COMPLEMENTARY MEDICINES - DISCIPLINE-SPECIFIC 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 SAHPRA's current thinking on the quality, safety, and efficacy of these medicines. It is not intended as an exclusive approach. SAHPRA 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 SAHPRA 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 CEO and the website: www.sahpra.org.za

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CHIEF EXECUTIVE OFFICER

SOUTH AFRICAN HEALTH PRODUCTS REGULATORY AUTHORITY

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1 INTRODUCTION i) Purpose

The purpose of this Guideline is to provide clear guidance with regards to the safety and efficacy (SE) requirements for registration of discipline-specific complementary medicines in South Africa in the Common Technical Document (CTD) format. The intent of this document is to ensure that the levels of evidence for SE are rigorous enough to protect public health and maintain consumer confidence, while providing a clearly defined pathway to bring into the market discipline-specific complementary medicines.

It should be read together with the current versions of the following guidelines, including those referred to therein:

- 7.03 Complementary Medicines – Use of the ZA CTD format in the preparation of a registration application
- 7.04 Complementary Medicines – Health Supplements: Safety and Efficacy
- 7.05 Complementary Medicines – Quality
- 2.24 Guidance for the submission of the South African CTD/eCTD – General & Module 1
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- 2.25 Pharmaceutical and Analytical – CTD/eCTD
- 2.36 Scheduling of Medicines
- 4.01 Guide to Good Manufacturing Practice for Medicines in South Africa • 16.01 Guideline for Licence to Manufacture, Import or Export and the forms:
- Application for Registration of a Medicine – South African Common Technical Document (ZACTD)
- 6.15 Screening Template for new application for registration
- 6.10 Licence Application to Manufacture, Import or Export Medicine ii) **Scope and Overview**

This SE Guideline applies to discipline specific complementary medicines (Category D) for human use. In addition, the requirements and restrictions outlined in this document do not apply to compounded medicines in terms of Section 14(4) of the Act.

In general Complementary Medicines (CMs) are used and sold by many people in the 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 for disciplinespecific CMs but should not in themselves be regarded as final. Where an applicant wishes to use and submit information not found in these guidelines, they may do so, but they would have to make thoroughly justified submissions on scientific, technical or traditional grounds.

To

C The CMs that will be the subject to these Guidelines are those associated with those disciplines as determined by Council. Currently six major disciplines have been identified and preparations associated

therewith, namely: **Homeopathy, Western Herbal Medicine, Traditional Chinese Medicine, Ayurveda, Unani Medicine (Unani-Tibb) and Aromatherapy**. In addition, a seventh category - Combination Products - is recognised and dealt with below. The disciplines of CMs are defined in this guideline and evidence required to substantiate the claims made for products falling under any of the disciplines, is divided into high risk or low risk categories.

For all CMs, quality and safety are non-negotiable, whereas, depending upon the discipline, proof of absolute efficacy may prove challenging, for a variety of reasons, and therefore concessions have been made in this area for tradition (discipline) based CMs that have a long history of use.

All manufacturers of CMs will be subject to compliance with Good Manufacturing Practice (GMP). 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.

The approach of these guidelines is to enable the applicant to present, to the SAHPRA, an application free of errors and easy to review. Each discipline will have its own set of requirements governed by its own references and pharmacopoeiae which are all subject to and compliant with the current science and knowledge of that particular discipline. Other relevant Guidelines of the SAHPRA should be consulted where necessary. Where guidelines are referred to, the latest (current) version should be used.

Discipline specific complementary medicines will be subject to the Scheduling of Medicines Guideline. CMs are not scheduled solely on the basis of toxicity. Although toxicity is one of the factors considered, 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, confirmed to relate to the relevant discipline and/or health supplements.

ANNEXURE A is included to help decide what would be regarded as a Category D substance, while **ANNEXURES B** and **C** describe the process of determination of relevant disciplines and origin of substances.

1.1 Definitions

i) The definition of a complementary medicine (CM) is provided as:

"Complementary medicine" means any substance or mixture of substances that—

(a) originates from plants, fungi, algae, seaweeds, lichens, minerals, animals or other substance as determined by Council, and

(b) is used or purporting to be suitable for use or manufactured or sold for use—

(i) in maintaining, complementing, or assisting the innate healing power or physical or mental state, or

(ii) to diagnose, treat, mitigate, modify, alleviate or prevent disease or illness or the symptoms or signs thereof or abnormal physical or mental state, of a human being or animal, and

(c) is used—

(i) as a health supplement, or

(ii) in accordance with those disciplines as determined by Council, or

(d) is declared by the Minister, on recommendation by the Council**,** by notice in the Gazette to be a complementary medicine.

ii) The definition of a health supplement (HS) is provided as:

"Health supplement" means any substance, extract or mixture of substances that—

(a) may—

(i) supplement the diet; ii) have a nutritional physiological effect; or iii) include pre- and probiotics classified as schedule 0; and

(b) are sold in pharmaceutical dosage forms not usually associated with a foodstuff and excludes injectables or substances schedule 1 or higher.

iii) The definition of a combination product is provided as:

Combination product means a single product that contains:

(a) a mixture of substances of different discipline-specific origins or philosophies;

(b) a mixture of at least one substance of discipline-specific origin and one or more health supplements; or

(c) a mixture of at least one substance of discipline-specific origin and one or more of its isolated constituents.

