



ZAMBIA MEDICINES REGULATORY AUTHORITY

GUIDELINES ON APPLICATION FOR REGISTRATION OF VETERINARY MEDICINES

First Edition

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Foreword

The Pharmaceutical Act (No. 14) of 2004 requires that veterinary medicinal products intended to be marketed in Zambia meet acceptable standards of quality, safety and efficacy and at the same time be assessed to have been manufactured in facilities which comply with current Good Manufacturing Practices (cGMP).

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

These guidelines have been prepared to provide information to applicants who intend to register veterinary medicinal products in Zambia.

This document has been developed by the Pharmaceutical Regulatory Authority (PRA) to provide guidance to applicants on the content and format of the dossier in respect of products submitted for registration. These guidelines also indicate the order of the material to be submitted and the minimum requirements for product registration.

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

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

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

Dr S.M. Miti
PERMANENT SECRETARY
Ministry of Health

Acknowledgements

The Ministry of Health (MoH) and the Pharmaceutical Regulatory Authority (PRA) wish to acknowledge the immense contributions of individuals and organisations that constituted the Technical Working Group in developing these guidelines. The principal contributors for this guidance document were:

- | | |
|----------------------------|--|
| 1. Professor Karashani: | Ethics & Research Committee, UTH |
| 2. Ms Esnat Mwape: | Director General, PRA |
| 3. Dr Yona Sinkala: | Veterinary Surgeon, Dept. of Veterinary
& Livestock Development, Lusaka |
| 4. Dr G. Chishimba: | Medical Practitioner, National AIDS
Council |
| 5. Ms Anne Zulu: | Pharmacist, Medical Stores Limited |
| 6. Dr K Choongo: | Lecturer, UNZA School of Veterinary
Medicine |
| 7. Ms Loyce Lishimpi: | National Profession Officer, WHO |
| 8. Mrs. Caroline M. Yeta: | Director-Inspectorate & Licensing, PRA |
| 9. Mrs. Bernice C. Mwale: | Director-Product Registration, PRA, |
| 10. Mr. Felix P. Chizu: | Regulatory Officer, PRA |
| 11. Dr Zuma Munkombwe: | Regulatory Officer, PRA |
| 12. Mr. Pelekelo Mangisha: | Assistant Regulatory Officer, PRA |

The MoH and PRA would further like to thank the World Health Organisation (WHO) for providing financial and technical support to the development of these guidelines.

Ms E. Mwape

DIRECTOR-GENERAL

Pharmaceutical Regulatory Authority

ABBREVIATIONS

µg Microgram

API Active Pharmaceutical Ingredient

ATC Anatomic Therapeutic Chemical classification

AUC Area under the plasma concentration time curve

BE Bioequivalence studies

BP British Pharmacopoeia

CASR Chemical Abstract Service Registry Number

cGMP current Good Manufacturing Practices

CI Confidence Interval

C_{max} Maximum plasma concentration

CV Coefficient of Variation

e.c Enteric coated

f.c Film coated

FDC Fixed Dose Combination

FDC Fixed dose combination

FP Finished Product

GCP Good Clinical Practice

GLP Good Laboratory Practice

GMP Good Manufacturing Practice

GS General Sale

GVCP Good Veterinary Clinical Practice

HPLC High power Liquid Chromatograph

i.m Intramuscular

i.v Intravenous

INN International Non-proprietary Name

IP International Pharmacopoeia

IR Infra red spectroscopy

IU International Unit

IUPAC International Union for Pure and Applied Chemistry

JP Japanese Pharmacopoeia

M.R Modified Release

mg Milligram

ml Millilitre

MRA Medicines Regulatory Authority

OIE Office International des Epizooties

P Pharmacy

Ph. Eur European Pharmacopoeia

POM Prescription Only Medicines

PRA Pharmaceutical Regulatory Authority

Requirements for Registration of Veterinary Medicines

RF values-Retention factors

RH Relative Humidity

s.c Sugar coated
SPC Summary of Product Characteristics
SR Sustained release
TE Therapeutic Equivalence
TLC Thin layer chromatography
T_{max} Time to reach maximum plasma concentration
USP United States Pharmacopoeia
VICH International Conference on Harmonization of Technical
VM Veterinary medicines
VMP Veterinary Medicinal Product.
WHO World Health Organization

DEFINITIONS 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).

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

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

Composition composition in relation to a 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.

Veterinary Medicines, Medicinal 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 Medicines 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 competent person.

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

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

General sale Medicines (GS) means any Medicines whose use does not need the direction or prescription by a Veterinary surgeon 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.

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

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

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

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

Manufacturer means .a firm that is engaged in the manufacture of products

Fixed dose combination means a product containing Medicines in combinations (qualitative content and/or proportions) different from those products that are subject of current pharmacopoeias

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

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

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

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

Retention fee means a fee paid annually to maintain product licence.

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

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

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

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

OIE World Organisation for Animal Health.

Meat animal tissue used as food.

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

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

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

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

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

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

1. GENERAL INFORMATION

- 1.1 These guidelines apply to all veterinary medicinal products (VMPs) except vaccines, 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 ENGLISH Language. Where originals are in another language, copies shall be presented together with certified English translations.

(a) 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 but stability study report is required for each package material of different technical specifications. Applications shall be made by submitting a dully filled in prescribed application form. An application should 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 ZAMBIA
- iii). A non-refundable application fee
- iv). 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 should 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 the BP, EU, USP or other recognized pharmacopoeias and other specifications may be accepted if they are validated.

Table I: Parts required for each type of medicinal product

APPLICATION TYPE		PARTS REQUIRED					
		I	II	III	IV	V	VI
		SPC	API	FP	Non clinical pharmacotoxicological data	Clinical Safety & Efficacy Data	TE
1	Innovator	√	√	√	√	√	X

	product						
2	Innovator fixed dose combination	√	√	√	√	√	X
3	Innovator variants: either as single or composite variation in dosage level, form, route of administration , or indication	√	√	√	Bridging studies data	Bridging studies data	X
4	Single active ingredient or fixed dose combination multi source/generic product	√	√	√	X	X	√

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

- v). Zambia-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.
- vi). Two (2) samples of the smallest commercial pack(s) with the respective certificate of analysis. However, in case of
 - a). Tablets or capsules if the total number of tablets of the five commercial packs is less than 200 tablets or capsules, additional packs should be supplied to bring the total to a minimum of 200.
 - (b) 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. additional samples maybe requested for in the event of extra requirements by the laboratory.
- vii). At least 100mg of sealed working standard for new medicinal products
- vii). 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 amendment of product licence

Whenever a product licence holder wishes to make any alteration to a registered product he should apply to and obtain approval from the Authority before introducing it in ZAMBIA. 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) Samples of the altered product.
- iii) A prescribed non-refundable amendment fee
- iv) Validation Data

(c) Application for renewal of registration

- 1.1 Applications for renewal of registration of products shall be submitted at least 90 days before the expiry date of registration.
- 1.2 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 Medicines 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.
 - vi. Non-refundable GMP inspection fee and updated site master file.
- 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 Director General, Pharmaceutical Regulatory Authority, P.O. Box 31890, LUSAKA.
- 1.5 All VMPs are registrable and should therefore be registered 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:
 - 2.1.1 A manufacturer,
 - 2.1.2 Patent holder/Owner of the formulation,
 - 2.1.3 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 should have a Local Distributor (DISTRIBUTOR) who is resident in ZAMBIA.

