MEDICINES CONTROL COUNCIL

COMPLEMENTARY MEDICINES - QUALITY, SAFETY, AND EFFICACY

This guideline is intended to provide recommendations to applicants wishing to submit applications for the registration of Complementary Medicines. It represents the Medicines Control Council's current thinking on the quality, safety, and efficacy of these medicines. It is not intended as an exclusive approach. Council reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. Alternative approaches may be used but these should be scientifically and technically justified. The MCC is committed to ensure that all registered medicines will be of the required quality, safety and efficacy. It is important that applicants also adhere to the administrative requirements to avoid delays in the processing and evaluation of applications.

Guidelines and application forms are available from the office of the Registrar of Medicines and the website.

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REGISTRAR OF MEDICINES
MS M HELA

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1 INTRODUCTION

A registerable complementary medicine may fall in Schedule 0, 1, 2 or 3.

Medicines are not scheduled solely on the basis of toxicity. Although toxicity is one of the factors considered, and is itself a complex of factors; the decision to include a substance in a particular Schedule also takes into account many other criteria such as the purpose of use, potential for misuse, abuse, safety in use and the need for the substance.

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

Essentially, if the substance is a designated active ingredient, as defined in the Regulations, that has an established identity and tradition of use, it is a complementary medicine substance.

1.1 Compliance with Good Manufacturing Practice and Good Dispensing Practice

1.1.1 Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP)

All manufacturers of complementary medicines shall comply with all aspects of Good Manufacturing Practice and Good Laboratory Practice.

1.1.2 Good Dispensing Practice

All dispensing and compounding of medicines by Practitioners shall comply with the provisions of Act 101 of 1965 and all aspects of Good Dispensing Practice in accordance with the provisions of Act 53 of 1974.

1.2 Format of submission

Data provided in applications for registration of complementary medicines should be in the CTD format.

1.3 Quality

Information is required for a product's active ingredients and its excipients. The data are evaluated to determine the quality of the product, including the identity, impurities and stability of the ingredients. The data assessment also takes into account information about the manufacturing processes and levels of good manufacturing practice (GMP), where appropriate.

Details of quality control measures are required to demonstrate that the product will be produced to a consistent quality. Stability data for the product are required to determine a shelf life over which the product's quality is maintained.

Should the results of any testing be outside the acceptable limits then appropriate action, which may include rejection or destruction, must be taken immediately.

1.4 Safety and Efficacy

Applications for the registration of complementary medicines must include appropriate data that demonstrate the safety and efficacy of the product.

The applicant must provide evidence (data) to support the product's efficacy for the proposed indication(s) and any claims that the applicant intends to make in the product labelling to determine whether the data supplied adequately support the requested indication(s)/claim(s).

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

Any complementary medicine that is of animal origin must comply with the importation requirements of the Veterinary Diseases Act.

1.5 The Naming of medicines and substances

1.5.1 General

(i) Chemical Substance Name

The approved name i.e. International Non-Proprietary Name (INN) or chemical name of substances used as inactive ingredients in topical products must be stated. In the absence of such name being available, a chemical description or characterisation of the substance should be given.

The approved name (INN) or chemical name of mineral, metal or chemical substances or prepared mineral substances used in Homoeopathic, Traditional Chinese, Ayurvedic or Unani Tibb medicines must be stated.

(ii) Biological Substance Name

In addition to the name of the organism, the part, preparation and / or biological descriptor may be required to fully name a biological substance.

(iii) Herbal Name

Herbal names are stated in the Latin binomial format which is the scientific genus and species name. If necessary the variant should be included.

Herbal Ingredient: The Latin binomial name the part and the preparation (including solvents and ratio if applicable) are used to fully name a herbal ingredient.

(iv) Herbal Substance

Pharmacopoeial names of herbal ingredients (e.g. olive oil) that are fully characterised in a monograph of an accepted pharmacopoeia[1] must be used.

(v) Herbal Component Name (HCN)

HCNs are names for classes of constituents that are found in herbal ingredients. The need for a HCN most often arises when a herbal extract is standardised to a particular class of constituents, or where particular classes of constituents are restricted (e.g. hydroxyanthracene derivatives). Where a herbal extract is standardised to a single constituent, the single constituent should have a chemical name. The HCN is not a stand-alone name and should be used only when expressing a herbal substance.

1.5.2 Nature identical oils are a blend of natural essential oils and aromatic compounds which are made in the laboratory. and have fewer synthetic compounds than 100 % synthetic oils. Nature identical essential oils are **NOT** suited for aromatherapy and therapeutic applications.

Nature identical' oils cannot be used therapeutically as complete substitutes for the naturally occurring aromatic materials

Wherever 'nature identical' oils are used, this must be clearly stated on all documentation including product labels.

1.5.3 Common names, *Materia Medica* Name, Traditional Chinese Pin Yin, Traditional Sanskrit and other Traditional Unani Tibb Names may be used in addition to the approved names.

The Pin Yin name of the plant may also be used in addition to the English names of the plant parts in the case of Traditional Chinese medicines.

[1] an earlier edition of another suitable pharmacopoeial reference may be used.

1.6 Accepted References

1.6.1 Herbal medicines

Herbal medicines or substances shall be described as herbal medicines or substances in at least one of the specified references on the herbal medicines reference lists:

- Australian Therapeutic Goods Authority List of Substances
- German Commission E Monograph
- German Commission D Monographs
- German Homoeopathic Pharmacopoeia

1.6.2 Traditional Chinese Ayurvedic, Unani Tibb

(i) A Traditional Chinese medicine or substance must be described as a Traditional Chinese medicine or substance in at least one of the following references:
- the Traditional Chinese pharmacopoeia
- Advanced Textbook on Traditional Chinese Medicine and Pharmacology. State Administration of Traditional Chinese Medicine, New World Press, Beijing, China
- The Yellow Emperor's Classic of Internal Medicine. Translated by Ilza Veith
- A Barefoot Doctor's Manual. The American Translation of the Official Chinese Paramedical Manual, Running Press, Philadelphia, Pennsylvania
- A Clinical Guide to Chinese Herbs and Formulae. Chen Song Yu and Li Fei. Translated by Jin Hui De
- The Practice of Chinese Medicine by Giovanni Maciocia
- Practical Traditional Chinese Medicine and Pharmacology. Herbal Formulas by Geng Junying *et al*
- Clinical Handbook of Internal Medicines by Will Maclean and Jane Lyttleton

(ii) An Ayurvedic medicine or substance must be described as an Ayurvedic medicine or substance in at least one of the following references
- Ayurvedic Materia Medica with Principles of Pharmacology & Therapeutics by H.V.Savnur
- Indian Materia Medica with Ayurvedic, Unani-tibbi, Siddha, Allopathic, Homeopathic, Naturopathic & Home Remedies, originally edited by the late Dr K.M.Nadkarni
- Caraka-Samhita by Prof. Priyavrat Sharma
- The Sushruta Samhita based on original Sanskrit text translated and edited by Kaviraj Kunjalal Bhishagratna M.R.A.S (LOND.)
- The Ayurvedic Pharmacopoeia of India
- The Aurvedic Formulary of India

(iii) A Unani Tibb medicine or substance must be described as a Unani Tibb medicine or substance in at least the Unani Tibb pharmacopoeia.