1.1.1 Active Ingredients Intended for Medicines Compounded in terms of Section 14(4)

The provisions of registration do not apply to Active Ingredients / raw materials that are supplied to practitioners for the purposes of compounding in terms of Section 14(4) of the Act. The exclusions relating to compounding apply where a practitioner prepares a medicine for an individual patient either following consultation with that particular patient, or to fill a prescription for that particular patient. This policy recognises the one-off nature of such medicines, the professional training and licensing of the practitioner to prepare a medicine for the specific needs of an individual patient. (This does not include otherwise available proprietary products or *bona fide* medicines for sale to the general public)

Manufacturers of substances for supply to individual practitioners for use in compounded medicines shall be duly licensed as a manufacturer or wholesaler and supply active ingredients / raw materials to registered and duly licensed practitioners only, provided that supply of such substance shall only be made to practitioners who are holders of combined dispensing and compounding licences as contemplated by Section 22C of the Act.

1.2 Compliance with Good Manufacturing Practice (GMP), Good Laboratory Practice (GLP) and Good Agricultural and Collection Practices (GACP)

All manufacturers of complementary medicines shall comply with all relevant aspects of Good Manufacturing Practice as outlined in the latest version of the SAHPRA's "GUIDE TO GOOD MANUFACTURING PRACTICE FOR MEDICINES IN SOUTH AFRICA" and Good Laboratory Practice as well as the WHO Guidelines on Good Agricultural and Collection Practices (GACP) for Medicinal Plants, if applicable. Any alternative standards must be specified, referenced and justified.

1.3 Format of submission

Data provided in applications for registration of complementary medicines should be in the latest version of the Common Technical Document (ZA-CTD) format as published by the SAHPRA.

1.4 Types of Substances and Preparations

1.4.1 Herbal substance / preparation

Herbal substance / preparation, in any discipline, means all or part of a plant, fungus, alga, seaweed or lichen, or other substance:

a) that is obtained only by drying, crushing, distilling, freezing, fermentation, 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 dosage form;

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; and d) that does not include:

i. a pure chemical or isolated constituent unless the isolated herbal constituent is formulated with the herbal substance from which it arises and is demonstrated to have "essentially the same"[1] action as the whole herbal substance; or ii. a substance of mineral, animal or bacterial origin.

1.4.2 Traditional Chinese, Ayurvedic and Unani Tibb substances

Traditional Chinese, Ayurvedic and Unani Tibb substances, in addition to herbal substances, may contain substances of animal or mineral origin.

1.4.3 Homeopathic substances / preparations

Homeopathic substances / preparations may be

a) of plant, fungal, animal, mineral or other origin prepared in accordance with homeopathic 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 homeopathic medicine;

b) formulated for use based on homeopathic 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 homeopathy; or

c) prepared or purported to be prepared according to the practices of homeopathic 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, and may include electronic preparations, homotoxicology, biochemic tissue salts, spagyric therapy, gemmotherapy and lithotherapy

1.4.4 Aromatherapy substances

Aromatherapy substances are essential (volatile) oils, hydrolates (hydrosols) or other aromatic extracts 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.

Synthetic aromatic compounds for medicinal purposes should follow the Category A registration route.

1.4.5 Anthroposophical, Gemmotherapeutic, Spagyric Substances and Flower Essences

In most cases these medicinal products 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 western herbal medicinal products. In case of overlap, they will be qualified as either homeopathic or Western herbal medicines, or a combination based on their presentation in the product.

[1] Guidance on equivalence of herbal extracts in complementary medicines; **https://www.tga.gov.au/publication/guidanceequivalenceherbal-extracts-complementary-medicines#not**

Applicants are permitted to make use of the wording: “Anthroposophical Preparation” "Gemmotherapeutic Preparation", "Spagyric Preparation" and "Flower Essence" where applicable, in addition to the specific discipline on any labelling, package insert, patient information leaflet of other product-related documentation.

1.5 The Naming of Substances and Ingredients used in Complementary Medicines

The following naming conventions will be relevant for names of substance / ingredients used in Complementary Medicines in respect of any application for registration of such or on any product labelling thereof.

1.5.1 Chemical Substance Name

The approved name i.e. International Non-Proprietary Name (INN) or chemical name of substances used 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 Homeopathic, Traditional Chinese, Ayurvedic or Unani Tibb medicines must be stated.

1.5.2 Biological Substance Name or Animal 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 or animal substance.

1.5.3 Herbal Name

For purposes of the registration procedure, herbal names are stated in the Latin binomial format, which must include the genus, species, subspecies, variety, sub-variety, form, sub-form or chemotype and author where appropriate. Reference must 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

1.5.3 Herbal Name - continued

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.

