GUIDELINE ON SUBMISSION OF DOCUMENTATION FOR REGISTRATION OF COMPLEMENTARY MEDICINES

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EFFECTIVE DATE: TBA

Medicines Control Authority of Zimbabwe
106 Baines Avenue
P O Box 10559
Harare

E-mail: mcaz@mcaz.co.zw

PROCESS AND ADOPTION OF THE GUIDELINE

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Contents

ABBREVIATIONS

API	Active Pharmaceutical Ingredient
BP	British Pharmacopoeia
EMA	European Medicines Agency
FDA	United States Food and Drug Agency
FPP	Finished Pharmaceutical Product
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
INN	International Non-proprietary Name
JP	Japanese Pharmacopoeia
PD	Product Dossier
Ph.Eur	European Pharmacopoeia
Ph.Int	International Pharmacopoeia
PIL	Patient Information Leaflet
SPC	Summary of Product Characteristics
USAN	United States Adopted Name
USP	United States Pharmacopoeia
WHO	World Health Organisation

GLOSSARY

Active pharmaceutical ingredient
Any substance or combination of substances used in a finished pharmaceutical product (FPP), intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment or prevention of disease, or to have a direct effect in restoring, correcting or modifying physiological functions in human beings.

Applicant
Person or entity by, or on whose behalf, an application for registration is made.

Complementary Medicine
―complementary medicine‖ means any substance or mixture of substances which is used, or is manufactured, sold or represented as suitable for use, in-
(a) the mitigation or prevention of disease or abnormal physical mental state or the symptoms thereof in human beings or in animals;
(b) restoring, correcting or modifying any physical, mental or organic function in man or in animals;

which originates from a plant, mineral, animal or insect and includes substances generally referred to as Aromatherapeutic Substances, Ayurvedic Medicines, Energy Substances or Medicines, Homeopathic Remedies, Nutritional Substances in Pharmaceutical Form, Traditional Chinese Medicines, Traditional Dutch Remedies, Unani Tibb Medicines, Western Herbal Medicines, and such other medicines or remedies as may be approved by the Authority;

Impurities
Any component of the new drug substance that is not the chemical entity defined as the new drug substance

Manufacturer
A company that carries out operations such as production, packaging, repackaging, labelling and re-labelling of pharmaceuticals.

Nutritional Substances/Nutraceuticals
A fortified food or a dietary supplement that is held to provide health or medical benefits in addition to its basic nutritional value in a pharmaceutical form. These include vitamins, minerals, amino acids (body building substances), probiotics etc.

Principal
Owner of the medicine

Traditional medicine
The sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness.

INTRODUCTION

This guideline is intended to assist applicants on the preparation of applications for approval (product dossiers) for complementary medicines.

SCOPE

This guideline applies to all applications for approval of complementary medicines made to MCAZ.

EXEMPTIONS

This guideline shall not apply to:

- Any person who compounds, dispenses or administers a complementary medicine to his patient in the practice of his profession at his premises.
- Cosmetics without any medicinal claims

BACKGROUND

Previously, the MCAZ was granting exemption from registration for products that did not make any form of medicinal claim on the labelling or package insert. Following the passing of the legislation known as the 'Medicines and Allied Substances Control (Complementary Medicines) Regulations, 2015' the MCAZ is mandated to assess all complementary medicines destined for public use in Zimbabwe. Not all medicinal claims may be permitted (see Annex B and C on permitted and non-permitted claims).

The content of this guideline should be read in conjunction with relevant information described in other existing MCAZ, WHO or ICH reference documents and guidelines. Scientific literature may be appropriate to fulfil the requirements for some of the information or parameters outlined in this guideline (e.g. efficacy data on herbal based complementary medicines)

Applicants interested in having their FPPs evaluated for registration in Zimbabwe should submit a product dossier reflecting the data and information requested below. The current version of any guideline or pharmacopoeia referred to in this guideline shall be applicable in all instances. Any deviations must be highlighted, justified and require approval by the MCAZ.

GUIDANCE ON PRESENTATION

Applicants are required to submit two copies of the dossier (one hard copy and one electronic copy {electronic copy where available}. The paper copies of the application should be bound for easy access of information.
Each section of the dossier is to be marked by use of clearly annotated tabs and the documentation should be filed in accessible files. *Lever arch files are not acceptable*. Each binder should be labelled with the non-proprietary name and the proprietary name of the FPP (e.g. Tribulus Terrestris Saponins "Trade name" 5% w/v) and the company name of the applicant. For ease of reference, the following information could also be included on the label of each binder (space permitting): the volume number for that binder (out of the total number of volumes for that module), the section(s) contained within each volume and the date of the application (month and year), e.g. FPP Non-proprietary name
"Name ABC"
Applicant "XYZ"
Volume x of y
Month/year

ADDITIONAL DOCUMENTATION

Cover letter

The cover letter submitted with the application for registration should include a clear statement from the responsible person submitting the dossier, indicating the contact details (telephone number, e-mail, and fax) of the person to whom all correspondence should be addressed.

A completed and signed C.M.1

A completed, signed and dated C.M.1 form should be submitted for each FPP. A copy of the form can be obtained from the MCAZ website: www.mcaz.co.zw. For clarity, the following considerations apply in determining whether the FPP requires one or separate applications.

a) Tablets/Capsules/Suppositories/Lozenges:
   i) Different pack-sizes of the same strength and formulation will require one application
   ii) Different strengths and/or formulations will require separate applications.

b) Syrups/Elixirs/Liquids/Solutions (non parenterals)/Creams/ointments
   i) Different container sizes of the same strength and formulation will require one application
   ii) Same container size of different strengths and/or formulations will require separate applications.

c) Different applicants/proprietary names for the same formula;
   i) Same formula applied under different proprietary names will require separate applications.
   ii) Same formula from different applicants will require separate applications.

Declaration by the applicant

A declaration should be made by the applicant or a responsible person nominated by the applicant and who has the requisite skills and necessary qualifications. It is stressed that only a person who can attest to the accuracy of the contents in the application should sign on behalf of the applicant.

Proof of payment of appropriate fees

A copy of the invoice or proof of payment of registration fees should be attached to the application for registration.

