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TANZANIA FOOD AND DRUGS AUTHORITY

GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR REGISTRATION OF HUMAN MEDICINAL PRODUCTS

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

Fifth Edition

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ABBREVIATIONS

API	-	Active Pharmaceutical Ingredient
ATC	-	Anatomic Therapeutic Chemical classification
AUC	-	Area under the plasma concentration time curve
BAN	-	British Approved Name
BP	-	British Pharmacopoeia
BSE	-	Bovine Spongiform Encephalopathy
CAS	-	Chemical Abstract Service
CEP	-	European Certificate of Suitability
Cmax	-	Maximum plasma concentration
CoA	-	Certificate of Analysis
CPP	-	Certificate of Pharmaceutical Product
DMF	-	Drug Master File
EC	-	European Commission
EU	-	European Union
FDC	-	Fixed Dose Combination
FPP	-	Finished Pharmaceutical Product
GMP	-	Good Manufacturing Practice
HIV	-	Human Immune-deficiency Virus
ICH	-	International Conference on Harmonization of Technical Requirements for Registration of Human Medicinal Products
INN	-	International Non-proprietary Name
JAN	-	Japanese Accepted Name
JP	-	Japanese Pharmacopoeia
LOD	-	Loss on Drying
MedDRA	-	Medical Dictionary for Drug Regulatory Authorities
NMT	-	Not More Than
PhEur	-	European Pharmacopoeia
PhInt	-	International Pharmacopoeia
PIL	-	Patient Information Leaflet
QA	-	Quality Assurance
RH	-	Relative Humidity
SMACS	-	Starting Materials Certification Scheme
SMF	-	Site Master File
SPC	-	Summary of Product Characteristics
TFDA	-	Tanzania Food and Drugs Authority
TFDCA	-	Tanzania Food, Drugs and Cosmetics Act
TRS	-	Technical Report Series
TSE	-	Transmissible Spongiform Encephalopathy
USAN	-	United States Approved Name
USP	-	United States Pharmacopoeia
WHO	-	World Health Organization

FOREWORD

The Tanzania Food and Drugs Authority (TFDA) was established under the Tanzania Food, Drugs and Cosmetics Act, 2003 with the mission of protecting and promoting public health by ensuring quality, safety and effectiveness of food, drugs, cosmetics and medical devices. The first step towards achieving this goal is to conduct pre-marketing evaluation of products so as to ensure that they meet standards of quality, safety and effectiveness before the products are allowed into the market. This is a fundamental requirement for authorisation of medicinal products in Tanzania.

In fulfilment of its mission, the Authority is duty-bound to ensure data submitted as evidence of quality, safety and efficacy is solid, credible and submitted in manner that is logical and consistent. Therefore, these guidelines have been reviewed to advise applicants on content and format of information in a product dossier and other general requirements to be submitted to TFDA when applying for registration of medicinal products. They are not intended to inhibit innovation and therefore whenever desirable applicants may submit additional data to elucidate the quality, safety and efficacy of the product.

Developments in pharmaceutical research broaden knowledge of medicines and therapy which also calls for new demands on standards of medicines. In the same manner, standards of obtaining scientific evidence on quality, safety and efficacy of medicines and presenting them to national medicines regulatory authorities for obtaining registration the medicines must be adhered to, to match the new demands. Such evidence is gathered during drug development and compiled into a medicinal product dossier.

Thus the "Guidelines on Submission of Documentation for Registration of Human Medicinal Products, 2008" were developed to cope with the new developments in line with the requirements of marketing authorization. Since their inception in November 2008, a number of typographical errors and unclear statements that mislead applicants on the required data have been noted. The errors have now been corrected as shown in the revision history at the end of the guidelines. Moreover the original text has been reformatted to comply with TFDA Quality Management System for Control of Documents. No conceptual changes have been made.

Adherence to these guidelines by submitting all the required data in the right format will facilitate efficient and effective evaluation as well as expediting the approval process. This will be of mutual consent as marketing authorization holders will be able to market their products in the shortest possible time and the public will have improved access to medicines of proven quality, safety and efficacy.

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INTRODUCTION

Section 51 (1) of the Tanzania Food, Drugs and Cosmetics Act, 2003 prescribes that a medicinal product shall be registered only if:

(a) The availability of the medicine is in the public interest;
(b) The medicine is proved to be safe, efficacious and of acceptable quality;
(c) The premises and manufacturing operations comply with the current Good Manufacturing Practices requirements;
(d) The medicine complies with any other requirements as may be prescribed by the Authority.

Furthermore, Section 22 (1) of the Act prohibits the sell, supply or importation of any drug unless it is registered in accordance with the provisions of the Act.

These guidelines prescribe data which is required to be submitted to TFDA to demonstrate the safety, efficacy and quality of medicinal products being applied for registration.

These revised guidelines have been improved by giving more details on requirements for active pharmaceutical ingredients (APIs) as well as finished pharmaceutical products (FPPs). In addition, requirements on bioequivalence and bio-waver(s) have been updated in line with the current state of knowledge. The improvements are based on the World Health Organization (WHO) Guidelines on Submission of Documentation for Prequalification of Multi-source Finished Pharmaceutical Products Used in the Treatment of HIV/AIDS, Malaria and Tuberculosis and the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for human use.

The guidelines consist of seven sections which are:

i. General Information;
ii. Summary of Product Characteristics;
iii. Active Pharmaceutical Ingredient(s);
iv. Finished Pharmaceutical Product(s);
v. Therapeutic Equivalence;
vi. Pharmacology, Toxicology and Efficacy of New Drugs; and
vii. Fixed-Dose Combination Medicinal Products; together with five annexes as follows:

i. Application Form: Quality Information Summary(QIS);
ii. Application Form: Bioequivalence Information Summary (BIS);
iii. Application Form for Renewal of a Registered Medicinal Product;
iv. Model Stability Report for Active Pharmaceutical Ingredients (APIs);
v. Model Stability Report for Capsules/Tablets; and

In the case of applications for marketing authorization of medicinal products containing new chemical entities or combinations of such entities, full and detailed information on safety and efficacy is required as prescribed in the most up to date ICH guidelines.

For fixed-dose combination medicinal products full and detailed information as defined in the WHO guidelines for registration of fixed-dose combination medicinal products (Technical Report Series 929 and its revisions) is required.

These guidelines apply only to human medicinal products. In the case of other medicinal products such as veterinary products, biological products, herbal drugs and traditional medicines, separate guidelines should be used. All these guidelines can be accessed online from TFDA website; www.tfda.or.tz.

Only information prescribed in the Application Form for Renewal of a Registered Medicinal Product will be required for application for renewal of a registered medicinal product.

Applicants are requested to carefully read these guidelines, fill in application forms for both Quality Information Summary and Bioequivalence Information Summary, prepare dossiers and other required documents and submit them in hard-copy as well as in electronic forms on a CD-ROM. The guidelines prescribe minimum information required. Evaluation of dossiers will as far as possible be based on these guidelines. However, since science is ever changing and taking into account that it is not always possible to keep pace in amending the guidelines, TFDA will in the interest of patient safety and well being not accept outdated methods and techniques and will evaluate products based on up to date scientific knowledge and standards known or existing at the time of evaluation. Applicants are therefore encouraged to keep abreast with scientific developments and apply the most up to date scientific information and technology to develop and test their products.

Applicants are also requested to read these guidelines together with the Tanzania Food, Drugs and Cosmetics Act, 2003 and Regulations made thereto.

GLOSSARY

In the context of these guidelines, the following words/phrases are defined as follows.

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.

Bioequivalence

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.

Certificate of Pharmaceutical Product

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

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.

Director General

Means the Chief Executive of the Tanzania Food and Drugs Authority.

Drug Master File

A drug master file (DMF) is a master file that provides a full set of data on an API. In some countries, the term may also comprise data on an excipient or a component of a product such as a container.

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.

Finished Pharmaceutical Product (FPP)

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.

Generic medicinal 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.

Innovator 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 (manufacturing)

Means all operations of purchase of materials and products, production, quality control, release, storage, shipment of finished products and the related controls.

Manufacturer

Means a person or firm that is engaged in the manufacture of product(s).

Medicinal product, 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.

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.

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 medicinal product

A medicinal product that contains a new API, a new combination of marketed APIs or a new multisource (generic) product.

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.

Quality Overall Summary

Means all information on the quality of active pharmaceutical ingredient and finished pharmaceutical product as stipulated under sections three and four of these guidelines

Registration of a medicine or Marketing authorization (registration)

Means an official authorization or registration of a product by TFDA for the purpose of marketing or free distribution in Tanzania after evaluation for safety, efficacy and quality.

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.

Specifications - 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.

Starting material

Means any substance of a defined quality used in the production of a pharmaceutical product, but excluding packaging materials.

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 are essentially the same, as determined from appropriate bioequivalence, pharmacodynamic, clinical or *in vitro* studies.

Variation

Means a change to any aspect of a pharmaceutical product, including but not limited to a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container and container labelling and product information.

Well-established active pharmaceutical ingredients

Means API which has been incorporated in medicinal products that have:

- been marketed for at least five years in countries that undertake active post-marketing surveillance;
- been widely used in a sufficiently large number of patients to permit the assumption that safety and efficacy are well known; and
- the same route of administration and strength, and the same or similar indications as in those countries.

Well-established drug products

Pharmaceutical products which contain well established active pharmaceutical ingredients and which:

- have been marketed for at least five years in countries that undertake active post-marketing monitoring;
- have been widely used in a sufficiently large number of patients to permit the assumption that safety and efficacy are well known; and
- have the same route of administration and strength, and the same or similar indications as in those countries.

SECTION ONE

GENERAL INFORMATION

This section describes application procedures and provides other useful information to applicants. Applicants are therefore advised to read carefully this section before compiling dossiers and assemble applications ready for submission to TFDA

1.1 Language

All applications and supporting documents shall be in Kiswahili or English.

1.2 Applicant

An applicant is a person who applies for registration of a medicinal product to TFDA, who must be the owner of the product. He may be a manufacturer or a person to whose order and specifications, the product is manufactured. After the product is registered the applicant shall be the Marketing Authorisation Holder (MAH) (registration holder).

The Marketing Authorization Holder shall have the primary responsibility of the product on the Tanzanian market that includes monitoring the safety of the registered medicinal product as well as making follow up on safety alerts from the world market concerning the product or other products with the same active ingredient(s). Whenever any serious safety concerns are noted the MAH shall take appropriate actions including but not limited to informing the authority, withdrawing registration, recalling the product from the market or revising labels by adding precautions or warnings.

Every applicant who is not resident in Tanzania shall appoint person (Natural or legal person) residing or a company incorporated in Tanzania and authorized by TFDA to deal in medicinal products to be a Local Agent. The appointment shall be notified to the Authority by submitting a letter of appointment supported by original copy of power of attorney that complies with Tanzanian laws.

The Local Agent shall be responsible for facilitating communication with the applicant and he shall also be responsible for the product on the Tanzanian market.

1.3 Data presentation

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.

1.3.1 Medicinal product dossier

A dossier is a file that contains detailed scientific information on the chemistry, formulation, manufacturing, quality control and biomedical studies that demonstrates quality, safety and efficacy of active pharmaceutical ingredient(s) and the corresponding finished pharmaceutical product. The information must be compiled in accordance with these guidelines as provided under sections 2-7. Different sections of the dossier shall be distinctly marked and page numbered in the style: ***page x of y*** and have a table of contents indicating the sections and page numbers. Where information is required in the application forms its location shall be cross referenced in the dossier.

Information for each section shall be printed on both sides of an A-4 paper which will be arranged sequentially on a 1.00 mm or more diameter stainless spring and clamped with a stainless steel binder of not less than 1.0 mm thick in an A4 expandable spring file. The file shall be of cardboard or paper material of not less than 600gsm.

Data for each section shall be bound in separate file(s) and Compact Discs (CDs)

The binding shall be in such a manner as to allow convenient up-dating by addition of new documents such as supplementary information, evaluation reports, query letters and responses.

One or more spring file covers may be used depending on the number of pages contained in each section and in this case the files shall be serially numbered in the format i.e. FILE NO. X of Y in the centre of the file. Every file shall be marked with the proprietary and non proprietary names of the product and number and title of the section in capital letters at the centre of the top cover (e.g. AMTETEXICIN, CLOPIDOGREL 75 MG TABLETS: SECTION 3 ACTIVE PHARMACEUTICAL INGREDIENT). The numbering of files should be cumulative for each product applied.

Files or filling that will not comply with the above description shall not be accepted.

1.3.2 Official references and texts

When direct reference is made to specifications, quality control procedures and test methods in official compendia, text books or standard publications, reprints or authenticated copies of relevant pages

shall be enclosed. References to pharmacopoeias should specify the year of issue.

1.3.3 Manuals

If the applicant has several products which are pharmaceutically similar with the same data which may be applicable to all these products e.g. specifications for named ingredients, standard analytical methods or test protocols, the information may be assembled in the form of a manual such as "Manual – Specifications for Ingredients" or Manual – Analytical Methods and Test Protocols".

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.

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

1.3.4 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").

1.4 Applications

An application consists of documentation in hard copies and electronic form, samples and fees. The application may be delivered physically or by courier to TFDA head office located at Mabibo External along Mandela Expressway, Dar es Salaam, Tanzania.

An application shall only be accepted by TFDA upon payment of the evaluation fees.

