names are written in italics; e.g. *Staphylococcus aureus.* After spelling out the whole name the first time in the Summary, Assessment, and main document, this is shortened to *S. aureus.* When the *S.* could perhaps be confused with *S.* for *Streptococcus,* the generic name can be shortened to *Staph.* Scientific specific names never have a capital, even if named after somebody: e.g. *Buggus wilsoni* is correct; *Buggus Wilsoni* is incorrect. The abbreviations sp. (singular) and spp. (plural) following a generic name are not italicised.

'Post mortem' is an adverb or an adjective; e.g the adverbial form is used as in 'examined post mortem' and the adjectival form in 'post-mortem examination'. Post mortem is increasingly used as a noun, as in 'They performed a post mortem', which is incorrect. Necropsies are performed on animals, autopsies on people.

'Commence' is a word that is correctly used for formal occasions. For example, theatrical performances and military tattoos 'commence'. Studies, doses etc. start or begin.

It is inappropriate to use nouns as adjectives, when commonly used adjectival forms are available. For example, use 'hepatic enzyme activity' rather than 'liver enzyme activity'; and 'viral replication' rather than 'virus replication'.

'However' is used to link a sentence with the preceding one. It should not be used within a sentence as a replacement for 'but'.
Correct: Blood glucose was reduced at all dose levels. However, this was not dose related.
Incorrect: Blood glucose was reduced at all dose levels, however this was not dose-related.
(Replace 'however' in the second sentence by 'but'. In addition, 'dose related' here is not acting

as an adjective and should not be hyphenated.)

6. SAVING EVALUATION REPORTS

Team members should save their individual evaluation reports into the sub-directory under cms\safety\ that refers to the substance under evaluation. Individual members should name their paper for the area of work they have been involved in. For example, if zinc ascorbate were being evaluated, and evaluator X was undertaking the toxicology of this substance, their paper would be saved under s:\tga\...\cms\safety\zinc ascorbate\toxicology.doc.

It is vital that evaluation reports are filed in the S drive so that all team members, and particularly the team leader, can access the files to edit them. Even if a report is being prepared by one evaluator alone, it must still be saved into the S drive so that other OCM staff can access it in the event of evaluator absence. However team members must not amend another evaluator's paper without good grounds and without informing that evaluator.

The draft of the overall safety evaluation should also be saved into the same sub-directory. Once the final evaluation report has been prepared and cleared by the OCM Director, the document should be saved into the relevant CMEC meeting subdirectory. For example, if the zinc ascorbate evaluation were to be presented to the 22nd CMEC meeting it would be saved as follows:
S:\tga\...\cms\cmec\cmec22\item 6\zinc ascorbate\evaluation report.

7. CLEARANCE OF EVALUATION REPORTS

After the team leader has prepared a first draft evaluation report based on the work of each team member (where relevant), the paper is presented to the Peer Review Panel for comment.

After the Peer Review Panel presentation, team members should update their papers as recommended by the Panel. The team leader should again collate the contributions, edit them (with particular emphasis on consistency of approach), prepare a draft CMEC briefing paper (see SOP - *CMEC briefing papers*) and provide these draft final papers to the Manager, Evaluation & Review Group.

After receiving comments from the Manager and amending the briefing and evaluation papers as recommended, the edited papers should be provided to the Director, Office of Complementary Medicines, for clearance.

After receiving comments and clearance from the Director, final versions of the briefing and evaluation papers, together with any attachments that do not form part of the electronic version of the document, should be provided to the Secretariat. These papers should not be stapled, for ease of photocopying.

8. CHECKLIST FOR EVALUATORS

1. Can you meet the agreed timetable? If not, advise the team leader or the Manager as soon as possible.

2. Is there an Australian Approved Name for this substance and is it acceptable? If it's not acceptable, or a name does not exist, you need to formally propose TGA publication *Approved Terminology for Drugs*, which is available on line. If you are evaluating the safety of a range of salts, derivatives or related compounds in the one evaluation report, ensure that you have AANs for each of these substances.