Applicants should consult the current fee schedule for the correct and appropriate fee. Note that Registration fees can be split into three main tiers, depending on the site of manufacture of the FPP. Fees for products wholly manufactured outside Zimbabwe attract a different fee from products wholly or partly (e.g. re-labelled and re-packaged) manufactured in Zimbabwe. All fees are payable according to the gazetted fee schedule.

Unless the full application fee is received, the application will not be accepted. Applicants can remit payment of fees in cash, telegraphic transfers and direct deposit into the

Authority account. Please note that direct transfers usually attract a commission charged by the banks leading to a shortfall in fees. Provision should, therefore, be made to cover such shortfalls. Applicants are further advised to specify very clearly in their instructions to the bank that such direct deposits are for application for registration of a medicine to avoid unnecessary delays.

Note that the application fee covers the cost of evaluating the initial submission and a single laboratory analysis of the product sample. Samples that require repeat analysis after failure of the first analysis, or as a result of modification or revalidation of the analytical method, attract an additional re-analysis fee. Any amendments to the original submission will attract amendment fees according to the gazetted fee schedule. The application fee excludes the GMP inspection fees, for which a separate charge is applicable.

Fees once received are not refundable, including those for rejected applications or voluntary withdrawals by the applicant.

Manufacturing and marketing authorisation(s)/international registration status

List the countries in which:

- the FPP (or set of FPPs) has been granted a marketing authorisation;
- the FPP (or one or more of the set of FPPs) has been withdrawn from the market; and
- an application for the marketing of the FPP (or one or more of the set of FPPs) has been rejected, deferred or withdrawn

The details of registration in the country of origin are required. Reasons for non-registration should be stated if the medicine is not registered in the country of origin.
Registration status in the country of manufacture should be indicated including any withdrawal, cancellations, suspension / revocations. The reasons for these should also be indicated.

Product Samples (e.g. FPP, device[s])

Draft labelling may be submitted at the time of dossier submission when labelling for marketing has not been finalised. Applicants should provide samples of the FPP in its final container and labelling as intended for presentation to the Zimbabwean market or closest reference packs when the labelling for marketing has not been finalised. Samples of the FPP in the market container should be provided to allow examination by the evaluators (assessors). In addition to the above, additional samples should be submitted for laboratory analysis by the MCAZ laboratory. The quantities of samples that should be submitted to the Authority for laboratory analysis should, in general, be twice the amount that is normally required for carrying out the full finished product analytical tests by the applicant's own quality control laboratory. This amount will enable repeat testing, if necessary. The precise quantities of samples required are indicated in *Annexure E*. The applicants may be required to submit reference analytical standards (where available) and their certificates of analysis to allow the MCAZ laboratory to expedite the analysis. Note that the MCAZ laboratory analyses a wide

range of medicines and it is almost impossible to keep analytical reference standards for all medicines.

GENERAL TECHNICAL AND ADMINISTRATIVE INFORMATION

SECTION A: ADMINISTRATIVE

Please note that the application for the approval of a complementary medicine shall be made only by: principal; applicant, manufacturer or an authorized Local Technical Representative (LTR) of the manufacturer or principal who shall be responsible for facilitating communication with the applicant and when the product is registered shall assume all legal responsibilities regarding the product on the market

i. Particulars of applicant: this includes the full name and address (physical address) of the applicant.
ii. Particulars of principal: this includes the full name and address (physical address) of the principal.
iii. Particulars of manufacturer: this includes the full name and address (physical address) of the manufacturer. The name, address, and responsibility of each manufacturer, including contractors, and each proposed production site or facility involved in manufacturing and testing should be provided. The list of manufacturers/companies should specify the *actual addresses* of production or manufacturing site(s) involved (including block[s] and unit[s]), rather than the administrative offices.
iv. LTR: this includes the full name and address (physical address) of the LTR.

SECTION B: PARTICULARS OF THE PRODUCT

i. **Product Name:** the trade and/or brand name which is unique to a particular medicine and by which it is generally identified (and by which it is registered in the country of manufacture).
ii. **Dosage form of the product:** the form in which the medicine is presented — a macerate, infusions, ashes, decoctions, tablet, capsule, solution, suspension, emulsion, ointment, suppository etc.
iii. **Strength of the product:** shall be given per unit dosage form or per specified quantity: e.g. mg per tablet, mg per capsule, mg/ml, mg per 5ml spoonful, mg per g, etc.
iv. **Therapeutic use(s):** the intended use should be only the major indication(s). The product may be multi-component with other pharmacological properties but the application should be restricted to the intended use.
v. **Visual description of the product:** a full description/appearance of the complementary medicine including colour, size, shape and other relevant features, e.g. green powder, brown liquid, pink film-coated tablets etc.
vi. **Type of container:** state the type of the primary package in which the complementary medicine is presented e.g. in HDPE bottles, aluminium sachets, etc.
vii. **Pack size(s):** the presentation of the product to be registered i.e. list all pack sizes intended for marketing.
viii. **Proposed Shelf life (in months):** the specified length of time prior to use for which a complementary medicine is deemed to remain fit for use under prescribed conditions supported by stability studies.

ix. **Storage conditions:** The proposed storage conditions should be indicated on the label and supported by stability studies.

x. **Country of origin:** The country of manufacture or production, of the complementary medicine to be registered or country of product release.

xi. **Status of registration of the product in the country of origin, authorization/registration number:** requires the applicant to provide the regulatory situation of the complementary medicine to be registered in the country of origin and other countries.

