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COMPLEMENTARY MEDICINES - DISCIPLINE-SPECIFIC SAFETY AND EFFICACY

This guideline provides recommendations to applicants wishing to submit applications for the registration of Complementary Medicines (Category D). It represents the South African Health Product Regulatory Authority's current thinking on the quality, safety, and efficacy of these medicines and is not intended as an exclusive approach. The 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 ensuring that all registered medicines will be of the required safety, quality 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 website: **www.sahpra.org.za**.

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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 documents, including those referred to therein:

- 6.18 Complementary Medicines – Screening Template for new applications for registration of a Complementary Medicine
- 7.02 Complementary Medicines – Roadmap and Transitional Process
- 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
- 7.06 Complementary Medicines – Guidance on Specified Substances

Other SAHPRA guidelines may be referred to where appropriate. A copied of the referenced guideline should also be supplied.

ii) Scope and Overview

This SE Guideline applies to complementary medicines (Category D) of the discipline specific sub-category 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 discipline-specific 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.

The CMs that will be the subject to these Guidelines are those associated with those disciplines as determined by the Authority herein. Currently, six major disciplines have been identified and preparations associated therewith, namely: **Aromatherapy, Ayurveda, Homeopathy, Traditional Chinese Medicine, Unani Medicine,** and **Western Herbal Medicine**. In addition, a seventh category - **Combination Products** - is recognised and dealt with below. The classification of **"Other Herbal"** may also be appropriated where any herbal substance of origin from a traditional discipline not listed above.

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) most appropriate to the context and nature of the product. 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) As per the General Regulations made in terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965):

"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 the Authority;

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

(i) in maintaining, complementing or assisting the 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 the Authority;

ii) As per the General Regulations made in terms of the Medicines and Related Substances Act, 1965 (Act 101 of 1965):

"health supplement" *means any substance, extract or mixture of substances as determined by the Authority, sold in dosage forms used or purported for use in restoring, correcting or modifying any physical or mental state by-*

(a) complementing health;

(b) supplementing the diet; or

(c) a nutritional effect,

and excludes injectable preparations, medicines or substances listed as Schedule 1 or higher in the Act;

iii) For the purposes of this guideline a combination product is (see also 1.6.2):

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 substances

Traditional Chinese, Ayurvedic and Unani 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 symptoms in a healthy person 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] Guidance on equivalence of herbal extracts in complementary medicines; **https://www.tga.gov.au/publication/guidance-equivalence-herbal-extracts-complementary-medicines#not**

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.

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. Refer also to Guideline 7.05: Annex B - Naming and labelling conventions for active ingredients in complementary medicines.

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 name a biological or animal substance fully.

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); or
d) 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 name an herbal ingredient fully.

For purposes of the product label, 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 isolated constituent 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 [ZA-CTD Modules 1.5.1]. **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

Western Herbal medicines or substances must be described as Western 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 related to Western Herbal Medicine,

which prove its origin and use within Western Herbal Medicine.

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 medicine or substance must be described as a Unani 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 *Only for non-eCTD electronic submission*	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 (Professional Information)	
1.3.1.1	Package insert (Professional Information)	Ensure that the proprietary name, pharmacological classification dosage form, active ingredient(s), strength,
1.3.1.2	Standard References	

Module	Heading	Comments/Notes
1.3.2	Patient Information Leaflet	composition, dosage regimen, identification, presentation and storage correspond with the information in all other Modules.
1.3.3	Labels	References listed that justify the medicine in terms of efficacy or safety claims (including traditional use and clinical evidence).
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.
		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. In order for a product to qualify to be registered as a CM in South Africa it must demonstrate origin from a recognised discipline. Provide references for the use of these substances in the specified discipline by providing references from the listed accepted sources. Traditional use within the discipline should be given, where possible for each of the following two aspects: a) origin/use of that herb within the discipline in general (as a demonstration of long-standing safe use); and b) use of the herb in the discipline for the indications claimed for this product or the particular API (demonstrating accordance with its clinical use in the discipline). Where (b) is not possible and rather relies on new or non-traditional evidence, this should be stated and the source of indications stated, e.g. clinical data from RCT.

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 search 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.
		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.

Module	Heading	Comments/Notes
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.
		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

Module	Heading	Comments/Notes
		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, five (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 the risk level of the claim (See 4.1).

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. Where the NMCD is referenced, care should be taken to consider the section from which information is taken (e.g., not safe, insufficient evidence or sufficient evidence for efficacy). Information quoted from such references when done so without this context and further substantiation is not acceptable. Information from sections such as "*People use this for:*" should be used with caution.

While this information may serve as limited substantiation of traditional use, it does not adequately substantiate claims 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.

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.

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.

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-risk level claims (i.e. the use of medicines for the treatment or prevention of a disease/disorder) 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 of SAHPRA.

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
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.
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 disease/disorder or sign/symptom of a named 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.

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 relevant health care provider".
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.

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; [2]

[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

- 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 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 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).

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 EFFICACY

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

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 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

means a noxious and unintended response to a medicine;

Animal

An invertebrate or vertebrate member of the animal kingdom.