1.6.3 Homoeopathy

The substance must be described as a homoeopathic substance in at least one of the specified Materia Medica or Homoeopathic Pharmacopoeiae

1.6.4 Aromatherapy

An aromatherapy substance must be described as an aromatherapy substance in at least one of the specified references on the Aromatherapy Substances Reference List - Can be obtained from a standard list – see the following reference *www.aromaweb.com/books/default.asp*

1.7 Types of Substances

1.7.1 **Herbal** substance means all or part of a plant or substance (other than a pure chemical or a substance of bacterial origin):

a) that is obtained only by drying, crushing, distilling, extracting, expressing, comminuting, mixing with an inert diluent substance or another herbal substance or mixing with water, ethanol, glycerol or aqueous ethanol; and

b) that is not subjected to any other treatment or process other than a treatment or process that is necessary for its presentation in a pharmaceutical form.

1.7.2 **Traditional Chinese, Ayurvedic** and **Unani Tibb** medicines or substances may be of plant, animal, or mineral origin. They may include fresh or dried substances, extracts or derivations from these extracts.

1.7.3 **Homoeopathic** substances may be of plant, animal, metal or mineral origin and may include allersodes, isodes, sarcodes, nosodes and allergens as well as allopathic substances, used in potentised form at acceptable potencies for use as a homoeopathic medicine.

1.7.4 **Aromatherapy** substances will be of plant origin. Reference must be made to the part of the plant(s) or the whole plant used to extract the aromatherapy substance.

2 QUALITY *Refer also to Pharmaceutical & Analytical Guideline*

Information on the quality of a complementary medicine substance is required to characterise the substance for the purpose of developing a compositional guideline *cf 2.1.2 below.*

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

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

Types of liquid extracts, and dried plant concentrate preparations include decoctions, macerations, infusions

This section is divided into two subsections:

2.1. Active Ingredient

2.2 Finished Product

Some complementary medicines are comprised of relatively simple ingredients[2] (e.g. amino acids, mineral salts, vitamins) and, unless the medicine contains multiple active ingredients, the quality parameters applying to such products are essentially the same as for pharmaceutical medicines.

However, complementary medicines that contain complex ingredients that are difficult to characterise and/or certain combinations of multiple active ingredients require special consideration.

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

[2] There is a wide range in the compositional complexity of complementary medicine ingredients. Simple complementary medicine substances are primarily single-constituent ingredients that can be readily characterised (methionine). Complex complementary medicine substances (e.g. herbal extracts) have a number of constituents.

2.1 ACTIVE INGREDIENT – Complementary Medicine Substance *(Module 3.2.S)*

The types of information and level of detail depend on the active ingredient and on the risk associated with the finished product.

In all cases, the application information must be sufficient to:

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

Description (Composition)

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

Nomenclature

Provide the name of the substance. Refer to Section 1.5

Structure

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

General properties

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

2.1.1 Manufacture of the Active Ingredient

The manufacture of the active ingredient must be described.

State the part of the plant or animal used and its form, i.e. whether it is a fresh or dried material, together with details of any processing it undergoes before use in the manufacture of the product.

Where appropriate it may be necessary to state the country or region of origin of the ingredient, or give other details such as time of harvesting and stage of growth, which are pertinent to the quality of the ingredient.

If the herb is processed to produce a galenical form, the extraction and any concentration processes should be described or a reference cited, indicating whether the extract or additives, such as calcium phosphate in dry extracts, are present in the final product formulation.

In the case of 'low dose' starting substances these must in all cases be manufactured according to suitable pharmacopoeiae to ensure reproducible quality and which form the basis for appropriate documented indications or claims, according to the particular method used.

Manufacturer(s)

Provide the manufacturer's name and address, and addresses of all sites involved in the manufacture/ testing of the substance.

2.1.2 Compositional Information

This is, in essence, a physicochemical definition of the substance.

The purpose of the compositional information is to provide detailed characterisation of the substance. For simple complementary medicinal substances, this is usually straightforward and may be a simple extension of the specifications. For complex complementary medicines, the compositional information is generally more detailed and contains a significant amount of additional qualitative and quantitative data.

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

Many complementary medicine substances have yet to be defined or characterised in a monograph that is acceptable to the MCC. Therefore specifications and control procedures that substantially characterise these substances should be proposed. In general, these 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.

Data on the nature or chemistry of the active component should be provided. This may include citation of pharmacopoeial monographs, photocopies from authoritative references, or in-house data.

Refer to the Australian guideline ARGCM Part III, Evaluation of Complementary Medicine Substances, Appendix 1 for guidance on the type and detail of information to be included.

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

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

2.1.3 Control of Active Ingredient / Substance – Specifications

Starting material specifications should be provided or a reference cited for each starting material. Where a pharmacopoeial reference does not apply to an ingredient, the specification should give details of the test methods and test specifications. Appropriate testing techniques are required in accordance with the SA Guide to GMP Annex 7 – *Manufacture of Herbal Medicinal Products*. These would need to cover identity and, where appropriate, adulteration and contamination, both chemical and microbiological. Where a herbal ingredient is standardised in terms of a component(s) and the statement of activity on the label is based on this standardisation, evidence of how the standardisation is achieved should be provided.

The active ingredient specifications are a set of tests and limits that are applied to the complementary medicine substance in order to ensure that every batch is of satisfactory and consistent quality. The specifications should monitor all parameters (generally by physico-chemical testing) where variation would be likely to affect the quality or safety of the product.

2.1.3 Control of Active Ingredient – Specifications - continued

The manufacturer of the active ingredient should apply specifications and control procedures for the substance at the time of its manufacture. The finished product manufacturer is also expected to ensure that the active ingredient complies with specifications before using the substance in the finished product at the time of manufacture. The two sets of specifications are not necessarily identical.

For most complementary medicines, the manufacturer of the active ingredient will not be controlled to the same extent as the finished product manufacturer, and therefore the focus will be on the specifications applied by the finished product manufacturer before the ingredient is used in the finished product. For some complex substances, or where the finished product will be a prescription only medicine, the specifications applied to the active ingredient by the ingredient manufacturer may be more closely scrutinised.

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

Where non-pharmacopoeial specifications are applied, a tabulated summary of the tests, test methods and limits should be provided. The specifications applied should be justified for their ability to assure the quality and consistency of the ingredients used.

Similarly, where a pharmacopoeial monograph is used as the specification, any modification to the pharmacopoeial requirements should be justified.

