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

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1 INTRODUCTION

Short overview

In general Complementary Medicines (CMs) are used and sold by many people in RSA. These guidelines accompany the regulations dealing with the registration and post-marketing control of these medicines. The guidelines give some direction with regard to the required information but should not in themselves be regarded as final. Where the applicant wishes to use and submit information not found in these guidelines these would have to be justified scientifically and technically.

The CMs that will be subject to these regulations are those associated with those disciplines regulated by the Allied Health Professions Council of South Africa (AHPCSA). These are commonly known as Homoeopathic medicines, Western Herbals, Traditional Chinese medicines, Ayurvedic medicines, Unani-Tibb and Aromatherapeutic medicines/oils. As per the Act, the term "practitioner" refers to a person registered as such under the Allied Health Professions Act, 1982 (Act No. 63 of 1982).

The administration and logistics of registration and regulation will be dealt with later in the form of further guidelines e.g. electronic registration possibilities and short and long applications arising from these latter processes.

All actions arising from the application and use of the guidelines are aimed at benefitting the stakeholders involved in their use for prevention and treatment of disease(s). These stakeholders include commercial concerns, users, practitioners and the regulators.

In general the categories (disciplines) of CMs are defined and can make high risk or low risk health claims. The CMs will be subject to compliance with Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP) and Good Dispensing Practice (GDP) as well as Good Regulatory Practice. In the process of complying with these practices the quality of the medicines is promoted and aimed at rendering them to be of acceptable quality, safety and efficacy.

It is thought that quality and safety is non-negotiable, whereas, depending upon the discipline, proof of absolute efficacy might prove challenging (for a variety of reasons). The approach of these guidelines is to enable the applicant to present, to the MCC, an application free of errors and easy to review. Each discipline will have its own set of requirements governed by its own references and pharmacopoeias which are all subject to and compliant with the current science and knowledge of that particular discipline.

The discussion which follows on Quality is dependent upon the Pharmaceutical and Analytical and related Guidelines of the MCC.

Where guidelines are referred to, the latest (current) version should be used.

A complementary medicine may fall in Schedules 0, 1, 2 or 3 or higher.

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, the need for specialised (professional) knowledge in its prescription 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 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 as outlined in the latest version of the MCC's "GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINES IN SOUTH AFRICA" and Good Laboratory Practice by 2016.

Also refer to WHO Guidelines on Good Agricultural and Collection Practices (GACP) for Medicinal Plants

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 latest version of the Common Technical Document (CTD) format as published by the MCC.

Data provided in applications for registration of new complementary medicines must 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 standards of good manufacturing practice (GMP), as required.

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**.**

The animal or plant should not be listed on the IUCN Red Data List, (http://www.iucnredlist.org/technical-documents/categories-and-criteria) or South African National Biodiversity Red List of South African Plants (http://redlist.sanbi.org/redcat.php), unless from a licensed cultivated, legal source and must adhere to the principles of the Convention on International Trade in Endangered Species of Wild Fauna and Flora (CITES) of which South Africa is a member.

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 as provided for in these guidelines.

1.4.1 Safety

Safety may be established by detailed reference to the published literature and/or the submission of original study data.

Any complementary medicine that is of animal origin must comply with the requirements of the Animal Diseases Act, 1984 (Act 35 of 1984).

1.4.2 Efficacy

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) as provided for in these guidelines. [Refer to Section 3, and Section 5 below.]

1.5 The Naming of complementary 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

For purposes of the registration procedure, herbal names are stated in the Latin binomial format, which should include the genus, species, subspecies, variety, subvariety, form, subform or chemotype and author where appropriate. Reference should be made to the internationally accepted name for the plant, fungus or alga by referring to the following databases where appropriate (in order of priority):

a) The Plant List (Available at: http://www.theplantlist.org)
b) The Index Fungorum (Available at: http://www.indexfungorum.org)
c) The International Plant Names Index (Available at: http://www.ipni.org)
d) OR other recognised major flora

Examples of correct herbal names include:

- *Olea europaea* subsp. *africana* (Mill.) P.S. Green
- *Crataegus curvisepala* Lindm.
- *Thymus zygis* subsp. *gracilis* (Boiss.) R.Morales ct. thymol

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

(iv) Herbal Substance

For purposes of labelling, a simple latin binomial or pharmacopoeial names of herbal ingredients that are fully characterised in a monograph of an accepted pharmacopoeia[1] may be used provided it is clear to the consumer exactly which herb is being 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] An earlier edition of another suitable pharmacopoeial reference may be used.

1.5.2 Nature identical oils are synthetic 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 or any therapeutic applications.

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

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.

1.6 Combination Products

A combination product means a single product that contains:

(a) a mixture of substances of various discipline specific origin or philosophy, or

(b) a mixture of at least one substance of discipline specific origin and other allowable substances which make no therapeutic claim.

In the case of combination products:

- applicants will need to demonstrate explicit, cogent philosophies of use amongst all ingredients or will be referred for Category A registration;
- the registration –sub-category will be "Combination Product" and the discipline(s) it relates to;
- where vitamins, minerals or other substances of food origin are included in a combination product (see definition) and where such items fall below prescribed maximum food levels and provided that no medicinal claim is made, CM registration will be permitted, and
- where classified foods further purport to make medical claims or are above prescribed maximum food levels, these products will be referred for Category A registration.

1.7 Accepted References

The following references (in addition to any further specified accepted references **[ANNEXURE A]** for each discipline) should be consulted for purposes of motivating that the product or substances used originate from the discipline indicated.

1.7.1 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 or any of the following:

- Australian Therapeutic Goods Authority List of Substances
- German Commission C Monograph[2]
- German Commission E Monograph
- WHO Monographs on Selected Medicinal Plants
- ESCOP Monographs
- EMEA Community Herbal Monographs
- British Herbal Pharmacopoeia
- Formal Herbal Materia Medicae, or
- Other national or international herbal monographs, pharmacopoeias or materiae medicae

[2] In most cases medicinal products used within the anthroposophic medical tradition cannot be distinguished on the basis of their methods of production, as these are largely shared with other medicinal product groups such as homeopathic and herbal medicinal products. In case of overlap, anthroposophic medicinal products are legally qualified as either homeopathic or traditional herbal medicinal based on their presentation in the product.

1.7.2 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 specified references or any of the following:
- the Traditional Chinese pharmacopoeia

(ii) An Ayurvedic medicine or substance must be described as an Ayurvedic medicine or substance in at least one of the following references
- 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 pharmacopoeia or one of the specified references.

1.7.3 Homoeopathy

The substance must be described as a homoeopathic substance in at least one of the specified Materia Medica, vade medicae, repertories or Homoeopathic Pharmacopoeiae or in any of the following:
- Australian Therapeutic Goods Authority List of Substances
- German Commission C Monograph
- German Commission D Monograph

1.7.4 Aromatherapy

The substance must be described as an aromatherapy substance in at least one of the specified references on the Aromatherapy Substances Reference List or listed in the “Accepted Aromatherapy Substance List”.

1.8 Types of Substances and Preparations

The following definitions provide for what types of substances will constitute each category listed.

1.8.1 **Herbal substance / preparation** means all or part of a plant, fungus, alga, seaweed or lichen, or other substance (other than a pure chemical or isolated constituent or a substance of mineral, animal or bacterial origin):

a) that is obtained only by drying, crushing, distilling, freezing, lyophilisation, extracting, expressing, comminuting, mixing with an inert diluent substance or another herbal substance or mixing with water, ethanol, glycerol, oil or aqueous ethanol; or other permitted solvents; with or without the addition of heat.

