Botswana Medicines Regulatory Authority

Approved _____ _____

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1. Purpose

This guideline provides guidance to applicants on how to correctly complete the application forms when applying for screening and registration of their complementary veterinary medicines.

2. Scope

This guideline is applicable to all applications to be submitted for registration of complementary veterinary medicines in Botswana. Applications for registration of homeopathic veterinary medicinal products should be submitted in accordance with EU guidelines for registration of homeopathic veterinary medicines and EC Directive 2001/82/EC.

3. Definitions and Abbreviations

3.1 Definitions

For the purposes of this guideline, the following definitions shall apply:

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

3.1.2 **Complementary Veterinary Medicine**: a product that:

a) Contains only natural ingredients as their active constituents.

b) Makes only general health claims, not specific therapeutic claims that refer to treatment, alleviation, or prevention of specific disease/conditions.

c) Usually administered orally or topically on the skin.

NB. All parenteral preparations (injections), eye preparations, nasal sprays, wound sprays will be covered by the guideline for registration of pharmaceutical.

3.1.3 **Shelf life**: The period from the date of manufacture when the complementary veterinary medicine is expected to remain safe and of good quality. Usually defined as the period from date of manufacture to date of expiry.

3.1.4 **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.

3.1.5 **Storage Condition**: Conditions at which a product should be kept for it retain its quality or safety profile. The storage conditions are established from the stability studies.

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 **CVM** - Complementary Veterinary Medicine

3.2.5 **GMP** - Good Manufacturing Practice

3.2.6 **HDPE** - High Density Polyethylene

3.2.7 **INN** - International Non-proprietary Name

3.2.8 **ISO** - International Organization for Standardization

3.2.9 **OIE** - Office International des Epizooties (World Organisation for Animal Health)

3.2.10 **SmPC** - Summary of Product Characteristics

3.2.11 **TSE** - Transmissible Spongiform Encephalopathy

3.2.12 **VICH** - International Cooperation on Harmonization of Technical Requirements for Registration of Veterinary Medicinal Products

4. Introduction

4.1 Background

4.1.1 BOMRA aims to ensure that all medicines manufactured, imported, or exported, distributed, or sold in Botswana are of acceptable quality, safety, and efficacy. To achieve this, the authority established a process for registration of medicines which involves evaluation of the scientific information provided by the manufacturer and/or applicants. Therefore, all medicines manufactured, imported/exported, distributed, or sold in Botswana should be registered.

4.1.2 The content of this guideline should be read in conjunction with the Medicines and Related Substances Act and its regulations, other relevant existing local and international guidance documents. If a CVM is intended for use in food producing animals, applicants are encouraged to refer to the SI No 76 of 2020 (Medicines and Related Substances Act), EU Commission Regulation 37/2010, Council Directives 96/22/EC and 96/23/EC as well as EC Regulation No 1831/2003 to ensure their ingredients are approved for use in food producing animals.

4.2 Determination of classification/registrability of a product

Where applicants are unsure whether a product falls within the definition of a medicine in terms of the Medicines and Related Substances Act, they should inquire with BoMRA before consideration for manufacture or importation into Botswana. The following information should form part of the enquiry:

4.2.1 The name of the product (brand name and approved name of the active constituents or ingredients).

4.2.2 The composition (active and inactive ingredients) and the dosage form of the product.

4.2.3 The intended use (indications and animal species).

Applicants can contact BoMRA using the email address info@bomra.co.bw or call +267 3731720 or Toll free 0800600216.

4.3 Requirement for Submission of applications for:

4.3.1 Screening

The following should be submitted:

4.3.1.1 Proof of payment for Screening application fee.

4.3.1.2 A dossier saved on a CD, as text searchable PDF documents.

4.3.1.3 The applicant should submit a cover letter, a duly completed and signed application form (hard copy). The dossier / application package prepared in English, typed in font New Times Roman, font size 12 and saved on the CD, in text searchable PDF format. All supporting documents should be scanned and saved in the CD with specific identification for easy of reference during assessments.