3. Has the sponsor supplied a compositional guideline and is it acceptable? You need to evaluate this in the paper and suggest amendments where necessary.

4. Has the literature search strategy been identified in the application? Pass to the Library for review.

5. Have you identified the experimental hypothesis for all papers reviewed?

6. Have you provided enough detail in your evaluation of individual studies for a CMEC member to be able to reach their own conclusion?

7. Have you checked with ADRU for adverse reaction reports?

8. Have you checked for regulatory status in other relevant arenas - e.g. Food Standards Code, Customs (Prohibited Imports) Regulations, SUSDP?

9. Have you checked for TGA restrictions on related substances, to ensure you are not proposing requirements out of step with other requirements?

10. Do you have a clear understanding of the area of work you are to prepare so that you are not doubling up on the work of other team members?

11. Have you followed the editing guidelines and saved your paper into the S drive?

12. Do you need help? Speak up if you do, don't leave it until the last day.

RECORD OF AMENDMENTS TO THIS STANDARD OPERATING PROCEDURE

Page and section number	Amendment (including reason for the amendment)	Cleared by, date
11, 13 & 32	Included relevant text from Evaluator checklist developed by Listings Unit	JC

LIST OF COMMONLY USED ABBREVIATIONS AND ACRONYMS

The following abbreviations can be used in evaluation reports but should be included in the table of abbreviations at the front of the report.

ADEC	Australian Drug Evaluation Committee
ADI	Acceptable daily intake
ADP	Adenosine diphosphate
ADRAC	Adverse Drug Reactions Advisory Committee
ALT (=GPT)	Alanine aminotransferase
AMP	Adenosine monophosphate
ANZFA	Australia New Zealand Food Authority
AP	Alkaline phosphatase
ARTG	Australian register of therapeutic goods
AST (=GOT)	Aspartate aminotransferase
ATP	Adenosine triphosphate
AUC	Area under the curve
BID	Twice daily
BUN	Blood urea nitrogen
bwt	Bodyweight
CD	Curative dose
cDNA	Complementary deoxyribonucleic acid
CPK	Creatine phosphokinase
CYP	Cytochrome
DNA	Deoxyribonucleic acid
EC_{50}	Effective concentraton 50
GC (or GLC)	Gas (liquid) chromatography
GGT	Gamma glutamyl transpeptidase
GLP	Good laboratory practice
GMP	Good manufacturing practice
Hb	haemoglobin
Hct (=PCV)	Haematocrit
HPLC	High performance liquid chromatography
IC_{50}	Inhibitory concentration 50
ID	Intradermal
IM	Intramuscular
IV	Intravenous
LD_{50}	Lethal dose 50
LDH	Lactate dehydrogenase
LOEL	Lowest observable effect level
MCH/C	Mean corpuscular haemoglobin/concentration
MEC	Medicines Evaluation Committee
mRNA	Messenger RNA
MRL	Maximum residue limit
NADH	Reduced nicotine adenine dinucleotide
NADPH	Reduced nicotine adenine dinucleotide phosphate
NOEL	No observable effect level

NOAEL	No observable adverse effect level
NMR	Nuclear magnetic resonance spectrometry
PCV	Packed cell volume
PO	By mouth
QA	Quality assurance
QD	Every day
QID	Four times a day
RBC	Red blood cell (erythrocyte)
RIA	Radioimmunoassay
RNA	Ribonucleic acid
SC	Subcutaneous
TID	Three times a day
TLC	Thin layer chromatography
UV	Ultraviolet
WBC	White blood cell (leucocyte)
WHO	World Health Organisationi

SI prefixes (International System of Units)

10^{1}	deka	10^{-1}	deci
10^{2}	hecto	10^{-2}	centi
10^{3}	kilo	10^{-3}	milli
10^{6}	mega	10^{-6}	micro
10^{9}	giga	10^{-9}	nano
10^{12}	tera	10^{-12}	pico