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, and

c) where part of a plant, fungus, seaweed or lichen refers to a structure such as a root, root bark, rhizome, mycelium, fruiting body, bulb, corm, tuber, stem, inner or outer bark, wood, meristematic tissue, shoot, bud, thallus, resin, oleoresin, gum, natural exudate or secretion, gall, leaf, frond, flower (or its parts), inflorescence, pollen, fruit, seed, cone, spores or other whole plant part.

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

1.8.3 **Homoeopathic substances** may be of plant, fungal, animal, mineral or other origin prepared in accordance with homoeopathic principles and may include starting substances as well as allersodes, isodes, sarcodes, nosodes, allergens, and allopathic substances all used in potentised form at acceptable potencies for use as a homoeopathic medicine.

1.8.4 **Homoeopathic preparations are**

a) formulated for use based 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; or

b) prepared or purported to be prepared according to the practices of homoeopathic pharmacy including starting substances using the methods described in a recognised pharmacopoeia which may include

(i) serial dilution and succussion of a mother tincture in water, ethanol, aqueous ethanol or glycerol; OR

(ii) serial trituration in lactose.

1.8.5 **Aromatherapy substances** are essential oils, hydrolate or other aromatic extract of plant origin where reference must be made to the part of the plant(s) or the whole plant and method used to extract the essential oils.

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 (chemical and/or morphological where possible) 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 MCC recognised pharmacopoeia (USP, BP, Ph. Eur.), a separate compositional guideline is usually not required.

This section is divided into two subsections:

2.1 Active Ingredient

2.2 Finished Product

Some complementary medicines are comprised of relatively simple ingredients (e.g. *single herb,* mineral salts) 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).*

2.1 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 information provided in the application 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 necessary information in addition to that included in the monograph/ standard description should be supplied.

Nomenclature

Provide the name of the substance. Refer to Section 1.5

Structure

Where possible 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.

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.

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

2.1.2 Compositional Information - continued

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, authoritative references, or in-house data that can be independently validated.

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.

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.

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.

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, explained, discussed and justified.

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 well-motivated 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, fungi, seaweed, algae or lichens will generally be identified according to a suitable morphological and histological description system (such as the Angiosperm Phylogeny Group III system [APGIII] system) where acceptable reference specimens are used and must be named according to the internationally accepted standard [see 1.5.1 (iii)]. The parts of the plant that are used or the whole plant must be specified.

(b) Where the plant or other material is examined for the first time in a powdered or crude form, it must be subjected to at least macroscopic and microscopic examination. A detailed description of any organoleptic properties used to assist in the confirmation of 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 be identified according to a suitable plant description and identification system (such as the Angiosperm Phylogeny Group III system [APGIII] 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 manufactured according to approved pharmacopoeiae. They must 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 be 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 must be used. Where plants are compared, reference to authenticated 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 applicant. An acceptable starting point may be to use monographs for similar substances as a model and adapt them to the substance in question.

2.1.3.1 Limits and Tests - continued

E Substances that are 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.

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.

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 in detail 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.

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, updated and maintained 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 sale 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, well-motivated 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 detailed 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 must be addressed.

2.1.7 Stability *Refer also to the Stability guideline*

Stability data must be provided for complementary medicine active ingredients to assist in identifying any particular degradants that may be formed and that must 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. Accelerated stability testing in the case of Homoeopathic Substances is not appropriate in situations where the active substance(s) cannot be (accurately) identified in dilutions generally greater than 4D).

(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.

2.1.7.2 Aromatherapy substances

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 (API)

Active ingredients in complementary medicines are those substances that have a therapeutic role in the formulation. The "therapeutic role" may be to mitigate, modify, alleviate, or prevent illnesses, or the symptoms thereof or abnormal physical or mental state 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.

No added substances should be included in the formulation as active ingredients that do not make a direct and proven contribution to the proposed indication(s) for the medicine.

2.2.1.2 Inactive Ingredients (IPI)

Inactive ingredients are substances used to aid in 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 as such.

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.

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 fully described 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 as defined in 2.2.5

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 with reference to the maximum allowed overage limit.

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 sufficient justification.

2.2.2 Product Development

Information on the development of and rationale for the finished product should be provided, including reference to and 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 and justification 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 described 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 accepted 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 accepted 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 limits stated for a specific Schedule.

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 stipulated by the MCC for a particular product, limits on impurities in finished products apply to impurities from all sources except water.

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.

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 then 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 and acceptability of the tests, limits and test methods proposed for the finished product should be justified 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.

2.2.5.7 Justification of Finished Product Specifications - continued

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

The limits applied at batch release should be justified 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 adequate explanation.

The reasons for proposed ranges in the quantities of any ingredients should be appropriately outlined and justified 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 and made available on request. 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.The batch certificate for the trial batch, as well as the first production batch (if available) must be submitted. 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 appropriately 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 may be considered per product

2.2.7 Container *(Refer to Pharmaceutical & Analytical Guideline)*

A description of the container and closure system should be provided, including the materials used. The suitability of the container should be justified in terms of its compatibility with the product and its ability to protect 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 but may not exceed 5 years for finished products.

(ii) Stability tests must be performed in accordance with the Stability Guidelines. Accelerated stability testing in the case of Homoeopathic Substances is not appropriate in situations where the active substance(s) cannot be (accurately) identified in dilutions generally greater than 4D).

(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 for retesting 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 but may not exceed 5 years for finished products.

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 is well described in standard sources it is possible to use these descriptions 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;*

Other sources should primarily include evidence-based references, such as the Natural Medicines Comprehensive Database, and the Natural Standard Databases.

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

Note also that anecdotal or limited clinical reports/mentions 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 or scans of the relevant pages are preferred) with particular references to the accepted indications, dosage and routes of administration of the active ingredients.

Refer to excipients that are generally regarded as safe (GRAS)

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.

Where more than one active ingredient is included in the product, the rationale for the inclusion of each active ingredient must be stated and justified. The inclusion of each active ingredient and the intended use of the product as a whole should be justified in terms of each ingredient's and the product as a whole's efficacy and safety.

For adverse events, the overview should provide, in humans, 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.

Where available an evidence-based approach using predetermined levels of evidence (e.g. systematic review and meta-analysis; randomised controlled trial; expert opinion) combined with a grading of the quality of the evidence should be developed.

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 peer-reviewed literature provided has been methodically investigated;
- the range of sources selected for submission is justified, and
- issues and concerns raised in the literature in relation to the product have been addressed.

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

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 differential 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 benefits, the risk from taking the medicine and the risks of untreated (and undiagnosed) diseases.

3.3 Benefits and Risks– Conclusion - continued

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 profile is also affected by the availability of accepted (proven) treatments, the risk profile of those accepted therapies, and the risks of foregoing treatment where such a medically acceptable option is available.

A benefits risk profile should be determined for every complementary medicine – even for so-called "minor" conditions.

3.4 Clinical Trials of Complementary Medicines

Where clinical trials are referenced, proposed or used, the relevant guidelines for clinical trials should be consulted and 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 two risk levels, namely High and Low risk indications or claims, as shown in Table 1.