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 may be used provided it is clear to the consumer exactly which herb (or part thereof) is being used.

1.5.4 Herbal Component Name (HCN)

HCNs are names for classes of constituents that are found in herbal ingredients. The need for a HCN most often arises when a herbal extract is standardised to a particular class of constituents, or where particular classes of constituents are restricted (e.g. hydroxyanthracene derivatives). Where a herbal

extract is standardised to a single constituent, the single constituent should have a chemical name. The HCN is not a stand-alone name and should be used only when expressing a herbal substance.

1.5.5 Common Names

Common names, *Materia Medica* Names and/or Discipline-specific names (e.g.: Traditional Chinese Pin Yin, Traditional Sanskrit or 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 Multi-component Formulations and Combination Products

1.6.1 Multi-component Formulations

For complementary medicines that contain multiple ingredients, the evaluation of quality, safety and efficacy also relies on the correct formulation of the product according to the principles of the discipline from which it arises. It is recognised that traditional medicine disciplines have their own innate systems for assuring quality, safety and efficacy. An applicant should demonstrate that their product has been formulated carefully and correctly in accordance with the principles of the discipline from which it arises and, if a product is not formulated according to traditional principles, then the applicant must provide a detailed rationale as to why the ingredients in the product are combined and address any potential concerns about potential incompatibility (physical, chemical, traditional) of any of the constituent parts.

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, including consideration of principles that relate to the additive, synergistic or modulating effects and compatibility of the various ingredients of a formula and the associated dosage justifications that these principles may merit. Each active ingredient must contribute to the overall efficacy of the medicine.

1.6.2 Combination Products

Refer to the definition of "combination product" as provided in 1.1.

a) In the case of combination products of a mixture of substances of various discipline-specific origin or philosophy applicants will need to demonstrate an explicit, cogent rationale for use of all discipline-specific ingredients in the formula.

b) In the case of combination products of a mixture of at least one substance of discipline-specific origin and one or more health supplements:

- detailed information must be provided to explain the rationale behind the inclusion of each substance together with the discipline-specific substances, and
- where any health supplements fall below minimum levels required for use of the associated health supplement claim, no claim related to its presence in the formula will be permitted.

c) In the case of a mixture of at least one substance of discipline-specific origin and one or more of its isolated constituents:

- the isolated constituent must be formulated with the herbal substance from which it arises; and
- the action of the isolate must be "essentially the same" (not significantly different) (See 1.4.1) as the action of the herbal substance.

In any instance (a, b or c) the registration sub-category will be "Combination Product" and the discipline(s) it relates to.

1.7 Accepted References

The following references (in addition to any further specified accepted references **[ANNEXURE D]** for each discipline) should be consulted for purposes of motivating that the product or substances used originate from the discipline indicated. Monographs from any other source equivalent in standard to any of those listed below would also be accepted, with suitable motivation of the standard provided. Copies of relevant sections of sources used must be provided and referenced.

1.7.1 Western Herbal Medicine

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

- Australian Therapeutic Goods Authority List of Substances
- Health Canada Monographs
- German Commission C Monograph (see 1.4.5)
- German Commission E Monograph
- WHO Monographs on Selected Medicinal Plants
- ESCOP Monographs
- EMA Community Herbal Monographs
- British Herbal Pharmacopoeia (any edition)
- American Botanical Council Monographs
- Official or Traditional Herbal Materia Medicae, or
- Other national or international herbal monographs, pharmacopoeiae or materiae medicae

1.7.2 Traditional Chinese, Ayurvedic, Unani Medicine

(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:

- Pharmacopoeia of the People's Republic of China. Compiled by The State Pharmacopeia Commission of P.R. China. Executive Editors: HE Hong mei, CUI Liping. China Medical Science Press. ISBN 978-7-5067-5013-4/ R 921.2

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

- The Ayurvedic Pharmacopoeia of India
- The Ayurvedic Formulary of India

(iii) A Unani Tibb medicine or substance must be described as a Unani Tibb medicine or substance in at least one of the specified references or any of the following:

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.

1.7.3 Homeopathy

The substance must be described as a homeopathic substance in at least one of the specified references or any of the following:

- Health Canada Monographs
- Australian Therapeutic Goods Administration List of Substances
- German Commission C Monograph (see 1.4.5)
- 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" (ANNEXURE E).

2 ZA-CTD FORMAT

This section applies to the safety and efficacy aspects of an application for registration of complementary medicines submitted in ZA-CTD format. Whilst the completed dossier should be checked for completeness, relevance and correctness, for ease of reference, relevant sections (not a complete list) of Module 1 and Module 2 with which information should be congruent/ should correspond, are indicated.

The requirements for the presentation, labelling, copies and relevant procedures for submission of applications, are stipulated in the General and Module 1 guidance.

The Technical Screening form should be completed to assist with checking of the contents before copying and submission.

Any information below should be provided in line with any further requirements stipulated in this Guideline.

The Guideline "Complementary Medicines – Use of the ZA-CTD Format in the Preparation of a Registration Application" should also be followed to determine completeness.

