GUIDELINES ON REGISTRATION OF IMPORTED HERBAL MEDICINE PRODUCTS FOR HUMAN OR VETERINARY USE IN UGANDA

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These guidelines shall be cited as the *"Professional Guidelines on Registration of Imported Herbal Medicine Products for Human or Veterinary Use in Uganda, Doc. No. DAR/GDL/029, Revision No. 0."*

Adoption and approval of these Professional Guidelines

In EXERCISE of the powers conferred upon the National Drug Authority by Section 5(i) of the National Drug Policy and Authority Act, Cap. 206 of the Laws of Uganda (2000 Edition), the National Drug Authority hereby ADOPTS and ISSUES these professional guidelines on; "**Registration of Herbal Medicine Products for Human or Veterinary Use in Uganda,** Doc. No. DAR/GDL/029, Revision No.:0", made this 29th day of July 2020, that take effect on 3rd Aug 2020

Signature

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1.0 BACKGROUND / INTRODUCTION

National Drug Authority (NDA) was established in 1993 by the National Drug Policy and Authority Statute which in 2000 became the National Drug Policy and Authority (NDP/A) Act, Cap. 206 of the Laws of Uganda (2000 Edition). The Act established a National Drug Policy and National Drug Authority to ensure the availability, at all times, of essential, efficacious and cost-effective drugs to the entire population of Uganda, as a means of providing satisfactory healthcare and safeguarding the appropriate use of drugs.

The Vision of NDA: "*A Uganda with safe, effective and quality medicines and health care products*".

The Mission of NDA: "*Promoting and protecting public health through the effective regulation of human and animal medicines and health care products*".

The National Drug Policy and Authority Act, Section 35 mandates the Drug Authority to scientifically examine any drug for purposes of ascertaining efficacy, safety and quality of the drug before registration for use in Uganda.

These guidelines shall be followed by all applicants when preparing applications for registration of Imported Herbal Medicine Products for Human & Veterinary use intended for submission to National Drug Authority

1.1 Objective of these guidelines

These guidelines are intended to provide guidance to applicants who intend to submit registration applications for imported Herbal medicine products for human or veterinary use in Uganda

1.2 Policy

These guidelines are developed in accordance with the National Drug Policy and Authority Act Cap 206, Section 35(1)(a): "the drug authority may scientifically examine any drug for the purposes of ascertaining efficacy, safety and quality of that drug"

Section 35(3) "if, on application made in the prescribed manner and on payment of the prescribed fee, the Authority is satisfied

(a) that the drug or preparation in respect of which the application is made has not previously been registered; and

(b) that the use of the drug or preparation is likely to prove beneficial,

the Authority shall register the name and description of that drug or preparation".

1.3 Scope

These guidelines apply to product dossiers for imported herbal medicine products.

2.0 ABBREVIATIONS

API	Active Pharmaceutical Ingredient
BMR	Batch Manufacturing Records
BP	British Pharmacopoeia
CPP	Certificate of Pharmaceutical Product (CPP)
GMP	Good Manufacturing Practice
ICH	International Conference on Harmonisation
Ph. Eur.	European Pharmacopoeia
USP	United States Pharmacopeia
WHO	World Health Organisation

3.0 TERMS AND DEFINITIONS

In these Guidelines, unless the context otherwise requires-

"Applicant" means a person who applies for registration of a medicinal product to NDA, who must be the owner of the product. He may be a manufacturer or a person to whose order and specifications, the product is manufactured. The applicant shall therefore be responsible for signing the registration application form. In the event that the applicant wants another person to register the medicine product on his behalf, then Powers of Attorney, duly notarised in the country of origin, and registered with the Registrar of Companies in Uganda shall be provided. After the product is registered, the applicant shall be the Marketing Authorisation Holder (MAH).

"Active pharmaceutical ingredient" means any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of a human being or animals

"Authorized person" means a person responsible for the release of batches of finished product for sale or distribution. The batch documentation of a batch of a finished product must be signed by an authorized person from the production department and the batch test results by an authorized person from the quality control department for batch release.

"Acceptance criteria" means numerical limits, ranges, or other suitable measures for acceptance of the results of analytical procedures.

"Chromatographic fingerprinting" refers to the application of chromatographic techniques to create a characteristic chromatographic pattern of phytochemical constituents which represents the multicomponent system typical of the herbal substance/herbal preparation/herbal medicine product.

"Constituents with known therapeutic activity" are chemically defined substances or groups of substances, which are generally accepted to contribute substantially to the therapeutic activity of a herbal substance, a herbal preparation or a herbal medicine product.

"Degradation product" means any impurity resulting from a chemical change in the composition of the active substance brought about during manufacture and/or storage of the active substance/medicine product by the effect of, e.g. light, temperature, pH, water, or by reaction with an excipient and/or the immediate container closure system. Due to the particular nature of herbals, for herbal substances/herbal preparations/HMPs, in general, only toxicologically relevant degradation products must be specified.

"Drug extract ratio (DER)" means the ratio between the quantity of herbal substance used in the manufacture of a herbal preparation and the quantity of herbal preparation obtained. The number (given as the actual range) written before the colon is the relative quantity of the herbal substance; the number written after the colon is the relative quantity of the herbal preparation obtained.

Two DER can be distinguished:

a) Genuine (Native) drug extract ratio (DER genuine): is the ratio between the quantity of herbal drug (herbal substance) used in the manufacture of an extract and the quantity of genuine (native) extract obtained.

b) Total drug extract ratio (DER total): is the ratio between the quantity of herbal drug (herbal substance) used in the manufacture of an extract and the quantity of whole extract

"Extraction solvents" are the solvents used for an extraction process.

"Genuine herbal preparation" refers to the preparation without excipients, even if for technological reasons the genuine herbal preparation is not available. However, for soft and liquid herbal preparations the genuine herbal preparation may contain variable amounts of (extraction) solvent.

"Herbal drugs" is a term synonymous with the term herbal substance, herbal preparations and herbal medicine products

"Herbal medicine products" refers to any medicine product, exclusively containing as active substances one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations. It is a finished, labeled herbal medicine product that contains as active ingredients, aerial or underground parts of plants, or other plant materials, or a combination of these, whether in the crude state or as plant preparations and which may contain conventional excipients in addition to the active ingredients and may also contain by tradition, natural organic or inorganic ingredients which are not of plant origin;

"Herbal preparations" are obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or

fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates.

"Herbal substances" refers to all mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen, animal, rocks or such natural components in an unprocessed, usually dried form but sometimes fresh.

Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).

"Herbal teas" consist exclusively of one or more herbal substance(s) intended for oral aqueous preparations by means of decoction, infusion or maceration. The preparation is prepared immediately before use. Herbal teas are usually supplied in bulk form or in sachets.

*"**Impurity"***

a) Any component of the herbal substance, which is not the entity defined as the herbal substance.

b) Any component of the herbal preparation/herbal medicine product that is not the entity defined as the herbal substance/preparation or an excipient in the herbal preparation/herbal medicine product.

"Markers" are chemically defined constituents or groups of constituents of a herbal substance, a herbal preparation or a herbal medicine product which are of interest for control purposes independent of whether they have any therapeutic or pharmacological activity. Markers serve to calculate the quantity of herbal substance(s) or herbal preparation(s) in the herbal medicine product if the marker has been quantitatively determined in the herbal substance or herbal preparation.

There are two categories of markers:

a) **Active markers** are constituents or groups of constituents, which are generally accepted to contribute to the therapeutic activity.

b) **Analytical markers** are constituents or groups of constituents that serve for analytical purposes, irrespective of any pharmacological or therapeutic activity which they may be reported to possess.

*"**Native herbal preparation"*** is a term synonymous with Genuine herbal preparation

"Pharmacopoeia (or related words)" refer to authorized pharmacopoeia as per the National Drug Authority and Policy Act (1993).

"Quantification" means adjusting the herbal preparation to a defined range of constituents exclusively achieved by blending different batches of herbal substances and/or herbal preparations (e.g. quantified extract).

"Solvent" means an inorganic or an organic liquid used for the preparation of solutions or suspensions in the manufacture of a herbal preparation or the manufacture of a herbal medicine product.

"Specification" is a list of tests, references to analytical and biological procedures, and appropriate acceptance criteria, which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a herbal substance/preparation or herbal medicine product should conform to be acceptable for its intended use. "Conformance to specification" means that the herbal substance/preparation and/or herbal medicine product, when tested according to the listed analytical procedures, will meet the listed acceptance criteria. Specifications are legally binding quality standards that are proposed and justified by the manufacturer/marketing authorization holder and approved by regulatory authorities or are prescribed in authorized pharmacopoeia.

"Specific test" is a test, which is considered to be applicable to a particular herbal substance/preparation or a particular herbal medicine product depending on their specific properties and/or intended use.

"Standardisation" means adjusting the herbal substance/preparation to a defined content of a constituent or a group of constituents with known therapeutic activity respectively either by adding excipients or by blending batches of the herbal substance and/or herbal preparation (e.g., standardized extracts).

Types of herbal substances / herbal preparations:

a) Standardized herbal substances/herbal preparations are adjusted to a defined content of one or more constituents with known therapeutic activity. This is achieved by adjustment of the herbal substance/herbal preparation with inert excipients or by blending batches of the herbal substance/herbal preparation.

b) Quantified herbal substances/herbal preparations are adjusted to one or more active markers, the content of which is controlled within a limited, specified range. Adjustments are made by blending batches of the herbal substance/herbal preparation.

c) 'Other' herbal substances/herbal preparations are not adjusted to a particular content of constituents. For control purposes, one or more constituents are used as analytical markers.

