ZANZIBAR FOOD AND DRUGS BOARD

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GUIDELINE ON APPLICATION OF SUBMISSION FOR VETERINARY PRODUCTS

(Made under section 52 (ii) of Zanzibar Food, Drugs and Cosmetics Act, 2006)

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ZANZIBAR FOOD DRUGS AND COSMETICS BOARD

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Protect and Enhance Health Care of Public Health

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Dr. Burhani Othman Simai

Registrar

Zanzibar Food and Drugs Board.

INTRODUCTION

This guidelines was intended to give the Zanzibar Food and Drugs Board's requirements for documentation and assembling of applications for registration of veterinary medicinal products in Zanzibar. It was intended to serve as technical requirements for the registration of veterinary medicinal products.

They prescribe the format and content of a registration dossier, number of samples, types and amount of fees payable and labeling and package insert information requirements.

The prescribed studies and data are considered minimum required to demonstrate the quality, safety and efficacy of veterinary medicinal products. However applicants may provide additional studies and/ or data to support claims on medicines being applied for registration. Compliance to these guidelines in the submission of applications will facilitate the speedy processing and evaluation the applications and hence market authorization. This will enable the registrants to market their products on time and make it 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

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
CI	Confidence Interval
Cmax	Maximum plasma concentration
CV	Coefficient of Variation
Eyd	Eye drops
Eyo	Eye ointment
FDC	Fixed Dose Combination
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HPLC	High Performance Liquid Chromatography
VICH	International Conference on Harmonization of Technical Requirements for Registration of Veterinary Medicines
i.m	Intramuscular
Inj	Injection
Inh	Inhaler
INN	International Non-proprietary Name
IP	International Pharmacopoeia
IU	International Unit

IUPAC	International Union for Pure and Applied Chemistry
i.v	Intravenous
JP	Japanese Pharmacopoeia
Ltd	Limited
mg	Milligram
ml	Millilitre
M.R	Modified Release
Oin	Ointment
Ph.	Eur European Pharmacopoeia
RH	Relative Humidity
SPC	Summary of Product Characteristics
Sr	Sustained release
TE	Therapeutic Equivalence
TLC	Thin Layer Chromatography
Tmax	Time to reach maximum plasma concentration
µg	Microgram
USA	United States of America
USP	United States Pharmacopoeia
WHO	World Health Organization
ZFDB	Zanzibar Food and Drugs Board
ZFDCA	Zanzibar Food, Drugs and Cosmetics Act, 2006

GLOSSARY OF TERMS

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

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).

Board

Means the Zanzibar Food and Drugs Board, or its acronym "ZFDB" established under Section 3(1) of the Zanzibar Food, Drugs and Cosmetics Act, (ZFDCA) 2006.

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 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.

Drug, medicine or pharmaceutical product

Means any substance or mixture of substances manufactured sold or represented for use in:

(a) The diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical or mental state, or the symptoms thereof, in an animal;

(b) Restoring, correcting or beneficial modification of organic or mental functions in an animal;

(c) Disinfections of premises in which drugs are manufactured, prepared or kept, animal hospitals or clinics and equipment;

(d) Articles intended for use as a component of any articles specified in clause (a), (b) or (c); but does not include medical devices or their components, parts or accessories.

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 expert on the subject.

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.

General sale drug

Means any drug whose use does not need the direction or prescription by a medical practitioner or dentist.

Generic products

Means products that are pharmaceutical equivalents or alternatives to innovator or reference products and which are intended to be therapeutically equivalent and can therefore be used interchangeably with the innovator or reference product.

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.

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 (according to the requirements at the time of authorization).

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 drug.

Manufacture

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

Manufacturer

Means a person or firm that is engaged in the manufacture of products.

New combination

Means a product containing drugs in combinations (qualitative content and/or proportions) different from those products that are subject of current pharmacopoeias.

New active pharmaceutical ingredient

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

Pharmacopoeia

Means a 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 marketing authorization

Specifications – expiry check or shelf life

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

Specification - release

Means the combination of physical, chemical, biological and microbiological test requirements that determine whether a drug 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.

PART I

1. GENERAL INFORMATION

1.1 These guidelines apply to all veterinary medicinal products (VMPs) except biological products, traditional medicinal products, diagnostic aids, medical appliances and public health chemicals.

1.2 All documents are to be submitted typewritten or computer printed (except for clinical trial data, which should be hand-written in ink and a copy, submitted) in KISWAHILI OR ENGLISH. Where originals are in another language, copies shall be presented together with certified English translations.

(a) First time applications

A separate application is required for each product. Products differing in active ingredient(s), strength, dosage forms, package size (preparations for injection only) or manufactured at different sites are considered to be different products and hence require separate applications. However pharmaceutically equivalent products bearing the same proprietary name and manufactured at the same manufacturing site, but differing only in packaging material or pack sizes require only one application.

Applications shall be made by submitting a dully filled in application form. An application must be accompanied by:

I. Two copies of complete checklist and index of the various parts and documents submitted
II. One copy of a motivation letter of not more than 500 words as to why the product should be registered in Zanzibar
III. A non-refundable application fee as stipulated in the current fee and charges regulations.
IV. A non refundable pre-registration inspection fee as stipulated in the current fee and charges regulations.
V. Hard and electronic copies one each of a medicinal product dossier containing prescribed information (as shown in table I) arranged in parts and filed sequentially in the order of; I, II, III, IV, V and VI as the case maybe. Each part shall be signed by authorized person and accompanied by a signed expert report.

NB All ingredients used in the formulation of generic medicinal products must comply with specifications prescribed either in the United States, British, European, International or Japanese pharmacopoeia. In-house specifications shall only be accepted if the limits are tighter than those prescribed in those pharmacopoeias and other specifications may be accepted if they are validated.

Table I: Parts required for each type of medicinal product

Product type	**Parts required**					
	I.	**II.**	**III.**	**IV.**	**V.**	**VI.**
	SPC	**API**	**FP**	**Pre-clinical Pharmaco-toxicological**	**Clinical safety and efficacy**	**TE**
Innovator	√	√	√	√	√	X
Innovator Fixed Dose Combination						X
Innovator Variants: either as single or composite variation in dosage level, form, route of administration or indication	√	√	√	Bridging studies data	Bridging studies data	X
Single Active Ingredient or Fixed Dose Combination	√	√	√	X	X	√

Key: SPC: Summary of Product Characteristics
API: Active Pharmaceutical Ingredient
FP: Finished Product
TE: Therapeutic Equivalence Data
√: Required
X: Not required

vi. Zanzibar specific Certificate of Pharmaceutical Product (WHO type) or equivalent document accompanied with the product's approved summary of product characteristics from the Medicines Regulatory Authority of the country of origin of the product.

vii. Five samples of the smallest commercial pack(s) with the respective Certificate of analysis. However:

(a) In case of tablets or capsules if the total number of tablets of the five commercial packs is less than 200 tablets or capsules, additional packs must be supplied to bring the total to a minimum of 200.

(b) In case of liquid preparations, 20 samples should be supplied if each pack contains less than 10ml and 10 samples should be supplied if each pack contains more than 10ml but less than 50ml and five samples for volumes of more than 50ml.

viii. At least 100mg of sealed working standard for new medicinal products

ix. Current Site Master File

NB: All documentation should be filed in accessible spring files made of biodegradable hardened material. Arch lever files are not acceptable.

(b) Application for alteration of a registered product

Whenever a marketing authorization holder wishes to make any alteration to a registered product he must apply to and obtain approval from the Board before introducing it in Zanzibar. An application for alteration shall be made on an Application Form for Alteration and shall be accompanied with:

(i) A detailed description of the alteration with supporting reasons.

(ii) Two samples of the altered product.

(iii) A non-refundable variation fee as stipulated in the current fee and charges regulations.

Note: A change of manufacturing site or active ingredient will require a separate application and submission of data and other requirements must be as first time application.

(c) Application for renewal of registration

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

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

(i) Consolidated report of all changes if any (reported and unreported) which had been made with respect to product during the validity of its registration.

(ii) Report of additional adverse drug reactions if any detected during the lifetime of the product.

(iii) Samples of the smallest commercial pack(s).

(iv) Working standard for new medicinal products

(v) A non-refundable renewal application fee as stipulated in the current fee and charges regulations.

(vi) Updated site master file and Non-refundable GMP inspection fee as stipulated in the current fee and charges regulation.

1.3 Registration procedures shall commence only if the Application Form with its appendices has been properly completed. Only the Information required in the appendices should be furnished.

1.4 All documents shall be addressed to the Registrar, Zanzibar Food and Drug Board, P.O. Box 3595, Zanzibar.

1.5 All VMPs are registrable and must therefore be registered in before being sold, imported or manufactured for sale or distribution.

2. APPLICANT

2.1 Application for the registration of a VMP shall be made only by:

- A manufacturer,
- Patent holder/Owner of the formulation,

- Person responsible for placing the product in the market with power of Attorney from or contract with the manufacturer or owner of the formulation.

2.2 Every applicant must have a Local Responsible Person (LRP) who must be resident in Tanzania.

2.3 (LRP) is a body corporate (company) licensed to handle pharmaceuticals in Zanzibar with legal authorization to take full responsibility for the product on behalf of the applicant.

3. PARTICULARS OF THE MANUFACTURER(S)

3.1 Manufacturer means a person engaged in the production, compounding, formulating, filling, packaging and labeling of a veterinary Medical Product (VMP).

3.2 The following information relating to the manufacturer shall be provided by the applicant:

3.2.1 The name, physical address, telephone number, fax number, and E- mail address of the manufacturer shall be provided.

3.2.2 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:

SN	Name	Address	Activity
1	A-Z Pharmaceuticals	Plot 102,Bububu Road, Zanzibar: Tel: +255-778-657854	Granulation
2.	SD Pharma LTD	Plot 74 ,Mazizini Road, Zanzibar: Tel: +255-777-678980	Compression and Coating
3.	FK Pharmaceuticals	Plot 244 ,Mbuyuni Road, Zanzibar: Tel: +255-777-669890	Packaging

3.3 A copy of current Good Manufacturing Practices (cGMP) certificates from the DRA of the country of manufacture shall be provided for each site.