2.1 Module 1: Administrative information

Refer to the General and Module 1 guidance.

The information under the following headings in particular should correspond with the information in Modules 5 if provided.

Module	Heading	Comments/Notes
1.0	Letter of application	Include a brief statement as to why the product meets the requirements for traditional use registration, specifically addressing the evidence of long standing use of the product or its ingredients.
1.1	Comprehensive Table of Contents (ToC) Modules 1 to 5	Ensure that the volume numbers indicated in the Table of Contents (ToC) correlate with the volume numbers of the final submission copies. Refer to the General and Module 1 guidance for 'Comprehensive Table of Contents' and 'Volume identification'
1.2.1	Application form	Ensure that the relevant product and other details correspond with all other Modules, e.g. the dosage form, active ingredient(s), strength, route of administration, manufacturer, packer
1.2.2.3	Dossier product batch information	Ensure that the batch information corresponds with that in the relevant sections of Module 3 e.g. 3.2.P.5 and 3.2.P.8 and also 3.2.R.1
1.3.1	South African Package Insert	
1.3.1.1	Package insert	Ensure that the proprietary name, pharmacological classification dosage form, active ingredient(s), strength, composition, dosage regimen, identification, presentation and storage correspond with the information in all other Modules. References listed that justify the medicine in terms of efficacy or safety claims (including traditional use and clinical evidence).
1.3.1.2	Standard References	
1.3.2	Patient Information Leaflet	
1.3.3	Labels	

1.5	Specific requirements for different types of applications	
1.5.1	Literature based submissions	A brief statement as to why the product meets the requirements for traditional use registration and addressing the evidence of long standing use of the product, expanded in Module 2.5.
Module	**Heading**	**Comments/Notes**
		Where a herbal monograph exists that is relevant to the proposed preparation, applicants should outline this fact in this section of the dossier and expand on it in Module 2.5. The circumstances of any form of Combination Product should be suitably motivated. A description as to the motivation of the selected risk level (LOW or HIGH) should also be provided.

2.2 Module 2: Common Technical Document summaries

The information under the following headings in particular should correspond with the information in Modules 1.3, 1.5, as well as 5 if provided.

Module	**Heading**	**Comments/Notes**
2.1	CTD Table of Contents (ToC) Modules 2 to 5	Ensure that the volume numbers indicated in the Table of Contents (ToC) correlate with the volume numbers of the final submission copies.
2.2	Introduction	Provide an introduction that would contextualise all presented information of the module including the relevance, necessity and appropriateness of Modules 2.4 and 2.5.

2.4	Non-clinical Overview	A bibliographic review of safety data together with a summary report, and where required, data necessary for assessing the safety of the medicinal product. The report on safety data should take into consideration the agreed format for the organisation of the non-clinical overview in the CTD. The list of relevant references for non-clinical data can be included at the end of module 2.4 Where a recognised monograph/reference standard has been established applicants should discuss this fact in the dossier taking into consideration that they do refer to the specific active ingredients and aspects related to the finished product. Furthermore, the applicant will need to demonstrate that the proposed product contains the CM substances which correspond to a CM substance listed in the monograph. A literature research should be provided to fill the gap between the compilation of any recognised reference source and the application, providing information about the research strategy. The relevance of the newer data and/or unpublished, specific data has to be discussed in relation of the known properties of the herbal substance(s) and the possible impact of such data on the existing assessment.

Module	**Heading**	**Comments/Notes**
		If the extract solvent and/or concentration is/are different from those given in the recognised reference/monograph, comparability has to be demonstrated by using appropriate analytical data. The same applies, if non-published data, which should be used (e.g. tests on mutagenicity) is referring to different extract solvent and/or concentration. For combination products the assessment should not only focus on the single CM substances, but also an assessment of the combination is necessary. If risks have been identified, the report must explain why a positive benefit/risk-balance for a traditional use is justified.

2.5	Clinical overview	A bibliographical evidence or expert evidence to the effect that the medicinal product in question, or its ingredients or a corresponding product, has a history of traditional medicinal use (as per the definition in the guideline) within the Republic of South Africa or within a country, the regulatory authority of which the SAHPRA aligns itself with. The evidence provided by traditional use should not be overstated and should be applicable to the level of indication provided. Sufficient reference and guidance as related to the claim and as per the guideline should be provided. Where reference is made to **recognised:** monographs or other reference standard: • Sources may be quoted but copies of the relevant text extract must be provided; and • Demonstration of how the product accords with such sources must be made. The plausibility of pharmacological effects or efficacy of the medicinal product as well as information on the safety of use should be addressed in this section. A summary of clinical evidence should also be included where required. For combination products the assessment should not only focus on the single CM substances, but also an assessment of the combination is necessary. A bibliographic review of safety data together with an expert report, and where required, data necessary for assessing the safety of the medicinal product. Evidence of widespread, long-standing use without significant safety problems emerging should form the basis of a typical safety report. Deficiencies in safety information should also be clearly addressed.
Module	**Heading**	**Comments/Notes**