SECTION C: COMPOSITION OF PRODUCT

Part 1: Herbal Substances

List all active ingredient(s) and all non-active ingredient(s) used
Composition, i.e. list of all components of the dosage form, and their amount on a per unit basis (including overages, if any), the function of the components, and a reference to their quality standards (e.g. compendial monographs or manufacturer's specifications).
The following should be provided where applicable.

i. **Scientific or Botanical Name of the plant(s)**: Name in Latin (genus and species) of the plant species and family e.g. *Vitex Agnus-Castus (Lamiaceae) Punica granatum (Lythraceae).*

ii. **The common name or synonym is the English name**. Where not known the local vernacular name may be used e.g. Abraham's balm (*Vitex Agnus-Castus),* Carthaginian apple *(Punica granatum)*

iii. **Part of Plant used**: The part used should be specified e.g. leaf, root, bark, etc.

iv. **Quality Standard**: Where the material is part of an established monograph then this should be stated e.g. WHO monograph or British Pharmacopoeia. Where the plant material is not subject to any established monograph the applicant must indicate so i.e. In-House.

v. **Quantity per dosage unit**: The strength of the product shall be given per unit dosage form or per specified quantity: e.g. mg per tablet, mg per capsule, mg/ml, mg per 5ml spoonful, mg per g, etc.

vi. **Chemical Constituent(s)**: For each of the active constituent(s) listed (e.g. *Catharanthus roseus*), indicate the major chemical compounds where known e.g. vincristine, or where not known major group of compounds e.g. indole alkaloids.

vii. **Reason for inclusion**: Where a material is included and is not the active ingredient indicate the purpose of its inclusion such as sugar as sweeter, honey as preservative.

Part II: Nutraceuticals

List all active ingredient(s) and all non-active ingredient(s) used

Provide full composition of the product including names of ingredient(s) and additives, official reference and in the absence of the official references in-house specifications, quantities per unit of measurement of each ingredient and reason of inclusion in a tabular form.

i. **Scientific of the Nutritional Substance** e.g. Cyanocobalamin, L-tyrosine

ii. **The common name or synonym is the English name** e.g. Vitamin A.

iii. Quality Standard: Where the nutritional substance is part of an established monograph then this should be stated e.g. USP Dietary Supplement or British Pharmacopoeia. Where the nutritional substance is not subject to any established monograph the applicant must indicate so i.e. In-House.

iv. **Quantity per dosage unit**: The strength of the product shall be given per unit dosage form or per specified quantity: e.g. mg per tablet, mg per capsule, mg/ml, mg per 5ml spoonful, mg per g, etc.

v. **Chemical Constituent(s)**: For each of the active constituent(s) listed (calcium), indicate the major chemical compounds where known e.g. calcium in form of calcium carbonate**.**

vi. **Reason for inclusion**: Where a material is included and is not the active ingredient indicate the purpose of its inclusion such as sugar as sweeter, honey as preservative.

SECTION D: SAFETY AND QUALITY ASSURANCE

SAFETY

Part I: Herbal Based

i. **Botanical identification/authentication** — The Latin (genus species and authority) of the plant species and family e.g. *Vitex Agnus-Castus* **(Lamiaceae)** *Punica granatum* **(Lythraceae)**. The local name of the plant should be supplied in addition to a herbarium specimen (Voucher number) verified by a recognized herbarium should be provided. For imported herbal or complementary products, a certificate of identification should be supplied from recognized herbarium.

ii. **Geographical source of the plant used** — It the country of origin and the region where the plant is collected, cultivated or wild natural distribution.

iii. **Harvesting and collection of the plant** — The method of collection of plant materials from cultivated or wild sources should be described including stage of plant development, time and season. The measures used to control adulteration of the plant material also should be described.

iv. **Method of drying** — the method used for drying the plant material should be described and justified.

v. **Storage and preservation of plant material** — the method used for storage and preservation of the plant material should be described and justified.

vi. **Biological information (via literature search/database)**

a) Biomedical information regarding the safety and efficacy of the product.
b) Biological information obtained from genetics or fingerprinting
c) In the absence of published results of toxicological studies, documented experience of long-term use should form the basis of the risk assessment. However, even in cases of complementary medicines used over a long period, chronic toxicological risk may have occurred but may not have been recognized.
d) Identification of toxic plants from national pharmacopoeia or international documents, such as the Pharmacopoeia or relevant WHO monographs and other well-established biomedical documentation.

vii. **Toxicity studies**

a) If the product has a long history of use without demonstrated harm, specific restrictive regulatory action is not necessary, unless new evidence indicates a need for a revised risk–benefit assessment.
b) If there is a known toxicological risk, standard toxicological studies are mandatory. Data derived from such studies should be appropriately documented and submitted to the Authority. Toxicity data should be submitted if long-term traditional use cannot be documented or if there are doubts about safety.
c) The absence of any reported or documented side-effects is not an absolute assurance of safety for complementary medicines; some toxicological tests may therefore be necessary. Suggested tests could include, not limited to, those for immunotoxicity (e.g. tests for allergic reactions), genotoxicity, carcinogenicity and reproductive toxicity through long-term use.

viii. **Posology**: The pharmacological determination of appropriate doses of drugs and medicines. Therapeutic prescribed amount of the medicine to be administered to the patient. The measures and age group should be included.

ix. **Dosage forms** in which the drug is presented, e.g. solution, liquid, suspension, emulsion, ointment, suppository, tablet, capsule, etc.

x. **Adverse reactions (Side effects)**: an unwanted effect that was not intended but happens when product is taken a subject suffers loose motion after taking an antimalarial product.

xi. **Contraindications:** A condition which makes a particular treatment or procedure inadvisable or against should be mentioned.

xii. **Warnings:** An intimation in case of any danger of effect after or during use of the product.

xiii. **Precautions:** Measures that should be taken in case of pregnancy, lactation, renal and hepatic failure etc. during use of the product.

Part II: Nutritional Substances

Maximum amounts of vitamins and minerals in vitamin and mineral food supplements per daily portion of consumption as recommended by the manufacturer shall be set, taking the following criteria into account:

i) Upper safe levels of vitamins and minerals established by scientific risk assessment based on generally accepted scientific data, taking into consideration, as appropriate, the varying degrees of sensitivity of different consumer groups;

ii) The daily intake of vitamins and minerals from other dietary sources.

QUALITY ASSURANCE

Active Raw Materials

Part I: Herbal Based

A. Identification of plant(s)

i. Definition (i.e. Latin name of the plant including Genus, species, varieties family);

ii. Synonyms (i.e. legitimate Latin binomial synonyms for the plant);

iii. Selected vernacular names (i.e. a selective list of vernacular names for the plant);

iv. Geographical distribution (i.e. the natural distribution in the country or region, and/or whether the plant(s) is cultivated or imported);

v. Description (i.e. a brief description of the living plant including photographs and/or drawings).