4. PARTICULARS OF THE VETERINARY MEDICINAL PRODUCT

4.1 Proprietary name means the (trade or brand) name, which is unique to a particular drug and by which it is generally identified (and by which it is registered in the country of manufacture).
4.2 Approved/ INN / generic name in relation to a drug means the internationally recognized non-proprietary name of such a drug.

4.3 Strength shall be given per unit dosage form or per specified quantity: e.g. mg per tablet, mg per capsule, mg/mL, mg per 5mL spoonful, mg per G, etc.

4.4 Dosage 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.

4.5 Description of the product shall mean a full visual description of the drug 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.

4.6 Commercial Presentation shall mean 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.)

4.7 ATC Classification means the Anatomical Therapeutic Chemical Classification system as described in Appendix I.

4.8 Country of manufacture means a country where the product was manufactured.

4.9 Storage conditions shall be stated in actual humidity and temperature range as shown below:-

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

4.9.2 Store between 2°C - 8°C (refrigeration, no freezing)

4.9.3 Store below 8°C (refrigeration)

4.9.4 Store between –5°C - O°C (in a freezer)

4.9.5 Store below –18°C (in a deep freezer)

Article II. 4.10 Pharmaceutical formula of the product

4.10.1 The approved / INN /generic name(s) and the chemical name(s) of the substances (active and inactive) shall be given, and in the absence of a chemical name, the chemical nature of the substance shall be described. Trade names shall not be used.

4.10.2 Quantities shall be given in terms of the dosage unit, eg. Mg/tablet, g/mL, etc.

4.10.3 Specifications or reference text shall be precisely stated, eg. BP 93 page 101.

4.10.4The reason for inclusion of each inactive ingredient in the formulation shall be stated. Any raw materials used, although not present in final dosage form, shall also be stated.

5. CURRENT REGISTRATION STATUS

5.1 State the names of all countries (including the country of manufacture) where the product is registered (attach certified copies of the certificate of Registration/product licence issued by the appropriate DRA in each case).

5.2 If not registered in country of manufacture, give reasons

5.3If the drug has been rejected/refused/deferred/cancelled/withdrawn in any country or territory supply details.

5.4 If the product is patented, provide details of the patent holder and the date of expiry.

6.0 SUPPORTING DOCUMENTS AND MATERIALS.

6.1 Samples:

Provide a minimum quantity of the product in commercial pack to conduct two sets of full analysis, For non-pharmacopoeial products, provide a minimum of 200mg of Reference standards with the corresponding Certificate of Analysis,

6.2 Product information:

Provide copies of package inserts, labels and samples of packaging materials,

Provide samples of the proposed advertising and promotional materials,

6.3 Certificate of pharmaceutical product (who type) Submit WHO Certification Scheme Certificate on the Quality of Pharmaceutical Products moving in International Commerce (use the current who format) together with a validated copy of the manufacturing licence issued by the appropriate DRA.

PART II
CHEMISTRY, MANUFACTURING AND QUALITY CONTROL DATA

1.0 Active pharmaceutical ingredient

Particulars under this section are required for products containing the following:-

i. New API or combination of new API.

ii. New API in combination with well established ingredients.

iii. Products containing little known ingredients or non-pharmacopoeia substances poorly documented in literature.

iv. Products containing pharmacopoeia substances when there is reason to doubt the validity of specifications i.e. when obtained from a new source using different method of manufacture/synthesis.

1.1 The international non proprietary name or chemical description of the active ingredient should be stated including structural formula, the empirical formula and molecular mass.

A comprehensive account of active ingredient specifications, Manufacture and analytical control procedures are required when the substance is wholly or partially synthetic.

1.2 Synthesis

1.2.1 Route of synthesis/chemical reactions/biological reactions and flow sheets for synthesis manufacture where applicable should be presented in form of flow sheet/scheme.

1.2.2 Indicate where possible approximate yield at each level of reaction or stage of manufacture; chemicals and solvents used during manufacture shall be stated.

1.3 Manufacturing process

Brief description of each stage of manufacturing/synthesis process, isolation and final purification steps is given. Include here information on:

(i) Methods used
(ii) Chemicals, materials used and specify whether solvent, reagent, catalyst etc
(iii) Reaction parameters and conditions where they are critical (i.e Temperature, pressure etc)
(iv) Information on intermediates that is isolated and purified.
(v) Details of final purification and solvents involved
(vi) In case of biological materials, state also source of material including as appropriate, species of animal, type of micro organism used in preparation of bulk active ingredient, method used to collect the material arrangements for storage and transportation.

1.4 Specifications and Analytical control of starting materials

State the specifications for starting material used in the manufacture of active ingredients (i.e. chemicals, reagents, solvents, biological materials etc used whether at the start of manufacture or added at various stages of manufacturing process.

1.4.1 If materials are of annalar grade or subject of current pharmacopoeias, it is sufficient to make appropriate references.

1.4.2 Information relevant to materials used for several products may be submitted in a "manual of specifications".

1.4.3 Detailed analytical methods and tests protocols should be available.

For non-pharmacopoeia active raw materials:

The following minimum information should be provided:

(a) Specifications and tests for all active raw materials:

(i) Description
(ii) Identification: test method should be selective

(iii) Assay: test method should be selective, sensitive and able to detect degradation compounds i.e. stability indicating.

(iv) Impurity limits

Organic impurities (generated during synthesis: starting materials, by- products like isomers and polymorphs, intermediates, degradation products, reagents, catalysts)

• If = 0.1% of active pharmaceutical ingredient (API) content it should be characterised (identified) and evidence of its safety provided

• If < 0.1%, characterisation is not necessary, and quantification only is required.

Inorganic impurities (used during synthesis: reagents, ligands, heavy metals and inorganic salts).

• Limits should be pharmacopoeial

Residual solvents (used during synthesis)

• In all cases where there are residual solvents, limits should be stated and justified.

(b) Additional specifications and tests for relevant active raw materials:

I. Physicochemical properties (e.g. melting point, pH in solution, refractive index)
II. Solid-state form (polymorphs and solvates)
III. Optical activity (to control enantiomeric purity)
IV. Water content (for hygroscopic or sensitive compounds)
V. Microbial limits (for susceptible compounds)
VI. Particle size, bulk density, flow
VII. Solubility in water and other solvents.

All tests should be performed unless development pre-formulation studies or process validation proves them unnecessary. Such proof should be provided in the application dossier.

Intermediate quality control, if any

Briefly give quality control checks, if any carried out at each stage of manufacture and specification and acceptance limits for intermediates isolated where applicable.

Details of quality control checks specifications, analytical methods, tests protocols should be included.

Impurities control

Impurities research and development studies

Give and briefly discuss on impurities considered and studies during research and development of ingredient, levels of impurity detected particularly those arising from synthesis/manufacturing process.

Studies showing that analytical methods deployed for impurity control in the API specifications are valid and sensitive should be included. Criteria for selecting limits and methods for impurity control should be discussed.

Note: Analytical methods shall be sufficiently detailed and precise, stating sensitivity and specificity to allow reproducible results in tests carried out by an independent body. For example chromatographic methods state:

(i) Sensitivity and limits of detection

(ii) Specificity for impurity detected

(iii) Materials used (mobile phase, stationary phase, equipment, apparatus, size of column or plate etc)

(iv) Test conditions – temperature, time, flow rate etc

(v) Actual loading of sample and reference impurities

(vi) Separation potential (RF values etc)

NB: The term "impurities "include:

(a) By product of synthesis arising from side reactions products in starting materials etc.
(b) Residual solvents and reagents

(c) Trace elements arising from other sources

(d) Products of degradation

Attach bibliography of works, reports papers or articles referenced.

(vii) Method of detection of visualization

(vii) Method of quantifying results

Visual evidence of chromatogram spectra and tabulation of results obtained with samples of material should be included.

1.5 Routine impurities control

Summary of impurities monitored or tested for during and after manufacture of ingredients as routine batch to batch impurities control should be given. Briefly state also analytical methods used for detection and qualification of impurities e.g. TLC, HPLC, Chemical tests, IR spectroscopy, atomic absorption etc and specify limits of acceptance of these impurities.

1.6 Tests and specifications (Release specifications)

List quality control tests/specifications for each batch of material (active ingredient) with limits or criteria for acceptance. State also whether the specification is BP/USP/ in house specification etc.

Indicate clearly which specifications are tested routinely on the batch at the time of manufacture. Tests which are not done for every batch shall be indicated, stating circumstances in which they are applied. For a typical synthetic drug the following criteria, at least, should be included in the specification for the material (Active ingredient):

(i) Appearance, colour, odour, taste, texture, crystallinity

(ii) Identity tests, UV, IR, melting point, chemical tests etc

(iii) Physico-chemical tests, solubility, pH, moisture loss on drying, particle size, optical rotation, polymorphism etc

(iv) Purity tests – chromatography, Ash values, trace elements, heavy metals, residual solvents, reagents etc.

(v) Assay – method should be sufficiently specific and sensitive.

1.7 Reference sample standards

Enclose analytical reports of recent batches of active ingredients (about 5 (five) batches), which are representative of material used in the manufacture of the product seeking registration.

Include also analytical reports for the batches used for toxicity tests and clinical works submitted in support of the application for registration. Reports should include; batch size, batch number, place of manufacture (factory premises), analytical method and results of analytical tests. Apparent inconsistent or anomalous results should be explained.

1.8 Structure activity relationship

State briefly the structure activity relationship of active ingredient and mode of action whenever possible, state also its activity in relation to other drugs of similar structure or group.

Copies of the supplier's or manufacturer's Certificates of Analysis shall be supplied for each raw material as proof of conformance to all declared specifications.