Applicant

means 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

means 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

means 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

means any substance or mixture of substances that-

(a) originates from plants, fungi, algae, seaweeds, lichens, minerals, animals or other substance as determined by the Authority;

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

(i) in maintaining, complementing or assisting the 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 the Authority;

Dosage form

The pharmaceutical form in which the active ingredients and excipients, and physical formulation of a medicine is presented. *See also General Information Guideline*

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

means 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 as determined by the Authority, sold in dosage forms used or purported for use in restoring, correcting or modifying any physical or mental state by-

(a) complementing health;

(b) supplementing the diet; or

(c) a nutritional effect,

and excludes injectable preparations, medicines or substances listed as Schedule 1 or higher in the Act;

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.

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.

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

Manufacture

means 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

General Regulations made in terms of 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

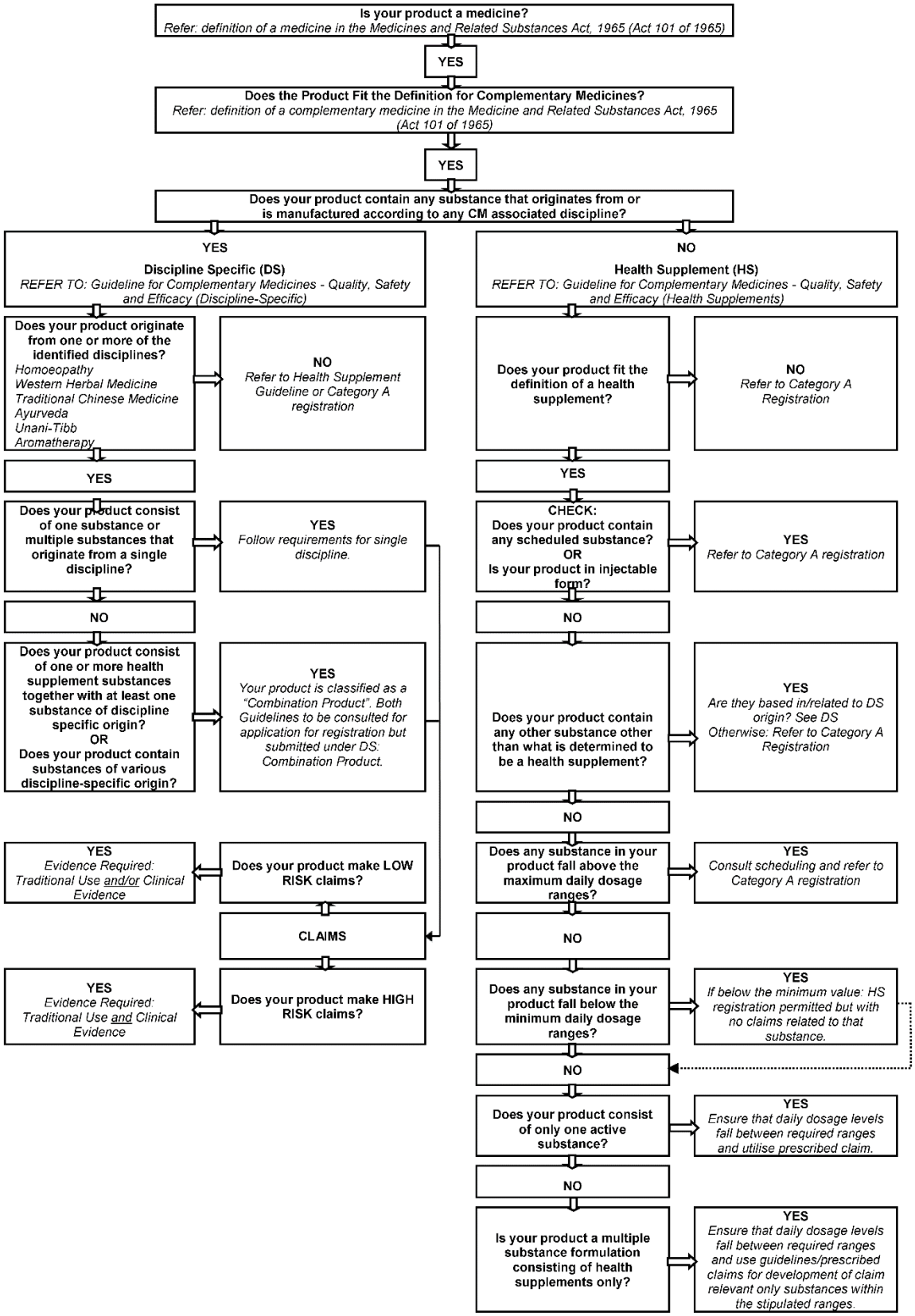
ADR	Adverse Drug Reaction
AHPCSA	Allied Health Professions Council of South Africa
BP	British Pharmacopoeia
CAS	Chemical Abstracts Service (Registry)
CM(s)	Complementary Medicine(s)
CPMP	Committee for Proprietary Medicinal Products (of the EMA)
CTD	Common Technical Document
EU	European Union
FDA	Food 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	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH)
IV	Intravenous
pH	Negative logarithm of hydrogen-ion concentration
Ph Eur	European Pharmacopoeia (also known as EP)
PI	Package insert
SAE	Serious Adverse Event
SAHPRA	South African Health Products Regulatory Authority
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 MCC 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 comment Due date for comment	v3 June 2016
June 2020	Amendment of SAHPR/Authority nomenclature Amendment of definitions and clarification of guidance Minor additions and corrections: Section 1, 1.7, 1.7.1 Section 3.1, par 3 Section 4.1, Table 1 (order of claims, wording of low risk, amendment of note 2) Annexure A: Correction of line direction Annexures B and D: Amendment and clarification Annexure E: Addition of accepted names	v3_1 June 2020