		The report should ideally consider the following aspects of safety: • the nature of the patient population and the extent of patient exposure/world-wide marketing experience to date • common and non-serious adverse events • serious adverse events • methods to prevent, mitigate or manage adverse events • reactions due to overdose • long-term safety if relevant data is available • special patient populations e.g. children and pregnant or lactating women • relevant animal toxicology and product quality information If risks have been identified, the report must explain why a positive benefit/risk-balance for a traditional use is justified. For example, if there are reports of serious adverse events, this must be balanced by sufficient evidence of appropriate benefit. In summary, 5 pivotal pieces of information must be discussed in this section of the dossier a) traditional use b) therapeutic indication and associated clinical evidence where necessary c) strength/type of substance d) posology e) specific information on safe use and evidence of safety

2.3 Module 4: Non-clinical study reports

Module	Heading	Comments/Notes
4.1	Table of contents of Module 4	
4.2	Study Reports	If data are available or have been requested these should be provided and summarised in Module 2.6, for which the corresponding non-clinical overview would be included in Module 2.4 Any reports or studies referenced should be provided in full. Product specific study reports should be provided if available.
4.3	Literature References	Such references should be indexed following the agreed format for the organisation of Module 4.

2.4 Module 5: Clinical study reports

Module	Heading	Comments/Notes

5.1	Table of contents of Module 5	
5.2	Study Reports	If applicable (High Risk only). If data are available or have been requested these should be provided and summarised in Module 2.7 for which the corresponding clinical overview would be included in Module 2.5
5.3	Literature References	Such references should be indexed following the agreed format for the organisation of Module 5.

3 SAFETY AND EFFICACY: GENERAL PRINCIPLES

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.

Applications for the registration of complementary medicines must include appropriate data that demonstrate the safety of the product as provided for in these guidelines. Safety may be established by detailed reference to the published literature and/or the submission of original study data.

A guiding principle should be that, if the product has been traditionally used without demonstrated harm, a review of the relevant literature should be provided with original articles or references to the original articles. If official monograph/review results exist, reference should be made to them. Toxicological studies, if available, should be part of the assessment. If a toxicological risk is known, relevant toxicity data must be submitted. The assessment of risk, whether independent of dose or related to dose, should be documented. 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.

Proof of efficacy, including the documentation required to support the indicated claims, should depend on the nature and level of the indications. For the treatment of minor disorders, for nonspecific indications, or for limited prophylactic uses, less stringent requirements (e.g. observational studies) may be adequate to prove efficacy, especially when the extent of traditional use and the experience with a particular herbal medicine and supportive pharmacological data are taken into account.

Where traditional use has not been established, appropriate pre-clinical and/or clinical evidence will be required, dependent on level of claim.

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.

3.1 Well-documented Ingredients – continued

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 Quality of Data

Since the evidence to demonstrate efficacy and safety of products may be literature based, it is important that a critical appraisal on the quality of the data is provided.

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.

3.2 Quality of Data - continued

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.

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 or its ingredients have been addressed.

3.3 Benefits and Risks– Conclusion

The evaluation of high-level claims (i.e. for the use of medicines for serious diseases) 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.

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 high risk complementary medicine (refer to Table 1).

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 SAHPRA website or from the office of the CEO.

4 SAFETY REQUIREMENTS

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.
Risk Level	**Type of Claim**	**Evidence required to support claim**

LOW RISK	• General health enhancement without any reference to specific diseases [1] • Health maintenance, including nutritional support. • Relief of minor symptoms (not related to a disease or disorder) [2]	• Clinical data to be evaluated [3] 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 D***

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.

4.2 Documenting safety

4.2.1 Safety

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.

4.2.2 Overview of Safety - continued

There should be a description of common and expected adverse events (both serious and nonserious). 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;[2]
- 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 Post Marketing Data

The applicant should include all data on the worldwide marketing experience, including all relevant PostMarketing 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 SAHPRA'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 SAHPRA in accordance with the ADR guideline (Reporting Adverse Drug Reactions in South Africa).

5 EFFICACY

Table 1 should be consulted to determine the type of evidence required to substantiate a claim.

[2] 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**.

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 Africanvalidated 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 homeopathic 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 relevant to high risk level claims.

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.

5.2.2 Study Reports and/or Publications - continued 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

Any motivation or proposal of a scheduling status should consider the safety of the medicine, level of indication and suitably justify for the level of access associated with the proposed schedule.

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 product has ingredients, components or characteristics that it does not have;
- if a name applied to the product 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 SAHPRA Naming Guideline);
- if the label of the product does not declare the presence of a therapeutically active ingredient;
- if a form of presentation of the product may lead to unsafe use of the product or suggests a purpose that is not in accordance with conditions applicable to the sale of the product in South Africa, or could be confused with an existing registered or unregistered “brand”; or
- if the format of the submissions does not comply with current SAHPRA 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 all terms applicable to the regulation of medicines and medical devices.

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

This glossary provides clarity on not only the use of terms in this document but also to the 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, and includes an Active Pharmaceutical Ingredient (API).