2.1.3.1 Limits and Tests

If there is a recognised pharmacopoeial monograph for the active substance, it must be used unless otherwise justified. Note that the most recent edition of any pharmacopoeial standard or monograph should be used, or a justification for not doing so provided. The requirements of the recognised pharmacopoeiae or applicable general monographs in these pharmacopoeiae must also be met except where a justification for not doing so is authorised by the MCC.

In some cases, the pharmacopoeial requirements may not in themselves be sufficient to adequately control the quality and consistency of an ingredient, and applicants may apply additional tests. However, it is generally not acceptable to:

- adopt only some of the tests from a pharmacopoeial monograph;
- selectively combine some tests and/or limits from one specific pharmacopoeial monograph with some from another pharmacopoeial monograph (without having ensured full compliance with either);
- adopt an earlier edition of the pharmacopoeial monograph or standard when there is a more recent edition that has been adopted by the MCC.

Where non-pharmacopoeial specifications are applied, a tabulated summary of the tests, test methods and limits should be provided *(e.g. assay (non-aqueous titrimetry): 99,0–101,0 %).* The specifications applied should be justified in respect of their ability to assure the quality and consistency of the ingredients used.

Similarly, where a pharmacopoeial monograph is used as the specification, any modification to the pharmacopoeial requirements should be justified.

The specifications for the active ingredient should be guided by the compositional information.

A The minimum tests and limits included in specifications for an active ingredient include:

(i) appearance/description;

(ii) identification:

(a) Plants will generally be identified according to a suitable morphological and histological description system, where acceptable reference specimens are used. The parts of the plant that are used or the whole plant must be specified.

(b) Where the plant material is examined for the first time in a powdered or crude form, it must be subjected to at least macroscopic and microscopic examination. The organoleptic properties that would confirm the identity must be included.

(c) Where it is not possible to confirm the identity by macroscopic and/or microscopic examination, suitable identification tests or assays must be performed by comparing the specimen to reference substances or known active ingredients or markers.

(d) Where relevant, extracts for identification by suitable and validated methods should be made.

(e) For homoeopathic medicines where Mother Tinctures or starting substances are prepared, the plant will ideally be identified according to a suitable plant description and identification system where reference authentic specimens are used

The identity of starting substances can, at Mother Tincture level, be established by means of suitable thin layer chromatograms which are congruent with reference chromatograms, or by other suitable methods. Thereafter product integrity and identity must be ensured by means of a carefully documented paper trail after positive identification by a suitably qualified person.

(f) 'Low dose' herbals are herbal extracts that are not manufactured to create standardized or higher levels of active ingredients in the extract. They are largely used as 'drainage' preparations and are manufactured according to approved pharmacopoeiae. They can be identified by a suitable description and identification system, where acceptable reference specimens and/or suitable and validated analytical methods are used.

(g) Therapeutic or pharmaceutical markers/active ingredients, can be used to identify standardized extracts or concentrates.

(h) Where materials other than plants are used, suitable systems and/or methods that are capable of confirming the identity of the substance must be employed.

(i) The identification of aromatherapy substances

- Appropriate methods or systems must used to confirm the identities of the plants and the parts of plants used to manufacture the aromatherapy substance. For this purpose suitable plant description and/or identification systems may be used. Where plants are compared, reference to authentic specimens may be made.
- Large variations, which are caused mainly by geographic and climatic variances may occur from batch to batch with respect to the active principles of aromatherapy substances. For this reason suitable plant description and/or identification systems should be used together with validated test methods and document trails.

(iii) content/assay;

Suitable pharmaceutical or therapeutic markers may be used in conjunction with suitable and validated test procedures to determine the concentration or strength of starting substances and/or final products.

Concentrations or quantities of scheduled substances must be specified and controlled within the Schedule limits

(iv) impurities (e.g. residual solvents, heavy metals, synthetic impurities and degradants).
See 2.1.3.2

B Additional tests and limits may be appropriate and will depend on the nature of the active ingredient. For example, tests for the presence or the proportion of isomers, optical rotation, microbial contamination, particle size distribution, and the clarity, colour and pH of solutions may also be relevant.

C The specifications might also include controls on the macro components, such as nitrogen content or sodium content. For complex liquid formulations, solvent content or viscosity might be important. Additional simple tests that could assist in characterisation could include colour, texture, smell and pH. More complex or specific tests should be used where there is a need to determine a component in a substance that is significant, such as sodium content in a sodium salt of a substance or gas chromatograph characterisation of key components in an oil.

D Significant minor components of a substance (e.g. content of a specific alkaloid) are particularly important. These components are often pivotal to the nature and/or safety of the substance, and their identification and analysis requires the attention of the sponsor. A good starting point may be to use monographs for similar substances as a model and adapt them to the substance in question.

E Substances that are intrinsic mixtures (e.g. synthetic polymers or fatty acid esters of glycerol) may require additional tests to control such aspects of the mixture as:

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

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

2.1.3.2 Impurities and Incidental Constituents

All herbal starting substances and intermediates must be free of contaminants.

The absence of orthodox pharmaceutical substances or chemicals must be confirmed.

The absence of herbal adulterants must be confirmed.

Information concerning impurities that are not dealt with in the monograph or standard should be provided. Applicants should be aware that the manufacturing process for the substance may differ from the process for the substance upon which the monograph is based and, consequently, different impurities may be present.

2.1.3.2 Impurities and Incidental Constituents - continued

One of the key purposes of raw material specifications for complementary medicines is to determine whether the active raw material is free of contaminants that may have safety implications. Therefore, incidental constituents and impurities need to be considered and tests and limits included in the active ingredient specifications.

Impurities and incidental constituents are those constituents that may be present in a substance as a by-product of the production, processing or storage of a substance, and are immaterial to the nature of the substance.

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

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

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

For further guidance on this matter, refer to the Australian guideline ARGCM Part III, Impurities and Incidental Constituents and ARGCM Part III, Guidance on Limits and Tests for Incidental Metals and Non-metals in Therapeutic Goods.

2.1.4 Control of Active Ingredient / Substance – Analytical Procedures and Validation

Details should be provided of all analytical methods used in the specifications, together with validation data that demonstrate the suitability of the method for the material in question. The information should cover accuracy, precision, specificity (e.g. freedom from interference by degradation products and other likely impurities) and linearity. Validation data are not required for methods described in an MCC-recognised monograph or standard.

Details of test methods and method validation data should be provided for all non-pharmacopoeial methods.

For homoeopathic substances the identity of starting substances can, at Mother Tincture level, be established by means of suitable thin layer chromatograms which are congruent with reference chromatograms, or by other suitable methods. Thereafter product integrity and identity must be ensured by means of a carefully documented paper trail after positive identification by a suitably qualified person.