"Unidentified impurity" is an impurity, which is defined solely by qualitative analytical properties, (e.g., chromatographic retention time).

"Universal test" is a test, which is considered to be potentially applicable to all herbal substances/preparations, or all herbal medicine products; e.g. appearance, identification, assay and impurity tests.

4.0 GENERAL

The requirements outlined in these guidelines shall apply to all imported herbal medicine products intended for sale by wholesale or retail sale to the general public.

4.1 Procedure for submission of an application for registration

a) The application should be typed in English. Any documents which are in any language other than English must be accompanied by a certified or notarized English translation.

b) The application must contain a complete index to the various appendices.

c) The documentation should be formatted as word document, and the body data in PDF format with bookmarks and optical character recognition (OCR) readable.

d) All pages of the application should be numbered in the style: page x of y.

e) Fees for Marketing Authorization applications should be paid before submitting
f) the application. Refer to the NDA website for the fees regulation

g) The application should be submitted in CD-ROM addressed to: The Secretary to the Authority, National Drug Authority.

h) A separate application is required for each product. The products as indicated in the table 1 below will be regarded as either being the same product or separate product applications.

i) All such submissions should be in the exact format/template prescribed in the appendices of this guideline.

Table 1

TYPE OF APPLICATIONS	**APPLICATION**	
	Same	**Separate**
1. Each individual dosage form of a particular medicine		**X**
2. Variations of the active pharmaceutical ingredient (API) of a product		**X**
3. Tablets/Capsules/Suppositories/Lozenges		
a) Different pack-sizes of exactly the same strength and formulation and primary packaging material.	**X**	
b) Different strengths and formulations.		**X**
c) Uncoated and coated tablets of the same strength and formulation.		**X**
4. Syrups/Liquids/Solutions (excluding parenterals) / Creams / Ointments		

TYPE OF APPLICATIONS	APPLICATION	
	Same	Separate
a) Different container sizes of the same strength and formulation where the primary packaging is the same	X	
b) The same container size of different strengths and formulations.		X

4.2 Additional information

a) Where the information or documents submitted in respect of an application for registration are not sufficient for the Authority to determine whether the product to be registered meets the quality, safety and efficacy requirements prescribed by the Authority, the Authority shall request the applicant to submit additional information necessary for the registration. A letter to this effect will be sent to the applicant.

b) Additional information provided should be complete and accurate. If the information provided is deemed insufficient by the Authority then additional information shall be requested for. This, however, shall only be done for a maximum of three times, after which if the information provided is still inadequate then the application for registration will be rejected. The applicant may however submit fresh applications for registration.

4.3 Application for registration

An application for the registration of an imported herbal medicine product shall be made to the Authority, in the prescribed Form 4 for imported herbal medicine product for human use or Form 5 for imported herbal medicine product for veterinary use, as the case may be.

4.4 Certificate of Registration for imported herbal medicine products.

The Authority shall issue a certificate of registration for an imported herbal medicine product in the prescribed Form 3 – Certificate for Registration of Human or Veterinary Drugs, Preparation and Vaccines or other Immunological Products (Appendix I). The holder of a certificate of registration shall pay an annual retention fee prescribed by the Authority for maintaining the registered imported human or veterinary herbal drug or preparation, on the Register

4.5 Suspension of Certificate of Registration.

A certificate of registration of an imported herbal medicine product shall be suspended for;

i) failure of the holder of the certificate to meet the quality specifications and standards of the registered herbal medicine product;

ii) for any other reasons as the Authority shall prescribe from time to time;

iii) for violation of any provision in the NDP/A Act, Regulations or these Guidelines

4.6 Application for alteration of a registered herbal medicine product

a) Whenever a marketing authorization holder wishes to make any alteration to a registered herbal medicine product, he/she shall be required to apply to and obtain approval from the Authority before executing the changes or alteration.

b) The guidelines for Variation of Registered Medicine Products (Doc No. DAR/GDL/005) shall be referred to for details. Application for alteration shall be done by submitting a dully filled in application form which shall be accompanied with:-

i) Detailed description of the alteration with supporting reasons as well as the classification of the alteration (major or minor).

ii) Sample or artwork of the altered product where applicable.

iii) Non-refundable alteration / amendment fees for each proposed amendment as stipulated in the prescribed fees

4.7 Maintenance of registration

Maintenance of registration status is subject to consistent quality and satisfactory performance of the herbal medicine product on the market

The holder of a certificate of registration shall pay an annual retention fee prescribed by the Authority, for maintaining the herbal medicine product on the Register.

4.8 Applicant

4.8.1 An application for registration of a product may be made by—

a) the patent holder;

b) licensed person approved by the manufacturer or patent holder;

c) the manufacturer; or

d) an agent authorised by the manufacturer or patent holder. The agent must hold a valid license to conduct pharmacy business

4.8.2 The name, physical address, telephone number, fax number, and e-mail address of the applicant shall be provided.

4.8.3 Every applicant who is not resident in Uganda shall appoint a person in Uganda authorized by NDA to deal in medicine products to be an AGENT. The appointment shall be notified to the Authority by submitting a letter of appointment supported by original copy of Powers of Attorney dully notarized in the country of origin, and registered with the Registrar of Companies in Uganda.

4.8.4 The supervising pharmacist of the appointed person shall sign the application form

4.9 Particulars of the Product

The applicant shall provide the following details in the prescribed manner;

a) **Proprietary name**. A proprietary name means the (trade or brand) name which is unique to a particular drug product and by which it is generally identified (and by which it is registered in the country of manufacture).

b) **Pharmaceutical form** shall mean the form in which the drug is presented, e.g., solution, suspension, eye drops, emulsion, ointment, suppository, tablet, capsule, etc. For injections, the type of presentation (e.g., vial, ampoule, dental cartridge, etc), and the type of content (e.g., powder for reconstitution, solution, suspension, oily solution, etc.) shall also be stated.

c) **Description of the drug** shall mean a full visual description of the product including colour, size, shape and other relevant features, eg. 'black and red gelatin capsule with the marks "Amp-250" on the side', 'pink film-coated tablets with word "PAN" embossed on one side' etc.

d) **Pack size(s)** applied for shall be those intended for marketing and should be the ones submitted as samples.

e) **Main indications** shall be those conditions for which the product is normally used and for which marketing authorisation is being sought. The applicable system of medicine should be mentioned, eg. Ayurveda, Sidda, Unani, Chinese traditional medicine, etc.

4.10 Labelling

The applicant shall ensure that the primary (immediate) packaging of the product and the secondary package are labelled according to the law applicable in Uganda. The following minimum information shall be required in English on the label of the immediate packaging:

a) brand name where applicable

b) International Non-proprietary Name (INN)/generic name or botanical name of the active ingredients

c) quantity of active ingredient per dosage unit

d) total number of units per pack

e) date of manufacture

f) date of expiry, where applicable debossed or embossed (e.g., for blister packs) onto the primary pack

g) batch number where applicable debossed or embossed (e.g., for blister packs) onto the primary pack

h) storage conditions

i) name and address of manufacturer

Note:

i) Due to lack of space, the date of manufacture, address of the manufacturer and storage conditions may be omitted on the primary container if it is a blister or strip pack, or a vial or an ampoule less than 10ml.

ii) The name of the manufacturer may be substituted with a trade-mark or other symbol. However, these details shall appear in full on the secondary packaging.

4.11 Information leaflet

The product packaging shall include a prescriber information leaflet in the case of prescription medicines, or a patient information leaflet in the case of non-prescription medicines. The leaflet shall include the following minimum information:

a) International Non-proprietary Name (INN) for each active ingredient, or botanical name where appropriate.

b) Names of all excipients

c) Pharmacology: a brief description of the mechanism of action and pharmacological effects

d) Clinical Information:

i) indications

ii) dosage regimens, including for children

iii) contraindications

iv) precautions in pregnancy, lactation, renal and hepatic failure

v) adverse reactions including their frequency

vi) clinically significant drug interactions

vii) symptoms and treatment of over-dosage

e) Pharmaceutical Information:

i) dosage form

ii) strength

iii) excipients

iv) storage conditions

v) shelf-life

vi) pack size

vii) description of product and package

viii) name and address of the manufacturer

4.12 Certificate of Pharmaceutical Product (CPP) Free sale

The CPP must be in accordance with WHO guidelines. However, if the CPP is not available, a marketing authorization or Free Sales Certificate from the country of origin should be submitted. Marketing authorization or free sales certificate should include the following: -

a) Product trade name in the country of origin.

b) Number and date of marketing authorization in the country of origin.

c) Name of active and inactive substances with their concentrations.

d) A statement that certifies the product is marketed in the country of origin.

e) Provide the Summary of Product Characteristics (SPC).

f) Provide a copy of the patient information leaflet (PIL).

4.13 Particulars of the Manufacturer(s) and Activity

4.13.1 For all herbal medicine products irrespective of the country of origin, all key manufacturing and/or processing steps in the production of finished pharmaceutical products must be performed in plants that comply with GMP standards. The Applicant must submit a valid GMP Certificate issued by competent Authority in the country of origin of the product

4.13.2 The name, physical addresses, telephone number, fax number, and e-mail address of the manufacturer shall be provided.

4.13.3 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 in the examples below.

