from ??

TRIM No. R12/P73440

Workshop: Compositional Guidelines

1. What has been the problem?

- **The AAN! Cannot rely purely on a name of a substance to regulate its use in listed medicines.**
- **May be little connectivity between the name and the material reviewed by CMEC. Example, three monographs for hydroxyapetite giving varied calcium levels and impurities.**
- **The AAN reference has never been a standard!**

2. What are Compositional Guidelines

- **Compositional Guidelines are developed during the evaluation process and link a physiochemical definition of substance(s) (actives and excipients), approved for use in listed medicines, with the regulatory (Australian Approved) names.**
- **Compositional Guidelines apply where there is no relevant (BP) pharmacopoeial monograph describing the substance(s).**
- **Advantage if Compositional Guidelines use authoritative documents such Australian Standards.**

3. How do Compositional Guidelines help sponsors?

- **To provide a definition for Industry and Stakeholders of the active or excipient, rather than requiring sponsors to obtain correct definitions (based on the Australian Approved Name) on an *ad hoc* basis.**

- **To ensure specific and general safety of the substance.**

- **To establish an action threshold based upon significant and unjustifiable deviation from the accepted Compositional Guideline.**

  Corollary: Action threshold determined at the listing interface during review/ audit of the product.

4. How do compositional guidelines help OCM

- **All of the above. Helping the sponsor assists in the prevention of problems at medicines listing interface.**

- **Passes the onus of determining the acceptability of substances to the manufacture / sponsor.**

  Corollary: Avoid sponsor requests to review substances against the Compositional Guidelines – onus rests with sponsors!

- **Allows OCM to determine the level of knowledge of the substance held by the sponsor. If the sponsor cannot define the substance does that impact on the safety data?**

- **Assists in determining the relevance of evaluation information data. Is the same substance used in all supporting evidence?**

5. Compositional Guidelines Don't Do!

- **Assure absolute safety of the substance and or medicine! Assists with inherent safety of the substance not necessarily specific safety of a particular batch of substance.**

- **Provide commercial exclusivity to the sponsor (by design).**

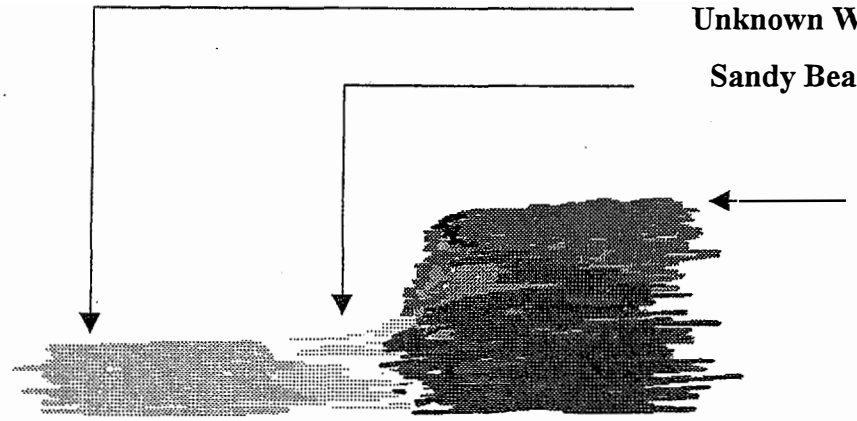
  Corollary: Evaluation needs to establish what is essential to the Compositional Guideline and what may be added to reduce commercial competition.

- **Always give analytical testing details. No access to proprietary testing methodology which remains the intellectual property of the sponsor without (written) permission of the sponsor.**

6. Compositional Guidelines and Standards

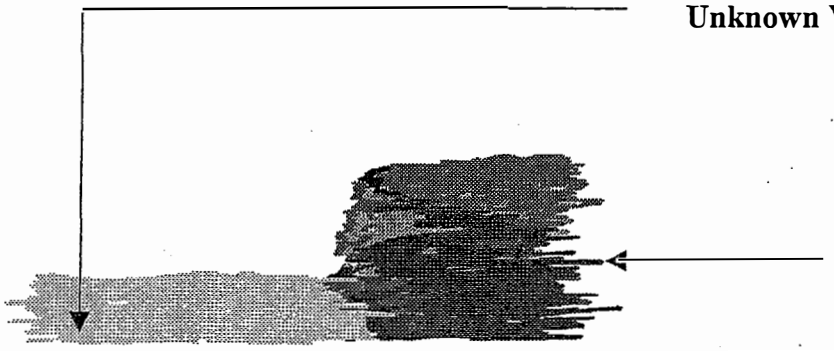
- **Compositional Guidelines are not <u>standards like the BP</u>.**

Compositional Guidelines: A firm but soft approach



Consider the dangerous waters beyond the sandy beach. The Beach slowly descends into the water and its still safe until you're in too deep.

Standard: Big Drop of the edge



The beach is gone. You're either on the land or in over your head!