ANNEXURE A

Category D Decision Tree



ANNEXURE B

Format for discussion of Traditional Use

Module 1.5.1

This module should demonstrate that the substance(s) used in the medicine:

1. are appropriately justified to originate from the stated discipline(s);
2. are appropriately justified to be used within the stated discipline(s) and that their traditional use:
   a) sufficiently demonstrates long-standing safe use; and
   b) accords directly with the intended indication;

   Where (b) is not possible and rather relies on new, non-traditional evidence such as accepted use in EMA monographs, this should be stated and the source of indications stated, e.g. clinical data from RCT; and
3. appear in the annexures to the Guideline Complementary Medicines – Health Supplements and that the dosage levels are used as prescribed. Stated warnings / additional information should also be highlighted for inclusion on relevant labelling.

Module 2.5

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 Authority aligns itself with.

In addition, 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.

Do not overstate the evidence provided by traditional use – give sufficient reference and guidance as related to the claim and as per guideline.

Two of the following four sources that demonstrates adequate support for the indications claimed:

Recognised Pharmacopoeia;
Recognised Monograph;
Three independent written histories of use in the classical or traditional medical literature.
Citations from other in vivo, in vitro studies, case reports or others.

Monographs

Monographs of equivalent standing to those specifically listed may be used.
Monographs may be quoted but applicants must provide copies of the relevant monograph.
Demonstration of how the product accords with such monograph must be made.

Pharmacopoeias

Copies of the relevant extract from the necessary pharmacopoeia must be provided.

Health Supplements

A bibliographical evidence or expert evidence to the effect that the medicinal product in question, or its ingredients or a corresponding product, accords with the claims and dosage levels as provided for in the annexures to the guideline.

In addition, 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.

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 the SAHPRA. 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 SAHPRA 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 7.01 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

Ayurveda

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

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.

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.

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.

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

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

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

Homeopathy

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 Homeopathique 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*. 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 including Boger's Boenninghausen repertory additions*

Traditional Chinese Medicine

A Barefoot Doctor's Manual. The American Translation of the Official Chinese Paramedical Manual. Running Press: Philadelphia.. ISBN: 0-914294-91-1

Chen, J & Chen, T. (2004) *Chinese Medical Herbology & Pharmacology.* Art of Medicine Press. ISBN 0-9740635-0-9.

Bensky, D. and Gamble, A. (1993). *Chinese Herbal Medicine: Materia Medica*. ISBN-13: 978-0939616152. ISBN-10: 0939616157.

Bensky, D and Barolet, R (1990). *Chinese Herbal Medicine: Formulas and Strategies*. Eastland Press:Seattle.. ISBN-13: 978-0939616107. ISBN-10: 0939616106.

Bensky, D., Clavey, S. & Stoger, E. (2004) *Chinese Herbal Materia Medica,* 3rd ed. ISBN-13: 978-0939616428. ISBN-10: 0939616424.

Bensky, D., Ellis, A.&Barolet, R.(2009) *Chinese Herbal Medicine: Formulas and Strategies.* 2nd Ed,. ISBN-13: 978-0939616671. ISBN-10: 093961667X.

Chen Song Yu and Li Fei. Transl. Jin Hui De. (1993). *A Clinical Guide to Chinese Herbs and Formulae.* Churchill Livingstone-Longman Group UK. ISBN: 0-443-04680-8.

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Maciocia, G. (2005). *The Foundations of Chinese Medicine: A Comprehensive Text for Acupuncturists and Herbalists*. 2nd Ed, . ISBN-13: 978-0443074899. ISBN-10: 0443074895.

Maclean, W. &Lyttleton, J.. *Clinical Handbook of Internal Medicine. The Treatment of Disease with Traditional Chinese Medicine*. University of Western Sydney Macarthur. ISBN: 1-875760-93-8.

Naesar, M. (1992). *Outline to Chinese Herbal Patent Medicines in Pill Form* (2nd Ed), Boston Chinese Medicine. ISBN-13: 0962565113. ISBN-10: 0962565113.

State Administration of Traditional Chinese Medicine *Advanced Textbook on Traditional Chinese Medicine and Pharmacology.* New World Press: Beijing. ISBN: 7-80005-301-6.

The Yellow Emperor's Classic of Internal Medicine. Transl. Ilza Veith. University of California Press. ISBN: 0-520-02158-4.

Unani

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.