4.3.1.4 A comprehensive table of contents should be included to facilitate easy reference or location of the information and attachments in the dossier (CD). **NB.** If folders are used to partition the information in the submission/dossier they should not be zipped.

4.3.2 Evaluation of new application for registration

The following documents should be submitted to enable evaluation of the new application,

4.3.2.1 Proof of payment for evaluation of new application for registration.

4.3.2.2 Evidence of an application passing screening (Screening Approval Letter).

4.3.2.3 Application cover letter.

4.3.2.4 Duly completed form.

4.3.2.5 Samples

A sealed sample (usually one sample), in the intended packaging for marketing should be submitted. BoMRA may request for more samples for testing as when required. Applicants should provide samples of the Finished Pharmaceutical Product (FPP) in its final container labelling as intended for presentation to the Botswana market. For larger pack sizes, a smaller pack sizes of same material of construct can be accepted.

4.3.2.6 Promotional material

Copies of existing and proposed promotional material should be submitted. All promotional material and/or advertisements should be in line with the information that has been approved by the authority.

5 Technical Requirements for Registration of Complementary Veterinary Medicines

The dossier, as described in clause 4.3.1.2 above, for registration of CVMs should satisfactorily cover the following aspects of the product, for it to attain marketing authorization in Botswana.

5.1 Administrative information (Applicant and Product details)

This part requires general information about the applicant, the product, and the manufacturer (the applicant may or may not be the actual manufacturer).

5.1.1 Applicant details

The name and address (both postal and physical) of the applicant should be provided. This information should also include the contact details such as telephone and email address.

5.1.2 Product details

The details of the product should include:

a) The INN or Botanical Name.

b) Proprietary name of the product.

c) Presentation, Strength, and dosage form.

d) Strength per dosage unit.

e) Target species.

f) Pack size(s).

g) Uses of the final product.

h) Source of the active ingredients.

i) Name and physical address of all the manufacturers. Provide Good Manufacturing Procedures (GMP) Certificate, Manufacturing license or ISO certificates.

j) List all the countries where the product is marketed and provide certificates or authorization letters of such.

k) Authorization letters from the applicant to the agent/local representative indicating the responsibility of the agent/representative.

l) Different dosage-forms (e.g., solution, suspension, emulsion, ointment etc) should have different applications.

m) 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.

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

5.2 Active ingredients or constituents

5.2.1 General Information

The information of all the active ingredients included in the CVM should be provided. This should include the name (Approved name, Botanical name, Scientific name and Pharmacopeial name where applicable), general properties and structure where applicable.

5.2.2 Safety aspects of the Active ingredients or Constituents

5.2.2.1 Botanical identification/authentication (plant-based products)

To facilitate verification of safety of the active ingredient(s), the applicant is required to provide the following:

a) The Latin name (genus species and authority) of the plant species and family e.g., Tribulus terrestris and Zygophyllaceae.

b) The local name of the plant should be supplied in addition to an herbarium specimen (Voucher number) verified by a recognized herbarium.

c) For imported herbal or complementary products, a certificate of identification should be supplied from recognized herbarium.

5.2.2.2 Safety and Toxicological information on the product

5.2.2.2.1 For plant-based products:

Published toxicological products should be provided. In the absence of published results of toxicological studies, documented evidence of experience of long-term use should be provided.

5.2.2.2.2 For Nutraceutical Products (Vitamins and Mineral products):

Maximum amounts of vitamins and minerals to be administered per day as recommended by the manufacturer shall be declared. This should take into account the upper safe levels of vitamins and minerals for each animal species, established by scientific data based on risk assessment/evaluation. Products with levels above established limits will be regarded as allopathic medicines.

5.2.3 Control of Active Ingredients

At the minimum, applicants will be required to provide signed and dated version-controlled specifications and analysis results of each of the active ingredients or constituents.

5.2.3.1 Specifications

The specifications should include tests and acceptance limits as given in recognized pharmacopoeias. As a guide, it may include the following:

5.2.3.1.1 For Plant Based Products:

The range of tests to be performed for plant-based products should include:

i. Definition (i.e., Latin name of the plant including Genus, species, varieties family and Part of the plant used, and the condition of the plant material used).

ii. Characteristics (a qualitative statement about the organoleptic properties)

iii. Identification (to discriminate between related species or potential adulterants).

iv. Purity tests / Assay and.

v. Other tests.