	Name	Location address of manufacturing site	Activity	Date of last inspection	Relevant line passed
1					
2					
3					

4.13.4 A copy of a valid manufacturing licence and GMP certificate shall be provided for each site.

4.14 Composition & Packaging Material

4.14.1 Specifications of the Packaging Material

a) Primary (immediate) container

This is the container in immediate contact with the drug. Detailed specifications of the type, nature, size and grade of the primary container shall be given including the method of closure and, for liquid products, the fill volume. Specifications for glass containers for aqueous solutions and rubber

closures for containers for parenteral products are as per BP, Phr Int. USP or Ph. Eur. specifications. The applicant shall specifiy the relevant pharmacopoeia concerning the primary container specifications

b) Outer packaging

The same requirements as with the primary packaging above shall apply.

4.15 Composition of the Product

4.15.1 *The **active ingredient(s)*** shall be the common English and scientific name of the processed plant material(s), or other natural material(s) in the product, possessing the medicine properties responsible for the product's medicine action (indications). Such processed material is derived from crude plant parts or crude plant materials, or other natural materials by processes such as extraction, distillation, comminution and heat treatment.

4.15.2 ***Source*** of the raw material (processed material) shall be the crude part of the plant used to obtain the processed plant material described above. The English and scientific name of the plant shall be stated. For other natural raw materials, the relevant source (eg. type of rock used, part of animal, etc) shall be stated.

4.15.3 ***Quantities*** of the active ingredients (processed material) shall be given in terms of the content per dosage unit, eg. mg/tablet, mg/ml, etc.

4.15.4 ***Species of plant*** used shall be the botanical name of the plant used.

4.15.5 ***The reason for inclusion*** of each inactive ingredient and active ingredient in the formulation shall be stated and justified with appropriate scientific reasons. Any raw materials used, although not present in final dosage form, shall also be stated.

4.16 Guidance on Quality Control (Specifications and Details of Analytical Methods)

4.16.1 Justification of Specifications and Scope

a) Justification should be presented for each procedure and each acceptance criterion included or excluded. The setting of a specification for a herbal substance/preparation and herbal medicines product is part of an overall control strategy.

b) The justification should refer to pharmacopoeial standards, the control of raw materials and excipients, relevant development data, in-process testing, process evaluation/validation, analytical validation, stability testing. A reasonable range of expected analytical and manufacturing variability should be considered. Acceptance criteria should be based on data obtained from batches used to demonstrate manufacturing consistency and historical batch data should be taken into account where available.

c) Linking a specification to a manufacturing process is important, especially with regard to phytochemical profile and potential impurities and contaminants. If

multiple manufacturing sites are planned, data from these sites in establishing the initial tests and acceptance criteria should be considered. If data from a single representative manufacturing site are used in setting tests and acceptance criteria, products manufactured at all sites should still comply with these criteria.

d) Since the specification is chosen to confirm the quality rather than to characterize the product, the applicant should provide the rationale and justification for including and/or excluding testing for specific quality attributes.

4.16.2 Specifications required for herbal substances:

a) **Botanical characteristics** of the plant (binomial scientific name: genus, species, variety and author, chemotype, where applicable; usage of genetically modified organisms), part of the plant, its state (e.g. whole, fragmented, fresh, dry);

b) **Macroscopical and microscopical** characteristics of the plant part;

c) **Phytochemical characteristics** constituents with known therapeutic activity or active or analytical markers, toxic constituents (identity, assay, limit tests);

d) **Biological / geographical variation,**

e) **Cultivation/harvesting / drying conditions** (microbial levels, mycotoxins (aflatoxins, ochratoxin A), heavy metals, pyrrolizidine alkaloids (PAs), polycyclic aromatic hydrocarbons (PAHs) etc.;

f) **Pre-/post-harvest chemical treatments** (pesticides, fumigants); and

g) **Profile and stability** of the constituents.

4.16.3 Specifications Required for herbal preparations:

a) Quality of the herbal substance (as indicated under required specifications for herbal substances);

b) Definition of the herbal preparation (genuine (native) drug extract ratio (DERgenuine), extraction solvent(s));

c) Method of preparation from the herbal substance;

d) Microscopical characteristics (comminuted and powdered herbal substances as herbal preparation);

e) Phytochemical characteristics of the herbal preparation: constituents with known therapeutic activity or active or analytical markers, toxic constituents (identification, quantitative determination, limit tests);

f) Contaminants (pesticide residues, fumigants, mycotoxins (aflatoxins, ochratoxin A), heavy metals, pyrrolizidine alkaloids (PAs), polycyclic aromatic hydrocarbons (PAHs) etc.);

g) Drying conditions (e.g. microbial levels, residual solvents in extracts);

h) Profile and stability of the constituents;

i) Microbial purity on storage; and

j) Batches used in pre-clinical/clinical testing (safety and efficacy considerations).

4.16.4 Specifications required for herbal medicine products:

a) The herbal substance and/or herbal preparation specifications as indicated under the respective sections;

b) Manufacturing process (temperature effects, residual solvents);

c) Pharmaceutical form (e.g. tablets, capsules, oral liquids), and the characteristics of the pharmaceutical forms;

d) Profile and stability of the active substance/formulation in the packaging;

e) Excipients (e.g. antimicrobial preservatives, antioxidants) microbial purity on storage;

f) Batches used in pre-clinical/clinical testing (safety and efficacy considerations); and

g) Conformation to a pharmacopoeial monograph (g)A copy of the manufacturer's or supplier's certificate of analysis shall be attached to confirm conformation to these specifications.

Note:

Due to the inherent complexity of HMPs, there may be no single stability-indicating assay or parameter that profiles the stability characteristics. Consequently, the applicant should propose a series of product-specific, stability-indicating tests (e.g. chromatographic fingerprint tests), the results of which will provide assurance that changes in the quality of the product during its shelf-life will be detected. The determination of which tests should be included should be product-specific and scientifically plausible.

4.16.5 Universal Tests and Acceptance Criteria

4.16.5.1 **Herbal substances**

Herbal substances are a diverse range of botanical materials including leaves, herbs, roots, flowers, seeds, bark etc. A comprehensive specification must be developed for each herbal substance. In the case of fatty or essential oils used as active substances of herbal medicine products, a specification for the herbal substance is required unless justified.

If a monograph for a herbal substance exists in an authorized pharmacopoeia, the herbal substance must be in accordance with this monograph. For non-pharmacopeial herbal substances the specification should be established on the basis of recent scientific data and should be set out in the same way the indicated authorized pharmacopoeia. The general monograph 'Herbal Drugs' of an authorized pharmacopoeia should be consulted for interpretation of the following requirements.

The following tests and acceptance criteria are considered generally applicable to all herbal substances.

a) Definition:

A qualitative statement of the botanical source, the binomial scientific name, plant part used and its state (e.g. whole, fragmented, fresh, dry).

b) Characters:

A qualitative statement about the organoleptic character(s) (smell,taste,texture,colour), the characteristic macroscopic and microscopic botanical characters of the herbal substance.

c) Identification:

i) Identification testing optimally should be able to discriminate between related species and/or potential adulterants/substitutes, which are likely to be present. Identification tests should be specific for the herbal substance and are usually a combination of three or more of the following: Macroscopical characters, microscopical characters, chromatographic fingerprinting procedures, chemical reactions.

ii) For the herbal substance, a characteristic fingerprint chromatogram should be established and included in the submission with details f the method of analysis used.

iii) The fingerprint shall be used for identity testing of the herbal substance. It can also be used to detect adulteration with other herbal substances.

d) Tests:

i) Foreign matter

1. Total ash
2. Ash insoluble in hydrochloric acid (might not apply to all herbal substances and must be justified by the applicant)
3. Water soluble extractive (might not apply to all herbal substances and must be justified by the applicant)
4. Extractable matter (might not apply to all herbal substances and must be justified by the applicant)

ii) Water content

This test is important when the herbal substances are known to be hygroscopic. For non pharmacopoeial herbal substances, acceptance criteria should be justified by data on the effects of moisture absorption. A Loss on drying procedure may be adequate; however, in some cases (essential oil containing plants) an analytical procedure that is specific for water is required.

iii) Potential contaminants

Should be considered and controls introduced, as appropriate. Acceptance criteria and suitable validated procedures should be used to control potential contaminants/residues. The analytical procedure and validation data should be provided considering the respective plant matrix. In the case of use of fresh herbal substances (e.g. to produce expressed juices, fatty or essential oils) testing for contamination of the herbal substance can be omitted, where fully justified, and should be performed on the herbal preparation, where appropriate. The limits for the herbal substance can be transferred accordingly.

iv) Pesticide and Fumigant residues

The potential for residues of pesticides and fumigant agents should be considered. For pesticide residues, the acceptance criteria and validated methods in authorized pharmacopoeia should be used. Regarding possible fumigant residues, confirmation by the supplier that fumigation of the herbal substance is not performed may be considered sufficient. However, it should be taken into account that fumigation of commodities is often required by quarantine or export/import regulations. Therefore, the herbal substance should be tested for fumigants if no information is provided by the supplier. Where a fumigant is known to be non-persistent and this is supported by appropriate batch data, reduced testing may be acceptable.

