Botswana Medicines Regulatory Authority

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Table of Contents

Revision status sheet

Page	Changes made	Issue No	Process owner's name	Date

1 Purpose

This guideline is intended to assist applicants on the preparation of documentation to support a variation of complementary medicines registered in Botswana.

2 Scope

This guideline applies to all variation applications of complementary medicines registered in Botswana. This guideline shall not apply to variations that require the submission of a new dossier.

3 Definitions and abbreviations

3.1 Definitions

3.1.1. Variation – changes that could have either minor or major changes to the overall safety, efficacy and quality of the finished product.

3.1.2. Applicant - a company/entity registered, licensed or operating in Botswana that submits an application for registration or licensing or Any person as defined by the Companies Act.

3.1.3. Complementary Medicine

—complementary medicine means a labelled substance or mixture of substances which is used, or is manufactured, sold or represented as suitable for use as adjuvants to conventional therapy in-

(a) the mitigation or prevention of an abnormal physical state; or

(b) restoring, correcting or modifying physical, mental or organic function in human, and;

originates from a plant, mineral, animal including microorganisms, homeopathic preparations Nutritional Substances I accepted pharmaceutical dosage forms, a combination of the above or any other such preparations as may be approved by the Authority.

3.1.4. Manufacturer

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

3.1.5. 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.

3.2 Abbreviations

3.2.1. COA- Certificate of analysis

3.2.2. EMA-European medicines agency

3.2.3. FPP-Finished pharmaceutical product

3.2.4. INN- International Non-proprietary Name

3.2.5. WHO- World Health Organisation

3.2.6. MAH- Marketing Authorisation Holder

4 Method

4.1 Background

Once a medicine is registered, any variations to the original information submitted with the application or set as conditions for registration must be submitted to the Authority to assess the request. Variations to a registered medicine may be due to numerous reasons that occur post-registration such as administrative changes, the emergence of new scientific knowledge concerning a product or improvements to a product's appearance.

The titles of the variations are numbered, and subcategories depicted by letters and numbers. The conditions necessary for a given variation are outlined for each subcategory and listed below each variation.

Applicants should present a summary of the intended variation in a tabulated format in which the current state/situation and the proposed situation are compared in order to outline the scope of the variation in a transparent manner. Each variation application should be accompanied by a justification.

4.2 General instructions

4.2.1. The following instructions are to be followed;

4.2.1.1. The variation application form duly filled, signed and stamped should be submitted.

4.2.1.2. The required documents must be submitted in the letter head of the Company responsible for the change.

4.2.1.3. All declarations should be on the letterhead of the company but can be signed by the responsible Pharmacist.

4.2.1.4. All variations are to be submitted in a compact disk (CD) and labelled accordingly i.e registration number(e.g. BWN18000xx) or application number (e.g. C13000xx) for Listed and exempted products, name of product initial variation/Q1 variation(for 1st response)/Q2 variation (for 2nd response to variation).

4.2.1.5. Applications should be accompanied by a cover letter from either the applicant or the manufacturer explaining the proposed variation in the product with justification. (The manufacturer explains changes in the product while the applicant explains changes in the admin or applicant changes).

4.2.1.6. For variations affecting the product label and package material, samples should be submitted (samples of the approved and proposed changes)

4.2.1.7. Declaration that correct information has been sent and no other changes have been done other than the stated ones should be submitted by either the applicant or manufacturer.

4.3. Types of variations

A. Variation in the name and/or address of the applicant/MAH

Conditions

I. The applicant shall remain the same legal entity.

Documentation

I. A formal document from the manufacturer/ relevant body in which the proposed name or address is mentioned.

II. Amended immediate label, outer label & package insert for the product with the proposed name if applicable.

B. Variation of MAH (Transfer of applicancy) of the FPP

Conditions

I. No change in the location of the manufacturing site and in the manufacturing operations.

Documentation

I. A formal document from the manufacturer or relevant official body [e.g. the national medicines regulatory authority (NMRA)] in which the new name and/or address is mentioned.