2.3 DISTRIBUTOR is a body corporate (company) licensed as an importer of pharmaceuticals in ZAMBIA with legal authorization to take full responsibility for the product on behalf of the applicant.

3. PARTICULARS OF THE MANUFACTURER(S)

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

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

3.1.2 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:

(i) Name & Address of manufacturing site

(ii) Activity

3.2 A copy of current Good Manufacturing Practices (cGMP) certificates from the Medicines Regulatory Authority (MRA) of the country of manufacture shall be provided for each site.

4. PARTICULARS OF THE VETERINARY MEDICINES

The following details of the veterinary medicines shall be submitted:

4.1 *Proprietary name*

4.2 *Approved/ INN / generic name*

4.3 *Strength*

4.4 *Dosage form*

4.5 *Description of the*

4.6 *Commercial Presentation*

4.7 *ATC Classification*

4.8 *Name and address of manufacturer*

4.9 *Storage conditions*

4.9.1 Store under normal storage conditions (15°C - 30°C/65+-5%RH-)

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 - 0°C (in a freezer)

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

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 2006 page -----.

4.10.4 *The 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 MRA in each case).

5.2 If not registered in country of manufacture, give reasons

5.3 If the Medicines 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 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-type 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 competent MRA.

PART II. CHEMISTRY, MANUFACTURING AND QUALITY CONTROL DATA

1.0 Active Pharmaceutical ingredient (API)

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

- i. New Medicinal substances or combination of new Medicines substances.
- ii. New Medicinal substances in combination with well established ingredients.
- iii. Products containing little known ingredients or non pharmacopoeial 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 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 annular 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.

v) 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 characterized (identified) and evidence of its safety provided
- If < 0.1%, characterization is not necessary, and quantification only is required.

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

- Limits should be pharmacopoeia 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.

(C) Impurities control and 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 Medicines substance 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)

Attach bibliography of works, reports papers or articles referenced.

- vii. Method of detection of visualization
- viii. 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 Medicines 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 Medicines 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, consistency 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:

Active ingredients/adjuvants and their quantities in:

- per unit dose
- percentage composition (w/w, w/v, v/v)
- weight per ml or
- 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 should 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.

- Quantity per unit dose;
- Percentage composition (w/w, w/v, v/v etc).

Reasons for inclusions of overage should be clearly stated.

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 or diagram 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 are 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 chart or diagram mention above.

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

- Tests of raw materials ;
- Tests on intermediate products ;and
- All operations concerning finished products ;

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 should 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 may 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:

Specifications and test methods (for all dosage forms)

- i. Description
- ii. Identity - test method should be specific for active ingredient(s)
- iii. Assay - test method should be specific and stability indicating for active ingredient(s)
- iv. Impurity limits - to determine the level of degradation products of active ingredients, and active ingredient-exciipient interaction impurities.

Additional specifications and test methods for hard gelatin capsules and tablets

- Dissolution (for relatively water insoluble active ingredients)
- Disintegration (for readily soluble active ingredients)
- Dissolution profiles for modified release preparations
- Hardness & friability
- Uniformity of content and mass (dosage units)
- Water content
- Microbial limits

Additional specifications and test methods for oral liquids

- pH
- Microbial limits
- Antimicrobial preservative content/ preservative efficacy test
- Antioxidant preservative content
- Extractables from primary container
- Alcohol content
- Dissolution of suspensions
- Particle size distribution
- Redispersibility
- Specific gravity
- Water content

Additional specifications and test methods for parenterals

- Uniformity of content and mass
- pH
- Sterility
- Endotoxins/pyrogens
- Particulate matter
- Water content
- Antimicrobial preservative content/PET
- Antioxidant preservative content
- Extractables
- Functionality of delivery systems, e.g. syringeability for prefilled syringes
- Osmolality
- Particle size distribution
- Redispersibility

All tests should be performed unless development pharmaceuticals 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:

- Raw material and packaging material requisition records
- Line clearance records
- Processing records
- Packaging records
- Reconciliation records

- Sterilization records
- Certificates of Analysis of the finished product.
- All other records as per standard 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 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, ophthalmics, 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, International Pharmacopoeia, or any other recognized 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 Medicines 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 Medicines substance or Medicines 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:

- Physical and chemical properties of the product;
- Pharmaceutical formulation
- Active ingredients
- Preservatives
- Other excipients
- Storage conditions

The storage conditions and shelf life of all pharmaceutical products should be provided. For reconstituted Medicines the manufacturer should state storage conditions and shelf life of 25 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.

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 Medicines substances, the experience gained from clinical formulation studies and stability studies on the Medicines substance. 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:

- Three (3) different batches for both stable and unstable active ingredients should be provided.
- Active ingredients should be from different raw material batches wherever possible.
- 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;

- Appearance
- Assay (stability indicating method shall be used)
- Content of decomposition products (impurities)
- Physicochemical properties, (e.g. hardness, disintegration, particulate matter, pH).
- Dissolution for all solids or semi-solid oral dosage forms;
- 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 should be done under controlled test conditions in stability chambers and not on open shelf as prescribed below. The applicant shall specify the type of stability test whether real time or accelerated.

a. Real time studies

- Test conditions $25\pm 2^{\circ}\text{C}$ / $65\pm 5\%\text{RH}$
- (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

- $40\pm 2^{\circ}\text{C}/75\pm 5\%\text{RH}$
- 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:

- New Medicines substances and product for urgent use
- New formulations for urgent use.
- New dosage forms.
- Photostability testing of new Medicines substances

4.3.3 Frequency of Testing

Frequency of testing should be sufficient to establish the stability characteristics of the Medicines substance. 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.

- Name, qualification, title and signature of the investigator should be provided.
- 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:

- Shelf life for solid dosage form should not exceed five years
- 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 Medicines 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. Pharmacodynamics
3. Toxicology
4. Expert report
5. Discussions and conclusions

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 Medicines to available data (in terms of selectivity, safety, potency etc.) on other Medicines 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 Pharmacodynamic 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 (Medicines 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 Medicines administration.

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

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

Where the product contains a combination of Medicines, the effect of use of two or more Medicines on the pharmacokinetics of one or the other Medicines 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 Medicines/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 Medicines, 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 Drug interactions

Discuss the pharmacokinetic interactions and mechanisms of interactions of the API with other compounds (Medicines 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 Medicines 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 Medicines and should be submitted for all new Medicines applications.

The investigation should, if possible, include experiments conducted with the Medicines 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 young animal 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 consumers

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 Safety assessment of veterinary Medicines residues in food of animal origin

Safety assessment of veterinary Medicines residues in food of animal origin should be performed for all new Medicines. 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 species.