v) Heavy metals and other toxic elements

The acceptance criteria described in the general monograph 'Herbal Drugs' of authorized pharmacopoeia shall be applied, unless otherwise justified. For other metals not listed in this monograph, acceptance criteria should be based on safety considerations. Where justified, herbal substances used for the production of extracts may exceed the limits for heavy metals specified in the monograph 'Herbal Drugs' provided that the resulting extract satisfies these requirements. The need for inclusion of additional tests and acceptance criteria for other toxic elements (e.g. arsenic) should be investigated during development using a risk assessment approach. In cases where authorized pharmacopoeia have a monograph where limits for specific heavy metals/toxic elements are included, these shall take precedence. Additionally, the origin of the plant (cultivation or wild collection, region) and the plant specific ability to accumulate heavy metals/toxic elements should be taken into account. The analytical procedures should be performed using pharmacopoeia methods where these exist or validated methods where they don't.

vi) Microbial limits

Routine testing is generally required for these substances because the microbial purity is linked to production and storage and to mycotoxin contamination. Acceptance criteria should be established in accordance with authorized pharmacopoeia limits. Higher microbial limits may be acceptable and should be set and justified in relation to the specific herbal substance, GACP concept and subsequent processing. Reduction of the microbial count at the level of the herbal substance (e.g. source, appropriate harvest/collection and drying procedures, treatment with water vapour), herbal preparation (processing) and/or HMP (boiling water) should be taken into account when setting the limits. The source of the herbal material should be taken into account when considering the inclusion of other possible pathogens (e.g. Campylobacter and Listeria species) in addition to those specified in authorized pharmacopoeia. Microbial counts should be determined using pharmacopoeial procedures or other comparable, validated procedures.

vii) Mycotoxins (aflatoxins, ochratoxin A)

The potential for mycotoxin contamination should be considered. For aflatoxins, the acceptance criteria and analytical procedure shall be as described in the respective authorized pharmacopoeia such as Ph. Eur. 2.8.18. The method's suitability for the herbal substances under test

must be demonstrated or another validated method used. For ochratoxin A, the analytical procedure and acceptance criteria are described in an authorized pharmacopoeia such as in Ph. Eur. 2.8.22. The suitability of the methods should be determined for the respective herbal substances, in the absence of which a validated method should be used. In cases where ochratoxin A contamination is relevant, the acceptance criteria given in the authorized pharmacopoeia is also be acceptable for other herbal substances.

viii) Impurities from extraneous sources

The potential for impurities from extraneous sources should be considered. Potentially toxic compounds arising from extraneous sources include, for example, pyrrolizidine alkaloids (PAs) from PA-containing weeds and polycyclic aromatic hydrocarbons (PAHs). It has been shown that PA-containing weeds can contaminate herbal substances used for the production of Herbal Medicine Products. PAH contamination of herbal substances can arise from environmental sources or specific conditions of processing of herbal substances. Suitable validated methods should be used and acceptance criteria justified. It is the responsibility of the applicant to establish at which stage testing for such impurities takes place. In order to ensure that the levels of PAs do not exceed the daily intake recommended for Herbal Medicine Products, it is anticipated that in most cases testing the herbal preparation will ensure a more homogeneous matrix than testing the herbal substance. With regard to the control and limits for PAs, relevant scientific references should be taken into account.

ix) Radioactivity

Radioactive contamination should be tested for, if there are reasons for concern.

x) Degradation products

Where relevant, appropriate limits should be proposed for potentially toxic degradants formed on storage or those that might arise as a result of decontamination treatments. Possible degradation products arising from irradiation of the herbal substance, should also be considered where such treatment is used.

xi) Toxic constituents

In the case of potentially toxic constituents, e.g.ascaridole, thujone, pulegone, menthofuran, quantitative determination of their content with details of the validated analytical procedure shall be required. If

relevant, information on their potential toxicity (either by reference to the literature or by presentation of data) should be given to justify the proposed limits.

xii) Other appropriate tests (e.g. swelling index)

xiii) Assay

In the case of herbal substances with constituents of known therapeutic activity or with active markers, assays of their content are required with details of the analytical procedure used and the validation data of the same. Where possible, a specific, stability-indicating procedure should be chosen. In cases where use of a non-specific assay is justified, other supporting analytical procedures should be used to achieve overall specificity, wherever required.

In the case of herbal substances where the constituents responsible for the therapeutic activity or active markers are unknown, assays of analytical markers or other justified determinations shall be required and the appropriateness of the choice of markers should be justified.

4.16.5.2 **Herbal preparations**

Herbal preparations are diverse in character ranging, ranging from simple, comminuted (powdered or cut) plant material to extracts, tinctures, essential oils, expressed juices and processed exudates. A comprehensive specification must be developed for each herbal preparation based on recent scientific data.

If a monograph for a herbal preparation exists in authorized pharmacopoeia as per the National Drug Authority and Policy Act, 1993, the herbal preparation must be in accordance with this monograph, and such applicable general chapters for on Herbal Drug Extracts.

For non-pharmacopeial herbal preparations the specification should be established on the basis of recent scientific data and should be set out in the same way as in authorized pharmacopoeia which shall be indicated by the applicant. The general monographs in the respective pharmacopoeia concerning ‘Herbal Drug Preparations’, ‘Herbal Drug Extracts’ and ‘Essential Oils’ should be consulted for the interpretation of the requirements below.

The following tests and acceptance criteria are considered generally applicable to all herbal preparations.

a) Definition:

i) A statement of the botanical source, and the type of preparation (e.g. dry or liquid extract). For extracts, the ratio between the quantity of herbal substance used in the manufacture of the extract, and the quantity of genuine (native) herbal extract obtained (DERgenuine) must be stated.

ii) Information on excipients included in the final extract should also be specified and the use should be justified.

b) Characters:

A qualitative statement about the organoleptic characters of the herbal preparation, where these are characteristic.

c) Identification:

i) Identification tests should be specific for the herbal preparation and optimally should be discriminatory with regard to substitutes/adulterants that are likely to occur.

ii) Identification solely by chromatographic retention time, for example, is not regarded as being specific; however, a combination of chromatographic tests (e.g. HPLC and TLC-densitometry) or a combination of tests into a single procedure, such as HPLC/UV-diode array, HPLC/MS, or GC/MS may be acceptable depending on the scientific sufficiency.

iii) Chromatographic fingerprinting: For the herbal preparation, a characteristic fingerprint chromatogram should be established by means of qualitative analysis. The parameter should be tested at release and during stability studies. During stability/retest testing the fingerprint chromatogram should remain comparable to the fingerprint at the initial time point value to demonstrate consistent quality.

d) Tests:

i) Water content

The acceptance criteria may be justified with data on the effects of hydration or moisture absorption. A Loss on drying procedure may be adequate; however, in some cases (essential-oil containing preparations), an analytical procedure that is specific for water is required.

ii) Particle size

This should be considered for cut or powdered herbal substances intended for use in herbal teas or solid dosage forms of Herbal Medicine Products and also for extracts for use in Herbal Medicine Products. Particle size can have a significant effect on disintegration time, dissolution rate, bioavailability, and/or stability. In such instances, testing

for particle size distribution should be carried out using an appropriate procedure, and acceptance criteria should be provided based on appropriate scientific rationale.

iii) Impurities

iv) Residual solvents in dry or soft extracts arising from the extraction process:

International guidance (ICH) on Residual solvents shall be considering in setting the acceptance limits as well as conducting the analysis of residual solvents.

v) Pesticides, fumigants, mycotoxins and heavy metal/toxic element residues:

Routine or periodic testing shall be required for pesticides, fumigants, mycotoxins (aflatoxins, ochratoxin A) and heavy metals. If it is justified that the contaminants do not accumulate during the manufacturing process, testing of these contaminants in the herbal preparation is usually considered not necessary if tested on the herbal substance. Particular attention should be paid to pesticide residues and mycotoxins that are soluble in lipophilic solvents and so can be concentrated in herbal preparations prepared with lipophilic extraction solvents. The limits for the herbal substance shall be as per the authorized pharmacopoeia.

vi) Microbial limits

Acceptance criteria for the microbiological quality of herbal preparations intended for oral use should be in-line the respective authorized pharmacopoeia. The microbiological quality of herbal preparations to be administered by routes other than oral use should correspond to the acceptance criteria for the intended route of administration according to the authorized pharmacopoeia and should be determined using pharmacopoeial procedures or other equivalent and validated procedures.

vii) Toxic constituents

In the case of potentially toxic constituents, e.g. ascaridole, thujone, pulegone, menthofuran, quantitative determination of their content with details of the validated analytical procedure are required. If relevant,

information on their potential toxicity (either by reference to the literature or by presentation of data) should be given to justify the proposed limits.

viii) Degradation products

Where relevant, appropriate limits should be proposed for potentially toxic degradants formed during processing or on storage.

ix) Impurities from extraneous sources

Potentially toxic compounds arising from extraneous sources include, PAs and PAHs should be tested and acceptable limits set. It is the responsibility of the applicant to establish at which stage testing for such impurities takes place. To ensure that the limits for PAs do not exceed the daily intake recommended for Herbal Medicine Products s it is anticipated that in most cases testing the herbal preparation will ensure a more homogeneous matrix than testing the herbal substance.

x) Assay:

a) In the case of herbal preparations with constituents of known therapeutic activity or with active markers, assays of their content are required with details of the analytical procedure and validation data. Where possible, a specific, stability-indicating procedure should be chosen. In cases where use of a non-specific assay is justified, other supporting analytical procedures may be used to achieve overall specificity, if required. For example, where a UV/visible spectrophotometric assay is used for hydroxyanthracene glycosides, a combination of the assay and a suitable test for identification (e.g. fingerprint chromatography) can be used.

b) In the case of herbal preparations where constituents of known therapeutic activity or active markers are not known, assays of analytical markers or other justified determinations are required. The appropriateness of the choice of markers should be justified.