For purposes of submission to TFDA, applications are classified into three categories as follows:

1.4.1 New application

This is an application for registration of a medicinal product that is intended to be placed on the Tanzanian market for the first time. A new application may only be made by the applicant and he shall be the person who signs the application form.

A separate application is required for each product.

Products that differ in active ingredient(s), strength, dosage forms, site of manufacture, proprietary names though containing the same ingredients, are considered to be different products and hence require separate applications. In case of parenteral preparations, differences in pack size also require separate applications.

However, products containing the same active ingredients at the same strength made by the same manufacturer at the same manufacturing site, to the same specifications and dosage form, but differing only in packing or pack sizes require only one application.

A new application for registration shall include submission of:

i. Cover letter
ii. A dully filled in application forms: Quality Information Summary and Bioequivalent Information Summary i.e. annexes 1 and 2 (where applicable) as prescribed in these guidelines.
iii. A table of contents listing all sections of the dossier and documents and their corresponding page numbers.
iv. Medicinal product dossier, copies of referenced literature and other supporting documents.
v. An original Certificate of Pharmaceutical Product (WHO Format) on official papers of the issuing competent authority.
vi. Five samples of the smallest commercial pack(s) from one batch with batch certificates of analysis provided that the total amount would not be less than 200 capsules/tablets, 400ml for liquid preparations and 250g for creams and ointments otherwise additional samples shall have to submitted to meet the total minimum required for the dosage form.
vii. A site master file in case the product is manufactured at a facility not inspected and approved by TFDA.
viii. Non refundable application fee for registration of human medicines in Tanzania and GMP inspection fees for facilities not yet inspected and approved by TFDA.

1.4.2 Application for Variation of a registered medicinal product

All applications for variation to a registered product shall be made according to requirements stipulated in the TFDA Application Guidelines for Variation of Registered Medicinal Products also available on TFDA website; www.tfda.or.tz.

1.4.3 Applications for Renewal of Registration

Applications for renewal of registration shall be made at least 180 days before the expiry of existing registration by submitting the following:

i. Dully filled in application form for renewal of registration as outlined in annex 3 of these guidelines.

ii. Batch Manufacturing Record (BMR) of a real batch manufactured within at most six months before the submission of the application.

iii. Two samples of the smallest commercial pack(s) from the same batch along with batch certificates of analysis.

iv. A site master files that describes the manufacturing facilities.

v. Non refundable application fee for registration of human medicines in Tanzania and GMP inspection fees for facilities not inspected and approved by TFDA within the last 3-5 years.

1.5 Payment of fees

Every application shall be accompanied by appropriate fees as specified in the Fees and Charges Regulations in force at the time of application.

Any application that will not be accompanied by appropriate fees will not be accepted.

The fees may be paid directly to TFDA or 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. P.O. Box 71625, Dar es Salaam Tanzania Swift Code: CITITZTZ.

Local applicants will deposit into Account No. 6503900110 at National Microfinance Bank, Kariakoo Branch OR by banker's draft.

When payment is made by bank transfer all bank charges shall be borne by the applicant who shall also make sure he sends an advice note giving details of the payment in particular the name of the applicant, the product or products paid for and amount of fees paid. If the product is already registered in addition to the aforementioned details, the registration number of the product must also be quoted.

For each registered product an annual retention fees shall be paid on or before the end of January of each year for which the fees are due.

1.6 Outline of the evaluation process

1.6.1 Evaluation

1.6.1.1 Evaluation of scientific data

Evaluation of applications will be done on a first in first out (FIFO) basis unless the product meets the fast track criteria as set out in these guidelines.

Assessment of product dossiers will involve evaluators from within or outside TFDA. The evaluation report produced by the evaluator will be reviewed by a second senior evaluator who does the quality assurance of the evaluation report and where necessary add comments and finalizes the report and recommendations. Evaluation will be done according to the requirements of these guidelines and in accordance with the Standard Operating Procedures for Evaluation. However, the Authority reserves the right to request information or material, or define conditions not specifically described in this guidance, in order to allow the Authority to adequately assess the safety, efficacy or quality of a medicinal product.

The Authority may during evaluation, request for clarification, certificates and/or samples through a query letter. Once a query has been raised and issued to the applicant, the evaluation process will stop until when TFDA receives a written response to the query. All queries issued in the same letter must be submitted together in one transaction within six months from the date they were issued, otherwise it will be deemed that the applicant has withdrawn the application. Thereafter, registration of the product may only be considered upon submission of a new application.

1.6.1.2 Laboratory analyses of product sample(s)

Laboratory analysis of the samples will be done against the claimed in-house or pharmacopoeia specifications using the analytical method provided by the applicant. The laboratory will generate a laboratory analysis report.

1.6.1.3 Good Manufacturing Practices (GMP) Certification

Good Manufacturing Practices (GMP) Certification of production lines of a manufacturing site of the respective medicinal product shall be mandatory before its registration is considered.

The validity of the GMP certification of production lines of manufacturing site shall, unless suspended, be valid for five years

after which it must be renewed by applying and paying inspection fees.

When inspection is conducted, an observation memorandum that details issues to be addressed by the applicant will be signed by representatives of the inspected parties and TFDA inspectors. The full report of the inspection will be sent to the applicant within 60 days of conducting the inspection. The applicant will be required to rectify the observed deficiencies and submit Corrective Actions and Preventive Actions (CAPA) report. Based on the report, the Authority may either approve the facility or conduct re-inspection.

When the site is found not to comply with GMP, data generated from it and submitted for application for registration of the respective medicinal product shall not be eligible for evaluation. All products from the site applied for or already registered will be rejected forthwith. Thereafter, registration of the rejected or withdrawn products shall only be considered if the site is confirmed to be GMP compliant, with subsequent submission of new application.

1.6.2 Consideration by Human Medicines Registration Technical Committee

A summary of recommendations of evaluation, laboratory analysis and GMP status reports will be presented before the *Human Medicines Registration Technical Committee* for consideration and making final recommendations for granting or rejecting registration of the product.

The committee will recommend registration of the product only if it is satisfied that adequate and scientifically sound evidence has been provided to demonstrate that the safety, efficacy and quality of product as required by Section 51 (1) of the Tanzania Food, Drugs and Cosmetics Act, 2003 and that the product is manufactured at a site that complies with Tanzanian Good Manufacturing Practice Guidelines, otherwise it will recommend rejection of the product. Also non compliance to the requirements prescribed in the guidelines in content and format shall lead to rejection of the product.

Recommendations of the Committee to register or reject the product will be submitted to Director General for approval.

1.6.3 Timelines

The Authority will implement the following timelines in processing applications for marketing authorization of human medicinal products

1.6.3.1 Evaluation of new applications

Complete applications will be evaluated within 180 working days of receiving the application including evaluation of documentation and consideration by a technical committee.

1.6.3.2 Fast-track evaluation

An application may be fast tracked and be evaluated within six (6) months of its submission if the applicant has requested and paid twice the prescribed evaluation fees and the product is life saving, or the product is indicated for diseases which at the time of application have no registered alternative medicine or evidence has been submitted in a motivation letter accompanying the application to show that the product has significant advantages in terms of safety and efficacy over existing products indicated for treatment or prevention of life threatening diseases (not a me too drug).

1.7. Validity of registration

The registration of a human medicinal product will subject to payment of annual retention fees be valid for five (5) years unless earlier suspended or revoked by TFDA or withdrawn by applicant. The Authority will give reasons in writing when it suspends or revokes, or amends conditions of registration. Likewise the applicant shall also give reasons for terminating registration of a product.

1.8. Application for review of refusal of registration

Any applicant who is not satisfied by the Authority's decision not to grant registration to his/her medicinal product may, within sixty days after the date of being notified of such refusal, apply to the Authority requesting it to review its decision. He shall do so by giving grounds for review for each reason given for the rejection of his product. The grounds for the request shall be based on the information that was submitted in the product's dossier. Any additional or new information that was not earlier submitted will only be considered upon submission of a new application. The Authority may review, reject or vary its own decision.

SECTION TWO

SUMMARY OF PRODUCT CHARACTERISTICS

Provide an A4 size and real size copies (both in hard copy and on a CD-ROM in MS-Word) of the package insert that contains a Summary of Product Characteristics (SPC) aimed at medical practitioners and other health professionals using the format outlined below. SPC for generic products shall be comparable to that of the corresponding innovator product. The SPC is an essential part of drug registration and it can only be changed with the consent of TFDA.

2.1 Name of the medicinal product

State the name under which the product 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 if any.

2.2 ATC and Forensic Classification

State the ATC class and the proposed distribution category of the product. For ATC refer to the current publication of The B Anatomical Therapeutic Chemical Classification System issued by the World Health Organization Collaborating Centre for Drug Statistics Methodology (WHOCC).

2.3 Qualitative and quantitative composition

Provide the qualitative and quantitative composition per unit dosage form in terms of the active substances and excipients.

2.4 Pharmaceutical form

State clearly the pharmaceutical dosage form of the product, e.g. tablets, capsules, injection, etc. Any descriptive terms to give an indication of the exact type of dosage form should also be included e.g. film-coated tablets, enteric-coated tablets, hard-gelatin capsules, soft-gelatin capsules, oily injection etc.

The visual and physical characteristics of the product should also be stated, including where applicable: shape, size, superficial markings for identification purposes, colour, odour, taste, pH, osmolarity, etc.

2.5 Clinical particulars

2.5.1 Therapeutic 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.

2.5.2 Posology and method 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.

2.5.3 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.

2.5.4 Special warnings and precautions for use

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 etc.

2.5.5 Interaction with other medicinal products and other forms of interaction

State briefly the interactions of the product with other drugs, food or any other substances and where applicable the mechanism of interaction.

2.5.6 Pregnancy and lactation

Provide information on the use of the product in pregnant women and lactating mothers. Results from reproduction toxicology should be included under section 2.6.3 below and cross-referenced here, if necessary.

2.5.7 Effects on ability to drive and use machines

Provide information on the effects of the product on the ability to drive and operate machines. Studies performed on the same should be provided or cross referenced, where applicable.

2.5.8 Undesirable effects

State the side effects and adverse reactions of the product as per the MedDRA frequency convention and system organ class database.

Within each frequency grouping, undesirable effects should be presented in order of decreasing seriousness.

2.5.9 Overdose

Describe symptoms of over-dosage or poisoning and the recommended treatment, emergency procedures and antidotes (if available).

2.6 Pharmacological properties

2.6.1 Pharmacodynamic properties

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

2.6.2 Pharmacokinetic properties

Give a concise summary of the pharmacokinetic properties (i.e. absorption, distribution, metabolism and excretion) of the drug(s).

2.6.3 Preclinical safety data

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

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use should also be outlined.

2.7 Pharmaceutical particulars

2.7.1 Incompatibilities

Provide information on incompatibilities of the product with other medicinal products. (e.g. mixing of medicinal products during administration).

2.7.2 Shelf life

Provide information on the finished product shelf life and on the in-use stability after first opening and/or reconstitution/dilution. Only one overall shelf life for the finished product should be given even if different components of the product may have a different shelf life (e.g. powder & solvent).

These should be stated in the following format:

<6 months><1 year><18 months><2 years><30 months><3 years>

2.7.3 Special precautions for storage

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 (see also 4.11.12 below for Core Storage Statements).

(b) Any special user instructions, e.g. dilution, reconstitution and storage and shelf life after reconstitution, etc.

2.7.4 Nature and contents of container

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.

2.7.5 Special precautions for disposal

Provide practical instructions for preparation and handling of the product including disposal of the medicinal product and waste materials derived from the used medicinal product.

2.8 Registrant

State the name and address of registration holder including telephone, fax number and e-mail.

2.9 Registration Number(s)

To be included after obtaining registration number.

2.10 Date of initial or renewed registration

The date should correspond to the initial registration of the medicinal product concerned (To be included after obtaining first registration or renewal of registration). It should not reflect individual strength or presentation approvals introduced via subsequent variations and/or extensions.

Both the date of first registration and, if the registration has been renewed, the date of the (last) renewal should be stated in the format given in the following example:

Date of first authorisation: 3 April 2008.
Date of last renewal: 3 March 2013.

2.11 Date of revision of the text

Date of revision of the text should be stated at the time of printing once a change to the SPC has been approved.

SECTION THREE

ACTIVE PHARMACEUTICAL INGREDIENT(S)

The information on the Active Pharmaceutical Ingredient(s) [API(s)] can be submitted according to the following order of preference:

- As the latest, valid European Certificate of Suitability (CEP) with all appendices. The information, which may not be covered by the CEP, should be provided under points 3.2.2, 3.5.2, 3.6 and 3.7.

- As (a) Drug Master File(s) [DMF(s)] submitted by the API manufacturer, provided that the DMF contains all the information listed in this section or

- By completing items **Section 3.1-3.7 of these guidelines**. In this case, the API manufacturer should provide a signed declaration that the synthesis and subsequent purification is conducted in accordance with what is presented in the dossier.