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 all animal feeds (e.g. poultry, pig and fish feeds)

- b. Anthelmintics in animals e.g. ivermectins
- c. Expired Medicines 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 parasiticides

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

- The target species and likelihood of and method of excretion of the product and its active metabolites into the environment.
- Pattern of use and therefore quantity Medicines to be used (herd/flock medication or individual medication)
- The method of administration and whether it may lead to direct entry of the product into the environment, e.g. sprays
- 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 and such studies shall include:

- fate and behaviour in the soil
- effects on soil organisms
- fate and behaviour in water
- Effects on air
- effect on aquatic organisms
- effects on other non-target organisms

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

Generic and well established dosage form

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

Presentation of safety studies

All toxicity studies shall be properly presented including the following:

- Objectives
- Experimental protocol including methodology and materials
- Summarized results and related statistical analysis
- Discussions and conclusions
- 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 drug substances.

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 **preclinical pharmaco- toxicological** studies were not done in target animals.

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

1. Pharmacodynamic 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 should 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 should 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 are 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 should 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 pharmacodynamic methods, the following requirements should 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 Medicines in target animals

The summary should outline;

- Particulars of principal investigators (name, curriculum vitae, affiliation and signature)
- Medicines and Medicines product information, batch details, batch number, manufacturing site and date, expiry date, specifications

The Medicines product should 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

- Protocol and study design; (objectives, animal selection, conduct of the study, Medicines 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 should be stated.

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

- Population

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

- 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:

- the title of the study
- particulars of principal investigator(s), location, justification and objectives, dates, time, duration, observation periods and justification thereof, study design (randomization methods description of design e.g. crossover or parallel etc), inclusion, exclusion, criteria, animal housing and feeding, methods and treatments, dosage used, concurrent treatments,

- specification of test Medicines and placebo,
- response variables – clinical endpoints measured, and recording clinical response (scoring system for endpoints).
- analysis of results including statistical methods used and their justification.
- Discussions and conclusions on efficacy and safety, including but not limited to adverse drug reactions observed and their relationship with the administered dose

PART V. THERAPEUTIC EQUIVALENCE/INTERCHANGEABILITY

1. Objectives

This section shall be applicable to all generic oral dosage forms

Generic product means a medicine that is a pharmaceutical equivalent or alternative to an innovator or reference Medicines and which is intended to be therapeutically equivalent and can therefore be used interchangeably with that innovator or reference Medicines.

Pharmaceutical equivalent; Medicinal 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; Medicines 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.

Reference or innovator product; this is a worldwide innovator product or any other product approved by the Pharmaceutical Regulatory Authority as a reference product.

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

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

2. Bioequivalence studies in target animals.

2.1 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:
 - indicated for life threatening diseases requiring rapid and/or assured therapeutic response,
 - with narrow therapeutic and/or safety indices,
 - with physicochemical properties conducive to or showing poor or highly variable absorption, non-linear pharmacokinetics, or extensive pre-systemic or first-pass metabolism
 - with high ratio of excipients to active ingredients
 - fixed dose combination products
- b. Medicines with special claim to absorptive properties or special formulation i.e. modified-release or enteric coated,
- c. Long acting injections
- d. Non-oral, non-parenteral products that are intended to undergo systemic absorption

2.2 Products for which bioequivalence studies are not necessary:

- Parenteral aqueous solutions with the same active ingredients, recipients and route of administration as the original product
- Oral products not intended for systemic absorption
- 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 indices
- Products reformulated by the original manufacturer to change inactive ingredients like colouring agents, flavouring and preservatives, which do not interfere with bioavailability
- Gases
- Powders for reconstitution as solutions to be used as in parenteral or oral solutions

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

2.3 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. Medicines and Medicines 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, Medicines 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 minimum intra and inter-animal variability and elimination of bias.

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

Medicinal product

Should be identical to the intended commercial product in every respect; same manufacturing site and same composition (qualitative)

Samples should be from commercial scale production.

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.

Parameters to be measured: (AUC, C_{max}, t_{max}, A_{et}, dA_{et}/dt_{max}.. The shape and area under plasma concentration curve or cumulative excretion profiles

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 C_{max} of the generic to the reference or innovator is within the acceptance limits.

2.4 In vitro dissolution testing

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

- a. Medicines not defined above (not applicable for Medicines defined above)
- b. Different strengths of a generic formulation manufactured by the same manufacturer at the same manufacturing site where:

The qualitative composition between strength is essentially the same.

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.

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

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

Highly soluble and highly permeable >80% in 15 minutes -

2.5 Biopharmaceutical Classification Systems (BCS)

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

Apparatus

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

Medium

Aqueous medium, pH 1.2, 4.5, 6.8 for sparingly water soluble Medicines: use of surfactants 500 - 1000mL; $37 \pm 0.5^{\circ}\text{C}$

Sampling time

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

Results

Dissolution profiles in different media (tables and graphs)

Statistical treatment

$$f_1 = \left\{ \left[\sum_{t=1}^n (R_t - T_t) \right] / \left[\sum_{t=1}^n R_t \right] \right\} \times 100$$

$$f_2 = 50 \times \log \left\{ \left[1 + \left(\frac{1}{n} \right) \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} k$$

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

f_1 is proportional to the average difference between the two profiles

(difference factor)

f_2 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, f_2 is used.

If the two products produce identical results at all time points, $f_2 = 100$.

If there is an average difference of 10% in the results at all time points results, $f_2 = 50$.

Acceptance criteria

f_2 should be between 50 and 100

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

3. Comparative pharmacodynamic studies in target species

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 should 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 should 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 should 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 pharmacodynamic methods, the following requirements should be satisfied:

- 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
- It should be possible to derive the common parameters of comparison.
- It should be possible to derive the common parameters of comparison like C_{max} , T_{max} and AUC

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

4. Comparative clinical trial in target species

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 there of, 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 can not be done i.e. when plasma concentration time profile data is not suitable to assess therapeutic equivalence or lack of meaningful pharmacodynamic 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. LABELLING AND PACKAGE INSERTS

1.0 Labelling

The applicant shall ensure that the primary (immediate) packaging of the product is labeled according to the law applicable in Member States. The following minimum information shall be required in English language on the label of the immediate packaging:

- brand name where appropriate
- International Non-proprietary Name (INN)/generic name
- quantity of active ingredient per dosage unit
- Route(s) of administration
- total contents of container
- date of manufacture
- date of expiry
- batch number
- storage conditions
- name and address of manufacturer
- "For Animal Use Only"
- Distribution category i.e. POM, P, GS.
- Warning and precautions
- Withdrawal period, where applicable
- Product licence number issued by PRA (?)

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

The name of the manufacturer may be substituted with a trademark or other symbol. However these details shall appear in full on the secondary packaging.