2.1.5 Batch Certificates of Analysis

Certificates of analysis should be provided for at least two recent commercial-scale production batches to demonstrate routine compliance with the specification or monograph. If data on commercial-scale batches are not available, certificates of analysis should be provided for pilot-scale batches manufactured using the same process as intended for commercial-scale batches.

Certificates of analysis should also be provided for any batches of material used in toxicity tests and clinical trials reported in support of the application. This will assist the MCC in determining whether the substance intended for supply is the same as that on which safety data have been provided. It is important that batch analysis data for the active ingredient are included for batches that were used in clinical trials reported in support of the application.

2.1.6 Justification of Specification

If an applicant proposes to use an alternative monograph or standard when a BP, Ph Eur or USP standard exists, justification for doing so is required. The justification should explain why the standard(s) cannot be met and detail what alternative(s) are proposed and why.

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

2.1.7 Stability *Refer also to the Stability guideline*

Stability data should be provided for complementary medicine active ingredients to assist in identifying any particular degradants that may be formed and that should be monitored as part of the overall stability program.

2.1.7.1 Homoeopathic substances

The following criteria shall apply with respect to shelf life and the determination of expiry dates:

(i) For D4 potencies upwards, with respect to products with single or multiple active ingredients, the shelf-life is consistent with the shelf-life of the vehicle substance containing the active potency.

(ii) Stability tests must be performed in accordance with the Stability Guidelines.

(iii) It must be noted that accelerated stability testing in the case of Homoeopathic Substances is not appropriate.

(iv) For mother tinctures and potencies up to and including the D3 or 3x potency (or equivalent potency), stability testing should be done by means of Thin Layer Chromatography on the Mother Tincture, or on the potencies, where this is applicable and possible. Standardised reference extracts and thin layer chromatograms can be used for comparison purposes.

2.1.7.2 Aromatherapy

The stability of aromatherapy substances and expiry dates may be related to the stability of the vehicles and/or excipients.

2.2 FINISHED PRODUCT *(Module 3.2.P)*

2.2.1 Description and Composition of the Product

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

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

The table of ingredients should provide greater detail than simply the product formulation. It should include overages (additional quantities of ingredients, over the amounts nominated in the product's formulation, added during manufacture) if any.

Components of a formulation are divided into active ingredients and inactive ingredients.

2.2.1.1 Active Ingredients

Active ingredients in complementary medicines are those substances that have a therapeutic role in the formulation. The therapeutic role may be to treat, prevent, cure or alleviate a disease, ailment, defect or injury or alleviate a symptom of a disease, ailment, defect or injury, or influence, inhibit or modify a physiological process. Also refer to the definition of a complementary medicine in the Regulations,

Substances included in the formulation as active ingredients must make a contribution to the proposed indications for the medicine.

2.2.1.2 Inactive Ingredients

Inactive ingredients are substances used to aid the manufacture of therapeutically active substances into dosage forms suitable for administration to consumers. Each inactive ingredient included in a formulation must have a justifiable excipient role and should be appropriately controlled by specifications.

Applicants should ensure that the intended use of an inactive ingredient is appropriate and that it is used in appropriate amounts to achieve its technical purpose. Applicants should also ensure that the excipient is approved for use.

2.2.1.3 Colouring and Flavouring Ingredients

Refer to the Pharmaceutical & Analytical Guideline.

2.2.1.4 Modified Release Products

Controlled release claims of modified release formulation must be demonstrated by both physico-chemical data (dissolution data) and clinical data (bioavailability data).

Refer to Dissolution and Biostudies guidelines.

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

(i) Routine variations in inactive ingredients

It is recognised that it may be necessary to vary the quantities of certain inactive ingredients from batch to batch in order to achieve acceptable results during manufacturing.

Table 1 lists the changes to the nominal amounts of certain inactive ingredients that may be made in the manufacture of immediate release complementary medicines.

2.2.1.5 Batch-to-batch variations in the amount of ingredients - continued

Table 1. Changes to the nominal amounts of certain excipients may be made as set out below.

Inactive ingredient type	Acceptable range around the nominal formulation
Quantity of ingredients whose function is to contribute to viscosity	+/– 10 %
Granulating fluid (fixed composition)	+/– 10 %
Disintegrant (even if the excipient serves more than one role in the formulation)	up to +25 %
Talc and water-soluble lubricants and glidants	–25 % to +100 %
Water-insoluble lubricants and glidants, except talc (e.g. magnesium stearate, stearic acid)	+/– 25 %
Filler (bulking agent) in hard gelatin capsules	+/– 10 %
Carriers and potency-adjusting ingredients for materials of biological and herbal origin	+ /– 10 %
Filler (bulking agent) in tablets and soft gelatin capsules to account for the changes in the item above	+ /– 10 %

(ii) Variations in content of some active ingredients

For some active ingredients, such as herbal substances, the mass of the active raw material used in a batch of the formulated product may vary according to its composition.

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

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

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

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

2.2.1.6 Overages

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

The application's product development summary should include a justification for the proposed overage. The use of an overage to compensate for poor analytical methodology or poor stability performance is not usually considered sufficient justification.

2.2.2 Product Development

Information on the development of the finished product should be provided, including a discussion of the studies that led to the proposed dosage form, formulation, method of manufacture and container.
Where a medicine has modified release characteristics or an unusual method of manufacture, the product development summary should include a detailed discussion of the development of those characteristics or method and any relationship with the finished product specifications. For example, for an enteric-coated tablet, dissolution and formulation studies performed during development should be discussed and related to the dissolution test in the finished product specifications.

If any overages are proposed, the developmental work that led to the proposed overage should also be discussed.

2.2.3 Manufacture of the Finished Product

2.2.3.1 Licensing and Control

The manufacturer's licence carries details of the types of manufacture permitted under the licence.

Where a product is imported, each nominated overseas manufacturer is expected to demonstrate an acceptable standard of GMP. *Refer to SA Guide to GMP.*

2.2.3.2 Batch Formulation

A batch formulation should be provided in table format. It should include all of the components that will be used in the manufacture of the finished product and their quantities on a per batch basis (including any overages), correlated to the unit formula.

2.2.3.3 Description of Manufacturing Process and In-Process Controls

Details of the manufacturing process for the finished product should be provided for each manufacturing site. These steps should include the manufacture of the dosage form, packaging and labelling, chemical and physical testing, microbiological testing and release for sale.

The manufacturing details should include information about:

- solvents that are used, even if they are evaporated from the product during manufacture;
- polishing agents that do not appear in the formulation.

2.2.4 Control of Inactive Ingredients – Specifications

All ingredients in complementary medicines, including inactive ingredients, should have suitable specifications.
If there is no relevant monograph or standard for an inactive ingredient, full details of the specifications for each excipient are required.

2.2.5 Control of the Finished Product – Specifications

The finished product specifications are a set of tests and limits that are applied to the finished medicinal product in order to ensure that every batch is of satisfactory and consistent quality at release and throughout its shelf life. The specifications should monitor all parameters (generally by physico-chemical testing) where variation would be likely to affect the safety or efficacy of the product.