II. Notarized (signed and dated) transfer of ownership documents. i.e Notification letter from the current applicant and acceptance letter from the proposed applicant.

III. Revised product information including label and package insert showing the proposed MAH name where applicable.

C. Variation in name and/or address of the FPP manufacturer

Conditions

I. The manufacturing site shall remain the same (No change in location of the manufacturing site and in the manufacturing operations).

Documentation

I. Declaration that the manufacturing process has not changed

II. Proof of change from local authority (regulatory or companies board) with the new manufacturer and address

III. Updated Label, Package insert reflecting change

IV. Replacement of relevant pages of the dossier.

D. Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FPP

Conditions

I. The manufacturing process should remain the same.

II. Method of transfer from the old to the new site or new test has been successfully completed.

Documentation

I. cGMP/ISO Certificates equivalent documentation of new site.

II. Comparison of manufacturing process of existing/old site vs new/additional site.

III. Specifications of Finished Pharmaceutical Product at new/additional site vs existing/old site

IV. Package Insert and label reflecting change

V. Replacement of relevant pages of the dossier.

E. Variation in the name of the FPP

Conditions

I. The product remains the same in qualitative and quantitative composition.

II. No change in the location of the manufacturing site and in the manufacturing operations.

III. No confusion with the international Non-proprietary Name (INN)

Documentation

I. A formal document from the National Medicines Regulatory Authority (NMRA) in which the new name is approved.
II. Declaration that there are no changes to manufacture or composition of the product.
III. Updated Package Insert and Label reflecting the change
IV. Replacement of relevant pages of the dossier

F. Change or addition of indication/Claim

Conditions

I. New indication is in line with permissible complementary medicine claims in Botswana.

Documentation

I. Evidence of indication from an acceptable source (Pharmacopoeia, WHO/EMA/Health Canada monographs; Traditional Chinese Materia Medica etc.).

II. Updated Package Insert and Label reflecting the change

G. Change in packaging in immediate contact with the product

Conditions

I. The proposed packaging material must be at least equivalent to the approved material in respect of its relevant properties.

II. Relevant stability studies in accordance with the relevant guidelines have been started with

Documentation

I. Replacement of relevant pages of the dossier.
II. Appropriate data/information on proposed packaging material.
III. Proof must be provided that no interaction between the content and the packaging material occurs.
IV.Copy of approved and proposed specifications of the packaging material.
V. The stability studies or commitment to conduct stability studies.

H. Change in packaging NOT in immediate contact with product

Conditions

N/A

Documentation

1. Approved and proposed artwork/ labels

I. Change or additional pack size

Conditions

I. Proposed pack size should be consistent with the posology and treatment duration as in the registered package insert.

II. The primary packaging material remains the same.

Documentation

I. Justification of the proposed pack size, showing that the proposed size is consistent with the dosage regime and duration as prescribed in the package insert

II. Specification of the approved and proposed packaging

III. Commitment to conduct stability studies in proposed pack sizes and report only on out of specification results

IV. Replace relevant pages of the dossier e.g the label and packaging material

J. Change in shelf life of the FPP (with/without change in storage condition)

Conditions

I. The shelf life is not less a year and does not exceed five years.

II. Container closure system should remain the same

Documentation

I. Revised stability data supporting the proposed shelf life

II. Approved and proposed release and end of shelf life specifications

III. Updated package insert and label with the changes and other relevant pages of the dossier

K. Change in Scientific or Botanical Name of the plant(s)

Condition

I. Declaration that the plant species is still the same as at registration.

Documentation

I. Provide evidence of the change of nomenclature and/or taxonomy of the plant e.g. Nomenclature and Taxonomy Advisory Group (NATAG) notification.