3.1 Nomenclature

3.1.1 International Non-proprietary Name (INN)

3.1.2 Compendial name if relevant

3.1.3 Chemical name(s)

3.1.4 Company or laboratory code, if applicable

3.1.5 Other non-proprietary name(s), e.g., national name, United States Adopted Name (USAN), Japanese Accepted Name (JAN); British Approved Name (BAN)

3.1.6 Chemical Abstracts Service (CAS) registry number

3.2 Properties of API(s)

3.2.1 API not described in BP, PhInt, JP, PhEur or USP

Provide the following information:

a) Chemical structure, including relative and absolute stereochemistry, the molecular formula and the relative molecular mass;

b) Isomeric nature including stereochemical configuration;

c) Documented evidence of structure and stereochemistry, such as clearly visible, Quality Assurance (QA)-certified copies of infrared, nuclear magnetic resonance (proton and C-13), ultraviolet and mass spectra, together with professional interpretation of the relevant parts of spectra, X-ray diffractograms, thermograms, and so on;

d) Physicochemical and other relevant properties of the API, such as solubility in water, other solvents such as ether, ethanol, acetone, and buffers of different pH; partition coefficient; existence/absence of

polymorphs and water/solvent of crystallization; results of hygroscopicity testing; particle size and so on.

3.2.2 API described in BP, PhInt, JP, PhEur, or USP

Identify physicochemical and other properties of the API, which are not included in a pharmacopoeial monograph and are relevant to product safety and efficacy, such as solubility in water, other solvents such as ether, ethanol, acetone, and buffers of different pH; partition coefficient; existence/absence of polymorphs and water/solvent of crystallization; results of hygroscopicity testing; particle size, and so on.

3.2.3 Information from literature

Supportive data and results from specific studies or published literature can be included within or attached to this section.

3.3 Site(s) of manufacture

State the name and street address of each facility where manufacture (synthesis, production) occurs. Provide phone number(s); fax number(s) and e-mail addresses. Include any alternative manufacturers.

Provide a valid Manufacturing Authorization for the production of APIs. If available, attach a certificate of GMP compliance.

Reference: WHO pharmaceutical starting materials certification scheme (SMACS): guidelines on implementation (WHO Technical Report Series, No. 917, 2003)

3.4 Route(s) of synthesis

3.4.1 API not described in BP, PhInt, JP, PhEur, or USP

Provide a flow diagram of the synthetic process(es) that includes molecular formulae, weights, yield ranges, chemical structures of starting materials, intermediates, reagents and API reflecting stereochemistry, and identifies operating conditions, purification steps, catalysts and solvents.

Submit a sequential procedural narrative of the manufacturing process. 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).

When the API is still to be produced in commercial quantities (pilot scale batches), it can be registered provided scale-up is immediately reported

to TFDA.

When the submitted route of synthesis consists of a limited number of steps (e.g., one to three), full details of the manufacture of the starting material(s) or key intermediates should be given and/or at least detailed specifications especially regarding the impurity profile including residual solvents and catalysts.

Process validation of critical steps of the synthesis and aseptic processing and sterilization, when applicable, should be included. The scale of manufacture / typical batch size should be stated.

A declaration on the use/non-use of material of animal or human origin should be provided.

Starting materials from vegetable origin should be fully characterized and a contaminant profile should be established and submitted.

Explain alternate processes and describe with the same level of detail as the primary process. It should be demonstrated that batches obtained by alternate processes have the same impurity profile as the principal process. If the obtained impurity profile is different, it should be demonstrated as to be acceptable according the requirements described further in the text for “impurities”.

Reprocessing steps should be identified and justified. Any data to support this justification should be either referenced or submitted.

Provide external environmental impact statement (aquatic, atmospheric and terrestrial environment, potential for harm, disposal sites and methods).

3.4.2 Specifications of raw materials and intermediates used in the synthesis

Provide specifications for starting materials, reagents, solvents, catalysts, and intermediates (if isolated during the process) in the synthesis. Provide information demonstrating that materials meet standards appropriate for their intended use (including the clearance or control of adventitious agents), as appropriate.

3.4.3 API described in BP, PhInt, JP, PhEur, or USP

An outline of the route of synthesis should be provided (a simplified flow chart and a qualitative description of the manufacturing method, including the name of solvents, reagents and catalysts) with special emphasis on the final steps including purification procedures.

3.5 Specifications

3.5.1 API not described in BP, PhInt, JP, PhEur or USP

Provide justification for the API specification.

Reference: ICH-Q6A — Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances + Decision trees.

http://www.ich.org/MediaServer.jser?@_ID=430&@_MODE=GLB

Characterize and analyze synthesis impurities, including residual solvents, which may be present in API. Particular attention should be given to justifying cases where testing for possible impurities are omitted, e.g., due to the fact that the impurity has not been detected in any batches or will not potentially be present due to a particular method of production.

References:

- Q3A(R) Impurities in New Drug Substances http://www.ich.org/MediaServer.jser?@_ID=422&@_MODE=GLB
- FDA (CDER) Guidance for Industry – ANDAs: Impurities in Drug Substances (Rev. 1, January 2005).http://www.fda.gov/cder/guidance/6422dft.htm
- Q3C Impurities: Guideline for Residual Solvents
- Q3C (M) Impurities: Residual Solvents (Maintenance) Permissible Daily Exposure (PDE) for Tetrahydrofuran and N. Methylpyrrolidine http://www.ich.org/MediaServer.jser?@_ID=423&@_MODE=GLB

Provide analytical validation information, including experimental data for the analytical procedures used for testing the API and impurities. Include test methods in sufficient detail for them to be replicated by another laboratory.

References:

- WHO Guideline: Validation of analytical procedures used in the examination of pharmaceutical materials.
- ICH-Q2A Text on Validation of Analytical Procedures http://www.ich.org/MediaServer.jser?@_ID=417&@_MODE=GLB
- ICH-Q2B Validation of Analytical Procedures: Methodology http://www.ich.org/MediaServer.jser?@_ID=418&@_MODE=GLB
- WHO Expert Committee on Specifications for Pharmaceutical Preparations. 32nd report. Geneva, WHO, 1992 (WHO Technical Report Series, No. 823) in "Quality assurance of pharmaceuticals – A compendium of guidelines and related materials." Volume 1. WHO, Geneva, pp. 119-124 (1997).

Provide information on the preparation and studies to establish the identity, purity and assay value of in-house primary (absolute) and secondary (working) standards.

Submit Certificate of Analysis (CoA) of in-house primary standards for use in assays, including:

- assay by two different validated methods,
- identification and control of impurities,
- storage instructions, and
- duration of use of the standards.

Reference:

ICH Q6A — Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.

Provide verified certificates of analysis for at least two batches produced at each site of manufacture by each synthetic method, including results for impurities.

3.5.2 API described in BP, PhInt, JP, PhEur or USP

Provide a copy of the monograph together with any test methods referenced in the monograph but not appearing in it. Note that the current monograph should always control the quality of the API.

The quality of the API should meet not only the requirements of specific monographs but also those described in the general monographs of a pharmacopoeia on APIs, excipients and other substance for pharmaceutical use.

Tests and limits should, as a minimum, comply with the relevant pharmacopoeial requirements. Whenever, an API has been prepared by a method liable to leave impurities not controlled in the pharmacopoeial monograph, these impurities (based on 3 to10 batch analysis results), including residual organic solvents, as well as their maximum tolerance limits should be declared and controlled by a suitable test procedure.
Provide details of any specifications for potentially critical quality variables (e.g. polymorphs, particle size, loss on drying, as identified during development chemistry) additional to those in the pharmacopoeia.

Provide verified certificates of analysis for at least two batches produced at each site of manufacture by each synthetic method, including results for impurities.

3.6 Container closure system

Provide a description of the container closure system(s), including the identity of materials of construction of each primary packaging component and their specifications. The specifications should include description and identification (and critical dimensions with drawings, where appropriate). Non-compendial methods (with validation) should be included, where appropriate.

Provide only a brief description for non-functional secondary packaging components (e.g., those that do not provide additional protection). Provide additional information on functional secondary packaging components.

The suitability should be discussed with respect to, for example, choice of materials, protection from moisture and light, compatibility of the materials of construction with the API, including sorption to container and leaching, if applicable, and/or safety of materials of construction.

3.7 Stability testing

3.7.1 Stress testing (forced degradation)

Publications from peer-reviewed literature could be submitted to support/replace experimental data.

Stress testing of the API can help to identify the likely degradation products, which can in turn help establish the degradation pathways and the intrinsic stability of the molecule and validate the stability indicating power of the analytical procedures used. The nature of the stress testing will depend on the individual API and the type of FPP involved.

Degradation paths for pharmaceutical compounds are typically reactions of hydrolysis, oxidation, photolysis, and/or acid-base chemistry. To force these reactions, the API or FPP is placed in solution expediently, for example, under the conditions shown in the following table.

Stress factor	Conditions
Heat	60°C
Humidity	75% RH or greater
Acid	0.1N HCl
Base	0.1N NaOH
Oxidative	3% H_2O_2
Photolytic	Metal halide, Hg , Xe lamp, or UV-B/fluorescent
Metal ions (optional)	0.05 M Fe2+ or Cu2+

The objective is not to completely degrade the active compound but to generate degradation to a small extent, typically 10-30% loss of active by assay when compared with non-degraded compound. This target is chosen so that some degradation occurs, but it is not so severe that secondary products are generated. (Secondary degradation products are degradation products of degradation products and in most cases are not observed during stability studies.) In the total absence of degradation products after 10 days, the API is considered stable. If degradation is detectable but its extent is less than 10%, then the stress factors or the stress conditions, or both, should be increased.

Stress testing is to be carried out on a single batch of the API. Photostability testing should be an integral part of stress testing. The standard conditions for photostability testing are described in ICH Q1B.

Solid-state degradation can also be considered. For APIs, placing a solid sample at elevated temperatures —e.g., 60-120 °C, or 5-10 °C below the melting point— can generate some degradation compounds. Because of the harsher conditions, these compounds may not be observed under the accelerated stress studies. However, this approach serves to generate degradation products that can be used as a worst case to assess the analytical method performance.

Examining degradation products under stress conditions is also useful in developing and validating suitable analytical procedures. However, it may not be necessary to examine specifically for certain degradation products if it has been demonstrated that they are not formed under accelerated or long term storage conditions. Results from these studies form an integral part of the information provided to TFDA.

For APIs not described in an official pharmacopoeial monograph, there are two options:

- When available, it is acceptable to provide the relevant data published in the “peer review” literature to support the proposed degradation pathways.

- When no data are available in the scientific literature, including official pharmacopoeias, stress testing should be performed. Results from these studies will form an integral part of the information provided to TFDA.

<u>Reference:</u>

ICH-Q1A (R2) Stability Testing of New Drug Substances and Products http://www.ich.org/MediaServer.jser?@_ID=419&@_MODE=GLB

3.7.2 Regulatory stability testing

Summarize the stability testing program and report the results of stability testing of not less than three (minimum one production scale and two pilot scale) batches of the API as described in **Annex 4**. The data for each attribute should be discussed, trends analyzed and a re-test date should be proposed. Information on the analytical procedures used to generate the data and validation of these procedures should be included.

Describe the methodology used during stability studies; if this is identical to methodology described elsewhere in the dossier, a cross-reference will suffice. If different methodology was used, provide validation of tests for impurities including degradants and assay and for other tests as necessary.

At the time of submitting the dossier, the general requirements are:

Storage temperature (°C)	**Relative humidity (%)**	**Minimum time period covered by data at submission (months)**
Accelerated: 40±2	75±5	6
Long term: 30±2	75±5	12

Provide the post-approval stability protocol and stability-testing commitment, when applicable.

References:

- Q1A (R2) Stability Testing of New Drug Substances and Products http://www.ich.org/MediaServer.jser?@_ID=419&@_MODE=GLB
- Q1B Stability Testing: Photostability Testing of New Drug Substances and Products http://www.ich.org/MediaServer.jser?@_ID=412&@_MODE=GLB
- Q1E Evaluation for Stability Data http://www.ich.org/MediaServer.jser?@_ID=415&@_MODE=GLB
- WHO list of stable APIs - Supplement 2, http://www.who.int/prequal/

A storage statement should be proposed for the labelling (if applicable), which should be based on the stability evaluation of the API.

A re-test period should be derived from the stability information, and the approved re-test date should be displayed on the container label and CoA.

Unless otherwise justified, the long-term stability studies should be conducted at 30°C ± 2°C/75± 5%RH conditions.

SECTION FOUR

FINISHED PHARMACEUTICAL PRODUCT(S)

The applicant shall be required to provide information on the finished pharmaceutical product(s) (FPP(s) as follows:-

4.1 Manufacturing and Marketing authorization

Submit a Certificate of Pharmaceutical Product in format recommended by the World Health Organization together with a valid Manufacturing Authorization for pharmaceutical production.

4.2 Pharmaceutical Development

The Pharmaceutical Development section should contain information on the development studies conducted to establish that the dosage form, the formulation, manufacturing process, container closure system, microbiological attributes and usage instructions are appropriate for the purpose specified in the application. The studies described here are distinguished from routine control tests conducted according to specifications.

References:

- ICH Q8 guidelines: Pharmaceutical Development
  http://www.ich.org/MediaServer.jser?@_ID=1707&@_MODE=GLB
- ICH Q9 guidelines: Quality Risk Management
  http://www.ich.org/MediaServer.jser?@_ID=1957&@_MODE=GLB

4.2.1 Company research and development

This section should identify, describe and document the formulation and process attributes (critical parameters) that can influence batch reproducibility, product performance and FPP quality, including stability.

(a) The compatibility of the API with excipients should be documented. 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 FPP should be discussed and supported by experimental data.