B. Part of the plant used and the condition of the plant material used

i. General appearance.

ii. Organoleptic properties

iii. Microscopic characteristics

iv. Powdered plant material.

C. General qualitative and quantitative tests of the plant materials
Chemical, biological or physical assays;

i. Medicinal plant material:

a) The quantity of plant material must be stated; or
b) The quantity of plant material may be given as a range, corresponding to a defined quantity of constituents of known therapeutic activity.

Example: *Name of active ingredient Quantity*
Sennae folium (a) 900 mg or (b) 830–1000 mg, corresponding to 25 mg of hydroxyanthracene glycosides, calculated as sennoside B.

ii. Plant preparation:

a) The equivalent quantity or the ratio of plant material to plant preparation must be stated (this does not apply to fatty or essential oils); or
b) The quantity of the plant preparation may be given as a range, corresponding to a defined quantity of constituents with known therapeutic activity (see example).

The composition of any solvent or solvent mixture used and the physical state of the extract must be indicated. If any other substance is added during the manufacture of the plant preparation to adjust the level of constituents of known therapeutic activity, or for any other purpose, the added substance(s) must be described as "other ingredients" and the genuine extract as the "active ingredient".
Example*: **Name of active ingredient Quantity***
Sennae folium (a) 125 mg ethanolic extract (8:1) or 125 mg ethanolic extract, equivalent to 1000 mg of Sennae folium or (b) 100–130 mg ethanolic extract (8:1), corresponding to 25 mg of hydroxyanthracene glycosides, calculated as sennoside B.

The determination of the presence of active components and quantity should be described in detail:

- Determination of extractable value (where applicable)
- For example *Datura stramonium*: the test of presence of alkaloids and the amount of atropine.

D. Purity tests

i. Microbiological tests should be described to demonstrate the absence of pathogenic microorganisms (e.g. *E. coli, P. aeroginosa, S aureus* and *Salmonella spp* etc.);

ii. Foreign organic matter;

iii. Total ash, acid-insoluble ash and sulfated ash;

iv. Water-soluble extractive;

v. Alcohol-soluble extractive;

vi. Loss on drying (where applicable);

vii. Swelling index;

viii. Pesticide residues.

ix. Heavy metals (Mercury, arsenic, lead);

x. Radioactive residues;

xi. Other purity tests.

Part II: Nutritional Substances

A. Identification of Substance

i. Definition (form of vitamin e.g. Ascorbic acid or its equivalent Calcium Ascorbate or Sodium Ascorbate)

ii. Synonyms

iii. Structure: The structural formula, including relative and absolute stereochemistry, the molecular formula, and the relative molecular mass should be provided.

iv. General Properties: A list should be provided of physicochemical and other relevant properties of the API. The physical and chemical properties of the API should be discussed including the physical description (e.g. appearance, colour, physical state), solubility in common solvents (e.g. water, alcohols, dichloromethane, acetone); pH and pKa values; UV absorption maxima and molar absorptivity; melting point; refractive index (for a liquid); hygroscopicity; partition coefficient, etc. This list is not

intended to be exhaustive, but provides an indication as to the type of information that could be included.

B. General and Specific Qualitative and Quantitative Tests

i. Assay (strength)

C. Specific Tests

Including but not limited to:

i. Solubility,

ii. Acid Value

iii. Absorbance ratio

iv. Impurities e.g. Lead, Arsenic, Sulfate etc

v. Loss on Drying,

vi. Microbiological tests should be described to demonstrate the absence of pathogenic microorganisms

EXCIPIENTS

Specification:
The specifications from the applicant or the FPP manufacturer should be provided for all excipients, including those that may not be added to every batch, those that do not appear in the final FPP and any others used in the manufacturing process.

If the standard claimed for an excipient is an officially recognised compendial standard, it is sufficient to state that the excipient is tested according to the requirements of that standard. If the standard claimed for an excipient is a non-compendial standard (e.g. House standard) or includes tests that are supplementary to those appearing in the officially recognised compendial monograph, a copy of the specification for the excipient should be provided.

For excipients of human or animal origin, information should be provided regarding adventitious agents (e.g. sources, specifications, description of the testing performed, and viral safety data)

The following excipients should be addressed in this section: gelatin, phosphates, stearic acid, magnesium stearate and other stearates. If from plant origin a declaration to this effect will suffice. For these excipients from animal origin, a letter of attestation should be provided

confirming that the excipients used to manufacture the FPP are *without* risk of transmitting agents of animal spongiform encephalopathies.

Materials of animal origin should be avoided whenever possible.

FINISHED PRODUCT

MANUFACTURE

Name of the Manufacturer: The name, physical address, telephone number, fax number, and e-mail address of the site of manufacture shall be provided. Where different activities of manufacture of a given product are carried out at different manufacturing sites, the above particulars shall be provided for each site and the activity carried out at the particular site shall be stated as shown in the table below.

Name of the Manufacturer	Full Physical address of the Manufacturing Site	Activity at the site

Description of manufacturing process and process controls (name, dosage form)
A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging that presents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g. tumble blender, in-line homogeniser) and working capacity, where relevant.

SPECIFICATIONS OF FINISHED PRODUCT

The minimum range of specifications for the finished products should be as given in recognized pharmacopoeias.

i. Microbiological contamination and tests for other toxins

ii. Uniformity of weight (for tablets, single-dose powders, suppositories, herbal tea in sachets and capsules, etc.), disintegration time (for tablets, capsules, suppositories and pills), hardness and friability (for example, uncoated tablets), viscosity (for internal and external fluids), consistency (semisolid preparations), and dissolution (tablets or capsules), if applicable.

iii. Physical appearance such as colour, odour, form, shape, size and texture

iv. Loss on drying or water content

v. Identity tests, qualitative determination of relevant substances of the plants (e.g. fingerprint chromatograms)

vi. Quantification of relevant active ingredients if they are identified and the adequate analytical methods are available

vii. Limit tests for residual solvents

viii. Performance tests e.g. disintegration and dissolution, weight.