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

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

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. *(where it pertains to Unani)*

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. *(where it pertains to Unani)*

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

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

Nadkarni, K. M., Nadkarni, A.K. (1976), "Indian Materia Medica", Bombay India. *(where it pertains to Unani)*

Western Herbal Medicine

Bone, K. & Mills, S. (2013). *Principles and Practice of Phytotherapy: modern herbal medicine*, 2nd ed. Churchill Livingstone:Edinburgh

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

British Herbal Medicine Association (1983). *British Herbal Pharmacopoeia.* British Herbal Medicine Association:Cowling (UK), (or any other edition,1-4 or later)

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

Cook, W (1869). *The Physiomedical Dispensatory.* (**http://www.henriettesherbal.com/eclectic/cook/index.html**)

Ellingwood (1983). *The American Materia Medica, Therapeutics and Pharmacognosy*. Eclectic Medical, (Reprint 1919)(http://www.henriettesherbal.com/eclectic/ellingwood/index.html)

ESCOP (2003). *ESCOP Monographs: The scientific foundation for herbal medicinal products*, 2nd ed. Thieme ISBN1-901964-07-8

Felter and Lloyd (1997). *King's American Dispensatory*. Eclectic Medical Publications, (Reprint 1898). (http://www.henriettesherbal.com/eclectic/kings/index.html)

Felter, H.W. (1922). *The Eclectic Materia Medica, Pharmacology and Therapeutics.* (**http://www.henriettesherbal.com/eclectic/felter/index.html**)

Grieve, M. (1971) *A Modern Herbal, Volume 1-2*. New York (NY): Dover Publications, [Reprint of 1931 Harcourt, Brace & Company publication]. (**http://botanical.com/botanical/mgmh/comindx.html**)

Health Canada NHPD monographs and other sources of Pre-Cleared Information

Hoffmann, D. (2003). *Medical Herbalism: the science and practice of herbal medicine*. Healing Arts Press:Rochester

Petersen, J. (1905). *Materia Medica and Clinical Therapeutics*. F.J. Peterson, 1905 (Reprint). (**http://www.henriettesherbal.com/eclectic/petersen/index.html**)

Remington *et al*.(1918). *The Dispensatory of the United States of America.* J.B. Lippincott Company, (**http://www.henriettesherbal.com/eclectic/usdisp/index.html**)

Romm, A.(2010). Botanical Medicine for Women's Health. Churchill Livingstone:St Louis.

Sayre, L. (1917). *A Manual of Organic Materia Medica and Pharmacognosy*. P. Blakiston's Son & Company. (http://www.henriettesherbal.com/eclectic/sayre/index.html)

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

Wren, RC. (1907). *Potter's Cyclopedia of Botanical Drugs and Preparations*. London (GB): Potter and Clark.

ANNEXURE E

Accepted Aromatherapy Substance List

In terms of Government Gazette Notice R. 44 in *Government Gazette* 16930 on 19 January 1996 preparations intended for aromatherapy for which no medicinal claims are made are not required to be submitted for registration: provided that **only** the descriptive words as listed in the Schedule to the notice (stated below) are used in advertisements for such preparations (or as their indications). Any other indications or wording (whether low or high risk) may subject such preparations to registration.

BALANCING COMFORTING NORMALISING REFRESHING RELAXING REVIVING

SOOTHING STIMULATING STRENGTHENING TONING UPLIFTING WARMING

The use of names for substances should take place in line with Annex B of Guideline 7.05. For the purposes of the table below:

Accepted name: This is the name currently identified to most accurately describe the specific substance and which should appear in the Professional Information and Patient Information Leaflet. Prior to use, applicants should verify the accepted name as per section 1.5 of this guideline.

Label name: This is the name that may appear on the outer or package label should space requirements not permit the use of the accepted name.

Synonym: Should only be used when determining when a substance is included by the accepted name.

Common name: The most appropriate common name should be used in terms of Annex 5 of Guideline 7.05.

ACCEPTED NAME	LABEL NAME	SYNONYM	COMMON NAME
Abelmoschus moschatus Medik.	*Abelmoschus moschatus*	*Hibiscus abelmoschus*	Ambrette seed, Musk seed, Egyptian alcee, Target-leaved hibiscus, Muskmallow
Abies alba Mill.	*Abies alba*	*Abies pectinata*	Silver fir needle, Whitespruce, European silver fir, Edeltanne, Weistanne
Abies balsamea (L.) Mill.	*Abies balsamea*	*Abies balsamifera, Pinus balsamea*	Canadian balsam, Balsam fir, Balsam tree, American silver fir, Balm of Gilead fir, Canada turpentine (oil)
Acacia dealbata Link	*Acacia dealbata*	*Acacia decurrens* var. *dealbata*	Mimosa, Sydney black wattle
Acacia farnesiana (L.) Willd.	*Acacia farnesiana*		Cassie, Sweet acacia, Huisache, Popinac, Opopanax
Achillea millefolium L.	*Achillea millefolium*		Yarrow, Milfoil, Millefolium, Common yarrow, Nosebleed, Thousand leaf
Acorus calamus var. *angustatus* Besser	*Acorus calamus*		Calamus
Agathosma betulina (P.J.Bergius) Pillans	*Agathosma betulina*	*Barosma betulina*	Buchu
Allium cepa L.	*Allium cepa*		Onion
Allium sativum L.	*Allium sativum*		Garlic
Aloysia citriodora Palau	*Lippia citriodora*	*Aloysia triphylla, Aloysia citriodora, Lippia triphylla, Verbena triphylla*	Lemon Verbena