(b) The choice of excipients, in particular their functions and concentrations should be documented.

(c) For fixed-dose combination products, the compatibility of APIs with each other should be studied and the results documented.

(d) A discriminating dissolution method should be developed for the final composition of the FPP, when applicable. Limits should be set for each API in fixed-dose FPPs. The dissolution method should be incorporated into the stability and quality control programs. Multipoint dissolution profiles of both the test and the reference FPPs should be compared [multipoint: at least five (5)]. Dissolution testing should be incorporated into the stability programme.

References:

- http://www.fda.gov/cder/guidance/1713bp1.pdf
- WHO guideline on dissolution testing – Supplement 1, http://www.who.int/prequal/

(e) A brief summary describing the development of the FPP should be provided, taking into consideration the proposed route of administration and usage.

(f) The selection and optimization of the manufacturing process, in particular its critical aspects, should be explained and documented. Where relevant, the method of sterilization should be explained and justified.

(g) Any overages in the formulation(s) should be warranted.

(h) Where appropriate, the microbiological attributes of the dosage form should be discussed, including, for example, the rationale for not performing microbial limits testing for non-sterile products and the selection and effectiveness of preservative systems in products containing antimicrobial preservatives. For sterile products, the integrity of the container closure system to prevent microbial contamination should be addressed.

Usually, in this phase the microbial challenge test could be performed to establish and justify the amount of the antimicrobial preservatives to be used. For this purpose, the drug product should be formulated with different concentrations of preservatives and a microbial challenge test on each of the formulations will give the answer on the “least necessary” but still effective concentration.

(i) The compatibility of the FPP with reconstitution diluent(s) or dosage devices (e.g., precipitation of API in solution, sorption on injection vessels, stability) should be addressed to provide appropriate and supportive information for the labelling.

(j) A tabulated summary of the compositions of the FPP batches (batch number, batch size, manufacturing date and certificate of analysis at batch release) used in clinical trials and in bioequivalence studies and a presentation of dissolution profiles

must be provided. A discussion of the documented information and data should be presented. Results from comparative in vitro studies (e.g., dissolution) or comparative in vivo studies (e.g., bioequivalence) should be discussed when appropriate.
Packaging should be selected to ensure the quality of the FPP throughout its shelf life.

Reference: Validation of manufacturing processes

http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf#page=46

Prospective validation is carried out during the development stage by means of a risk analysis of the production process, which is broken down into individual steps; these are then evaluated on the basis of past experience to determine whether they might lead to critical situations. Where possible critical situations are identified, the risk is evaluated, the potential causes are investigated and assessed for probability and extent, the trial plans are drawn up, and the priorities set. The trials are then performed and evaluated, and an overall assessment is made. If, at the end, the results are acceptable, the process is satisfactory. Unsatisfactory processes must be modified and improved until a validation exercise proves them to be satisfactory.

4.2.2 Information from literature

Supportive data and results from specific studies or published literature can be included within or attached to the Pharmaceutical Development section.

4.3 Formulation

Provide the formulation in tabular form for a typical batch and for an administration unit, e.g. one tablet, 5 ml of oral solution, or the contents of an ampoule or bag of large volume parenteral solution.

Include excipients that may be removed during processing, those that may not be added to every batch (e.g. acid and alkali), and the qualitative and quantitative composition of any tablet coating, capsule shell and inked imprint on the dosage form. State and justify any overages. State the function(s) of each excipient (e.g. antioxidant, lubricant and binder).

Where applicable special technical characteristics of excipients should be indicated, e.g. lyophilized, micronised, solubilized, emulsified. The type of water (e.g. purified, demineralized), where relevant, should be indicated.

Indicate any substances whose content may be varied (e.g. inked imprint, tablet coating). Ranges in the content of excipients need justification and explanation how the content is decided for each batch.

4.4 Sites of manufacture

State the name and street address of each facility where any aspect of manufacture occurs, including production, sterilization, packaging and quality control. Indicate the activity performed at each site. Provide phone number(s); fax number(s) and e-mail addresses. Include any alternative manufacturers.

For each site where the major production step(s) is/are carried out, submit a valid GMP Certificate and attach an original Certificate of a Pharmaceutical Product (CPP) issued by the competent authority in terms of the WHO Certification Scheme on the Quality of Pharmaceutical Products Moving in International Commerce.

4.5 Manufacturing process

A flow diagram should be presented giving the steps of the process and showing where materials enter the process. The critical steps and points at which process controls, intermediate tests or final product controls are conducted should be identified.

A narrative description of the manufacturing process, including packaging that represents the sequence of steps undertaken and the scale of production should also be provided. Novel processes or technologies and packaging operations that directly affect product quality should be described with a greater level of detail. Equipment should, at least, be identified by type (e.g., tumble blender, in-line homogenizer) and working capacity, where relevant.

Steps in the process should have the appropriate process parameters identified, such as time, temperature, or pH. Associated numeric values can be presented as an expected range. Numeric ranges for critical steps should be justified (e.g., blending parameters, loss on drying (LOD) of the compression blend and in-process as well as final yields). In certain cases, environmental conditions (e.g., experimentally documented temperature and relative humidity for hygroscopic FPPs) should be stated.

Proposals for the reprocessing of materials should be justified. Any data to support this justification should be either referenced or filed in this section.

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.

Indicate stages of manufacture at which sampling is carried out for in-process control tests. The in-process tests should be described in full, though reference to methods in other parts of the dossier or an acknowledged pharmacopoeia will suffice.

Documented evaluation of at least three (3) production scale batches should be submitted to provide assurance that the manufacturing process will reliably meet predetermined specifications.

4.6 Manufacturing Process Controls of Critical Steps and Intermediates

Critical Steps: Tests and acceptance criteria should be provided (with justification, including experimental data) performed at the critical steps of the manufacturing process, to ensure that the process is controlled.

Intermediates: Information on the quality and control of intermediates isolated during the process should be provided.

4.7 Process Validation and Evaluation

4.7.1 New (for the generic manufacturer) FPPs

Data should be submitted in the application for demonstrating the validity of a given process.

Reference: Validation of manufacturing processes

http://whqlibdoc.who.int/trs/WHO_TRS_908.pdf#page=46

Concurrent validation is carried out during normal production. This method is effective only if the development stage has resulted in a proper understanding of the fundamentals of the process. The first three production-scale batches must be monitored as comprehensively as possible. (This careful monitoring of the first three production batches is sometimes regarded as prospective validation.) The nature and specifications of subsequent in-process and final tests are based on the evaluation of the results of such monitoring.

One of the most practical forms of process validation, mainly for non-sterile products, is the final testing of the product to an extent greater than that required in routine quality control. It may involve extensive sampling, far beyond that called for in routine quality control and testing to normal quality control specifications, and often for certain parameters only. Thus, for instance, several hundred tablets per batch may be weighed to determine unit dose uniformity. The results are then treated statistically to verify the "normality" of the distribution, and to determine the standard deviation from the average weight. Confidence limits for individual results and for batch homogeneity are also estimated. Strong assurance is provided that samples taken at random will meet

requirements if the confidence limits are well within compendial specifications.

Similarly, extensive sampling and testing may be performed with regard to any quality requirements. In addition, intermediate stages may be validated in the same way, e.g. dozens of samples may be assayed individually to validate mixing or granulation stages of low-dose tablet production by using the content uniformity test. Products (intermediate or final) may occasionally be tested for non-routine characteristics. Thus, sub-visual particulate matter in parenteral preparations may be determined by means of electronic devices, or tablets/capsules tested for dissolution profile if such tests are not performed on every batch.

Simulation process trials are used mainly to validate the aseptic filling of parenteral products that cannot be terminally sterilized. This involves filling ampoules with culture media under normal conditions, followed by incubation and control of microbial growth. In the past, a level of contamination of less than 0.3% was considered to be acceptable; however, the current target level should not exceed 0.1%.

Challenge experiments are performed to determine the robustness of the process, i.e. its capacity to operate smoothly when parameters approach acceptable limits. The use of ranges of parameters for the quality of the starting materials in experimental batches may make it possible to estimate the extent to which the process is still capable of producing an end-product that meets the specifications.

The progress from pre-formulation → formulation → pilot manufacture → industrial scale manufacture should be shown in the dossier submitted to be logical, reasoned and continuous.

Laboratory scale batches are produced at the research and early development laboratory stage; they may be of very small size (e.g. 100-1000x less than production scale). These batches may find many uses, for example to support formulation and packaging development, clinical and/or pre-clinical studies.

Pilot Batches may be used to support formal stability studies and also to support pre-clinical and clinical evaluation. Pilot batch size should correspond to at least 10% of the production scale batch, i.e. such that the multiplication factor for the scale-up does not exceed 10. For oral solid dosage forms this size should generally be 10% of production scale or 100,000 units whichever is the greater.

Full validation studies should be completed for each FPP at the production scale.

Where ranges of batch sizes are proposed, it should be shown that variations in batch size would not adversely alter the characteristics of

the finished product. It is envisaged that those parameters listed in the following validation scheme will need to be re-validated once further scale-up is proposed after registration.

Where validation data on production scale batches are not provided with the application, the applicant shall submit the validation protocol described below. This should outline the formal process validation studies to be conducted on production scale batches [usually not less than three (3) consecutive batches]. The applicant should submit a written commitment that information from these studies will be available for verification during inspection. The protocol should be in the dossier submitted and should include the following information as a minimum:

Provide a short description of the process with a summary of the critical processing steps or critical parameters to be monitored during validation.

- FPP specification (release).
- Details of analytical methods (references to appropriate parts in the dossier). In-process controls proposed with acceptance criteria.
- Additional testing intended to be carried out (e.g. with proposed acceptance criteria and analytical validation as appropriate).
- Sampling plan — where, when and how the samples are taken.
- Drug content uniformity is considered essential for FDC-FPPs and should be addressed in the final process validation.
- Details of methods for recording and evaluation of results.
- Proposed timeframe

Following completion of the programme, a validation report containing the following information and signed by the appropriate authorized person should be generated for examination.

- Batch Analytical Data
- Certificates of Analysis
- Batch Production Records
- Report on unusual findings, modifications or changes found necessary with appropriate rationale
- Conclusions

Where the results obtained show significant deviations from those expected, TFDA need to be informed immediately. In such cases corrective actions should be proposed and any changes proposed in the manufacturing process should receive prior TFDA approval by way of variation.

4.7.2 Established (for the generic manufacturer) FPPs

Manufacturing as well as in-process and quality control testing data should be evaluated. A total of 10-25 consecutive batches (or more), manufactured over the period of the last 12 months, should be used when reviewing the results, to provide a statistically significant picture. Trend analysis should be presented.

Rejected batches should not be included in the analysis but must be reported together with the reports of failure investigations.

4.8 Specifications for excipients

Include microbiological limits in the specification for excipients of natural origin. Skip testing is acceptable, if justified. For excipients of human, animal or microbial origin, provide information regarding adventitious agents (e.g., sources specifications; description of the testing performed; viral safety data).

Provide detailed information on the avoidance and control of non-viral adventitious agents (e.g., transmissible spongiform encephalopathy agents (TSE-CEP is preferred), bacteria, mycoplasma, and fungi). This information can include, for example, certification and/or testing of raw materials and excipients, and control of the production process, as appropriate for the material, process and agent.

For oils of plant origin (e.g., soy bean oil, peanut oil) demonstrate the absence of aflatoxins or biocides. Only colours permitted by the EU's "List of permitted food colours", the FDA's "Inactive ingredient guide" or "Japanese Pharmaceutical Excipients" may be used.

References:

- List of permitted food colours, Official journal of the European Communities, 1994. L237. (European Commission Directive 94/36/EC).
- Inactive ingredient guide. Rockville, MD, United States Food and Drug Administration, Division of Drug Information and Research, 1996.
- Japanese pharmaceutical excipients. Tokyo, Pharmaceutical and Cosmetics Division, Pharmaceutical Affairs Bureau, Ministry of Health and Welfare (updated annually or biennially).

4.8.1 Excipients not described in PhInt, JP, BP, PhEur or USP

For non-compendial excipients(s) and those used for the first time in a FPP or by a new route of administration, full details of manufacture, characterization, and controls, with cross references to supporting safety data (non-clinical and/or clinical) should be provided according to the API format. Certificate of analysis for one batch of each excipient should be provided.

4.8.2 Excipients described in PhInt, JP, BP, PhEur or USP

Provide a copy of the monograph together with any test methods referenced in the monograph but not appearing in it. Note that the current monograph should always control the quality of the excipient. Provide details of any specifications additional to those in the pharmacopoeia. Certificate of analysis for one batch of each excipient should be provided.