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

Risk Level	Type of Claim	Evidence required to support claim
HIGH RISK	• Treats/cures/manages any disease/disorder. • Prevention of any disease or disorder. • Reduction of risk of a disease/disorder. • Aids/assists in the management of a named symptom/disease/ disorder. • Relief of symptoms of a named disease or disorder[2] • Treatment of proven vitamin or mineral deficiency diseases.	• Clinical data to be evaluated[3]. AND • Two of the following four sources that demonstrates adequate support for the indications claimed: 1. Recognised Pharmacopoeia[4]; 2. Recognised Monograph[4]; 3. Three independent written histories of use in the classical or traditional medical literature, or 4. Citations from other *in vivo, in vitro* studies, case reports or others.
LOW RISK	• General health enhancement without any reference to specific diseases or conditions [1] • Health maintenance, including nutritional support. • Relief of minor symptoms (not related to a disease or disorder)[2]	• Clinical data to be evaluated AND/OR: • Two of the following four sources that demonstrates adequate support for the indications claimed: 1. Recognised Pharmacopoeia[4]; 2. Recognised Monograph[4]; 3. Three independent written histories of use in the classical or traditional medical literature. [5,6], or 4. Citations from other *in vivo, in vitro* studies, case reports or others.

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 *Refer to section 5.1 i) – vi)*

4 *Refer to section 5.1 vii) – ix) and Annexure A*

5 *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 or confirm the classical or traditional literature may be used to support claims. Traditional claims should refer to corresponding traditional descriptions of the condition(s).*

6 *Terms used must be in accordance with the practice of the associated discipline registered with the AHPCSA.*

4.2 Documenting safety

4.2.1 The safety section should include the following:

- overview of safety;
- any studies that address specific safety issues;
- reports (where possible) of adverse effects reported to the National Adverse Drug Event Monitoring Centre

- reports of adverse effects from accepted international sources
- any studies not submitted in the efficacy section that have been referred to in the overview;
- post-marketing data.

Full evidence of tissue residue data of products which have been used in animals destined for human consumption must be included.

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 may be motivated using relevant *in vitro*, *in vivo* evidence or clinical studies. The data should be outlined in a detailed, clear and objective manner. Tabulations of adverse events are often helpful.

There should be a description of common and expected adverse events (both serious and non-serious). An accepted causality assignment determination protocol to show the relationship between the product and an event, or lack of relationship, should be provided.

The following issues should be considered:

- the use of the term "natural" should not be used to infer safety;
- all known interactions should be considered and detailed in the application process;
- adverse effects that are expected because of the mechanism of action;
- any likely adverse effects anticipated from 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); an outline of safety data collection in efficacy trials, with appropriate definitions of adverse events, serious adverse events, etc;
- 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
- evidence of lack of efficacy.[4]

[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

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 and thereafter should be highlighted and any regulatory action relating to safety taken by an overseas regulatory agency should be detailed.

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. This usually requires special "pharmacovigilance" techniques such as prescription event monitoring.

The data should be presented as a tabulation of the adverse events that have been reported, including any serious adverse events using the definition of SAE's in the MCC's ADR guideline and any potentially serious interactions with other medicines.

Furthermore, the applicant should collect, collate and maintain a record of all adverse reactions after they have been 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

The criteria to be considered in the evaluation of efficacy for all complementary medicines may include established traditional use, pre-clinical data and evidence from clinical trials in animals and human beings as well as those references specified below appropriate for the risk level of associated claim.

Generally acceptable evidence in support of efficacy include:

(i) Appropriately designed clinical trials using the product for which an application is being made.

(ii) Appropriately designed qualitative and observational studies preferably using South African-validated instruments/methods.

(iii) Published systematic reviews such as in the Cochrane database.

(iv) Published clinical trials

(v) Published case reports

(vi) Evidence-based databases (e.g. Natural Medicines Comprehensive Database, Natural Standards Database)

(vii) Accepted Herbal monographs or pharmacopoeiae.

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

(ix) In the case of homoeopathic medicines, justification of the use of the medicines from the relevant ***Materia Medica*** or ***Repertory*** listing

5.2 Documenting efficacy

The efficacy must be documented from studies in humans for human complementary medicines and in the relevant animal species for animal/veterinary complementary medicines relevant to high risk level claims.

[4] "adverse drug reaction" means a response in human or animal to a medicine which is harmful and unintended and which occurs at any dosage and can also result from lack of efficacy of a medicine, off-label use of a medicine, overdose, misuse or abuse of a medicine; [Regulation 1 "Definitions" in the Regulations of the Medicines Act.

5.2.1 Information to include

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 Study Reports and/or Publications

If a clinical trial has been conducted by the applicant of the product then a study report should be provided. The study report should be written to comply with prescribed guidelines. As stated in the guideline, the structure and format required is intended to assist applicants 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 applicant's study has been published, the published paper should also be included. It is important that the applicant ensures that the data in the study report and the publication are consistent. Any differences should be explained in detail.

Evidence of non-interference by the applicant and the independence of the researchers must be given. If in-house studies are done this must be explicit and all steps taken to reduce bias disclosed.

6 SCHEDULING

To follow as a separate document

7 UNACCEPTABLE PRESENTATION

The presentation (including package inserts, patient information leaflets, labelling and packaging) of complementary medicines is unacceptable if it is capable of being misleading or confusing as to the content or proper use of the medicines. Particular care must be taken in South Africa to ensure that any translation of languages is not only accurate, but idiomatically sound so that incorrect messages are not conveyed.

In addition, the presentation of complementary medicines is unacceptable:

- if the words "natural" and "gentle" are used to imply safety
- 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 already supplied in South Africa, where those other products contain additional or different therapeutically active ingredients (refer to the current MCC Naming Guideline);
- if the label of the products does not declare the presence of a therapeutically active ingredient;
- 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 sale of the products in South Africa, or could be confused with an existing registered or unregistered "brand";
- in certain prescribed cases; or
- if the format of the submissions does not comply with current MCC guidelines. In such a case, the submission may be returned to the applicant and any fee forfeited.

8 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. See also Regulations for Medical Devices.

This glossary provides clarity on not only the use of terms in this document but specific use of related terminology that may be relevant to the registration process or CMs in general.

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 or pharmacological action which may include a whole substance such as a single herb.

Active pharmaceutical ingredient (API)

Therapeutically active component in the final formulation of the medicine, or

A substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active ingredient.

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 deconstruction and interpretation of data, examination and testing.

Animal

An invertebrate or vertebrate member of the animal kingdom.

Applicant

Holder / Proposed holder of certificate of registration

Application

An application for registration of a medicine made to MCC in terms of the provisions of Act 101 of 1965.

Aromatherapy substance

Essential oils, hydrolate or other aromatic extract of plant origin where reference must be made to the part of the plant(s) or the whole plant and method used to extract the substance.

Batch

"batch" or "lot" in relation to a medicine means a defined quantity of a medicine manufactured in a single manufacturing cycle and which has homogeneous properties;
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 substances or to which the medicines or substances 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

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

Clinical trial

“clinical trial" means an investigation in respect of a medicine for use in humans that involves human subjects and that is intended to discover or verify the clinical, pharmacological or pharmacodynamic effects of the medicine, identify any adverse events, study the absorption, distribution, metabolism and excretion of the medicine or ascertain its safety or efficacy;

Combination product

means a single product that contains:

a) a mixture of substances of various discipline specific origin or philosophy, or
b) a mixture of at least one substance of discipline specific origin and other allowable substances which make no therapeutic claim.