4.16.5.3 **Vitamins and minerals in traditional herbal medicine products**

Vitamin(s) and mineral(s), which could be ancillary substances in herbal medicine products should meet such established use

The following tests and acceptance criteria are considered generally applicable to vitamins/minerals included (added) to herbal medicine products.

i) Identification:

Identification tests should establish the specific identity of the vitamin(s) and/or mineral(s).

ii) Assays:

Validated assays of vitamins and minerals are required.

iii) Impurities:

Impurities and 'Residual solvents' shall be tested as per the guidelines on registration of medicines for human or veterinary use as applicable. Impurities arising from degradation of the vitamin(s) should be monitored in the herbal medicine products. When it has been demonstrated conclusively by provision of a significant body of data, generated using appropriate analytical methods, that the vitamin(s) do not degrade in the specific formulation and under the specific storage conditions proposed in the application, degradation product testing may be reduced or eliminated upon approval by the National Drug Authority.

4.16.5.4 **Herbal medicine products**

The following tests and acceptance criteria are considered generally applicable to all herbal medicine products:

i) Description:

A qualitative description of the dosage form should be provided (e.g. size, shape, colour). The acceptance criteria should include the final acceptable appearance at the end of the shelf-life. If colour changes occur during storage, a quantitative procedure shall be appropriate.

ii) Identification:

Identification tests should establish the specific identity of the herbal substance(s) and/or herbal preparation(s), in the herbal medicine product and optimally should be discriminatory with regard to substitutes/adulterants that are likely to occur.

Identification solely by chromatographic retention time, for example, is not regarded as being specific; however, a combination of chromatographic tests (e.g. HPLC and TLC-densitometry) or a combination of tests into a single procedure, such as HPLC/UV-diode array, HPLC/MS, or GC/MS may be acceptable. In the case of Herbal Medicine Products containing comminuted (powdered or cut) herbal substances, microscopical and macroscopical characterisation could be used for identification in combination with other methods, if justified.

iii) Chromatographic fingerprinting:

A characteristic fingerprint chromatogram should be established and justified taking account of the fingerprints for the active substance(s). With

regard to combination products a more detailed assessment following robust scientific procedure shall be applied. For this purpose. The scientific procedure may be adopted from stringent regulatory agencies.

Chromatograms from identification or assay test methods can often be used as a basis for chromatographic fingerprinting. The parameter should be tested at release and during stability studies.

In the shelf-life specification, the acceptance criteria should specify that the fingerprint chromatogram is comparable to the initial fingerprint obtained at release.

iv) Impurities:

ICH guidance in 'Note for guidance on impurities in new drug products'/'Guideline on impurities in new veterinary medicine products' (CPMP/ICH/2738/99 and CVMP/VICH/838/99 as revised) and authorized pharmacopoeia information on the same shall be applied with priority being given to whichever is more stringent.

Impurities arising from the herbal substance(s) and/or herbal preparations, e.g. contaminants such as pesticide/fumigant residues, heavy metals, mycotoxins, PAs, PAHs: If controlled during the testing of the herbal substance/preparation, it is not necessary to test for these in the herbal medicine product.

Similarly, residual solvents arising from the manufacture of the herbal preparation (e.g. an extract) do not need not to be controlled in the herbal medicine product, provided they are appropriately controlled in the extract specification. However, solvents used, for example in tablet coating, will need to be controlled in the herbal medicine product.

In cases where potentially toxic degradation products of the herbal substance/preparation are evident (e.g. aglycones from hydroxyanthracene glycosides), they should be monitored in the herbal medicine product and acceptance limits should be stated for such degradation products.

v) Toxic constituents:

In the case of potentially toxic constituents, e.g. ascaridole, thujone, pulegone, menthofuran, quantitative determination of their content with details of the validated analytical procedure are required. If relevant, information on their potential toxicity (either by reference to the literature or by presentation of data) should be given to justify the proposed limits.

vi) Microbial limits:

Acceptance criteria for the microbiological quality of herbal medicine products intended for oral use should be in-line with the relevant authorized pharmacopoeia. The microbiological quality of herbal medicine products to be administered by routes other than oral use should correspond to the acceptance criteria for the intended route of administration according to the authorized pharmacopoeia. Microbial counts should be determined using pharmacopoeial procedures or equivalent validated methods.

vii) Assay:

In the case of products containing herbal substances and/or herbal preparations with constituents of known therapeutic activity, validated assays of the content of these constituents are required along with details of the analytical procedure(s).

Where appropriate, a specific, stability-indicating procedure should be chosen. In cases where use of a non-specific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. For example, where a UV/visible spectrophotometric assay is used e.g. with hydroxyanthracene glycosides, a combination of the assay and a suitable test for identification (e.g chromatographic fingerprinting) can be used.

In the case of herbal medicine products containing herbal substance(s) and/or herbal preparation(s) where the constituents with known therapeutic activity are not known, validated assays of active or analytical markers or other justified determinations are required, as described above.

In cases where use of a non-specific assay is justified, other supporting analytical procedures may be used to achieve overall specificity.

In cases where a specific assay of each active substance of herbal medicine product, is not possible other justified determinations are required following such appropriate guidance such as the Europeans Medicines Agency's 'Guideline on quality on combination of herbal medical products / traditional herbal medical products' (EMA/HMPC/CHMP/CVMP/214869/2006).

viii) Vitamins and/or minerals:

For Herbal Medicine Products containing vitamins and/or minerals, the vitamins and/or minerals should also be qualitatively and quantitatively determined as detailed in 4.16.5.3.

ix) Specific tests and acceptance criteria for herbal medicine products

In addition to the universal tests listed above, the following provides examples of tests which shall be considered applicable to herbal medicine products on a case-by-case basis. The relevant pharmacopoeia chapters on the different pharmaceutical forms shall also be considered.

Individual tests/criteria should be included in the specification when the tests have an impact on the quality of the herbal medicine product for batch control. Tests other than those listed below may be needed in particular situations or as new information becomes available.

Additional tests and acceptance criteria generally should be included for particular herbal medicine products. The following selection presents a representative sample of both the herbal medicine products and the types of tests and acceptance criteria, which may be appropriate.

The specific dosage forms addressed include solid oral, and liquid formulations. Application of the concepts in this guideline to other dosage forms is encouraged.

4.16.5.5 **Tablets (coated and uncoated) and hard capsules**

One or more of these tests may also be applicable to soft capsules and granules.

i) Dissolution / disintegration:

In the case of immediate release herbal medicine products for which constituents with therapeutic activity are not known, the test for in-vitro active substance release can be omitted.

For immediate release products containing herbal preparations, which are highly soluble throughout the physiological pH range, disintegration testing may sometimes be sufficient. Disintegration testing is most appropriate when a relationship to dissolution has been established or when disintegration is shown to be more discriminating than dissolution. In such cases, dissolution testing may not always be necessary, or may be proposed as a periodic test. Development information should be provided to support the robustness of the formulation and manufacturing process with respect to the selection of dissolution vs. disintegration testing.

Single-point measurements are normally considered to be suitable for immediate-release dosage forms. For modified-release dosage forms,

appropriate test conditions and sampling procedures should be established. For example, multiple-time-point sampling should be performed for extended-release dosage forms, and two-stage testing (using different media in succession or in parallel, as appropriate) may be appropriate for delayed-release dosage forms. In these cases it is important to consider the populations of individuals or target animal species who will be taking the herbal medicine products (e.g. achlorhydric, elderly) when designing the tests and acceptance criteria.

Where multiple-point acceptance criteria are necessary, in vitro/in vivo correlation may be used to establish these criteria when human or target animal species bioavailability data are available for formulations exhibiting different release rates. Where such data are not available, and drug release cannot be shown to be independent of in vitro test conditions, then acceptance criteria must be established on the basis of available batch data. Normally, the permitted variability in release rate at any given time point should not exceed a total numerical difference of ± 10% of the labelled content of herbal substance or herbal preparation (i.e. a total variability of 20%: a requirement of 50% ± 10% thus means an acceptable range from 40% to 60%), unless a wider range is justified.

ii) Hardness/friability:

It is normally appropriate to perform hardness and/or friability testing as an in-process control. Under these circumstances, it is normally not necessary to include these attributes in the specification. If the characteristics of hardness and friability have a critical impact on herbal medicine product's quality (e.g. chewable tablets), acceptance criteria should be included in the specification.

iii) Uniformity of mass:

The pharmacopoeial procedure should be used. If appropriate, this test may be performed as in-process control; the acceptance criteria should be included in the specification.

iv) Water content:

A test for water content should be included when appropriate. The acceptance criterion may be justified with data on the effects of or water absorption on the herbal medicine product. In some cases, Loss on drying procedure may be adequate; however, in certain cases (e.g. essential-oil containing preparations), a more specific procedure (e.g. Karl Fischer titration) is required.

v) Oral liquids

One or more of the following specific tests will normally be applicable to oral liquids and to powders intended for reconstitution as oral liquids. Likewise, one or more of the following specific tests will normally be applicable to liquid preparations intended for routes other than oral use.

vi) Uniformity of mass:

Generally, acceptance criteria should be set for weight variation, fill volume, and/or uniformity of fill. Pharmacopoeial procedures should be used.