ACCEPTED NAME	LABEL NAME	SYNONYM	COMMON NAME
Alpinia galanga (L.) Willd.	*Alpinia galanga*		Siamese Ginger, Galangal Root
Amyris balsamifera L.	*Amyris balsamifera*		Sandalwood WI, Amyris
Anethum graveolens L.	*Anethum graveolens*	*Graveolens anethum, Peucedanum graveolens*	Dill, European Dill, American Dill
Angelica archangelica L.	*Angelica archangelica*	*Angelica officinalis*	Angelica, European Angelica, Garden Angelica
Aniba rosaeodora Ducke	*Aniba rosaeodora*	*Aniba rosaeodora* var. *amazonica*	Rosewood, Bois de rose, Brazilian Rosewood
Anthoxanthum odoratum L.	*Anthoxanthum odoratum*		Flouve/ Sweet Vernal Grass
Apium graveolens L.	*Apium graveolens*		Celery
Arnica montana L.	*Arnica montana*		Arnica, Leopard's Bane, Mountain Tobacco
Artemisia abrotanum L.	*Artemisia abrotanum*		Southenwood
Artemisia absinthium L.	*Artemisia absinthium*		Wormwood
Artemisia annua L.	*Artemisia annua*		Sweet Annie , Annual Wormwood
Artemisia arborescens (Vaill.) L.	*Artemisia arborescens*		Tree Wormwood
Artemisia dracunculus L.	*Artemisia dracunculus*		Tarragon, Estragon, Russian tarragon
Artemisia herba-alba Asso	*Artemisia herba-alba*		Armoise, White Wormwood
Artemisia pallens Wall. ex DC.	*Artemisia pallens*		Davana
Artemisia vulgaris L.	*Artemisia vulgaris*		Mugwort
Asarum canadense L.	*Asarum canadense*		Snakeroot, Wild ginger
Betula lenta L.	*Betula lenta*		Sweet Birch
Betula pubescens Ehrh.	*Betula pubescens*	*Betula alba, Betula odorata, Betula pendula, Betula verrucosa*	European white birch, Silver birch
Boronia megastigma Nees ex Bartlett	*Boronia megastigma*		Boronia
Boswellia frereana Birdw.	*Boswellia frereana*		Coptic Frankincense, Dhidin, Maydi
Boswellia sacra Flueck.	*Boswellia sacra*	*Boswellia carteri*	Frankincense, Olibanum, Gum Thus
Brassica nigra (L.) K.Koch	*Brassica nigra*		Black Mustard
Bulnesia sarmientoi Lorentz ex Griseb.	*Bulnesia sarmientoi*		Argentine Lignum Vitae, Palo Santo
Bursera glabrifolia (Kunth) Engl.	*Bursera glabrifolia*		Copal, Macho Copal
Calendula officinalis L.	*Calendula officinalis*		Marigold, Calendula, Pot marigold, Common marigold
Cananga odorata (Lam.) Hook.f. & Thomson	*Cananga odorata*	*Unona odoratissimum*	Ylang Ylang, Cananga
Canarium luzonicum (Blume) A.Gray	*Canarium luzonicum*		Elemi, Elemi gum, Elemi resin, Elemi oleoresin
Carum carvi L.	*Carum carvi*	*Apium carvi, Bunium carvi*	Caraway
Cedrus atlantica (Endl.) Manetti ex Carrière	*Cedrus atlantica*		Atlas Cedarwood, Atlantic Cedar, Atlas Cedar, African Cedar, Moroccan cedarwood
Chamaemelum nobile (L.) All.	*Chamaemelum nobile*	*Anthemis nobilis, Chamomilla romana*	Roman chamomile, English chamomile, Garden Chamomile, Sweet Chamomile, True Chamomile
Chrysopogon zizanioides (L.) Roberty	*Chrysopogon zizanioides*	*Andropogon muricatus*	Vetiver
Chrysopogon zizanioides (L.) Roberty	*Chrysopogon zizanioides*	*Vetiveria zizanoides, Andropogon muriaticus, Anatherum muriaticum*	VETIVER, Vetivert, Khus khus