2. PHARMACEUTICAL DOSAGE FORM

2.1 Description of the product

A concise description of the product should be presented here. These should include; physical characteristics, consistence of the product, shape, size, colour, odour, taste, type of tablet (i.e. s.c, f.c, e.c, SR etc). Liquids should be clearly stated if it is emulsion, elixir, suspension etc.

2.2 Composition of the product

The composition of the product should be set out under the following topics:

(i) Active ingredients/adjuvants and their quantities in:

(a) per unit dose
(b) percentage composition (w/w, w/v, v/v)
(c) weight per ml or
(d) quantity per measured dose

INN or approved names or pharmacopoeia names should be used for injectable preparations; total content in each unit container should be given.

Exact quantities are not required for ingredients used in tablet coating or capsule shell although the constituents of these must be included.

Comprehensive details of the procedures involved in the various stages of manufacture, including packaging shall be given. This shall be in the form of a detailed flow diagram accompanied by a list of equipment used at each stage. Specifications and acceptance limits for intermediates should be given where applicable.

2.3 Complete manufacturing master formula

Give the actual batch manufacturing master formula with names and quantities of ingredients with the reasons for inclusion (Active and otherwise). Substances which are removed in the course of manufacture should be included.

2.4 Overage

Where an overage is included, give here the name of the ingredient and amount i.e.

(a) quantity per unit dose;

(b) % age composition (w/w, w/v, v/v etc).

Reasons for inclusions of overage should be clearly stated i.e. to cover losses during manufacturing etc.

2.5 Manufacturing processes

All stages involved in the manufacture of the dosage form should be described. Basic principles involved should be clearly set out i.e. for a tablet.

Stages: 1. Dispensing of ingredients

2. Mixing of ingredients
3. Moist granulation
4. Fluid bed drying at 60°C
5. Rotatory punching etc.

All steps involved and their operations should be carefully described including the conditions subjected to each operation i.e. temperature, PH adjustments, processing time etc. All the details should be made clear and sequenced to the logic. Flow charts would be useful.

A brief description of how the product is packaged into final immediate and outer containers should be given. All stages should be illustrated i.e. filling, weight checking, labelling, packing in hardboard and sealing. Steps, equipment, flow and precautions for each packaging stage be included.

2.6 Quality control

Analytical, microbiological and other in-process control procedures together with the frequency and sequence in which they are carried out during the manufacturing process shall be stated. These processes shall be included in the flow diagram above.

. Details of in-process control and specifications of quality assurance of product should be given here;

. Tests of raw materials should be carried;
. Tests on intermediate products should also be carried;
. All operations concerning finished products also be carried.

Information to cover the following should be supplied by manufacturers:

(i) Methods of control of receipt/issue of all raw materials; released/reject procedures of starting materials;

(ii) Record keeping batch production records control charts, packing and labelling material control release/quarantine records;

(iii) Specifications, analytical controls and other tests on starting material/intermediates. Analytical methods and test protocols must be in details;

(iv) Sampling plan and sampling methods should be available;

(v) Precautions and actions taken to reduce or eliminate breakdowns or defective products;

(vi) Methods of plant maintenance, sanitation, safety, cleaning of equipment, prevention of contamination and cross contamination.

(vii) Control of procedure of operations, i.e. filling, labelling, packaging and or rejection of final products;

(viii) Storage conditions for products before release for sale or quarantine procedures.

2.6.1 Finished product specifications

Summarized specifications of the final product shall be given, i.e. the acceptable limits of the entire physical, chemical, biological and (where applicable) microbiological parameters. A full description of analytical and other control procedures carried out to ascertain the final product specifications stated above should be given. Where analytical procedures in various parts of the application coincide, these procedures may be described fully in one part and may be subsequently referred to in other parts, provided that the relevant page and paragraph are clearly identified.

- For pharmacopoeial finished products, photocopies of the relevant monographs shall be provided.

- For pharmacopoeial finished products where the methods of analysis used are non-pharmacopoeial, detailed analytical validation of such methods shall be provided (see Appendix 2). However, the limits used should not be inferior to the Pharmacopoeial limits.

- For non-pharmacopoeial (in-house) finished products the following minimum information shall be provided:

(i) Specifications and test methods (for all dosage forms)

a) Description
b) Identity - test method should be specific for active ingredient(s)
c) Assay - test method should be specific and stability indicating for active ingredient(s)
d) Impurity limits - to determine the level of degradation products of active ingredients, and active ingredient-excipient interaction impurities.

(ii) Additional specifications and test methods for hard gelatin capsules and tablets

a) Dissolution (for relatively water insoluble active ingredients)
b) Disintegration (for readily soluble active ingredients)
c) Dissolution profiles for modified release preparations
d) Hardness & friability
e) Uniformity of content and mass (dosage units)
f) Water content
g) Microbial limits

(iii) Additional specifications and test methods for oral liquids

a. pH
b. Microbial limits
c. Antimicrobial preservative content/ preservative efficacy test
d. Antioxidant preservative content
e. Extractables from primary container
f. Alcohol content
g. Dissolution of suspensions
h. Particle size distribution
i. Redispersibility
j. Specific gravity
k. Water content

(iv) Additional specifications and test methods for parenterals

a) Uniformity of content and mass

b) pH
c) Sterility
d) Endotoxins/pyrogens
e) Particulate matter
f) Water content
g) Antimicrobial preservative content/PET
h) Antioxidant preservative content
i) Extractables
j) Functionality of delivery systems, e.g. syringeability for pre-filled syringes
k) Osmolality
l) Particle size distribution
m) Redispersibility

All tests should be performed unless development pharmaceutics studies or process validation prove that they are unnecessary. Such proof should be provided in the application dossier.

2.7 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 QC 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) Reconciliation records
f) Sterilization records
g) Certificates of Analysis of the finished product.
h) All other records as required by WHO GMP guidelines

Exemption from provision of batch manufacturing records by applicants for research based innovator products may be granted on a case-by-case basis, upon application for such an exemption.

3. Container-closure System and Pack Size

The following information shall be provided:

a) A general description of the container and closure system including primary (inner) and secondary (outer) packaging, and other components such as spoons and syringes pack sizes e.g. tablets B/100's, 500's, blister pack - 50's, 20's etc should be given.

3.1 The chemical identity of materials for each component of the system

3.2 Detailed specifications and tests for primary (immediate) packaging components such as:

3.2.1 Glass containers

3.2.2 Plastic containers and closures for solid dosage forms, opthalmics, parenterals, blood products

3.2.3 Rubber closures

3.3 Such specifications and tests shall be as per the British Pharmacopoeia, European Pharmacopoeia, or United States Pharmacopoeia, or in-house, and certificates of analysis shall be provided as proof that the packaging conforms to specifications.

3.4 Evidence of suitability of the container and closure system for the finished product:

3.5 Compatibility of primary packaging components with finished product.

3.6 Performance of system in drug delivery, e.g. actual volumes of teaspoons and eye drop bottles, extractable volumes of vials and ampoules.

4. STABILITY TESTING

4.1 Objectives of stability testing

The purposes of stability testing shall be to provide evidence of how the quality of a API or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. This will enable recommended storage conditions; re-test periods and shelf life to be established.

4.2 Factors determining stability of the product

Stability of a product shall be dependent on the following parameters:

(a) Physical and chemical properties of the product;
(b) Pharmaceutical formulation
(i) Active ingredients
(ii) Preservatives
(iii) Other excipients

(c) Storage conditions

The storage conditions and shelf life of all pharmaceutical products should be provided. For reconstituted drugs the manufacturer should state storage conditions and shelf life of the reconstituted preparations and provide data to support shelf life.

Multi-dose vial for liquid injectables, test should be done to determine stability after punching.

Multi-dose solid dosage forms (i.e. in jars, tins etc.), test should be done to determine stability after opening.

(d) Packaging
Packaging materials should be appropriate for the physical and chemical properties of particular product. The containers to be used for real time stability evaluation shall be the same as for storage and distribution.

4.3. Protocol for stability testing

The design of the stability testing program for the finished product should be based on the knowledge of the behavior and properties of the API, the experience gained from clinical formulation studies and stability studies on the API. The likely changes on storage and the rationale for the selection of product variables to be included in the testing program should be stated.

A storage temperature range may be used in accordance with relevant national/regional requirements. The use of terms such as ambient conditions or room temperature is totally unacceptable.

4.3.1 Test procedures and test criteria

Test samples shall be from pilot or production batches:

a) Three (3) different batches for both stable and unstable active ingredients should be provided.
b) Active ingredients should be from different raw material batches wherever possible.
c) The selection of samples for testing from each batch shall be random.

The testing should cover those features susceptible to change during storage and likely to influence quality, safety and efficacy. Analytical test procedures should be fully validated and the assays should be stability indicating. For products with official monographs, the procedures in the current edition of the official compendium will apply. Results of validation studies will determine the need for the extent of replication.

Any evaluation should cover the following parameters;
(a) Appearance
(b) Assay (stability indicating method shall be used)
(c) Content of decomposition products (impurities)
(d) Physicochemical properties, (e.g. hardness, disintegration, particulate matter, pH).
(e) Dissolution for all solids or semi-solid oral dosage forms;
(f) Preservative efficacy tests,

The length of the studies and the storage conditions should be sufficient to cover storage, shipment, and subsequent use.

A description of the sampling plan used to select the samples from the test batch, for storage and subsequent testing, shall be given.

4.3.2 Type of stability studies

All stability studies must be done under controlled test conditions in stability chambers and not on open shelve as prescribed below
The applicant shall specify the type of stability test whether real time or accelerated.

(a) Real time studies

(i) Test conditions 30°C±2°C/75%±5%RH

(ii) a minimum of 12 months stability data should be submitted together with the application

(iii) Studies should continue to the end of the proposed shelf life (a written commitment to this effect should be made by the applicant).