If appropriate, tests may be performed as in-process controls; however, the acceptance criteria should be included in the specification. This concept may be applied to both single-dose and multiple-dose packages. The dosage unit is considered to be the typical dose taken by the patient. If the actual unit dose, as taken by the patient, is controlled, it may either be measured directly or calculated, based on the total measured weight or volume of drug, divided by the total number of doses expected.

If dispensing equipment (such as medicine droppers or dropper tips for bottles) is an integral part of the packaging, this equipment should be used to measure the dose. Otherwise, a standard volume measure should be used. The dispensing equipment to be used is normally determined during development.

For powders for reconstitution, uniformity of mass testing is generally considered acceptable.

vii) pH value:

Acceptance criteria for pH should be provided where applicable and the proposed range justified.

viii) Antimicrobial preservative content:

For oral liquids needing an antimicrobial preservative, acceptance criteria for identification and assay of the preservative content must be included in the specification. These criteria should be based on the levels necessary to maintain microbiological product quality throughout the shelf-life.

The lowest specified concentration of antimicrobial preservative should be demonstrated to be effective in controlling microorganisms by using an authorized pharmacopoeial test which should be specified under the antimicrobial preservative effectiveness test.

Release testing for antimicrobial preservative content should normally be performed. Under certain circumstances, in-process testing may suffice in lieu of release testing. When antimicrobial preservative content testing is

performed as an in-process test, the acceptance criteria should remain part of the specification.

Antimicrobial preservative effectiveness should be demonstrated during development, during scale-up, and throughout the shelf-life (e.g. in stability testing), although chemical testing for preservative content is the attribute normally included in the specification.

ix) Antioxidant preservative content:

Release testing for antioxidant content should normally be performed. Under certain circumstances, where justified by developmental and stability data, shelf-life testing may be unnecessary, and in process testing may suffice in lieu of release testing. When antioxidant content testing is performed as an in-process test, the acceptance criteria should remain part of the specification. If only release testing is performed, this decision should be reinvestigated whenever either the manufacturing procedure or the container/closure system changes.

x) Extractables and leachables:

Generally, where development and stability data show no significant evidence of extractables/leachables from the container/closure system, elimination of this test may be proposed. This should be reinvestigated if the container/closure system changes.

Where data demonstrate the need, tests and acceptance criteria for extractables/leachables from the container-closure system components (e.g. rubber stopper, cap liner, plastic bottle, etc.) are considered appropriate for oral solutions packaged in non-glass systems or in glass containers with non-glass closures. The container-closure components should be listed and data collected for these components as early in the development process, as possible.

xi) Ethanol content:

Where it is declared quantitatively on the label in accordance with pertinent regulations, the ethanol content should be tested and specified.

xii) Dissolution:

In addition to the attributes recommended immediately above, it may be appropriate (e.g. where constituents of the herbal substance or herbal preparation are sparingly soluble) to include dissolution testing and acceptance criteria for oral suspensions and dry powder products for resuspension. The testing apparatus, media, and conditions should be pharmacopoeial, if possible, or otherwise justified. Dissolution procedures

using either pharmacopoeial or non-pharmacopoeial apparatus and conditions should be validated.

Single-point measurements are normally considered suitable for immediate-release dosage forms. Multiple-point sampling, at appropriate intervals, should be performed for modified-release dosage forms.

Acceptance criteria should be set based on the observed range of variation, and should take into account the dissolution profiles of the batches that showed acceptable performance in vivo. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure.

Dissolution testing may be performed as an in-process test, or as a release test, depending on its relevance to product performance. The discussion of dissolution for solid oral dosage forms (above), and of particle size distribution (immediately following), should also be considered here.

xiii) Particle size distribution:

Quantitative acceptance criteria and a procedure for determination of particle size distribution may be appropriate for oral suspensions. Developmental data should be considered when determining the need for either a dissolution procedure or a particle size distribution procedure for these formulations.

Particle size distribution testing may be performed as an in-process test or as a release test, depending on its relevance to product performance. If these products have been demonstrated during development to have consistently rapid drug release characteristics, exclusion of a particle size distribution test from the specification may be proposed.

Particle size distribution testing may also be proposed in place of dissolution testing; justification should be provided. The acceptance criteria should include acceptable particle size distribution in terms of the percent of total particles in given size ranges. The mean, upper and/or lower particle size limits should be well defined.

Acceptance criteria should be set, based on the observed range of variation, and should take into account the dissolution profiles of the batches that showed acceptable performance in vivo, as well as, the intended use of the product. The potential for particle growth should be investigated during product development; the acceptance criteria should take the results of these studies into account.

xiv) Redispersibility:

For oral suspensions, which settle on storage (produce sediment) acceptance criteria for redispersibility may be appropriate. Shaking may be an appropriate test. The procedure (mechanical or manual) should be indicated. Time required to achieve re-suspension by the indicated procedure should be clearly defined. Data generated during product development may be sufficient to justify skip testing, or elimination of this attribute from the specification.

xv) Rheological properties:

For relatively viscous solutions or suspensions, include rheological properties (viscosity) in the specification. The test and acceptance criteria should be stated. Data generated during product development may be sufficient to justify skip testing, or elimination of this attribute from the specification.

xvi) Specific gravity:

For oral suspensions, or relatively viscous or non-aqueous solutions, acceptance criteria for specific gravity should be included. Testing may be performed as an in-process control.

xvii) Reconstitution time:

Acceptance criteria for reconstitution time should be provided for dry powder products, which require reconstitution. The choice of diluent should be justified. Data generated during product development may be sufficient to justify skip testing or elimination of this attribute from the specification.

xviii) Water content:

For oral products requiring reconstitution, a test and an acceptance criterion for water content should be proposed when appropriate. Loss on drying is generally considered sufficient if the effect of absorbed moisture vs. water of hydration has been adequately characterised during the development of the product. In certain cases (e.g. essential-oil containing preparations), a more specific procedure (e.g. Karl Fischer titration) is required.

xix) Oromucosal preparations

These are oromucosal preparations which are solid, semi-solid or liquid preparations, containing one or more active substances intended for administration to the oral cavity and/or the throat to obtain a local or systemic effect. For many oromucosal preparations, it is likely that some proportion of the active substance(s) will be swallowed and may be absorbed via the gastrointestinal tract.

Oromucosal preparations may contain suitable antimicrobial preservatives and other excipients such as dispersing, suspending, thickening, emulsifying, buffering, wetting, solubilising, stabilising, flavouring and sweetening agents. Solid preparations may in addition contain glidants, lubricants and excipients capable of modifying the release of the active substance(s).

Several categories of preparations for oromucosal use may be distinguished:

Gargles; mouthwashes; gingival solutions; oromucosal solutions and oromucosal suspensions; semi solid oromucosal preparations (including for example gingival gel, gingival paste, oromucosal gel, oromucosal paste); oromucosal drops, oromucosal sprays and sublingual sprays (including oropharyngeal sprays); lozenges and pastilles; compressed lozenges; sublingual tablets and buccal tablets; oromucosal capsules; mucoadhesive preparations; orodispersible films.

The requirements under Oral Liquids shall apply for Oromucosal preparations.

4.16.5.6 Herbal medicine products containing exclusively herbal substances (e.g. herbal teas)

In addition to the universal tests one or more of these tests may be applicable to herbal medicine products containing exclusively herbal substances.

i) Loss on drying:

To be specified depending on the plant parts present in the herbal medicine products, if not performed on the herbal substance.

ii) Uniformity of mass/Average mass of the sachet (e.g. herbal tea):

Generally, acceptance criteria should be set for weight variation and/or fill volume. Authorized Pharmacopoeial procedures should be used for example Ph.Eur. ”Herbal teas” and ”Herbal teas, instant”. If appropriate, tests may be performed as in-process controls; however, the acceptance criteria should be included in the specification. This concept may be applied to both single-dose and multi-dose products.

The dosage unit is considered to be the typical dose taken by the patient. If the actual unit dose, as taken by the patient, is controlled, it may either be measured directly or calculated, based on the total measured weight or volume of herbal substance, divided by the total number of doses expected.

If dispensing equipment is an integral part of the packaging, this equipment should be used to measure the dose. Otherwise, a standard volume measure should be used. The dispensing equipment to be used is normally determined during development.

iii) Assay:

In the case of such herbal medicine products containing herbal substances with constituents of known therapeutic activity, validated assays for these constituents are required along with details of the analytical procedure(s).

Where appropriate, a specific, stability-indicating procedure should be chosen. In cases where use of a non-specific assay is justified, other supporting analytical procedures should be used to achieve overall specificity. (e.g. a UV/visible spectrophotometric assay for anthraquinone glycosides in combination with fingerprint chromatography for identification). In the case of products containing herbal substance(s) where the constituents with known therapeutic activity are not known, assays of active or analytical markers or other justified determinations are required. The choice of such markers should be justified.

For herbal medicine products consisting of one herbal substance without any excipients, the assay can be carried out on the herbal substance, if justified.

