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

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

4.4. Compositional Guidelines

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

4.4.1. Simple / Complex Complementary Medicine Substances

4.4.1.1. Simple complementary medicine substances

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

4.4.1.2. Complex complementary medicine substances

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

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