2.0 Package inserts

The product packaging shall include a prescribing information leaflet in the case of prescription medicines, or a patient information leaflet in the case of non-prescription medicines (i.e. P, GS). The leaflet shall include the following minimum information:

- International Non-proprietary Name (INN) for each active ingredient
- Pharmacology: a brief description of the mechanism of action and pharmacological effects
- Clinical Information:
 - i. Indications
 - ii. Dosage regimens
 - iii. Contraindications
 - iv. Precautions in pregnancy, lactation, renal and hepatic failure, etc
 - v. Adverse reactions including their frequency
 - vi. Clinically significant Medicines interactions
 - vii. Symptoms and treatment of overdose
 - viii. Withdrawal period
 - ix. Pharmaceutical Information:
 - Dosage form
 - Strength
 - Excipients
 - Storage conditions
 - Shelf-life
 - Pack size
 - Description of product and package
 - 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 pharmaceuticals, pharmacokinetic and pharmacodynamic studies of FDCs in category II and III should demonstrate that the individual components:-

- a. Are pharmaceutically compatible,
 - b. Compatible pharmacokinetics,
 - c. Do not require relative dose adjustments,
 - d. Have no potential of deleterious Medicines interactions between them,
 - e. 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:-

Developed as a generic equivalent to an existing FDC.

Whose APIs are already approved, well characterised, with well documented clear evidence of safety and /or efficacy advantage of being used together or concurrent use of component Medicines 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 Medicines 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 pharmacodynamic studies data (studies should be appropriate to the claim) of studies carried out to investigate the potential for favourable or unfavourable interactions between the components. These include:

- a. Pre clinical toxicological studies and dose escalation studies when there is potential for a Medicines 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 demonstrate clinical superiority or non-inferiority and contribution each component within the combination to the claimed effect.

The clinical superiority or advantages may include:

- Increased efficacy (additive or synergistic)
- Reduced toxicity
- Prevention of antimicrobial resistance
- Bolstering of Medicines 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:

- 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 recommended dosing regimens. Consideration should be given to ethnic, environmental, co-morbid, and nutritional variations between populations

- 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.

- 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.

- i. Microbiologic activity in vitro against laboratory strains and clinical isolates of the targeted pathogen(s):
- ii. Microbiological activity in appropriate animal models of infection with the targeted pathogen(s),
- iii. 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
- iv. Characterization of the mechanism by which the active ingredients exhibit additive, or synergistic, microbiologic effect(s) on the targeted pathogen(s).
- v. In addition, the potential for antagonistic effects should be excluded, as this may compromise clinical efficacy.
- vi. 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 Medicines resistance, endpoints might be the frequency of new Medicines resistance, as well as the overall clinical outcome following the use of the Medicines.

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 anatomical therapeutic chemical system serves as a basis for classifying medicines according to therapeutic indications. The *ATCvet* system for the classification of veterinary medicines is based on the same overall principles as the *ATC* system for substances used in human medicine. In most cases an ATC code exists which can be used to classify a product in the ATCvet system. The ATCvet code is then created by placing the letter Q in front of the ATC code. In some cases, however, specific ATCvet codes are created, e.g. Antibacterials for intramammary use (QJ51) and Immunologicals (QI).

In both the ATC and the ATCvet systems, preparations are divided into groups, according to their therapeutic use. First, they are divided into 15 *anatomical groups* (1st level), classified as QA-QV in the ATCvet system, on the basis of their main therapeutic use.

Within most of the 1st level groups, preparations are subdivided into different *therapeutic main groups* (2nd level), coded for example as QA01, QA02, QA03 etc. Two levels of *chemical/therapeutic/pharmacological subgroups* (3rd and 4th levels), e.g. QA02A, QA02B etc. at the 3rd level and QA02AA, QA02AB etc at the 4th level, provide further subdivisions. At a 5th level, e.g. QA02AA01, *chemical substances* are classified. (This subdivision does not apply to QI - Immunologicals.)