II. Revised package insert and label indicating the change of name

L. Change or additional part of plant used

Condition

I. Plant remains the same

II. Active ingredient is also found in the additional part.

III. Quantity of the active ingredient remain the same

Documentation

I. Provide evidence to support that the active ingredient is also found in the additional part.

II. Specifications and COA of the old plant part and the new one

III. Replace relevant pages of the dossier e.g composition table

M. Change in Scientific name of nutritional substance

Condition

1. Nutraceutical is still the same as at registration

Documentation

I. Provide evidence of the change of nomenclature of the nutraceutical from acceptable sources

II. Revised package insert and label indicating the change of name and other relevant pages of the dossier

N. Replacement of excipient with a comparable excipient

Conditions

I. Same functional characteristics of the excipient.

II. The proposed excipient does not include the use of materials of human or animal origin for which assessment is required of safety data.

Documentation

I. Justification for the change of excipient

II. Evidence that the change of excipient does not drastically change the finished product specifications of the product eg. approved and proposed specifications of the FPP

O. Variation in the manufacturing processes of the finished pharmaceutical product

Conditions

I. The overall manufacturing principle remains the same.

II. The proposed manufacturing process must lead to an identical product regarding all aspects of quality, safety and efficacy.

Documentation

I. Provide finished product release and end of shelf life specifications and / COA of the approved and proposed manufacturing process

II. Updated post-acceptance stability protocol and stability commitment to place the first production-scale batch of the proposed product into the long-term stability programme

P. Variation in the Finished Product Specification

I.	Variation in the Finished Product Specification	Conditions to be fulfilled	Required documentation
a.	Tightening of specification limits	I, II	I
b.	Addition of a new test parameter	I, II, III	I,II
c.	Replacement of a test parameter	I, II	I,II
d.	Deletion of a test parameter	I	I,II

Conditions

I. The variation should not be the result of unexpected events arising during manufacture.

II. Any variation should be within the range of registered limits.

III. The proposed test(s) method does not concern a novel non-standard technique, or a standard technique used in a novel way.

Documentation

I. Comparative table of approved and proposed specifications and COA

II. Justification for change

Q. Change in source of an excipient from a TSE risk to a material of vegetable or synthetic origin.

Conditions

1. No change in the excipient, FPP release and shelf-life specifications.

Documentation

1. Declaration from the manufacturer of the excipient that it is entirely of vegetable or synthetic material

R. <u>Variation or addition of imprints, embossing or other markings on tablets or printing on capsules, including replacement, or addition of inks used for product marking</u>

Conditions

I. Finished product specifications have not been amended (except for appearance).

II. Any ink must comply with the relevant standards

Documentation

I. Provide approved and proposed finished product specifications

II. Submit a sample of the product for the approved and proposed.

Appendix I

Variations types

A. Variation in name and/or address of the applicant and/or principal
B. Variation in Marketing Authorization Holder of the FPP
C. Variation in name and/or address of the FPP manufacturer
D. Replacement or addition of a manufacturing site for part or full manufacturing process of the FPP
E. Variation in the name of the Finished Product
F. Change or addition of therapeutic use
G. Change in packaging in immediate contact with product
H. Change in packaging NOT in immediate contact with product
I. Change or additional pack size
J. Change in shelf life (with/without change in storage condition)
K. Change in Scientific or Botanical Name of the plant(s)
L. Change or additional part of plant used
M. Change in Scientific name of nutritional substance
N. Replacement of excipient with a comparable excipient
O. Minor variation in the manufacture of the finished product
P. Variation in the Finished Product Specification
Q. Change in source of an excipient from a TSE risk to a material of vegetable of synthetic origin
R. Variation or addition of imprints, embossing or other markings on tablets or printing on capsules, including replacement, or addition of inks used for product marking

Appendix II

Variations requiring new applications

- Variation of the API to a different API
- Variation in the strength of one or more APIs
- Inclusion of an additional API to a multi-component product
- Removal of one API from a multi-component product
- Variation of dosage form e.g. capsule to tablet
- Variation of release profile of product e.g. sustained release to immediate release