ANALYTICAL METHODS

Details of the test methods described here should be those applied to confirm compliance with specifications listed under the above section attaching the certificate of analysis.

The control tests for the finished product must be such as to allow the qualitative and quantitative determination of the active ingredients. If the therapeutic activity of constituents is known, this must be specified and determined quantitatively. When this is not feasible, specifications must be based on the determination of markers. If either the final product or the preparation contains several plant materials and a quantitative determination of each active ingredient is not feasible, the combined content of several active ingredients may be determined. The need for such a procedure must be justified.

STABILITY STUDIES

The physical and chemical stability of the product in the marketing container should be determined under defined storage conditions to support the shelf-life. This section should include a summary of the studies undertaken (environmental conditions, batches, analytical procedures) and a brief discussion of the results and conclusions, the proposed storage conditions or shelf-life.

The WHO stability guideline *Stability testing of active pharmaceutical ingredients and finished pharmaceutical products* (WHO Technical Report Series, No. 953, Annex 2, 2009) should be consulted for recommendations on the core stability data package required for the registration of products.

Accelerated and long-term testing

Stability data must demonstrate stability of the medicinal product throughout its intended shelf life under the climatic conditions for Climatic Zone IVb.

The minimum data required at the time of submitting the dossier (in the general case):

	Storage temperature (ºC)	Relative humidity (%)	Minimum time period
Accelerated	40±2	75±5	6
Long-term	30±2	65±5*	12

To establish the shelf-life, data should be provided on not less than one batch of at least pilot scale and a second batch which may be smaller of each proposed strength of the FPP. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full production-scale batch.
The stability testing programme should be summarised and the results of stability testing should be reported in the dossier and summarised using the tables below.

Storage conditions (◦C, % RH)	**Strength and batch number**	**Batch size**	**Container closure system**	**Completed (and proposed) test intervals**

PACKAGING

The product shall be packed in containers which will safeguard the hygienic and other qualities of the complementary medicine. The containers, including packaging material, shall be made only of substances which are safe and suitable for their intended use.

LABELLING

The Primary Packaging Label should comply with the Medicines and Allied Substances Control (Complementary Medicines) Regulations, 2015 (S.I. 97 0f 2015) with at least the following:

- **i.** The name of the FPP
- **ii.** Route of administration
- **iii.** A list of API(s) (using INNs if applicable) with the amount of each present in a dosage unit, and a statement of the net contents of the container, e.g. number of dosage units, weight or volume
- **iv.** List of excipients known to be of safety concern for some patients, e.g. lactose, gluten, metabisulfites, parabens, ethanol
- **v.** Instruction on use
- **vi.** The batch number assigned by the manufacturer
- **vii.** The manufacturing AND expiry date in an un-coded form
- **viii.** Storage conditions or handling precautions that may be necessary. The labelled storage conditions should be achievable in practice in the distribution network
- **ix.** Directions for use, and any warnings or precautions that may be necessary
- **x.** The name and physical address of the manufacturing site(s)
- **xi.** For containers of capacity less than or equal to 10 ml that are marketed in an outer pack such as a carton, and the outer pack bears all the required information, the

immediate container need only contain items (a), (b), (c), (f) and (g) —or a logo that unambiguously identifies the company— and the name of the dosage form or the route of administration

xii. The disclaimer **"NO APPROVED THERAPEUTIC CLAIMS"** on the label, unless otherwise exempted by the Authority from complying with this requirement.

PACKAGE INSERT

The package insert should comply with the Medicines and Allied Substances Control (Complementary Medicines) Regulations, 2015 with at least the following:

i. the name and address of the principal;
ii. the name and address of the manufacturer;
iii. the approved name of the active ingredient of the medicine which shall be of greater size and prominence than the proprietary name (trade mark), if any, of the medicine;
iv. the house-mark, if any, of the principal or manufacturer of the medicine;
v. the quantity and strength of the active ingredient of the medicine;
vi. the name and percentage of any bacteriostatic or bactericidal agent which is added to the medicine as a preservative;
vii. the strength of the medicine where applicable;
viii. the requirements for the method of storage or other necessary precautions for the preservation of the medicine;
ix. the category of distribution of the medicine which may be represented by words or symbols as set out in the Sixth Schedule;
x. the pharmacological classification of the medicine determined in terms of section 34;
xi. the dosage of the medicine and the directions for use;
xii. the description of the pharmacological action of the medicine;
xiii. indications of the medicine;
xiv. contra – indications of the medicine;
xv. warnings relating to the use of the medicine and such warning shall be printed in a colour as approved by the Authority;
xvi. the side-effects and special precautions of the medicine;
xvii. known symptoms of over dosage and particulars of its treatment;
xviii. the identification of the medicine;
xix. the form in which the medicine is presented, whether tablet, capsule, liquid, etc., and the colour thereof;
xx. the date of publication of the package insert;
xxi. any necessary warning concerning the administration or use of the medicine by children, old people, pregnant women or patients suffering from certain diseases, or the use of the medicine in conjunction with the consumption of alcohol or any particular food or any other medicine;
xxii. a summary of relevant information concerning the purpose and the beneficial, detrimental, injurious or other effects of the medicine, and the possible dangers that may arise from the prolonged use of the medicine;
xxiii. relevant information, including particulars in regard to a specific medicine as an

xxiv. antidote (if known), concerning the treatment of a patient in cases where an overdose of the medicine has been administered or where a patient reacts adversely to the medicine;

xxv. Any other particulars or warning notices as may be directed by the Authority.