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.

Adverse Drug Reaction

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, off label use of a medicine, overdose, misuse or abuse of a medicine.

Animal

An invertebrate or vertebrate member of the animal kingdom.

Applicant

A person who submits an application for the registration of a medicine, an update or amendment to an existing registration.

Application

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

Aromatherapy substance

Essential (volatile) oils, hydrolates (hydrosols) or other aromatic extracts 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.

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; To describe further, it is 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 product

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

Biological substance

Substance of biological origin, which is frequently chemically complex and has 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.

Clinical trial

An investigation in respect of a medicine for use in humans and animals that involves human subjects or animals 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

A single product that contains:

a) a mixture of substances of various discipline specific origin or philosophy;
b) a mixture of at least one substance of discipline specific origin and one or more health supplements, or
c) a mixture of at least one substance of discipline-specific origin and one or more of its isolated constituents.

Complementary medicine

Any substance or mixture of substances that—

(a) originates from plants, fungi, algae, seaweeds, lichens, minerals, animals or other substance as determined by Council, and

(b) is used or purporting to be suitable for use or manufactured or sold for use—

(i) in maintaining, complementing, or assisting the innate healing power or physical or mental state, or

(ii) to diagnose, treat, mitigate, modify, alleviate or prevent disease or illness or the symptoms or signs thereof or abnormal physical or mental state, of a human being or animal, and

(c) is used—

(i) as a health supplement, or

(ii) in accordance with those disciplines as determined by Council, or

(d) is declared by the Minister, on recommendation by the Council, by notice in the Gazette to be a complementary medicine.

Dosage form

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

Drug See **Medicine 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 up to which a medicine will retain the strength and other properties which are mentioned on the label which strength and other properties can change after the lapse of time and after which date the medicine shall not be sold to the public or 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.

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

Health supplement means any substance, extract or mixture

of substances that— a) may—

i) supplement the diet; ii) have a nutritional physiological effect, or

iii) include pre- and probiotics classified as schedule 0, and

b) are sold in pharmaceutical dosage forms not usually associated with a foodstuff and excludes injectables or substances schedule 1 or higher.

Herbal substance / preparation in any discipline, means all or part of a plant, fungus, alga, seaweed or lichen, or other substance:

a) that is obtained only by drying, crushing, distilling, freezing, fermentation, 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, and d) that does not include:

i) a pure chemical or isolated constituent unless the isolated herbal constituent is formulated with the herbal substance from which it arises and is demonstrated to have "essentially the same"[3] action as the whole herbal substance, or

ii) a substance of mineral, animal or bacterial origin. **Homeopathic substances / preparations** may be

a) of plant, fungal, animal, mineral or other origin prepared in accordance with homeopathic 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 homeopathic medicine;

b) formulated for use based on homeopathic 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 homeopathy, or

c) prepared or purported to be prepared according to the practices of homeopathic 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, and may include electronic preparations, homotoxicology, biochemic tissue salts, spagyric therapy, gemmotherapy and lithotherapy

Inactive ingredient(s)

A substance or compound that is used in the manufacture of a pharmaceutical product and does not contribute to the therapeutic effect of the product, but is intended to enhance the consistency, appearance, integrity, stability, release characteristics, or other features of the product.

Indications

The specific therapeutic uses of medicines.

[3] Guidance on equivalence of herbal extracts in complementary medicines;
https://www.tga.gov.au/publication/guidance-equivalence-herbal-extracts-complementary-medicines#not

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 General Regulations published in terms 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.

Medicine

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 homeopathic preparations are made.

Nature identical oil

An oil which has had a component added, either natural or artificial, with a chemical structure identical or similar 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 means a person registered as such under the Allied Health Professions Act, 1982 (Act No. 63 of 1982)

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 unique 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.

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 maintaining, complementing, or assisting the innate healing power or physical or mental state, or to diagnose, treat, mitigate, modify, alleviate or prevent disease or illness or the symptoms or signs thereof or abnormal physical or mental state of a human being.