Finally, in cases of multi-component herbal medicine products where an assay of each herbal substance is not possible, the applicant must justify how reproducibility of the finished product is guaranteed and tested. Guidelines from acceptable regulatory bodies such as 'Guideline on quality on combination of herbal medical products/traditional herbal medical products' (EMA/HMPC/CHMP/CVMP/214869/2006) may be used in this assessment.

iv) Particle size:

Suitable acceptance criteria have to be given by the manufacturer

Note

a) Where analytical procedures in various parts of the application coincide, these procedures may be reflected in one part and may be subsequently referred to, provided that the relevant page and paragraph are clearly identified. Reference only to standard books of reference will not be acceptable.

b) Omission of any of the above specifications and tests should be well-justified.

c) Where applicable, a Certificate of Pharmaceutical Product (CPP) in accordance with the WHO Certification scheme/or Free sale certificate and issued by the statutory regulatory authority in the country of origin of the product, shall be submitted along with a certificate of analysis

4.16.6 Evidence of Stability shall be submitted as follows:

a) Stability studies on imported finished product should:

i) be on the market pack

ii) have a detailed protocol

iii) have summarised results

iv) have conclusions on:

v) proposed storage conditions

vi) proposed shelf life

vii) in-use storage conditions and shelf life

b) Labelling recommendations shall be stated as follows:

i) Store under normal storage conditions (15°C - 30°C)

ii) Store between 2°C - 8°C (i.e. refrigeration, no freezing)

iii) Store below 8°C (i.e. refrigeration)

iv) Store between –5°C - O°C (i.e. in a freezer)

v) Store below –18°C (i.e. in a deep freezer)

Note

a) That these recommendations must be present on the product samples submitted with the application.

b) Stability studies shall be conducted for 3 (three) trial batches of production and the proposed shelf-life and storage conditions must be determined, based on these results.

c) WHO Zone IV a climatic conditions

Condition	Accelerated	Real Time
Storage Temperature	40 +2°C	30°C
Relative Humidity	75 ±5% RH	65 ±5% RH
Duration	6 months	Until end of shelf life

d) The stability study shall be conducted in the container closure system in which it will be marketed in Uganda.

4.17 Batch Manufacturing Records (BMR)

Copies of original documents used in the manufacture of one complete batch, i.e. from release of raw materials to release of final product for marketing, shall be submitted including Quality Control reports.

Batch records for one particular batch should include:

a) raw material and packaging material requisition records

b) line clearance records

c) processing records

d) packaging records

e) sterilisation records

f) Certificates of Analysis for the finished product.

4.18 Safety and efficacy

4.18.1 Evidence of safety

a) toxicological studies proving safety are necessary, and should be submitted in the dossier. These include

i) acute,

ii) chronic

iii) and sub-chronic toxicity test reports of the finished product.

b) Study reports

A bibliographic review of the safety data and data necessary for assessing the safety of the product should be provided. The study report must clearly indicate the following information:

i) Route of administration

ii) Dose levels

iii) Number of animals or subjects per dose level

iv) Animals" or subjects" origin, gender, weight range and age

v) frequency at which observations were made

vi) Duration of each study

vii) The relationship between the time of administration and the onset of the effects observed; and

viii) All measurements made.

c) Toxicology

Refer ICH Note for Guidance on Toxicokinetics: The Assessment of Systemic Exposure in Toxicity Studies (S3A) for guidance on developing test strategies in toxicokinetics and the need to integrate pharmacokinetics into toxicity

testing, in order to aid in the interpretation of the toxicology findings and promote rational study design development.

d) Single-Dose Toxicity (in order by species by route)

Reports of acute oral toxicity studies on at least one mammalian species should be provided, if available. The inclusion of the results of LD50 testing for each species and route of administration is not mandatory. If acute toxicity studies could not be performed due to presence of studies from similar herbal substance or preparation, it should be documented in the application.

e) Repeat-Dose Toxicity

i) Repeat-dose studies (short-term, sub-chronic and chronic toxicity) allow proper, long-term assessment of the substance or its metabolites, which may accumulate in the body. The length of the repeat-dose study should be related to the duration of the proposed therapeutic use of the substance

ii) Generally, short-term use (up to a week) would need to be supported by a short-term, 28-day toxicity study; longer therapeutic use would require a sub-chronic (90 days) study; and prolonged use must be supported by long-term, chronic-exposure studies.

iii) Refer to “The Committee for Human Medicine Products (CHMP) Guidelines” on repeated dose toxicity for guidance on the conduct of repeated dose toxicity studies of active substances intended for human use.

iv) Refer to the “ICH Guideline on Duration of Chronic Toxicity Testing in Animals (Rodent and Non Rodent Toxicity Testing) (S4)” for the considerations that apply to chronic toxicity testing in rodents and non-rodents as part of the safety evaluation of a medicine product. The text incorporates the guidance for repeat-dose toxicity tests.

f) Literature References

A list of cited references should be provided. References that have not been provided should be available upon request

14.18.2 Evidence of efficacy in use

Evidence should be submitted as follows:

a) Pharmacological and clinical effects of active ingredients and their active constituents if known should be described, and should be relevant to the main indications of the product

b) For products with long-term traditional use, used for minor disorders or non-specific indications or for prophylactic use: bibliographical evidence of efficacy should be submitted, eg. literature (textbooks, journals etc), case reports, pharmacopoeial monographs.

c) For products without bibliographical evidence of efficacy in traditional use: reports of clinical studies proving efficacy

d) Combination products: for new combinations of active ingredients, the therapeutic justification, compatibility and dose range should be given. For well established combinations, photocopies of references in traditional texts (eg. Ayurveda, traditional Chinese) will be acceptable as evidence of efficacy

14.18.3 Special labelling requirements

a) For products containing Camphor, the following warning should be stated on the label:-

i) "Can cause convulsion, contraindicated in children below 2 years of age. Caution must be exercised when older children are treated. Avoid direct application into nostrils."

ii) Precaution: "It is dangerous to place any camphor – containing product into the nostril of children. A small amount applied this way may cause immediate collapse"

iii) Avoid contact with the eyes

iv) Do not apply to wounds or damaged skin

b) For products containing Ginseng (including all Panaxgenus) state:

i) Safe use of ginseng in pregnant women and children has not been established.

ii) Safety on long term use has not been established

c) For products containing Flower parts, state:

i) This product may contain pollen which may cause severe allergic reactions, including fatal anaphylactic reactions in susceptible individuals.

ii) Asthma and allergy sufferers may be at greater risks.

d) For product containing Chelidonium Majus, state:

Warning: This Product may cause adverse reaction to the liver.

e) For product containing Senna Leaf (Cassia) and Rhubarb/Radix et, Rhizoma Rhei, state:

i) Do not use when abdominal pain, nausea or vomiting is present.

ii) Frequent or prolonged used of this preparation may result independence towards the product and „imbalanced electrolytes".

f) For product containing Alfalfa (*Medicago Sativa)*, state:

Text Box: This product contains Alfalfa (*Medicago Sativa)*. Individuals with a predisposition to systemic lupus erythematosus should consult their physician before consuming this product.

g) For product containing St. John‟s Wort, state:

The product may interact with other medicines. Please consult a doctor / pharmacist before using it.

h) For product containing *Pelargonium Sidoides,* state:

In very rare cases, pelargonium sidoides may cause hypersensitivity reactions.

i) For product containing Benzyl Alcohol/ Phenylmethanol (as preservative), state:

As this preparation containing Benzyl Alcohol, its use should be avoided in children under 2 years of age. Not to be used in neonates.

j) For product containing *Ginkgo Biloba / Ginkgo Extract*, state:

“Please consult your physician/ pharmacist if you are on or intend to start using any other medicines and before you undergo any surgical/dental procedure‟ as the use of Ginkgo may increase the tendency of bleeding.”

k) For product containing royal jelly, state:

This product contains royal jelly and may cause severe allergic reactions including fatal anaphylactic reactions insusceptible individuals. Asthma and allergy sufferers may be at the greater risk.

l) For product containing Propolis (topical preparation), state:

Propolis may cause allergic skin reaction.

m) For product containing “Anti-diarrhoea”, state:

Contraindicated in children below 1 year old.

n) For product with indication “To regulate menstruation / to improve menstrual flow”, state:

Contraindicated in pregnant women.

o) For product with indication “To reduce body weight”, state:

Balanced diet and regular exercise are essential.

4.19 Application Forms

The following shall be submitted:

a) The proposed patient information leaflet for products intended for self-medication

b) The proposed prescriber information leaflet for intended prescription-only products

c) Any proposed advertising material

d) Two physical samples of each pack size intended for marketing

e) Digital copies of the mock up samples inclusive of the label, primary packaging and secondary packaging.

f) A copy of marketing authorisation in the country of manufacture

g) Form 4 for imported herbal medicine product for human use (Appendix II) or

h) Form 5 for imported herbal medicine product for veterinary use (Appendix III)

5.0 REFERENCES

Guideline on declaration of herbal substances and herbal preparations in herbal medicinal products/traditional herbal medicinal products in the SPC (EMEA/HMPC/CHMP/CVMP/287539/2005)

Guideline on quality of herbal medicinal products/traditional herbal medicinal products' (CPMP/QWP/2819/00, EMEA/CVMP/814/00).