ACCEPTED NAME	LABEL NAME	SYNONYM	COMMON NAME
Cinnamomum camphora (L.) J.Presl	*Cinnamomum camphora*	*Laurus camphora, Camphora officinalis*	Camphor, True camphor
Cinnamomum cassia (L.) J.Presl	*Cinnamomum cassia*	*Cinnamomum aromaticum*	Cassia Cinnamon, Cassia Bark, Cassia
Cinnamomum verum J.Presl.	*Cinnamomum verum*	*Cinnamomum zeylanicum, Laurus cinnamomum*	Cinnamon, Ceylon Cinnamon, Seychelles Cinnamon, Madagascar Cinnamon, True Cinnamon
Cistus creticus L..	*Cistus creticus*	*Cistus ladaniferus*	Labdanum, Cistus, Gum cistus, Ciste, Labdanum gum, European Rock Rose
Citrus aurantiifolia (Christm.) Swingle	*Citrus aurantiifolia*	*Citrus medica* var. *acida*, *Citrus latifolia*	Lime, Mexican lime, West Indian lime, Sour lime
Citrus bergamia Risso.	*Citrus bergamia*	*Citrus aurantium* subsp. *bergamia* (Risso & Poit.) Wight & Arn. ex Engl.	Bergamot
Citrus limon (L.) Osbeck	*Citrus limon*	*Citrus* x *limonum*	Lemon
*Citrus paradi*si Macfad.	*Citrus paradisi*	*Citrus* x *paradisi*	Grapefruit
Citrus reticulata Blanco	*Citrus reticulata*	*Citrus nobilis, Citrus madurensis, Citrus unshiu, Citrus deliciosa, Citrus tangerina*	Mandarin, European mandarin, True mandarin, Tangerine, Satsuma
Citrus sinensis (L.) Osbeck	*Citrus sinensis*		Sweet Orange, China Orange, Portugal Orange
Citrus x *aurantium* L.	*Citrus aurantium* (flower)	*Citrus aurantium* subsp. *amara, Citrus vulgaris, Citrus bigaradia*	Orange blossom, Neroli, Neroli bigarade
Citrus x *aurantium* L.	*Citrus aurantium* (leaf)	*Citrus aurantium* subsp. *amara*	Petitgrain, Petitgrain bigarade, Petitgrain Paraguay
Citrus x *aurantium* L.	*Citrus aurantium* (fruit)	*Citrus aurantium* subsp. *amara, Citrus vulgaris, Citrus bigaradia*	Bitter orange, Seville orange, Sour orange bigarade (oil). Sweet orange
Clinopodium menthifolium (Host) Stace	*Clinopodium menthifolium*	*Calamintha sylvatica*	Wood Calamint
Clinopodium nepeta (L.) Kuntze.	*Clinopodium nepeta*	*Calamintha nepeta*	Lesser Calamint
Clinopodium nepeta subsp. *glandulosum* (Req.) Govaerts.	*Clinopodium nepeta subsp. glandulosum*	*Calamintha officinalis, Calamintha clinopodium, Melissa calaminta*	Calamintha, Calamint, Common Calamint
Commiphora myrrha (Nees) Engl.	*Commiphora myrrha*	*Balsamodendron myrrha, Commiphora molmol*	Myrrh, Gum myrrh, Common myrrh, Myrrha
Copaifera officinalis L.	*Copaifera officinalis*	*Copaiba officinalis*	Copaiba balsam, Copahu balsam, Copaiba, Copaiva, Jesuit's balsam, Maracaibo balsam, Para balsam
Coriandrum sativum L.	*Coriandrum sativum*		Coriander
Corymbia citriodora (Hook.) K.D.Hill & L.A.S.Johnson	*Corymbia citriodora*	*Eucalyptus citriodora*	Lemon-scented Eucalyptus, Lemon-scented Gum, Citron-scented Gum
Croton eluteria (L.) W.Wright	*Croton eluteria*		Cascarilla, Cascarilla bark
Cuminum cyminum L.	*Cuminum cyminum*	*Cuminum odorum*	Cumin, Cummin
Cupressus sempervirens L.	*Cupressus sempervirens*	*Cupressus australis, Cupressus fastigiata*	Cypress, Italian Cypress, Mediterranean Cypress
Curcuma longa L.	*Curcuma longa*	*Curcuma domestica, Amomum curcuma*	Turmeric
Cymbopogon citratus (DC.) Stapf	*Cymbopogon citratus*	*Andropogon citratus, Andropogon schoenanthus*	Lemongrass: West Indian / Madagascar / Guatemala lemongrass
Cymbopogon flexuosus (Nees ex Steud.) W.Watson	*Cymbopogon flexuosus*	*Andropogon flexuosus*	Lemongrass: East Indian / Cochin / Native / British India lemongrass

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Cymbopogon martini (Roxb.) W.Watson	*Cymbopogon martini*	*Andropogon martini, Andropogon martini*	Palmarosa, East Indian geranium, Turkish geranium, Indian rosha, Motia
Cymbopogon nardus (L.) Rendle	*Cymbopogon nardus*	*Andropogon nardus*	Citronella,Sri Lanka Citronella Lenebatu Citronella
Daucus carota L.	*Daucus carota*		Carrot seed, Wild carrot, Queen Anne's Lace
Dryobalanops sumatrensis (J.F.Gmel.) Kosterm.	*Dryobalanops sumatrensis*	*Dryobalanops camphora, Dryobalanops aromatica*	Borneo camphor, East Indian Camphor, Sumatra Camphor, Malay Camphor
Dysphania ambrosioides (L.) Mosyakin & Clemants.	*Dysphania ambrosioides*	*Chenopodium ambrosioides*	Wormseed
Elettaria cardamomum (L.) Maton	*Elettaria cardamomum*		Cardamom, True Cardamom, Green Cardamom
Eriocephalus africanus L.	*Eriocephalus africanus*		Cape Snowbush, Kapokbos, Wild Rosemary
Eriocephalus punctulatus DC.	*Eriocephalus punctulatus*		Cape Chamomile, boegoekapok
Eucalyptus dives Schauer	*Eucalyptus dives*		Broad-leaved Peppermint Eucalyptus, Menthol-scented Gum
Eucalyptus globulus Labill.	*Eucalyptus globulus*	*Eucalyptus globulus* subsp. *globulus*	Eucalyptus, Blue gum, Gum tree, Southern blue gum, Tasmanian blue gum, Fever tree, Stringy bark
Ferula assa-foetida L.	*Ferula assa-foetida*	*Ferula foetida, Narthex assafoetida*	Asafetida, Asafoetida, Gum Asafetida, Devil's Dung
Ferula gummosa Boiss.	*Ferula gummosa*	*Ferula galbaniflua*	Galbanum, Galbanum gum / resin, Bubonion
Foeniculum vulgare Mill.	*Foeniculum vulgare*		Fennel
Guaiacum officinale L.	*Guaiacum officinale*		Guaiacum, Guaiacwood, Lignum Vitae
Helichrysum italicum (Roth) G.Don	*Helichrysum italicum*	*Gnaphalium italicum* Roth	Helichrysum, Immortelle, Everlasting
Humulus lupulus L.	*Humulus lupulus*	*Lupulus humulus*	Hops, Common Hop, European Hop, Lupulus
Hyacinthus orientalis L.	*Hyacinthus orientalis*	*Scilla nutans*	Hyacinth, Bluebell
Hyssopus officinalis L.	*Hyssopus officinalis*		Hyssop
Illicium verum Hook.f.	*Illicium verum*		Star Anise, Chinese Anise, Illicium, Chinese Star Anise
Jasminum officinale L.	*Jasminum officinale*		Jasmine, Jasmin, Jessamine, Common Jasmine
Juniperus ashei J.Buchholz	*Juniperus ashei*	*Juniperus mexicana*	Ashe Juniper, Mountain Cedar, Mexican Cedar, Mexican Juniper
Juniperus communis L.	*Juniperus communis*		Juniper, Common Juniper
Juniperus oxycedrus L.	*Juniperus oxycedrus*		Cade, Cade Juniper, Prickly Cedar, Prickly Juniper
Juniperus virginiana L.	*Juniperus virginiana*	*Juniperus virginianus*	Virginian cedarwood, Red Cedar, Eastern Red Cedar, Virginian Juniper
Laurus nobilis L.	*Laurus nobilis*		Bay Laurel, Sweet Bay, Grecian Laurel, True Bay, Mediterranean Bay, Roman Laurel, Noble Laurel
Lavandula × *intermedia* Emeric ex Loisel.	*Lavandula x intermedia*	*Lavandula* hybrida, *Lavandula* hortensis	Lavandin, Bastard lavender
Lavandula angustifolia Mill.	*Lavandula angustifolia*	*Lavandula officinalis, Lavandula vera*	True Lavender, Garden Lavender, Common Lavender

