Botswana Medicines Regulatory Authority

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Revision status sheet

Page	Changes made	Issue No	Process owner's name	Date
5	4.1 the background has been updated.	2	Kesolofetse Keakile	30/01/2020
6-13	4.3 Submission requirements have been changed to align to the Regulations of 2018.	2	Kesolofetse Keakile	30/01/2020
14-20	Addition of annex 1 and 2	2	Kesolofetse Keakile	30/01/2020

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1. Purpose

These guidelines provide guidance to applicants to correctly complete the application forms when applying for screening and registration of their products.

2. Scope

These guidelines are applicable to all complementary medicines applications to be assessed in Botswana by BOMRA.

3. Definitions and Abbreviations

3.1 Definitions

For the purpose of these guidelines, the following definitions shall apply:

3.1.1 **Act -** The Medicines and Related Substances Act, 2013 and as subsequently amended.

3.1.2 **Complementary Medicine**: means a labelled substance or mixture of substances manufactured, sold or represented for use as adjuvants to conventional therapy in:

i. the mitigation or prevention of or abnormal physical states;
ii. restoring, correcting or modifying physical, mental or organic functions in human and animals as determined by the Authority;

and originate from plant, mineral, animal (including microorganisms), homeopathic preparations, nutritional substances in accepted pharmaceutical dosage forms, a combination of the above or any other such preparations as may be approved by the Authority.

3.1.3 **Product:** This refers to the complementary medicine.

3.1.4 **Shelf life**: The period that product is expected to remain safe and of good quality. The expiry date of an individual batch is based on the known shelf life.

3.1.5 **Stability**: The capacity of an active ingredient or product or dosage form to remain safe and of good quality and maintain its identity, purity, strength.

3.1.6 **Storage Condition**: The storage condition, which shall guarantee the maintenance of the quality of the product in relation to its safety, acceptability throughout the shelf life.

3.2 Abbreviations

The following abbreviations shall apply:

3.2.1 BOMRA – Botswana Medicines Regulatory Authority

3.2.2 BSE - Bovine Spongiform Encephalopathy

3.2.3 CoA - Certificate of Analysis

3.2.4 GMP- Good Manufacturing Practice

3.2.5 HDPE - High density Polyethylene

3.2.6 ISO - International Organization for Standardization

3.2.7 TSE - Transmissible Spongiform Encephalopathy

4. Activity description

4.1 Background

BOMRA aims at ensuring that all medicines manufactured, imported or exported, distributed or sold in Botswana are of acceptable quality, safety and efficacy. The process of medicine registration forms an important basis for evaluating and assuring drug safety, efficacy and quality. Therefore, all medicines manufactured, imported/exported, distributed or sold in Botswana should be registered.

The content of this guideline should be read in conjunction with relevant information described in other existing BoMRA, 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. evidence of claim on complementary medicines)

This guideline applies to all applications for the registration of complementary medicines made to BoMRA

The guideline is not applicable to:

i. Cosmetic products
ii. Fortified Foods such as replacement meals
iii. Any person who compounds, dispenses or administers a complementary medicine to his patient in the practice of his profession at his premises.

4.2 Determination of classification/registrability of a product

Where applicants are unsure whether a product falls within the definition of a drug in terms of the Medicines and Related Substances Act, 2013 the following information shall be forwarded to BoMRA:

i. The proposed name of the product;
ii. The composition (especially active ingredients and the quantities thereof) and formulation of the product;
iii. The intended use;
iv. The intended marketing/promotional strategy and material;
v. A written reply will be issued by as to whether the product is a conventional, complementary product, medical device or a cosmetic;

4.3 Submission requirements (all documents shall be in English)

4.3.1 Submission for screening

4.3.1.1 Proof of payment for Screening or Re-Screening

4.3.1.2 A CD with all the information from 4.3.2.5 till end of the document.

4.3.2 Submissions for New application for registration (Post passing screening)

4.3.2.1 **Proof of payment for New application for registration**

4.3.2.2**. Successful screening letter**

4.3.2.3 **Application form and Cover Letter**

The applicant shall submit one hard copy of the signed and completed application form

The Soft copy (Word Format on the CD) of the application must be typed in font New Times Roman, font size 12. Attachments should be scanned and included in the CD arranged as per the guideline.

The Completed application shall be submitted with a covering letter. To expedite unpacking of documents the covering letter should itemise the contents of the submission.

4.3.2.4 **Samples**

Sealed samples (at least two samples), in the actual distribution container shall be submitted. BoMRA may request for more samples for testing. Applicants should provide samples of the Finished Pharmaceutical Product (FPP) in its final container and labelling as intended for presentation to the Botswana market or closest reference packs when the labelling for marketing has not been finalised.

4.3.2.5 **Promotional material**

Copies of existing and proposed promotional material should be submitted.

