ZAMBIA MEDICINES REGULATORY AUTHORITY

# GUIDELINES ON APPLICATION FOR REGISTRATION OF HERBAL MEDICINES

First Edition

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**Foreword**

There has been a marked increase in the use of herbal medicines in the recent past. Herbal medicines are not only used for primary health care of the poor in developing countries but also in countries where conventional medicines are predominant in the national health care system.

With the expansion in the use of these medicines world wide, quality, safety and efficacy have become a challenge both to medicines regulatory authorities and the public. These guidelines have been developed to provide requirements in support of quality, safety and efficacy in respect of herbal medicines meant to be placed on the Zambian market.

One of the means for ensuring that a herbal medicinal product meets the required standards of quality, safety and efficacy is by conducting product specific pre-marketing assessments to determine whether the product should be registered.

Submission of adequate documentation on quality, safety and efficacy of a herbal medicine will enable the PRA to use the information and other factors to assess the suitability of the product for the intended use.

Compliance to these guidelines in the submission of applications will facilitate the speedy processing and evaluation of the applications and subsequent registration of the products. This will enable the product prospective licence holders to market their products on time and make them available to the consumers in a timely manner.

It is therefore my sincere hope that these guidelines will provide the necessary information in preparing and submitting documents for registration of herbal medicinal products in Zambia.

Finally, I wish to urge our esteemed readers and applicants to read this first edition of guidelines carefully and make as many suggestions as possible so that we have a version of the guidelines that are commensurate with current practices.

Dr S.M. Miti
**PERMANENT SECRETARY**
**Ministry of Health**

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1. Professor Karashani: Ethics & Research Committee, UTH
2. Ms Esnat Mwape: Director General, PRA
3. Dr Yona Sinkala: Veterinary Surgeon, Dept. of Veterinary & Livestock Development, Lusaka
4. Dr G. Chishimba: Medical Practitioner, National AIDS Council
5. Ms Anne Zulu: Pharmacist, Medical Stores Limited
6. Dr K Choongo: Lecturer, UNZA School of Veterinary Medicine
7. Ms Loyce Lishimpi: National Profession Officer, WHO
8. Mrs Bernice C. Mwale: Director-Product Registration, PRA,
9. Mr. Felix P. Chizu: Regulatory Officer, PRA
10. Dr Zuma Munkombwe: Regulatory Officer, PRA
11. Mr. Pelekelo Mangisha: Assistant Regulatory Officer, PRA

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Ms E. Mwape
**DIRECTOR-GENERAL**
**Pharmaceutical Regulatory Authority**

## Introduction

The Pharmaceutical Act No 14 of 2004 requires that products intended to be marketed in Zambia meet appropriate standards of good quality, safety and efficacy. Also they should be manufactured in facilities, which comply with cGMP requirements. One of the means for ensuring that Herbal Medicinal products meet the required standards of good quality, safety and efficacy is by conducting product specific pre-marketing assessments to determine whether the product should be registered.

These Guidelines have been prepared to provide information to applicants who intend to register Herbal Medicinal products in Zambia.

This document has been developed by the Pharmaceutical Regulatory Authority (PRA) to provide guidance to applicants on the content and format of the Chemistry and pharmaceutical data of such products required for their complete scientific evaluation for quality, safety and efficacy. These guidelines also indicate the order of the material to be submitted and the minimum requirements for product registration. Compliance to these guidelines in the submission of applications will facilitate the speedy processing and evaluation of the application and hence the product licensing. This will enable the prospective licence holders to market their products on time and make them available to the consumers. In view of this, applicants are advised to read these guidelines carefully and adhere in full to the prescribed instructions.

## Abbreviations

**µg** Microgram
**API** Active Pharmaceutical Ingredient
**ATC** Anatomic Therapeutic Chemical classification
**AUC** Area under the plasma concentration time curve
**BE** Bioequivalence studies
**BP** British Pharmacopoeia
**CASR** Chemical Abstract Service Registry Number
**cGMP** current Good Manufacturing Practices
**CI** Confidence Interval
**Cmax** Maximum plasma concentration
**CV** Coefficient of Variation
**e.c** Enteric coated
**f.c Film** coated
**FDC** Fixed Dose Combination
**FP** Finished Product
**GCP** Good Clinical Practice
**GLP** Good Laboratory Practice
**GMP** Good Manufacturing Practice
**GS** General Sale
**HPLC** High power Liquid Chromatograph
**i.m** Intramuscular
**i.v** Intravenous
**INN** International Non-proprietary Name
**IP** International Pharmacopoeia
**IR** Infra red spectroscopy
**IU** International Unit
**IUPAC** International Union for Pure and Applied Chemistry
**JP** Japanese Pharmacopoeia
**M.R** Modified Release
**mg** Milligram
**ml** Millilitre
**MRA** Medicines Regulatory Authority
**P** Pharmacy
**Ph. Eur** European Pharmacopoeia
**POM** Prescription Only Medicines
**PRA** Pharmaceutical Regulatory Authority
**RF values**-Retention factors
**RH** Relative Humidity
**s.c** Sugar coated
**SPC** Summary of Product Characteristics
**SR** Sustained release
**TE** Therapeutic Equivalence
**TLC** Thin layer chromatography
**Tmax** Time to reach maximum plasma concentration
**USP** United States Pharmacopoeia
**VICH** International Conference on Harmonization of Technical
**WHO** World Health Organization