The specifications against which a finished product is tested before release for sale are referred to as the "batch release" specifications in this document; those against which the product is tested to ensure satisfactory quality throughout its shelf life are referred to as the stability specifications.

The finished product specifications should be provided, defining the physical, chemical and microbiological characteristics of the product and detailing quality-control test methods and test specifications.

2.2.5.1 Data Requirements

Release and stability specifications must be tabulated separately.

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

The batch release limits must be chosen in order to guarantee that all batches will comply with the expiry specifications throughout the product's shelf life.

As a minimum, the stability specifications should include all of the tests in the batch release specifications.

Identification

- The final product must be identified by suitable pharmacopoeial methods or, when not available, by validated in-house methods. Product identification must be supported by a carefully documented paper trail.

Assay

- Suitable pharmaceutical or therapeutic markers may be used in conjunction with suitable and validated test procedures to determine the concentration or strength of starting substances and/or final products.
- Concentrations or quantities of scheduled substances must be specified and controlled within the Schedule limits

2.2.5.2 Impurity Requirements for Non-pharmacopoeial Products

The specifications for finished products for which there is neither a BP, Ph Eur nor USP monograph for a closely related finished product, should include tests and limits for impurities related to the active ingredient.

For impurity limits, the results of stability studies should be taken into account and reference should be made to information on toxicity. Specifically, the amount and types of impurities that were detected in the stability studies should be consistent with the stability specifications and the proposed shelf life.

Consideration also needs to be given to the materials examined in the toxicity studies so that the product is consistent with the submitted safety data.

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

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

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

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

2.2.5.3 Residual Solvents

In addition to controlling residual solvents in the active ingredient, it is necessary to consider the total quantity of residual solvents that may be present in the finished product. This includes solvent residues that are present in the active ingredient and all inactive ingredients and solvent residues resulting from the manufacture of the finished product.

Depending on the quantities and types of solvent residues from each of these sources, it may be appropriate to include a test and limits for residual solvents in the finished product specifications.

2.2.5.4 Microbiological Requirements

Sterile Products

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

Non-Sterile Products

All non-sterile dosage forms should include limits for microbial content in the finished product batch release and stability specifications.

Microbial specifications for solid oral or dry powder products may not be necessary if their absence can be justified in the application by establishing during product development that the product is at a very low risk of contamination and microbial growth is not supported.

Products with significant water content (e.g. creams, gels and oral liquids) are likely to support microbial growth. Such products should include tests and limits for microbial content in both the batch release and expiry specifications.

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

If animal-derived proteins are used as raw materials or in the manufacturing process, there must be evidence of no risk of transmitting infectious viral agents (such as BSE) or effective viral inactivation or removal in the manufacturing process.

2.2.5.5 Tablets and Capsules

Dissolution may be an indicator for bioavailability and is considered an important part of quality control for solid oral dosage forms. *Refer to Dissolution Guideline.*

Modified release products must include dissolution testing in the finished product specification.

2.2.5.6 Analytical Procedures & Validation

Details should be provided of all analytical methods used in the specifications, together with validation data that demonstrate (among other things) accuracy, precision, specificity (e.g. freedom from interference by degradation products and other likely impurities), and linearity.

2.2.5.7 Justification of Finished Product Specifications

The suitability of the tests, limits and test methods proposed for the finished product should be discussed with reference to the results of the method validation studies and the ability of the specifications to guarantee the quality and consistency of the finished product.

A detailed commentary or justification for any unusual features in the finished product specifications should be included.

The limits applied at batch release should be discussed in terms of their ability to ensure that the product will remain within the expiry specification throughout its shelf life. For example, if the batch release and stability limits for assay are identical, the implication is that there will be no loss of the active ingredient throughout the shelf life. Any changes or unusual variability in the results obtained in the stability studies require comment.

The reasons for proposed ranges in the quantities of any ingredients should be discussed in the application.

2.2.6 Batch Certificates of Analysis

At least three certificates of analysis for the final product to demonstrate compliance with batch release specifications must be provided. These certificates should relate to one or more production batches of the medicine or to trial batches if production batches have not been manufactured. In such a case, the applicant should identify any differences between the trial process and the manufacturing process.

For imported products, each batch must be accompanied by a Certificate of Analysis and an identification and assay test must be performed locally before such a batch is released for sale in order to demonstrate that product integrity has not been prejudiced during transit, unless exemption from this requirement has specifically been granted by the Council. Nothing prohibits applicants from returning locally drawn samples to foreign suppliers for reanalysis to verify product integrity.

If the transport method is monitored and the transport complies with the storage conditions, then only a description and an identification test by the importer are required.

Exemption from these requirements hall be considered per product.

2.2.7 Container

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

2.2.8 Finished Product Stability *Refer to Stability Guideline*

All applications to register a complementary medicine must include stability data for the proposed finished product. The stability data must be sufficient to demonstrate, or indicate with a high probability, that the product intended for market will remain safe, of consistent quality and efficacious throughout the product's shelf life. The stability data will form the basis for setting a shelf life and recommended storage conditions for the product.

The following headings are recommended:

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

The maximum permitted shelf life is five years.

2.2.8.1 Homoeopathic medicines

(i) For D4 potencies upwards, with respect to products with single or multiple active ingredients, the shelf-life is consistent with the shelf-life of the vehicle substance containing the active potency.

(ii) Accelerated stability testing in the case of Homoeopathic Substances is not appropriate.

(iii) For mother tinctures and potencies up to and including the D3 or 3x potency (or equivalent potency), stability testing should be done by means of Thin Layer Chromatography on the Mother Tincture, or on the potencies, where this is applicable and possible. Standardised reference extracts and thin layer chromatograms can be used for comparison purposes.

2.2.8.2 Aromatherapy

The stability of aromatherapy products/substances and expiry dates may be related to the stability of the vehicles and/or excipients.

2.3 Amendments

For any amendments or changes, refer to the Amendments Guideline.

3 SAFETY AND EFFICACY – GENERAL PRINCIPLES

3.1 Well-documented Ingredients

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

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

- *Martindale: The Complete Drug Reference*, Sweetman SC (ed), Pharmaceutical Press, United Kingdom;
- *Handbook of Non-Prescription Drugs, American Society of Health System Pharmacists, United States;*
- *Remington's Pharmaceutical Sciences, Gennaro AR (ed), Mack Publishing Company, United States;*
- *Handbook of Pharmaceutical Excipients, Kibbe AH (ed), American Society of Health System Pharmacists, United States;*

Note that indications and dosage must be the same as described in these textbooks. Any use outside the documented indications and/or dosages, or any new route of administration, will require evidence of efficacy and safety, unless otherwise justified.

