THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH

TANZANIA FOOD AND DRUGS AUTHORITY

APPLICATION GUIDELINES FOR REGISTRATION OF HUMAN MEDICINAL PRODUCTS

(Made under section 52 (1) of the Tanzania Food, Drugs and Cosmetics Act, 2003)

THIRD EDITION

JUNE 2004

Table of Contents

1. Abbreviations.....3
2. Preface.....4
3. Preamble.....5
3. Glossary of Terms.....6
4. General information.....9
5. Part I: Summary of Product Characteristics.....16
6. Part II: Documentation for Active Pharmaceutical Ingredient (s).....19
7. Part III: Documentation on Quality of Finished Product.....21
8. Part IV: Documentation on Pre-Clinical Data.....29
9. Part V: Documentation on Clinical Data.....42
10. Part VI: Documentation on Fixed Dose Combination Products.....47
11. Part VII: Documentation on Therapeutic Equivalence studies.....50
12. Appendix I: Application form.....67
13. Appendix II: Anatomic Therapeutic Chemical Classification system.....73
14. Appendix III: International comparator products for equivalence assessment of interchangeable multisource (generic) products.....82

ABBREVIATIONS

API	Active Pharmaceutical Ingredient
ATC	Anatomic Therapeutic Chemical classification
AUC	Area under the plasma concentration time curve
BE	Bioequivalence studies
BMS	Bristol-Myers Squibb
BP	British Pharmacopoeia
CASR	Chemical Abstract Service Registry Number
Chtab	Chewable tablet
CI	Confidence Interval
Cmax	Maximum plasma concentration
CV	Coefficient of Variation
Eyd	Eye drops
Eyo	Eye ointment
FDC	Fixed Dose Combination
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
GSK	GlaxoSmithkline
HCL	Hydrochloride
ICH	International Conference on Harmonization of Technical Requirements for Registration of Human Medicines
i.m	Intramuscular
Inj	Injection
Inh	Inhaler
INN	International Pre-proprietary Name
IP	International Pharmacopoeia
IU	International Unit
IUPAC	International Union for Pure and Applied Chemistry
i.v	Intravenous
JP	Japanese Pharmacopoeia
Ltd	Limited
MAOI's	Monoamine Oxidase Inhibitors
mg	Milligram
ml	Millilitre
M.R	Modified Release
MSD	Merck Sharp and Dohme
Oin	Ointment
Ph. Eur	European Pharmacopoeia
RH	Relative Humidity
SPC	Summary of Product Characteristics
Sr	Sustained release
TE	Therapeutic Equivalence
TFDA	Tanzania Food and Drugs Authority
TFDCA	Tanzania Food, Drugs and Cosmetics Act, 2003
Tmax	Time to reach maximum plasma concentration
µg	Microgram
UK	United Kingdom
USA	United States of America
USP	United States Pharmacopoeia
WHO	World Heath Organization

PREFACE

Access to quality medicines is one way of fighting against diseases that form one part of the three big enemies (diseases, ignorance and poverty) which the government of Tanzania declared war against since independence. One of the strategies to achieve this is through medicinal products registration, a process that involves pre-marketing evaluation to confirm their compliance to acceptable standards of quality, safety and efficacy.

Laws regulating trade in therapeutic substances have existed in Tanzania since 1937. These included the Food and Drugs Ordinance; Cap 93, the Pharmacy and Poisons Ordinance; Cap 94, the Dangerous Drugs Ordinance; Cap 95 the Pharmaceutical and Poisons Act; 1978 and the most recent one Tanzania Food, Drugs and Cosmetics Act; 2003. However, it was until 1990, when regulations were made to prohibit the manufacture for sale, sell, import or export of any medicinal product unless it was registered. Prior to 1990, pharmaceutical products were introduced by way of promotion through medical practitioners, dentists, veterinary surgeons and pharmacists who were given information on the product.

Registration was gradually introduced in Tanzania to have a smooth transition, beginning with one-year provisional registration christened as notification from 1998. This gave ample time for the then Pharmacy Board to prepare guidelines to assist applicants and evaluators to respectively submit and evaluate correctly the required information.

Following the preparation of the guidelines the first application was received in 1997 and the first product was registered in April 1999. I am happy that the review of these guidelines is coinciding with the coming into force of the TFDC 2003, and the first renewal of registration.

The review of these guidelines has been necessitated by the need to incorporate regional and international requirements, advances in science and technology, experience gained from the former guidelines and comments gathered from applicants in relation to the previous guidelines.

Lastly, I would like to thank the many people whose combined efforts have made the review of these guidelines possible and successful. In particular I would like to express my sincere thanks to members of the pharmaceutical industry, the major contributors; Profs. A. Masele and Karim Manji, Drs. M.H.S Chambuso, M. J. Moshi, and Stella Chale from Muhimbili University College of Health Sciences, Dr.Salim Abdulla of National Institute of Medical Research, Dr. P. Wambura of Sokoine University of Agriculture, Dr.F. Rutachunzibwa of Kairuki Memorial University, Mr. L. R. Mhangwa, Dr. N.B. Chukilizo, Dr S. H. Luwongo, Mr. Hiiti B. Sillo, Mr. Akida Khea, Ms Rosemary Aaron Mr. Adonis Bitegeko, Mr. Mitangu Fimbo, Ms Siya Augustine and Mr. Ngemera Mwemezi from TFDA for their invaluable contributions in drafting, editing and proofreading these revised version. I also extend my thanks to Ms Mariam Mirambo and Joyce Komba who tirelessly and meticulously did all the tedious and daunting secretarial work.

M. Ndomondo-Sigonda
DIRECTOR GENERAL
TANZANIA FOOD AND DRUGS AUTHORITY

PREAMBLE

The aim of these revised guidelines remain the same as the previous one that is of giving the Authority's requirements for documentation and assembling of application for registration of human medicinal products in Tanzania. The guidelines provide comprehensive information on the preparation of an application covering regulatory expectations regarding the format and content.

The updating of these guidelines was based on the need for clear, simple and concise guidelines that would be easy to follow. Inclusion of other critical requirements which were either missing or inadequately described in the earlier editions such as *in vivo* therapeutic equivalence studies for generic medicines, stability studies of API and finished product as well as the regional and international harmonised technical requirements for registration of human medicinal products has also been taken into consideration.

The guidelines are organised into parts that include: Summary of product characteristics, documentation of quality data of active pharmaceutical ingredient(s), documentation of quality data of finished product, documentation of safety data, documentation of efficacy data, documentation of therapeutic equivalence data and documentation of fixed dose combination products
Administrative data and details of data requirements for each type of medicinal product are provided under general information.

Registration of medicinal products implements one of the legal requirements for marketing of medicinal products in Tanzania. The Tanzania Food, Drugs and Cosmetics Act, 2003 under Section 22 subsection (1)(a) prohibits the sale, offer or supply of unregistered drugs. The Act also prescribes that drugs shall only be registered if they are in the public interest, meet appropriate standards of safety, efficacy and quality and are manufactured in facilities, which comply with GMP requirements.

It is therefore essential that every person who intends to market a medicinal product in Tanzania reads the whole of these guidelines carefully and follows strictly the instructions prescribed herein. Applications, which do not comply with the requirements prescribed in these guidelines, shall be rejected.

GLOSSARY OF TERMS

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

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

Authority
Means the Tanzania Food and Drugs Authority, or its acronym "TFDA" established under Section 4 of the Tanzania Food, Drugs and Cosmetics Act, (TFDCA) 2003.

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

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

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

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

Drug, medicine or pharmaceutical product
Means any substance or mixture of substances manufactured sold or represented for use in:

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

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

(c) Disinfection in premises in which drugs are manufactured, prepared or kept, hospitals and equipment;

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

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

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

Expert report
Means a summary and interpretation of data, with conclusions, prepared by an independent expert on the subject.

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

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

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

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

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

Innovator (or pioneer) pharmaceutical product
Means a pharmaceutical product, which was first authorized for marketing (normally as a patented product) on the basis of documentation of efficacy, safety and quality (according to the requirements at the time of authorization).

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

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

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

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

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

Pharmacopoeia
Means a current edition of the British Pharmacopoeia, European Pharmacopoeia, United States Pharmacopoeia, International Pharmacopoeia and Japanese Pharmacopoeia.

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

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

Retention fee
Means a fee paid annually to maintain marketing authorization

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

Specification - release
Means the combination of physical, chemical, biological and microbiological test requirements that determine whether a drug product is suitable for release at the time of its manufacture.

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

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

GENERAL INFORMATION

All applications shall be made by submitting a dully filled in application form accompanied with prescribed information as detailed in these guidelines. All documents shall be in Kiswahili or English. Applications that do not comply to requirements prescribed in these guidelines will be rejected and returned to the applicant at his own cost. All applications before being accepted for consideration must comply with the following:

(a) First time applications

A separate application is required for each product. Products differing in active ingredient(s), strength, dosage forms, package size (preparations for injection only) or manufactured at different sites are considered to be different products and hence require separate applications.

However pharmaceutically equivalent products bearing the same proprietary name and manufactured at the same manufacturing site, but differing only in packaging material or pack sizes require only one application.

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

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

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

Table I: Parts required for each type of medicinal product

Product type		Parts required					
		I	**II**	**III**	**IV**	**V**	**VI**
		SPC	**API**	**FP**	**Pre-clinical Pharmaco-toxicolgical**	**Clinical Safety and efficacy**	**TE**
1.	Innovator	√	√	√	√	√	x
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 generic	√	√	√	x	x	√

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

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

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

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

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

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

ix. Current Site Master File

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

(b) Application for alteration of a registered product

Whenever a marketing authorization holder wishes to make any alteration to a registered product he must apply to and obtain approval from the Authority before introducing it in Tanzania. 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 non-refundable alteration fee as prescribed in the TFDA fees and charges regulations.

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

(c) Application for renewal of registration

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

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

i. Requirements prescribed in (a) i, ii, iii, vi, vii, viii and ix
ii. Renewal application form.
iii. Consolidated report of all post registration changes if any (reported and unreported) which had been made on the product.
iv. Report of additional adverse drug reactions observed after the product was registered.

3. Documentation

(a) Paper type and binding

Data shall be presented on A4 and 80g/m^2 paper with readily readable letters of at least 12 font sizes. Every page shall be numbered sequentially.

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

All parts must be bound separately and arranged sequentially in A4 size accessible spring file covers with flexible seat. One or more covers may be used depending on the number of pages contained in a part.

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

The file cover should be made of hard, non-collapsible biodegradable material. Arch lever files are strictly not permissible. The thickness should be expandable or reducible depending on the total thickness of the contents.

(b) Official references, texts

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

(c) Expert reports

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

(d) Manuals

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

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

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

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

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

(e) Cross Reference between Products

There shall be no cross reference of particulars or documentation between one product and another (other than reference to above-mentioned "Manuals") except in the following circumstances:

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

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

Separate application forms are required for each such product but supporting

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

4. Submission, payment of fees and processing of applications

(a) Submission of application

All applications shall be addressed and submitted in person or by courier to:

The Director General, Tanzania Food and Drugs Authority, Off Mandela Road, Mabibo External, P. O. Box 77150, Dar es *Salaam, Tanzania*

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

(b) Payment of fees

Fees shall be paid either by bank transfer to:

Tanzania Food and Drugs Authority, Account No. 100380013 USD, Citibank, Tanzania Ltd. Dar es Salaam – Head office Peugeot House, 36 Upanga Road, P. O. Box 71625, Dar es Salaam Tanzania Swift Code: CITITZTZ. OR Account No. 6503900110 National Microfinance Bank, Kariakoo Branch (for local manufacturers). *OR by bankers draft in favour of the Tanzania Food and Drugs Authority.*
Note: *All bank charges shall be borne by the applicant.*

(c) Processing of applications

Once an application has been accepted for consideration it will be placed in the evaluation queue. The Authority may during evaluation of the product request for clarification or additional data or samples. Once a query or a request has been raised, the processing shall halt until after the Authority has received the response to the query.
If no response to the query or request has been received within six months the application will be rejected.

The processing of an application takes about 12 months. However applications for registration of new medicines (not me too drugs) intended for treatment or prevention of malaria, tuberculosis and HIV or medicines intended for diseases for which there are no registered medicines will be fast tracked by evaluating them immediately they are received.

The Authority as part of the evaluation of the product may conduct pre-registration GMP inspection to verify compliance thereof.

5. Naming of medicinal products

When naming medicinal products the following should be taken into consideration:

a). Names of medicinal products should not be suggestive either directly or indirectly to food or be liable to cause confusion to the purchaser or consumer.

b). Names shall not be inconveniently long (e.g. during naming avoid esters and salts of these products).

c). Names should be distinctive in sound and spelling

d). Names that are likely to convey to a patient an anatomical, physiological, pathological or therapeutic suggestion will not permissible.

f). To avoid confusion, which could jeopardize the safety of patients, trade names cannot be derived from pre proprietary names and in particular, must not include their common stems.

h). Two different pharmaceutical products, with different pharmacological action but using the same brand name will not be registered as they may cause confusion. If they are from different companies the first registrant must be considered and favoured.

6. Registration

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

(a) Validity of registration

The registration of a product shall be valid for five years unless sooner suspended, cancelled or revoked by the Authority or terminated by the registration holder. The validity of registration shall be subject to payment of annual retention fees for the product immediately after a product is registered.

(b) Termination of product registration

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

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

(c) Appeals

Any person aggrieved by a decision of the Authority in relation to any application for registration of a drug may make representations in writing to the Authority, by submitting additional evidence based reasons to support the representations.

If after reconsideration of the representations, the Authority still rejects the application, the applicant may if not satisfied with the decision appeal to the Minister for Health.

The appeal shall or English. However, where original certificates are in another language, copies shall be presented together with certified Kiswahili or English translations. These guidelines should be read together with the Tanzania Food, Drugs, and Cosmetic Act 2003 and regulations made there under.

PART I: SUMMARY OF PRODUCT CHARACTERISTICS

1. Name and Dosage form of product

State the name under which the product is or will be marketed in Tanzania. In case of 'generic' products, the International Non– Proprietary Name (INN) in block letters and a trade mark name in small letters in brackets if any.

State clearly also the pharmaceutical_dosage form of the product, e.g. tablet, capsule, injection, etc.

Any descriptive terms to give an indication of the exact type of dosage form should also be included e.g. sustained – release tablet, oily injection.

2. Anatomic Therapeutic Chemical Classification and Distribution Category

State the ATC class and the proposed distribution category of the product. (Refer to Appendix 1 for guidance on ATC classification).

3. Description

State briefly visual and physical characteristics of the product, including where applicable: Shape, size, superficial markings for identification purposes, colour, odour, taste, consistency, type of tablet coating, type of capsule type of liquid etc.

4. Name(s) and Strength(s) of Active Ingredient(s)

Give the name(s) and strength(s) of the active ingredient(s).