QA ALIMENTARY TRACT AND METABOLISM

QA01 STOMATOLOGICAL PREPARATIONS

A Stomatological preparations

QA02 ANTACIDS, DRUGS FOR TREATMENT OF PEPTIC ULCER AND FLATULENCE

A Antacids

B Drugs for treatment of peptic ulcer

D Antiflatulents

E Antiregurgitants

X Other antacids, drugs for treatment of peptic ulcer and flatulence

QA03 ANTISPASMODIC AND ANTICHOLINERGIC AGENTS AND PROPULSIVES

A Synthetic antispasmodic and anticholinergic agents

B Belladonna and derivatives, plain

C Antispasmodics in combination with psycholeptics

D Antispasmodics in combination with analgesics

E Antispasmodics and anticholinergics in combination with other drugs

F Propulsives

QA04 ANTIEMETICS AND ANTINAUSEANTS

A Antiemetics and antinauseants

QA05 BILE AND LIVER THERAPY

A Bile therapy

B Liver therapy, lipotropics

C Drugs for bile therapy and lipotropics in combination

QA06 LAXATIVES

A Laxatives

**QA07 ANTIDIARRHEALS, INTESTINAL
ANTIINFLAMMATORY/ANTIINFECTIVE AGENTS**

A Intestinal antiinfectives

B Intestinal adsorbents

C Electrolytes with carbohydrates

D Antipropulsives

E Intestinal antiinflammatory agents

F Antidiarrheal microorganisms

X Other antidiarrheals

QA08 ANTI OBESITY PREPARATIONS, EXCL. DIET PRODUCTS

A Antiobesity preparations, excl. diet products

QA09 DIGESTIVES, INCL. ENZYMES

A Digestives, incl. enzymes

QA10 DRUGS USED IN DIABETES

A Insulins and analogues

B Oral blood glucose lowering drugs

X Other drugs used in diabetes

QA11 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, combinations

QA12 MINERAL SUPPLEMENTS

A Calcium

B Potassium

C Other mineral supplements

QA13 TONICS

A Tonics

QA14 ANABOLIC AGENTS FOR SYSTEMIC USE

A Anabolic steroids

B Other anabolic agents

QA15 APPETITE STIMULANTS

QA16 OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS

A Other alimentary tract and metabolism products

Q Other alimentary tract and metabolism products for veterinary use

QB BLOOD AND BLOOD FORMING ORGANS

QB01 ANTITHROMBOTIC AGENTS

A Antithrombotic agents

QB02 ATIHEMORRHAGICS

A Antifibrinolytics

B Vitamin K and other haemostatic

QB03 ANTIANEMIC PREPARATIONS

A Iron preparations

B Vitamin B12 and folic acid

X Other antianemic preparations

QB05 BLOOD SUBSTITUTES AND PERFUSION SOLUTIONS

A Blood and related products

B IV solutions

C Irrigating solutions

D Peritoneal dialytics

X IV solution additives

Z Hemodialytics and hemofiltrates

QB06 OTHER HEMATOLOGICAL AGENTS

A Other hematological agents

QC CARDIOVASCULAR SYSTEM

QC01 CARDIAC THERAPY

A Cardiac glycosides

B Antiarrhythmics, class I and III

C Cardiac stimulants, excl. cardiac glycosides

D Vasodilators used in cardiac disease

E Other cardiac preparations

QC02 ANTIHYPERTENSIVES

A Antiadrenergic agents, centrally acting

B Antiadrenergic agents, ganglion-blocking

C Antiadrenergic agents, peripherally acting

D Arteriolar smooth muscle, agents acting on

K Other antihypertensives

L Antihypertensives and diuretics in combination

N Combinations of antihypertensives in QC02

QC03 DIURETICS

A Low-ceiling diuretics, thiazides

B Low-ceiling diuretics, excl. thiazides

C High-ceiling diuretics

D Potassium-sparing agents

E Diuretics and potassium-sparing agents in combination

QC04 PERIPHERAL VASODILATORS

A Peripheral vasodilators

QC05 VASOPROTECTIVES

A Antihemorrhoidals for topical use

B Antivaricose therapy

C Capillary stabilizing agents

QC07 BETA-BLOCKING AGENTS

A Beta-blocking agents

B Beta-blocking agents and thiazides

C Beta-blocking agents and other diuretics

D Beta-blocking agents, thiazides and other diuretics

E Beta-blocking agents and vasodilators

F Beta-blocking agents and other antihypertensives

QC08 CALCIUM CHANNEL BLOCKERS

C Selective calcium channel blockers with mainly vascular effect

D Selective calcium channel blockers with direct cardiac effect

E Non-selective calcium channel blockers

G Calcium channel blockers and diuretics

QC09 AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM

A Angiotensin converting enzyme (ACE) inhibitors, plain

B Angiotensin converting enzyme (ACE) inhibitors, combinations

C Angiotensin II antagonists, plain

- D Angiotensin II antagonists, combinations
- X Other agents acting on the renin-angiotensin system

QC10 SERUM LIPID REDUCING AGENTS

- A Cholesterol and triglyceride inhibitors

QD DERMATOLOGICALS

QD01 ANTIFUNGALS FOR DERMATOLOGICAL USE

- A Antifungals for topical use
- B Antifungals for systemic use

QD02 EMOLLIENTS AND PROTECTIVES

- A Emollients and protectives
- B Protectives against UV-radiation

QD03 PREPARATIONS FOR TREATMENT OF WOUNDS AND ULCERS

- A Cicatrizants
- B Enzymes

QD04 ANTIPRURITICS, INCL. ANTIHISTAMINES, ANESTHETICS ETC.

- A Antipruritics, incl. antihistamines, anesthetics etc.

QD05 ANTIPSORIATICS

- A Antipsoriatics for topical use
- B Antipsoriatics for systemic use

QD06 ANTIBIOTICS AND CHEMOTHERAPEUTICS FOR DERMATOLOGICAL USE

- A Antibiotics for topical use
- B Chemotherapeutics for topical use
- C Antibiotics and chemotherapeutics, combinations

QD07 CORTICOSTEROIDS, DERMATOLOGICAL PREPARATIONS

- A Corticosteroids, plain
- B Corticosteroids, combinations with antiseptics
- C Corticosteroids, combinations with antibiotics
- X Corticosteroids, other combinations

QD08 ANTISEPTICS AND DISINFECTANTS

- A Antiseptics and disinfectants

QD09 MEDICATED DRESSINGS

- A Medicated dressings

QD10 ANTI-ACNE PREPARATIONS

- A Anti-acne preparations for topical use
- B Anti-acne preparations for systemic use

QD11 OTHER DERMATOLOGICAL PREPARATIONS

- A Other dermatological preparations

QG GENITO-URINARY SYSTEM AND SEX HORMONES

QG01 GYNECOLOGICAL ANTIINFECTIVES AND ANTISEPTICS

- A Antiinfectives and antiseptics, excl. combinations with corticosteroids
- B Antiinfectives/antiseptics in combination with corticosteroids

QG02 OTHER GYNECOLOGICALS

- A Oxytocics
- B Contraceptives for topical use
- C Other gynecologicals

QG03 SEX HORMONES AND MODULATORS OF THE GENITAL SYSTEM

- A Hormonal contraceptives for systemic use
- B Androgens
- C Estrogens
- D Progestogens

- E Androgens and female sex hormones in combination
- F Progestogens and estrogens in combination
- G Gonadotrophins and other ovulation stimulants
- H Antiandrogens
- X Other sex hormones and modulators of the genital system

QG04 UROLOGICALS

- B Other urologicals, incl. antispasmodics
- C Drugs used in benign prostatic hypertrophy

QG51 ANTIINFECTIVES AND ANTISEPTICS FOR INTRAUTERINE USE

- A Antiinfectives and antiseptics for intrauterine use
- B Antiinfectives/antiseptics for intrauterine use, combinations

QG52 PRODUCTS FOR THE CARE OF TEATS AND UDDER

- A Disinfectants
- B Teat canal devices
- C Emollients
- X Various products for the care of teats and udder

QH SYSTEMIC HORMONAL PREPARATIONS, EXCLUDING SEX HORMONES

QH01 PITUITARY, HYPOTHALAMIC HORMONES AND ANALOGUE

- A Anterior pituitary lobe hormones and analogues
- B Posterior pituitary lobe hormones and analogues
- C Hypothalamic hormones and analogues

QH02 CORTICOSTEROIDS FOR SYSTEMIC USE

- A Corticosteroids for systemic use
- B Glucocorticosteroids for systemic use, combinations
- C Antiadrenal preparations

QH03 THYROID THERAPY

- A Thyroid preparations
- B Antithyroid preparations
- C Iodine therapy

QH04 PANCREATIC HORMONES

- A Glycogenolytic hormones

QH05 CALCIUM HOMEOSTASIS

- A Parathyroid hormones
- B Anti-parathyroid hormones

QI IMMUNOLOGICALS

QI01 IMMUNOLOGICALS FOR AVES

- A Domestic fowl
- B Duck
- C Turkey
- D Goose
- E Pigeon
- F Pheasant
- G Quail
- H Partridge
- I Ostrich
- K Pet birds
- X Aves, others

QI02 IMMUNOLOGICALS FOR BOVIDAE

- A Bovine/Cattle
- B Buffalo

X Bovidae, others

QI03 IMMUNOLOGICALS FOR CAPRIDAE

A Caprine/Goat

X Capridae, others

QI04 IMMUNOLOGICALS FOR OVIDAE

A Ovine/Sheep

X Ovidae, others

QI05 IMMUNOLOGICALS FOR EQUIDAE

A Equine/Horse

B Azinine/Donkey

C Hybride

X Equidae, others

QI06 IMMUNOLOGICALS FOR FELIDAE

A Feline/Cat

X Felidae, others

QI07 IMMUNOLOGICALS FOR CANIDAE

A Canine/Dog

B Fox

X Canidae, others

QI08 IMMUNOLOGICALS FOR LEPORIDAE

A Rabbit

B Hare

X Leporidae, others

QI09 IMMUNOLOGICALS FOR SUIDAE

A Porcine/Pig

X Suidae, others

QI10 IMMUNOLOGICALS FOR PISCES

A Atlantic salmon

B Rainbow trout

C Carp

D Turbot

E Ornamental fish

X Pisces, others

QI11 IMMUNOLOGICALS FOR RODENTS

A Rat

B Mouse

C Guinea-pig

X Rodents, others

QI12 IMMUNOLOGICALS, OTHER SPACIES

A Red deer

B Reindeer

C Mink

D Ferret

E Snake

F Bee

X Others

QJ GENERAL ANTIINFECTIVES FOR SYSTEMIC USE

QJ01 ANTIBACTERIALS FOR SYSTEMIC USE

A Tetracyclines

B Amphenicols

C Beta-lactam antibacterials, penicillins

- D Other beta-lactam antibacterials
- E Sulfonamides and trimethoprim, incl. derivatives
- F Macrolides and lincosamides
- G Aminoglycoside antibacterials
- M Quinolone antibacterials
- R Combinations of antibacterials
- X Other antibacterials