SECTION E: EFFICACY

PART 1: HERBAL BASED

Therapeutic activity refers to the successful prevention, diagnosis and treatment of physical and mental illness; the improvement in the symptoms of illness; as well as the beneficial alteration or regulation of the physical and mental status of the body. The active ingredients of a complementary medicine are those that have therapeutic activity.

i. Assessment of efficacy

a) In the case of complementary medicines, the requirements for proof of efficacy will depend on the kind of indications for use and individual experiences as recorded in reports from physicians, traditional practitioners or treated patients. Experience from herbal or complementary practitioners; experiences from treated patients and clinical evidence will be required in cases where traditional use has not been documented; scientific literature validated by clinical trials;

b) If use of a complementary medicine has not been documented, or in cases where a new medicine consists of traditionally-used plants for a new indication, appropriate clinical evidence of efficacy is required.

ii. Active ingredients

a) The preparation of medicines whose active ingredients have been identified should be standardized so that each batch contains a defined amount of the active ingredients, assuming adequate analytical methods are available;

b) In cases where it is not possible to identify the active ingredients, the whole complementary medicine may be considered as one active ingredient.

iii. Evaluation of efficacy

a) For uses supported by clinical data (i.e. including medical indications which are well-established in some countries and which have been validated by clinical trials, the results of which are recorded in the scientific literature);

b) For uses described in pharmacopoeias and other well-recognized documents (i.e. medicinal uses that have been well-established in many countries and are included in official pharmacopoeias or official government monographs);

c) For uses described in traditional medicine (i.e. indications described in non-official pharmacopoeias and other forms of literature or purely traditional uses).

PART II: NUTRITIONAL SUBSTANCES

No evidence for efficacy is required. However for vitamins and minerals, the minimum level of each vitamin and/or mineral contained in a vitamin and mineral food supplement per daily portion of consumption as suggested by the manufacturer should be 15% of the recommended daily intake as determined by FAO/WHO.

SECTION F: POST-MARKET SUIVELLAINCE

A satisfactory post-market surveillance plan must be provided in the application for approval of a complementary medicine. The plan must include but not limited to: adverse drug reaction form, product defect form. **This requirement is applicable to herbal-based substances.**

ANNEX A: PROHIBITED COMPLEMENTARY MEDICINE INGREDIENTS

Herbal Substance	**Reason**
Aconitum	Extremely Poisonous. Causes 'rabies-like' symptoms
Akebia quinata, Akebia trifoliata	See Aristolochia below
Aristolochia, Aristolochia clematis, Aristolochia contorta, Aristolochia debelis, Aristolochia fang-chi, Aristolochia manshuriensis, Aristolochia serpentaria	Carcinogenic, nephrotoxicity,
Clematis armandii, Clematis montana	Known to cause internal haemorrhage
Cocculus laurifolius, Cocculus orbiculatus, Cocculus trilobus	High levels of allergens
Senecio	hepatotoxicity
Stephania tetrandra	Products have been known to contain aristolochia-like components. See above

ANNEX B: ACCEPTABLE INDICATIONS FOR COMPLEMENTARY MEDICINES

The tables and list below serve as guidance on indications that may be permissible in product for approval. The table is not exhaustive and will be constantly under review as more experience and information is acquired. The specific indication permitted on any individual product will depend on the ingredients (safety and efficacy profile) and the category of distribution assigned amongst other things.

System or part of the body or disease[1]	Permitted traditional use
1. Cardiovascular system	'symptomatic relief of': Chilblains Haemorrhoids by relief of symptoms by means of locally effective preparations or stool softening agents and lubricants.
2. Endocrine system	Weight reduction dependent upon mechanism involving a reduced calorie or joule intake
3. Gastro-intestinal system	symptomatic relief of': Indigestion, heart burn, hyperacidity, dyspepsia, halitosis or flatulence Colicky pain, stomach ache or nausea Occasional or non-persistent diarrhoea or constipation Travel sickness or related symptoms
4. Genito-urinary system and mammary glands	symptomatic relief of': Dysmenorrhea. Sore nipples during lactation by means of local applications.
5. Infections including viral, bacterial and fungal infections	symptomatic relief of': Minor cutaneous infections where a medicinal product is to be administered to a n external surface of the body, including treatment by means of preparations for the relief of pruritus or exanthematous rashes of

[1] The Medicines and Healthcare Products Regulatory Agency (**MHRA**)

	childhood infection and treatment of boils and the treatment or prevention of athlete's foot. Aphthous ulcers Common colds, coughs, conditions commonly referred to as influenza and similar upper respiratory tract infections. Minor acute inflammatory conditions of the buccal cavity and pharynx.
6. The musculo-skeletal system	symptomatic relief of': Muscular pain and stiffness including backache, sciata, lumbargo, fibrositis, rheumatic pain and cramp.
7. Nervous System	symptomatic relief of': Headache including migrainous headache Neuralgia Difficulties falling sleep Agitation, anxiety, irritability, nervous tension, stresses, strains, tenseness
8. Optical and auditory system	symptomatic relief of': by means of local administration of eye preparations
9. Parasitic diseases	Head lice, scabies,
10. The respiratory system	'symptomatic relief of' Hay fever, rhinitis or catarrh Blocked up sinuses
11. The skin, hair and scalp	'symptomatic relief of' Where applied to an external surface of the body of acne Dandruff by means of external applications Psoriasis by application to an external surface of the body

	Where applied to an external surface of the body of eczema and skin allergies Hard skin and corns Contact dermatitis by means of protective applications Common minor skin conditions including dry and chapped skin, cold sores, nettle rashes, pruritus, insect bites and napkin rash
12. The teeth and gums	'symptomatic relief of': Gingivitis and pyorrhoea by means of oral hygiene.

ANNEX C: ACCEPTABLE CLAIMS FOR NEUTICEUTICAL MULTIVITAMIN/MULTIMINERAL PREPARATIONS/AMINO ACID PREPARATIONS

VITAMINS/MINERALS/AMINO ACIDS	Acceptable 'Functional Claims'
Vitamin A (Retinol)	• Helps in maintenance of good health • Has a role in maintaining normal vision, skin, bones and muscles • Has a role in maintaining normal growth processes • Is involved in normal reproductive performance • Has a role in maintaining integrity of skin and mucous membranes
Vitamin C (Ascorbic Acid)	• Helps in maintenance of good health • Has a role in maintaining healthy cartilage, tendons and bone
Vitamin D **(D2 –Ergocalciferol)** **(D3 - Cholecalciferol)**	• Helps in maintenance of good health • Has a role in the absorption of calcium & phosphorous • Has a role in normal growth and health of bones and teeth.
Vitamin E (Tocopherol)	• Helps in maintenance of good health • Is an antioxidant
Vitamin B1 (Thiamin)	• Helps in maintenance of good health • Has a role in the metabolism and maintenance of normal muscle and nerve function • Has a role in assisting in the maintenance of normal appetite and bodyweight • Has a role in helping body to metabolize carbohydrates
Vitamin B2 (Riboflavin)	• Helps in maintenance of good health • Is required for normal general metabolism and growth • Has a role in maintaining integrity of skin,mucous membranes • Has a role in helping the body to utilize energy from food/metabolize proteins, fats and carbohydrates