Note also that anecdotal or limited clinical reports of efficacy alone (e.g. in Martindale, "xxx has also been used in …") are not considered evidence of efficacy and safety.
Applications for products with well-documented ingredients should include details of the relevant texts (photocopies of the relevant pages are preferred) with particular references to the accepted indications and dosage of the active ingredients.

3.2 Other Points to Consider in Preparing an Application for Registration

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

3.2.1 Quality of Data

It is likely that many submissions to demonstrate efficacy and safety will be bibliographic, or literature based (i.e. they will consist solely of published papers). In these cases it is important that applicants are able to comment on the quality of the data submitted and place it in context to the body of data which exists.

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

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

The non-clinical and clinical overviews should include a critical appraisal of the quality of the data generated from each trial and the relevance of the results to the efficacy and safety of the product.

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

3.2.1 Quality of Data - continued

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

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

3.2.2 Searching the Literature on Complementary Medicines

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

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

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

For further information refer to the Australian Regulatory Guidelines for Complementary Medicines (ARGCM), Part I: Registration of Complementary Medicines

3.3 Benefits and Risks – Conclusion

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

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

3.4 Clinical Trials of Complementary Medicines

The relevant guidelines for clinical trials are available on the MCC website or from the office of the Registrar of Medicines

4 SAFETY

4.1 Criteria for determining the safety of indications and health claims

The indications and health claims will be classified into three risk levels, namely High, Medium and Low risk indications or claims, as shown in table 1.

Table 1 – Risk Level, type of claim and evidence required

Level of Claim	Type of Claim	Evidence required to support claim
HIGH	• Treats/cures/manages any disease/disorder. • Prevention of any disease or disorder. • Treatment of vitamin or mineral deficiency diseases.	Clinical data to be evaluated.
MEDIUM	• Health enhancement[1] • Reduction of risk of a disease/disorder. • Reduction in frequency of a discrete event. • Aids/assists in the management of a named symptom/disease/ disorder. • Relief of symptoms of a named disease or disorder[2]	Primary evidence: Two of the following three sources that demonstrate adequate support for the indications claimed: 1. Recognised Pharmacopoeia. 2. Recognised Monograph. 3. Three independent written histories of use in the classical or traditional medical literature[4,5,6]
LOW	• Health maintenance, including nutritional support. • Vitamin or mineral supplementation[3] • Relief of symptoms (not related to a disease or disorder)[2]	Primary evidence: One of the following three sources that demonstrates adequate support for the indications claimed: 1. Recognised Pharmacopoeia. 2. Recognised Monograph. 3. Three independent written histories of use in the classical or traditional medical literature. [4,5,6]

1 Health enhancement claims apply to enhancement of normal health. They do not relate to enhancement of health from a compromised state.

2 All claims relating to symptoms must be accompanied by the advice "If symptoms persist consult your healthcare practitioner".

3 Vitamin or mineral supplementation claims are only permitted where the recommended daily dose of the product provides at least 25 percent of the Recommended Dietary Intake (RDI) for that vitamin or mineral. Where vitamins or minerals are the subject of other kinds of claims, the dose must be consistent with the evidence to support the claim being made. Claims should not refer to the presence of vitamins or minerals unless they are present in the recommended daily dose of the product to at least the level of 10 % of the RDI, unless there is evidence to support a therapeutic effect below this level.

4 In cultures where an oral tradition is clearly documented, evidence of use from an oral tradition would be considered acceptable provided the history of use is authenticated. Modern texts that accurately report the classical or traditional literature may be used to support claims.

5 Terms used must be in accordance with the general practice of the specific discipline.

6 This evidence does not stand alone and may only be used in conjunction with primary evidence.

4.2 Documenting safety

4.2.1 The safety section should include the following:

- overview of safety;
- any studies that address specific safety issues;

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

Products for use in animals destined for human consumption must include full evidence of tissue residue data.

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

4.2.2 Overview of Safety

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

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

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

The following issues should be considered:

- adverse effects that are expected because of the mechanism of action;
- any likely adverse effects expected because of animal data or product quality information (manufacturing processes);
- the nature of the patient population and the extent of exposure;
- any limitations of the safety data derived from the clinical trials (e.g. inclusion/exclusion criteria, trial subject demographics);
- relationship of adverse events to dose, dose regimen and treatment duration;
- similarities and differences in results among studies, and their effect on the interpretation of the safety data;
- any differences in the rates of adverse events in population subgroups, such as those defined by demographic factors, gender, age, race, weight, concomitant illness or concomitant therapy;[3]
- long-term safety;
- any methods to prevent, mitigate or manage adverse events;
- overdose reactions, potential for dependence, rebound phenomena and abuse, or the lack of data on these aspects.

4.3 Post Marketing Data

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

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

[3] Because of greater awareness of the potential for interactions between concomitantly administered medicines, there has been an international focus on interaction studies rather than on *ad hoc* observational studies. Guidance on points to consider when assessing interaction studies is given in CPMP/EWP/560/95. Additional information is contained in the US FDA CDER Guidance – *Drug Metabolism/Drug Interaction Studies in the Drug Development Process: Studies In Vitro* (April 1997) – CLIN 3.

4.3 Post Marketing Data - continued

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

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

Furthermore, the applicant should collect, collate and maintain a record of all adverse reactions reported for the registered product and this should be available for inspection to the MCC in accordance with the ADR guideline (Reporting Adverse Drug Reactions in South Africa).

5 EFFICACY

5.1 Criteria

5.1.1 Herbal medicines

Generally acceptable evidence in support of efficacy include:

(i) Appropriately designed clinical trials.

(ii) Accepted Herbal monographs or pharmacopoeiae.

(iii) Monographs from any other source equivalent in standard to any of the above.

5.1.2 Traditional Chinese, Ayurvedic, Unani Tibb medicines

Generally acceptable evidence in support of efficacy of medicines and substances include:

(i) Recognized or approved *Pharmacopoeiae, Materia Medica* and other peer reviewed publications on Traditional Chinese, Ayurvedic and Unani Tibb medicines.

(ii) Appropriately designed human clinical trials and other human safety and efficacy studies conducted in recognized research centres.*

(iii) Appropriate research work from reputable research institutions and investigators.*

5.1.3 Homoeopathic Medicines

Acceptable criteria relating to the establishment of efficacy shall include:

(i) Drug symptom pictures according to accepted ***Materia Medica***

(ii) Accepted Homoeopathic Pharmacopoeiae

(iii) The German Commission D Monographs

(iv) Monographs from the Homeopathic Pharmacopoeia Committee of the United States and the French Pharmacotechny

(v) Appropriate clinical trials

(vi) Monographs from any other source equivalent in standard to any of the above.