QJ02 ANTIMYCOTICS FOR SYSTEMIC USE

- A Antimycotics for systemic use

QJ04 ANTIMYCOBACTERIALS

- A Drugs for treatment of tuberculosis
- B Drugs for treatment of lepra

QJ05 ANTIVIRALS FOR SYSTEMIC USE

- A Agents affecting the virus directly

QJ51 ANTIBACTERIALS FOR INTRAMAMMARY USE

- A Tetracyclines
- B Amphenicols
- C Beta-lactam antibacterials, penicillins
- D Other beta-lactam antibacterials
- E Sulfonamides
- F Macrolides and lincosamides
- G Aminoglycoside antibacterials
- R Combinations of antibacterials
- X Other antibacterials

QJ54 ANTIMYCOBACTERIALS FOR INTRAMAMMARY USE

- A Drugs for mycobacterial infections

QL ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS

QL01 ANTINEOPLASTIC AGENTS

- A Alkylating agents
- B Antimetabolites
- C Plant alkaloids and other natural products
- D Cytotoxic antibiotics and related substances
- X Others antineoplastic agents

QL02 ENDOCRINE THERAPY

- A Hormones and related agents
- B Hormone antagonists and related agents

QL03 IMMUNOSTIMULANTS

- A Cytokines and immunomodulators

QL04 IMMUNOSUPPRESSIVE AGENT

- A Immunosuppressive agents

QM MUSCULO-SKELETAL SYSTEM

QM01 ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS

- A Antiinflammatory and antirheumatic products, non- steroids
- B Antiinflammatory/antirheumatic agents in combination
- C Specific antirheumatic agents

QM02 TOPICAL PRODUCTS FOR JOINT AND MUSCULAR PAIN

- A Topical products for joint and muscular pain

QM03 MUSCLE RELAXANTS

- A Muscle relaxants, peripherally acting agents
- B Muscle relaxants, centrally acting agents

C Muscle relaxants, directly acting agents

QM04 ANTIGOUT PREPARATIONS

A Antigout preparations

QM05 DRUGS FOR TREATMENT OF BONE DISEASES

B Drugs affecting mineralization

QM09 OTHER DRUGS FOR DISORDERS OF THE MUSCULO-SKELETAL SYSTEM

A Other drugs for disorders of the musculo-skeletal system

QN NERVOUS SYSTEM

QN01 ANESTHETICS

A Anesthetics, general

B Anesthetics, local

QN02 ANALGESICS

A Opioids

B Other analgesics and antipyretics

C Antimigraine preparations

QN03 ANTIEPILEPTICS

A Antiepileptics

QN04 ANTI-PARKINSON DRUGS

A Anticholinergic agents

B Dopaminergic agents

QN05 PSYCHOLEPTICS

A Antipsychotics

B Anxiolytics

C Hypnotics and sedatives

QN06 PSYCHOANALEPTICS

A Antidepressants

B Psychostimulants and nootropics

C Psycholeptics and psychonaleptics in combinations

QN07 OTHER NERVOUS SYSTEM DRUGS

A Parasympathomimetics

C Antivertigo preparations

X Other nervous system drugs

QN51 PRODUCTS FOR ANIMAL EUTHANASIA

A Products for animal euthanasia

QP ANTIPARASITIC PRODUCTS, INSECTICIDES AND REPELLENTS

QP51 ANTIPROTOZOALS

A Agents against protozoal diseases

B Agents against coccidiosis

C Agents against amoebosis and histomonosis

D Agents against leishmaniosis and trypanosomosis

E Agents against babesiosis and theileriosis

X Other antiprotozoal agents

QP52 ANTHELMINTICS

A Anthelmintics

B Agents against trematodosis

C Agents against nematodosis

D Agents against cestodosis

X Other anthelmintic agents

QP53 ECTOPARASITICIDES, INCL. INSECTICIDES AND REPELLENTS

- A Ectoparasitocides for topical use
- B Ectoparasitocides for systemic use
- G Repellents

QP54 ENDECTOCIDES

- A Macrolytic lactones

QR RESPIRATORY SYSTEM

QR01 NASAL PREPARATIONS

- A Decongestants and other nasal preparations for topical use
- B Nasal decongestants for systemic use

QR02 THROAT PREPARATIONS

- A Throat preparations

QR03 ANTI-ASTHMATICS

- A Adrenergics, inhalants
- B Other anti-asthmatics, inhalants
- C Adrenergics for systemic use
- D Other anti-asthmatics for systemic use

QR05 COUGH AND COLD PREPARATIONS

- C Expectorants, excl. combinations with cough suppressants
- D Cough suppressants, excl. combinations with expectorants
- F Cough suppressants and expectorants, combinations
- X Other cold combination preparations

QR06 ANTIHISTAMINES FOR SYSTEMIC USE

- A Antihistamines for systemic use

QR07 OTHER RESPIRATOR SYSTEM PRODUCTS

- A Other respiratory system products

QS SENSORY ORGANS

QS01 OPHTHALMOLOGICALS

- A Antiinfectives
- B Antiinflammatory agents
- C Antiinflammatory agents and antiinfectives in combination
- E Antiglaucoma preparations and miotics
- F Mydriatics and cycloplegics
- G Decongestants and antiallergics
- H Local anesthetics
- J Diagnostic agents
- K Surgical aids
- X Other ophthalmologicals

QS02 OTOLOGICALS

- A Antiinfectives
- B Corticosteroids
- C Corticosteroids and antiinfectives in combination
- D Other otologicals
- Q Antiparasitics

QS03 OPHTHALMOLOGICAL AND OTOLOGICAL PREPARATIONS

- A Antiinfectives
- B Corticosteroids
- C Corticosteroids and antiinfectives in combination
- D Other ophthalmological and otological preparations

QV VARIOUS

QV01 ALLERGENS

- A Allergens

QV03 ALL OTHER THERAPEUTIC PRODUCTS

A All other therapeutic products

QV04 DIAGNOSTIC AGENTS

B Urine tests

C Other diagnostic agents

QV06 GENERAL NUTRIENTS

A Diet formulations for treatment of obesity

B Protein supplements

C Infant formulas

D Other nutrients

QV07 ALL OTHER NON-THERAPEUTIC PRODUCTS

A All other non- therapeutic products

QV08 CONTRAST MEDIA

A X-ray contrast media, iodinated

B X-ray contrast media, non-iodinated

C Magnetic resonance imaging contrast media

D Ultrasound contrast media

QV09 DIAGNOSTIC RADIOPHARMAEUTICALS

A Central nervous system

B Skeleton

C Renal system

D Hepatic and reticulo endothelial system

E Respiratory system

F Thyroid

G Cardiovascular system

H Inflammation and infection detection

I Tumour detection

X Other diagnostic radiopharmaceuticals

QV10 THERAPEUTIC RADIOPHARMACEUTICALS

A Antiinflammatory agents

B Pain palliation (bone seeking agents)

X Other therapeutic radiopharmaceuticals

QV20 SURGICAL DRESSINGS

Appendix II: Guidelines to Analytical method validation

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

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

2.5.1 Definition: 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

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

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

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
- Medicines
- Accuracy X X
- Repeatability precision X 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

Appendix III.