Vitamin B3 (Niacin)	• Has a role in maintaining of good health • Has a role in helping normal growth and development • Has a role in helping the body to utilize energy from food
Vitamin B6 (Pyridoxine)	• Helps in maintenance of good health • Has a role in normal general metabolism, nervous system function and vision • Is involved in red blood cell formation • Has a role in maintaining normal healthy skin and vision • Has a role in helping the body to metabolize proteins, fats and carbohydrates
Vitamin B12 (Cyanocobalamin)	• Has a role in general metabolism, nervous and reproductive function • Has a role in blood cell production
Vitamin K (Menadione)	• Has a role in maintaining normal blood clotting process
Folic Acid	• Involved in general metabolism • Involved in the formation of red and white blood cells and haemoglobin • Has a role in blood cell production
Beta Carotene	• Helps in maintenance of good health • Has a role in maintenance of growth, vision and tissue differentiation
Biotin	• Helps in maintenance of good health • Helps to metabolize fats and carbohydrates
Choline	• Is involved in metabolism of fats • Has a role in transmitting nerve impulses
Inositol	• Has a role in the metabolism of fats and integrity of hair coat • Has a role in maintaining a normal health coat
Niacin	• Involved in general metabolism and red blood cell formation • Has a role in maintaining normal healthy skin and hair condition
Panthothenic Acid	• Helps in maintenance of good health • Helps to metabolize fats and carbohydrates

Calcium	• Helps in maintenance of good health • Helps in the formation and maintenance of bones and teeth
Chromium	• Has a role in the regulation of glucose metabolism
Cobalt	• Is involved in the formation of vitamin B12 and subsequent formation of red blood cells and haemoglobin • Has a role in maintaining normal nerve cell function
Copper	• Has a role in iron metabolism, bone development, and maintenance of elastic connective tissue
Iodine	• Helps in maintenance of good health • Helps in the function of the thyroid glands
Iron	• Helps in maintenance of good health • Helps in the formation of red blood cell • Helps to prevent anaemia due to iron deficiency
Magnesium	• Helps in maintenance of good health • Helps the body to metabolize carbohydrate
Manganese	• Helps in maintenance of good health • Helps the body to metabolize carbohydrate and proteins
Molybdenum	Has a role in general metabolism
Potassium	• Has a role in maintaining cellular integrity and healthy nerve and muscle function • Is involved in normal digestion and utilization of dietary nutrients • Has a role in muscular contraction, nerve function and relaxation of the heart muscle
Phosphorus	• Helps in maintenance of good health • Helps in the formation and maintenance of bones and teeth
Selenium	• Has a role in preventing cellular oxidation • Necessary for normal growth and fertility
Sodium and Chloride	• Has a role in maintaining normal electrolyte

	balance in body tissues during heavy exercise • Has a role in recovery after strenuous exercise
Sulphur	• Has a role in general metabolism and protein synthesis • Has a role in maintaining healthy hair, skin and hooves • Has a role in maintaining normal healthy joints
Zinc	• Helps in maintenance of good health • Helps to metabolize carbohydrates, fats and protein
Copper	• Helps in maintenance of good health • Helps in the formation of red blood cell
Arginine	• Has a role in promoting release of metabolic hormones-insulin, growth hormone • Is involved in the immune response • Is a component of urea cycle
Histidine	• Is involved in normal growth
Isoleucine	• Is involved in normal protein synthesis and energy production
Leucine	• Has a role in normal protein synthesis and energy production
Lysine	• Has a role in normal protein synthesis
Methionine	• Aids liver in detoxification mechanisms
Phenylalanine	• Has a role in normal protein synthesis
Threonine	• Required for normal growth, feed conversion and nitrogen balance in tissues
Tryptophan	• Has a role in normal growth • Involved in synthesis of niacin (vitamin B3)
Valine	• Has a role in normal energy metabolism and protein synthesis

ANNEX D: PROHIBITED INDICATIONS FOR COMPLEMENTARY MEDICINES

A complementary medicine may not be suitable for use in:

(a) the mitigation or prevention of disease or abnormal physical mental state or the symptoms thereof in human beings or in animals;
(b) restoring, correcting or modifying any physical, mental or organic function in man or in animals;

for the conditions listed below.

Alcoholism
Appendicitis
Arteriosclerosis
Cardiovascular disease
Cataract
Diabetes
Epilepsy
Gallstones
Gangrene
Glaucoma
Hernia
HIV-AIDS
Hypertension
Hypotension
Infantile diarrhoea
Kidney stone
Locomotor or any other ataxia
Malignant disease
Meningitis (all types)
Multiple sclerosis
Nephritis
Osteoarthritis
Parkinson's disease
Plague
Pleurisy
Pneumonia
Pneumoconiosis
Poliomyelitis
Prostate gland disorders
Rheumatic fever
Rheumatoid arthritis
Sexually transmitted infections
Thrombosis
Tuberculosis

ANNEX E: QUANTITIES OF SAMPLES REQUIRED FOR LABORATORY ANALYSIS

The following is the minimum sample size required for analysis. However as a guiding principle the applicant should provide adequate sample for a full spectrum of analysis based on the proposed finished product specifications and repeat if required.

NB: Samples **MUST be** submitted in their original containers intended for marketing.

APPLICANTS please note:

1. Ensure that you have attached **Copy of the certificate of analysis CoA.**
2. Ensure that you have attached **Finished Product Specifications** & **Method of Analysis**
3. Ensure that you have provided all **Chemical Reference Standards**, **Decomposition products** and **Related substances** required for a full monograph analysis when submitting **Registration samples**.