## Definitions

***Active pharmaceutical ingredient (API)*** means a substance or compound that is intended to be used in the manufacture of a pharmaceutical product as a therapeutically active compound (ingredient).

***Authority*** Means the Pharmaceutical Regulatory Authority established under Section 4 of the Pharmaceutical Act No 14 of 2004.

***Bio-equivalence*** Two pharmaceutical products are bioequivalent if they are pharmaceutically equivalent or alternatives and their bio-availabilities (rate and extent of availability), after administration in the same molar dose, are similar to such a degree that their effects can be expected to be essentially the same.

***Composition*** Composition in relation to a Herbal medicinal product means the ingredients of which it consists, proportions, degree of strength, quality and purity in which those ingredients are contained.

***Container*** Means a bottle, jar, box, packet, sachet or other receptacle which contains or is to contain in it, not being a capsule or other article in which the product is or is to be administered or consumed, and where any such receptacle is or is to be contained in another receptacle, includes the former but does not include the latter receptacle.

***Container labelling***
Means all information that appears on any part of a container, including that on any outer packaging such as a carton.

***Established active pharmaceutical ingredient***
Means APIs which are subject of the current pharmacopoeias or those well documented in the literature and generally recognized as safe and effective for use as a medicine.

***Excipient***
Means any component of a finished dosage form which has no therapeutic Value

***Expert report***
Means a summary and interpretation of data, with conclusions, prepared by an independent competent person.

***Finished product***
Means a product that has undergone all stages of production, including packaging in its final container and labelling

***Formulation***
Means the composition of a dosage form, including the characteristics of its raw materials and the operations required to process it.

***Herbal Medicine*** means any medicinal product that contains, as active ingredients, aerial or underground parts of plants other plant material or combination thereof,

whether in a crude state or as plant preparations and includes herbal medicines which contain, organic or inorganic active ingredients and are processed or packed in such a manner that they appear like medicines under the western system but do not include medicines containing plant materials combined with chemically defined active substances, or chemically isolated constituents of plants.

***Immediate release dosage form***
Means a dosage form that is intended to release the entire active ingredient on administration with no enhanced, delayed or extended release effect.

**Impurities** include by-product of synthesis arising from side reactions products in starting materials etc., residual solvents and reagents, trace elements arising from other sources and products of degradation

***Innovator (or pioneer) pharmaceutical product***
Means a pharmaceutical product which was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality

***Label*** Means any tag, brand, mark, pictorial or other descriptive matter, written, printed, stenciled, marked, embossed or impressed on or attached to a container of any Medicines

***Manufacture*** Means production, quality control, release and packaging of a product.

***Manufacturer*** Means a firm that is engaged in the manufacture of products

***New active pharmaceutical ingredient*** Means a Medicine (active ingredient), including its salts, esters, derivatives, etc. or biological agent, which is not a subject of current pharmacopoeias.

***Pharmacopoeia*** Includes but not limited current edition of the British Pharmacopoeia, European Pharmacopoeia, United States Pharmacopoeia, International Pharmacopoeia and Japanese Pharmacopoeia.

***Pharmaceutical alternatives*** Two or more medicinal products are said to be pharmaceutical alternatives if they contain the same active ingredients, but which may differ in salt, esters, dosage forms, strength and/ or route of administration.

***Pharmaceutical equivalents*** Products are pharmaceutical equivalents means products that contain the same amount of the same active substance(s) in the same dosage form; if they meet the same or comparable standard; and if they are intended to be administered by the same route.

***Retention fee***
Means a fee paid annually to maintain product licence.

***Shelf life Specifications***

Means the combination of physical, chemical, biological and microbiological test requirements that an active ingredient should meet up to its retest date or a Medicines product should meet during its shelf life.

***Shelf Life***
Means the combination of physical, chemical, biological and microbiological test requirements that determine whether a Medicines product is suitable for release at the time of its manufacture

***Therapeutic equivalence***
Two pharmaceutical products are therapeutically equivalent if they are pharmaceutically equivalent and, after administration in the same molar dose, their effects with respect to both efficacy and safety essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or *in vitro* studies.

***WHO-type certificate***
Means a certificate of pharmaceutical product of the type defined in the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce

***Proprietary name***
Means the (trade or brand) name, which is unique to a particular Medicines and by which it is generally identified (and by which it is registered in the country of manufacture).