Strengths should be expressed in weights, volume or percentage per dosage units and must be in SI units.

5. Pharmacology

Give a concise summary of the pharmacodynamic and pharmacokinetic properties of the drug(s) relevant to the proposed indications.

6. Toxicology

State briefly the safety profile of the product in relation to single dose toxicity, repeated dose toxicity, carcinogenicity, genotoxicity, reproduction effects and dependence liability.

7. Indications

State briefly recommended therapeutic use(s) of the product. Indications should be specific; phrases such as 'associated conditions' or 'allied diseases' should be avoided.

8. Posology and Route of Administration

State the dose (normal dose, dose range), dosage schedule (frequency,

duration) and route of administration appropriate for each therapeutic indication. Dosages for adults, children, should be stated clearly.

Dosage adjustments for special conditions, e.g. renal, hepatic, cardiac, nutritional insufficiencies, where relevant, should be stated.

Distinction should be made between therapeutic and prophylactic doses and between dosages for different clinical uses where applicable.

9. Contraindications

Outline situations where patients should never or generally not be treated with the product and in rare cases where the product should not be used.

10. Side Effects and Adverse Reactions

State the side effects and adverse reactions of the product.

11. Interactions

State briefly the interactions of the product with other compounds (drug or other substances) and the mode or mechanism of interaction if known.

12. Precautions and warnings

State briefly the precautions and warnings that should be taken when or before using the product. Describe the conditions under which the product may be recommended for use in subgroups of patients at risk provided that the special conditions of use are fulfilled. Emphasis should be given to a serious risk by underlining the seriousness (i.e. possibility of death).

State also any special pharmaceutical precautions e.g. incompatible diluents additives or admixtures etc.

13. Over dosage

State briefly the symptoms of over dosage or poisoning and the recommended treatment and antidotes for over dosage or poisoning.

14. Packing and Pack size(s)

State briefly the type(s) of packing and pack size(s) being applied for registration. The pack sizes declared here should correspond with the samples submitted.

15. Storage conditions and user instructions

State briefly:

(a) The recommended storage conditions (temperature, humidity, light, etc.) as established by stability studies. The storage temperature must be stated in figures e.g. Store below 30˚c protected from light.

(b) Any special user instructions, e.g. dilution, reconstitution, storage and

shelf life after reconstitution, etc.

16. Name and signature of the authorized person:

Date:

Official stamp:

PART II: DOCUMENTATION ON QUALITY OF ACTIVE PHARMACEUTICAL INGREDIENT (S)

1. Identity of active ingredient(s)

1.1 Nomenclature

State the INN and IUPAC name or other names, if any. The CAS Registry number should as well be given.

1.2 Description of physical chemical characteristics

Give a brief description of physico-chemical characteristics, including, where applicable: colour, physical state (powders, amorphous, crystalline, liquid, etc) odour, taste, solubility in water, acid, alkali, common solvents (chloroform, ether, acetone, alcohol, etc), melting point, hygroscopicity, polymorphism, pKa, pH values and any other characteristics.

Give the structural formula with molecular formula and molecular weight. Molecular weight of base or acid should also be given where a substance is a salt.

1.3 Evidence of Chemical Structure

Confirmation of structure based on synthetic route and spectral analyses with interpretation should be provided. Information such as potential for isomerism, identification of stereochemistry or potential for forming polymorphs should also be included.

2. Manufacture of Active Ingredient

A flow diagram of the synthetic process (es) should be provided which includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and drug substance reflecting stereochemistry, identified operating conditions and solvents.

A sequential procedural narrative of the manufacturing process should be submitted. The narrative should include, for example, quantities of raw materials, solvents, catalysts and reagents reflecting the representative batch scale for commercial manufacture, identification of critical steps, process controls, equipment and operating conditions (e.g. temperature, pressure, pH, time).

Alternate processes should be explained and described with the same level of detail as the primary process. Reprocessing steps should be identified and justified.

3. Quality Control

A list of tests and limits for results for the active pharmaceutical ingredient is needed. Include test methods in sufficient detail for them to be replicated by another laboratory. Results of validation of the methods for assay of the active pharmaceutical and of impurities are needed. Potential impurities

originating from the route of synthesis and arising during the production and purification must be clearly stated and described.

4. Expert Report

Provide an independent expert report critically examining data and making considered opinions supported with references from peer review literature.

5. Name and signature of the authorized person:

Date:

Official stamp:

PART III: DOCUMENTATION ON QUALITY OF PHARMACEUTICAL DOSAGE FORM

1. Description

State briefly visual and physical characteristics of the product, including where applicable: shape, size, superficial markings for identification purposes, colour, odour, taste, consistency, type of tablet coating, type of capsule type of liquid etc.

2. Composition per dosage unit

Provide complete composition per dosage unit as set out in Table II below.

TABLE II

S/N	Name of ingredient	Qty (SI units)	Referenced monograph (e.g. B.P, U.S.P)	Reasons for Inclusion	Name and Address of manufacturer

Strength of each ingredient should be expressed in weight, volume or percentage per dosage units. The quantity of overages added, if any should be indicated with the reasons for inclusion provided.

3. Formulation Development

A brief summary describing the development of the finished product should be provided, taking into consideration the proposed route of administration and usage. The differences between clinical formulations and the formulation (i.e. composition) should be discussed. Results from comparative in vitro studies (e.g. dissolution) or comparative in vivo studies (e.g. bioequivalence) should be discussed where appropriate.

3.1 Active Pharmaceutical Ingredient

The compatibility of the API with excipients should be discussed. Additionally, key physicochemical characteristics (e.g. water content, solubility, particle size distribution, polymorphic or solid state form) of the API that can influence the performance of the finished product should be discussed. For combination products, the compatibility of drug substances with each other should be discussed.

3.2 Excipients

The choice of excipients their concentration, their characteristics that can

influence the finished product performance should be discussed relative to their respective function.

3.3 Overages

Any overages in the formulation(s) should be justified.

3.4 Physicochemical and Biological Properties

Parameters relevant to the performance of the finished product, such as pH, ionic strength, dissolution, redispersion, reconstitution, particle size distribution, aggregation, polymorphism, rheological properties, biological activity or potency, and/or immunological activity, should be addressed.

3.5 Manufacturing process development

The selection and optimisation of the manufacturing process in particular its critical aspects, should be explained. Where relevant, the method of sterilization should be explained and justified.

Difference between the manufacturing process (es) used to produce pivotal clinical batches and the process that can influence the performance of the product should be discussed.

4. Manufacture of Product

Provide an outline of the manufacturing procedure for the finished product, including packaging. Provide a copy of the master formula and a copy of a manufacturing record for a real batch.

For sterile products, details of sterilization processes and/or aseptic procedures used must be described.

State the stage of manufacture at which sampling is carried out for in-process control tests. List the in-process quality control tests and checks performed, the stages at which such tests and checks are done, the frequency of sampling and number of samples taken each time.

5. Specifications

State the name and address of the laboratory (ies) performing quality control tests if not done in-house.

5.1 Specifications for starting materials

For ingredients described in the pharmacopoeia, state the referenced pharmacopoeia and provide a copy of the relevant monographs.

Provide details of any specifications additional to those in the pharmacopoeia

For ingredients not described in the pharmacopoeia, provide a list of tests and limits for results for each excipient, including solvents, liquids to adjust pH, coatings, capsule shell, and inked imprint (on the dosage form), including description of test methods in sufficient detail for them to be replicated by

another laboratory.

Include microbiological limits for materials of natural origin.

5.2 Specifications for the finished product

Two separate sets of specifications should be set out, at manufacture (at release) and at the end of shelf life. A list of general characteristics, specific standards, tests and limits for results for the finished product must be provided.

All analytical test procedures used must be described in sufficient details including biological and microbiological methods where relevant to enable the procedures to be repeated if necessary.

The following control methods must be included in the specification:

(i) General characteristics of the finished product (physicochemical properties);

(ii) Identification tests of the active pharmaceutical ingredient(s);

(iii) Quantitative determination of the active pharmaceutical ingredient (s) Unless there is appropriate justification, the maximum acceptable deviation in the active pharmaceutical ingredient content of the finished product shall not exceed +/-5% at the time of manufacture.

(iv) Purity tests (breakdown products, residual solvents or other process related impurities, microbial contamination)

(v) Pharmaceutical tests, e.g. dissolution;

(vi) The identification tests for colouring materials used and identification and assay of antimicrobial or chemical preservatives with limits. The preservatives content limits of 90-110% at release are acceptable without further justification except in special cases.

All procedures need to be validated. Results of the validation studies, comments on the choice of routine tests and standards must be provided.

If the product is tested on the basis of a monograph in a pharmacopoeia, it is sufficient to provide a copy of the monograph together with any test methods referenced but not duplicated in the monograph. Provide any details of any specifications additional to those in the pharmacopoeia. Provide the results of validation of the assay method for this formulation.

For pharmacopoeia methods, provide data which demonstrate that the method is applicable to this formulation.

Results of batch analysis (including date of manufacture, place of manufacture, batch size and use of batch tested) must be presented. The batch analysis must include the results obtained for all specifications at release.

6. Container/closure system(s) and other packaging(s)

Give a detailed description of the container/closure system(s), including any liner or wadding, and provide details of the composition of each component. Describe other (e.g. outer) packaging, and state what materials they are made from. Provide the specifications for any part of the container/closure system(s) which comes into contact with the product or is protective. For parenteral products, components that will at any stage come into contact with any part of the product must comply with requirements specified by the BP, EP, JP or USP.

7. Stability studies

Stability testing provides evidence of how the quality of an API or finished product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light. In this way the recommended storage conditions, re-test periods and shelf life are established.

Applicants are required to provide stability study report conducted on at least three batches of the product, which must include the study design (protocol), type of container, results and conclusions.

The proposed shelf life, containers and storage conditions must be supported by evidence from the studies. The shelf life of reconstituted solutions as well as after opening of sealed bottle should also be stated wherever applicable.

Testing must be conducted using containers and closures intended for marketing of the product in Tanzania. Each pack size intended for marketing shall be subjected to stability testing and results submitted to the Authority for evaluation. For bulk products, testing in prototype containers that simulate the actual packaging is allowed. Information about the type, size and source of containers and closures must be provided to enable determine the expiry period of the product in its container and closure.

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

In any case the proposed shelf life for:

(a) Solid dosage forms should not exceed five years.

(b) Large volume parenterals should not exceed three years.

7.1 Stability of the active pharmaceutical ingredient

Provide the results of stability testing of the active pharmaceutical ingredient. Describe the methodology used during stability studies. Results should be

included for physical as well as chemical tests e.g. particle size and polymorph form. The proposed shelf life (or retest date) should be justified by the stability testing.

7.2 Stability of the finished product

7.2.1 Accelerated stability studies

Give brief description of the accelerated stability studies conducted to establish the effects of the increase of the rate of chemical degradation and physical change of a drug product using exaggerated storage conditions

These studies shall be conducted at **40±2°C/75±5%RH** for six months at a sampling frequency of initial, 1, 2, 3, and 6 months.

Attributes (parameters) to be tested should be those susceptible to change and are likely to influence the quality, safety and efficacy of the pharmaceutical product. These parameters should at least cover:

(a) Appearance for all dosage forms
(b) Assay (stability indicating) for all dosage forms
(c) Degradation products/impurities for all dosage forms
(d) Physicochemical properties such as disintegration, hardness, particulate matter etc., for solid dosage forms
(e) Dissolution for all solid and semi solid oral dosage forms.
(f) Microbial limit for liquid preparations
(g) Sterility for parenterals
(h) pH for parenterals and liquid preparations

Samples from three different batches which are randomly selected to represent the whole batches should be used for the study.

Where different batches of active ingredient(s) are used, then all the batches should be subjected to stability studies.
y
It should be clearly noted that these results could only propose a tentative shelf life of 24 months which shall later be confirmed by submission of completed real time stability studies.

The requirement of orientation of containers and container closure systems is equally applicable here as is in the case for real time stability studies.

7.2.2 Real time stability studies

Describe briefly the real time stability studies performed on three batches to establish the shelf life and storage conditions of the product.

Real time studies should be conducted under controlled conditions (in stability chambers and not on open shelves).

They should be carried out under Zone IV of the world climatic conditions (hot/humid), which are fixed at **30±2°C/65±5%RH** except as may otherwise be recommended for those drugs which require special storage conditions.

Sampling should be done at initial, 3, 6, 9, 12, 18, 24, 36 etc. months to establish the stability characteristics of the drug product.

Samples from three different batches which are randomly selected to represent the whole batches should be used for the study.

Where different batches of active ingredient(s) are used, then all the batches should be subjected to stability studies.

The parameters to be examined, type of packaging and analytical test procedures shall be similar to those described under accelerated stability studies.

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

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

Results of stability studies for three batches tested shall be provided along with the name, qualification, designation and signature of the investigator(s).

Results should be presented in a tabular form and graphs wherever possible.

Acceptance criteria should be fixed for each test included in the stability study. The criteria can be in the form of numerical limits if results are quantitative (e.g. assay, degradation products, particle size, viscosity). For qualitative tests, the criteria can be pass or fail (e.g. odour, colour, appearance).

Analytical test procedures shall be fully validated and assays shall be stability indicating. For products with official monographs, the procedures in the current edition of the official compendia stipulated in these guidelines will apply.

8. Labelling and package insert information requirements.

Ten copies each of package inserts and labels printed on A4 paper shall be included in the application file.

8.1 Labelling requirements

Every immediate container of any product shall be affixed with a label bearing the following particulars pertaining to the contents of such container in clearly legible and indelible letters in English, Swahili or both languages:

(a) International non- proprietary (in bold letters) and proprietary name (in light letters) and the dosage form of the product

(b) The name and strength of the active ingredient(s) and the total content of the product in the container expressed in the appropriate unit or volume of the pharmaceutical product.

(c) The name and concentration (content) of preservatives, where present

(d) Name and address of registrant (product owner). In case of contract manufacturing, the name and address of manufacturer printed in the same letter size as those of the registrant as follows: *"Manufactured for……(name and address of registrant) by…….(name and address of manufacturer)"*.

(e) Distribution category

(f) The Precautions "Keep out of reach of children" and where applicable the instructions:
"For external use only"
"Shake well before use"

(g) Where practicable, indications and recommended dosage of the pharmaceutical product.

(h) In case of products for injection, route of administration by suitable words or abbreviations such as im, iv etc.

(i) The batch or lot number of the product

(j) Storage instructions and shelf life. Storage instructions must be as clear as possible. Storage temperature shall be indicated in numerical figures as derived from stability testing e.g. store between 8-30° C. Instructions such "store under cool conditions" are vague and therefore not acceptable.