5.1.4 Aromatherapy Preparations

Acceptable criteria relating to the establishment of efficacy include:

(i) References on the Aromatherapy Reference List

(ii) Monographs from any other source equivalent in standard to any of the References on the Aromatherapy List of References

5.2 Documenting efficacy

5.2.1 The efficacy section of the application should consist of the following:

- an overview and summaries; (Modules 2E / 2.5. 2.7)
- study reports and/or publications. (Module 5)

5.2.2 Overview of Efficacy

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

The overview should contain the following subsections:

- pharmacodynamics;
- pharmacokinetics;
- bioavailability
- clinical studies.

5.2.2.1 Pharmacodynamics

The pharmacodynamics section should include information on the mechanism of action, if known.

It should also include information to justify the proposed dose and dose interval, and any information that may be relevant to formulation differences in the submitted studies and to possible interactions with other medicinal products or substances.

5.2.2.2 Pharmacokinetics

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

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

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

5.2.2.3 Bioavailability *Refer also to Biostudies guideline*

Bioavailability describes the proportion of administered medicine reaching the systemic circulation; the formal definition is the rate at and extent to which the API, or its active moiety, is absorbed from a pharmaceutical product and becomes available at the site of action.

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

5.2.2.3 Bioavailability - continued

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

The main parameters measured in bioavailability studies are the maximal blood concentration (C_{max}) and the area under the blood medicine concentration-time curve (AUC) which reflects the total amount of medicine that reaches the systemic sampling site. The time to maximal blood concentration (T_{max}) and the half-life of the product (time for the C_{max} to fall to half the C_{max}) are also calculated.

Bioavailability is important because to exert a therapeutic effect the active ingredient of a medicine must be delivered to its site of action in an effective concentration for the required time period to initiate and maintain the action of the medicine.

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

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

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

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

Applicants planning to market a dosage form different from that described in the published papers presented in their submission may need to conduct a bioavailability study. It may be to prove that the active ingredient is delivered into the systemic circulation or to demonstrate bioequivalence to the formulation used in the published papers.

In order to conduct bioavailability studies, it is essential that the active ingredient of the medicine is known and that there is a method for testing the level of active ingredient in the systemic circulation.

The test method (assay) must be accurate, precise, selective for the active ingredient, sensitive (able to test to the level present in circulation) and reproducible.

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

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

5.2.2.4 Clinical Studies

The applicant should differentiate those studies considered pivotal to the submission from those considered to be supportive.

The following issues should be considered and discussed:

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

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

5.2.3 Study Reports and/or Publications

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

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

6 SCHEDULING

To follow as a separate document

7 UNACCEPTABLE PRESENTATION

The presentation of complementary medicines is unacceptable if it is capable of being misleading or confusing as to the content or proper use of the medicines.

In addition, the presentation of complementary medicines is unacceptable:

- if it states or suggests that the products have ingredients, components or characteristics that they do not have;
- if a name applied to the products is the same as the name applied to other products that are supplied in South Africa, where those other products contain additional or different therapeutically active ingredients;
- if the label of the products does not declare the presence of a therapeutically active ingredient or Nature Identical Essential Oils;
- if a form of presentation of the products may lead to unsafe use of the products or suggests a purpose that is not in accordance with conditions applicable to the supply of the products in South Africa;
- in certain prescribed cases; or
- if the format of the submissions does not comply with current MCC guidelines.

8 REFERENCES

Australian Regulatory Guidelines for Complementary Medicines (ARGCM), Part I: Registration of Complementary Medicines, Version 4.0, March 2011

9 GLOSSARY OF TERMS

This glossary is not exhaustive and does not include many terms that are 'technically' specific to only some areas of MCC; in particular, it does not interpret terms, which are used exclusively for, or in connection with the manufacture of prescription medicines or therapeutic devices.

Refer also to The Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended, for definitions.

This document includes terms used only in relation to medicines. It does not include terms related only to medical devices.

Act

The *Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended*

Active ingredient

The therapeutically active component in a medicine's final formulation that is responsible for its physiological action.

Active pharmaceutical ingredient (API)

Therapeutically active component in the final formulation of the medicine.

Active raw material

The unformulated active chemical substance, usually a powder or a liquid, in the form in which it is used to manufacture a dosage form, usually in combination with excipients.

Analysis

Includes examination and testing.

Animal

An invertebrate or vertebrate member of the animal kingdom.

Antibiotic

A selective antimicrobial agent, other than disinfectants, antiseptics and substances used solely as antineoplastics, that, on application to living tissue or by systemic administration, kills or prevents the growth of susceptible micro-organisms.

Applicant

Holder / Proposed holder of certificate of registration

Application

An application made to MCC under Act 101 of 1965.

Batch

A quantity of a product that is:

a. uniform in composition, method of manufacture and probability of chemical or microbial contamination; and
b. made in one cycle of manufacture and, in the case of a product that is sterilised or freeze dried, sterilised or freeze dried in one cycle.

Bioburden

The quantity and characteristics of micro-organisms present in the medicines or to which the medicines may be exposed in a manufacturing environment.

Biological products

Products in which the active ingredient is a biological substance including antisera, antivenins, monoclonal antibodies and products of recombinant technology.

Biological substance

Substances of biological origin, which are frequently chemically complex and have a molecular mass greater than 1 000, such as hormones, enzymes and related substances, but not including herbal substances and antibiotics. Biological substances are not uniquely defined by a chemical name because their purity, strength and composition cannot readily be determined by chemical analysis. Substances which can be isolated as a low molecular mass pure substance, such as purified steroids, digoxin and ergotamine, are considered to be chemical substances.

British Pharmacopoeia[1]

The edition of the book of that name, including any additions or amendments.

Clinical trial

A planned study in humans designed to investigate or report upon the effectiveness and / or safety of a medicines

Complementary medicine

A medicine that is used

(a) or intended to be used for, or manufactured or sold for use in assisting the innate healing power of a human being or animal; and

(b) in accordance with the practice of the professions regulated under the Allied Health Professions Act, 1982 (Act 63 of 1982)

Contract manufacture

Where all or part of the manufacturing process of the medicine is carried out on a contract basis by a person other than the applicant. Can include principal manufacturers and other (sub)manufacturers.

Counterfeit

Complementary medicines which contain false representations in the label or presentation of the products, any document or record relating to the products or their manufacture or in any advertisement for the products.

Dosage form

The pharmaceutical form in which a product is presented for therapeutic administration, e.g. tablet, cream.

Drug

See **Medicine**. Note that legislative definitions apply in both singular and plural forms.

Excipient

Any component of a finished dosage form other than an active ingredient (in some cases the distinction between an active ingredient and an excipient may not be clear cut, e.g. use of sodium chloride to adjust tonicity of an injection is an excipient). An inactive ingredient.

Expiry date

The date (expressed as the month and year) after which the medicines should not be used.

Finished product

The finished or final dosage form of the complementary medicines when all stages of manufacture, other than release for sale, have been completed.

Formulation

A list of the ingredients used in the manufacture of a dosage form and a statement of the quantity of each ingredient in a defined weight, volume, unit or batch.