Complementary medicine

means any substance or mixture of substances which

a) originates from plants, minerals or animals;
b) is used or intended to be used for, or manufactured or sold for use in assisting the innate healing power of a human being or animal to mitigate, modify, alleviate, or prevent illnesses, or the symptoms thereof or abnormal physical or mental state, and
c) in accordance with the practice of the professions regulated under the Allied Health Professions Act, 1982 (Act No 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 GMP licenced person other than the applicant. Can include principal manufacturers and other (sub) manufacturers.

Counterfeit medicine

A medicine in respect of which a false representation has been made with regard to its contents, identity or source by any means including its labelling and packaging.

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.

Essential Oil

Concentrated, unadulterated, unaltered, pure, volatile aromatic extract from a plant.

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)

Good Manufacturing Practice is that part of Quality Assurance which ensures that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the medicine registration or product specification and is concerned with both production and quality control.

Herbal substance / preparation

means all or part of a plant, fungus, alga, seaweed or lichen, or other substance (other than a pure chemical or isolated constituent or a substance of mineral, animal or bacterial origin):

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

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, provided that none of the therapeutic capacity or characteristics of such a herbal substance are in any way changed by such a treatment or process, and

c) where part of a plant, fungus, seaweed or lichen refers to a structure such as a root, root bark, rhizome, mycelium, fruiting body, bulb, corm, tuber, stem, inner or outer bark, wood, meristematic tissue, shoot, bud, thallus, resin, oleoresin, gum, natural exudate or secretion, gall, leaf, frond, flower (or its parts), inflorescence, pollen, fruit, seed, cone, spores or other whole plant part.

Homoeopathic substances

May be of plant, fungal, animal mineral or other origin prepared in accordance with homoeopathic principles and may include starting substances as well as allersodes, isodes, sarcodes, nosodes, allergens, and allopathic substances all used in potentised form at acceptable potencies for use as a homoeopathic medicine.

Homoeopathic preparations

are:

a) formulated for use based 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; or

b) prepared or purported to be prepared according to the practices of homoeopathic pharmacy including starting substances using the methods described in a recognised pharmacopoeia which may include

   (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 medicines.

Individual patient data

In relation to complementary medicines, individual patient data means information, derived from clinical trials or observational data recorded during clinical practice, 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 **AND**

in accordance with Regulation 8 of the Regulations to the Medicines Act.

Licence

A licence under Section 22C of the Act

Manufacture

All operations including purchasing of material, processing, production, packaging, releasing, storage and shipment of medicines and related substances in accordance with quality assurance and related controls;

Manufacturer

A person manufacturing a medicine and includes a manufacturing pharmacy.

Manufacturing licence

A licence granted under Section 22C 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 sale, 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.

Practitioner

"practitioner" means a person registered as such under the Allied Health Professions Act, 1982 (Act No. 63 of 1982) (as per the Medicines and Related Substance Act, 1965 (Act 101 of 1965)

Primary pack

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

Product

The commercial presentation or marketed entity of complementary medicine, *excluding pack size*.

Proprietary name

"proprietary name", "brand name" or "trade name" means the name which is unigue to a particular medicine and by which the medicine is generally identified and which in the case of a registered medicine is the name approved in terms of section 15(5) of the Act.

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.

Scheduling

In relation to a substance, means the schedule or schedules in which the name or a description of the substance is already or is to be included in the list of scheduled substances made in terms of Section 22A(2) of the Medicines Act.

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.

Sell

'sell' means sell by wholesale or retail and includes import, offer, advertise, keep, expose, transmit, consign, convey or deliver for sale or authorize, direct or allow a sale or prepare or possess for purposes of sale, and barter or exchange or supply or dispose of to any person whether for a consideration or otherwise; and 'sale' and 'sold' have corresponding meanings;

Strength

The quantity or quantities of an ingredient or ingredients in a medicine or a formulation 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.

Therapeutic use / Therapeutic role

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) 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 reliably established, according to the accepted philosophy or accumulated experience of a particular discipline that may be verified in any of the listed accepted references which may apply to each discipline and accords with well-established traditional procedures of preparation, application and dosage. New combinations of active ingredients previously used separately or in different combinations, must be suitably justified according to the philosophy / principles of the associated discipline.

9 ABBREVIATIONS AND ACRONYMS

ADR	Adverse Drug Reaction
AHPCSA	Allied Health Professions Council of South Africa
BP	British Pharmacopoeia
CAS	Chemical Abstracts Service (Registry)
CM(s)	Complementary Medicine(s)
CPMP	Committee for Proprietary Medicinal Products (of the EMA)
CTD	Common Technical Document
EU	European Union
FDA	Food and Drug Administration (of the United States of America)
GLP	good laboratory practice
GMP	good manufacturing practice
GRAS	General Regarded As Safe
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
pH	Negative logarithm of hydrogen-ion concentration
Ph Eur	European Pharmacopoeia (also known as EP)
PI	Package insert
SAE	Serious Adverse Event
TGA	Therapeutic Goods Administration
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

10 UPDATE HISTORY

Date	**Reason for update**	**Version & publication**
Aug 2011	First publication released for comment	v1 August 2011
Oct 2011	Deadline for comment extended	v1_1 August 2011
Nov 2013	Publication for implementation	v1_5 Nov 2013

ANNEXURE A

SPECIFIED ACCEPTED REFERENCE LISTS

Below appear the list of acceptable and authoritative texts for each discipline which could be consulted in addition to those standard references stipulated in the MCC Guideline entitled, "COMPLEMENTARY MEDICINES - QUALITY, SAFETY, and EFFICACY" to which this annexure relates. Such reference would be to provide substantiation or confirmation of the categorisation of a particular substance under a particular discipline. This list shall be amended from time to time and is inclusive of any later / English edition of the stipulated text.

Herbal Medicine

Bradley, P.(ed.) (2006). British Herbal Compendium, Vol's 1 & 2. British Herbal Medicines Association: Bournemouth. ISBN 0-903032-12-0

Brendler, T., Eloff, J., Gurib-Fakim, A. & Phillips, A.(eds.) (2010). African Herbal Pharmacopoeia. Association for African Medicinal Plants Standards. ISBN-10: 9990389098

BHMA (2003). A Guide to Traditional Herbal Medicines. British Herbal Medicines Association: Bournemouth. ISBN 0-903032-11-2.

Tobyn, G., Denham, A. & Whitelegg, M. (2011). The Western Herbal Tradition: 2000 years of medicinal plant knowledge. Churchill Livingstone: Edinburgh. ISBN 978-0-443-10344-5 or authors or references referred to therein

Traditional Chinese Medicine

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

Ayurveda

Savnur, H.V. (1988) *Ayurvedic Materia Medica.* Reprint edition. New Delhi: Sri Satguru Publications

Nadkarni, K.M. (1976) *Indian Materia Medica*, Volume1 and 2. Reprint of third revised and enlarged edition. New Delhi : Popular Prakashan Pvt. Ltd.

Sharma, P.V (1994) *Caraka-Samhita.* Volumes 1, 2, 3 and 4. First Edition. New Delhi : Chaukhambha Orientalia

Bhishagratna, K.L. (1991) *Sushruta Samhita* .Volumes 1, 2 and 3. 4th Edition. Varanasi: Chowkhamba Sanskrit Series office

India, Department of Indian Systems of Medicine and Homeopathy. (2001) *The Ayurvedic Pharmacopoeia of India*, Part 1, Volume 1. First Edition. New Delhi: The Controller of Publications Civil Lines.