<u>Difference between standard and Guideline is that deviation(s) can be justified by the sponsor provided the safety evidence considered by OCM /CMEC is not breached.</u>

7. Example of a Compositional Guideline

Draft Compositional Guidelines for Alpha lipoic acid

Definition: Chemical Abstract Service Registry Number for alpha lipoic acid is 62-46-4

Note: Regulations provide approval for *R* and racemic mixture *R/S* not pure *S* isomer.

Requirement	Method	Result
Description Yellow crystalline powder with characteristic odour	Visual	Complies
Identification	(a) UV (b) IR	Complies spectra corresponds with standard
Assay	HPLC	98 to 102%
Melting Point	NS	59.5 to 62.0°C
Loss on Drying	NS	NMT 0.5%
Heavy Metals	NS	20 ppm

Legend: ICH - International Conference on Harmonization topic Q3C (CPMP/ICH/283/95)
AGRD2 - Australian Guide to the Registration of Drugs Vol 2., page 89.
NS - Not Specified. Any analytical method of appropriate analytical rigour is acceptable. Details of the methodology and validation may be requested by the TGA in some circumstances.

Comments invited

You are invited to make a written submission containing technical or other relevant information that may assist the TGA in the development of Compositional Guidelines. Information relevant to the Compositional Guideline above, including consideration of its regulatory impact, from individuals and organisations, would contribute to the decision making process. Technical information should be presented in sufficient detail to allow independent scientific review.

If you wish any confidential information contained in a submission to remain confidential to the TGA, you should clearly identify the sensitive information and provide justification for treating it in confidence.

Address for submissions:

Information Officer
Office of Complementary Medicines, TGA
PO Box 100
WODEN ACT 2606
Fax: (02) 6232 8577

Submissions must be received by close of business 2000.

8. Treatment of Deviations

- **Consider Compositional Guideline for alpha lipoic acid**
- **Scenario: sponsor provides C of A (and / or material specifications) which deviate from the Compositional Guideline. Need to consider model to assess significance!**

Impact of deviations from Compositional Guidelines on safety

Same Substance

Low

Minor differences in:
(Analytical inaccuracy)
Moisture content higher
Assay limit by ± 5%
Appearance

Separate and Distinct (CMEC)

Profound difference in:
Assay ± 25%
Related substances > 10%
Pure *S* isomer

Unacceptable Substance

High

High Heavy metal limits
Solvent residues
Microbiology

- **Needs development of regulatory criteria for**
  - **separate and distinct substances**
  - **Breaches of substance safety**

8. How Do We Handle Compositional Guidelines?

Overview of decision making steps in application processing.

Step 1: Generation of a compositional Guideline
Responsibilities: Evaluator / Teamleader

Process Aim: To develop, in consultation with the sponsor, Compositional Guideline(s) for proposed substance, while considering: * Section 9 *

1. The minimalist requirements for the Guideline.
2. The analytical basis for the guideline (analytical rigour)
3. Value added safety of the substance (assumed global supply)
4. Attempts to "exclusify" substance(s) through ancillary requirements.

Step 2: CMEC consideration of a draft compositional Guideline
Responsibilities: CMEC / evaluator / Teamleader

Process Aim: CMEC review of the Compositional Guideline.

Possible Outcomes

CMEC acceptance of draft

CMEC recommended change
Discussions with sponsor / Delegate

Step 3. Dissemination and finalisation of the draft Compositional Guidelines

Process Aim: To disseminate the draft to stakeholders and finalise the draft in accordance with stakeholder comments.

Note: Comments to be reviewed with consideration of what is a justifiable alteration of the original Compositional Guideline without invalidating the CMEC safety conclusion!

9. New OCM approach to Compositional Guidelines?

- **Prescriptive requirements for Compositional information within the evaluation. The sponsor may justify omissions.**

  Model document provided for review.

- **Establishes "weaknesses" within the data package at application lodgement.**

- **Need to develop Guideline requirements for herbal and biological substances!**

Attachment 1

Draft Compositional Guidelines for Complementary Medicinal Chemical Substances

1. General Principles for Compositional Guidelines

An application submitted to the TGA for the evaluation of a new complementary medicine must include a physicochemical definition of the substance proposed for medicinal use. If the substance is already defined in a relevant monograph of the British Pharmacopoeia, the TGA expects that the substance will meet all requirements of that standard. If the proposed substance is the subject of a pharmacopoeial monograph other than the BP, for example the United States Pharmacopoeia (USP), Commission E Monographs, European Pharmacopoeia (EP) or Peoples Republic of China Pharmacopoeia (PRCP), the TGA will expect that monograph to apply to the proposed substance, unless otherwise justified in the application.

Often there are no current pharmacopoeial references for substances proposed for use in complementary medicines. Nevertheless, the TGA still expects draft compositional guidelines to be provided in applications. Compositional data must be present in sufficient detail to allow characterisation of the proposed substance, before the application evaluation process is commenced. Applications lodged with the OCM without relevant data may be rejected or the application evaluation process delayed.