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

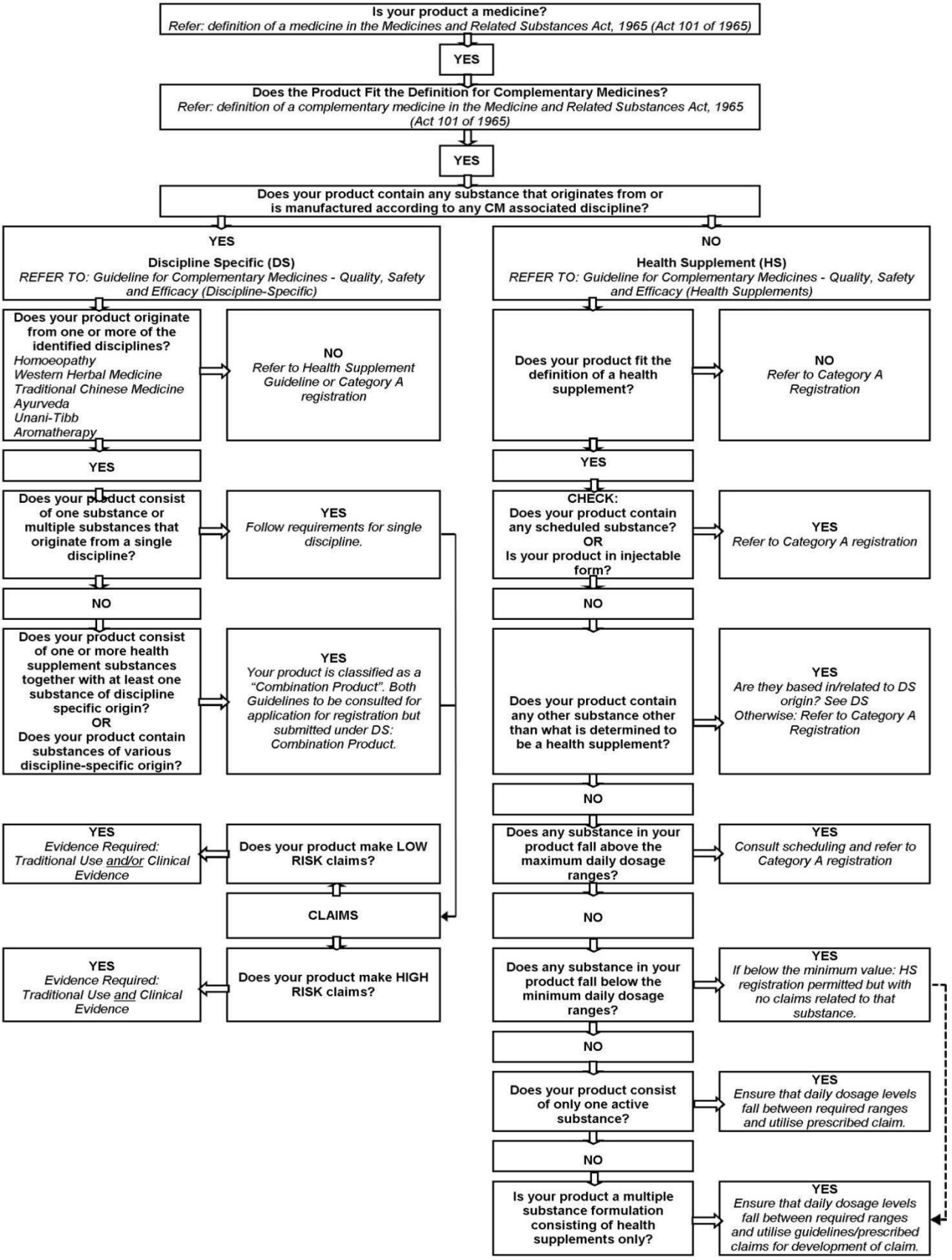
ADR	Adverse Drug Reaction
AHPCSA	Allied Health Professions Council of South Africa
BP	British Pharmacopoeia
CAS	Chemical Abstracts Service (Registry)
CM(s)	Complementary Medicine(s)
CPMP	Committee for Proprietary Medicinal Products (of the EMA)
CTD	Common Technical Document
EU	European Union
FDA	Food 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
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
Dec 2013	v1_5 Approved by SAHPRA for implementation	v2 Dec 2013
Feb 2014	Amendment of section 2.2.1.1	v2_1 Feb 2014
June 2016	Removal of Section 2 for inclusion in separate guideline Publication for implementation	v3 June 2016

ANNEXURE A Category D Decision Tree



ANNEXURE B

Consultation with the AHPCSA

Regulation 25A of the General Regulations made in terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965), provides for the subdivision of Complementary Medicine into such disciplines as determined by Council after consultation with the Allied Health Professions Council of South Africa (AHPCSA). Such consultation shall consist of a meeting of representatives of the SAHPRA and the Allied Health Professions Council of South Africa (AHPCSA) by way of request by either party. The requesting party shall provide the intended agenda for discussion. The intention of identification of any specific discipline must consider that:

i) It is a recognised discipline with documented, verifiable historical usage of the associated medicines;

ii) It is distinctly separate from any other existing or proposed discipline;

iii) There is a significant usage and/or demand for a form of proprietary product associated with the discipline in South Africa, and

iv) It may be associated with the use of any professionals registered or that could be registered with the AHPCSA.

The AHPCSA shall be granted the opportunity of making recommendation to representatives of the SAHPRA. Following discussion, the representatives of the SAHPRA shall minute proceedings of the meeting and make further recommendations for discussion to the Complementary Medicines Committee (CMC) which shall in turn make the required recommendations to the SAHPRA for inclusion as a discipline of Complementary Medicine.