(k) The manufacturing and expiry dates of the product

(l) Tanzania drug registration number

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

8.2 Package inserts requirements

Each package of a pharmaceutical product shall be accompanied by a package insert either as a separate entity or as an integral part of the package on which are printed in legible letters in English, Swahili or both under the headings and in the format specified below:

(a) Name (both proprietary and international non-proprietary names) and dosage form of the product

(b) Identification (description of the product and package)

(c) Name and strength of active ingredient(s) in a dosage unit or suitable mass or volume or unit of the product

(d) Therapeutic class

(e) Indications

(f) Dosage regimen and directions for use

(g) Contraindications

(h) Side effects and adverse reactions

(i) Drug interactions

(j) Precautions and warnings

(k) Symptoms and treatment of overdose

(l) Presentation (packing and pack size)

(m) Storage instructions and shelf life. Storage instructions must be as clear as possible. Storage temperature shall be indicated in numerical figures as derived from stability testing e.g. store between 8-30º C. Instructions such "store under cool conditions" are vague and therefore not acceptable.

(n) Name and address of registrant (product owner). In case of contract manufacturing, the name and address of manufacturer printed in the same letter size as those of the registrant as follows: *"Manufactured for……(name and address of registrant) by…….(name and address of manufacturer*

(o) Date of publication of the insert

(p) Any other relevant information

9. Name and signature of the authorized person:

Date:

Official stamp:

PART IV: DOCUMENTATION ON PRE-CLINICAL DATA

I. Overview of pre-clinical testing strategy

The pre-clinical overview should present an integrated and critical assessment of the pharmacologic, pharmacokinetic and toxicologic evaluation of the API. There should be comment on the Good Laboratory Practice (GLP) status of the studies submitted.

The pre clinical safety study recommendations for the marketing approval of an API should include single and repeated dose toxicity studies, reproduction toxicity studies, genotoxicity studies, local tolerance studies and for drugs that have special cause for concern or are intended for a long duration of use, an assessment of carcinogenic potential.

Studies conducted to establish the pharmacodynamic effects, the mode of action, and potential side effects should be evaluated and consideration should be given to the significance of any issues that arise.

The assessment of the pharmacokinetic, toxicokinetic, and metabolism data should address the relevance of the analytical methods used, the pharmacokinetic models, and the derived parameters. It might be appropriate to cross-refer to more detailed consideration of certain issues within the pharmacology or toxicology studies (e.g. impact of the disease states, changes in physiology, antiproduct antibodies, cross-species consideration of toxicokinetic data). Inconsistencies in the data should be discussed. Inter-species comparisons of metabolism and systemic exposure comparisons in animals and humans (AUC, Cmax, and other appropriate parameters) should be discussed and the limitations and utility of the pre-clinical studies for prediction of potential adverse effects in humans highlighted.

The onset, severity, and duration of the toxic effects, their dose dependency and degree of reversibility (or irreversibility) and species or sex related differences should be evaluated and important features discussed, particularly with regard to:

(i) Pharmacodynamics

(ii) Toxic signs

(iii) Causes of death

(iv) Pathologic findings

(v) Genotoxic activity, the chemical structure of the compound, its mode of action, and its relationship to known genotoxic compounds.

(vi) Carcinogenic potential in the context of the chemical structure of the compound, its relationship to known carcinogens, its genotoxic potential, and the exposure data.

(vii) The carcinogenic risk to humans if epidemiological data are available, they should be taken into account.

(viii) Fertility, embryo-foetal development, pre and postnatal toxicity

(ix) Studies in juvenile animals

(x) The consequences of use before and during pregnancy, during lactation, and during development of the animal.

The evaluation of toxicology studies should be arranged in a logical order so that all relevant data elucidating a certain effect/phenomenon are brought together. Extrapolation of the data from animals to humans should be considered in relation to:

(i) Animal species used

(ii) Number of animals used

(iii) Routes of administration employed

(iv) Dosage used

(v) Duration of treatment or of the study

(vi) Systemic exposures in the toxicology species at no observed adverse effect levels and at toxic doses, in relation to the exposures in humans at the maximum recommended human dose. Tables or figures summarising this information are recommended.

(vii) The effect of the API observed in pre-clinical studies in relation to that expected or observed in humans.

If alternatives to whole animal experiments are employed, their scientific validity should be discussed.

II. Content and Structural Format

The Pre-clinical documentation should be presented in the following sequence:

1. **Pharmacodynamics**
2. **Pharmacokinetics**
3. **Toxicology**
4. **Integrated overview and conclusions**
5. **Expert report**

1. Pharmacodynamics

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

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.

1.2 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 (drug or other substances), which are relevant to proposed therapeutic use. Where there is evidence of antagonism or additive/synergistic effects, these should be well elucidated.

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

2. Pharmacokinetics

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

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

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

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

If it is expected that the product will be used in children and paediatrics, studies should include young animals.

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.

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.

2.2 Distribution of API and metabolites

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

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

2.3 Biotransformation

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

2.4 Pharmacokinetic interactions

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

2.5 Excretion

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

3. Toxicology

The principal findings of toxicology studies should be briefly summarized. The extent of toxicological evaluation can be indicated by the use of table listing the principal 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, pathology, teratology, reproduction effects, carcinogenicity, genotoxicity, dependence liability, etc) is required to establish the safe use of the drug.

Toxicity should be studied in several animal species of all sexes, three or more in single dose experiments and two or more in repeated dose investigations (including chronic toxicity, carcinogenicity, genotoxicity). One of the species in all studies should be a pre-rodent.

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

For drugs/products intended for topical application, the possibility of toxic reactions following systemic absorption should be explored. Positive as well as negative results should be reported.

3.1 General Toxicity Studies

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

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

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

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

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

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

Comparative studies with other standard drugs and extrapolation (correlation) of results to man should be included wherever possible.

3.1.2 Single dose toxicity

The single dose toxicity data should be very briefly summarised, in order by species and by route. Data may be presented in the form of a table.

3.1.3 Repeat dose toxicity

Studies should be summarised in order by species, by route and by duration giving brief description of the methodology and highlighting important findings (e.g. nature and severity of target organ toxicity, dose/response relationships, pre observed effect levels etc).

Duration and frequency of repeat dose toxicity studies should be determined by the proposed duration of usage in man and the pharmacokinetics of the drug.

Observation should be extended over the period during which signs are present or may be expected; at least one week after administration of drug may be necessary.

Detailed observation should be made throughout the course of an experiment on pertinent parameters such as: food consumption, body weight, toxic symptoms-convulsions, vomiting, etc. change in appearance, behaviours, locomotion, general conditions, etc. tissue reactions ophthalmic, respiratory, cardiovascular effects haematology (sub acute/chronic only) biochemistry and urinalysis, (sub acute/chronic only).

Discuss the therapeutic margin in animal species tested, whether toxic effects

are reversible or irreversible and which tissues, organs or other effects affect the systems.

3.2 Genotoxicity studies

Studies should be summarised in the following order:

(i) In vitro pre mammalian cell system
(ii) In vitro mammalian cell system
(iii) In vivo mammalian cell system
(iv) Other systems

Genotoxicity testing of existing and new drugs will be required in the following categories:

(a) Compounds, which are chemically, biochemically or pharmacologically related to known or suspected mutagens.

(b) Compounds that exhibit certain toxic effects in animals, such as:

(i) Depression of bone marrow at tolerated doses.

(ii) Inhibition of spermatogenesis or oogenesis at maximum tolerated doses.

(iii) Inhibition of mitosis (e.g. intestinal epithelium and other rapidly growing tissues) at maximum tolerated doses.

(iv) Carcinogenic effects

(v) Teratogenic effects at maximum tolerated doses.

(vi) Causation of sterility or semi-sterility in reproduction studies.

(vii) Stimulation or inhibition of growth or synthetic activity of a specific organ, cell or virus.

(viii) Inhibition of immune response at maximum tolerated dose.

(c) Drugs that are often used over a period of years particularly in children and young adults.

(d) Drugs that are prescribed for a large proportion of the population

(e) Drugs used for general prophylaxis

(f) Drugs subject to widespread abuse

3.3 Carcinogenicity

Carcinogenic studies in animals will be required in the following circumstances:

(a) Where the active pharmaceutical ingredient or its metabolite has a chemical structure or pharmacological properties that suggest carcinogenic potential/resemble known carcinogens.

(b) Where the API causes concern as a result of:

(i) Some specific aspects of its biological action (e.g. damages rapidly crossing tissues such as the haemopoietic system, intestinal mucosa; affects mitosis, spermatogenesis, oogenesis; shows teratogenic, mutagenic effects, etc.)

(ii) Its pattern of toxicity or retention (substances likely to be retained in body tissues for a prolonged period)

(c) Where the API would be used in man continuously for long periods (more than 12 months) or have frequent intermittent usage as in treatment of chronic illness.

3.4 Reproductive and developmental toxicity

Studies should be summarised in the following order, giving brief description of the methodology and highlighting important findings:

3.4.1 Fertility and early embryonic development

Provide summary of effects of the API on fertility and reproductive performance of males and females. This includes effects in gonadal function, the oestrous and menstrual cycle, mating behaviour, fecundation, and early stages of gestation, parturition, lactation and weaning, growth, development, fertility and behaviour of F2 generation.

3.4.2 Perinatal and Postnatal development

Give a summary of effects of the API administered during the period of gestation in which dosing was not conducted in above and during the third trimester of pregnancy, throughout period of lactation up to weaning.

The female animals dosed in these studies should be allowed to litter spontaneously.
Results of studies should report:

a) Effects on the mother
b) Effects on parturition
c) Effects on the foetus or neonate
d) Effects on lactation and growth of the weaning
e) Late effects on the offspring.

3.4.3 Pharmacokinetics in Pregnancy

Give a summary of results of studies on pharmacokinetics during pregnancy.

When reproduction studies are made, opportunity should be taken to determine whether the pharmacokinetics of the drug differ in pregnant from that in pre-pregnant animals.

Plasma levels or tissue concentrations of drug in mother and foetus should be established wherever practicable.

If pharmacokinetic studies in pregnancy are performed separately, they should be conducted with the same species of animals as those used in reproduction studies.

3.5 Dependence Liability

Studies should be made to establish the liability of the API to produce dependence effects such as tolerance, physical and psychic dependence.

Give a summary of results of in-vitro/animal studies for tolerance, physical and psychic dependence effects of the API.

Drugs of the following categories should be evaluated for potential dependence liabilities:

a) Drugs structurally related to compounds known to have dependence liability in man.

b) Drugs acting on the central nervous system such as analgesics, depressants, hallucinogens, stimulants, anorexiants, etc.

3.6 Local Tolerance

If local tolerance studies have been performed they should be summarised in order by species, by route and by duration giving brief description of the methodology and highlighting important findings.

3.7 Other toxicity studies

If other studies as shown below have been performed they should be summarised. When appropriate the rationale for conducting such studies should be provided.

a) Antigenicity
b) Immunogenicity
c) Mechanistic studies (if not reported anywhere)
d) Studies on metabolites
e) Studies on impurities
f) Other studies

4. Integrated overview and conclusions

The Integrated overview and conclusions should clearly define the characteristics of the human pharmaceutical as demonstrated by the pre-clinical studies and arrive at logical, well-argued conclusions supporting the safety of the product for the intended clinical use. Taking the pharmacology, pharmacokinetics, and toxicology results into account, the implications of the pre-clinical findings for the safe human use of the pharmaceutical should be discussed (i.e. as applicable to labelling).

For each study conducted a summary report in the following format shall be submitted. A safety report must contain sufficient details to enable independent conclusions to be drawn on the pharmacological activities and potential hazards (toxicities) of the API and proper assessment of validity of techniques.

a) Name(s), qualification(s) and address (es) of investigators

b) Objectives

Objectives of the study should be stated explicitly

c) Test materials

Provide specifications for API used in the study, including formulation, composition, source, batch number, manufacturer, etc. If specifications are not the same as those given in Part B and C, detailed specifications must be enclosed here including solvent, vehicles, suspending agents, etc. used in tests.

d) Test systems

Studies shall be made on several mammalian species, at least one of which must be a pre-rodent. Animal species selected should be those whose reactions to the test substance are as similar as possible to those of man: rat, hamster, guinea pig, rabbit, cat, dog, monkey, etc.

Where it is reasonable and feasible to provide an animal model for a disease state analogous to that for which the API is indicated, studies on such animals shall also be made.

Species and strain, sex, age, weight, number of test animals, positive control and negative control should be stated. Diet, housing conditions and state of health of animals (physiological and pathological states) shall be also given. Where applicable numbers used should be sufficient to permit valid estimation of incidence and frequency of effect. Justification should be given for selection of a particular animal model or test system.

e) Methodology

Describe study design and justification for the chosen design. Under this section the following should be well addressed:

(i) Procedures employed for the study

(ii) Dosage and administration i.e. range of dose/dose levels, dosage schedule (timing, frequency and duration of treatment), route of administration and duration of study controls, where applicable (positive and negative controls)

(iii) Methods of observation and monitoring of effects (histopathological examination, behavioural examination, criteria for malformation, autopsy findings, etc.). Accuracy, specificity, sensitivity of methods shall be discussed.

(iv) Methods for detection and measurement of API/metabolite in body fluids, tissue or blood

f) Study results

(i) Results of all studies must be presented in a clear and organized form and where appropriate both tables and graphs should be adopted. Positive and negative results should be included.

(ii) Analysis of data - The form of analysis and the tests of statistical significance used should be appropriate to the type of data and to the basic experimental design. The statistical procedure used should be clearly stated.

(iii) Interpretation of results- Types of response, dose-response relationship, time-effect curves, AUC, ED 50, role of modifying factors (enhancing and inhibiting) should be discussed.

(iv) Extrapolation of results to man and evaluation of benefit and risk to patient use should be included wherever possible.

g) Discussion and Conclusions

Discussion and conclusion should be integrated across studies and across species, and exposure in the test animals should be related to exposure in humans given the maximum intended doses. Whenever appropriate, age and gender related effects should be discussed. Relevant findings with stereoisomers and/or metabolites should be included.

h) Bibliography

Bibliography of all studies conducted on the API shall be provided.
The list should include relevant report of studies made by the manufacturer/applicant or on his behalf, articles and papers published in reputable scientific journals, monographs or official compendia, dated reports and protocols from named laboratories.

References, whether or not cited in the summary shall be listed.

5. Expert Report

The expert should clearly define the beneficial and advantageous aspects of the API as demonstrated by toxico-pharmacological studies. Any necessary conditions for its use should be specified including, for radiopharmaceuticals any precautions necessary because of the radioactive nature of the product.