(b) Accelerated studies

(i) 40°C±2°C/75%±5%RH

(ii)A minimum of 6 months stability data should be submitted together with application

Accelerated stability data should be used to predict expiry date of a product. It may be accepted for the following:

(iii) New API and product for urgent use

(iv) New formulations for urgent use.

(v) New dosage forms.

(vi) Photostability testing of new drugs substances

4.3.3 Frequency of Testing

Frequency of testing should be sufficient to establish the stability characteristics of the API. Testing under the defined long term conditions will normally be at zero, every three months over the first year, every six months over the second year and thereafter annually. For accelerated condition, testing frequency should be at 0,1,2,3, and 6 months.

4.3.4 Orientation of containers

For liquid and semi-solid products, samples should be stored in upright, horizontal and inverted positions to ensure full interaction with all primary packaging materials.

4.3.5 Presentation of results.

(i) Name, qualification, title and signature of the investigator should be provided.

(ii) The results should be presented in tables and where applicable in graphs.

4.3.6. Shelf life

The proposed shelf life shall be supported by the stability data and should take into consideration the following:

(a) Shelf life for solid dosage form should not exceed five years

(b) Shelf life for liquids and other dosage forms should not exceed three years.

PART III

PRECLINICAL PHARMACO- TOXICOLOGICAL DATA

Information on this part is required for new pharmaceutical active ingredients. The objective of toxicological/safety studies is to define the pharmacological actions (pharmacodynamics and pharmacokinetics) and toxicological effects of the active ingredient in test animals and target species, users, consumers and the environments. This normally involves initial studies in laboratory animals and later on pre-clinical studies in the target species, which should take into consideration the following:

1.1 Selection of the relevant animal species
1.2 Age of the animals
1.3 Physiological state of the animals
1.4 The manner of delivery, including dose, route of administration and treatment regimen and the effect on the animals

1.5 Stability of the test material or drug under the condition of use

1.6 Safety of personnel.

Data Presentation
The pre-clinical documentation should be presented in the following sequence:

1. Pharmacology
2. Toxicology
3. Discussions and conclusions
4. Expert report

1.1.0 Pharmacodynamics

Provide a full description of tests performed to establish the pharmacological actions that are relevant to the proposed indication(s) of the API and mechanisms of action. Where possible it will be helpful to relate the pharmacodynamics of the drug to available data (in terms of selectivity, safety, potency etc.) on other drugs in the same class.

1.1.1 Other actions (desired/undesired)

Give evaluation summary of action(s) other than those of therapeutic use. The results of two or three dosage levels studied should be submitted, with the lowest level representing the ED50 for the API's primary action on the animal species being investigated.

For effects, which may be expected to have significant adverse reactions, attempts should be made to estimate the threshold levels.

1.1.2 Pharmacodynamics interactions

The applicant shall submit data either to establish that such interactions do not occur or that they are clearly recognised and defined.

Discuss the pharmacodynamic interactions and mechanisms of interactions of the API with other compounds (drug or other substances), which are relevant to proposed therapeutic use. Where there is evidence of antagonism or additive/synergistic effects, these should be well elucidated.

In case of fixed dose combination or combination packs appropriate data to justify the benefit of combination against single API should be given.

1.2.0 Pharmacokinetics

Pharmacokinetics studies should be made with single dose by various routes. Repeated dose studies should also be performed when relevant, to establish the pharmacokinetics of chronic drug administration.

Metabolic studies should be conducted on species used in toxicological and reproduction studies using the proposed clinical routes of administration.

Where radioactive labelled materials are used in studies, position of label stability and specificity of material should be stated.

Where the product contains a combination of drugs, the effect of use of two or more drugs on the pharmacokinetics of one or the other drugs should be established.

Provide studies done to establish the pattern and time course of absorption, distribution, biotransformation, pharmacokinetic interactions and excretion of the API and/or its metabolites as described below.

1.2.1 Absorption

Provide summary of mechanism of absorption, factors affecting absorption, rate and extent of absorption, plasma levels of the API and metabolites (peak levels, half-life, etc.). This information should be discussed for different routes. Correlation between plasma levels and pharmacological effects should be discussed.

1.2.2 Distribution of API and metabolites

Provide a summary and time course of distribution of the API and metabolites in body fluids, tissues, and organs.

Accumulation, retention of the drug/metabolites in tissues, organs, penetration of blood-brain and placental barriers, plasma binding all these parameters should be reported in quantitative form.

1.2.3 Biotransformation

Give the pattern and time-course of biotransformation of the drug, i.e. sites of metabolism and their importance, metabolic pathway(s), nature and quantities of metabolites, rate of metabolism, pre-systemic metabolites enzyme inhibition or induction, activity of metabolites, if any.

1.2.4 Pharmacokinetic interactions

Discuss the pharmacokinetic interactions and mechanisms of interactions of the API with other compounds (drug or other substances), which are relevant to proposed therapeutic use. Where there is evidence of antagonism or additive/synergistic effects, these should be well elucidated.

1.2.5 Excretion

Summarise the routes and extent of excretion of the drug and its metabolites. State also its excretion in milk in case of lactating animals. Discuss the rate of elimination and factors influencing elimination.

2. Toxicological studies

The scope of toxicological evaluation should be described in relation to the proposed clinical use. Information obtained from experimental and biological studies of all aspects of toxicology (general toxicity, acute toxicity studies, sub-acute toxicity and long term toxicity studies including teratology, reproduction effects, carcinogenicity, genotoxicity, immunogenicity, Microbial affects (e.g. development of resistance), local tolerance (potential for adverse effects at site of administration, etc) is required to establish the safe use of the drug and must be submitted for all new drug applications.

The investigation should, if possible, include experiments conducted with the drug in the vehicle intended for therapeutic application or its final pharmaceutical formulation (product).

2.1 General Toxicity Studies

In general toxicity studies, at least three or more routes of administration should be used including one for therapeutic use and at least one other which ensures systemic absorption, i.e. intravenous, intramuscular or subcutaneous.

Different dose levels spaced logarithmically should be used. The maximum tolerated dose should be indicated.

All animals dying during the experiment should be autopsied and cause of death determined where possible.

Full post-mortem should be carried out on all animals and histopathological studies undertaken on control and dosed groups.

Results should be tabulated. Full data for all parameters measured, with mean, range for groups, should be included.

If it is expected that the product will be used in children, studies should be conducted on both adult and young (weaning) animals.

2.2 Acute, sub-acute and long term toxicity studies

Principles governing general toxicity studies shall be applicable to acute, sub-acute and long term toxicity studies and local tolerability studies.

2.3 Safety to users

Residue study data should be provided to justify withdrawal periods for milk, meat, eggs for each species for which the product is indicated.

Studies on potential harmful effects to exposure by various routes, e.g. inhalation, topical contact, oral ingestion, performed on laboratory animals, shall be presented. The implications to humans using the product should be described and, where appropriate, precautions during preparation and use of the product should be proposed.

2.4 Risk assessment of veterinary drugs residues in food of animal origin

Safety assessment of veterinary drugs residues in food of animal original should be performed for all new drugs. Relevant pharmacological, toxicological, microbiological end points should be used to establish acceptable daily intake. Maximum residue limits in food producing animals should be provided. Withdrawal period should be indicated on the labels. All the analytical methods used should be provided.

Pre and post antimicrobial resistance surveillance should be performed on indicator pathogens e.g. *E.coli, Salmonella spp.* Quinolones - usage should be restricted to avoid resistance in zoonotic pathogens.

2.5 Toxicity to the environment

Assessment of the environmental safety should be given for all veterinary medicinal products. Requirements for safety are important to avoid persistent damage to the environment.

Products requiring environmental assessment include:

(a) Antibiotics in poultry, pig and fish feeds
(b) Antihelmintics in large animals e.g. invermectins
(c) Expired drugs from veterinary hospitals/clinics, pharmacies
and manufacturing plants
(d) Effluents from manufacturing plants
(e) Hazardous or potentially hazardous non pharmaceutical materials (used devices e.g. needles, syringes and gloves)
(f) External parasticides.

An assessment of the potential of exposure of the drug and its active metabolites to the environment shall be made taking into account:

(i) The target species and likelihood of and method of excretion of the product and its active metabolites into the environment.
(ii) Pattern of use and therefore quantity drug to be used (herd/flock medication or individual medication)
(iii) The method of administration and whether it may lead to direct entry of the product into the environment, e.g. sprays
(iv) The method of disposal of the unused, used products and containers

Studies on potential harmful effect of the product to the environment shall be provided. The environment shall include soil, water and air such studies shall include:

(i) fate and behaviour in the soil
(ii) effects on soil organisms
(iii) fate and behaviour in water
(iv) effect on aquatic organisms
(v) effects of other non-target organisms

Proposed measures to minimize the above potential risks during use of the product shall be described.

3 Generic and well established dosage form

In case of generic or interchangeable multi-source drugs and dosage forms provide bioequivalence studies data corroborated with literature review.

3. Presentation of safety studies

All toxicity studies shall be properly presented including the following:

(i) Objectives
(ii) Experimental protocol including methodology and materials
(iii) Summarized results and related statistical analysis
(iv) Discussions and conclusions
(v) Proposed measures to minimize potential toxicity during use of the product

PART IV

EFFICACY DATA

OBJECTIVES

This section shall only be applicable to new Chemical entities.

Original efficacy data will be required for all veterinary medicinal products containing new chemical entities (NCE) whether when mono or in fixed dose combination with another NCE or a well known API.

A summary of well presented, controlled blinded clinical trials conducted in target animals investigating the pharmacological and therapeutic properties, and adverse reactions is required.
Pharmacological studies are only required if the biological studies were not done in target animals.

The principles of Good Veterinary Clinical Practice (GVCP) should be adhered to during the study.

1. Pharmacodynamics studies (target animals)

Describe the study protocol including the study design, pharmacological or biochemical response measured, measuring instruments used results, statistical methods used and their justification. Tabulation and graphical illustration of results and conclusion.