4.9 Quality Control of the FPP

4.9.1 Specifications for the finished pharmaceutical product

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

The following control methods must be included in the specification:

- General characteristics of the pharmaceutical form (physicochemical properties and appearance);
- Identification tests of the API(s);
- Quantitative determination of API(s);
- Unless there is appropriate justification, the maximum acceptable deviation in the API content of the FPP shall not exceed ± 5% of the label claim at the time of manufacture;
- Purity tests [degradation products, residual solvents or other product (e.g. incompatibilities of APIs in a fixed-dose-combination (FDC) FPP] or process related impurities, microbial contamination);
- Pharmaceutical tests, e.g. dissolution;
- Physical tests appropriate to the dosage form, e.g. loss on drying, hardness, friability, particle size and apparent density;
- Uniformity of dosage units, where applicable;
- The identification tests for colouring materials used and identification and assay of antioxidants, antimicrobial or chemical preservatives with limits. The preservatives content limits of 90-110% at release are normally acceptable without further justification;
- For FDC-FPPs, analytical methods that can distinguish each API in the presence of the other APIs should be developed and validated;
- Acceptance criteria for degradants in FDC-FPPs should be established with reference to the API they are derived from. If an impurity results from a chemical reaction between two or more APIs, then its acceptance limits should be calculated with reference to the worst case (API with the smaller area under the curve). Alternatively, the content of such impurities could be calculated in relation to their reference standards;

- Dissolution testing specifications should include all APIs of the finished dosage form and utilize relevant media.

Information on the reference standards or reference materials used for testing of the FPP should be submitted if not previously provided in API part.

Reference:

ICH Q6A — Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances.

4.9.2 Analytical procedures

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

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 in the monograph but not appearing in it. Provide details of any specifications and test methods additional to those in the pharmacopoeia.

4.9.3 Validation of analytical procedures

All non-compendial test procedures need to be validated. Results of the validation studies, comments on the choice of routine tests and standards must be provided. For pharmacopoeial methods, provide data to demonstrate that the method is applicable to this formulation.

Reference(s)

- WHO Guideline: Validation of analytical procedures used in the examination of pharmaceutical materials
- WHO Expert Committee on Specifications for Pharmaceutical Preparations. 32nd report. Geneva, WHO, 1992 (WHO Technical Report Series, No. 823) in "Quality assurance of pharmaceuticals – A compendium of guidelines and related materials." Volume 1. WHO, Geneva, pp. 119-124 (1997)
- ICH-Q2A Text on Validation of Analytical Procedures
- http://www.ich.org/MediaServer.jser?@_ID=417&@_MODE=GLB
- ICH-Q2B Validation of Analytical Procedures: Methodology
- http://www.ich.org/MediaServer.jser?@_ID=418&@_MODE=GLB

4.9.4 Batch analysis

Results of not less than three (3) batch analyses (including the 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.

4.10 Container/closure system(s) and other packaging

The suitability of the container closure system used for the storage, transportation (shipping) and use of the FPP should be discussed. This discussion should consider, e.g., choice of materials, protection from moisture and light, compatibility of the materials of construction with the dosage form (including sorption to container and leaching) safety of materials of construction, and performance (such as reproducibility of the dose delivery from the device when presented as part of the FPP).

Give a detailed description of the container/closure system(s), including any liner or wadding, and provide details of the composition of each component. 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, Ph.Eur, JP or USP.

The specifications should include description and identification (and critical dimensions, with drawings where appropriate). Non-compendial methods (with validation) should be included where appropriate.

Describe other (e.g. outer) packaging, and state what materials they are made from.

4.11 Stability testing

The design of the formal stability studies for the finished product should be based on knowledge of the behaviour and properties of the API and the dosage form.

Describe the methodology used during stability studies; if this is identical to methodology described elsewhere in the data set, a cross-reference will suffice. If different methodology was used, the test procedures applied to the stability tests on the finished product should be validated or verified, and the accuracy as well as the precision (standard deviations) should be recorded. Characterize the possible degradants identified by stress stability testing (see 3.7.1 Stress testing (forced degradation) for details) during development pharmaceutics (compatibilities of the APIs with each other and with the excipients as well as the effect of temperature on the rate of degradation reactions). The tests for degradants should be validated to demonstrate that they are specific to the FPP being examined and are of adequate sensitivity.

Stability studies should be performed on each individual strength and container size of the finished product unless bracketing or matrixing is applied. Other supporting data can be provided.

4.11.1 Stability-indicating quality parameters

Stability studies should include testing of those attributes of the FPP that are susceptible to change during storage and are likely to influence quality, safety and/or efficacy. Analytical procedures should be fully validated and stability indicating. Whether and to what extent replication should be performed will depend on the results of validation studies.

Characteristics studied should be those in the finished product specification that are likely to be affected by storage and/or not monitored routinely at the time of manufacture, but which may be indicative of the stability/instability of the particular dosage form. These include:

- Physical characteristics (such as organoleptic properties, physical properties characteristic to the dosage form, important quality parameters, e.g., in vitro dissolution, moisture content and change of polymorphs, if relevant). As regards tablets and capsules packed with semi-permeable blister films, loss or uptake of water must be tested during stability studies.
- Efficacy of additives, such as antimicrobial agents, to determine whether such additives remain effective and within the accepted validated range throughout the projected shelf life.
- Chemical characteristics (assay of the API, content of degradation products, content of other ingredients such as preservatives, antioxidants, as well as enantiomeric purity, if relevant).
- Study of the container and closure interaction with the contents, when applicable.
- Where the product is to be diluted or reconstituted before being administered to the patient (e.g. a powder for injection or a concentrate for oral suspension) “in use” stability data must be submitted to support the recommended in-use storage time and conditions for those storage forms.

It may be appropriate to have justifiable differences between the shelf life and release acceptance criteria based on the stability evaluation and the changes observed on storage. Any differences between the release and shelf life acceptance criteria for antimicrobial preservative content should be supported by a validated correlation of chemical content and preservative effectiveness demonstrated during drug development on the product in its final formulation (except for preservative concentration intended for marketing. A single primary stability batch of the finished product should be tested for antimicrobial preservative effectiveness (in addition to preservative content) at

the proposed shelf life for verification purposes, regardless of whether there is a difference between the release and shelf life acceptance criteria for preservative content.

Report and discuss the results of stability testing as described in **Annex 5.** Organize data for all attributes separately and evaluate each attribute in the report. No statistical analysis is required, if the stability data do not show variability or a trend over the time.

Shelf life acceptance criteria should be derived from consideration of all available stability information. The proposed storage conditions should be achievable in practice in Tanzania.

The summary should include conclusions with respect to in-use storage conditions and shelf life, when applicable.

Long-term studies should cover the whole shelf life. When available long-term stability data on primary batches do not cover the proposed shelf-life period granted at the time of approval, a commitment should be made in writing to continue the stability studies post approval in order to firmly establish the shelf-life period. The post-approval stability protocol should also be provided and should be the same as that for the primary batches, unless otherwise scientifically justified.

Repackaging of bulk finished product will require stability studies in the bulk container and the final container closure system. Expiration dating is linked to the manufacturing date of the dosage form.

4.11.2 Photostability Testing

Photostability testing should be conducted on at least one primary batch of the FPP, if not included in the stress stability tests.

Reference:

- ICH-Q1B: Photostability Testing of New Active Substances and Medicinal Products.
  http://www.ich.org/MediaServer.jser?@_ID=412&@_MODE=GLB

4.11.3 Selection of Batches

At the time of submission data from stability studies should be provided for batches of the same formulation and dosage form in the container closure system proposed for marketing.

Stability data on three primary batches are to be provided. One of the three batches should be of production scale, the remaining two batches at least pilot scale. The composition, batch size, batch number and manufacturing date of each of the stability batches should be documented and the certificate of analysis at batch release should be attached.

The manufacturing process used for primary batches should simulate that to be applied to production batches and should provide product of the same quality and meeting the same specification as that intended for marketing. Where possible, batches of the finished product should be manufactured by using different batches of the API.

4.11.4 Container Closure System

Stability testing should be conducted on the dosage form packaged in the container closure system proposed for marketing (including, as appropriate, any secondary packaging and container label). Any available studies carried out on the product outside its immediate container or in other packaging materials can form a useful part of the stress testing of the dosage form or can be considered as supporting information, respectively.

4.11.5 Testing Frequency

At the accelerated storage condition, a minimum of three points, including the initial and final time points (e.g., 0, 3, and 6 months), from a 6-month study is recommended. Where an expectation (based on development experience) exists that results from accelerated testing are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or by including a fourth time point in the study design.

At long term storage condition, sampling should be done at initial, 3, 6, 9, 12, 18, 24, 36 etc. months to establish the stability characteristics of the FPP.

Reduced designs, i.e., matrixing or bracketing, where the testing frequency is reduced or certain factor combinations are not tested at all, can be applied, if justified.

Reference:

- ICH Q1D: Bracketing and Matrixing Designs for Stability Testing of New Drug Substances and Products
  http://www.ich.org/LOB/media/MEDIA414.pdf

4.11.6 Storage Conditions

In general, a FPP should be evaluated under storage conditions (with appropriate tolerances) that test its thermal stability and, if applicable, its sensitivity to moisture or potential for solvent loss. The storage conditions and the lengths of studies chosen should be sufficient to cover storage, shipment, and subsequent use.

Stability testing of the finished product after constitution or dilution, if applicable, should be conducted to provide information for the labelling on the preparation, storage condition, and in-use period of the constituted or diluted product. This testing should be performed on the constituted or diluted product through the proposed in-use period on primary batches as part of the formal stability studies at initial and final time points and, if full shelf life long term data will not be available before submission, at six months or the last time point for which data will be available. In general, this testing need not be repeated on commitment batches.

Note: in-use stability testing should be performed on at least two different batches one of which should be investigated close to the end of shelf life.

The long term testing should cover a minimum **of 12 months duration** at the time of submission and should be continued for a period of time sufficient to cover the proposed shelf life. Additional data accumulated during the assessment period of the registration application should be submitted to TFDA if requested.

Data from the accelerated storage condition can be used to evaluate the effect of short-term excursions outside the label storage conditions (such as might occur during shipping).

Long term and accelerated storage conditions for finished products are detailed in **Annex 5**. The general case applies if a subsequent section does not specifically cover the finished product.

4.11.7 General case

Storage temperature (°C)	**Relative humidity (%)**	**Minimum time period covered by data at submission**
Accelerated: 40±2	75±5	6
Long term: 30±2	75±5	12

Note. Unless otherwise justified, 30°C ± 2°C/75% RH ± 5% RH is the long term stability condition for products to be marketed in Tanzania.

When a “significant change" occurs at any time during 6 months' testing at the accelerated storage condition, these should be evaluated during long term stability testing.

In general, “significant change” for a finished product is defined as:

- A 5% change in assay from its initial value; or failure to meet the acceptance criteria for potency when using biological or immunological procedures.
- Any degradation product exceeding its acceptance criterion.
- Failure to meet the acceptance criteria for appearance, physical attributes, and functionality test (e.g., colour, phase separation, hardness).
- And, as appropriate for the dosage form:

  - Failure to meet the acceptance criterion for pH; or
  - Failure to meet the acceptance criteria for dissolution for 12 dosage units.

4.11.8 Finished products packaged in impermeable containers

Sensitivity to moisture or potential for solvent loss is not a concern for finished products packaged in impermeable containers that provide a permanent barrier to passage of moisture or solvent. Thus, stability studies for products stored in impermeable containers can be conducted under any controlled or ambient humidity condition.

4.11.9 Finished products packaged in semi-permeable containers

Aqueous-based products packaged in semi-permeable containers should be evaluated for potential water loss in addition to physical, chemical, biological, and microbiological stability. This evaluation can be carried out under conditions of low relative humidity, as defined below.

Study	**Storage condition**	**Minimum time period covered by data at submission (months)**
Long term	25±2°C/40±5% RH or 30±2°C/75±5% RH	12
Accelerated	40±2°C/NMT 25±5% RH	6

Note. Unless otherwise justified, 30 ± 2°C and 75 ± 5% RH is the long term stability condition for products to be marketed in Tanzania.

Ultimately, it should be demonstrated that aqueous-based finished products stored in semi-permeable containers could withstand low relative humidity environments. Other comparable approaches can be developed and reported for non-aqueous, solvent-based products.

A 5% loss in water from its initial value is considered a significant change for a FPP packaged in a semi-permeable container after three (3) months storage at 40 ± 2°C and NMT 25 ± 5% RH.

4.11.10 Evaluation

A systematic approach should be adopted in the presentation and evaluation of the stability information, which should include, as appropriate, results from the physical, chemical, biological and microbiological tests, including particular attributes of the dosage form (for example, dissolution rate for solid oral dosage forms, hardness, LOD, etc.).

The purpose of the stability study is to establish, based on testing a minimum of three batches of the finished product, a shelf life and label storage instructions applicable to all future batches of the finished product manufactured and packaged under similar circumstances. The degree of variability of individual batches affects the confidence that a future production batch will remain within specification throughout its shelf life.

Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

An approach for analyzing data on a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate. This can be done by first applying appropriate statistical tests (e.g., p values for level of significance of rejection of more than 0.25) to the slopes of the regression lines and zero time intercepts for the individual batches. If it is inappropriate to combine data from several batches, the overall shelf life should be based on the minimum time a batch can be expected to remain within acceptance criteria.

The nature of any degradation relationship will determine whether the data should be transformed for linear regression analysis. Usually the relationship can be represented by a linear, quadratic, or cubic function on an arithmetic or logarithmic scale. Statistical methods should be employed to test the goodness of fit of the data on all batches and combined batches (where appropriate) to the assumed degradation line or curve.

Reference:

- ICH-Q1E Evaluation For Stability Data http://www.ich.org/MediaServer.jser?@_ID=415&@_MODE=GLB

4.11.11 Extrapolation of data

An API is considered as stable if it is within the defined specifications when stored at 30 ± 2°C/75 ± 5 % RH (2 years) and 40 ± 2°C/75 ± 5 % RH (6 months). If long term data are supported by results from accelerated studies the re-test period/shelf life may be extended beyond the end of long-term studies. The proposed retest period or shelf life can be up to twice, but should not be more than 12 months beyond, the period covered by long-term data.