Guideline on specifications: test procedures and acceptance criteria for herbal substances, herbal preparations and herbal medicinal products/traditional herbal medicinal products' (CPMP/QWP/2820/00, EMEA/CVMP/815/00). EMEA/HMPC/CHMP/CVMP/214869/2006 © EMEA 2008

Container closure and packaging specifications as per BP , Phr Int , USP or Ph Eur

Guideline on repeated dose toxicity CPMP/SWP/1042/99 Rev 1 Corr* Committee for Human Medicinal Products (CHMP)

Good manufacturing practices: Supplementary guidelines for the manufacture of herbal medicinal products - Annex 8 in WHO Expert Committee on specifications for pharmaceutical preparation. 34 Report, WHO, (WHO Technical Report Series, No. 863)

Guidelines for the Appropriate use of Herbal Medicines (WHO/WPRO)

Guidelines for the assessment of herbal medicines - Annex 11 in WHO Expert Committee on specifications for pharmaceutical preparation. 35 Report, WHO, 1996 (WHO Technical Report Series, No. 863)

Guidelines on packaging for pharmaceutical products. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report. Geneva, World Health Organization, 2002, Annex 9 (WHO Technical Report Series, No. 902).

ICH S3A Toxicokinetics: the assessment of systemic exposure in toxicity studies.

ICH S4 Duration of chronic toxicity testing in animals (rodent and non-rodent toxicity testing)

Operational guidance: Information needed to support clinical trials of herbal products (TDR/GEN; 2005)

Quality control methods for herbal Materials, Updated edition (WHO; 2011;

Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines (WHO/WPRO)

Stability testing of active pharmaceutical ingredients and finished pharmaceutical products. In WHO Expert Committee on specifications for pharmaceutical preparation. 43rd Report, WHO, 2009, Annex 2 (WHO Technical Report Series, No. 953, 2009)

Supplementary guidelines on good manufacturing practices for the manufacture of herbal medicines - Annex 3 in WHO Expert Committee on specifications for pharmaceutical preparations. 40 Report, WHO, 2006 (WHO Technical Report Series, No. 937) (WHO; 2006; 22 pages)

WHO good practices for pharmaceutical microbiology laboratories. In: WHO Expert Committee on Specifications for Pharmaceutical Preparations. Forty fifth report. Geneva, World Health Organization. (WHO Technical Report Series, No. 961, 2011, Annex 2)

WHO Guidelines for assessing quality of herbal medicines with reference to contaminants and residues (WHO Geneva, 2007)

WHO Guidelines for assessing quality of herbal medicines with reference to contaminants and residues (WHO Geneva, 2007, 105 pages)

WHO guidelines on safety monitoring of herbal medicines in pharmacovigilance systems (WHO; 2004; 82 pages)

Appendix I: FORM 3 - CERTIFICATE FOR REGISTRATION OF HUMAN OR VETERINARY DRUGS, PREPARATION AND VACCINES OR OTHER IMMUNOLOGICAL PRODUCTS

Regulation 14 (1)

NATIONAL DRUG POLICY AND AUTHORITY ACT, CAP 206

Registration number:……

Date of registration:…….

Expiry date of registration:……

Category of drug or preparation:

Human Veterinary

1. Product information

Proprietary (trade) name:…….

Generic name (the International Nonproprietary name; for herbal product, state botanical name):……

Dosage form:…….. Strength(s) per dosage unit:……

Description of drug or preparation:……

Therapeutic category:……..

Indication:……

2. Approved manufacturer(s) information for the product

Production stage	*Name of manufacturer*	*Street address of site*	*Manufacturing step*

3. Product shelf-life

The approved shelf-life of this product when packaged and labeled as detailed in the application and modified in subsequent correspondence is as follows.

Pack Description	*Shel-life*	*Storage conditions*

4. Restrictions on sale or distribution of drug or preparation

☐ Scheduled narcotic;

☐ Restricted prescription-only distribution (specify - for example,hospitals only);

☐ Prescription only;

☐ Pharmacy only;

☐ Over-the-counter (OTC)

Appendix II: FORM 4 - APPLICATION FOR REGISTRATION OF IMPORTED HERBAL MEDICINE PRODUCTS FOR HUMAN USE

Regulation 19 (1)

NATIONAL DRUG POLICY AND AUTHORITY ACT, CAP 206

SECTION A: GENERAL INFORMATION

Particulars of the applicant

Name……

Physical address (Plot No./street No./country) ……

Postal address (if different) ……

Phone:……Fax: ……e-mail:……

Particulars of the Product

Proprietary name (Trade name): ……

Pharmaceutical form: ……Pack size(s) applied for:……

Description of the drug (colour, shape, size etc.):……

Main indication(s):……

Particulars of the manufacturer and activities of the manufacturer

	Name	*Physical Address of the manufacturing plant*	*Activities undertaken at the manufacturing plant*
1.			
2.			
3.			

Authorised agent in Uganda

Name of agent: ……

I the undersigned hereby apply for registration of the above-mentioned product and declare that all the information herein and in the appendices is correct and true.
I enclose a fee of ……
Date: …… Signed: ……
Full name of signatory: ……

Designation and qualifications:……

SECTION B: PACKAGING SPECIFICATIONS AND PRODUCT COMPOSITION

1. Specifications of the packaging material

   a) Primary (inner) container(s):

b) Outer packing:

2. Product composition (*Give the formula of the product in terms of a dosage unit)*

a) Active ingredients

Processed plant/other natural material	*Source (part of plant or non-plant material used)*	*Quantity per unit dose*	*Plant species*

b) Inactive ingredients

Approved name	*Quantity per unit dose*	*Reason for inclusion*

3. Additional raw materials *(Give details of any additional raw materials used in the manufacturing process but not found in the final product):*

SECTION C: CHEMISTRY AND PHARMACEUTICAL ASPECTS

1. Raw material specifications and analytical control methods used:
   a) Crude plant/non-plant material (source of active ingredients)
   b) Processed plant/non-plant material (active ingredients)……
   c) Inactive ingredient ……
2. Details of manufacturing procedures (incl. packaging) and summary of equipment used:
   a) Summary of manufacturing process:
      i) Preparation of processed raw material from crude plant/non-plant material
      ii) Preparation of manufactured product from processed raw material
   b) Summary of equipment used
3. Details of in-process control procedures……
4. Specifications and analytical tests of manufactured product …….
5. Test methods……
6. Stability studies on manufactured product (based on two batches ……
7. Complete, filled batch manufacturing records for one commercial batch

SECTION D: SAFETY AND EFFICACY

1. Safety
   i) Evidence of safety in use
   ii) Side effects, contra-indications, precautions etc.
2. Efficacy
   i) Main pharmacological and clinical effects
   ii) Evidence of efficacy in use for proposed indications
   iii) Justification for combination products

Appendix III: FORM 5 - APPLICATION FORM FOR REGISTRATION OF IMPORTED HERBAL MEDICINE PRODUCTS FOR VETERINARY USE

Regulation 19 (1)

NATIONAL DRUG POLICY AND AUTHORITY ACT, CAP 206

SECTION A: GENERAL INFORMATION

Particulars of the applicant

Name……

Physical address (Plot No./street/country)……

Postal address (if different)……

Phone: …… Fax: ……e-mail:……

Particulars of the product

Proprietary name (Trade name): ……

Pharmaceutical form: …… Pack size(s) applied for:……

Description of the drug (colour, shape, size etc.):……

Main indication(s):……

Species of animals for which it is intended:
……

Particulars of the manufacturer and activities of manufacturer

	Name	*Physical Address of the manufacturing plant*	*Activities undertaken at the manufacturing plant*
1.			
2.			
3.			

Authorised agent in Uganda

Name of agent ……
I the undersigned hereby apply for registration of the above-mentioned product and declare that all the information herein and in the appendices is correct and true.
I enclose a fee of ……

Date:……Signed: ……

Full name of signatory: ……

Designation and qualifications: .....

SECTION B: PACKAGING SPECIFICATIONS AND PRODUCT COMPOSITION

1. Specifications of the packaging material

a) Primary (inner) container(s):

b) Outer packing:

2. Product composition (*Give the formula of the product in terms of a dosage unit)*

a) Active ingredients

Processed plant/other natural material	*Source (part of plant or non-plant material used)*	*Quantity per unit dose*	*Plant species*

a) Inactive ingredients

Approved name	*Quantity per unit dose*	*Reason for inclusion*

3. Additional raw materials Give details of any additional raw materials used in the manufacturing process but not found in the final product:

SECTION C: CHEMISTRY AND PHARMACEUTICALASPECTS

1. Raw material specifications and analytical control methods used:

a) Crude plant/non-plant material (source of active ingredients)……

b) Processed plant/non-plant material (active ingredients)…….

c) Inactive ingredients ……

2. Details of manufacturing procedures (including packaging) and summary of equipment used:

a) Summary of manufacturing process:

i) Preparation of processed raw material from crude plant/non-plant material

ii) Preparation of manufactured product from processed raw material

b) Summary of equipment used

3. Details of in-process control procedures…….

4. Specifications and analytical tests of manufactured product……

5. Test methods ……

6. Stability studies on manufactured product (based on two batches)

7 Complete, filled batch manufacturing records for one commercial batch

SECTION D: SAFETY AND EFFICACY

1. Safety
    1) Evidence of safety in use
    2) Side effects, contra-indications, precautions etc.
    3) Withdrawal periods for meat, milk, eggs, etc.
2. Efficacy
    1) Main pharmacological and clinical effects
    2) Evidence of efficacy in use for proposed indications
    3) Justification for combination products

6.0 DOCUMENT REVISION HISTORY

Date of revision	Revision number	Document Number	Author(s)	Changes made and/or reasons for revision
29 Jul 2020	0	DAR/GDL/029	*Authors* Mutyaba Michael *Reviewers* Amoreen Naluyima Comfort E. W. Abdulhakim Ssenyange Martin Okeng Juliet Okecho	First Issue of document

End of document