Notes:

a) A cross-over design is preferred and where it is not appropriate a parallel design is acceptable. The study design must consider the pathology and natural history of the condition.

b) Studies should be done in healthy animals or in sick animal if the disease affects the actions/responses studied.

c) Inclusion/exclusion criteria must be stated and non-responders should be identified and excluded prior to the study commencement

d) Measured pharmacological response should be relevant to the claimed therapeutic uses where there is more than one therapeutic use studies should be done to demonstrate the therapeutic use for each indication.

e) Measurement of responses should as far as possible be quantitative, measured under double blind conditions and be recorded in an instrument producer/instrument recorded fashion. The methodology must be validated for precision, accuracy, reproducibility and specificity.

f) Where possible the effect can be graphically illustrated using the area under the effect time curve, maximum effect and time of maximum effect.

In using pharmacodynamics methods, the following requirements must be satisfied:

a) The response can be measured precisely over a reasonable range

The response can be measured repeatedly to obtain time-course from the beginning to end of the response

2. Pharmacokinetics and Bioavailability of the drug in target animals

The summary should outline;

a) Particulars of principal investigators (name, curriculum vitae, affiliation and signature)

b) Drug and drug product information, batch details, batch number, manufacturing site and date, expiry date, specifications The Drug product must be identical to the intended commercial product in every respect; same manufacturing site and same composition (qualitative and quantitative)
Samples should be from commercial scale production

c) Protocol and study design; (objectives, animal selection, conduct of the study, drug administration, food intake, sample collection, storage, bioanalytical methods and validation results, pharmacokinetics parameters measured and results.

Justifications for the chosen design (e.g. cross over or replicated design), measures taken to minimize intra and inter-animal variability and elimination of bias must be stated.

All possible factors that may influence the product pharmacokinetics must be standardized e.g. fluid intake, food intake, exercise, etc.

d) Population

Population size of 12 – 24 (sample size shall depend on the animal o-efficient of variation CV if low say < 15%; n = 14, > 30%; n = 44) healthy young animals

e) The results, data and statistical procedures should be detailed enough to allow for repeat analysis if necessary.

3. Efficacy clinical end point studies in target species

Describe in detail the study protocol, which should, include:

a) The title of the study

b) Particulars of principal investigator(s), location, justification and objectives, dates, time, duration, observation periods and justification thereof,

c) Study design (randomization methods description of design e.g. cross-over or parallel etc), inclusion, exclusion, criteria, animal housing and feeding, methods and treatments, dosage used, concurrent treatments,

d) Specification of test drug and placebo,

e) Response variables – clinical endpoints measured and recording clinical response (scoring system for endpoints).

f) Analysis of results including statistical methods used and their justification.

g) Discussions and conclusions on efficacy and safety, including but not limited to:

Adverse reactions observed and their relationship with the administered dose.

PART V

THEREPEUTIC EQUIVALENCE/INTERCHANGEABILITY

1. OBJECTIVES

This section shall be applicable to all generic oral dosage form Generic drugs means a drug product that is a pharmaceutical equivalent or alternative to an innovator product and which is intended to be therapeutically equivalent and can therefore be used interchangeably with innovator product.

Pharmaceutical equivalent; drug products are said to be pharmaceutically equivalent if they contain the same active ingredients (same esters, salt, etc.) in identical strength, in the same dosage form intended to be administered by the same route but not necessary the same inactive ingredient(s)
Pharmaceutical alternative; drug products are said to be pharmaceutical alternatives if they contain the same active ingredients which may differ in salt, esters, dosage form, strength and or route of administration.

All generic drug products applied for registration must conform to the same standards of quality, efficacy and safety (therapeutic equivalence) as the innovator product. Proof of efficacy, safety and withdrawal period is substantiated by therapeutic equivalence studies.

Applicants for registration of generic drugs must submit evidence showing that the generic drug is therapeutically equivalent to its innovator product in the relevant animals by either submitting reports of bioequivalence studies, comparative pharmacodynamic studies or comparative clinical trials and which must have been conducted in compliance with Good Veterinary Clinical Practice (GVCP) and Good Laboratory Practice (GLP).

2. Bioequivalence studies in target animals.

Bioequivalence studies data shall be required for the following product

a) Products where the innovator manufacturer changes the composition or manufacturing method of his original product b) Products where the route of administration is changed from the original product c) Oral solid dose immediate-release products:

i) indicated for life threatening diseases requiring rapid and/or assured therapeutic response,
ii) with narrow therapeutic and/or safety indices,
iii) with physicochemical properties conducive to or showing poor or highly variable absorption, non-linear pharmacokinetics, or extensive pre-systemic or first-pass metabolism
iv) with high ratio of excipients to active ingredients
v) fixed dose combination products

d) Drug with special claim to absorptive properties or special formulation i.e. modified-release or enteric coated,
e) Long acting injections
f) Non-oral, non-parenteral products that are intended to undergo systemic absorption

Products for which bioequivalence studies are not necessary:
a) Parenteral acqueous solutions with the same active ingredients, recipients and route of administration as the original product.

b) Oral products not intended for systemic absorption

c) Oral solutions with the same active ingredients as the original products and with no excipient interfering with their absorption, and not containing active ingredients with narrow therapeutic and/or safety indicies.

d) Products reformulated by the original manufacturer to change inactive ingredients like colouring agents, flavouring and preservatives, which do not interfere with bioavailability
e) Gases
f) Powders for reconstitution as solutions to be used as in parenteral or oral solutions

g) Ophthalmic or topical aqueous solutions with the same active ingredient(s), similar excipients and similar quantitative composition as the original product Inhalation liquid products containing the same active ingredients and with a similar quantitative composition as the original product

2.1 in vivo bioequivalence studies

Provide details of bioequivalence studies, conducted to establish the bioequivalence of the product, which is the subject of the application to the reference product. The study report should include among other things the following;

i)Justification for the selected procedure to establish bioequivalence

ii)Drug and drug product information (for test and reference); batch details, number, manufacturing site and date, expiry date, specifications

iii) Responsible investigators their curriculum vitae, affiliation and signature

iv) Protocol and study design; (objectives, ethical considerations, subject selection, conduct of the study, drug administration, food intake, sample collection, storage, bioanalytical methods and validation results, pharmacokinetics parameters measured and results Justification for the chosen design (e.g. cross over or replicated design) measures taken to minimize intra and inter-animal variability and elimination of bias.

(a) All possible factors that may influence the product pharmacokinetics must be standardized e.g. fluid intake, food intake, exercise etc.

(b) Drug product
Must be identical to the intended commercial product in every respect; same manufacturing site and same composition (qualitative)
Samples should be from commercial scale production.

(c) Population

Sample size shall depend on the intra-animal co-efficient of variation CV if low say < 15%; n = 14, > 30%; n = 44) healthy young animal.

(d) Parameters to be measured: (AUC, Cmax, tmax, Aet. dAet/dtmax.. The shape and area under plasma concentration curve or cumulative excretion profiles.

(vi) The results, data and statistical procedures should be detailed enough to allow for repeat analysis if necessary.

Preferably the two one sided statistical test should be carried out using log – transformed data to show that the ratio of AUC and Cmax of the generic to the

reference or innovator is within the acceptance limits of 0.8-1.25 at the 90% confidence interval.

2.2 In vitro dissolution testing

Therapeutic equivalence may be assessed by the use of in vitro dissolution testing in the following circumstances:

a) Drugs not defined above (not applicable for drugs defined above)

b) Different strengths of a generic formulation manufactured by the same manufacturer at the same manufacturing site where:

i) The qualitative composition between strength is essentially the same.

ii) The ratio of active ingredients and excipients is essentially the same or, in the case of small strengths, the ratio between the excipients is the same.

iii) An appropriate equivalent study has been performed on at least one of the strengths of the formulation.

iv) In case of systemic availability pharmacokinetics have been shown to be linear over the therapeutic dose range.

v) Highly soluble and highly permeable >80% in 15 minutes - Biopharmaceutical Classification System (BCS).

c) The dissolution profile is determined rather than a single point determination. The protocol of individual comparative dissolution profile studies shall include:

i) Apparatus

Use the basket method at 50/120 rpm, or paddle method at 50/75 rpm

ii) Medium

- aqueous medium, pH 1.2, 4.5, 6.8
- for sparingly water soluble drugs: use of surfactants

- 500 - 1000mL; 37°C ± 0.5°C

iii) Sampling time

- 15 minute intervals until 85% dissolution (immediate release products)
- 60 minutes, at 50% dissolution, and at 80% dissolution (for modified release products)

iv) Results

Dissolution profiles in different media (tables and graphs)

Statistical treatment

$f1 = \{ [\sum_{t=1}^{n} (R_t - T_t)] / [\sum_{t=1}^{n} R_t] \} \times 100$

$f2 = 50 \times \log \{ [1 + (1/n) \sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \times 100 \} k$

where Rt and Tt are the cumulative % of dissolved active substance at each of the selected n time points.

f1 is proportional to the average difference between the two profiles (difference factor)

f2 is inversely proportional to the average squared difference between two profiles and measures the closeness between the two profiles (similarity factor)

Since the interest is to know how similar the profiles are, f2 is used.
If the two products produce identical results at all time points, f2 = 100.

If there is an average difference of 10% in the results at all time points results, f2 = 50.

Acceptance criteria

f2 should be between 50 and 100

In cases where bioequivalence studies are not suitable e.g. for non solution drug product for non systemic use, example oral, nasal, ocular, dermal, rectal or vaginal: comparative clinical or pharmacodynamics studies can be done to prove therapeutic equivalence.