Reference:

- ICH-Q1E Evaluation For Stability Data http://www.ich.org/MediaServer.jser?@_ID=415&@_MODE=GLB

4.11.12 Core Storage Statements

Testing conditions where stability has been shown	Required labelling statement	Additional labelling statement*, where relevant
30°C/75% RH (long term) 40°C/75% RH (accelerated)	Do not store above 30°C, or Store below 30°C	Do not refrigerate or freeze

* Depending on the pharmaceutical form and the properties of the product, there may be a risk of deterioration due to physical changes if subjected to low temperatures. Low temperatures may also have an effect on the packaging in certain cases. An additional statement may be necessary to take account of this possibility.

4.12 Primary and secondary packaging labels

Every immediate and outer container of any medicinal product shall be labelled in clearly legible indelible letters in Kiswahili or English or both. Over the counter or general sales medicines shall be labelled in Kiswahili or Kiswahili and English. The batch number, manufacturing and expiry dates must unless otherwise justified be embossed or engraved in the label of the container. The immediate and where available the outer container packaging label shall include at least the following:

4.12.1 Immediate and outer packaging

The immediate and where available the outer container packaging labelling should include at least the following:

(a) The name of the FPP.
(b) Method of administration.
(c) A list of API(s) (using INNs if applicable) showing the amount of each present in a dosage unit, and a statement of the net contents of the container, e.g. number of dosage units, weight or volume.
(d) List of excipients known to be a safety concern for some patients, e.g. lactose, gluten, metabisulfites, parabens, ethanol, or tartrazine.
(e) Indication(s) and recommended dosage, where practicable
(f) The batch number assigned by the manufacturer.
(g) The manufacturing and expiry dates in an uncoded form.
(h) Storage conditions or handling precautions that may be necessary.
(i) Directions for use and any warnings or precautions that may be necessary.
(j) The name and address of the manufacturer
(k) The name and address of the company or person responsible for placing the product on the market if different from the manufacturer
(l) Tanzania marketing authorization number (to be included after approval)
(m) Distribution category

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

4.12.2 Blisters and strips

Blisters and strips should include, as a minimum, the following information:

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

(b) Name of the manufacturer

(c) The batch number assigned by the manufacturer

(d) The manufacturing and expiry dates in an uncoded form

4.13 Patient information and package inserts

Provide copies of all package inserts and any information intended for distribution with the product to the patient. The patient information leaflet (PIL) should be in conformity with the SPC. It should be written in Kiswahili and/or English, should be legible, indelible and comprehensible.

Reference:

http://pharmacos.eudra.org/F2/eudralex/vol-2/home.htm#2c

SECTION FIVE

THERAPEUTIC EQUIVALENCE

The applicant shall when applying for registration of any generic medicinal product provide reports of bioequivalence studies conducted to demonstrate that the generic product is therapeutically equivalent to the corresponding innovator product as surrogate of preclinical and clinical studies to demonstrate the safety and efficacy of the generic medicinal product. To avoid carrying out multiple interchangeability studies, applicant shall begin with a generic that will be tested for efficacy and safety against the innovator's highest available strength. In case of absence of an innovator product on the world market, the applicant must obtain prior approval from the Authority to use a different proposed comparator product.

In the context of these guidelines medicinal products are considered to be therapeutic equivalents only if they are pharmaceutical equivalents and bioequivalent.

Medicinal products are deemed bioequivalent if "The rate and extent of absorption of the test medicinal product do not show a significant difference from the rate and extent of absorption of the reference medicinal product when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses.

Therapeutic equivalent medicinal products are expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling and thus suitable for generic substitution (interchangeable with an innovator product).

No generic medicinal product may be registered unless it is of proven safety and efficacy, which may either be done by submitting bioequivalence study reports or preclinical and clinical studies reports or comparative clinical trial using clinical or pharmacodynamic endpoints studies reports. The endpoints should be justified and validated for the compound and the trial should be designed to show equivalence. Trial showing the absence of significant difference cannot be accepted.

If the product meets biowaiver criteria, in vitro studies recommended in the WHO guidelines referenced below may be submitted in *lieu of in vivo* bioequivalence.

All studies to demonstrate therapeutic equivalence shall be done and reported in accordance with the WHO guidelines on registration requirements to establish interchangeability.

Reference:

The World Health Organization Expert Committee on Specifications for Pharmaceutical Preparations. The Fortieth report. Geneva, World Health Organization, 2006: 347-458 (WHO Technical Report Series, No.937).

A Bio-equivalence study report should contain at least the following items:

- Description of study design. The most appropriate study type is two-period, randomized, crossover study. If other study types were used (e.g. parallel group design), these should be justified by the applicant. In general, single-dose study with sufficiently long period for blood samples collection is acceptable.
- Information about investigators, study site and study dates.
- Data about preparations used: manufacturer, place of manufacture, batch number etc.
- Characterization of study subjects. Bio-equivalence study should be normally performed in healthy volunteers. If patients were used, this should be justified by the applicant. Number of subjects should not be less than 12. Study report should contain inclusion and exclusion criteria, listing of demographic data of all subjects.
- Description of study procedures. Administration of test products, meals, and times of blood sampling or urine collection periods should be described in the clinical report.
- Description and validation of drug determination methods in investigated material. Analytical method should be validated over the measured drug concentration range. Validation should contain methodology and results of sensitivity, specificity, accuracy, precision and repeatability determination.
- All measured drug concentrations should be presented.
- Calculation methodology of pharmacokinetic parameters. Preferred is non-compartmental analysis. If modelled parameters were used, these models should be validated for the compound. All measured and calculated pharmacokinetic parameters should be presented in the report.
- Description of statistical methodology and results of statistical calculations. Statistical calculations should be based on the equivalence evaluation. The statistical method of choice is the two one-sided test procedure and the calculation of 90% confidence intervals of the test/reference ratios of pharmacokinetic parameters. The main parameters to assess the bio-equivalence are area under the plasma concentration-time curve (AUC) and maximum concentrations (C_{max}) ratios.

  The 90% confidence interval for the AUC-ratio should lie within a bio-equivalence range of 80-125%. In some specific cases of drugs with a narrow therapeutic range the acceptance range may need to be tightened.

  The 90% confidence interval for the C_{max}-ratio should lie within a bio-equivalence range of 80-125%. In some specific cases of drugs with a narrow therapeutic range the acceptance range may need to be tightened. In certain cases for drugs with an inherently high intra-subject variability, a wider acceptance range (e.g., 75-133%) may be acceptable. The range used must be defined prospectively and should be justified, taking into account safety and efficacy considerations.

SECTION SIX

PHARMACOLOGY, TOXICOLOGY AND EFFICACY OF NEW PRODUCTS

In case of products containing new active ingredients and new combinations of active ingredients provide full information on safety and efficacy as set down in the up-to-date ICH guidelines which shall include:

6.1 Nonclinical Overview
6.2 Clinical Overview
6.3 Nonclinical Summary
6.4 Clinical Summary
6.5 Nonclinical Study Reports
6.6 Clinical Study Reports

References:

http://www.ich.org/products/guidelines/efficacy/article/efficacy-guidelines.html

http://www.ich.org/products/guidelines/safety/article/safety-guidelines.html

SECTION SEVEN

FIXED DOSE COMBINATION MEDICINAL PRODUCTS

In case of fixed-dose combination (FDC) FPPs, provide full information as defined in the WHO guidelines for registration of fixed-dose combination medicinal products.

Reference:

WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-ninthreport. Geneva, World Health Organization, 2005: Annex 5, (WHO Technical Report Series, No.929).

ANNEX 1: Application Form for Registration of Human Medicinal Product (Quality Information Summary)

APPLICATION FORM FOR REGISTRATION OF HUMAN MEDICINAL PRODUCT
(QUALITY INFORMATION SUMMARY)

General Instructions:

Please read all the instructions carefully prior to completing this Application form.

Provide accurate, concise, but as far as possible complete summary of all necessary data and relevant particulars in all areas of the form. Note that all areas are to be filled out by the applicant EXCEPT where indicated by grey areas which are for TFDA Official Use Only!

Please state the exact location (Annex number) of any appended documents in the relevant sections of the form.

Before submitting the completed form, check that you have provided all requested information.

Should you have any questions regarding this form, please contact the Tanzania Food and Drugs Authority (TFDA).

A properly filled out and signed original copy of the form with all its annexes (including a copy in MS Word on a CD-ROM) must be submitted together with the Quality Overall Summary. The entire dossier should be submitted both as hard-copy and on CD-ROM. The application should be sent to the following address:

Director General
Tanzania Food and Drugs Authority
P.O. Box 77150
EPI Mabibo
Off Mandela Road
Dar-es-Salaam
Tanzania

1. For official use only

1.1 Application Number		
1.2 Date of submission of the dossier		
1.3 Evaluator	Name	Signature
1.4 Auditor	Name	Signature
1.5 Date of evaluation		
1.6 Date of auditing		
1.7 Number of files		
1.8 Conclusion of the assessment *If the dossier is* **RECOMMENDED** *specify:* • *Primary packaging and shelf-life of product,* • *Storage condition of product and special precautions.* • *Distribution category*	**RECOMMENDED (no outstanding issues)** **QUERY RAISED** **REJECTED** **(*Please delete which does not apply*)**	

2. To be filled in by the applicant

2.1Registration number	
2.2Date of expiry of current registration	
2.3Proprietary Name of the Product	
2.4International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API), strength, pharmaceutical form.	
2.5 Anatomic Therapeutic Classification (ATC) Code	
2.6 Name and address of applicant (who must be the holder of the marketing authorization) Name: Physical Address: Postal Address: City: District:	

Region/State: Country: Email: Fax: Phone Name of contact person in the company:	
2.7 Name and address(es) of the manufacturer(s) of the active pharmaceutical ingredient(s). *(Add as many rows as necessary)* Name: Physical Address: Postal Address: City: District: Region/State: Country: Email: Fax: Phone: Name of contact person in the company:	
2.8 site/location of manufacture of API (s)	
2.9 Name(s) and complete address (es) of the manufacturer(s) of the finished product(s), including the final product release if different from the applicant. *(Add as many rows as necessary)* Name: Physical Address: Postal Address: City: District: Region/State: Country:	

Email: Fax: Phone: Name of contact person in the company:			
2.10. Site/location of manufacture FPP			
2.11 Local Agent: Name: Physical Address: Postal Address: City: District: Region/State: Country: Email: Fax: Phone Name of contact person in the company:			
2.12 Visual description of the FPP			
2.13 Visual description of the packaging			
2.14 Sample			
2.15 Current registration status in other countries including East African community (EAC) and the Southern African Development Community (SADC) countries			
2.16 Visual description of the FPP			
2.17 Visual description of the packaging			
2.18 Sample			
2.19 Registration status in other countries (e.g. SADC and EAC)			
Batch number(s) of the FPPs used in			
2.20 Clinical/bioequivalence studies			
2.21 Stability studies			

2.21 Validation/production scale batches			
2.22 Comments [e.g., batch size, explanation of NA (not applicable) answers]			
2.23 Composition of clinical, primary stability and validation/production FPP batches (kg)			

Ingredients	Unit (mg)	Clinical	Stability	Production
Core tablet/Contents of capsule				
Subtotal 1				
Film coating/Hard capsule				
Subtotal 2				
Grand total				
Equivalence of the composition or justified differences				

This product assessment report should be written in clear unambiguous language referring to deficiencies or lack of data submitted, as communication with the manufacturer may result from the assessment.

The report should be completed by an evaluator and auditor

The assessment report should be typed with “Bookman Old Style 11” fonts. The format of tables must not be changed.