India, Department of Indian Systems of Medicine and Homeopathy. (1999) *The Ayurvedic Pharmacopoeia of India*, Part 1, Volume 2. First Edition. New Delhi: The Controller of Publications Civil Lines.

India, Department of Indian Systems of Medicine and Homeopathy. (2000) *The Ayurvedic Formulary of India*, Parts 1 and 2. First Edition. New Delhi: The Controller of Publications Civil Lines.

Unani Tibb

AYUSH, National formulary of Unani Medicine (Part 1-6), Ministry of Health and Family Welfare, Govt of India.

AYUSH, The Unani Pharmacopoeia of India (Part 1..Volume 1-6), Ministry of Health and Family Welfare, Govt of India.

AYUSH, The Unani Pharmacopoeia of India (Part 2..Volume 1-2), Ministry of Health and Family Welfare, Govt of India.

Brown, D, (1995) Encyclopaedia of Herbs, "The Royal Horticultural Society Dorling Kindersley, UK & USA

Chughtai, G.M., Bayaz-e-Feerozi, Hakeem Lahore, Pakistan.

CSIR, The Wealth of India, Raw Materials, New Delhi, India.

Culbreth, D.M.R. (1927) - "A Manual of Materia Medica and Pharmacology", USA.

Gujrati, K.B. Hakim, Miftahul-Khazain, Pakistan.

Ibn Sina, A. A., "Al-Qanoon-fil-Tibb" (Philosophy of Tibb), India.

Khan, O. G, "Indusyunic Medicine", Pakistan.

Khan, N.M. Hakim, Khazain-al-Adviyah (Khazainat-ul-Adviyah), Shaikh Mohammad Bashir and sons, Lahore, Paksitan

Khan, M.N.G. Hakim, Qarabadeen Najmul Ghani, Pakistan.Khare, C.P., Indian Medicinal Plants - An Illustrated dictionary, India.

Said, M. Hakim, Hamdard Pharmacopea, Hamdard Foundation, Pakistan.

Said, M. Hakim, (1996) - "Medicinal Herbal", Hamdard, Pakistan

Nadkarni, K. M., Nadkarn, A.K. (1976), "Indian Materia Medica", Bombay India.

Van Wyk B. E., (1997) - "Medicinal Plants of South Africa", South Africa

Wagman, R. J.(1997) - "The New Complete Medical and Health Encyclopedia", USA.

Homoeopathy

Allen, H.C. (1910). The Materia Medica of the Nosodes. India: Boericke et Tafel.

Allen, T.F. (1877). The Encyclopedia of Pure Materia Medica. A record of the positive effects of drugs upon the healthy human organism. New Delhi (India): Jain Publishers.

Allen T.F. (1974). Encyclopedia of Pure Materia Medica. (10 vol). Edit. New York, (NY): Boericke et Tafel.

Boericke, W. (1899). The Twelve tissue remedies of Schussler. Boericke & Tafel [OR REFERENCE OF EQUIVALENT VALUE REGARDING TISSUE SALTS]

Boericke, W. (1985). Pocket Manual of Homeopathic Materia Medica with Repertory (9th Ed.): New Delhi (India): Jain Publishers Pvt. Ltd.

Boericke, W. (1996). Materia Medica with Repertory. New Delhi (India): Pratap Medical Publishers PVT Ltd.

Bradford, L. (1901) Th. Index to Homeopathic Provings. India: Boericke et Tafel.

Clarke, J.H. (1902). A Dictionary of Practical Materia Medica. (3 vol.). London (U.K.): The Homeopathic Publishing Co.; 1902.

Clarke, J.H. (1925). Dictionary of Practical Materia Medica. New Delhi (India): The Homeopathic Publishing Company; 1925.

Coulamy A., Jousset C. (2000) Basses dilutions et drainage en homéopathie. Paris (France): Similia.

Ecalle H., Delpech L., Peuvrier A. (1898). Pharmacopée Homoeopathique française. Paris (France): Librairie J.B. Baillière et Fil.

European Pharmacopoeia. (Ph. Eur.) Strasbourg (France), European Directorate for the Quality of Medicines and Healthcare (EDQM)

Fare, Ch. (1993). Éléments de matière médicale homéopathique vétérinaire. France: CEDH.

Farrington, E.A. (1887). A Clinical Materia Medica. Philadelphia (PA): Sherman & Co..

German Commission D. Keller K., Greiner S., Stockebrand P. Homöopathische Arzneimittel - Materialien zur Bewertung (Commission D). Francfort (Allemagne): Govi Verlag, Band I, II, III.

Ghose, S.C. (1970). Drugs of Hindoosthan. Calcutta (India): Hahnemann Publishing Co. Private Ltd..

Hering, C. (1974). The Guiding Symptoms of our Materia Medica. New Delhi (India): Jain Publishers.

Homoepathic Pharmacopoeia of India. (1971). India: Government of India, Ministry of Health.

Homöopathisches Arzneibuch 2000 (German Homeopathic Pharmacopoeia). (2003). Stuttgart (Germany): medpharm GmbH Scientific Publishers.

Jouanny, J. (1984). The Essentials of Homeopathic Materia Medica. France: Boiron.

Julian, O.A. (1962). Biothérapiques et Nosodes. Paris (France): Librairie Maloine S.A.

Kent, J.T. (1996). Repertory of Homeopathic Materia Medica. Delhi (India): B. Jain Publishers (P) Ltd.

Murphy, R. (2000). Homeopathic Remedy Guide (2nd edition). Blacksburg (Virginia): H.A.N.A. Press.

Nash, E.B. (1913). Leaders in Homeopathic Therapeutics: with Grouping and Classification, Philadelphia, Boericke & Tafel, 1899(1st Ed), 1900 (2nd Ed), 1907 (3rd Ed), 1913(4th Ed)

Schroyens, F. (2001). Synthesis - Repertorium Homeopathicum Syntheticum (edition 8.1). London (United Kingdom): Homeopathic Book Publishers.

Schwabe W. (1933). Pharmacopoea homeopathica Polyglotta. Leipzig (Germany): Edition française Willmar Schwabe.

The Homeopathic Pharmacopeia of United States (HPUS). (2004). United States: published by the Pharmacopeia Convention of the American Institute of Homeopathy: Boston (U.S.A).

Vermeulen, F. (1994). Concordant Materia medica. Haarlem (The Netherlands): Ary Bakker.

Vermeulen, F. (2005). *Monera: Kingdom Bacteria & Viruses*. Spectrum Materia Medica Vol.1. Emryss Publishers:Haarlem. ISBN 90-76189-15-3

Vermeulen, F. (2007). *Fungi: Kingdom Fungi*. Spectrum Materia Medica Vol.2. Emryss Publishers:Haarlem. ISBN 978-90-76189-20-8

Vermeulen, F. & Johnston, L. (2011). Plants: Homeopathic and Medicinal Uses from a Botanical Family Perspective. Saltire Books: Busby. ISBN 9780955906596

Wyrth Post Baker. (1974). Compendium of Homeotherapeutics. Leesburg Pike, Falls Church (VA): American Academy of Homeotherapeutics.

Zandvoort, R.V. (1998). The complete repertory mind including Boger's Boenninghausen repertory additions (3rd revised edition). IRHIS.