APPLICATION FORM For registration of a veterinary medicine in Zambia

PART 1A ADMINISTRATIVE INFORMATION

<i>For official use</i>	
Date	Application number

The Guidelines on registration of a medicine to be consulted in completing this form and preparing of dossiers for submission to the PRA

<i>1 Details of Applicant (who must be the prospective holder of the product licence)</i>			
Name:			
Physical Address:			
Postal Address:			
Country:			
Phone:	Fax:	Mobile:	E-mail:

<i>1.1 Details of a Distributor (who must be appointed by the applicant and submit evidence of power of attorney)</i>			
Name:			
Physical Address:			
Country:			
Phone:	Fax:	Mobile:	E-mail:

<i>1.2 Manufacturer(s), site(s) for the pharmaceutical dosage form</i>			
NAME (each site involved in the manufacture of the dosage form)	ACTIVITY -Dosage form compounding (for each stage where applicable, including labelling)	SITE (Physical Address, Phone and Country)	

1.3 Source (s) (manufacturer(s) of Active Pharmaceutical Ingredient(s):

Name:

Physical Address:

Postal Address:

Country:

Phone:

Fax:

Mobile:

E-mail:

2 Proprietary Name and dosage form

Generic (INN) name

Description

2.1 Name of the Active Pharmaceutical Ingredient (s) (International Non-proprietary Name in English) and strength

2.2 Pharmacotherapeutic Classification (Anatomic-Therapeutic Classification system)

2.3 Dosage and Strength

3 Pharmaceutical Dosage Form

3.1 Dosage and Route of administration (in case of veterinary medicine, the dosage and route of administration for each species of animal for which the product is intended to be specified)

3.2 Container, closure and administration devices

3.3 Package sizes

3.4 Shelf life

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

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

(iii) The shelf life after reconstitution

3.5 Storage conditions

3.6 Categories for Distribution

☐

Narcotic

☐

Prescription only

☐

Pharmacy only

	General Sales Medicines
Other information	

4 Status of /Registration in the Country of Original Development and /Registration Number and Date, Where Applicable. Country of Manufacture	
5 Registration Status for this Medicine in the SADC Member States and in Other Countries	
5.1 Registered:	Country: Date of registration: Proprietary name:
5.2 Pending:	Country: Date of submission: Application number:
5.3 Rejected:	Country: Date of rejection: Application number: Reason for rejection:
5.4 Withdrawn (by applicant before registration)	Country: Date of withdrawal: Reason for withdrawal: Proprietary name:
5.5 Withdrawn (by applicant after registration)	Country: Date of registration: Date of withdrawal: Reason for withdrawal: Proprietary name:
5.6 Suspended/ revoked/cancelled/Withdrawn by competent authority	Country: Date of withdrawal: Reason for withdrawal: Proprietary name:

6 Therapeutic Indications for the Product (In case of a medicinal product for veterinary use, the target species are to be specified)				
7 Unit (Master) Formulation				
Name (INN) of	Reason for inclusion	Quantity	Unit	Reference standards

-API				
1.				
2.				
3. etc.				
-Excipients:				
1.				
2.				
3. etc.				

8 Declaration by an Applicant:

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

- 8.1 The current edition of the WHO guideline on “**Good Manufacturing Practice for Pharmaceutical products**”, and/or equivalent national guideline, is applied in full in all premises involved in the manufacturer of this medicine.
- 8.2 The formulation per dosage form correlates with the master formula and with the batch manufacturing record.
- 8.3 the manufacturing procedure is exactly as specified in the master formula and batch manufacturing record.
- 8.4 Each batch of all starting materials is either tested or certified (in accompanying certificate of analysis for that batch) against the full specifications in the accompanying documentation and must comply fully with those specifications before it is released for manufacturing purposes.
- 8.5 All batches of the active pharmaceutical ingredient (s) (Raw materials are obtained from the source(s) specified in the accompanying documentation.
- 8.6 No batch of active pharmaceutical(s) will be used unless a copy of the batch certificate established by the active ingredient manufacturer is available.
- 8.7 Each batch of the container/closure system is tested or certified against the full specifications in the accompanying documentation and complies fully with those specifications before it is released for the manufacturing purposes.
- 8.8 Each batch of the finished product is either tested, or certified (in an accompanying certificate of analysis for that batch), against the full specifications in the accompanying documentation and complies fully with release specifications before it is released for sale.
- 8.9 The person releasing the product an authorized person as defined by the WHO guideline “**Good Manufacturing Practices: Authorized person - the role, functions and training**” and /or an equivalent national guideline.
- 8.10 The procedures for control of the finished product have been validated for this information. The assay method has been validated for accuracy, precision, specify and linearity.
- 8.11 The holder of marketing authorization/Product licence is obliged to follow national requirements for handling adverse reaction on its products.
- 8.12 The holder of Product licence is obliged to follow national requirements for handling batch recalls of its products.
- 8.13 All the documentation referred to in this certificate is available for review during a GMP inspection.
- 8.14 Clinical Trials were conducted in accordance with Good Clinical Practice.

Name:

Qualification:

Position in the company:

Signature:

Date:

PART IB PRODUCT PROFILE

9	Summary of Product Characteristics (if not identical to package insert)
9.1	Proprietary name of the medicine
9.2	Approved generic name(s) (use the INN if applicable)
9.3	Qualitative and quantitative composition
9.4	Dosage form
9.5	Clinical particulars
5.1	Therapeutic indication (s)
5.2	Route of administration
5.3	Contra-indications
5.4	Special warnings and precautions for use (In case of veterinary medicine, include special precautions for each target species and precautions to be taken by the person administering the medicinal product to the animals, withdrawal periods for the various animals meant for food, including those for which withdrawal period is zero)
5.5	Interactions
5.6	Pregnancy and lactation (Include lay for veterinary medicines)
5.7	Effects on the ability to drive and operate machinery
5.8	Undesirable effects
5.9	Overdose
9.6	Pharmacological properties
6.1	Pharmacodynamic properties
6.2	Pharmacokinetic properties
6.3	Preclinical safety data
9.7	Pharmaceutical particulars
7.1	List of excipients
7.2	Incompatibilities
7.3	Shelf-life
7.4	Special precautions for storage
7.5	Nature and composition of container
7.6	Instructions for use/handling
7.7	Restriction on sale/distribution
9.8	Administrative data
8.1	Holder of a Product licence
8.2	Registration number
8.3	Date of first registration/renewal of a Product licence
8.4	Date of revision of the text
9.9	Registration in a SADC member state
10	Package Insert
11	Patient Information Leaflet