The expert should especially and in each case refer to the following:

(i) The effects of an active substance(s) observed in toxico – pharmacological studies in relation to those expected or observed in man

(ii) The consequences of the use of the medicinal product before and during pregnancy and during lactation

(iii) Mutagenic effects

(iv) The tumorigenic risk to man if epidemiological data are available they should be taken into account

(v) Possible irreversible toxic effects

(vi) The consequence of the product being a radiopharmaceutical

5.1 Pharmacodynamics

Studies conducted to establish the pharmacodynamic effects and the mode of action should be evaluated in the following order:

(i) Studies demonstrating desired therapeutic effects

(ii) Studies demonstrating effects in addition to desired effects

(iii) Studies to detect drug interactions

5.2 Pharmacokinetics

The data of absorption, distribution, biotransformation, excretion, protein binding and the occurrence of metabolites necessary for extrapolation to humans should be assessed considering the relevance of:

(i) The methods used (including sensitivity and validation of assays

(ii) The pharmacokinetic models

(iii) The pharmacokinetic parameters

5.3 Toxicity

The appearance and duration of the toxic effects, the dose-dependency and the reversibility or irreversibility, and all species or sex related differences should be reviewed and important features discussed particularly with regard to:

(i) Toxic symptoms

(ii) Clinical-chemical and haematological findings

(iii) Interactions between excipients of the medicinal product (fixed combinations)

(iv) Fertility, embryotoxicity (particularly teratogenicity), and peri/postnatal toxicity

(v) Mutagenic activity, for which the chemical structure of the compound, its mode of action and the relationship to known mutagens should be taken into account,

(vi) Oncogenic/carcinogenic potential in the context of the chemical structure, the relationship of known carcinogens, the mutagenic potential, and the pharmacokinetics

(vii) Local toxicity

(viii) Immunotoxicity

(ix) Studies conducted to clarify special problems

The evaluation of toxicological studies should be arranged in a logical order so that all relevant data elucidating a certain effect or phenomenon are brought together. Extrapolation of data from one animal species to another and from animals to man should be discussed considering the relevance of:

(i) Animal species used

(ii) Number(s) of animals used

(iii) Route(s) administration employed

(iv) Dosage(s) used

(v) Duration of treatment or of the study

If alternatives to whole animal experiments are employed, their validity should be proved.

If the dose response relationship changes, e.g. with increasing doses or during repeated or long term dosing, an explanation should be proposed.

5.4 Conclusions

Conclusions should be drawn as outlined above.

5.5 Reference list

A list of references used, in addition to those contained in the dossier, should be given and stated in accordance with internationally accepted standards of the 1979 Vancouver Declaration on "Uniform Requirements for Manuscripts Submitted to Biomedical Journals" or the system used in "Chemical Abstracts".

5.6 Curriculum Vitae of the toxico-pharmacological expert(s)

The qualifications and experience of the toxico-pharmacological expert(s) should be briefly summarised. Although only one expert may assume responsibility for the expert report, other experts may contribute to its preparation, according to their expertise.

PART V: DOCUMENTATION ON CLINICAL DATA

The purpose of this section is to present a critical analysis of important issues that might affect the efficacy and/or safety of the to-be-marketed formulation(s) (for instance, dosage form or strength proportionality, differences between the to-be-marketed formulation and the formulation(s) used in clinical trials, and influence of food on exposure).

The section also presents a critical analysis of the clinical data pertinent to the efficacy of the medicinal product in the intended population. The analysis should consider all relevant data, whether positive or negative and should explain why and how the data support the proposed indication and prescribed information.

Detailed reports of clinical trials and supporting documents should be submitted.

Sufficient details must be provided in all reports to enable:

(i) Independent conclusions to be drawn on the pharmacological activities, pharmacokinetics, efficacy and potential hazard (toxicities) of the product.

(ii) Assessment of validity of techniques.

(iii) For products containing more than one active pharmaceutical ingredient, state clearly whether the information refers to a particular ingredient. Information for combination products should cover individual ingredients as well as the effects of the combination.

The efficacy reports should be presented in the following format:

1. Product used in the study

Give particulars of the product (source, formulation and specifications), if different from that proposed for marketing.

Give particulars (source, formulation, characteristics, packaging etc) of placebos, controlling agents, if any. If product used is different from that proposed for marketing (registration), the equivalence of the products should be discussed and appropriate data included providing evidence of equivalence.

2. Particulars of subjects

Give the total number of subjects involved in the study (sufficient to allow dropouts and variability of effects). The age of subjects appropriate to problem under study should also be provided. Mention the sex of subjects, including reasons for limitations, if any.

State the selected health/disease states (with diagnostic criteria and confirmatory tests), socio-economic and cultural factors, geographical areas, criteria for exclusion, withdrawal of subjects, compatibility of study group, etc.

3. Study design

Mention the study groups, number per group, and number of groups.
Explain the methods of allocation (complete random assignments, blocking on baseline status or other statistically acceptable methods).

Mention the types of controls:
Placebo, positive control, standard treatment, no treatment
Single blind, double blind, pre-blind, cross-over (within patient comparison), concurrent/retrospective controls (in between patient comparison) etc

4. Treatment profiles

Give dosage (route, amount, frequency, duration).
Mention concurrent, subsequent therapy, if any and washout period, where applicable.

5. Study parameters

Mention the indices, variables etc, for measuring parameter under study (effect, reaction) etc.

Indicate the methods of measurement, assessment of observation, details of technique of measurement, assessment, quantitation of response, laboratory and analytical methods.

Indicate also the rationale for choice of indices, variables and their methods of determination; specificity, sensitivity and precision of methods selected.

6. Examination procedures

Give the qualifications of personnel, number of examiners, etc other than investigators named above (where relevant).

Indicate the frequency of examination, observation and measurement.
List the equipment and facilities used.

Give details of operational aspects – treatment schedule of groups, individuals, preparation of products, dispensing, administration, storage of products between treatment, monitoring of potency and stability of product, methods of ensuring blind design etc, where relevant.
Indicate the modifications from protocol, if any (withdrawals, dropouts, adjustments, review of criteria from measurement, observation, assessment, etc).

Give details of record keeping (treatment rosters, inventory of supplies, etc) relevant to the study. Indicate the observations and recordings of effects studied.

7. Results and observations

Give a summary of baseline data, such as by groups, categories treated, location, investigator. Tabulation and graphical representation should be included where relevant and possible.

8. Statistical considerations

Give details of protocol design, including statistical hypothesis to be tested, considerations in determining sample size and possible stratification of study subjects. Give details of analysis of results and software used to analyse the results (e.g. EPI-INFO, SPSS and SAS etc. Statistical analysis of response variables, indices, comparison between treatment groups and rationale for statistical methods should also be given.

9. Discussion and conclusions

The purpose of this section is to integrate all of the conclusions reached in the previous sections about bio-pharmaceutics, clinical pharmacology, efficacy and safety of the medicinal product and to provide an overall appraisal of the benefits and risks of its use in clinical practice.

The analysis of benefits and risks is expected to be very brief but it should identify the most important conclusions and issues concerning each of the following points:

a) The efficacy of medicinal product for each proposed indication
b) Significant safety findings and any measures that may enhance safety
c) Dose-response and dose-toxicity relationships, optical dose ranges and dosage regimens
d) Efficacy and safety in sub-populations e.g. those defined by age, sex, ethnicity, organ function, disease severity and genetic polymorphisms
e) Data in children in different age groups, if applicable and any plans for a development programme in children
f) Any risks to the patient of known and potential interactions including food-drug and drug-drug interactions and recommendations for the product use
g) Any potential effect of the medicinal product that affect ability to drive or operate heavy machinery.

Details of results, discussion and conclusions should be well presented. Give a summary and comparison of results with data from other investigations/studies, explaining differences from other centres/sources, if any. Limitations of study (withdrawals, dropouts, failure, etc) should be given together with reasons.

CLINICAL TRIALS

Efficacy of a medicinal product can be demonstrated through clinical trials.
Clinical trials are generally divided into three phases (Phase I-III), the fourth phase for additional studies and post marketing surveillance especially on efficacy and adverse reactions may sometimes be conducted.

For each phase a summary of well presented, controlled clinical trials, investigating the product pharmacological and therapeutic properties and adverse reactions should be submitted.

For each phase give a concise summary of clinical study conducted and major findings. This should include names of investigators, their addresses, qualifications and official status. The aims, specific objectives and rationale of the study should be given as well as the addresses of institutions where the clinical trials were conducted, if different from above.

Evidence must be shown that there was compliance to Good Clinical and Laboratory Practices.

a) Phase I

Phase I clinical trials are intended to provide evidence of safety, pharmacological effects, safe dose, and dose related side effects of drug (single dose and repeated dose administration), etc.

It also aim at providing information regarding drug pharmacokinetics (absorption, distribution, metabolism and excretion), determination of relationship between dose, drug-concentration in blood and clinical response for both desirable and undesirable effects and support choice of dose selection and dosing interval and any other instructions regarding individualization of dosage.

Biopharmaceutics studies present a critical analysis of any important issues related to bioavailability that might affect safety and/or efficacy of the formulation e.g. dosage form, strength proportionality, effect of food etc.

Healthy adult volunteer subjects or selected patients may be used. Number of subjects/patients varies with the drug.

Phase I studies should ideally be conducted on "hospitalised" subjects or in settings which permit close observation.

b) Phase II

Phase II clinical trials are required to identify types of disease/conditions, which may be responsive to the drug (product), i.e. establish effectiveness, estimate appropriate clinical dosage and duration of effect and identify adverse effects i.e. establish safety. Studies should be closely monitored patients (100-200 subjects).

c) Phase III

Studies in this phase provide more specific information about incidence of common and rare adverse effects as well as more specific information about types of conditions for which product is especially effective.

It also intend to establish optimal dosage in populations for which it is intended, duration of continued effectiveness if given up to six months or more, where relevant and safety when product is given daily for up to six months or more, where relevant.

Details of on-going trials and stage of progress should be included. Reports of such studies must be submitted on completion of studies

Data should be obtained to ascertain whether the product confers clinical benefit in the disease condition for which effectiveness is claimed, over its adverse effects.

In the case of combination products, studies showing that the combination as such is of therapeutic value and confers advantages over and above those conferred by the ingredient when taken separately in therapeutic doses are to be submitted. Adverse reactions resulting from such combination should also be studied.

d) Phase IV

This phase begins after drug approval and it includes all studies performed after drug approval and related to the approved indications. These are studies often important for optimising the drug's use.

If the drug has been already marketed, all relevant post-marketing data available to the applicant (published and unpublished including periodic safety update reports if available) should be summarised.

Details of on-going studies and stage of progress as well as reports of such studies shall be submitted on completion.
A summary of special studies elucidating use of product in special circumstances (e.g. during pregnancy, breastfeeding, in infants and children, geriatric patients, patients with diseases complicating the monitoring of efficacy of the drug such as kidney disease etc.) shall be submitted.

Particular attention should be paid to various factors under special circumstances e.g. Pregnancy and breast-feeding, toxic effects to mother, foetus, newborn, infant, labour drug level in breast milk etc.
.
In case of paediatrics determination of dosage (documented evidence for suitable dosage) at various stages, from infancy to puberty should be well documented.

Special dosage consideration should be made for geriatric and patients with complicating diseases.

10. Expert report

Provide an expert report on clinical studies conducted to evaluate safety and efficacy of the product.

The report should be presented in the following sequence:

a) Problem statement
b) Clinical pharmacology
c) Clinical trials (efficacy and safety)
d) Post marketing experience
e) Other information
f) Conclusions
g) Reference list
h) Curriculum vitae of the experts

Although only one expert may assume responsibility for the expert report, other experts may contribute to its preparation, according to their expertise.

PART VI: DOCUMENTATION FOR FIXED DOSE COMBINATION PRODUCTS (FDCs)

A fixed dose combination is a medicinal product consisting of two or more active ingredients co-formulated into a single product or two different drugs co-packaged together for the purposes of being co-administered in a fixed ratio of doses.
All information prescribed for single active ingredient products shall be submitted together with the following additional information under the respective parts.
For the purposes of these guidelines FDCs are grouped into three categories; generic FDCs or FDCs whose all APIs are well established and their concurrent use is standard of care; FDCs whose all APIs are well established but their concurrent use are unknown; and FDCs with one or more new chemical entities.
Developmental pharmaceutics, pharmacokinetic and pharmacodynamic studies of FDCs in category II and III should demonstrate that the individual components: -

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

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

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

For such products documentation of studies done to demonstrate bioequivalence shall be sufficient. Generally no toxicology studies are needed, provided international acceptable excipients are used
The documentation shall include data or literature in support of the safety and efficacy of the combination. However non-clinical pharmacology or toxicology studies and clinical efficacy studies in support of the proposed indication may be required if the proposed indication involves either a higher dose level or duration than currently licensed for one or more of the active ingredients in the fixed dose combination. Alternatively, toxicological studies may be needed if there is potential for a drug interaction or overlapping toxicity.

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

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

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

Appropriate pharmacokinetic and/or pharmacodynamic studies data (studies must 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 drug interaction or overlapping toxicity.
b) Comparative clinical studies of the FDC versus a reference product or a regimen used as part of standard of care for the same indication to demonstrate clinical superiority or non-inferiority and contribution each component within the combination to the claimed effect.

The clinical superiority or advantages may include:

(i) Increased efficacy (additive or synergistic)
(ii) Reduced toxicity
(iii) Prevention of antimicrobial resistance
(iv) Bolstering of drug levels

In situations where monotherapy does not satisfy the standard of care, the aggregate of data supporting the combination may include historical clinical data on the components used alone, pharmacokinetic data, animal data, in vitro microbiological data, etc.
The risks and benefits should be clearly defined and weighed.

3. FDCs with one or more new APIs.

These consist of one or more new molecular entities.
Documentation required in appropriate Parts includes:
(i) Complete data demonstrating the quality, safety and efficacy of each of the individual active ingredients.
Individual components that are being considered for inclusion in a FDC should have a well-established risk-benefit profile in the target population at the recommend dosing regimens. Consideration should be given to ethnic, environmental, co-morbid, and nutritional variations between populations

(ii) comparative preclinical and clinical studies safety and efficacy data of the FDC demonstrating clinical superiority or non-inferiority when compared to another product or regimen used as part of standard of care for the same indication.
Comparators or comparator regimens should represent the current state of the art treatment for the indication in question.
The comparators should be licensed innovator products.

iii) Microbiological evaluation

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

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

a) Microbiological activity in appropriate animal models of infection with the targeted pathogen(s),

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

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

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

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

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

4.0 Bioequivalence studies for FDC

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

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

PART VII: #part7DOCUMETATION FOR THERAPEUTIC EQUIVALENCE STUDIES **

Therapeutic equivalence

Unless otherwise expressly exempted in these guidelines, documentation on studies done to demonstrate therapeutic equivalence of all generic medicinal products must be submitted.

Therapeutic equivalence/interchangebility may subject to the prescribed conditions be demonstrated by in vivo bioequivalence, comparative clinical or pharmacodynamic studies or in-vitro dissolution profiles.
The comparator product shall an innovator or other prescribed reference product. The generic product must be a pharmaceutical equivalent or alternative.