(i) Comparative pharmacodynamics studies

Describe the study protocol including the study design, pharmacological or biochemical response measured, measuring instruments used results, statistical methods used and their justification. Tabulation and graphical illustration of results and conclusion.

a. A cross-over design is preferred and where it is not appropriate a parallel design is acceptable. The study design must consider the pathology and natural history of the condition.

b. Studies should be done in healthy subjects or in patient if the disease affects the actions/responses studied.

c. Inclusion/exclusion criteria must be stated and non-responders should be identified and excluded prior to begin the study.

d. Measured pharmacological response should be relevant to the claimed therapeutic uses where there are more than one therapeutic use studies should be done to demonstrate the therapeutic equivalence for each use.

e. Measurement of responses should as far as possible be quantitative, measured under double blind conditions and be recorded in an instrument producer/instrument recorded fashion. The methodology must be validated for precision, accuracy, reproducibility and specificity.

f. The principles of Good Veterinary Clinical Practice (GVCP) and Good Laboratory Practice (GLP) should be adhered to during the study.

g. Where possible the effect can be graphically illustrated using the area under the effect time curve, maximum effect and time of maximum effect.

In using pharmacodynamics methods, the following requirements must be satisfied:

i) The response can be measured precisely over a reasonable range

ii) The response can be measured repeatedly to obtain time-course from the beginning to end of the response

iii) It should be possible to derive the common parameters of comparison.

iv) It should be possible to derive the common parameters of comparison like Cmax, Tmax and AUC

The test and reference product should not produce a maximal response during the course of study.

(ii) Comparative clinical trial Describe in detail the study protocol, which should, include the title of the study investigator(s), location, justification and objective, dates, time, duration, observation periods and justification thereof, study design (randomization methods description of design e.g. cross-over or parallel etc), inclusion, exclusion, criteria, methods and treatments, specification of comparator and placebo, results (definition of ethical endpoints measured, methods, measured and recording clinical response (scoring system for endpoints).

Statistical methods used and their justification.

a) Comparative clinical studies is required in cases where bioequivalence or pharmacodynamic studies cannot be done i.e. when plasma concentration time profile data is not suitable to assess therapeutic equivalence or lack of meaningful
b) pharmacodynamics parameters which, are measured (quantified).

b) The number of animal chosen and acceptance limits should be justified (usually higher than for BE studies).

PART VI

1.0 LABELING AND PACKAGE INSERTS

1.1. Labelling

Every immediate and outer container of any medicinal product shall be labelled in clearly legible indelible letters in Kiswahili or English or both.

The batch number, manufacturing and expiry dates must unless otherwise justified be embossed or engraved in the label of the container

Over the counter or general sales medicines shall be labelled in Kiswahili or Kiswahili and English.

The immediate and where available the outer container packaging label shall include at least the following:

(a) The name of the VMP.

(b) Method of administration.

(c) A list of active substance(s) (using INNs if applicable) showing the amount of each present in a dosage unit, and a statement of the net contents of the container, e.g. number of dosage units, weight or volume.

(d) Indication(s) and recommended dosage per target species where practicable

(e) The batch number assigned by the manufacturer.

(f) The manufacturing and expiry dates.

(g) Storage conditions or handling precautions that may be necessary.

(h) Directions for use and any warnings or precautions that may be necessary.

(i) "For Animal use only"

(j) Withdrawal period

(k) The name and address of the manufacturer

(l) The name and address of the company or person responsible for placing the product on the market if different from the manufacturer

(m) Tanzania registration number (to be included after approval)

(n) Forensic category

For containers of less than or equal to 10 ml capacity that are marketed in an outer pack such as a carton, and the outer pack bears all the required information, the immediate container need only contain items (a), (b), (c), (e), (f), (g), (i), (j) and (k) — or a logo that unambiguously identifies the company and the name of the dosage form or the route of administration.

1.1.1 Blisters and strips

Blisters and strips should include, as a minimum, the following information printed direct on blister or/and strip:

(a) Name, strength and pharmaceutical form of the VMP

(b) Name of the manufacturer

(c) The batch number assigned by the manufacturer

(d) The manufacturing and expiry dates

1.2. Package inserts

The product packaging shall include a prescribing information leaflet. The leaflet shall include the following minimum information:

i) International Non-proprietary Name (INN) for each active ingredient
ii) Pharmacology: a brief description of the mechanism of action and Pharmacological effects
iii) Clinical Information:

a) Indications

b) Dosage regimens

c) Contraindications

d) Precautions in pregnancy, lactation, renal and hepatic failure, etc

e) Adverse reactions including their frequency

f) Clinically significant drug interactions

g) Symptoms and treatment of overdose

h) Withdrawal period

iv) Pharmaceutical Information:

a) Dosage form

b) Strength

c) Excipients

d) Storage conditions

e) Shelf-life

f) Pack size

g) Description of product and package

h) Name and address of the manufacturer

PART VII:

DOCUMENTATION FOR FIXED DOSE COMBINATION PRODUCTS (FDC)

Documentation on fixed dose combinations with regard to summary of product characteristics, quality of active ingredients and chemistry, manufacturing and quality controls of finished product, stability and bioequivalence should be in the way as for the other products. However the following additional information shall be provided under the relevant Parts.

For the purposes of these guidelines FDCs are grouped into three categories; generic FDCs or FDCs whose all APIs are well established and their concurrent use is standard of care; FDCs whose all APIs are well established but their concurrent use are unknown; and FDCs with one or more new chemical entities.

Developmental pharmaceutics, pharmacokinetic and pharmacodynamics studies of FDCs in category II and III should demonstrate that the individual components:-

a) Are pharmaceutically compatible,
a) Have similar pharmacokinetics,
b) Do not require relative dose adjustments,
c) Have no potential of deleterious drug interactions between them,
d) Their chemistry is compatible with co-administration.

1. Generic FDCs, or FDCs whose all APIs are well established and their concurrent use is standard of care

This category consists of FDC products:-
a) Developed as a generic equivalent to an existing FDC.
b) Whose APIs are already approved, well characterized, with well documented clear evidence of safety and /or efficacy advantage of being used together or concurrent use of component drugs is already standard of care at the same dosage regimen (well characterized as safe and effective e.g. antituberculous combinations).

For such products documentation of studies done to demonstrate bioequivalence shall be sufficient. Generally no toxicology studies are needed, provided international acceptable excipients are used .The documentation shall include data or literature in support of the safety and efficacy of the combination. However non-clinical

pharmacology or toxicology studies and clinical efficacy studies in support of the proposed indication may be required if the proposed indication involves either a higher dose level or duration than currently licensed for one or more of the active ingredients in the fixed dose combination. Alternatively, toxicological studies may be needed if there is potential for a drug interaction or overlapping toxicity.

2. FDC whose all components are well established but their concurrent use effects are unknown

These consist of individual components which are well characterized for safety and efficacy when used alone, however, the efficacy and safety of their concurrent use is not well established (risks), or where two or more well characterized individual products are combined using novel dosage regimens or where the claimed benefit of the combination is untested or hypothetical.

For such products formulation studies should be carried out to establish pharmaceutical compatibility and finished product quality control specifications and the following data be submitted in appropriate Parts:

Appropriate pharmacokinetic and/or pharmacodynamics studies data (studies must be appropriate to the claim) of studies carried out to investigate the potential for favorable or unfavorable interactions between the components. These include:

a) Pre clinical toxicological studies and dose escalation studies when there is potential for a drug interaction or overlapping toxicity.

b) Comparative clinical studies of the FDC versus a reference product or a regimen used as part of standard of care for the same indication to be demonstrate clinical superiority or non-inferiority and contribution each component within the combination to the claimed effect.

The clinical superiority or advantages may include:

(i) Increased efficacy (additive or synergistic)
(ii) Reduced toxicity
(iii) Prevention of antimicrobial resistance
(iv) Bolstering of drug levels
In situations where monotherapy does not satisfy the standard of care, the aggregate of data supporting the combination may include historical clinical data on the

components used alone, pharmacokinetic data, animal data, in vitro microbiological data, etc

3. FDCs with one or more new APIs.

These consist of one or more new molecular entities.
Documentation required in appropriate Parts includes:

(i) Complete data demonstrating the quality, safety and efficacy of each of the individual active ingredients.
Individual components that are being considered for inclusion in a FDC should have a well-established risk-benefit profile in the target population at the recommend dosing regimens. Consideration should be given to ethnic, environmental, co-morbid, and nutritional variations between populations

(ii) comparative preclinical and clinical studies safety and efficacy data of the FDC demonstrating clinical superiority or non-inferiority when compared to another product or regimen used as part of standard of care for the same indication.

Comparators or comparator regimens should represent the current state of the art treatment for the indication in question.

The comparators should be licensed innovator products.

iii) Microbiological evaluation

Microbiological evaluations may be done to determine the advantage of combinations of active ingredients over individual active ingredients for a given pathogen where clinical trials of monotherapy are inappropriate or unethical. Data from the following types of studies shall be submitted.

a) Microbiologic activity in vitro against laboratory strains and clinical isolates of the targeted pathogen(s):

a) Microbiological activity in appropriate animal models of infection with the targeted pathogen(s),
b) Microbiologic activity against resistant isolated/strains of the targeted pathogen(s) in the geographic areas in which the product is intended to be used in patients, and

c) Characterization of the mechanism by which the active ingredients exhibit additive, or synergistic, microbiologic effect(s) on the targeted pathogen(s).

d) In addition, the potential for antagonistic effects should be excluded, as this may compromise clinical efficacy.

e) Investigation of microbiologic activity at Cmin concentrations may be needed where concerns exist about sub therapeutic trough levels. For such cases Cmin should be evaluated in human bioequivalence studies,(see bioequivalence section).

Clinical and microbiological endpoints should be selected that are relevant for the indication. For example, where a combination is designed to reduce the development of anti-malarial drug resistance, endpoints might be the frequency of new drug resistance, as well as the overall clinical outcome following the use of the drug.

4.0 Bioequivalence studies for FDC

Bioequivalence studies for generic FDC are essentially conducted and documented in a similar way as for other generic products except that the FDC may be compared to a single active ingredient reference product (principle of pharmaceutical equivalence is disregarded).

In conducting pre clinical, clinical or bioequivalence studies Good Laboratory and Clinical Practices should be adhered to.