12A Immediate Container Label

1. Proprietary Name
2. Generic name in English
3. Name of active pharmaceutical ingredient, (INN) quantity of each
4. Pharmaceutical Dosage form and pack size
5. Scheduling status
6. Specific excipients
7. Dosage and route of administration (In case of veterinary medicines, include target species)
8. Store out of reach of children
9. Special warnings
10. Date of Manufacture
11. Storage Conditions
12. Expiry date (month/year)
13. Name and address of holder of marketing authorization/Product licence /registration number
14. Manufacturer's batch number
15. Manufacturer's name and Address
16. In the case of general sales products, indication for use (outer label will comply with the above as minimum)

In the case of veterinary medicines, the product label shall have the words 'for animal treatment only'

17. Blisters
 - Proprietary name
 - Name of manufacturer
 - Storage Instructions
 - Name of licence holder
 - Name and address of manufacturer
 - Expiry date (month/year)
 - Batch number

In the case of veterinary medicines, the product label shall have the words 'for animal treatment only'

16. Small units (5ml container)
 - Proprietary name
 - Method of administration
 - Batch number
 - Contents by mass/volume/units
 - Expiry Date

In the case of veterinary medicines, the product label shall have the words 'for animal treatment only'

	12B	Outer packaging label
1.	The proprietary name of the medicine followed immediately below by the generic name of the API in equal print size where the medicine contains only one API. With the exception of multicomponent products	
2	Pharmaceutical dosage form and strength per unit dose.	
3.	Pack size.	
4.	A list of specific excipients.	
5.	The route of administration.	
6.	Store out of reach of children.	
7.	Special warnings, if necessary for the medicine.	
8.	The expiry date (monthly/year).	
9.	Storage requirements and necessary precautions	
10.	If appropriate, special precautions for disposal of unused medicine or waste materials derived from such medicine, for example cytotoxics and radiopharmaceuticals	
11.	The name and address of the holder of marketing authorization/ Product licence	
12.	The name and address of the manufacturer	
13.	The registration number	
14.	The manufacturers batch number	
15.	In the case of General Sales products, instructions on the use of the medicines; (Not applicable to prescription medicines)	
16.	Categorization for distribution purposes	
17.	The outer packaging may include symbols or pictograms designed to clarify certain information mentioned in paragraph 1 and other information compatible with the summary of the product characteristics, which is useful for health education, to the exclusion of any element of a promotional nature.	
In the case of veterinary medicines, the product label shall have the words ‘for animal treatment only’		

PART II **BIOAVAILABILITY / BIOEQUIVALENCE DATA**
EXPERT REPORTS

Bioavailability and Bioequivalence Studies (see Bioavailability Guidelines)		
1.	Chemical and pharmaceutical documentation	(No. of volumes)
		(No. of pages)
2.	Toxicological and pharmacological documentation	(No. of volumes)
		(No. of pages)
3.	Clinical Documentation	(No. of volumes)
		(No. of pages)
Add: Bioavailability / Bioequivalence data		

PART IIIA Composition

- Medicine
- Container/packaging
- Clinical trial formula(e) where applicable

PART IIIB Development Pharmaceuticals

PART IIIC Control of Starting Materials

- Active Pharmaceutical Ingredients**
 - Route of synthesis including impurities
 - Physical and chemical characteristics
 - Specifications
 - API(s) described in the pharmacopoeia
 - API(s) not described in the pharmacopoeia
 - Certificate of Analysis (CoA)
 - Analytical Validation
 - Stability for the API(s) (NCEs only)
- Excipients**
 - Specifications
 - Excipients described in the pharmacopoeia
 - Excipients not described in the pharmacopoeia
 - Additional tests
 - Scientific data (excipients used for the first time in a medicine)
 - Nomenclature:

- | | |
|-------|--|
| 2.3.2 | International non proprietary name (INN) |
| 2.3.3 | Chemical name |
| 2.3.4 | Other names |
| 2.3.5 | Laboratory code |
| 2.3.6 | Physiochemical Properties |
| 2.3.7 | Potential and actual Isomerism |
| 2.3.8 | Specifications |

PART IIID Packaging Material (Immediate Packaging)

1. Type of material
2. Construction
3. Specifications
4. Development studies on packaging material
5. Batch analysis results

PART IIIE Control Tests on Intermediate Products

1. Identification of intermediate (e.g. powder mix, or granules ready for compression)
2. Specifications
3. Justification for tests

PART IIIF Control Tests on Finished Product

1. Specifications
 - (a) pharmacopoeial (include copy of monograph)
 - (b) in-house (supply details)
2. Justification for tests
3. Analytical validation

PART IIIG Method of Preparation for the Finished Product

1. Batch Formulation including details of batch size
2. Site of Manufacturer
 - 2.1 Name and business address of each facility where any aspect of manufacture occurs including activity performed in each site.
 - 2.2 GMP Certificate
3. For domestic companies supply the current license number issued by a regional or national PRA.
4. Manufacturing procedure
 - 4.1 Detailed manufacturing procedure including equipment, in-process controls, processing conditions and packaging procedure.
 - 4.2 Flow chart of the entire manufacturing procedure (including packaging and labeling)
 - 4.3 Manufacturing process validation protocol or report
 - 4.4 Copy of Master Formula
 - 4.5 Copy of batch manufacturing record

PART IIIH Stability Testing of the Finished Product (See Stability Guidelines)

1. Specifications
2. Characteristics to be tested
3. Batch sizes
4. Packaging material
5. Real time and accelerated conditions
6. Validation of stability-indicating tests
7. Tabulated results
8. Discussion
9. Conclusion

PART IV: SUMMARY OF TOXICO-PHARMACOLOGY OF THE MEDICINE

- | | |
|------|---|
| Part | IV A: Single dose toxicity |
| | IV B: Repeat dose toxicity |
| | IV C: Reproduction studies |
| | 1. Fertility/general reproduction Performance |
| | 2. Embryotoxicity |
| | 3. Peri-/Post natal effects |
| | IV D: Mutagenic potential |
| | 1. <i>In vitro</i> |
| | 2. <i>In vivo</i> |
| | IV E: Oncogenic/Carcinogenic potential |
| | IV F: Pharmacodynamics |
| | IV G: Pharmacokinetics |
| | IV H: Local tolerance |
| | IV J: Other information |

PART V CLINICAL STUDIES

V A: Human pharmacology

1. Pharmacodynamics
2. Pharmacokinetics

V B: Clinical Documentation

1. Clinical trials (Phase I, II and III)
2. Post marketing experience
3. Published and unpublished experience
4. Other relevant information