Aromatherapy

Lists and Manuals:

South African list of essential oils as per attached

Australian Therapeutic Goods Authority List of Substances

Integrated Aromatic Medicines [Proceedings from International Symposia – 1998 onwards]

International Journal of Aromatherapy – all volumes

Sylla *Sheppard-Hanger*, 1995. *The Aromatherapy Practitioner Reference Manual*.

Reference Books:

Salvatore Battaglia, 1962. *The Complete Guide to Aromatherapy*. Edition. Perfect Potion. ISBN 0 6464 2896 9

Shirley Price Cert Ed FISPA MIFA FIAM, 1999. *Aromatherapy for Health Professionals, 2e*. 2 Edition. Churchill Livingstone. ISBN 0 443 06210 2

Robert Tisserand, 1995. *Essential Oil Safety: A Guide for Health Care Professionals, 1e*. 1 Edition. Churchill Livingstone. ISBN 0 443 05260 3

Len Price, 2000. *Carrier Oils: For Aromatherapy and Massage*. 4th Edition. Riverhead. ISBN 1 874353 02 6

Robin Higgins, 1993. *Approaches to Case-Study: A Handbook for Those Entering the Therapeutic Field*. 1 Edition. Jessica Kingsley Pub. ISBN 1 85302 182 2

Julia Lawless, 2013. *The Encyclopedia of Essential Oils: The Complete Guide to the Use of Aromatic Oils In Aromatherapy, Herbalism, Health, and Well Being*. 1 Edition. ISBN 157324614X

Patricia Davis, 2005. *Aromatherapy: An A-Z: The Most Comprehensive Guide to Aromatherapy Ever Published*. Revised Edition. Random House UK. ISBN 009190661X

Jean Valnet, 2012. *The Practice Of Aromatherapy*. Edition. Ebury Digital ISBN 0 85207 143 4

Other reference books:

Nye S, *Clinical Aromatherapeutics: A Reference Manual*

Guenther E, *The Essential Oils* [all volumes]

Pénoël, Dr D, *L'aromathérapie exactement*

Pénoël, Dr & R-M, *Urgences & Soins Intensifs*

Berkowsky, Dr B, *Essential Oils and the Cancer Miasm*

Lautié, R and Passebecq, A, *Aromatherapy: The Use of Plant Essences in Healing*

Gattefosse, Rene-Maurice, *Gattefosse's Aromatherapy*

Maury, Margeurite - *Margeurite Maury's Guide to Aromatherapy*

Tisserand, Robert The Art of Aromatherapy

Sellar, Wanda Directory of Essential Oils

Schnaubelt, Kurt *Advanced Aromatherapy, The Science of Essential Oil Therapy*

Schnaubelt, Kurt *Medical Aromatherapy, Healing with Essential Oils*

Price, Shirley, *Aromatherapy Workbook*

Grace, Ulla-Maija, *Aromatherapy for Practitioners*

Buckle, Jane, *Clinical Aromatherapy in Nursing*

Wildwood, Chrissie, *The Bloomsbury Encyclopedia of Aromatherapy*

Worwood, Valerie Ann,*The Fragrant Pharmacy*

Worwood, Valerie Ann, *The Fragrant Mind*

Fischer-Rizzi, Susanne, *Complete Aromatherapy Handbook*

Ulla-Maija Grace, *Aromatherapy for Practitioners*

Lunny, Dr V, *Aromatherapy*

Catty, S *Hydrosols*

Caddy, Rosemary, *The Essential Blending Guide*

Damian, P & K, *Aromatherapy: Scent & Psyche*

Mojay, Gabriel, *Aromatherapy for Healing the Spirit*

Davis, Patricia, *Subtle Aromatherapy*

Berwick, Ann, *Holistic Aromatherapy*

Grosjean, Nelly, *Veterinary Aromatherapy*

Accepted Aromatherapy Substance List

LABEL NAME	SYNONYM	COMMON NAME
Abelmoschus moschatus	Hibiscus abelmoschus	Ambrette seed, Musk seed, Egyptian alcee, Target-leaved hibiscus, Muskmallow
Abies alba	Abies pectinata	Silver fir needle, Whitespruce, European silver fir, Edeltanne, Weistanne
Abies balsamea	Abies balsamifera, Pinus balsaamea	Canadian balsam, Balsam fir, Balsam tree, American silver fir, Balm of Gilead fir, Canada turpentine (oil)
Acacia dealbata	Acacia decurrens var. dealbata	Mimosa, Sydney black wattle
Acacia farnesiana	Cassia ancienne	Cassie, Sweet acacia, Huisache, Popinac, Opopanax
Achillea millefolium	Millefolium, Milfoil	Yarrow, Milfoil, Millefolium, Common yarrow, Nosebleed, Thousand leaf
Acorus calamus, var. angustatus asarone		Calamus
Agathosma Betulina		Buchu
Allium Cepa	Allii cepae bulbus	Onion
Allium Sativum		Garlic
Alpinia galange		Siamese Ginger, Galangal Root
Amyris balsamifera		Sandalwood WI, Amyris
Andropogon muricatus		Vetiver
Anethum graveolens	Graveolens anethum, Peucedanum graveolens, Fructus anethi	Dill, European dill, American dill
Angelica archangelica	Angelica officinalis	Angelica, European angelica, Garden angelica
Aniba rosaeodora	Aniba rosaeodora var. amazonica	Rosewood, Bois de rose, Brazilian rosewood
Anthemis nobilis	Chamaemelum nobile, Chamomilla romana	Roman chamomile, English chamomile, Garden chamomile, Sweet chamomile, True chamomile
Anthoxanthum odoratum		Flouve/ Sweet vernalgrass

LABEL NAME	SYNONYM	COMMON NAME
Apium graveolens		Celery
Arnica montana		Arnica, leopards bane, mountain tobacco
Artemisia abrotanum		Southenwood
Artemisia absinthium	Artemisia afra	Wormwood
Artemisia annua		Annie sweet, annual wormwood
Artemisia darborescens		Mugwort, Artemisia
Artemisia dracunculus		Tarragon, Estragon, Little dragon, Russian tarragon
Artemisia herba alba		Armoise, mugwort white
Artemisia pallens		Davana
Artemisia vulgaris		Mugwort
Asarum canadense		Snakeroot, Wild ginger, Indian ginger.
Asteracease eriocephalus afticanus		Cape Snowbush, Kapokbos, wild rosemary - indigenous
Asteracease eriocephalus punctulatus		Cape Camomile, boegoekapok - indigenous
Betula alba	Betula alba var. pubescens, Betula odorata, Betula pendula, Betula verrucosa	European white birch, Silver birch
Betula lenta		Birch sweet
Boronia megastigma		Boronia
Boswellia carteri	Boswellia Sacra	Frankincense, Olibanum, Gum thus, Beeyo
Boswellia Frereana		Frankincense, Gum thus, meydi
Brassica nigra		Mustard, black
Bulnesia sarmienti		Guaiacwood, Champaca wood, Palo santo
Bursera glabrifolia	Bursera delpechiana	Linaloe, Mexican linaloe, Copal limon
Calamintha nepeta		Wild Basil
Calamintha officinalis	Calamintha clinopodium, Melissa calaminta	Calamintha, Calamint, Common calamint, Mill mountain, Mountain balm, Mountain mint, Basil thyme, Nepeta (oil), French marjoram (oil), Wild basil (oil), Catnip (oil)
Calamintha sylvatica		Calamintha, Calamint, Common calamint, Mill mountain, Mountain balm, Mountain mint, Basil thyme, Nepeta (oil), French marjoram (oil), Wild basil (oil), Catnip (oil)
Calendula officinalis		Marigold, Calendula, Marygold, Marybud, Gold-bloom, Pot marigold, Hollygold, Common marigold, Poet's marigold
Cananga odorata	Cananga odoratum var. macrophylla	Cananga