***Approved/ INN / generic name***
In relation to Medicines mean the internationally recognized non-proprietary name of such Medicines.

***Dosage form***
Means the form in which the Medicines 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.

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

***Commercial Presentation***
Means the final product pack as it will be presented in the market (e.g. 10 ampoules of 2ml each, 10 blister packs of 10capsules each, etc.)

**Prescription Only Medicine (POM)**
The products in this category are available from pharmacies/dispensaries only.
All products in the above three categories are available upon presentation of a prescription from a prescriber to a licensed pharmacy/dispensary.

**Pharmacy Medicine (P)**

These products are available from licensed pharmacies only.

**General Sales Medicines (GS)**
Medicines in this category are available in pharmacies, dispensaries and all licensed trade supermarkets.

**Strength of the medicinal product**
Means the content of the active ingredient expressed quantitatively per dosage unit, per unit of volume or mass or weight according to the dosage form;

**Immediate packaging**
Means container or other form of packaging, which is immediately in direct contact with the medicinal product;

**Outer packaging**
Means the packaging into which is placed the immediate packaging;

**Labelling**
Means the information contained on the immediate or outer packaging;

**Package insert**
Means a leaflet containing information for the prescriber and the dispenser;

**Patient information leaflet**
Means a leaflet containing information for the patient;

**Product licence Holder** means a person or company under whom a medicinal product has been registered. This party is responsible for all aspects of the medicinal product including quality, safety, efficacy and compliance with conditions of registration.

## PART A. GENERAL REQUIREMENTS

All application shall be made by submitting a duly filled in application form accompanied with information as prescribed in these guidelines.
All documents shall be in English language
Where original licences are in another language, copies shall be presented together with certified English version.

### Applicants

An application for registration of herbal medicines can be made by owner of the product (an individual, body corporate, partners or registered business) responsible for the manufacture or to whose order the product is manufactured for sale in Zambia.

The applicant shall be responsible for the product information supplied in support of his/her application for registration and amendments thereof.

### Responsible local Distributor

Every applicant who is not resident in Zambia shall nominate a licensed pharmaceuticals importer in Zambia to be responsible local distributor. Every nominee shall submit a power of attorney as evidence of his/her nomination.

### Responsibilities of local Distributor, applicant and manufacturer

The responsibilities of the local agent, applicant and manufacturer shall be –

i. To monitor the product on the market and inform the Authority immediately after the detection of any problem relating to registered product such as serious manufacturing defects which may endanger public health.
ii. The Local Distributor shall facilitate communication between the applicant and the Authority on matters relating to the product
iii. Handle product recalls according to Pharmaceutical Regulatory Authority Recall procedures.
iv. Detect and report adverse drug reactions or events to the Pharmacovigilance Unit of the Pharmaceutical Regulatory Authority

### Applications

A separate application is required for each product, i.e. products containing the same ingredients but made to a different specification (in terms of strength or content of active ingredients, dosage form, etc) or by a different manufacture.

However, product other than injectable, made by the same manufacturer to the same specifications, strength (content) of ingredients and form, but differing in

packaging or pack size requires only one application but separate stability studies reports should be submitted for each packaging material and container differing in technical specifications

Applications shall be made by submitting a dully filled in application form which shall be accompanied with:

i). Complete documentation as per these guidelines supported by independent expert reports on quality, safety and efficacy.

All ingredients must comply with specification prescribed either in International & national Herbal medicines Pharmacopoeias. In-house specification may be acceptable if justified by validation reports

ii). Original Licence of Pharmaceutical Product (WHO-type) from the Drug Regulatory Authority of the country of origin of the product. This shall be accompanied with approved product information.

iii). Prescribed Non refundable fee per product to be imported or produced locally.

iv). Three commercial samples of each package size being applied for registration or sufficient samples to carry out quality control tests as declared in the dossier whichever is higher. The samples must be in the form and container in which they will be marketed.

v). An appropriate and complete index / list of the various chapters and documents of submission.

vi). Current Site Master File

*It should be noted that the above fees may be changed as shall be prescribed under the Fees and Charges Regulations.*

**Application for amendment of a registered product**

Whenever a product licence holder wishes to make any amendment to a product he must apply to and obtain approval from the Authority in respect of a registered product before introducing it is Zambia. An application for amendment shall be made on an Application Form for Amendments and shall be accompanied with:

i). Detailed description of the amendment with supporting reasons

ii). Samples of the amendments

iii). Prescribed non refundable amendment fee.

## Application for renewal of registration

Application for renewal of registration of products shall be submitted at least 90days before expiry date of registration.