Appendix I:
ANATOMIC THERAPEUTIC CHEMICAL CLASSIFICATION SYSTEM (ATC)

The anatomic therapeutic chemical system serves as a basis for classifying drugs according to therapeutic indications. It is made up of an alphabet, 2 numerals and ends with an alphabet. Example A01B and interpreted as shown below:

A - Anatomical main group
01 - Therapeutic main group
B - Therapeutic subgroup

The main group of the ATC classification system is:-

A - Alimentary tract and metabolism
B - Blood and blood forming organs
C - Cardiovascular system
D - Dermatological
G - Genito-Urinary System and Sex Hormones
H - Systemic hormonal preparations, excl. sex hormones
J - General anti-infectives, systemic
L - Anti-neoplastic and immunosuppressive drugs
M - Musculo – skeletal system
N - Central nervous system
P - Anti-parasitic products
R - Respiratory system
S - Sensory organs
V - Various

A: ALIMENTARY TRACT AND METABOLISM

A01 Stomatologicals, mouth preparations

A Stomatologicals, mouth preparations

A02 Antacids, antiflatulents and antipeptic ulcerants

A Antacids and antiflatulents

B Antipeptic ulcerants

C Others

A03 Gastrointestinal antispasmodics and anticholinergics

A Synthetics, incl. Papaverine

B Belladonna and derivatives, pain

C Antispasmodics in combination with psycholeptics

D Antispasmodics in combination with analgesics

E Other combinations

A04 Antiemetics and antinauseants

A Anti-emetics and antinauseants

A05 Cholagogues and hepatic protectors

A Bile therapy, cholagogues and choleretics

B Hepatic protectors, lipotropics

C Cholagogues and lipotropics in combination

A06 Laxatives

A Laxative

A07 Antidiarrhoeals, intestinal antiinflammatory/antiinfective agents

A Intestinal anti-infectives

B Intestinal adsorbents

C Electrolytes with carbohydrates

D Antipropulsives

E Intestinal anti-inflammatory agents

F Antidiarrhoeal microorganisms

X Various antidiarrhoeals

A08 Antiobesity preparations excl. diet products

A Antiobesity preparations, excl. diet products

A09 Digestives, incl. Enzymes

A Digestives, incl. Enzymes

A10 Antidiabetic therapy

A Insulins and other parenterals

B Oral antidiabetics

A11 Vitamins

A Multivitamins, combinations

B Multivitamins, plain

C Vitamin A and D, incl. combinations of the two

D Vitamin B1, plain and in combination with Vitamin B6 and B12

E Vitamin B – Complex incl. combinations

G Ascorbic acid (Vitamin C), incl. combinations

H Other plain vitamin preparations

J Other vitamin products, combination

AB12 Mineral Supplements

A Calcium

B Potassium

C Other Mineral supplements

A13 Tonics

A Tonics

A14 Anabolics, systemic

A Anabolic steroids

B Other anabolic agents

A15 Appetite stimulants

A16 Other alimentary tract and metabolism products

B BLOOD AND BLOOD FORMING ORGANS

B01 Anticoagulants

A Anticoagulants

B02 Antihaemorrhagics

A Antifibrinolytics

B Vitamin K and Others

B03 Antianaemic preparations

A Haematinics, iron and all combinations

B Vitamin B12 and folic acid

B04 Cholesterol reducers, antiatheroma preparation

A Cholesterol reducers, antiatheroma preparations

B05 Plasma substitutes and perfusion solutions

A Blood and related products

B I.V. solutions

C Irrigating solutions

D Peritoneal dialytics

X I.V. solution additives

Z Haemodialytics

B06 Other haematological agents, incl. Fibrinolytics and hyaluronidase

A Other haematological agents, incl. Fibrinolytics and hyaluronidase

C CARDIOVASCULAR SYSTEM

C01 Cardiac therapy

A Cardiac glycosides

B Antiarrhythmics

C Antiadrenergic agents, ganglion – blocking

D Arteriolar smooth muscle, agents acting on

E Renin – angiotensin system, agents acting on

K Other hypotensives

L Hypotensives and diuretics in combination

C02 Diuretics

A Low – ceiling diuretics, thiazides

B Low – ceiling diuretics, excl. thiazides

C High – ceiling diuretics

D Potassium – sparing drugs

E Diuretics and potassium – sparing drugs in combination

C03 Peripheral vasodilators

A Peripheral vasodilators

C04 Vasoprotectives

A Antihaemorrhoidals, topical preparations

B Antivaricose therapy

C Capillary stabilizing agents

C05 Beta blocking agents

A Beta blocking agents, plain

D DERMATOLOGICALS

D01 Antifungals, dematological

A Antifungals, topical preparations

B Antifungals, systemic preparations

D02 Emollients and protectives

A Emollients and protectives

D03 Cicatrizants, excl. medicated dressings

D04 Antipruritics, incl. Antihistamines, Anaesthetics, etc.

A Antipruritics, incl. Antihistamines, Anaesthetics, etc.

D05 Coal tar, sulphur and resorcinol products

A Coal tar, sulphur and resorcinol products

D06 Antibiotics and chemotherapeutics, dermatologicals

A Antibiotics, topical preparations

B Chemotherapeutics, topical preparations

C Antibiotics and chemotherapeutics, combinations

D07 Corticosteroids, dermatological preparations

Corticosteroids, plain

B Corticosteroids, combinations with antiseptics

C Corticosteroids, combinations with antibiotics

X Corticosteroids, other combinations

D08 Antiseptics and disinfectants

A Antiseptics and disinfectants

D09 Medicated dressings

A Medicated dressings

D10 Antiacne preparations

A Anti – acne preparations

D11 Other dermatological preparations

G GENITO-URINARY SYSTEM AND SEX HORMONES

G01 Gynaecological antiinfectives and antiseptics

A Antiinfectives, excl. combinations with corticosteroids

B Antiinfectives and corticosteroids in combination

G02 Other gynaecologicals

A Oxytocics

B Topical contraceptives

C Other gynaecologicals

G03 Sex hormones and stimulants of the genital system

A Hormonal contraceptives, systemic

B Androgens and combinations, excl. G03E

C Estrogens and combinations, excl. G03E, G03F and antiandrogens and estrogens

D Progesterones and combinations, excl. G03E and G03F

E Androgens and female sex hormones in combination

F Progestogens and estrogens in combination

G Gonadotrophins and other ovulation stimulants

H Antiandrogens and combinations

X Other sex hormones

G04 Urologicals

A Urinary antiseptics and antiinfectives

B Other urologicals, incl. Antispasmodics

H SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES

H01 Pituitary hormones

A Anterior pituitary lobe hormones

B Posterior pituitary lobe hormones

H02 Systemic corticosteroids

A Systemic corticosteroids, plain

B Systemic corticosteroids, combinations

C Antiadrenal preparations

H03 Thyroid therapy

A Thyroid preparations

B Antithyroid preparations

C Iodine therapy

H04 Pancreatic hormones

A Glycogenolytic hormones

H05 Calcium homeostasis

A Parathyroid hormones

B Antiparathyroid hormones

J GENERAL ANTIINFECTIVES, SYSTEMIC

J01 Systemic antibiotics

A Tetracyclines

B Chloramphenicol

C Penicillins with increases effect on Gram – negative bacilli

D Cephalosporins

E Trimethoprim, excl. combinations with sulphonamides

F Macrolides

G Streptomycins

H Penicillins

J Penicillin and streptomycin in combination

K All other antibiotics

J02 Systemic antimycotics, excl. griseofulvin

A Systemic antimycotics, excl. griseofulvin

J03 Systemic chemotherapeutics

A Sulfonamides

B Sulfonamides and antiinfectives in combination

C Other chemotherapeutics

J04 Tuberculostatics, excl. streptomycin

A Tuberculostatics, excl. streptomycin

J05 Systemic antivirals

A Agents affecting the virus directly

B Immunostimulating agents

C Agents with immunostimulants and antiviral activity

J06 Immune sera and immunoglobulins

A Immune sera

B Immunoglobulins

J07 Vaccines

A Vaccines

J08 Other antiinfectives, incl. Leprostatics

A Other antiinfectives, incl. Leprostatics.