1. Bioequivalence Studies

Bioequivalence studies (BE) are scientific investigations in man designed to establish the comparability of bioavailabilities of two or more medicinal products.

Bioequivalence studies data is required for all generic medicinal products except those expressly exempt in these guidelines

BIOEQUIVALENCE STUDIES FOR ORAL SOLID DOSAGE FORMS

The following are the requirements for the design and conduct of bioequivalence studies.

3.1 Study design

The study design should be such that the formulation effects can be differentiated from other effects. If the formulations are two, a balanced two-period, two-sequence crossover design is preferred. However, subject to the study design, data collection and statistical analyses being scientifically sound, alternative designs such as parallel designs for very long half-life substances may be acceptable.

Generally, single dose studies will suffice, but in situations in which they do not suffice steady-state studies will be required.

To avoid carry-over effects, treatments should be separated by adequate wash-out periods.

The sampling schedule should be planned to provide an adequate estimation of C_{max} and to cover the plasma drug concentration time curve long enough to provide a reliable estimate of the extent of absorption. This is generally achieved if the AUC derived from measurements is at least 80 % of the AUC extrapolated to infinity.

If a reliable estimate of terminal half-life is necessary, it should be obtained by collecting at least three to four samples above the Limit of Quantification during the terminal log linear phase. For long half-life drugs (> 24 hours) the study should cover a minimum of 72 hours unless 80 % is recovered before 72 hours.

For immediate release dosage forms, studies should be done under fasting conditions, unless food effects influence bioavailability. If the reference product dosage directions specifically state administration with food or without food, the study should be designed accordingly

For modified release dosage forms, the influence of food should be demonstrated to exclude any possibility of dose dumping; hence, both fed and fasted studies are required**.**

3.2 Study population

3.2.1 Number of Subjects

It is recommended that the number of subjects should be justified on the basis of providing at least 80 % power of meeting the acceptance criteria. The minimum number of subjects should not be less than 12. If 12 subjects do not provide 80 % power, more subjects should be included.

A minimum of 20 subjects is required for modified release oral dosage forms.

The number of subjects required to provide an 80 % power of meeting and passing the acceptance criteria for the 0,8 to 1,25 acceptable interval, can be determined from Reference 1.

Alternatively, the sample size can be calculated using appropriate power equations, which should be presented in the protocol.

The provision for add-ons should be made in the protocol *a priori* clearly reflecting the maximum number of subjects to be included.

3.2.2 Selection of Subjects

The subject population for bioequivalence studies should be selected with the aim to minimise variability and permit detection of differences between pharmaceutical products. Therefore, the studies should normally be performed with healthy volunteers.

The inclusion/exclusion criteria should be clearly stated in the protocol.

In general, subjects should exhibit the following characteristics:

a) **Sex:** Subjects may be selected from either sex. However, the risk to women of childbearing potential should be considered on an individual basis.

b) **Age:** Subjects should be between 18 and 55 years of age.

c) **Mass:** Subjects should have a body mass within the normal range according to accepted normal values for the Body Mass Index (BMI = mass in kg divided by height in meters squared, i.e. kg/m^2), or within 15 % of the ideal body mass, or any other recognised reference.]

d) **Informed Consent**: All subjects participating in the study should be capable of giving informed consent.

e) **Medical Screening:** Subjects should be screened for suitability by means of clinical laboratory tests, an extensive review of medical history, and a comprehensive medical examination. Depending on the drug's therapeutic class and safety profile, special medical investigations may have to be carried out before, during and after the completion of the study.

f) **Smoking/Drug and Alcohol Abuse:** Subjects should preferably be non-smokers and without a history of alcohol or drug abuse. If

moderate smokers are included they should be identified as such and the possible influences of their inclusion on the study results should be discussed in the protocol.

3.2.3 Inclusion of Patients

If the API under investigation is known to have adverse effects and the pharmacological effects or risks are considered unacceptable for healthy volunteers, it may be necessary to use patients instead, under suitable precautions and supervision. In this case the applicant should justify the use of patients instead of healthy volunteers.

3.2.4 Genetic Phenotyping

Phenotyping and/or genotyping of subjects can be considered for exploratory bioavailability studies. It may also be considered in crossover studies (e.g. bioequivalence, dose proportionality, food interaction studies) for safety or pharmacokinetic reasons.

If a drug is known to be subject to major genetic polymorphism, studies could be performed in cohorts of subjects of known phenotype or genotype for the polymorphism in question.

3.3 STANDARDISATION OF THE STUDY CONDITIONS

The test conditions should be standardised in order to minimise the variability of all factors involved, except that of the products being tested. Therefore, standardisation of the diet, fluid intake and exercise is recommended.

3.3.1 Dosing: The time of day for ingestion of doses should be specified.

3.3.2 Fluid Intake at Dosing: As fluid intake may profoundly influence the gastric transit of orally administered dosage forms, the volume of fluid administered at the time of dosing should be constant (e.g. 200 ml).

3.3.3 Food and Fluid Intake: In fasted studies the period of fasting prior to dosing should be standardised and supervised. All meals and fluids taken after dosing should also be standardised in regard to composition and time of administration and in accordance with any specific requirements for each study.

3.3.4 Concomitant Medication: Subjects should not take other medicines for a suitable period prior to, and during, the study and should abstain from food and drinks which may interact with circulatory, gastrointestinal, liver or renal function (e.g. alcoholic or xanthine-containing beverages or certain fruit juices).

3.3.5 Posture and Physical Activity: As the bioavailability of an active moiety from a dosage form can be dependent upon gastrointestinal transit times and regional blood flows, posture and physical activity may need to be standardised.

3.4 SAMPLE COLLECTION AND SAMPLING TIMES

Under normal circumstances, blood should be the biological fluid sampled to measure the concentrations of the drug. In most cases the drug may be measured in serum or plasma. However, in some cases, whole blood may be more appropriate for analysis.

3.4.1 When blood is collected:

a) The duration of blood sampling in a study should be sufficient to account for at least 80 % of the known AUC to infinity (AUC_{∞}). This period is approximately three terminal half-lives of the drug.

b) For most drugs 12 to 18 samples including a pre-dose sample should be collected per subject per dose.

c) Sample collection should be spaced such that the maximum concentration of drug in blood (C_{max}) and the terminal elimination rate constant (K_{el}) can be estimated.

d) At least three to four samples above LOQ should be obtained during the terminal log-linear phase to estimate K_{el} by linear regression analysis.

e) The actual clock time when samples are collected, as well as the elapsed time relative to drug administration, should be recorded.

If drug concentrations in blood are too low to be detected and a substantial amount (> 40 %) of the drug is eliminated unchanged in the urine, then urine may serve as the biological fluid to be sampled.

3.4.2 When urine is collected:

a) The volume of each sample should be measured immediately after collection and included in the report.

b) Urine should be collected over an extended period and generally no less than seven times the terminal elimination half-life, so that the amount excreted to infinity (Ae_{∞}) can be estimated.

c) Sufficient samples should be obtained to permit an estimate of the rate and extent of renal excretion. For a 24-hour study, sampling times of 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 hours post-dose are usually appropriate.

d) The actual clock time when samples are collected, as well as the elapsed time relative to drug administration, should be recorded.

3.5 CHARACTERISTICS TO BE INVESTIGATED

3.5.1 Blood/Plasma/Serum Concentration *versus* Time Profiles

In most cases evaluation of bioavailability and bioequivalence will be based upon measured concentrations of the parent compound (i.e. the API) where the shape of, and the area under, the plasma concentration *versus* time curves are generally used to assess the rate and extent of absorption.

In some situations, however, measurements of an active or inactive metabolite may be necessary instead of the parent compound. Instances where this may be necessary are as follows:

a) If the concentration of the API is too low to be accurately measured in the biological matrix.

b) If there is a major difficulty with the analytical method.

c) If the parent compound is unstable in the biological matrix.

d) If the half-life of the parent compound is too short, thus, giving rise to significant variability.

Justification for not measuring the parent compound should be submitted by the applicant and bioequivalence determinations based on metabolites should be justified in each case.

Sampling points should be chosen such that the plasma concentration *versus* time profiles can be defined adequately, thereby allowing accurate estimation of relevant parameters.

The following bioavailability parameters are to be estimated:

a) AUC_t, AUC_∞, C_{max}, t_{max} for plasma concentration *versus* time profiles.

b) AUC_∞, C_{max}, C_{min}, fluctuation (% PTF) and swing (% Swing) for studies conducted at steady state.

c) Any other justifiable characteristics (cf. Appendix I).

d) The method of estimating AUC-values should be specified.

3.5.2 Urinary Excretion Profiles

In the case of API's predominantly excreted renally, the use of urine excretion data may be advantageous in determining the extent of drug input. However, justification should also be given when this data is used to estimate the rate of absorption.

Sampling points should be chosen so that the cumulative urinary excretion profiles can be defined adequately so as to allow accurate estimation of relevant parameters.

The following bioavailability parameters are to be estimated:

a) Ae_t, Ae_∞ as appropriate for urinary excretion studies.

b) Any other justifiable characteristics (cf. Appendix I).

c) The method of estimating AUC-values should be specified.

3.5.3 Pharmacodynamic Studies

If pharmacodynamic parameters/effects are used as bioequivalence criteria, the applicant should submit justification for their use. Bioequivalence determinations based on these measurements should be justified in each case. In addition:

a) A dose-response relationship should be demonstrated.

b) Sufficient measurements should be taken to provide an appropriate pharmacodynamic response profile.

c) The complete dose-effect curve should remain below the maximum physiological response.

d) All pharmacodynamic measurements/methods should be validated with respect to specificity, accuracy and reproducibility.

3.6 Bio analysis

The bio analytical part of bioequivalence trials should be conducted according to the applicable principles of Good Laboratory Practice (GLP) and cGMP**.**

Bioanalytical methods used to determine the active moiety and/or its metabolic product(s) in plasma, serum, blood or urine, or any other suitable

matrix, should be well characterised, and fully validated and documented to yield reliable results that can be satisfactorily interpreted.

The main objective of method validation is to demonstrate the reliability of a particular method for the quantitative determination of an analyte(s) in a specific biological matrix. Validation should, therefore, address the following characteristics of the assay (Reference 2):

a) Stability of stock solutions.

b) Stability of the analyte(s) in the biological matrix under processing conditions and during the entire period of storage.

c) Specificity.

d) Accuracy.

e) Precision.

f) Limits of detection and quantification.

g) Response function.

i) Robustness and ruggedness.

A calibration curve should be generated for each analyte in each analytical run, and it should be used to calculate the concentration of the analyte in the unknown samples in the run.

A number of separately prepared Quality Control samples should be analysed with processed test samples at intervals based on the total number of samples.

All procedures should be performed according to pre-established Standard Operating Procedures (SOPs).

All relevant procedures and formulae, used to validate the bioanalytical method, should be submitted and discussed.

Any modification of the bioanalytical method, before and during analysis of study specimens, may require adequate revalidation, and all modifications should be reported and the scope of revalidation justified.

3.7 Study Products

3.7.1 Reference Products

Refer to the Pharmaceutical and Analytical guideline**.**

3.7.2 Retention samples

A sufficient number of retention samples of both test and reference products used in the bioequivalence study, should be kept for one year in excess of the accepted shelf-life, or two years after completion of the trial or until approval, whichever is longer, in order to allow re-testing if required by the Authority.

3.7.3 Sample handling

A complete audit trail of procurement, storage, transport and use of both the test and reference products should be recorded.

3.8 Data analysis

The primary concern of bioequivalence assessment is to quantify the difference in bioavailability between the test and reference products, and to demonstrate that any clinically important difference is unlikely.

3.8.1 Statistical Analysis

The statistical method for testing relative bioavailability (i.e. average bioequivalence) is based upon the 90 % confidence interval for the ratio of the population means (Test/Reference) for the parameters under consideration.

Pharmacokinetic parameters derived from measures of concentration, e.g. AUC_t, AUC_∞ and C_{max} should be analysed using ANOVA. Data for these parameters should be transformed prior to analysis using a logarithmic transformation.

If appropriate to the evaluation, the analysis technique for t_{max} should be non-parametric and should be applied to untransformed data.

In addition to the appropriate 90 % confidence intervals, summary statistics such as geometric and arithmetic means, SD and % RSD, as well as ranges for pharmacokinetic parameters (minimum and maximum), should be provided.

3.8.2 Acceptance Range for Pharmacokinetic Parameters

The pharmacokinetic parameters to be tested, the procedure for testing and the acceptance ranges, should be stated beforehand in the protocol.

a) Single-Dose Studies

In single-dose studies designed to determine average bioequivalence, acceptance criteria for the main bioequivalence parameters are as follows:

i) AUC_t - ratio

The 90 % confidence interval for the test/reference ratio should lie within the acceptance interval of 0,80-1,25 (80 – 125 %).

In certain cases an alternative approach may be acceptable.

Justification for the use of alternative methods, e.g. scaled average bioequivalence (ABE) based on sound scientific principles for the evaluation of the bioequivalence of highly variable drugs, has been described in the literature (References 2 and 3). Use of alternative methods should be stated *a priori* in the protocol and cannot be added retrospectively.

ii) C_{max} - ratio

The 90 % confidence interval for the test/reference ratio should lie within an acceptance interval of 75 – 133 %, calculated using log-transformed data, except for narrow therapeutic range API's when an acceptance interval of 80 – 125 % will apply.

In certain cases, e.g. in the case of highly variable API's, a wider interval or other appropriate measure may be acceptable, but should be stated *a priori* and justified in the protocol (See references 3 and **4).**

b) Steady-State Studies

i) Immediate Release Dosage Forms

The acceptance criteria are the same as for single dose studies but using AUC_{∞} instead of AUC_t

ii) Controlled/Modified Release Dosage Forms

The acceptance criteria are as follows:

- **AUC_{∞} - ratio**
  The 90 % confidence interval for the test/reference ratio should lie within the acceptance interval of 0,80-1,25 (80 – 125 %).
- **$C_{max\ (ss)}$ and $C_{min\ (ss)}$**
  The 90 % confidence interval for the test/reference ratio should lie within the acceptance interval of 0,75-1,33 (75 – 133 %), calculated using log-transformed data.
- **% Swing and % PTF**
  The 90 % confidence interval for the test/reference ratio should lie within the acceptance interval of 0,80-1,25 (80 – 125 %), calculated using log transformed data.

3.9 Study Report

The report of a bioavailability or a bioequivalence study should give the complete documentation of its protocol, conduct and evaluation, complying with GCP, GLP and cGMP.