The origin of the data submitted in the draft compositional guideline might be from any source which is appropriate and authoritative. For example, data published in literature or the results of testing of the substance using proprietary methods.

The draft compositional guideline will be reviewed in the application evaluation process and modifications may be proposed by the TGA. Further, the Complementary Medicines Evaluation Committee (CMEC) will advise the TGA of any modifications that the committee feels are appropriate following consideration of the application. This will usually be followed by consultation on the draft guidelines with industry and stakeholders. Any requests for significant alteration to submitted compositional guidelines, following CMEC review, may necessitate a re-review of the substance by CMEC.

This process occurs separately from the gazettal process for a newly approved substance. As soon as a new listable substance is gazetted, it may be used in listed therapeutic goods, as defined in the gazette notice. Usually the compositional guideline will be finalised some time after Gazettal. Sponsors should be aware of the details of the draft guidelines that are circulated for consultation, however, its specifications are not binding. It should also be noted that it would be rare for a compositional guideline to become more restrictive as a result of consultation. Once a compositional guideline is finalised, the "new" substance should comply with it unless the sponsor holds justification as to why the substance they are using should differ in composition from the compositional guideline.

2. Specific Advice For Chemical Substances

For the purposes of this advice, a substance that has been refined to a high degree of purity is defined as a **"chemical substance"**. The function of this document is to offer guidance in the development of a workable draft compositional guideline for a **chemical substance**, and allow judgement of whether sufficient specific information is held by sponsors to lodge an application with the OCM.

It should be noted that compositional guidelines for medicinal substances of **herbal and biological origin will be expected to meet different requirements and are not considered in this advice.**

2.1 Guidance Notes for the preparation of Draft Compositional Guidelines

2.1.1. The draft compositional guidelines must be presented in a format in accordance with the requirements set out below in "Format for Draft Compositional Guidelines for Chemical Substances".

2.1.2. The primary requirements of the Draft Compositional Guidelines are considered to be the minimum amount of descriptive information to characterise the proposed substance. Applicants may wish to include additional requirements, to that presented in the format below, if such information is applicable to the proposed substance.

The TGA acknowledges the diversity of data that may be used to define medicinal substances and understands that there may be situations where the guidelines do not address all needs. If insufficient information is available to address requirements of the guideline, 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 must be provided in the application. The validity of any justifications will be considered in the application pre-assessment process.

It should be noted, however, that any omissions of primary compositional requirements will be reviewed to determine whether the omission is indicative of limited knowledge and / or uncertainty of the composition of the substance. The TGA may challenge any justification(s) and request further information (under section 31 of the *Therapeutic Goods Act* 1989) before proceeding with the application, or under some circumstances the application may be rejected.

2.1.3 Please indicate the method of analysis used to establish the corresponding limit in the "method" column of the guideline, ie. HPLC, GC or TLC. If the method and limits are based on a pharmacopoeia or published reference please provide all details in the relevant section of the Guidelines.

Please note that if any proprietary methods are presented in the Draft Compositional Guidelines a brief description should be detailed in the application form.

Unless written approval is provided in the application, details of proprietary methodology will not be distributed as stakeholder information on the final Compositional Guideline. By default methods used in the analyses of the substance will be presented as abbreviations. For example, HPLC, TLC, GC and IR.

2.1.4 Secondary requirements are those that may be ancillary for the substances and should be included, where possible, in the guidelines. No justification is required for the omission of secondary requirements.

Format for Draft Compositional Guidelines for Chemical Substances

Name of the Chemical Substance: This name must refer to the current or proposed Australian Approved Name of the substance

General Requirements to be addressed

Please present the draft compositional guideline in this format including, but not limited to, the following primary and secondary requirements.

Requirement	Method(s)	Limits / Result
Description Give a physical description of the substance such as, physical form, colour, texture, viscosity, crystallinity (if solid) and organoleptic qualities For example, white to straw crystalline solid.	Visual or otherwise	Complies
Identification What is being identified? Present identification of all relevant compounds.	List relevant methods of identification	Complies
Assay What is determined in the assay? Present assay of all relevant compounds or elements.	List relevant methods of assay	Relevant limits for assay(s)

Organic or inorganic impurities What impurities are assayed?	List relevant methods of assay	Total limit of impurities in substance Impurity specific limits
Solvent Residues What solvents?	List relevant methods of assay	Total limit of solvents Solvent specific limits
Heavy Metals What metals?	List relevant methods of assay	Total limit of heavy metals Metal specific limits
Microbiology	List relative methods	Total and specific microbiological loading

Secondary Requirements for solids

Moisture	List relevant methods	Moisture limit per unit mass

Secondary Requirements for Liquids

Relative Density	List relevant methods	Relative density limit
pH	List relevant methods	pH limit

Methodology

If analytical methods are referred to in the above table, for example HPLC, then please document details of the method in this section of the Draft Compositional Guideline. Where a published method has been cited, please provide full text copies of the literature.

Justification

Please give detailed justification(s) for the omission of any primary requirement detailed above.