LABEL NAME	SYNONYM	COMMON NAME
Cananga odorata var. genuina	Unona odoratissimum	Ylang ylang, Flower of flowers
Canarium luzonicum	Canarium commune	Elemi, Manila elemi, Elemi gum, Elemi resin, Elemi oleoresin
Carum carvi	Apium carvi, Bunium carvi	Caraway, Carum, Alcaravea
Cedrus atlantica		Atlas Cedarwood, Atlantic cedar, Atlas cedar, African cedar, Moroccan cedarwood (oil), Libanol (oil)
Chenopodium ambrosioides		Wormseed
Cinnamomum camphora	Laurus camphora, Camphora officinalis	Camphor, True camphor, Hon-sho, Laurel camphor, Gum camphor, Japanese camphor, Formosa camphor
Cinnamomum cassia	Cinnamomum aromaticum	Cassia bark, Chinese cinnamon
Cinnamomum zeylanicum	Cinnamomum verum, Laurus cinnamomum	Cinnamon, Ceylon cinnamon, Seychelles cinnamon, Madagascar cinnamon, True cinnamon
Cistus ladaniferus		Labdanum, Cistus (oil), Gum cistus, Ciste, Labdanum gum, Ambreine, European rock rose
Citrus aurantifolia	Citrus medica var. acida, Citrus latifolia	Lime, Mexican lime, West Indian lime, Sour lime
Citrus aurantium	Citrus aurantium var. amara, Citrus vulgaris, Citrus bigaradia	Orange blossom, Neroli, Neroli bigarade
Citrus aurantium var.	Citrus vulgaris, Citrus bigaradia	Petitgrain, Petitgrain bigarade, Petitgrain Paraguay
Citrus aurantium var. amara	Citrus vulgaris, Citrus bigaradia	Bitter orange, Seville orange, Sour orange bigarade (oil). Sweet orange
Citrus bergamia	Citrus aurantium subsp. Bergamia	Bergamot
Citrus limon	Citrus limonum	Lemon
Citrus paradisi	Citrus racemosa, Citrus maxima var. racemosa	Grapefruit
Citrus reticulata	Citrus nobilis, Citrus madurensis, Citrus unshiu, Citrus deliciosa, Citrus tangerina	Mandarin, European mandarin, True mandarin, Tangerine, Satsuma
Citrus sinensis	Citrus aurantium var. dulcis, Citrus aurantium var. sinensis	Sweet orange, China orange, Portugal orange
Commiphora myrrha	Balsamodendron myrrha	Myrrh, Gum myrrh, Common myrrh, Hirabol myrrh, Myrrha
Copaifera officinalis		Copaiba balsam, Copahu balsam, Copaiba, Copaiva, Jesuit's balsam, Maracaibo balsam, Para balsam

LABEL NAME	SYNONYM	COMMON NAME
Coriandrum sativum		Coriander, Chinese parsley
Croton elutheria		Cascarilla bark, Sweetwood bark, Swwet bark, Bahama cascarilla, Aromatic quinquina, False quinquina
Cuminum cyminum	Cuminum odorum.	Cumin, Cummin, Roman caraway
Cupressus sempervirens	Cupressus australis, Cupressus fastigiata	Cypress, Italian cypress, Mediterranean cypress
Curcuma longa	Curcuma domestica, Amomoum curcuma	Turmeric, Curcuma, Inian saffron, Indian yellow root
Cymbopogon citratus	1. Andropogon citratus, Andropogon schoenanthus. 2. Andropogon flexuosus, Cymbopogon flexuosus	Lemongrass 1. West Indian / Madagascar / Guatemala lemongrass 2. East Indian / Cochin / Native / British India lemongrass, Vervaine Indienne, France Indian verbena
Cymbopogon martinii var. martinii	Andropogon martinii, Andropogon martinii var. motia	Palmarosa, East Indian geranium, Turkish geranium, Indian rosha, Motia
Cymbopogon nardus	Andropogon nardus	Citronella, Sri Lanka citronella, Lenebatu citronella
Daucus carota		Carrot seed, Wild carrot, Queen Anne's lace, Bird's nest
Dryobalanops aromatica	Dryobalanops camphora	Borneol, Borneo camphor, East Indian camphor, Baros camphor, Sumatra camphor, Malayan camphor
Elettaria cardamomum	Elettaria cardamomum var. cardamomum	Cardamom, Cardomon, Cardamomi, Mysore cardomom
Eucalyptus citriodora		Lemon-scented eucalyptus, Lemon-scented gum, citron-scented gum, Scented gum tree, Spotted gum, Boabo
Eucalyptus dives var. Type		Broad-leaved peppermint eucalyptus, Blueb peppermint, Menthol-scented gum
Eucalyptus globulus var. globuls		Eucalyptus, Blue gum, Gum tree, Southern blue gum, Tasmanian blue gum, Fever tree, Stringy bark
Ferula asafoetida	Ferula narthex, Ferula scorodosma, Scorodosma foetidum	Asafetida, Asafoetida, Gum asafetida, Devil's dung, food of the gods, Giant fennel
Ferula galbaniflua	Ferula gummosa	Galbanum, Galbanum gum / resin, Bubonion
Foeniculum vulgare	Foeniculum officinale, Foeniculum capillaceum, Anethum foeniculum	Fennel, Fenkel
Guaiacum officinale	G. sanctum, Bulnesia sarmienta	Guaiacwood, Champaca wood, Palo santo
Helichrysum angustifolium		Helichrysum, Immortelle, Everlasting, St. John's herb

LABEL NAME	SYNONYM	COMMON NAME
Humulus lupulus	Lupulus humulus	Hops, Common hop, European hop, Lupulus
Hyacinthus orientalis	Scilla nutans	Hyacinth, Bluebell
Hyssopus officinalis		Hyssop, Azob
Illicium verum		Star anise, Cinese anise, Illicium, Chinese star anise
Jasminum officinale		Jasmine, Jasmin, Jessamine, Common jasmine, Poet's jasmine, Spanish jasmine
Juniperus ashei	Juniperus mexicana	Texas cedarwood, Mountain cedar, Mexican cedar, Rock cedar, Mexican juniper
Juniperus communis		Juniper, Common juniper
Juniperus oxycedrus		Cade, Juniper tar, Prickly cedar, Medlar tree, Prickly juniper
Juniperus virginiana	Juniperus virginianus	Virginian cedarwood, Red cedar, Eastern red cedar, Southern red cedar, Bedford cedarwood (oil)
Laurus nobilis		Bay laurel, Sweet bay, Grecian laurel, True bay, Mediterranean bay, Roman laurel, Noble laurel, Laurel leaf (oil)
Lavandula angustifolia	Lavandula officinalis, Lavandula vera	True lavevder, Garden lavender, Common lavender
Lavandula latifolia	Lavandula spica	Spike lavender, Broad-leaved lavender, Lesser lavender, Spike
Lavandula x intermedia	Lavandula hybrida, Lavandula hortensis	Lavandin, Bastard lavender
Levisticum officinale	Angelica levisticum, Ligusticum levisticum	Lovage Root, Smellage, Maggi herb, Garden lovage, Common lovage, old English lovage, Italian lovage, Cornish lovage
Lippia citriodora	Aloysia triphylla, Aloysia citriodora, Lippia triphylla, Verbena triphylla	Lemon Verberna, Verbena
Liquidambar orientalis	Balsam styracis	LEVANT STYRAX, Balsam Styracis, Oriental sweetgum, Turkish sweetgum, Asiatic styrax, Storax
Litsea cubeba	Litsea citrata.	LITSEA CUBEBA, 'May chang', Exotic verbena, Tropical verbena
Matricaria recutita	Chamomilla recutita, Chamomilla vulgaris, Matricaria chamomilla	CHAMOMILE (CAMOMILE) GERMAN Blue chamomile, Matricaria, Hungarian chamomile, Sweet false chamomile, Single chamomile, Chamomile blue (oil)
Melaleuca alternifolia		TEA TREE, Narrow-leaved paperbark tea tree, Ti-tree, Ti-trol, Melasol
Melaleuca cajeputi	Melaleuca minor, Melaleuca aetheroleum	CAJEPUT, Cajuput, White tea tree, White wood, Swamp tea tree, Punk tree, Paperbark tree.
Melaleuca viridiflora	Melaleuca quinquenervia	NIAOULI 'Gomenol'