Renewal of registration shall be made on a Renewal Application Form which shall be accompanied with:

iv). Consolidated report of all changes if any (reported and unreported) which had been with respect to product during the validity of its registration.
v). Report of additional adverse drug reactions if any detected during the lifetime of the product.
vi). Five commercial samples of each package size being applied for registration or sufficient samples to carry out quality control tests as declared in the dossier whichever is higher. The samples must be in the form and container in which it shall be marketed.
vii). Prescribed Non refundable renewal application fee per product to be imported or for produced locally.
viii). Current Site Master File.

## Documentation

## Paper type and binding

Data shall be presented on A4 and 80g/m2 paper with readable letters of at least 12 font sizes. Every page shall be numbered sequentially.

Extension sheets, tables, diagrams and other supporting documents shall be as far as possible be of the same size, well annotated, numbered and appropriately referenced or cross referenced.

All chapters must be bound separately and arranged sequentially in or more file covers depending on the number of pages contained in a chapter.

However, if two or more chapters are bound in a single file, cover marked dividers should separate them. The binding shall be in such a manner as to allow chapters to be detached for evaluation by different experts.

The file cover should be of hard, non-collapsible biodegradable material. Lever arch files and spring files are not permissible. The thickness should be expandable or reducible depending on the thickness of the contents. The allowable file size is A4 size.

## Official References, Texts

When direct reference is made to specification, quality control procedures, test methods, data etc. in official compendia, texts or standard publication other than the current pharmacopoeias, reprints or authenticated copies of relevant pages shall be enclosed. References to pharmacopoeias should specify the year of issue.

## Expert Reports

Expert reports shall accompany documentation on quality, safety and efficacy. All copies should be authenticated by authorised signatories and stamped officially by the applicant.

## Manuals

An applicant may have several products which are pharmaceutical similar and the same data may be applicable to these products e.g. specifications for named ingredients, standard analytical methods or test protocols.

In order to avoid unnecessary duplication, this information may be assembled in the form of a manual for e.g. “Manual – Specifications for Ingredients” or “Manual Analytical Methods and Test Protocols”.

One hard copy a manual and CD-ROM if any should be submitted together with the first application. In subsequent applications appropriate reference may then be made to the “Manuals”.

Such manuals must be clearly headed with the company name, title e.g.” Manual – Specifications for Ingredients” and date of compilation. The Authority must be notified of any change of particulars in the manuals.

Binding of manuals should be such as to allow convenient up-dating, revision, additions or removals.

## Cross Reference between Products

There shall be no reference of particulars or documentation between on product and another (Other than reference to above-mentioned “Manuals”) except in the following circumstances:

i) Two or more products in the same pharmaceutical dosages form containing the same active ingredient in different strengths or

ii) Two or more products in the same pharmaceutical dosage form containing a mixture in different strengths of the same two or more active ingredients in the same proportion.

Separate application forms are required for each product but supporting documentation if similar, may be cross-referenced provided the application for registration of these products are made at the same time, or within five years of the application for registration of the first product in the group. Appropriate reference must be clearly stated.

## Submission, payment of fees and processing of applications

### Submission of application

All application accompanied by prescribed fees shall be addressed and submitted in person or by courier to: The Director General, Pharmaceutical Regulatory Authority, Plot No. 6903, Tuleteka Road, Rhodespark, P.O Box 31890, Lusaka, Zambia

When an application has been received, an acknowledgement will be issued together with reference number for each product.

### Payment of Fees

Fees shall be paid into the following bank account:

| | |
|---|---|
| Name of Account: | Zambia Medicines Regulatory Authority |
| Name of Bank: | Standard Chartered Bank, North-end Branch<br>Cairo Road. Lusaka, Zambia |

| | |
|---|---|
| US Dollar Bank Account No | 8700211468100 |
| ZMK Bank Account No. | 0100122033800 |
| Swift Code: | SCBL2MLX |

## Processing of applications

Processing of applications shall only be done on complete applications, incomplete applications shall not be processed. The Authority may during evaluation of the product request for clarification or additional data or samples and the applicant is obliged to comply. Once a query has been raised, the processing may be halted until the query has been clarified.

The processing of an application takes about 180days. Immediately after the processing is completed applicants will be informed.

The Authority as part of the evaluation of the product may conduct pre-registration Good manufacturing process (GMP) inspection to verify compliance thereof. The applicant shall bear the cost of conducting pre-registration GMP inspection.

## Registration

When a product is found to have complied with all the prescribed registration requirements, the applicant will be informed to that effect. A product licence together with such conditions as the Authority may determine shall be issued.

A duplicate of the licence may be issued upon request and on payment prescribed non refundable fee.

## Validity of registration

The registration of a product shall be valid for five (5) years unless sooner suspended, cancelled or revoked by the Authority or terminated by the registration holder. The validity of registration shall be subjected to payment of prescribed annual retention fees product one year after a product is registered.

## Termination of product registration

The Authority may by giving in writing refuse, suspend, cancel or revoke the registration of a product or amend the conditions of its registration.