L ANTI-NEOPLASTIC AND IMMUNOSUPPRESSIVE DRUGS

L01 Cytostatic drugs

A Alkylating agents

B Antimetabolites

C Plant alkaloids and other natural products

D Cytotoxic antibiotics

X Various cytostatics

L02 Hormone therapy

A Hormones

B Anti-hormones

M MUSCULO – SKELETAL SYSTEM

M01 Anti-inflammatory and anti-rheumatic products

A Anti-inflammatory and anti-rheumatic products pre – steroids

B Combinations with corticosteroids

M02 Topical products for joint and muscular pain

A Topical products for joint and muscular pain

M03 Muscle relaxants

A Peripherally acting agents

B Centrally acting agents

C Directly acting agents

M04 Antigout preparations

A Antigout preparations

M05 Other drugs for disorders of the musculo – skeletal system

A Other drugs for disorders of the musculo – skeletal system

N CENTRAL NERVOUS SYSTEM

N01 Anaesthetics

A Anaesthetics, general

B Local anaesthetics, excl. dermatologicals

N02 Analgesics

A Narcotics

B Other analgesics and antipyretics

C Anti-migraine preparations

N03 Anti-epileptics

A Anti – Parkinson drugs

N04 Psycholeptics

A Neuroleptics

B Tranquilizers

C Hypnotics and sedatives

N05 Psychoanaleptics

A Antidepressants

B Psychostimulants

C Psycholeptics and psychoanaleptics in combination

N06 Other CNS drugs, incl. Parasympathomimetics

A Parasympathomimetics

P ANTI-PARASITIC PRODUCTS

P01 Antiprotozoals

A Amoebicides and similar

B Antimalarials

X Other antiprotozoals

P02 Antihelmintics

A Schistosomicides

X Other antihelmintics

P03 Ectoparasiticides, incl. Scarbicides

A Ectoparasiticides, incl. Scarbicides

R RESPIRATORY SYSTEM

R01 Nasal preparations

A Nasal decongestants, topical preparations

R02 Throat preparations

A Throat preparations

R03 Anti-asthmatics

A Bronchodilators and other anti – asthmatics, excl. R03B

B Respiratory stimulants

R04 Chest rubs and other inhalants

A Chest rubs and other inhalants

R05 Cough and cold preparations

A Cold preparations without antiinfectives

B Cold preparations with antiinfectives

C Expectorants, excl. combinations with antitussives

D Antitussives, excl. combinations with expectorants

E Systemic nasal decongestants

F Antitussives and expectorants, combination

R06 Antihistamines for Systemic use

A Antihistamines for systemic use

S SENSORY ORGANS

S01 Ophthalmologicals

A Antiinfectives

B Corticosteroids

C Corticosteroids and antiinfectives in combination

D Other ophthalmologicals

S02 Otologicals

A Antiinfectives

B Corticosteroids

C Corticosteroids and antiifectives in combination

D Other otologicals

S03 Ophthalmological and otological preparations

A Antiinfectives

B Corticosteroids

C Corticosteroids and antiinfectives in combination

D Other ophthalmological preparations

V VARIOUS

V01 Allergens

A Allergens

V02 Immunosuppressive drugs

C Immunosuppressive drugs

V03 All other therapeutic products

A All other therapeutic products

V04 Diagnostic agents

A Contrast media

B Urine tests

C Other diagnostic agents

V05 Surgical antiseptics

V06 General nutrients

A Slimming preparations

B Protein supplements

C Infant formulas

D Other nutrients

V07 All other pre – therapeutic products

A All other pre – therapeutic product

Appendix II: Guidelines to Analytical method validation

1. Types of analytical procedures requiring validation

a) Identification tests
b) Quantitative test for impurities content
c) Limit tests for control of impurities
d) Quantitative tests for active ingredients assay

2. Analytical performance parameters

2.1 Accuracy

2.1.1 Definition: exactness of result obtained by analytical method relative to the true value

2.1.2 Expressed as % recovery:

Ratio of mean of observed measurements x 100 true mean

2.1.3 Measurements: minimum of three measurements each at three concentrations spanning 50% - 150% of the working range of the method using reference standards

2.1.4 Acceptance criteria: recovery should be 98% - 102%.

2.2 Precision

2.2.1 Definition: degree of deviation from mean of observed measurements using the method.

2.2.2 Repeatability precision: same instrument, analyst, laboratory and day

2.2.3 Intermediate precision: same laboratory and instrument, different analyst

2.2.4 Reproducibility: different instrument, analyst, laboratory and day.

2.2.5 Measurements: minimum of 3 measurements each at 3 different concentrations within the range, and six measurements at 100% of the expected normal working concentration, using reference standards

2.2.6 Acceptance criteria: RSD = 2%

2.3 Specificity

2.3.1 Definition: ability of the method to discriminate quantitatively and qualitatively between test substances from related substances.

2.3.2 Measurements: resolution between chromatographic peaks of test substances and added impurity for assay methods. Presence of positive control peak and absence of peak for negative control in identification methods

2.3.3 Acceptance criteria: chromatogram analysis.

2.4 Limit of detection

2.4.1 Definition: lowest concentration detectable by the method

2.4.2 Measurement: chromatography analysis

2.4.3 Acceptance criteria: the ratio of the peak to background height (signal: noise ratio) should be at least 3:1.

2.5 Limit of quantitation

2.5.1Definition: the lowest concentration measurable with precision and accuracy by the method.

2.5.2 Measurement: chromatography analysis

2.5.3 Acceptance criteria: signal: noise ratio should be at least 10:1

2.6 Linearity

2.6.1 Definition: the ability of the method to produce results that are directly proportional to the actual concentration of test substances within a given range

2.6.2 Measurements: minimum of 6 measurements each at 5 different concentrations covering 50% - 150% of expected normal working concentrations. Plot graph of true concentration (x) versus observed result (y), determine Y intercept and coefficient of regression.

2.6.3 Acceptance criteria:
i) Regression coefficient should be = 0.98

ii) Y intercept should be at 0.

2.7 Range

2.7.1 Definition: the interval between the lowest and highest concentration at which the method is demonstrated to be precise, accurate and linear

2.7.2 Measurement: as above

2.7.3 Acceptance criteria

i) Active Pharmaceutical Ingredient (API): 80% -120% of expected test concentration

ii) Uniformity of content of Final Product (FP): 70% - 130% of expected test concentration

iii) Impurity tests: from reporting level to 120% of the maximum allowable limit.

2.7.4 Therefore linearity range should be greater than working range.

2.8 Robustness

2.8.1 The ability to remain unaffected by small variations in instrument conditions.

2.9 Ruggedness

2.9.1 Reproducibility precision.

3. Types of validation tests for different analytical tests

Analytical performance **Parameter to be tested**	**Identification test**	**Assay of impurity**	**Limit test for impurity**	**Assay of active drug**
Accuracy	X	✓	X	✓
Repeatability precision		✓	X	✓
Intermediate precision	i. X	✓	X	✓
Reproducibility precision	X	✓	X	✓
Specificity				
Limit of detection	X	X		X
Limit of quantitation	X	✓	X	X
Linearity	X	✓	X	✓
Range	X	✓	X	✓

Text Box: For official Use Only
Application No.:……..
Date Received:…….

Appendix III

APPLICATION FORM FOR REGISTRATION OF A VETERINARY MEDICINAL PRODUCT

1. Particulars of applicant
Name:……

Physical Address:……..

Postal address:……..

Telephone No.:…….Telefax No.:……

Email:……

Website:…….

2. Particulars of the Manufacturer(s) and Activity

Name Physical address of Activity

Production Site

1. ……..……..

2. ……..……..

3. ……..……..

(Attach copies of cGMP certificate from the country of origin drug Regulatory Authority local (DRA) for each site)

3. Particulars of Local Responsible Person
Name:…….……

Postal Address:……..

……

Telephone No.:…….…. Telefax No.:……

E-mail:……

Website:…….

4. Particulars of the medicinal Product
Proprietary name (Trade name)…….
Approved name
(INN/Generic)…….……

Dosage form……

Strength……..

Description of the product (colour, shape, size, etc)
……

Commercial presentation (packaging and pack sizes applied for in which stability studies were conducted):
……..……

Route of administration……..

…….

Distribution category requested (POM/OTC):
……..……

ATC Classification:

……

Country of manufacture ……....

Shelf life in months:……..

Storage conditions:……...

Pharmaceutical formula of the product in terms of unit dose:

Description of the ingredients:

Name(s)of ingredients and specification(s)	**Quantity**	**State whether Active/excipient/other**	**Reason(s) for inclusion**	

The chemical name, molecular and structural formulae of the active ingredient(s):

…….
…….
…….

6. Specifications of Packaging material

Primary container(s):
……
……..
…….

Secondary container(s):

……..
……
……..……

7. Current Registration Status

State the names of all countries (including the country of manufacture) where the product is registered

……
……..…
……

If not registered in country of manufacture, give reasons

……
……
……

If the drug has been rejected/refused/deferred/cancelled/withdrawn in any country or territory supply details:

……
……..

Is the product under patent?
Yes/No:……....

If yes, provide name of Patent holder:……

Expiry date of the Patent:……

8. Certificate of a Pharmaceutical Product (WHO type)

Submit a certificate of a pharmaceutical product WHO type (current format) together with a copy of approved product information sheet.

9. Chemistry and Pharmaceutical Data on Dosage Form

Raw material (active /inactive) specifications including manufacturing processes and analytical control procedures carried out as release requirements:

……
……

Details of manufacturing procedures including packaging and equipment used:
……
……..
……..

In-process controls performed:
……
……
……

Final product specifications and analytical control procedures carried out as release requirements:
……..
……..…
……..

Stability data based on a minimum of three batches:
……
……..…

Complete batch records relating to one production batch:

……
……

Summary of the experiments and results performed on the drug to confirm its physiological availability:
……
……

10. Toxicology and Pharmacology

Particulars of toxicological studies done (target species, users,consumers and the environment):

……..…
……..

Particulars of therapeutic effects and indications:

……
……

Particulars of clinical trials and pharmacological studies:

……..
……..

For specified category of products, provide proof of field trials performed in a member state/region, endorsed by the relevant authority:

……..
……

Particulars of side effects, contraindications, etc. of the product:

……
……

Data relating to the pharmacokinetics and bioavailability of the drug in animals, bioequivalence data for generics including full reference product details:

……
……..……

Details of drug residues and withdrawal periods in species intended for human consumption:

……
……..…

11. Supporting documents and materials

Samples:

Provide a minimum quantity of the product in commercial pack to conduct two sets of full analysis,

For non-pharmacopoeia products, provide a minimum of 200mg of reference standards with the corresponding Certificate of Analysis,

Product information:

Provide copies of package inserts, labels and samples of packaging materials,

Provide samples of the proposed advertising and promotional materials,

12. Declaration

I, the undersigned hereby apply for registration of the product detailed above and declare that all the information contained herein and in the annextures is correct and true.

I enclose a fee of US $:…… Bankers Cheque No……

Date:……

Signed:…….……

Full name of Signatory:……

Official designation and qualification:…….

(Official Stamp)

NB

The signatory shall be a person responsible for the release of the product working for and/or authorized by the applicant. The designation and qualification shall be stated.

Appendix IV Schedule of Fees

1. Application fee for registration of a generic medicinal product to be imported……..US$ 500.00 and locally manufactured……. US$ 100
2. Application fee for registration of a new medicinal product……..US$ 500.00
3. Application fee for registration of a medicinal product for clinical trial……..US$ 500.00
4. Application fee for a minor variation of a registered medicinal product ……..US$ 20.00
5. Pre-registration inspection fee for of a manufacturing facility ……..US$ 3000.00 per site for overseas facilities and US$ 100.00 for Tanzania based facilities