LABEL NAME	SYNONYM	COMMON NAME
Melissa officinalis		MELISSA, Lemon balm, Common balm, bee balm, Sweet balm, Heart's delight, Honey plant
Mentha arvensis		MINT, Cornmint, Japanese Mint, Chinese Mint
Mentha piperita		PEPPERMINT, Brandy mint, Balm mint
Mentha pulegium	Hedeoma pulegoides	PENYROYAL
Mentha spicata	Mentha viridis.	SPEARMINT, Common spearmint, Garden spearmint, Spire mint, Green mint, Lamb mint, Pea mint, Fish mint
Myristica fragrans	Myristica officinalis, Myristica aromata, Myristica aromtica, Nux moschata, Nuphar pumilum	NUTMEG, Myristica (oil), Mace (husk), Macis (oil)
Myrocarpus fastigiatus		CABREUVA, Cabureicica, "Baume de Perou brun"
Myroxylon balsamum var. balsamum	Toluifera balsamum, Balsamum tolutanum, Balsamum americanum, Myrospermum toluiferum	TOLU BALSAM, Thomas balsam, Resin Tolu, Opobalsam
Myroxylon balsamum var. pereirae	Toluifera pereira, Myrospermum pereira, Myroxylon pereirae	PERU BALSAM, Peruvian balsam, Indian balsam, Black balsam
Myrtus communis		MYRTLE, Corsican pepper
Nardostachys jatamansi		SPIKENARD, Nard, False Indian valerian root
Ocimum basilicum		BASIL, French Basil, Common basil, Joy-of-the-mountain, "True" sweet basil, European basil
Origanum majorana	Majorana hortensis, Origanum hortensis	MARJORAM SWEET, Knotted marjoram
Origanum vulgare		ORIGANUM
Ormenis multicaulis	Ormenis mixta, Anthemis mixta	MAROC CHAMOMILE
Pelargonium graveolens	Pelargonium radens, pelagnium capitatum	GERANIUM, Rose geranium, Pelargonium
Petroselinum sativum	Petroselinum crispum, Petroselinum hortense, Apium petroselinum, Carum petroselinum	PARSLEY, Common parsley, Garden parsley
Pimenta dioica	Pimenta officinalis	PIMENTO, Allspice, Pimenta, Jamaica pepper
Pimenta racemosa	Myrcia acris, Pimenta acris	BAY, West Indian Bay, Myrcia, Bay, Bay rum tree, Wild cinnamon, Bayberry, Bay leaf (oil)
Pimpinella anisum	Anisum officinalis, Anisum vulgare	ANISEED, Anise, Sweet cumin
Pinus palustris		TEREBRINTH, Turpentine, Therebintine, Gum thus, Gum turpentine, Turpentine balsam, Spirit of turpentine (oil)

LABEL NAME	SYNONYM	COMMON NAME
Pinus palustris *		LONGLEAF PINE, Longleaf yellow pine, Southern yellow pine, Pitch pine, Pine
Pinus sylvestris	Pinus silvestris	SCOTCH PINE, Forest pine, Scotch pine, Norway pine, Scotch fir
Piper cubeba	Cubeba officinalis	CUBEB, Cubeba, Tailed pepper, Cubeb berry, false pepper
Piper nigrum		BLACK PEPPER, Piper, Pepper
Pistacia lentiscus		MASTIC, Mastick, Mastix, Mastich, Lentisk, Chios
Pogostemon cablin	Pogostemon patchouli	PATCHOULI, Patchouly, Puchaput, Paradise flower
Rosa centifolia		CABBAGE ROSE, Rose maroc, French rose, Provence rose, Hundred-leaved rose
Rosa damascena		ROSA DAMASCENA, DAMASK ROSE, Summer damask rose, Bulgarian rose, Turkish rose
Rosmarinus officinalis	Rosmarinus coronarium.	ROSEMARY, Compass plant, Incensier
Salvia lavendulaefolia	Salvia officinalis	SAGE SPANISH , Lavender-leaves sage
Salvia sclarea		CLARY SAGE, Clary, Clary wort, Muscatel sage, Clera eye, See bright, Common clary, Clarry, Eye bright
Santalum album		SANDALWOOD, White sandalwood, Yellow sandalwood, East Indian sandalwood, Sandalwood Mysore, Sanders-wood
Santolina chamaecyparissias		SANTOLINA
Saussurea costus	Saussurea lappa, Aucklandia costus, Aplotaxis lappa, Aplotaxis auriculata	COSTUS
Schinus molle		SCHINUS MOLLE, Peruvian pepper, Peruvian mastic, Californian pepper tree
Styrax benzoin		BENZOIN, Gum benzoin, Gum benjamin
Syzygium aromaticum	Caryophyllus aromaticus, Caryophyllus aromaticum, Eugenia aromatica, Eugenia caryophyllata, Eugenia caryophyllus	CLOVE
Tagetes minuta	Tagetes glandulifera	TAGETTES, Tagette, Taget, Mexican marigold, Khakibos
Thymus vulgaris	Thymus aestivus, Thymus ilerdensis, Thymus webbianus, Thymus valentianus	THYME, Common thyme, French thyme, Garden thyme

LABEL NAME	SYNONYM	COMMON NAME
Tilia vulgaris	Tilia europaea	LINDEN, Lime tree, Common lime, Lyne, Tillet, Tilea
Tsuga canadensis	Pinus canadensis, Abies canadensis, Abies balsamea	HEMLOCK SPRUCE, Spruce, Eastern hemlock, Common hemlock, Canadian pine
Valeriana officinalis	Valeriana officinalis var. angustifolium, Valeriana officinalis var. latifolia, Valeriana fauriei	VALERIAN, European valerian, Common valerian, Belgian valerian, Fragrant valerian, Garden valerian
Vanilla planifolia		VANILLA (ABSOLUTE)
Vetiveria zizanoides	Andropogon muriaticus, Anatherum muriaticum	VETIVER, Vetivert, Khus khus
Viola odorata		ViIOLET, English violet, Garden violet, Blue violet, Sweet-scented violet
Zingiber officinale	Zingiber officinalis	GINGER, Common ginger, Jamaica ginger