3.9.1 Clinical Report

In addition to the protocol the clinical section of the bioequivalence study report should include the following:

a) A statement indicating the independence of the ethics committee.

b) Documented proof of ethical approval of the study.

c) A complete list of the members of the ethics committee, their qualifications and affiliations.

d) Names and affiliations of the all investigator(s), the site of the study and the period of its execution.

e) The names and batch numbers of the products being tested.

f) The name and address of the applicant of both the reference and the test products.

g) Expiry date of the reference product and the date of manufacture of the test product used in the study.

h) Assay and dissolution profiles for test and reference products.

i) Certificate of analysis of the API used in the test product bio-batch.

j) A summary of adverse events, which should be accompanied by a discussion on the influence of these events on the outcome of the study.

k) A summary of protocol deviations (sampling and non-sampling) which should be accompanied by a discussion on the influence of these adverse events on the outcome of the study.

l) Subjects who drop out or are withdrawn from the study should be identified and their withdrawal fully documented and accounted for.

3.9.2 Analytical Report

The analytical section of the bioequivalence report should include the following clearly presented:

a) The full analytical validation report.

b) All individual subject concentration data.

c) Calibration data, i.e. raw data and back-calculated concentrations for standards, as well as calibration curve parameters, for the entire study.

d) Quality control samples for the entire study.

e) Chromatograms from analytical runs for 20 % of all subjects (or a minimum of 4 subjects) including chromatograms for the associated standards and quality control samples.

f) A summary of protocol deviations which should be accompanied by a discussion on the influence of these deviations on the outcome of the study. Protocol deviations should be justified.

3.9.3 Pharmacokinetic and Statistical Report

The pharmacokinetic and statistical section of the bioequivalence report should include the following, which should be clearly presented:

a) All individual plasma concentration *versus* time profiles presented on a linear/linear as well as log/linear scale (or, if appropriate, cumulative urinary excretion data presented on a linear/linear scale).

This data should be submitted in hard copy and also formatted on a diskette in a format compatible for processing by SAS software. Individual subject data should be in rows and arranged in columns, which reflect the subject number, phase number, sequence, formulation, and sample concentration *versus* time data (Appendix 2).

b) The method(s) and programmes used to derive the pharmacokinetic parameters from the raw data.

c) A detailed ANOVA and/or non-parametric analysis, the point estimates and corresponding confidence intervals for each parameter of interest.

d) Tabulated summaries of pharmacokinetic and statistical data.

e) The statistical report should contain sufficient detail to enable the statistical analysis to be repeated, e.g. individual demographic data, randomisation scheme, individual subject concentration *vs*. time data, values of pharmacokinetic parameters for each subject, descriptive statistics of pharmacokinetic parameters for each formulation and period.

3.9.4 Quality Assurance (QA)

a) A signed QA statement, confirming release of the document should accompany the study report.

b) A declaration should be made by the applicant to indicate whether the site(s) (clinical and analytical) where the study was performed was subjected to a pre-study audit to ascertain its/their status of GCP and GLP and/or cGMP conditions. All audit certificates should clearly

indicate the date of audit and the name(s), address(es) and qualifications of the auditor(s).

c) The applicant should submit an independent monitor's certificate on the clinical portion of the study. This certificate should clearly indicate the date of monitoring and the name, address and qualifications of the monitor, and should be included in the study report**.**

3.10 EXPIRY DATES OF BIOSTUDIES

The bioequivalence study should have been completed not longer than five years prior to the date of submission.

4 BIOAVAILABILITY AND BIOEQUIVALENCE REQUIREMENTS

4.1 ORALLY ADMINISTERED DRUG PRODUCTS INTENDED FOR SYSTEMIC ACTION

4.1.1 Antibiotics and Anti-microbials (such as for tuberculosis)

Unless otherwise exempted by the Authority

- bioequivalence studies should be carried out for all antibiotic preparations and
- Bioavailability studies for anti-microbial preparations.

4.1.2 Solutions

A bioequivalence waiver may be granted for oral solutions, elixirs, syrups or other solubilised forms containing the same API(s) in the same concentration(s) as the innovator or other reference product, and containing no ingredient known to significantly affect absorption of the medicinal ingredient(s).

4.1.3 Suspensions

Bioequivalence for a suspension should be treated in the same way as for immediate release solid oral dosage forms.

4.1.4 Immediate Release Products – Tablets and Capsules

In general bioequivalence studies are required. *In vivo* BE studies should be accompanied by *in vivo* dissolution profiles on all strengths of each product. Waivers for *in vivo* bioavailability and bioequivalence studies for immediate release solid oral dosage forms, based on comparative dissolution studies, may be acceptable (see 5 below and Dissolution guideline).

4.1.5 Modified Release Products

Modified release products include delayed release products and extended (controlled) release products. In general, bioequivalence studies are required. In addition to the studies required for immediate release products, a food-effect study is necessary. Multiple dose studies are generally not recommended.

4.1.6 Miscellaneous Oral Dosage Forms

Rapidly dissolving drug products, such as buccal and sublingual dosage forms, should be tested for *in vitro* dissolution and *in vivo* BA and/or BE.

Chewable tablets should also be evaluated for *in vivo* BA and/or BE. Chewable tablets (as a whole) should be subject to *in vitro* dissolution because a patient, without proper chewing, might swallow them. In general, *in vitro* dissolution test conditions for chewable tablets should be the same as for non-chewable tablets of the same active ingredient/moiety.

4.2 ORALLY ADMINISTERED DRUGS INTENDED FOR LOCAL ACTION

Generally BE studies with clinical efficacy and safety endpoints and/or suitably designed and validated *in vitro* studies are required.

4.3 PARENTERAL SOLUTIONS

The applicant is not required to submit a bioequivalence study if the product is to be administered as an aqueous intravenous solution containing the same API in the same concentration as the currently approved product.

4.3 *Parenteral solutions continued*

In the case of parenteral routes other than intravenous, e.g. intramuscular or subcutaneous - if the test product is of the same type of solution (aqueous) as the reference product, contains the same concentration of the same API, and the same or comparable excipients as the reference, then bioequivalence testing is not required; provided that the formulation does not contain an excipient(s) known to significantly affect absorption of the active ingredient(s).

For all other parenterals bioequivalence studies are required.

For intramuscular dosage forms, monitoring is required until at least 80 % of the AUC_{∞} has been covered.

4.4 TOPICAL PRODUCTS

4.4.1 Local Action

Topical preparations containing corticosteroids intended for application to the skin and scalp, the human vasoconstrictor test (blanching test) is recommended to prove bioequivalence. Validated visual and/or chromometer data will be necessary**.**

For topical formulations, other than simple solutions with bacteriostatic, bactericidal, antiseptic and/or antifungal claims, clinical data (comparative clinical efficacy) will be required. Microbial growth inhibition zones will not be acceptable as proof of efficacy. Simple solutions, however, may qualify for a waiver based on appropriate *in vitro* test methods.

Proof of release by membrane_diffusion will not be accepted as proof of efficacy, unless data are presented that show a correlation between release through a membrane and clinical efficacy.

Whenever systemic exposure resulting from locally applied/locally acting medicinal products entails a risk of systemic adverse reactions, systemic exposure should be measured.

4.4.2 Systemic Action

For locally applied products with systemic action, e.g. transdermal products, a bioequivalence study is always required.

4.5 Products intended for other routes of administration

Products for local use (e.g. oral, nasal, inhalation, ocular, dermal, rectal, vaginal) intended to act without systemic absorption, the approach to determine bioequivalence based on systemic measurements, is not applicable and pharmacodynamic or comparative clinical studies are required. However, pharmacokinetic studies may be required as measures of safety.

4.6 Variations or post-registration amendments

For all post-registration changes that require proof of efficacy in accordance with the Post-registration amendment guideline, the requirements of this guideline will be applicable.

5 Waivers of *in vivo* bioequivalence studies

Biowaivers will be considered under the circumstances detailed below.

5.1 IMMEDIATE RELEASE PRODUCTS

5.1.1 Biopharmaceutics Classification System (BCS) Class 1 Drug Substances

When the medicinal product contains a Class 1 active pharmaceutical ingredient(s) (based on the BCS), and the inactive ingredients used in the dosage form do not significantly affect absorption of the active ingredients, a biowaiver may be acceptable.

The drug substances should be highly soluble, highly permeable and the dosage form rapidly dissolving (Dissolution guideline).

Relevant information to prove that the drug substance falls within the Class 1 classification (Reference 5) should be provided.

The API is uncomplicated, i.e. it does not exhibit any of the following:

- A narrow therapeutic range or safety margin, e.g. it does not require careful dosage titration or patient monitoring.
- A steep dose-response relationship.
- A risk of serious undesired effects.
- Complicated or variable pharmacokinetics, e.g.:
  - non linear pharmacokinetics,
  - variable or incomplete absorption,
  - an absorption window, i.e. site-specific absorption,
  - substantial first-pass metabolism (>40 %), or
  - an elimination half-life of 24 hours or more.
- There is no documented evidence of bioavailability problems related to the API(s) or the pharmaceutical product, or products of similar chemical structure or formulations.
- Is not a pro-drug.

In the case of generic products, the reference product should be a conventional, immediate-release oral dosage form and the test and reference products should exhibit similar dissolution profiles.

Dosage forms should not be intended for absorption in the oral cavity, e.g. sublingual or buccal tablets.

BCS based biowaivers are intended only for BE studies. They do not apply to food effect BA studies or similar pharmacokinetic studies.

The reference product should be a conventional, immediate-release oral dosage form.

5.1.2 Different Strength Dosage Forms

When the drug product is the same dosage form but of a different strength and is proportionally similar (section 2.9 of this guideline) in its API and IPIs, a biowaiver may be acceptable.

Dissolution profiles are required for all strengths. The f_2 similarity factor should be used to compare dissolution profiles from different strengths of a product. An f_2 value ≥ 50 indicates a sufficiently similar dissolution profile such that further *in vivo* studies are not necessary. For an f_2 value < 50, it may be necessary to conduct an *in vivo* study. The difference factor, f_1, should also be submitted but will not be used as an acceptance criterion (Reference 6).

a) Lower strength dosage forms

The demonstration of bioequivalence *in vivo* of one or more of the lower strength(s) may be waived based on dissolution tests (Dissolution guideline) and an *in vivo* study on the highest strength**.**

b) Higher strength dosage forms

Conducting an *in vivo* study on a strength that is not the highest may be appropriate for reasons of safety. In this case a waiver may be considered for the higher strength if an *in vivo* BE study was performed on a lower strength of the same drug product provided that:

i) Generic medicinal products

- Linear elimination kinetics has been shown over the therapeutic dose range.
- The higher strength is proportionally similar to the lower strength.
- Comparative dissolution on the higher strength of the test and reference products is similar.

ii) New Chemical Entities

- Clinical safety and/or efficacy studies including dose desirability of the higher strength,
- linear elimination kinetics over the therapeutic dose range,
- the higher strength being proportionally similar to the lower strength, and

- the same dissolution procedures being used for both strengths and similar dissolution results obtained.

Note: Details on conducting dissolution studies are described in the Dissolution guideline.

5.2 Modified Release Products

5.2.1 Beaded Capsules - Lower Strength

For extended release beaded capsules where the strength differs only in the number of beads containing the active ingredient, a single-dose, fasting BE study should be carried out on the highest strength. A biowaiver for the lower strength based on dissolution studies can be requested.

Dissolution profiles in support of a biowaiver should be generated for each strength using the recommended dissolution test methods described in the Dissolution guideline.

5.2.2 Tablets – Lower strength

For extended release tablets when the drug product is:

a) in the same dosage form but in a different strength, and

b) is proportionally similar in its active and inactive ingredients, and

c) has the same drug release mechanism,

an *in vivo* BE determination of one or more lower strengths may be waived based on dissolution testing as previously described. Dissolution profiles should be generated on all the strengths of the test and the reference products.

For sections 5.2.1 and 5.2.2 above, the f_2 factor should be used to compare profiles from the different strengths of the product. An f_2 value of ≥ 50 can be used to confirm that further *in vivo* studies are not needed (Dissolution guideline). The difference factor, f_1, should also be submitted but will not be used as an acceptance criterion (Reference 6).

6.0 Criteria for waiver of Bioequivalence studies

The requirement for *in vivo* bioequivalence studies will not be generally required for products meeting the following criteria;

Products having the same active drug substance in the same concentration and the same excipients in comparable concentrations in the following form:

(i) Parenteral solutions.

(ii) Oral solutions.

(iii) Topically applied solutions not meant to be absorbed and act systemically.

(iv) Inhalation volatile anaesthetic solutions, sprays, gaseous.

(v) Powder for reconstitution as solution
(vii) highly soluble, highly permeable, and absorbed (BCS Classification)

7.0 Bio-equivalence studies report

Provide details of in vivo 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:

a) Drug and finished product information (for test and reference): batch details, manufacturing site and date, expiry dates.

The finished product must be identical to the intended commercial product in every respect; same manufacturing site, same composition.

Samples should be from commercial scale production.

b) Responsible investigators, their curriculum vitae, affiliation and signature.

c) Protocol and study design: (objectives, ethical considerations, subject selection, conduct of the study, drug administration, food intake, sample collection, storage, bioanalytical methods and validation results, pharmacokinetic parameters obtained results. Justification for the chosen design (e.g. cross over or parallel design), measures taken to minimize intra and intersubject variability and eliminate bias.

Population size of 12-24 (sample size shall depend on the intra-subject co-efficient of variation CV) healthy male volunteers of 18-55 years of age and with weight within normal ranges to accepted life tables.

d) Parameters to be measured: [AUC, C max tmax, Ae, Aet, dAe/dtmax)
Shape and area under plasma concentration curve or profile of cumulative excretion and excretion rate. Justification for the selected procedure to establish bioequivalence

All possible factors that may influence the product pharmacokinetics must be standardized e.g.: fluids in-take, and food in-take, exercise etc.

The data and statistical procedures should be detailed enough to allow for repetition of analysis if necessary.

e) Statistical analysis
Preferably the two one - sided statistical tests should be carried out using log –transformed data to show that the ratio of AUC and Cmax of the generic to the reference/innovator is within the acceptance limits of 0.8-1.25 at the 90% confidence interval (CI).

f) Tabulation and graphical illustration of results.

g) Conclusions.

8.0. Comparative Clinical or Pharmacodynamic Studies

In case of oral-solution drug products for oral-systemic use (oral, nasal, ocular, dermal, rectal, vaginal etc) or when drug produces no measurable concentrations in accessible fluid therapeutic equivalence can be demonstrated by pharmacodynamic studies.

When neither measurable concentration in accessible fluid nor measurable pharmacodynamic responses are elicited, comparative clinical studies shall be used to demonstrate therapeutic equivalence.

9.0 Pharmacodynamic Studies

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

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

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

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

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 therapeutic equivalence for each use.

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

The principles of good clinical practice (GCP) should be adhered to during the study.