3. ACTIVE PHARMACEUTICAL INGREDIENT(s) [API(s)]
3.1 Nomenclature
3.1.1 International Nonproprietary Name (INN)
3.1.2 Compendial name if relevant
3.1.3 Chemical name(s)
3.1.4 Company or laboratory code, if applicable
3.1.5 Other nonproprietary name(s)**,** e.g., national name, United States Adopted Name (USAN), Japanese Accepted Name (JAN); British Approved Name (BAN)
3.1.6 Chemical Abstracts Service (CAS) registry number
3.2 Properties of API(s)
3.2.1 API not described in BP, PhInt, PhEur, or USP
(a) List of studies performed (e.g., IR, UV, NMR, MS, elemental analysis) and summary of the interpretation of evidence of structure: (b) Discussion on the potential for isomerism and identification of stereochemistry (e.g., geometric isomerism, number of chiral centres and configurations): (c) Summary of studies performed to identify potential polymorphic forms (including solvates): (d) Summary of studies performed to identify the particle size distribution of the API: (e) Potentially critical, additional characteristics: ▪ Physical description (e.g., appearance, colour, physical state): ▪ Physical form (e.g., polymorphic form, solvate, hydrate): ▪ Solubilities (e.g., in common solvents, aqueous/nonaqueous solubility profile): ▪ Partition coefficient ▪ Hygroscopicity ▪ Others (e.g., pH and pKa values, melting or boiling points, optical rotation, refractive index (for a liquid), UV absorption maxima and molar absorptivity):

3.2.2 API described in BP, PhInt, PhEur, or USP
(a) Summary of studies performed to identify potential polymorphic forms (including solvates): (b) Summary of studies performed to identify the particle size distribution of the API: (c) Potentially critical, additional characteristics: ▪ Physical description (e.g., appearance, colour, physical state): ▪ Physical form (e.g., polymorphic form, solvate, hydrate): ▪ Solubilities (e.g., in common solvents, aqueous/nonaqueous solubility profile): ▪ Partition coefficient ▪ Hygroscopicity ▪ Others (e.g., pH and pKa values, melting or boiling points, optical rotation, refractive index (for a liquid), UV absorption maxima and molar absorptivity):
3.2.3 Information from literature
3.3 Site(s) of manufacture
List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF letters of access), if applicable):
3.4 Route(s) of synthesis
3.4.1 API not described in BP, PhInt, PhEur, or USP
Controls of Critical Steps and Intermediates Summary of the controls performed at critical steps of the manufacturing process and on intermediates: Process Validation and/or Evaluation Description of process validation and/or evaluation studies (e.g., for aseptic processing and sterilization): *Manufacturing Process Development* Description and discussion of the significant changes made to the manufacturing process and/or manufacturing site of the API used in producing clinical, comparative, stability, scale-up, pilot, and, if available, production scale batches: *Impurities* (a) Identification of potential and actual impurities arising from the synthesis, manufacture and/or degradation: List of impurities (e.g., starting materials, by-products, intermediates, chiral impurities, degradation products), including chemical name, structure, and

origin:

API-related Impurity (chemical name or descriptor)	Structure	Origin
		Potential impurity of the starting material(s)
		Unreacted starting material(s)
		Unreacted intermediate(s)
		By-product(s)
		Reagent(s)
		Catalyst(s)
		Residual solvent(s)
		Potential degradant(s)

(b) Basis for setting the acceptance criteria for impurities:

- Maximum daily dose (i.e., the amount of API administered per day), ICH Reporting/Identification/Qualification Thresholds for drug-related impurities, and Concentration Limits (ppm) for process-related impurities (e.g., residual solvents):

- Data on observed impurities for relevant FPP batches (e.g., clinical, comparative):

Impurity (API- and process-related)	Acceptance criteria	Results [FPP batch number* and use (e.g., clinical, comparative)]		

* include strength, if reporting impurity levels found in the FPP (e.g., for comparative studies)

- Justification of proposed acceptance criteria for impurities:

3.4.2 Specifications of raw materials and intermediates used in the synthesis

For APIs or APIs manufactured with reagents obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) agents (e.g., ruminant origin), a letter of attestation (with supporting documentation) should be provided confirming that the material is not from a BSE/TSE affected country/area.

3.4.3 API described in BP, PhInt, PhEur, or USP

List process-related impurities not included in the monograph(s) (e.g., key intermediates, residual solvents), which can be identified from the simplified flow diagram and text-book level narrative of the synthetic process:

3.5 Specifications

3.5.1 API not described in BP, PhInt, PhEur, or USP

Standard Claimed (e.g., In-house, BP, PhEur, PhInt, USP)		
Specification Reference Number and/or Version		
Test	Analytical Procedure (Type/Source/Version)	Acceptance Criteria

Batch Analyses

(a) Description of the batches:

Batch Number	Batch Size	Date and Site of Production	Use (e.g., clinical, comparative)

(b) Summary of results for relevant batches (e.g., clinical, comparative):

Justification of Specification

Justification of the API specification (e.g., evolution of tests, analytical procedures, and acceptance criteria, differences from compendial standard):

Reference Standards or Materials

(a) Source of reference standards or reference materials (e.g., In-House, USP, BP, PhEur, PhInt):

(b) Characterization and evaluation of non-official (e.g., non-compendial) reference standards or reference materials (e.g., method of manufacture, elucidation of structure, certificate of analysis, calibration against an official standard):

3.5.2 API described in BP, PhInt, PhEur, or USP

3.6 Container closure system

3.7 Stability testing

3.7.1 Stress testing (forced degradation)

Summary of stress testing (e.g., heat, humidity, oxidation, photolysis, acid/base): and results:

Treatment	Conditions	Observations
Temperature		
Humidity		
Light		
Oxidation		
Acid		
Base		
Metal ions (optional)		
Other		

3.7.2 Regulatory stability testing

Storage Conditions (°C, % RH)	Batch Number	Batch Size	Container Closure System	Completed (and Proposed) Test Intervals (in months)

(a) Copies of API CoA(s) at the start of stability studies

(b) Stability protocol for commitment batches (e.g., storage conditions (including tolerances), testing frequency, number of batches and batch sizes, container closure system(s), tests and acceptance criteria):

(c) Evaluation of the submitted stability results

4. FINISHED PHARMACEUTICAL PRODUCT(s) [FPP(s)]

4.1 Manufacturing and Marketing authorization

4.2 Pharmaceutical Development

4.2.1 Company research and development

Discussion of the:

- 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 FPP:
- for FDC products, compatibility of APIs with each other:

Discussion of the:

- choice of excipients (e.g., their concentrations, their characteristics that can influence the FPP performance):
- compatibility of the API(s) with excipients:

Formulation Development

(a) Summary describing the development of the FPP (e.g., route of

administration, usage):

(b) Discussion of the differences in the formulations for the batches used the in the *in vivo* studies (e.g., pivotal clinical, comparative bioequivalence) and the formulation described in 4.3:

(c) Description of batches used in the comparative *in vitro* studies (e.g., dissolution) and in the *in vivo* studies (e.g., pivotal clinical, comparative bioequivalence), including strength, batch number, and type of study:

(d) Summary of results for comparative *in vitro* studies (e.g., dissolution) and comparative *in vivo* studies (e.g., bioequivalence):

(e) Summary of any information on *in vitro*-*in vivo* correlation (IVIVC) studies:

(f) For scored tablets, provide rationale/justification for scoring:

Overages

Justification of overages in the formulation(s) described in 4.3:

Physicochemical and Biological Properties

Discussion of the parameters relevant to the performance of the FPP (e.g., pH, ionic strength, dissolution, particle size distribution, polymorphism, rheological properties):

Manufacturing Process Development

(a) Discussion of the development of the manufacturing process of the FPP (e.g., optimization of the process, selection of the method of sterilization):

(b) Discussion of the differences in the manufacturing process(es) for the batches used the in the *in vivo* studies (pivotal clinical, comparative bioequivalence) and the process described in 4.5:

Container Closure System

Discussion of the suitability of the container closure system (described in 4.10) used for the storage, transportation (shipping), and use of the FPP (e.g., choice of materials, protection from moisture and light, compatibility of the materials with the dosage form):

Microbiological Attributes

Discussion of microbiological attributes of the dosage form (e.g., preservative

effectiveness studies):

Compatibility

If applicable, discussion of the compatibility of the FPP, e.g., with reconstitution diluent(s) or dosage devices, co-administered drugs, etc.:

4.2.2 Information from literature

4.3 Formulation

Strength (label claim)					
Master Production Document Reference Number and/or Version					
Batch Size (number of dosage units)					
Ingredients	Quality standard	Unit composition		Batch quantities	
		mg	%	Kg	%

Composition of all *components that are mixtures* (e.g., colourants, coatings, capsule shells, imprinting inks):

Description of accompanying reconstitution diluent(s), if applicable:

4.4 Sites of manufacture

…..

List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF

letters of access are attached to **Section 4.4 Sites of manufacture** in the dossier submitted for registration).
4.5 Manufacturing process
4.6 Manufacturing Process Controls of Critical Steps and Intermediates
Summary of controls performed at the critical steps of the manufacturing process and on isolated intermediates:
4.7 Process Validation and Evaluation
4.7.1 New (for the generic manufacturer) FPPs
Summary of the process validation and/or evaluation studies conducted (e.g., batch numbers, batch sizes, testing parameters, acceptance criteria) or a summary of the proposed validation protocol for the critical steps or critical assays used in the manufacturing process (e.g., protocol number, parameters, results):
4.7.2 Established (for the generic manufacturer) FPPs
4.8 Specifications for excipients
4.8.1 Excipients not described in BP, PhInt, PhEur, or USP
Summary of the specifications for non-compendial excipients:
4.8.2 Excipients described in BP, PhInt, PhEur, or USP
(a) Summary of the specifications compendial excipients which include supplementary tests not included in the monograph(s): (b) List of excipients that are of human or animal origin (including country of origin): (c) Summary of the information (e.g., sources, specifications, description of the testing performed, viral safety data) regarding adventitious agents for excipients of human or animal origin: (d) For excipients obtained from sources that are at risk of transmitting Bovine Spongiform Encephalopathy (BSE)/Transmissible Spongiform Encephalopathy (TSE) agents (e.g., ruminant origin), a letter of attestation (with supporting documentation) should be provided confirming that the material is not from a BSE/TSE affected country/area. A copy of the letter

may be found in:

(b) List of referenced Drug Master Files (DMFs) and DMF Numbers:

4.9 Quality Control of the FPP

4.9.1 Specifications for the FPP

Standard Claimed (e.g., In-house, BP, PhEur, PhInt, USP)			
Specification Reference Number and/or Version			
Test	Analytical Procedure (Type/Source/Version)	Acceptance Criteria	
		Batch release	Shelf life

Justification of the specifications (e.g., evolution of tests, analytical procedures, and acceptance criteria, exclusion of certain tests, differences from compendial standard):

Information on the characterization of impurities, not previously provided in 3.4 (e.g., summary of actual and potential degradation products, basis for setting the acceptance criteria):

4.9.2 Analytical procedures

Reference Standards or Materials

(a) Source of reference standards or reference materials (e.g., In-House, USP, BP, PhEur, PhInt):

(b) Characterization and evaluation of non-official (e.g., non-compendial) reference standards or reference materials (e.g., method of manufacture,

elucidation of structure, certificate of analysis, calibration against an official standard):

4.9.3 Validation of analytical procedures

4.9.4 Batch analyses

4.10 Container/closure system(s) and other packaging

(a) Description of the container closure systems, including unit count or fill size, container size or volume:

(b) Materials of construction of each primary packaging component:

(c) Summary of specifications of each primary and functional secondary (e.g., foil pouches) packaging components:

(d) List of referenced Drug Master Files (DMFs) and DMF Numbers, if applicable:

4.11 Stability testing

Stability protocol for commitment batches:

Protocol Parameter	Description
Storage conditions (including tolerances)	
Testing frequency	
Number of batches per strength and batch sizes	
Container closure system(s)	
Tests and acceptance criteria	
Other	

Stability protocol for continuing (i.e., ongoing) batches:

Protocol Parameter	Description
Storage conditions (including tolerances)	
Testing frequency	
Number of batches per strength and batch sizes	

Container closure system(s)	
Tests and acceptance criteria	
Other	

4.11.1 Stability-indicating quality parameters

4.11.2 Photostability testing

4.11.3 Selection of batches

4.11.4 Container closure system

4.11.5 Testing frequency

4.11.6 Storage conditions

4.11.7 General case

4.11.8 FPPs packaged in impermeable containers

4.11.9 FPPs packaged in semi-permeable containers

4.11.10 Evaluation

(a) Summary of stress testing and results (e.g., photostability studies, cyclic studies for semi-solids, freeze-thaw studies):

(b) Summary of accelerated and long term testing (e.g., studies conducted, protocols used, results obtained):

(i) Description of stability study details:

Storage Conditions (°C, % RH)	Batch Number	Batch Size	Container Closure System	Completed (and Proposed) Test Intervals (in months)

(ii) Summary and discussion of stability study results:

(c) Proposed storage conditions and shelf life (and in-use storage conditions and in-use period, if applicable):

4.11.11 Extrapolation of data
4.11.12 Core storage statements
4.12 Container labelling
4.12.1 Outer packaging or, where there is no outer packaging, on the immediate packaging
4.12.2 Blisters and strips
4.13 Patient information and package inserts

5. Declaration of the 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:-

5.1 The current edition of the Tanzania **"**Good Manufacturing Practices Guidelines for Pharmaceuticals Products"

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

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

5.4 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.

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

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

5.7 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.

5.8 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.

5.9 The person releasing the product is an authorized person as defined by the Tanzania "Good Manufacturing Practices Guidelines for pharmaceuticals.

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

5.11 All the documentation referred to in this application is available for review during GMP inspection.

5.12 Clinical trials (where applicable) were conducted in accordance with Good Clinical Practice,

I also agree that:

5.13 As a holder of marketing authorization/registration of the product I will adhere to Tanzanian requirements for handling adverse reactions.

5.14 As holder of registration I will adhere to Tanzanian requirements for handling batch recalls of the products.

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

QUERIES TO BE COMMUNICATED TO THE APPLICANT

Please copy all relevant observation and information to be communicated to the manufacturer in the query letter (format to be provided) and save it accordingly

A. General remark, if applicable

B. Observations, queries

ACTIVE PHARMACEUTICAL INGREDIENT(s) (INN)

FINISHED PHARMACEUTICAL PRODUCT (INN .mg PHARMACEUTICAL FORM)

C. Overall conclusion

Please fill in the relevant conclusion, based on the review of the data on quality, in the first part of the document.

The dossier can be recommended for registration only, if minor issues are pending.

Please mark on the top of the cover page the in capital word RECOMMEDED if the product is recommended for registration or QUERIED if it is not recommended pending resolution of queries or REFUSED if it is recommended not to be granted registration.