Name of Product	Pack Size	Number of Containers
Tablets and Capsules	24 30 60 90 100 120 500 1000	4 3 2 1 1 1 1 1
Oral Suspensions	60 ml 100 ml 240 ml	5 5 5
Powders for Oral Suspensions	Market pack size	5
Creams and Ointments	15g 25g 30g ≥100g	10 5 4 3

ANNEX F: FREQUENTLY ASKED QUESTIONS

FREQUENTLY ASKED QUESTIONS

1. **What are complementary medicines?**

   Complementary medicines have different and varied definitions dependent on the region. The Medicines and Allied Substances Control (Complementary Medicines) Regulations, 2015 define a complementary medicine as follows:

   A complementary medicine means any substance or mixture of substances which is used, or is manufactured, sold or represented as suitable for use, in-

   (a) the mitigation or prevention of disease or abnormal physical mental state or the symptoms thereof in human beings or in animals;

   (b) restoring, correcting or modifying any physical, mental or organic function in man or in animals;

   which originates from a plant, mineral, animal or insect and includes substances generally referred to as Aromatherapeutic Substances, Ayurvedic Medicines, Energy Substances or Medicines, Homeopathic Remedies, **Nutritional Substances in Pharmaceutical Form**, Traditional Chinese Medicines, Traditional Dutch Remedies, Unani Tibb Medicines, Western Herbal Medicines, and such other medicines or remedies as may be approved by the Authority;

   This serves as the basis of a complementary medicine in Zimbabwe

2. **What is the difference between complementary medicine, alternative medicine and integrative health care?**

   Complementary medicines is used in conjunction with conventional therapy, whilst alternative medicine is used in place of it. Integrative medicine" refers to a therapeutic approach that integrates conventional, complementary, and alternative medicine and re-emphasizes the relationship between health care practitioners and patients[2]

3. **Should the manufacturing site of the complementary medicine be inspected before the product is registered?**

   The Authority requires that the all premised where manufacturing occurs conforms to some standard of cGMP. The Authority is aware that some countries do not inspect manufacturers of some products, however evidence of a standard of cGMP is required. The MCAZ may insist that its inspectors inspect the site on a case by case basis.

[2] National Center for Complementary and Alternative Medicine (NCCAM) The Use of Complementary and Alternative Medicine in the United States Bethesda, Md: National Institutes of Health; December2008. Available at: http://nccam.nih.gov/news/camstats/2007/camsurvey_fs1.htm Accessed June 15, 2010.

4. **What does the registration process of complementary medicine entail?**

   The Authority assesses the Safety, Quality and Efficacy of all medicines destined for public use in Zimbabwe. The same applies to complementary medicines. Evaluators assess the quality of documentation, analysts test the samples submitted and inspectors deal with GMP issues. A committee of experts overlooks the procedure to ensure consistency, transparency and guidance. Applicants are informed of the status of their products periodically. Products that are successful are granted market authorization whilst those that have not satisfied the Authorities requirement are refused authorization.

5. **What are the requirements at submission to the Authority?**

   A complete application consists of a product dossier, samples and application fees. A screening checklist is included in the submission guideline which assists in ensuring completeness of the dossier. The guideline also states the quantity of sample(s) required at submission.

6. **My product contains a vitamins, minerals and herbal substances. Which sections should I complete in my dossier?**

   The guideline is composed of one section for purely herbal main ingredients and another for isolated nutraceuticals (vitamins, minerals, amino acids, probiotics etc). If a product contains both groups then both sections should be provided.

7. **Are all herbal medicines permitted under this procedure?**

   No. The guideline contains a list of herbal substances that have profound toxicity when ingested. The list is not exhaustive and is continually updated as more information becomes available.

8. **Are body building products registerable with the Authority?**

   Body-building products that contain nutraceuticals should be approved by the authority unless there are declared as purely foods without medical, health and/or structure/functional claims. These three concepts are defined below.

   I. Medical claim: claims specified to treat, cure or prevent a disease or restore, correct or modify physiological functions. Most of these products with medical claims have to be registered by a regulating authority before being placed on the market.

   II. Health claims: any statement, suggestion or implication in labelling or advertising that a product carries a specific health benefit, but not nutritional claims or medicinal claims.

   III. Structure/function claims : a substance to an effect on a structure or function of the body

9. **Are cosmetic preparations containing vitamins and/or herbal substances registerable with the Authority?**

   No. Cosmetic products do not fall under the Authorities' mandate.

10. **May I advertise my complementary medicine?**

    All intended advertisements for complementary medicines should be approved by the authority in writing. There are some conditions for which advertisement is strictly prohibited. These are listed in the Sixth Schedule of the Medicines Allied Substances Control (Complementary Medicines) Regulations, 2015.

11. **Where can I sell my approved product?**

    Approved products are placed in two categories for distribution. Complementary medicines Pharmacy and Complementary Medicine General Sale depending on indication and safety profile of product amongst other reasons. Complementary Medicines Pharmacy can be sold in Pharmacies only where there is continuous supervision of practice. Complementary Medicines General Sale may be sold in health shops, supermarkets, pharmacies etc.

12. **The country of origin does not regulate complementary medicines. Can I still submit my product for registration to the Authority**?

    Yes. The Authority is aware that some countries do not regulate complementary medicines. The Authority may conduct an inspection of any premises that manufacture complementary medicines for which approval is sought, on payment by the applicant of a fee as determined by the Authority from time to time**.**

13. **What are the maximum (Upper limits) Recommended Daily Allowances (RDA) for Vitamins and Minerals permitted by the authority**?

    A Tolerable Upper Intake Level (UL) is the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population[3]. There are numerous authoritative sources regarding the maximum RDA limits for Vitamins and Trace elements (minerals). The MCAZ currently uses World Health Organization (WHO), United States Department of Agriculture and the Recommended Daily Allowances 10th edition by the United States National Research Council as sources of current data. Manufacturers are advised to quote their sources for Upper limits of Vitamins and Minerals.

[3] Dietary Reference Intakes (DRIs): Tolerable Upper Intake Levels, Elements Food and Nutrition Board, Institute of Medicine, National Academies