The product licence holder may by giving a 60 days written notice and reasons to the Authority terminate the registration of registered product.

## Appeals

Any person aggrieved by decision of the Authority in relation to any application for registration of a herbal medicines may take representation to the Authority, whereby he shall submit information and arguments to convince the Authority to reconsider its decision. However, if after reconsideration of the application, the Authority still rejects the application, the applicant may appeal to the Minister

## PART B. SUMMARY OF PRODUCT CHARACTERISTICS

The following summary of product characteristics shall be submitted for every application: -

1. Trade name and dosage form of the product

2. Physical description of the product
3. Botanical name or any other name, family of the plant(s) from which the drug(s) has been extracted including plants part(s) used. Synonym if available should be given. The English name if available shall be provided. For locally produced products the local name and geographical distribution shall be provided.
4. Plant used whether wild or cultivated
5. Brief pharmacology of the medicines
6. Therapeutical indications
7. Dosage regimen and route of administration
8. Brief toxicological information of the medicine
9. Contra-indications
10. Warnings and precautions
11. Drug Interactions

12. Adverse reactions

13. Side Effects

14. Shelf-life and storage conditions

15. Presentation or pack size(s)

## PART C. QUALITY REQUIREMENTS

The following information shall be submitted in support of the quality of herbal medicines:

*1. **Raw material specifications and details of analytical methods** to test compliance to these specifications should be described. Where references to pharmacopoeial specifications and analytical methods are given, full photocopies of those references (monographs) should be supplied. Such pharmacopoeias include the **British Herbal Pharmacopoeia, Ayurvedic Pharmacopoeia of India, or the list of WHO herbal monographs.***

*In all other cases specifications and analytical methods should be described for the processed material and the crude material from which it is processed as follows:*

(a) **Crude plant parts or plant material/non-plant material**:

- Definition:
  - name of plant
  - part of plant
  - Nature/condition of material: whole, powdered, fresh, dried, etc.

- Authentication: confirmation of:
  - Correct geographical origin
  - Correct stage of growth

- Absence of foreign matter:
  - other plant parts or materials
  - soil, stones, dust
  - insects and other animal matter (as determined by microscopy, macroscopy, chromatography - see below).

- Microscopic characteristics confirming identity:
  - qualitative features
  - quantitative features, e.g. stomatal number

- Radioactive contamination limits: arising from environmental pollution or microbial decontamination procedures.

- Assay: for materials containing constituents of known therapeutic activity, or known unique (marker) compounds. Non-specific assay methods for groups of compounds may be used where specific assay methods are not available for single compounds.
- Conformation to a pharmacopoeial monograph

- A copy of the manufacturer's or supplier's certificate of analysis should be attached to confirm conformation to these specifications

(b) **Processed plant materials/non-plant materials (extracts, tinctures, comminutions etc):**

Definition: liquid, solid, etc

Organoleptic characteristics:

- macroscopy
- smell
- taste
- texture
- colour

- Chromatographic profile using more than one method:
  - to confirm presence of unique compounds (markers)
  - to confirm characteristic TLC chromatogram
  - to confirm characteristic HPTLC chromatogram (TLC + densitometry = HPTLC)
- Water content (for hygroscopic materials)

- Ash values: indicate extent of contamination with inorganic material. Determined by incineration. Values include acid insoluble and sulphated ash

- Volatile matter: for plants containing volatile oils. Determined by steam distillation
- Powdered material – test method and acceptable limits for particle size, distribution
- If the product is a mix of plant materials, the supplier must provide evidence that each component plant has been individually tested.
- Heavy metal limits: from environmental pollution and pesticides

- Microbial contamination limits: microbial contamination arises from cultivation, harvesting, processing and storage:

- confirmation of absence of *E. coli*, *S. aureus*, *P. aeruginosa* and *salmonella*
- limits for aflatoxins (fungal toxins)

- Residual solvents from processing

- Pesticide residue limits: arising from cultivation (FAO and WHO limits)

- Extractive values: extraction by different solvents indicates proportion of polar and non-polar components

- Assay: for materials containing constituents of known therapeutic activity, or known unique (marker) compounds. Non-specific assay methods for groups of compounds may be used where specific assay methods are not available for single compounds

**(c) Inactive ingredients**: as per pharmacopoeial monograph, or in-house monographs where no pharmacopoeial monographs exist.