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 must be satisfied:

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

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

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

(iv) It should be possible to derive the common parameters of comparison i.e. Cmax, Tmax and AUC

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

10.0 Comparative Clinical Trials

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

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 (randomisation 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 clinical endpoints measured, methods, measuring and recording clinical response (scoring system for endpoints)

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

Statistical methods used and their justification.

11. In-vitro dissolution testing

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

(a) Drugs, which are not defined above (not applicable for drugs defined above)

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

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

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

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

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

(v) Highly soluble and highly permeable more than 80% in 15 minute

***Adopted from South Africa Development Community (SADC) bioequivalence draft guidelines.*

Appendix I:

THE UNITED REPUBLIC OF TANZANIA
MINISTRY OF HEALTH

TANZANIA FOOD AND DRUGS AUTHORITY

For Official Use Date..... Application No.....

APPLICATION FORM

For registration of a Human medicinal product in Tanzania

1. Proprietary name	
1.1 Name of the active ingredient(s) (International Non-proprietary Name in English)	
1.2 Pharmacotherapeutic classification (Anatomic-Therapeutic Classification system)	
2. Pharmaceutical Dosage form	
2.1 Route of administration	
2.2 Container, closure and administration devices 2.3 Package sizes 2.4 Shelf life 2.5 Shelf life (after first opening of container) 2.6 Shelf life (after reconstitution)	

2.7 Storage conditions

2.8 Proposed conditions of sale

☐ Narcotic or ☐ Psychotropic

☐ Prescription only

☐ Pharmacy only

☐ General sale

Other information

3. Details of applicant (who must be the future holder of the marketing authorization/registration certificate)

Name:

Business Address:

Postal Address:

Country:

Phone: Fax: Email:

3.1 Details of a locally responsible person (who must be nominated by the applicant and submit evidence of power of attorney)

Name:

Business Address:

Country:

Phone: Fax: Email:

3.2 Manufacturer(s), site(s) and authorized person(s) for the pharmaceutical dosage form

NAME (Attach WHO certification of each)	ACTIVITY	SITE (Business Address, Phone and Country)	AUTHORIZED PERSON
			Name: Business Address:

Source (manufacturer) of active pharmaceutical ingredient(s):

Name:

Street Address:

Business Address:

Country:

Phone: Fax: Email:

4. Status of marketing authorization/registration in the country of origin and authorization/registration number and date where applicable

5. Registration status for this medicine in the SADC member states and in other countries	
Registered:	Country: Date of authorization: Authorization number: Trade name:
Pending:	Country: Date of submission: Application number:
Rejected:	Country: Date of rejection: Application number: Reason for rejection:
Withdrawn (by applicant before registration)	Country: Date of withdrawal: Reason for withdrawal: Trade name:
Withdrawn (by applicant after registration)	Country: Date of withdrawal: Reason for withdrawal: Trade name:
Suspended/Revoked/Withdrawn (by competent authority)	Country: Date of withdrawal: Reason for withdrawal: Trade name:

6. Proposed indications of the product

7. Complete composition per dosage unit				
Name (INN) of	Reason for inclusion	Quantity	Unit of measure	Referenced monograph
- 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 correctness:

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 manufacture of this medicine.

2. The formulation per dosage form correlates with the master formula and with the batch manufacturing record.

3. The manufacturing procedure is exactly as specified in the master formula and batch manufacturing record.

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.

5. All batches of the active pharmaceutical ingredient(s) are obtained from the source(s) specified in the accompanying documentation.

6. No batch of active pharmaceutical ingredient(s) will be used unless a copy of the batch certificate established by the manufacturer is available.

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 released for the manufacturing purposes.

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 released for sale.

9. The person releasing the product is an authorized person as defined by the WHO guideline **"Good Manufacturing Practices: Authorized person – the role, functions and training"** and/or an equivalent Tanzania guideline.

10. The procedures for control of the finished product have been validated for this information. The assay method has been validated for accuracy, precision, specificity and linearity.

11. All the documentation referred to in this certificate is available for review during GMP inspection.

12. Clinical Trials were conducted in accordance with Good Clinical Practice, where applicable.

I also agree that:

1. The holder of marketing authorization/registration certificate is obliged to follow Tanzanian requirements for handling adverse reactions of its products.

2. The holder of registration certificate is obliged to follow Tanzanian requirements for handling batch recalls of its products.

Name:
Qualification:
Position in the company:
Signature:
Date: **Official stamp:**

Appendix II:

ANATOMIC THERAPEUTIC CHEMICAL CLASSIFICATION SYSTEM (ATC)

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

A - Anatomical main group

01 - Therapeutic main group

B - Therapeutic subgroup

The main group of the ATC classification system are:-

A - Alimentary tract and metabolism

B - Blood and blood forming organs

C - Cardiovascular system

D - Dermatologicals

G - Genito-Urinary System and Sex Hormones

H - Systemic hormonal preparations, excl. sex hormones

J - General anti-infectives, systemic

L - Anti-neoplastic and immunosuppressive drugs

M - Musculo – skeletal system

N - Central nervous system

P - Anti-parasitic products

R - Respiratory system

S - Sensory organs

V - Various

A ALIMENTARY TRACT AND METABOLISM

A01 Stomatologicals, mouth preparations
- A Stomatologicals, mouth preparations

A02 Antacids, antiflatulents and antipeptic ulcerants
- A Antacids and antiflatulents
- B Antipeptic ulcerants
- C Others

A03 Gastrointestinal antispasmodics and anticholinergics
- A Synthetics, incl. Papaverine
- B Belladonna and derivatives, pain
- C Antispasmodics in combination with psycholeptics
- D Antispasmodics in combination with analgesics
- E Other combinations

A04 Antiemetics and antinauseants
- A Anti-emetics and antinauseants

A05 Cholagogues and hepatic protectors
- A Bile therapy, cholagogues and choleretics
- B Hepatic protectors, lipotropics
- C Cholagogues and lipotropics in combination

A06 Laxatives
- A Laxative

A07 Antidiarrhoeals, intestinal antiinflammatory/antiinfective agents
- A Intestinal anti-infectives
- B Intestinal adsorbents
- C Electrolytes with carbohydrates
- D Antipropulsives
- E Intestinal anti-inflammatory agents
- F Antidiarrhoeals micro organisms
- X Various Antidiarrhoeals

A08 Antiobesity preparations excl. diet products
- A Antiobesity preparations, excl. diet products

A09 Digestives, incl. Enzymes
- A Digestives, incl. Enzymes

A10 Antidiabetic therapy
- A Insulins and other parenterals
- B Oral antidiabetics

A11 Vitamins
- A Multivitamins, combinations
- B Multivitamins, plain
- C Vitamin A and D, incl. combinations of the two
- D Vitamin B_1, plain and in combination with Vitamin B_6 and B_{12}
- E Vitamin B – Complex incl. combinations
- G Ascorbic acid (Vitamin C), incl. combinations

H Other plain vitamin preparations
J Other vitamin products, combination

AB12 Mineral Supplements
A Calcium
B Potassium
C Other Mineral supplements

A13 Tonics
A Tonics

A14 Anabolics, systemic
A Anabolic steroids
B Other anabolic agents

A15 Appetite stimulants

A16 Other alimentary tract and metabolism products

B BLOOD AND BLOOD FORMING ORGANS

B01 Anticoagulants
A Anticoagulants

B02 Antihaemorrhagics
A Antifibrinolytics
B Vitamin K and Others

B03 Antianaemic preparations
A Haematinics, iron and all combinations
B Vitamin B_{12} and folic acid

B04 Cholesterol reducers, antiatheroma preparation
A Cholesterol reducers, antiatheroma preparations

B05 Plasma substitutes and perfusion solutions
A Blood and related products
B I.V. solutions
C Irrigating solutions
D Peritoneal dialytics
X I.V. solution additives
Z Haemodialytics

B06 Other haematological agents, incl. Fibrinolytics and hyaluronidase
A Other haematological agents, incl. Fibrinolytics and hyaluronidase

C CARDIOVASCULAR SYSTEM

C01 Cardiac therapy
A Cardiac glycosides
B Antiarrhythmics
C Antiadrenergic agents, ganglion – blocking
D Arteriolar smooth muscle, agents acting on
E Renin – angiotensin system, agents acting on

K Other hypotensives
L Hypotensives and diuretics in combination

C02 Diuretics
A Low – ceiling diuretics, thiazides
B Low – ceiling diuretics, excl. thiazides
C High – ceiling diuretics
D Potassium – sparing drugs
E Diuretics and potassium – sparing drugs in combination

C03 Peripheral vasodilators
A Peripheral vasodilators

C04 Vasoprotectives
A Antihaemorrhoidals, topical preparations
B Antivaricose therapy
C Capillary stabilizing agents

C05 Beta blocking agents
A Beta blocking agents, plain

D DERMATOLOGICALS

D01 Antifungals, dematological
A Antifungals, topical preparations
B Antifungals, systemic preparations

D02 Emollients and protectives
A Emollients and protectives

D03 Cicatrizants, excl. medicated dressings

D04 Antipruritics, incl. Antihistamines, Anaesthetics, etc.
A Antipruritics, incl. Antihistamines, Anaesthetics, etc.

D05 Coal tar, sulphur and resorcinol products
A Coal tar, sulphur and resorcinol products

D06 Antibiotics and chemotherapeutics, dermatologicals
A Antibiotics, topical preparations
B Chemotherapeutics, topical preparations
C Antibiotics and chemotherapeutics, combinations

D07 Corticosteroids, dermatological preparations
A Corticosteroids, plain
B Corticosteroids, combinations with antiseptics
C Corticosteroids, combinations with antibiotics
X Corticosteroids, other combinations

D08 Antiseptics and disinfectants
A Antiseptics and disinfectants

D09 Medicated dressings
A Medicated dressings

D10 Antiacne preparations
- A Anti – acne preparations

D11 Other dermatological preparations

G GENITO-URINARY SYSTEM AND SEX HORMONES

G01 Gynaecological antiinfectives and antiseptics
- A Antiinfectives, excl. combinations with corticosteroids
- B Antiinfectives and corticosteroids in combination

G02 Other gynaecologicals
- A Oxytocics
- B Topical contraceptives
- C Other gynaecologicals

G03 Sex hormones and stimulants of the genital system
- A Hormonal contraceptives, systemic
- B Androgens and combinations, excl. G03E
- C Estrogens and combinations, excl. G03E, G03F and antiandrogens and estrogens
- D Progesterones and combinations, excl. G03E and G03F
- E Androgens and female sex hormones in combination
- F Progestogens and estrogens in combination
- G Gonadotrophins and other ovulation stimulants
- H Antiandrogens and combinations
- X Other sex hormones

G04 Urologicals
- A Urinary antiseptics and antiinfectives
- B Other urologicals, incl. Antispasmodics

H SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES

H01 Pituitary hormones
- A Anterior pituitary lobe hormones
- B Posterior pituitary lobe hormones

H02 Systemic corticosteroids
- A Systemic corticosteroids, plain
- B Systemic corticosteroids, combinations
- C Antiadrenal preparations

H03 Thyroid therapy
- A Thyroid preparations
- B Antithyroid preparations
- C Iodine therapy

H04 Pancreatic hormones
- A Glycogenolytic hormones

H05 Calcium homeostasis
- A Parathyroid hormones
- B Antiparathyroid hormones

J GENERAL ANTIINFECTIVES, SYSTEMIC

J01 Systemic antibiotics
- A Tetracyclines
- B Chloramphenicol
- C Penicillins with increases effect on Gram – negative bacilli
- D Cephalosporins
- E Trimethoprim, excl. combinations with sulphonamides
- F Macrolides
- G Streptomycins
- H Penicillins
- J Penicillin and streptomycin in combination
- K All other antibiotics

J02 Systemic antimycotics, excl. griseofulvin
- A Systemic antimycotics, excl. griseofulvin

J03 Systemic chemotherapeutics
- A Sulfonamides
- B Sulfonamides and antiinfectives in combination
- C Other chemotherapeutics

J04 Tuberculostatics, excl. streptomycin
- A Tuberculostatics, excl. streptomycin

J05 Systemic antivirals
- A Agents affecting the virus directly
- B Immunostimulating agents
- C Agents with immunostimulants and antiviral activity

J06 Immune sera and immunoglobulins
- A Immune sera
- B Immunoglobulins

J07 Vaccines
- A Vaccines

J08 Other antiinfectives, incl. Leprostatics
- A Other antiinfectives, incl. Leprostatics.

L ANTI-NEOPLASTIC AND IMMUNOSUPPRESSIVE DRUGS

L01 Cytostatic drugs
- A Alkylating agents
- B Antimetabolites
- C Plant alkaloids and other natural products
- D Cytotoxic antibiotics
- X Various cytostatics

L02 Hormone therapy
- A Hormones
- B Anti-hormones

M MUSCULO – SKELETAL SYSTEM

M01 Anti-inflammatory and anti-rheumatic products
- A Anti-inflammatory and anti-rheumatic products pre – steroids
- B Combinations with corticosteroids

M02 Topical products for joint and muscular pain
- A Topical products for joint and muscular pain

M03 Muscle relaxants
- A Peripherally acting agents
- B Centrally acting agents
- C Directly acting agents

M04 Antigout preparations
- A Antigout preparations

M05 Other drugs for disorders of the musculo – skeletal system
- A Other drugs for disorders of the musculo – skeletal system

N CENTRAL NERVOUS SYSTEM

N01 Anaesthetics
- A Anaesthetics, general
- B Local anaesthetics, excl. dermatologicals

N02 Analgesics
- A Narcotics
- B Other analgesics and antipyretics
- C Anti-migraine preparations

N03 Anti-epileptics
- A Anti – Parkinson drugs

N04 Psycholeptics
- A Neuroleptics
- B Tranquilizers
- C Hypnotics and sedatives

N05 Psychoanaleptics
- A Antidepressants
- B Psychostimulants
- C Psycholeptics and psychoanaleptics in combination

N06 Other CNS drugs, incl. Parasympathomimetics
- A Parasympathomimetics

P ANTI-PARASITIC PRODUCTS

P01 Antiprotozoals
- A Amoebicides and similar
- B Antimalarials
- X Other antiprotozoals

P02 Antihelmintics
- A Schistosomicides
- X Other antihelmintics

P03 Ectoparasiticides, incl. Scabicides
- A Ectoparasiticides, incl. Scabicides

R RESPIRATORY SYSTEM

R01 Nasal preparations
- A Nasal decongestants, topical preparations

R02 Throat preparations
- A Throat preparations

R03 Anti-asthmatics
- A Bronchodilators and other anti – asthmatics, excl. R03B
- B Respiratory stimulants

R04 Chest rubs and other inhalants
- A Chest rubs and other inhalants

R05 Cough and cold preparations
- A Cold preparations without antiinfectives
- B Cold preparations with antiinfectives
- C Expectorants, excl. combinations with antitussives
- D Antitussives, excl. combinations with expectorants
- E Systemic nasal decongestants
- F Antitussives and expectorants, combination