ANNEXURE C

Origin of Complementary Medicines

The origin of any complementary medicine is defined to be from plants, fungi, algae, seaweeds, lichens, minerals, animals or other substance as determined by Council. Where any medicine is not to be of plants, fungi, algae, seaweeds, lichens, minerals or animals the applicant should demonstrate that such a substance accords with its use within the relevant discipline within the provided literature with respect to substantiation of traditional use. The Council will evaluate the use of such a substance and provided that it accords with the relevant discipline, allow for the use of such substance on recommendation from the Complementary Medicines Committee (CMC).

ANNEXURE D

Specified Accepted Reference Lists

Below appears the list of acceptable and authoritative texts for each discipline which could be consulted in addition to those standard references stipulated in the SAHPRA Guideline entitled, “COMPLEMENTARY MEDICINES - SAFETY, and EFFICACY” to which this annexure relates. This list shall be amended from time to time and is inclusive of any later / English edition of the stipulated text. The latest edition of any of the mentioned texts or other directly associated versions is allowable.

Aromatherapy

Lists and Manuals:

Aroma SA: Journal of the Aromatherapy Association of South Africa– all volumes

Australian Therapeutic Goods Authority List of Substances

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

International Journal of Aromatherapy – all volumes South

African list of essential oils (**ANNEXURE E**) Reference

Books:

Battaglia, S. (1962). *The Complete Guide to Aromatherapy*. 1st & 2nd Edition. Perfect Potion. ISBN 0 6464 2896 9

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

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

Lawless, J. (2013). *The Encyclopaedia of Essential Oils: The Complete Guide to the Use of Aromatic Oils In Aromatherapy, Herbalism, Health, and Well Being*. Harper Collins. ISBN 157324614X

Price, L. (2000). *Carrier Oils: For Aromatherapy and Massage*. 4th Ed. Riverhead. ISBN 1 874353 02 6 **Price**, S. (1999). *Aromatherapy for Health Professionals*, 2nd Ed. Churchill Livingstone. ISBN 0 443 06210 2

Schnaubelt, K.(2011). *The Healing Intelligence of Essential Oils: The Science of Advanced Aromatherapy.* ISBN 978-1594774256.

Sheppard-Hanger, S. (1997). *The Aromatherapy Practitioner Reference Manual*: The Complete Reference Book of Over 350 Aromatic Plant Extracts, Index of Biologically Active Phytochemicals, Clinical Index and Taxonomical Index, Vol. 1 & 2. Atlantic Institute of Aromatherapy: Tampa.

Tisserand, R. (1995). *Essential Oil Safety: A Guide for Health Care Professionals.* Churchill Livingstone. ISBN 0
443 05260 3

Tisserand, R. (1977). *The Art of Aromatherapy.*, New York; Inner Traditions Int. ISBN 9780852071403 **Valnet**, J. (2012). *The Practice Of Aromatherapy.* Ebury Digital ISBN 0 85207 143 4

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ANNEXURE E 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 galanga		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
Apium graveolens		Celery
Arnica montana		Arnica, leopards bane, mountain tobacco
Artemisia abrotanum		Southenwood
Artemisia absinthium	Artemisia afra	Wormwood
Artemisia annua		Annie sweet, annual wormwood

LABEL NAME	SYNONYM	COMMON NAME
Artemisia arborescens		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.
Eriocephalus africanus		Cape Snowbush, Kapokbos, wild rosemary - indigenous
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, Goldbloom, Pot marigold, Hollygold, Common marigold, Poet's marigold
Cananga odorata	Cananga odoratum var. macrophylla	Cananga
Cananga odorata var. genuina	Unona odoratissimum	Ylang ylang, Flower of flowers
Canarium luzonicum	Canarium commune	Elemi, Manila elemi, Elemi gum, Elemi resin, Elemi oleoresin

LABEL NAME	SYNONYM	COMMON NAME
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

LABEL NAME	SYNONYM	COMMON NAME
Guaiacum officinale	G. sanctum, Bulnesia sarmienta	Guaiacwood, Champaca wood, Palo santo

Helichrysum angustifolium		Helichrysum, Immortelle, Everlasting, St. John's herb
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 lavender, 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

LABEL NAME	SYNONYM	COMMON NAME
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'
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-ofthemountain, "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

LABEL NAME	**SYNONYM**	**COMMON NAME**

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		TEREBINTH, Turpentine, Therebintine, Gum thus, Gum turpentine, Turpentine balsam, Spirit of turpentine (oil)
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		SAGE SPANISH , Lavender-leaves sage
Salvia sclarea		CLARY SAGE, Clary, Clary wort, Muscatel sage, Clera eye, See bright, Common clary, Clarry, Eye bright
Salvia africana-lutea *Salvia africana-ceroelia*		AFRICAN SAGE
Salvia officinalis		COMMON SAGE
Santalum album		SANDALWOOD, White sandalwood, Yellow sandalwood, East Indian sandalwood, Sandalwood Mysore, Sanders-wood
LABEL NAME	**SYNONYM**	**COMMON NAME**
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	TAGETES, Tagette, Taget, Mexican marigold, Khakibos
Thymus vulgaris	Thymus aestivus, Thymus ilerdensis, Thymus webbianus, Thymus valentianus	THYME, Common thyme, French thyme, Garden thyme

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