2. Whereas fresh plant materials are to be used, processing should commence as soon as possible after harvesting. If processing cannot be initiated within a few hours, harvesting should not be done under damp weather conditions when plants are wet or covered with dew. If the delay in processing will be greater than 8 hours, the plant material will need to be stored under appropriate conditions to conserve the medicinal properties, preferably refrigerated and used within 48 hours.
3. *Comprehensive details of the* ***procedures involved in the various stages of manufacture****, including packaging (e.g. a description of the type of equipment, duration of treatment, etc.) should be given.*

4. ***Analytical, microbiological and other in-process control procedures*** *together with the frequency and sequence in which they are carried out during the manufacturing process should be stated.*

5. ***Summarised specifications of the final product*** *should be given, i.e. the acceptable limits of all the physical, chemical and (where applicable) microbiological parameters. A full description of analytical and other control procedures carried out to ascertain the final product specifications should also be given. The following specifications and relevant analytical methods should be described:*
6. **Specifications and test methods (for all dosage forms)**
   - Description of dosage form
   - Identity
   - Assay: specific or non-specific; stability-indicating

- Impurities
  - degradation product of active raw materials
  - microbial limits

7. Additional tests for specific dose-forms

**Hard Gelatin capsules and tablets (coated & uncoated)**

a) Dissolution/Disintegration
b) Hardness & friability
c) Uniformity of content and mass (dosage units)
d) Water content

**Oral liquids**

a) Uniformity of content and mass
b) pH
c) Microbial limits
d) Antimicrobial preservative content
e) Antioxidant preservative content
f) Extractable from container/closure system
g) Alcohol content
h) Dissolution for suspensions and powders for suspension
i) Re-dispensability for suspensions.
j) Viscosity for suspensions or viscous solutions
k) Specific gravity for suspensions or viscous solutions
l) Water content for powders for reconstitution.

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.

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

Brief description of the finished product

8. Herbal medicines Stability

*Evidence of Stability should be submitted as follows:*

***8.1 Stability studies on imported finished product should:***

(i) be on the market pack
i) have a detailed protocol
ii) have summarised results
iii) have conclusions on:
- proposed storage conditions
- proposed shelf life
- in-use storage conditions and shelf life

- ***Labelling recommendations should be stated as follows:***
  - Store under normal storage conditions ($15^oC$ - $30^oC$)
  - Store between $2^oC$ - $8^oC$ (i.e. refrigeration, no freezing)
  - Store below $8^oC$ (i.e. refrigeration)
  - Store between $^-5^oC$ - $O^oC$ (i.e. in a freezer)
  - Store below $^-18^oC$ (i.e. in a deep freezer)

  Note that these recommendations must be present on the product samples submitted with the application.

- ***Stability studies on local finished product****:*
  - All local products should have a shelf life of not more than one year.
  - copy of certificate of analysis one year from the date of manufacture should be submitted

Accelerated stability data (6 months) and real time stability studies conducted for minimum of 12 months should be submitted together with the application. However, studies should continue to the end of the proposed shell-life (a written commitment to this effect should be made by the applicant).

The following are the guidelines on submission of the stability data

| **INSTRUCTIONS** | **EXPLANATORY NOTES** |
|---|---|
| **Accelerated stability studies**<br><br>Give brief description of the accelerated stability conducted to establish the effects of the increase of change of the rate of chemical degradation and physical change of a drug using exaggerated storage conditions. | 1. These studies shall be conducted at $40\pm2^oC$/75%RH for six months at a sampling frequency of initial 1, 2, 3 and 6 months in humidity chambers.<br><br>2. The parameters to be examined, number of batches, sampling plan, type of packaging and analytical test procedures shall be similar to those |

| | |
|---|---|
| | under real-time stability (see below).<br><br>3. Accelerated stability data results shall enable proposition of a tentative shelf-life of 24months, which shall later be confirmed by completed real-time stability studies.<br><br>4. The requirement of orientation of containers and container closure systems is equally applicable here as is the case for real time stability studies. |
| **Real time stability studies**<br><br>Describe briefly the real time stability studies performed to establish the shelf-life and storage conditions of the product. | 1. Real time stability studies should be conducted under controlled conditions in stability chambers and not open shelves.<br><br>2. They should be carried out under zone III of the world climatic conditions (hot/dry) which are fixed at $25\pm2^{o}C/65\pm5\%$.<br>3. Sampling should be done at initial 3, 6, 9, 12, 18, 24, 36 etc. Months to establish the stability characteristics of the drug product.<br>4. Samples from three different batches, which are randomly selected to represent the whole batch, should be issued for the study.<br>5. Attributes (parameters) to be tested should be those susceptible to change and are likely to influence the quality, safety and efficacy of the pharmaceutical product. These parameters should be at least cover:<br>a. Appearance for all dosage forms<br><br>b. Assay (Stability indicating) for all dosage forms |

| | |
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| | c. Degradation products / impurities for all dosage forms.<br><br>d. Physiological properties such as disintegration, hardness, particle matter etc, for all solid dosage forms.<br><br>e. Dissolution for all solid and semi solid oral dosage forms.<br><br>f. Microbial limits for all dosage forms.<br><br>g. pH for liquid preparations.<br><br>6. A description of the sampling plan used to select the samples from the test batch for storage and subsequent testing should be given.<br><br>7. For liquids, dispersed systems and semi-solid products, samples should be stored in upright, horizontal and inverted positions to ensure full interactions with all primary packaging materials. |
| **Provide results of stability studies for the three batches tested.** | 1. Results should be presented in tabular form or graphs (wherever possible).<br>2. Acceptable criteria should be fixed for each test included in the stability study. The criteria can be in the form of numerical limits if results are quantitative (e.g. assay degradation products, particle size and viscosity). For qualitative tests, the criteria can be pass or fail (e.g. odour, colour, appearance).<br>3. Analytical test procedures shall be fully validated and assay shall be stability indicating. For products with official monographs, the procedures in the current edition of the official compendia |