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Lavandula latifolia Medik.	*Lavandula latifolia*	*Lavandula spica*	Spike Lavender, Broad-leaved Lavender, Lesser Lavender
Levisticum officinale W.D.J.Koch	*Levisticum officinale*	*Angelica levisticum, Ligusticum levisticum*	Lovage Root, Maggi herb, Garden/Common Lovage
Liquidambar orientalis Mill.	*Liquidambar orientalis*	*Balsam styracis*	LEVANT STYRAX, Balsam Styracis, Oriental sweetgum, Turkish sweetgum, Asiatic styrax, Storax
Litsea cubeba (Lour.) Pers.	*Litsea cubeba*	*Litsea citrata.*	May Chang, Aromatic Litsea
Matricaria chamomilla L.	*Matricaria chamomilla*	*Chamomilla recutita, Chamomilla vulgaris, Matricaria recutita*	GERMAN CHAMOMILE (CAMOMILE) Blue Chamomile, Matricaria, Hungarian Chamomile, Wild Chamomile
Melaleuca alternifolia (Maiden & Betche) Cheel	*Melaleuca alternifolia*		TEA TREE, Narrow-leaved paperbark tea tree, Ti-tree, Ti-trol, Melasol
Melaleuca leucadendra (L.) L. OR *Melaleuca cajuputi* Powell OR *Melaleuca squarrosa* Sm.	*Melaleuca cajeputi, M. squarrosa or M. leucadendra*	*Melaleuca minor, Melaleuca aetheroleum*	CAJEPUT, Cajuput, White Tea Tree, White Wood, Paperbark tree.
Melaleuca viridiflora Sol. ex Gaertn.	*Melaleuca viridiflora*	*Melaleuca quinquenervia*	NIAOULI, Broad-leaved Paperbark, Paper Bark Tea Tree
Melissa officinalis L.	*Melissa officinalis*		MELISSA, Lemon Balm, Common Balm
Mentha × *piperita* L.	*Mentha piperita*		PEPPERMINT
Mentha arvensis L.	*Mentha arvensis*		MINT, Cornmint, Japanese Mint, Chinese Mint
Mentha pulegium L.	*Mentha pulegium*	*Hedeoma pulegoides*	PENNYROYAL
Mentha spicata L.	*Mentha spicata*	*Mentha viridis.*	SPEARMINT, Common Spearmint, Garden Spearmint
Myristica fragrans Houtt.	*Myristica fragrans*	*Myristica officinalis, Myristica aromata, Myristica aromtica, Nux moschata, Nuphar pumilum*	NUTMEG, Myristica, Mace (husk)
Myrocarpus fastigiatus Allemao	*Myrocarpus fastigiatus*		CABREUVA, Cabureicica, "Baume de Perou brun"
Myroxylon balsamum (L.) Harms	*Myroxylon balsamum*	*Toluifera balsamum, Balsamum tolutanum, Balsamum americanum, Myrospermum toluiferum, Myroxylon balsamum var. balsamum*	TOLU BALSAM
Myroxylon balsamum var. *pereirae* (Royle) Harms	*Myroxylon balsamum var. pereirae*	*Toluifera pereira, Myrospermum pereira, Myroxylon pereirae*	PERU BALSAM, Peruvian Balsam, Balsam of Peru
Myrtus communis L.	*Myrtus communis*		MYRTLE, Common Myrtle
Nardostachys jatamansi (D.Don) DC.	*Nardostachys jatamansi*		SPIKENARD, Nard, Indian Spikenard, Jatamamsi
Ocimum basilicum L.	*Ocimum basilicum*		BASIL, French Basil, Common Basil, Sweet Basil,
Origanum majorana L.	*Origanum majorana*	*Majorana hortensis, Origanum hortensis*	MARJORAM SWEET
Origanum vulgare L.	*Origanum vulgare*		ORIGANUM
Ormenis multicaulis Braun-Blanq. & Maire	*Ormenis multicaulis*	*Ormenis mixta, Anthemis mixta*	MAROC CHAMOMILE