5.2.3.1.2 For Nutraceuticals

The range of tests to be performed for nutraceuticals should include:

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

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

iii. Characteristics.

iv. Assay (strength).

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

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

For all in-house active constituents/ingredients, the tests and acceptance criteria should be adequately justified.

5.2.3.2 Batch Analysis

Analysis results of each active ingredient or constituent used in the manufacture of the complementary veterinary medicines should be submitted. Certificates of analysis of at least two batches of each active ingredient should form part of the submission.

5.3 Finished Product or Complementary Veterinary Medicine (CVM)

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

5.3.1 Qualitative and quantitative composition of the CVM

All the ingredients (active and inactive), the quantities, purpose for inclusion, the reference standard for each should be declared. This information should be presented in a table as shown below:

Ingredients	Ref standard	Quantity (mg/ unit)	Purpose for inclusion	Uses for ingredient
e.g., Ingredient A	e.g., British Pharmacopoeia	X mg/g	e.g., active	e.g., helps with colds and flu
e.g., Ingredient B	e.g., European pharmacopoeia	Y mg/g	e.g., inactive	e.g., diluent
e.g., Ingredient C	e.g., In-house	Z mg/g	e.g., inactive	e.g., bulking agent

5.3.2 Control of Excipients or inactive ingredients

5.3.2.1 At the minimum applicants will be required to provide the signed, dated and version-controlled specifications of all the excipients. 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.

5.3.2.2 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.

5.3.2.3 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 together with a BSE/TSE free certificate should be provided.

5.3.3 Manufacture of the Complementary Veterinary Medicines

5.3.3.1 Manufacturer

The applicant should declare the name and physical address of all the manufacturing sites involved and their responsibilities in the manufacture of the finished product. In addition, the following contact details of the manufacturers should be provided i.e., telephone number and email addresses.

Name and physical address of the Manufacturer	Responsibility
Manufacturer A	Bulk manufacturing
Manufacturer B	Packing, Testing & release
etc.	

A valid GMP certificate or some form of certification (ISO) should be provided for each of the declared manufacturing sites.

5.3.3.2 Description of the Manufacturing Process

A flow diagram should be presented giving the steps of the process of manufacture of the complementary veterinary medicine 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.

5.3.4 Control of the Finished product (CVM)

At a minimum the applicant should submit signed, dated and version-controlled specifications and batch analysis data including certificates of analysis.

5.3.4.1 Specifications

The specifications should include tests and acceptance limits as given in recognized pharmacopoeias. In cases where there are no recognized monographs, the following tests can be considered depending on the formulation:

5.3.4.1.1 Solid oral dosage forms e.g., tablets and capsules

i. Appearance (colour, odour, form, shape, size, and texture).
ii. Identification e.g., fingerprint chromatograms.
iii. Uniformity of dosage units.
iv. Water content.
v. Dissolution.
vi. Assay.
vii. Residual solvents (if there are any organic solvents used during manufacture).
viii. Microbial limits and Bacterial Endotoxins.

5.3.4.1.2 Oral liquids

i. Appearance (colour, odour, form, shape, size, and texture)
ii. Identification e.g., fingerprint chromatograms
iii. Uniformity of dosage units
iv. Dissolution, resuspendability, rheology may be applicable for suspensions.
v. Assay
vi. pH
vii. Residual solvents (if there are any organic solvents used during manufacture)

viii. Microbial limits and Bacterial Endotoxins

Control of the finished product is not only limited to the above tests. An applicant may perform additional tests as they see fit.

5.3.4.2 Batch Analysis

Analysis results of the complementary veterinary medicine (finished product) should be submitted. Certificates of analysis of at least three batches of finished product should form part of the submission.