Good manufacturing practice (GMP)

The acronym GMP is used internationally to describe a set of principles and procedures which, when followed by manufacturers of medicines, helps ensure that the products manufactured will have the required quality. A basic tenet of GMP is that quality cannot be tested into a batch of product but must be built into each batch of product during all stages of the manufacturing process.

Herbal substance

All or part of a plant or substance (other than a pure chemical or a substance of bacterial origin):

a. that is obtained only by drying, crushing, distilling, extracting, expressing, comminuting, mixing with an inert diluent substance or another herbal substance or mixing with water, ethanol, glycerol or aqueous ethanol
b. that is not subjected to any other treatment or process other than a treatment or process that is necessary for its presentation in a pharmaceutical form.

Homoeopathic preparation

A preparation:

a. formulated for use on homoeopathic principles, which may include being capable of producing in a healthy person symptoms similar to those which it is administered to alleviate, or those principles related to classical, clinical or combination homoeopathy; and

b. prepared according to the practices of homoeopathic pharmacy using the methods of

(i) serial dilution and succussion of a mother tincture in water, ethanol, aqueous ethanol or glycerol OR
(ii) serial trituration in lactose.

Indications

The specific therapeutic uses of complementary medicines.

Individual patient data

In relation to complementary medicines, individual patient data means information, derived from clinical trials, relating to individuals before, during and after the administration of the medicines to those individuals, including but not limited to, demographic, biochemical and haematological information.

Label

A display of printed information:

(a) on or attached to the complementary medicine **OR**

(b) on or attached to a container or primary pack in which the medicines are supplied OR

(c) supplied with such a container or pack.

Licence

A licence under Section 22C of the Act

Licence number

The number of the licence issued by the MCC to a manufacturer of complementary medicines for use in humans.

Manufacture

The production of medicines or any part of the process of producing medicines or bringing the medicines to their final state, including engaging in the processing, assembling, packaging, labelling, storage, sterilising, testing or releasing for supply of the medicines or of any component or ingredient of the medicines as part of that process.

Manufacturer

Corporation or person carrying out one or more of the steps specified in the definition of manufacture.

Manufacturing licence

A licence granted under Section 22 of the Act, relating to manufacturing of complementary medicines.

Medicine

'medicine' means any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in-

(a) the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in man; or
(b) restoring, correcting or modifying any somatic or psychic or organic function in man, and includes any veterinary medicine.

Medicinal product

An alternative term to medicine for the finished, packaged product.

Mother tincture

A product of the process of solution, extraction or trituration, from which homoeopathic preparations are made.

Nature identical oil

An oil which has had a component added, either natural or artificial, with a chemical structure identical to that found in nature

Oral

Taken through the mouth into the gastrointestinal system.

Pack size

The size of the product in terms of the quantity contained in the container (e.g. volume in a multi-use container) and / or the number of items in the primary / unit pack (e.g. number of tablets in a bottle).

Presentation

The way in which the complementary medicines are presented for supply, and includes matters relating to the name of the medicines, the labelling and packaging of the medicines, and any advertising or other informational material associated with the medicines.

Primary pack

The complete pack in which the complementary medicine, or the medicines and their container, are to be supplied to consumers.

Principal manufacturer

The manufacturer who manufactures the medicines or who performs one or more steps in the manufacture of the medicines and also contracts with, or controls the use of other manufacturers for the performance of the remaining steps in manufacture of the medicines.

Product

The commercial presentation or marketed entity of complementary medicine, *excluding pack size*. Where a therapeutic device, it excludes such fine details as size or gauge; and, where a kit / tray or pack containing one or more medicines, it is an individual medicine entity within the kit.

Proprietary name

The registered trademark of the complementary medicine or the unique name assigned to the medicines by the applicant and appearing on the label.

Quality

Includes the composition, strength, potency, stability, sterility, purity, bioburden, design, construction and performance characteristics of the medicine.

Regulations

Regulations to the Medicines and Related Substances Act, 1965 (Act 101 of 1965), as amended.

Route of administration

Route by which a complementary medicine is applied on or introduced into the body.

Sample

Includes part of a sample.

Scheduling

In relation to a substance, means determining the schedule or schedules in which the name or a description of the substance is to be included.

Step in manufacture

Any part of the process of bringing medicines to their final state and which may be completed separately from other parts of the process.

Strength

The quantity of an ingredient in a medicines or a formulated or medicated device expressed: for discrete units, as the nominal weight of the ingredient in the unit for other dosage forms, as the nominal weight or volume per unit weight or volume.

Supply

Includes supply by way of sale, exchange, gift, lease, loan, hire or hire purchase. It also includes whether free of charge or otherwise, samples or advertisements, supply for testing the safety or efficacy, and for treatment of person or animal.

Therapeutic use

Use in or in connection with:

a. preventing, diagnosing, curing or alleviating a disease, ailment, defect or injury in persons or animals; **OR**
b. influencing, inhibiting or modifying a physiological process in persons or animals; **OR**
c. testing the susceptibility of persons or animals to a disease or ailment; **OR**
d. influencing, controlling or preventing conception in persons; **OR**
e. testing for pregnancy in persons; **OR**
f. the replacement or modification of parts of the anatomy in persons or animals.

Topical

Applied to a certain area of the skin for a localised effect.

Traditional use

Use of a designated active ingredient that is well-documented, or otherwise established, according to the accumulated experience of many traditional healthcare practitioners over an extended period; and accords with well-established procedures of preparation, application and dosage.

10 ABBREVIATIONS AND ACRONYMS

ADR	Adverse Drug Reaction
AUC	area under the curve
BP	British Pharmacopoeia
CAS	Chemical Abstracts Service (Registry)
CHMP	Committee for Medicinal Products for Human Use (previously CPMP)
C_{max}	Maximal blood concentration
CPMP	Committee for Proprietary Medicinal Products (of the EMA)
CTD	Common Technical Document
EMA	European Medicines Agency (previously European Agency for the Evaluation of Medicinal Products)
EU	European Union
FDA	Food and Drug Administration (of the United States of America)
GLP	good laboratory practice
GMP	good manufacturing practice
HPCSA	Health Professions Council of South Africa
ICH	International Conference on Harmonisation (of Technical Requirements for Registration of Pharmaceuticals for Human Use)
IV	Intravenous
MCC	Medicines Control Council
nmt	not more than
pH	Negative logarithm of hydrogen-ion concentration
Ph Eur	European Pharmacopoeia (also known as EP)
PI	Package insert
TGA	Therapeutic Goods Administration
T_{max}	Time to maximal blood concentration
USP	United States Pharmacopoeia
USP-NF	United States Pharmacopoeia – The National Formulary
US FDA	Food and Drug Administration (of the United States of America)
WHO	World Health Organization

11 UPDATE HISTORY

Date	Reason for update	Version & publication
Aug 2011	First publication released for comment	v1 August 2011