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Pelargonium graveolens L'Hér.	*Pelargonium graveolens*		GERANIUM, Rose geranium, Pelargonium
Petroselinum crispum (Mill.) Fuss	*Petroselinum crispum*	*Petroselinum sativum, Petroselinum hortense, Apium petroselinum, Carum petroselinum*	PARSLEY, Common Parsley, Garden Parsley
Pimenta dioica (L.) Merr.	*Pimenta dioica*	*Pimenta officinalis*	PIMENTO, Allspice, Pimenta, Jamaica pepper
Pimenta racemosa (Mill.) J.W.Moore	*Pimenta racemosa*	*Myrcia acris, Pimenta acris*	West Indian Bay, Bay Rum tree
Pimpinella anisum L.	*Pimpinella anisum*	*Anisum officinalis, Anisum vulgare*	ANISEED, Anise
Pinus palustris Mill.	*Pinus palustris* Mill.*		LONGLEAF PINE, Longleaf Yellow Pine, Southern Yellow Pine, Pitch Pine, Pine
Pinus sylvestris L.	*Pinus sylvestris*		SCOTCH PINE, Forest pine, Scotch pine, Norway pine, Scotch fir
Piper cubeba L.f.	*Piper cubeba*	*Cubeba officinalis*	CUBEB, Cubeba, Tailed pepper, Cubeb berry, False Pepper
Piper nigrum L.	*Piper nigrum*		BLACK PEPPER
Pistacia lentiscus L.	*Pistacia lentiscus*		MASTIC, Mastick, Mastix, Mastich, Lentisk, Chios
Pogostemon cablin (Blanco) Benth.	*Pogostemon cablin*	*Pogostemon patchouli*	PATCHOULI, Patchouly, Puchaput, Paradise Flower
Rosa × *damascena* Herrm.	*Rosa damascena*		DAMASK ROSE, Summer Damask Rose, Bulgarian Rose, Turkish Rose
Rosa centifolia L.	*Rosa centifolia*		CABBAGE ROSE, Rose Maroc, French Rose, Provence Rose
Rosmarinus officinalis L.	*Rosmarinus officinalis*	*Salvia rosmarinus*	ROSEMARY
Salvia africana-lutea L. *Salvia africana-caerulea* L.	*Salvia africana-lutea* *Salvia africana-caerulea*	*Salvia aurea / Salvia africana*	AFRICAN SAGE
Salvia officinalis L.	*Salvia officinalis*		COMMON SAGE
Salvia officinalis subsp. *lavandulifolia* (Vahl) Gams	*Salvia lavendulaefolia*		SAGE SPANISH , Lavender-leaves Sage
Salvia sclarea L.	*Salvia sclarea*		CLARY SAGE, Clary
Santalum album L.	*Santalum album*	*Sirium myrtifolium* L.	SANDALWOOD, White Sandalwood, Yellow Sandalwood, East Indian Sandalwood, Sandalwood Mysore
Santolina chamaecyparissus L.	*Santolina chamaecyparissis*		SANTOLINA
Saussurea costus (Falc.) Lipsch.	*Saussurea costus*	*Saussurea lappa, Aucklandia costus, Aplotaxis lappa, Aplotaxis auriculata*	COSTUS
Schinus molle L.	*Schinus molle*		Pink Pepper, Peruvian pepper, Peruvian mastic, Californian pepper tree
Styrax benzoin Dryand.	*Styrax benzoin*		BENZOIN, Gum Benzoin, Gum Benjamin
Syzygium aromaticum (L.) Merr. & L.M.Perry	*Syzygium aromaticum*	*Caryophyllus aromaticus, Caryophyllus aromaticum, Eugenia aromatica, Eugenia caryophyllata, Eugenia caryophyllus*	CLOVE
Tagetes minuta L.	*Tagetes minuta*	*Tagetes glandulifera*	TAGETES, Tagette, Taget, Mexican Marigold, Khakibos
Thymus vulgaris L.	*Thymus vulgaris*		THYME, Common Thyme

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Tilia × *europaea* L.	*Tilia europaea*	*Tilia vulgaris*	LINDEN, Lime tree, Common Lime, Lyne, Tillet, Tilea, Tilia
Tsuga canadensis (L.) Carrière	*Tsuga canadensis*	*Pinus canadensis, Abies canadensis, Abies balsamea*	HEMLOCK SPRUCE, Spruce, Eastern Hemlock, Common Hemlock, Canadian Pine
Valeriana officinalis L.	*Valeriana officinalis*		VALERIAN, Common Valerian, Garden Valerian
Vanilla planifolia Jacks. ex Andrews	*Vanilla planifolia*		VANILLA
Viola odorata L.	*Viola odorata*		VIOLET, English violet, Garden violet, Blue violet, Sweet-scented violet
Zingiber officinale Roscoe	*Zingiber officinale*	*Zingiber officinalis*	GINGER, Common Ginger, Jamaica Ginger