4.3.2.6 **Supporting Documentation**

The following sections should be satisfactorily addressed for a product to attain marketing authorization

i. Administrative. (Applicant and Product details)
ii. Composition
iii. Safety and Quality Assurance
iv. Quality assurance of Active Ingredients
v. Pharmaceutical documentation;
vi. Package insert and labelling
vii. Evidence of Claim/indication
viii. Post-Market Surveillance Plan

4.3.2.6.1 Administrative

a. Applicant details

This part requires general information about the applicant, the product and the manufacturer (the applicant may or may not be the actual manufacturer). The name and address (both postal and physical) of the applicant should be provided.

b. Product details

The details of the product should include:

i. The INN or Botanical Name
ii. Proprietary name of the product
iii. Presentation, Strength and dosage form
iv. Strength per dosage unit;
v. Pack size(s)
vi. Uses of the final product
vii. Source of the active ingredients
viii. Name and physical address of all the manufacturers. Provide Good Manufacturing Procedures (GMP) Certificate, Manufacturing license or ISO certificates.
ix. List all the countries where the product is marketed and provide certificates or authorization letters of such.
x. Authorization letters from the applicant to the agent/local representative indicating the responsibility of the agent/representative.
xi. Different dosage-forms (e.g. solution, suspension, emulsion, ointment etc) should have different applications.

xii. All the various package sizes intended for marketing should be submitted. Any distinguishing unique characteristics of each package should be described. A sample label bearing all the labelling information (in English) as would appear on the immediate container should be attached to the application.

xii. The declaration form must be completed and signed by the responsible person in the manufacturing facility and applicant as specified.

4.3.2.6.2 Composition

This section should be presented in a table as shown on the Form. It should include the following:

i. Approved name;
ii. Quantity per dosage unit or other suitable unit of mass or of volume of the product.
iii. Purpose of inclusion, i.e. active or inactive.

iv. Uses of the ingredient. On this column it must be stated what the ingredients are used for in the final product. e.g. Helps in weight loss, diluent etc

v. 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.

4.3.2.6.3 Safety of Active Ingredients

a. Botanical identification/authentication (plant based products only)

i. The Latin (genus species and authority) of the plant species and family e.g. *Tribulus terrestris* and Zygophyllaceae. 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. Safety and Toxicological information on the product

iii. For plant based products: Published toxicological products should be provided. In the absence of published results of toxicological studies, documented experience of long-term use should be provided.

b. For Nutraceutical Products (Vitamins and Mineral products): 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; Products with levels above established limits will be regarded as allopathic medicines.

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

4.3.2.6.4 Quality assurance of Active Ingredients

The specifications of the active ingredients (with a Certificate of analysis) should be provided. The minimum range of specifications for the active ingredients should be as given in recognized pharmacopoeias. As a guide, it may include the following:

a. For Plant Based Products:

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

iv. General qualitative and quantitative tests of the plant materials such as chemical, biological or physical assays;

v. Purity tests

b. For Nutraceuticals:

i. Definition (form of vitamin e.g. Retinol)

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:

v. Assay (strength)

vi. Specific Tests: Including but not limited to Solubility, Acid Value, Absorbance ratio, Impurities e.g. Lead, Arsenic, Sulfate etc

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

4.3.2.6.5 Pharmaceutical Documentation

Information required in the pharmaceutical documentation should indicate details of the following:

a. Specifications for Excipients

i. 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.

ii. 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.

iii. 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.

iv. For excipients obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) agents (e.g., ruminant origin), a letter of attestation with supporting documentation should be provided confirming that the material is not from a BSE/TSE affected country/area.

b.Manufacture

i.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/ contract manufacturers 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

ii. 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.

iii.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.

c. Specifications of the 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.

Attach Certificates of Analysis for Final product. The CoA must include Control for Heavy Metals.

d. Stability studies and expected shelf life.

i.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 IV.

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

ii.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.

iii.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**

e. Container Closure System:

Describe the materials of the immediate container (e.g. HDPE, amber glass bottle) and of other components of the packaging (e.g. stopper, secondary container (box).

4.3.2.6.6. Package Insert and Labelling:

a. The Package Insert should include the following:

- **i.** the name and address of the manufacturer;
- **ii.** the house-mark, if any, of the principal or manufacturer of the medicine;
- **iii.** the quantity and strength of the active ingredient of the medicine;
- **iv.** the strength of the medicine where applicable;
- **v.** the requirements for the method of storage or other necessary precautions for the preservation of the medicine;

vi. the dosage of the medicine and the directions for use;

vii. the description of the pharmacological action of the medicine;

viii. indications of the medicine;

ix. contra – indications of the medicine;

x. warnings relating to the use of the medicine and such warning shall be printed in a colour as approved by the Authority;

xi. the side-effects and special precautions of the medicine;

xii. known symptoms of over dosage and particulars of its treatment;

xiii. the identification of the medicine;

xiv. the form in which the medicine is presented, whether tablet, capsule, liquid, etc., and the colour thereof;

xv. the date of publication of the package insert;

xvi. 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;

xvii. 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;

xviii. relevant information, including particulars in regard to a specific medicine as an 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;

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

b. The label should include the following:

A sample label as would appear on the immediate container should be attached bearing information in English

i. Name of the Product

ii. Package size;

iii. Quantity of the active ingredient per dosage unit;

iv. Batch number;

v. Expiry date;

vi. Storage conditions;

vii. Warnings and precautions;

viii. Directions for use;

ix. Manufacturer's name and address

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

4.3.2.6.7 Evidence of claim

Provide proof of claim supported by:

i. 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);

ii. 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.

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

4.3.2.6.8 Post Market Surveillance Plan

A satisfactory post-market surveillance plan must be provided in the application for registration 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 I

Acceptable Claims For Nutraceutical 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 2:

Acceptable Claims/Indications for Complementary Medicines

System or part of the body or disease	Permitted traditional use
1. Cardiovascular system	'symptomatic relief of': Chilbrains 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 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.