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| | stipulated in these guidelines will apply. |

9. Labelling Requirements

9.1 Information on the label

Every immediate container of any product shall be affixed with a label bearing the following particulars pertaining to the contents of such container in clearly legible and indeligible letters in English

i. Proprietary / trade name
ii. Local names based on the seven official local languages for locally manufactured herbal medicines.
iii. Dosage form of the product
iv. Quantitative list of active ingredient(s) in the container expressed in the appropriate unit or volume of the pharmaceutical product.
v. Name and address of manufacturer
vi. In case of contract manufacturing, the name and address of manufacturer printed in the same letter size as those of the registrant as follow: “Manufactured for ….(name and address of registrant) by …..(name and address of manufacturer)”.
vii. Distribution category
viii. Precautions ( e.g. the instruction:
“Shake well before use or “For external use only”, where applicable)
ix. Indications and recommended dosage of the pharmaceutical product
x. In case of products for injection, route of administration by suitable words or abbreviations such as im, iv, etc.
xi. The batch or lot number of the product
xii. The manufacturing and expiry date of the product
xiii. Zambian product registration number
xiv. The name and concentration (content) of preservatives, where present
xv. Storage instruction and shelf-life and the instruction “keep out of the reach of children”.

In case the product’s package bears both the immediate container label and outer container label, the above requirements shall apply to the outer label as well.

9.2 Requirements for package inserts

Each package of a product shall be accompanied by a package insert as a separate entity or as an integral part of the package on which the following information is printed in legible letters in English both under the headings specified below:

i. Name and dosage form of the product
ii. Identification (description of the product and package)
iii. Quantitative list of active ingredients in a dosage unit or suitable mass or volume or unit of the product.
iv. Indications
v. Dosage regimen and directions for use.
vi. Contraindications
vii. Side effects and adverse reactions
viii. Drug interactions
ix. Precautions and warnings
x. Symptoms and treatment of overdose
xi. Presentation (packing and pack size)
xii. Storage instructions and shelf-life
xiii. Name and address of manufacture and country of origin
xiv. Date of publication of the insert

## PART D. SAFETY DATA

The requirement for submission of safety data is applicable for products which are not official in current editions of pharmacopoeia and for herbal medicines which are not listed in the current WHO Monographs on Selected Medicinal Plants.

a) *For products of long-term traditional use:* bibliographical (documentary) evidence of safety should be submitted including the following:

i) Evidence of long-term use (in terms of decades)
ii) Specification of the system of traditional medicine, disorders treated, numbers of users and countries of use (as found in literature, monographs, etc)
iii) Indication of the lack of toxicity problems over the documented period of time
iv) If toxicity problems are revealed by the documentation, toxicological studies should be done to determine safe dosage, and risk assessment made and presented in the dossier
v) Details of the potential for misuse, abuse or dependence
vi) Bibliographical evidence sources include reference literature (textbooks, journals etc), case reports, pharmacopoeial monographs

vii) In the case of local products where there may not be much bibliographical evidence available, the applicant should write a summary clearly confirming the safety of the product.

b) *For foreign products where there is no bibliographical evidence of safety in long-term use:* toxicological studies proving safety are necessary, and should be submitted in the dossier.

c) Non clinical studies

Provide full information to support safety of the herbal medicines by submitting results of the following tests.

i). Acute toxicity tests using at t least two species one of them being a non rodent.
ii). Subacute toxicity tests
iii). Chronic toxicity tests
iv). Mutagenic tests using salmonella (Ames test) or other tests
v). Teratogenicity tests if a product is to be administered to pregnant women
vi). Immuno toxicity (test for allergic reactions)
vii). Carcinogenicity tests
viii). Reproductive toxicity tests

For each of the above tests applicants will be required to provide protocol or study plan and amendments bearing signatures of study director and quality assurance person.

i) Name of study director, principal investigators, their qualifications and full addresses
ii) Details of all tests items including transportation, storage formulation data and quality control data.
iii) Information on tests system (supplier, animal husbandry, species, justification for use, strain).
iv) Curriculum vitae (CV) of all personnel involved in the study
v) Copies of standard operating procedures and revisions if any for each of the tests.
vi) Copies of all raw data including procedures and revisions if any for each of the tests.
vii) Copy of final report on safety of the product signed by the study director and quality assurance person.