R06 Antihistamines for Systemic use
- A Antihistamines for systemic use

S SENSORY ORGANS

S01 Ophthalmologicals
- A Antiinfectives
- B Corticosteroids
- C Corticosteroids and antiinfectives in combination
- D Other ophthalmologicals

S02 Otologicals
- A Antiinfectives
- B Corticosteroids
- C Corticosteroids and antiinfectives in combination
- D Other otologicals

S03 Ophthalmologicals and otologicals preparations
- A Antiinfectives
- B Corticosteroids
- C Corticosteroids and antiinfectives in combination
- D Other ophthalmologicals preparations

V VARIOUS

V01 Allergens
- A Allergens

V02 Immunosuppressive drugs
- C Immunosuppressive drugs

V03 All other therapeutic products
- A All other therapeutic products

V04 Diagnostic agents
- A Contrast media
- B Urine tests
- C Other diagnostic agents

V05 Surgical antiseptics

V06 General nutrients
- A Slimming preparations
- B Protein supplements
- C Infant formulas
- D Other nutrients

V07 All other pre – therapeutic products
- A All other pre – therapeutic product

Appendix III: International comparator products for equivalence assessment of interchangeable multisource (generic) products

Pharmaceutical Name	Dosage forms and strengths	Comparator pharmaceutical products		
		Trademark	Manufacturer	Primary market
Albendazole	chtab, 200mg	Zentel	GSK	France
Amiloride, HCL	Tab, 5mg	Midamor	MSD	UK
Aminophylline	Tab, 100mg, 200mg (Sr), 125mg	Aminophylin	BYK Gulden Lomberg	Germany
Amitriptyline, HCL	Tab, 25mg	Elavil	Astra Zeneca	USA
Amoxicillin	Cap, 250mg, 500mg pwosp, 125mg/5ml tab, 250mg, 500mg	Amoxil	GSK	UK
Atenolol	Tab, 50mg, 100mg	Tenormin	Astra Zeneca	UK
Atropine, sulfate	Eyd, 0.5%, 1%	Atropin Dispersa	Ciba Vision (Novatis)	Switzerland
Benznidazole	Tab, 100mg	Radanil	Roche	Argentina, Brazil, Switzerland
Biperiden, HCL	Tab, 2mg	Akineton	Knoll	Germany
Captopril	Sctab, 25mg	Capoten	BMS	USA
Carbamazepine	Actab, 100mg, 200mg (Sr)	Tegretol	Novartis	Switzerland
Chloramphenicol	Cap, 250mg	Chloromycetin	Parke-Davis	USA
Chloramphenicol, sodium succinate	Oilspinj, 0.5g/2ml	Chloromycetin sodium phosphate	Parke-Davis/Parkedale	USA
Chlorpheniramine, hydrogen maleate	Tab, 4mg	Chlortrimeton	Schering-Plough	USA
Ciclosporin	Cap, 25mg	Sandimmun	Novartis	Switzerland
Cimetidine	Tab, 200mg	Tagamet	GSK	France
Ciprofloxacin, HCL	Tab, 250mg	Ciprobay	Bayer	Germany
Clofazimine	Cap, 50mg, 100mg	Lamprene	Novartis	Switzerland
Clomifene, citrate	Tab, 50mg	Clomid	Hoechst Marion Roussel	USA
Clomipramine, HCL	Cap, 10mg, 25mg	Anafranil	Novartis	Switzerland
Clonazepam	Sctab, 500ug	Rivotril	Roche	Switzerland
Cloxacillin, sodium	Cap, 500mg pwsl, 125mg/5ml	Penstaphon Tegopen	BMS	Belgium USA
Cyclophosphamide	Tab, 25mg, 50mg	Endoxana	ASTA Medica	UK
Dapsone	Tab, 25mg, 100mg	Dapsone	Jacobus	USA

Pharmaceutical Name	Dosage forms and strengths	Comparator pharmaceutical products		
		Trademark	Manufacturer	Primary market
Desmopressin, acetate	Nsp, 10ug/ metered dose	DDAVP	Ferring	USA
Dexamethasone	Tab, 500ug, 4mg	Decardron	MSD	USA
Diazepam	Sctab, 2mg, 5mg	Valium	Roche	USA
Doxazosin mesilate	Tab, 1mg, 2mg, 4mg	Caldura	Pfizer	Germany
Doxycycline, hyclate	Cap, 100mg Tab, 100mg	Vibramycin	Pfizer	Germany
Epinephrine, HCL	Eyd, 2%	Suprarenin	Hoechst Marion Roussel	Germany
Ergocalciferol	Cap, 1.25mg (50 000IU), Osl, 250ug/ ml (10000IU), Tab, 1.25mg (50000IU)	Drisdol	Sanofi Synthelabo	USA
Ethinylestradiol	Tab, 10ug, 20ug, 50ug	Pregypre C	Schering Plough	Germany
Ethinylestradiol + levonorgestrel	Tab, 30ug + 150ug, 50ug + 250ug	Nordette-21	Wyeth-Ayerst	USA
Ethosuximide	Cap, 250mg Syr, 250mg/ 5ml	Zarontin	Parke-Davis	USA
Etoposide	Cap, 100mg	Vepesid	BMS	Netherlands
	Inj, 20mg/ml			USA
Flucytosine	Cap, 250mg	Ancobon	ICN Pharmaceuticals	USA
Fludrocortisone, acetate	Tab, 100ug	Florinef	BMS	USA
Fluorouracil	Oin, 5%	Efudix	Roche	USA
Fluphenazine, decanoate	Depot inj, 25mg/ml	Prolixin decanoate	BMS	USA
Fluphenazine, enantate	Depot inj, 25mg/ml	Prolixin enanthate	BMS	USA
Furosemide	Tab, 40mg	Lasix	Hoechst Marion Roussel	Germany
Glyceryl trinitrate	Chcap, 800ug	Nitroglycerin wander	Novartis	Switzerland
Griseofulvin	Cap, 125mg, 250mg	Grisactin	Astra Zeneca	USA
	Tab, 125mg, 250mg	Fulcin		USA
Haloperidol	Tab, 2mg, 5mg	Haldol	Janssen Cilag	Belgium
Hydralazine, HCL	Tab, 25mg, 50mg Pwinj, 20mg	Apresoline	Novartis	Netherlands, UK
Hydrochlorothiazide	Tab, 25mg	Hydrosaluric	MSD	UK

Pharmaceutical Name	Dosage forms and strengths	Comparator pharmaceutical products		
		Trademark	Manufacturer	Primary market
	Tab, 25mg, 50mg			
Ibuprofen	Tab, 200mg	Nurofen	Boots	UK
Idoxuridine	Eyd, 0.1% Eyo, 0.2%	Herplex	Allergan	USA
Imipenem (monohydrate) + cilastin (sodium)	Pwinj, 250mg + 250mg, 500mg	Tienam	MSD	Italy
Insulin (soluble)	Inj, 40IU/ml	Actrapid	Novo Nordisk	Germany
	Inj, 100IU/ml	Actrapid		Zimbabwe
	Inj, 100IU/ml	Novolin R		Japan, USA
Intermediate-acting insulin (as compound insulin zinc suspension)	Inj, 40IU/ml, 80IU/ml, 100IU/ml	Humulin L	Eli Lilly	USA
Intermediate-acting insulin (as isophane insulin)	Inj, 40IU/ml, 80IU/ml, 100IU/ml	Humulin N	Eli Lilly	USA
Ipratropium bromide	Inh, 20ug/ metered dose	Atrovent	Boehringer Ingelheim	USA
Iron dextran	Inj, equiv. To 50mg iron/ml	Infed	Shein Pharmaceuticals	USA
Isosorbide dinitrate	Sbltab, 5mg	Isordil	Wyeth-Ayerst	USA
Ivermectin	Sctab, 6mg	Mectizan/Stromectol	Merck, Sharp & Dohme	Netherlands
Ketoconazole	Osp, 100mg/5ml Tab, 200mg	Nizoral	Janssen Cilag	Belgium
Levamisole, HCL	Tab, 50mg, 150mg	Ergamisol	Janssen Cilag	Belgium
Levodopa + Carbidopa	Tab, 100mg + 10mg, 250mg + 50mg	Sinemet	MSD	Italy
Levonorgestrel	Tab, 30ug	Microval	Wyeth-Ayerst	Germany
Lithium carbonate	Cap, 300mg Tab, 300mg	Quilonum	GSK	Germany
Mebendazole	Chtab,100mg , 500mg	Vermox	Janssen Cilag	Belgium
Medroxyprogesterone acetate	Depot inj, 150mg/ml Tab, 5mg	Depo-Provera Provera	Pharmacia Ltd	USA
Mefloquine, HCL	Tab, 250mg	Lariam	Roche	Switzerland
Methyldopa	Tab, 250mg	Aldomet	MSD	Spain
Metoclopramide, HCL	Tab, 10mg	Primperan	Sanofi Synthelabo	France
Miconazole, nitrate	Cream, 2%	Daktarin	Janssen Cilag	Belgium
	Oin, 2%			
Nalidixic acid	Cap, 500mg	Neggran	Sanofi Synthelabo	USA

Pharmaceutical Name	Dosage forms and strengths	Comparator pharmaceutical products		
		Trademark	Manufacturer	Primary market
Neostigmine, bromide	Tab, 15mg	Prostigmin	Roche	Germany
Niclosamide	Chtab, 500mg	Yomesan	Bayer	Germany
Nifedipine	Cap, 10mg (Sr)	Adalat 10	Bayer	Germany
	Tab, 10mg (Sr)	Adalat T 10		
Nifurtimox	Tab, 30mg, 120mg	Lampit	Bayer	Argentina
Nitrofurantoin	Tab, 100mg	Furadantin	Procter & Gamble	Ireland, UK
Norethisterone enantate	Oilsl, 200mg/ml	Noristerat	Schering Plough	Mexico, South Africa
Nystatin	Loz, 100000IU	Nystan	BMS	UK
	Tab, 100000IU			France
	Tab, 500000IU			USA
	Vagtab, 100000IU			France
Oxamniquine	Cap, 250mg	Mansil/Vansil	Pfizer	Brazil
	Syr, 250mg/5ml			
Paracetamol	Sup, 125mg, 250mg, 500mg, 1000mg	Ben-U-Ron	Bene	Germany
Penicillamine	Cap, 250mg	Cuprimine	MSD	USA
	Tab, 250mg	Depen	Cater-Wallace	
Phenobarbital	Tab, 15 – 100mg	Luminal (100mg)	Desitin	Germany
		Luminaletten (15mg)		
Phenoxymethylpenicillin, potassium	Pwosp, 250mg/5ml Tab, 250mg	V-Cillin K	Eli Lilly	USA
Phenytoin, sodium	Cap, 30mg, 100mg	Dilantin Kapseals	Parke-Davis	USA
	Tab, 50mg	Dilantin Infatabs		
Phytomenadione	Tab, 10mg	Konakion	Roche	Switzerland
Praziquantel	Tab, 150mg, 600mg	Biltricide	Bayer	Germany
	Tab, 600mg			
Prednisolone	Tab, 5mg	Scherisolon	Schering Plough	Colombia, Uruguay
	Tab, 5mg			
	Tab, 1mg,			

Pharmaceutical Name	Dosage forms and strengths	Comparator pharmaceutical products		
		Trademark	Manufacturer	Primary market
	5mg			
	Eyd, 0.5%	Ultracortenol	Ciba Vision (Novartis)	Germany
Procainamide, HCL	Tab, 250mg, 500mg	Pronestyl	BMS	USA
Procarbazine, HCL	Cap, 50mg	Natulan	Roche	Switzerland
Proguanil, HCL	Tab, 100mg	Paludrine	Astra Zeneca	UK
Propranolol, hydrochloride	Tab, 20mg, 40mg	Inderal	Astra Zeneca	Japan
	Tab, 10mg, 40mg			UK
Pyrantel, embonate	Chtab, 250mg	Combantrin	Pfizer	Germany
	Osp, 50mg/ml			
Pyrazinamide	Tab, 500mg	Zinamide	MSD	UK
Pyridostigmine, bromide	Tab, 60mg	Mestipre	Roche	Switzerland
Rifampicin	Cap, 150mg, 300mg Tab, 150mg, 300mg	Rifadin	Gruppo Lepetit	Italy
Rifampicin + isoniazid	Tab, 150mg + 100mg, 300mg + 150mg	Rifinah	Gruppo Lepetit	Italy
Rifampicin + isoniazid + pyrazinamide	Tab, 150mg + 75mg + 400mg, 150mg + 150mg + 500mg	Rifater	Hoechst Marion Roussel	Italy
Silver sulfadiazine	Cream, 1%/500g	Silvadene	Hoechst Marion Roussel	USA
Sulfadoxine + Pyrimethamine	Tab, 500mg + 25mg	Fansidar	Roche	Switzerland
Sulfamethoxazole + Trimethoprim	Osp, 200mg + 40mg/5ml Tab, 100mg + 20mg, 400mg + 80mg	Bactrim	Roche	Switzerland
Sulfasalazine	Tab, 500mg	Azulfidine	Pharmacia Ltd	USA
Tamoxifen, citrate	Tab, 10mg, 20mg	Nolvadex	Astra Zeneca	UK
Testosterone, enantate	Inj, 200mg/ml, 250mg/ml	Testorion depot	Schering Plough	Argentina, Germany, Mexico
Theophylline	Tab, 125mg, 250mg, 375mg, 500mg	Euphylong	BYK-Gulden	Germany

Pharmaceutical Name	Dosage forms and strengths	Comparator pharmaceutical products		
		Trademark	Manufacturer	Primary market
Timolol, maleate	Sl (Eyd), 0.25%, 0.5%	Timoptol ophthalmic solution	MSD	France
	Eyd, 0.25%, 0.5% (unit dose)	Timoptol Ocudose		
	Gel (Eyd), 0.25%, 0.5%	Timoptol LP		
Tolbutamide	Tab, 500mg	Rastipre	Hoechst Marion Roussel	Germany
Triclabendazole	Tab, 250mg	Egaten	Novartis	Egypt
Tropicamide	Eyd, 0.5%	Mydriacyl	Alcon	UK
Verapamil, HCL	Tab, 40mg, 80mg (Sr)	Isoptin	Knoll	Germany

Appendix IV Schedule of Fees

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

References:

1. European Union Directives.
2. International Conference on Harmonisation of Technical Requirements for the Registration Pharmaceuticals for Human Use.
3. Marketing Authorization of Pharmaceutical Products with Special Reference to Multisource (Generic) Products, 1999.
4. Medicines Control Council of South Africa Guidelines for Biostudies, 2003
5. SADC Draft harmonised guidelines for registration of medicinal products. 2004
6. USFDA-CDER, Guidances for Industry.