5.3.5 Container Closure System

A description of the primary packaging material or container intended for use on the market should be provided. The description should include exact material of construct of the container e.g., HDPE, amber Type I glass bottle etc., and of other components of the packaging such as the closure or stopper. In addition, the secondary container e.g., the carton box if applicable should be described.

5.3.6 Stability Data

5.3.6.1 Applicants are required to declare the shelf-life and storage conditions of the complementary veterinary medicines. The shelf-life and the stated storage conditions should be adequately supported by satisfactory stability study results.

5.3.6.2 The Accelerated and long-term stability data must be submitted to demonstrate stability of the medicinal product throughout its intended shelf life under the climatic conditions for Climatic Zone IV.

5.3.6.3 To establish the shelf-life, data should be provided on not less than one batch of at least pilot scale and a second batch of commercial scale. Bracketing or matrixing approach is allowed in cases where there are multiple strengths and/or pack sizes. These batches should be manufactured by a procedure fully representative of and simulating that to be applied to a full commercial/production-scale batch.

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

5.3.6.4 The stability testing programme should be summarized, and the results of stability testing should be reported in the dossier and summarized using the tables below.

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

5.3.6.5 The full stability data should be submitted, and it should include the test parameters, acceptance criteria and results at each stability testing time point.

5.3.7 Labelling Information

5.3.7.1 Package Insert

The Package Insert should be compiled in accordance with established international SmPC structure. At a minimum it should include the following:

i. the name of the medicinal product.
ii. qualitative and quantitative composition of the product.
iii. dosage form.
iv. indications and directions of use.
v. Contraindications.
vi. Special warnings and precautions for use.
vii. Interaction with other medicinal products.
viii. the description of the pharmacological action of the medicine.
ix. the side-effects.
x. known symptoms of over dosage and particulars of its treatment.
xi. presentation of the medicine.
xii. the name and address of the manufacturer and proposes Marketing Authorization Holder.
xiii. the house-mark, if any, of the principal or manufacturer of the medicine.
xiv. the date of publication of the package insert.
xv. provisions for registration details.
xvi. Any other particulars as may be directed by the Authority.

5.3.7.2 Label

The label should be in English, font Times New Roman size 12, using indelible ink and should include the following:

i. Approved name of the medicine as used in official pharmacopoeias/formulary (INN).
ii. Brand name, if applicable.
iii. Package size/contents of the container.
iv. Quantity of the active ingredient per dosage unit.
v. Manufacturer's name and address.
vi. Batch number.
vii. Manufacturing date.
viii. Expiry date.
ix. Storage conditions.
x. Warnings and precautions
xi. Directions for use.
xii. provisions for registration details
xiii. Any other particulars as may be directed by the Authority.

For labels intended for use on small pack sizes e.g., vial/ampoule less than 10ml some of the information may be waived, but should be included in the package insert and/or carton pack.

5.4 Efficacy Data

A reduced efficacy data package as evidence in support of the claim should be provided. This should be in the form of:

i. Clinical data from well-structured clinical trials or case studies in target species, and relevant/established scientific publications from literature.
ii. Established pharmacopeial monographs.

5.5 Safety Data

Evidence of safety of the formulation in the target species should be submitted. This information should include tolerance studies, persistence studies to establish withdrawal periods in food producing animals etc. This data should be obtained from well-structured clinical trials or case studies in the target species, and relevant/established scientific publications from literature. Documented experience of long history of usage can be considered acceptable evidence.

5.6 Pharmacovigilance Plan

A satisfactory Pharmacovigilance and 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 and product defect reporting. This requirement is applicable to herbal-based substances only.

ANNEXURE 1

Examples of Acceptable Claims for Complementary Veterinary Medicines

Example of the CVM	Example of acceptable claims
Vitamin A	• Helps in the maintenance of good health. • Has a role in the maintenance of normal vision, skin, bones, and muscles.
Calcium	• Helps in the formation and maintenance of bones and teeth. • Enhances the production of milk.

NOTE.

1. Any specific therapeutic claims that refer to treatment, alleviation, or prevention of specific disease/conditions will not be accepted.
2. Parenteral preparations (injections), eye preparation, nasal and wound sprays will not be accepted as complementary VMP.