An independent expert report critically examining data and making considered opinions supported with references from peer review literature should be provided.

## PART E. EFFICACY DATA

The requirement for submission of efficacy data is applicable for products which are not official in current editions of pharmacopoeia and for herbal medicines which are not listed in the current WHO Monographs on Selected Medicinal Plants. It shall be noted that only those therapeutic uses which are established through clinical studies are acceptable for herbal medicines listed in the current WHO monographs on Selected Medicinal Plants. The rest of the herbal medicines shall be required to provide evidence of efficacy as outlined below.

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, e.g. 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

e) In the case of local products where there may be little or no bibliographical evidence available, the applicant should write a summary clearly explaining the efficacy of the product.

**PART F. APPLICATION FORM**

# PHARMACEUTICAL REGULATORY AUTHORITY

## APPLICATION FORM

***For registration of Herbal Medicines for Human use in Zambia***

For official use only

Date of receipt of application:

Application Number:

**In completing this form and preparing of dossiers for submission to the Authority, the applicant is advised to refer to the guidelines on registration of Herbal Medicines for Human use in Zambia.**

**1. Product Particulars**

1.1. Product Name:-

***1.2. Therapeutic Indications for the Product:-***

***1.3. Pharmaceutical Dosage Form***

1.3.1 Dosage and Route of administration:-

1.3.2 Container, closure and administration devices:-

1.3.3 Package sizes:-

1.3.4 Shelf life:-

(i) The shelf life of the product in each of the different package type(s) and sizes:-

(ii) The shelf life after first opening of container where applicable:-

(iii) The shelf life after reconstitution:-

1.3.5 Storage conditions:-

1.3.6 Categories for Distribution

☐ Prescription only Herbal Medicines

☐ Pharmacy Herbal Medicines

☐ General Sales herbal Medicines

Other information

| ***2. Product composition*** | | | | |
|---|---|---|---|---|
| Name (INN) of | Reason for inclusion | Quantity | Unit | Reference standards |
| Names of ingredients | | | | |
| i. | | | | |
| ii. | | | | |
| iii. | | | | |
| iv. | | | | |
| v. | | | | |
| vi. | | | | |
| vii. | | | | |

***3. Status of/ Registration in the Country of Original Development and /Registration Number and Date, Where Applicable, Country of Manufacture:-***

***4. Registration Status for this herbal Medicines in the SADC Member States and in Other Countries***

| | |
|---|---|
| 4.1 Registered: | Country:<br>Date of registration:<br>Proprietary name: |
| 4.2 Pending: | Country:<br>Date of submission:<br>Application number: |
| 4.3 Rejected: | Country:<br>Date of rejection:<br>Application number:<br>Reason for rejection: |

| | |
|---|---|
| 4.4 Withdrawn (by applicant before registration) | Country:<br>Date of withdrawal:<br>Reason for withdrawal<br>Proprietary name: |
| 4.5 Withdrawn (by applicant after registration) | Country:<br>Date of registration:<br>Date of withdrawal:<br>Reason for withdrawal<br>Proprietary name: |
| 4.6 Suspended/ revoked/ cancelled/Withdrawn by competent authority | Country:<br>Date of withdrawal:<br>Reason for withdrawal<br>Proprietary name: |

**5.** ***Details of Applicant*** (who must be the prospective holder of the product licence)

Name:

Physical Address:

Postal Address:

Country:

Phone: Fax: Mobile: E-mail:

**5.1** ***Details of a Distributor/local agent*** (who must be appointed by the applicant and submit evidence of power of attorney)

Name:

Physical Address:

Country:

Phone: Fax: Mobile: E-mail:

| |
|---|
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| |

**5.2** Manufacturer(s), site(s) for the pharmaceutical dosage

| NAME (each site involved in the manufacture of the dosage form) | ACTIVITY –Dosage form compounding (for each stage where applicable, including labelling) | SITE (Physical Address, Phone and Country) | Name, address & qualifications of key personnel |
|---|---|---|---|
| | | | |
| | | | |
| | | | |

**5.3** Source(s) manufacturer(s) of Active Pharmaceutical Ingredient(s)

Name:

Physical Address:

Postal Address:

Country:

Phone: Fax: Mobile: E-mail:

**6.** ***Declaration by an Applicant***:

I, the undersigned certify that all the information in this form and all accompanying documentation is correct. I further certify that I have examined the following statements and I attest to their accuracy.

I also agree that I am obliged to follow the provisions of the Pharmaceutical Regulatory Authority which relate to Herbal Medicines.

All the documentation referred to in this licence is available for review during a GMP inspection.

Name:

Qualification:

Position in the company:

Official
Date stamp

Signature:

Date:

**References**


- WHO/AFRO guidelines for registration of herbal medicines