D. Outstanding commitments

Please list the outstanding commitments, which should be answered before the product can be authorized for marketing.

RECOMMENDATIONS FOR INSPECTION

ANNEX 2: Application Form for Registration of Human Medicinal Product (Bioequivalence Information Summary)

APPLICATION FORM FOR REGISTRATION OF HUMAN MEDICINAL PRODUCT
(BIOEQUIVALENCE INFORMATION SUMMARY)

General Instructions:

Please read all the instructions carefully before completing this Application form.

Provide accurate, concise, but as far as possible complete summary of all necessary data and relevant particulars in all areas of the form. Note that all areas are to be filled out by the applicant EXCEPT where indicated by grey areas which are for TFDA Official Use Only!

Please state the exact location (Annex number) of any appended documents in the relevant sections of the form.

Before submitting the completed form, kindly check that you have provided all requested information and enclosed all requested documents.

Should you have any questions regarding this form, please contact the Tanzania Food and Drugs Authority (TFDA).

A properly filled out and signed original copy of the form with all its annexes (including a copy in MS Word on CD-ROM) must be submitted together with the Bioequivalence Study Reports. The entire dossier should be submitted both as hard-copy and on CD-ROM. The application should be sent to the following address:

Director General
Tanzania Food and Drugs Authority
P.O. Box 77150
EPI Mabibo
Off Mandela Road
Dar-es-Salaam
Tanzania

1. For official use only

Application Number		
Date of submission of the dossier		
Evaluator	Name	Signature
Auditor	Name	Signature
Quality evaluator (e.g., when dissolution profiles are submitted for comparison of the compositions of clinical, stability and validation batches, or a biowaiver for additional strengths is requested)	Name	Signature
Date of evaluation		
Date of auditing		
Number of files		
Conclusion of the assessment	**RECOMMENDED (no outstanding issues)** **QUERY RAISED** **REJECTED** **(*Please delete which does not apply*)**	
SPC , PIL submitted	(state location in submission)	
SPC, PIL, Package Labelling acceptable	Yes:_____// No:_____	
2. To be filled in by the applicant		
Proprietary Product Name (if relevant)		
International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API), strength, pharmaceutical form.		
Name and address of applicant (who must be the holder of the marketing authorization) Name: Physical Address: Postal Address: City: District: Region/State: Country: Email: Fax: Phone		

Name of contact person in the company:	
Name and address of the Contract Research Organisation(s) where the clinical studies proving efficacy and safety of the product were conducted. *(Add as much rows as necessary)* Name: Physical Address: Postal Address: City: District: Region/State: Country: Email: Fax: Phone Name of contact person in the company:	

1.0 Summary of Bioavailability/Bioequivalence Studies Performed

(Provide a brief description of each comparative bioavailability study included in the submission)
*…

2.0 Tabulation of the Composition of the Formulation(s) Proposed for Marketing and those Used for Bioequivalence Studies

(State the location of the master formulae in the Quality Overall Summary of the submission)

(Tabulate the composition of each product strength using the table below. For solid oral dosage forms the table should contain only the ingredients in tablet core /contents of a capsule. A copy of the table should be filled in for the film coating / hard capsule, if any.
Important: If the formulation proposed for marketing and those used for bioequivalence studies are not identical, copies of this table should be filled in for each formulation with clear identification in which bioequivalence study the respective formulation was used)
*…

Component and Quality Standard	Function	Strength (label claim)			
		XX mg		XX mg	
		Quantity per unit	%*	Quantity per unit	%*

TOTAL					

*each ingredient expressed as a percentage of the total core or coating weight

Composition of the batches used for clinical, bioequivalence or dissolution studies				
Batch number				
Batch size (number of unit doses)1				
Comments, if any				
Comparison of unit dose compositions and of clinical FPP batches (duplicate this table for each strength, if compositions are different)				
Ingredients	Unit dose (mg)	Unit dose (%)	Biobatch (kg)	Biobatch (%)
Equivalence of the compositions or justified differences				

2.1 Has comparative bioavailability data been submitted for all strengths?

(If comparative bioavailability data has not been submitted for all strengths, provide a scientific justification for not submitting such data; append copies of all references cited in the justification. Justification should include – but is not limited to – argumentation related to dose-proportional composition, dose-linearity of pharmacokinetics (Cmax and AUC,), discriminatory (with regard to bioavailability differences) power of dissolution tests employed)
*…

Sections 3.0 – 11.0 below should be copied and completed separately for each bioequivalence study performed.

3.0 CLINICAL STUDY REPORT

1 Bioequivalence batches should be at least of pilot scale (10% of production scale or 100,000 capsules/tablets whichever is the greater) and manufacturing method should be the same as for production scale.

Study #:
Study Title:
Location of Study Protocol:
Start and stop dates for each phase of the clinical study:
*…

3.1 ETHICS

(a) Name of review committee, date of approval of protocol and consent form, location of approval letter in the submission
*…

(b) State location of a reference copy of the informed consent form
*…

3.2 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

(a) Name of principal investigator(s) *(State location of C.V. in the submission)*
*…

(b) Clinical Facility *(Name and full mailing address)*
*…

(c) Clinical Laboratories *(Name and full mailing address)*
*…

(d) Analytical Laboratories *(Name and full mailing address)*
*…

(e) Company performing pharmacokinetic/statistical analysis *(Name and full mailing address)*
*…

3.3 STUDY OBJECTIVES

Briefly state the study objectives.
*…

3.4 INVESTIGATIONAL PLAN

3.4.1 Overall Study Design and Plan – Description
(Describe the type of study design employed in 1-2 sentences)
*…

3.4.2 Selection of Study Population
*…

3.4.2.1 Inclusion Criteria
*…

3.4.2.2 Exclusion Criteria
(List the exclusion criteria applied to subjects)

*…

3.4.2.3 Removal of Trial subjects from Trial or Assessment
*…

(a) Number of subjects enrolled in the study
(All subjects including alternates, withdrawals, and dropouts)
*…

(b) Withdrawals
(Identify each withdrawal by subject and provide the reason for withdrawal and at what point in the study the withdrawal occurred)
*…

3.4.2.4 Health Verification
(Individual data should be included in the submission)
*…

(a) List criteria used and all tests performed in order to judge health status
*…

(b) Indicate when tests were performed
*…

(c) Study site normal values
(State location in submission of study site normal values for blood clinical chemistry, haematology, and urinalysis clinical screen)
*…

(d) Report any results that were outside of study site normal values
(State location in submission of the summary of anomalous values)
*…

3.4.3 Products Administered

3.4.3.1 Test Product
*…

(a) Batch number, size and date of manufacture for the test product
*…

(b) Potency (measured content) of test product as a percentage of label claim as per validated assay method
(This information should be cross-referenced to the location of the certificate of analysis in the submission)
*…

3.4.3.2 Reference Product
(Append to this template a copy of product labelling (summary of product characteristics), as authorised in country of purchase, and English translation if appropriate)
*…
(a) Name and manufacturer of the reference product

*…

(b) Batch number and expiry date for the reference product
*…

(c) Purchase, shipment, storage of the reference product
(This information should be cross-referenced to location in submission of documents (e.g. receipts) proving conditions)
*…

(d) Potency (measured content) of the reference product as a percentage of label claim, as measured by the same laboratory and under the same conditions as the test product
(This information should be cross-referenced to the location of the certificate of analysis in the submission)
*…

(e) Justification of choice of reference product
(Provide short summary here and cross-reference to location of comprehensive justification in study protocol)
*…

3.4.4 Selection of Doses in the Study
*…

(a) State dose administered
(Indicate the number of dosage units comprising a single dose, e.g., 400 mg as 1 x 400 mg or 2 x 200 mg tablets)
*…

3.4.5 Selection and Timing of Dose for Each Subject
(a) State volume and type of fluid consumed with dose
*…

(b) Interval between doses *(i.e., length of washout)*
*…

(c) Protocol for the administration of food and fluid
*…

(d) Restrictions on posture and physical activity during the study
*…

3.4.6 Blinding
3.4.6.1 Identify which of the following were blinded. If any of the groups were not blinded, provide a justification for not doing so
a) study monitors: Yes ☐ / No ☐ If No, justify:_____
b) subjects: Yes ☐ / No ☐ If No, justify:_____
c) analysts: Yes ☐ / No ☐ If No, justify:_____
*…

3.4.6.2 Identify who held the study code and when the code was broken
*…

3.4.7 Drug Concentration Measurements
*…

3.4.7.1 Biological fluid(s) sampled
*…

3.4.7.2 Sampling Protocol
*…

(a) Number of samples collected per subject
*…

(b) Volume of fluid collected per sample
*…

(c) Total volume of fluid collected per subject per phase of the study
*…

(d) List the study sampling times
*…

(e) Identify any deviations from the sampling protocol
(State location of summary in the submission)
(Describe and explain reasons for deviations from sampling protocol. Comment on impact on study. Indicate whether the deviations were accounted for in the pharmacokinetic analysis)
*…

3.4.7.3 Sample Handling
*…

(a) Describe the method of sample collection
*…

(b) Describe sample handling and storage procedures
*…

3.5 Comments from review of Section 3.0 – *TFDA use only*

4.0 Trial subjects

4.1 Demographic and Other Baseline Characteristics
*…

(a) Identify study population (i.e., normal, healthy adult volunteers or patients)
*…

(b) Summary of ethnic origin and gender of subjects
*…

(d) Range and mean age ± SD of subjects
*…

(e) Range and mean height and weight ± SD of subjects
*…

(f) Identify subjects whose ratio is not within 15% of the values given on a standard height/weight table
*…

4.2 Number of smokers included in the study
*…

(a) Indicate how many cigarettes smoked per day per subject
*…

(b) Comment on the impact on study
*…

4.3 Comments from review of Section 4.0 – *TFDA use only*

5.0 PROTOCOL DEVIATIONS

5.1 Protocol deviations during the clinical study
(Describe any such deviations and discuss their implications with respect to bioequivalence)
*…

5.2 Comments from review of Section 5.0 – *TFDA use only*

6.0 SAFETY EVALUATION

6.1 Identify adverse events observed
(List any adverse events by subject number. State whether a reaction occurred following administration of the test or reference product, identify any causal relationships, and note any treatments required. State location of this summary in the submission)
(Discuss the implications of the observed adverse events with respect to bioequivalence)
*…

6.2 Comments from review of Section 6.0 – *TFDA use only*

7.0 EFFICACY EVALUATION – Efficacy Results and Tabulations of Individual Trial Subjects Data

7.1 Presentation of Data

*…

(a) State location in submission of tables of mean and individual subject concentrations

*…

(b) State location in submission of (mean and individual) linear and semi-logarithmic subject drug concentration vs. time plots

*…

Pharmacokinetic (PK) Parameters

	Test			Reference		
Parameter	Arithmetic Mean	Standard deviation	Inter-individual coefficient of variation (%)	Arithmetic Mean	Standard deviation	Inter-individual coefficient of variation (%)
AUC_T (units)						
AUC_I (units)						
C_{max} (units)						
T_{max} (units)						
$T_{½}$ (units)						

(State method of AUC calculation and method of extrapolation. Indicate location of description in protocol)

*…

(b) Ratio of AUC_T to AUC_I

(State mean ratio for both test and reference, state location in submission where individual ratios can be found,)

*…

7.3 Statistical Analysis

(Provide the following results from the ANOVA (non-parametric) on the logarithmically transformed AUC_T and C_{MAX} and other relevant parameters, e.g. in the case of steady-state designs, AUC_τ , C_{MAX} , and C_{MIN} ; state software which has been used for computing ANOVA)

*…

(a) Geometric means, Results from ANOVA, Degrees of Freedom (DF) and derived CV (intra-individual)

Parameter	Test	Reference	% Ratio of Geometric Means	90 % Confidence Interval	DF	CV (%)
AUC_T (units)						
AUC_I (units)						
C_{max} (units)						

*…

(b) Period and/or sequence effects
(State whether any period- and/or sequence-effects have been found. If yes, provide short discussion of effects here, and state location in submission where comprehensive explanation is provided)
*…

7.4 DISCUSSION OF RESULTS
(State location of the discussion of the results in the submission. If the discussion currently included in the study report does not include comparisons of results, including inter- and intra-individual variability, of this study with published results (literature, product information of reference product (innovator), such a discussion should be provided here and copies of the references used should be appended to this document)
*…

7.5 Comments from review of Section 7.0 – *TFDA use only*

8.0 ANALYTICAL STUDY REPORT

8.1 Analytical Technique
*…

8.1.1 Analytical protocol
(State the location of the analytical protocol)
*…

8.1.2 Identify analyte(s) monitored
*…

8.1.3 Comment about source and validity of reference standard
*…

8.1.4 Identify analytical technique employed
*…

8.1.5 Identify method of detection
*…

8.1.6 Identify internal standard
*…

8.1.7 If based on a published procedure, state reference citation
*…

8.1.8 Identify any deviations from protocol
*…

8.1.9 Dates of subject sample analysis
*…

8.1.10 Longest period of subject sample storage
(Identify the time elapsed between the first day of sample collection and the last day of subject sample analysis)
*…

8.1.11 State whether all samples for a given subject were analysed together in a single analysis run
*…

8.2 Standard Curves
(State location in submission of tabulated raw data and back calculated data with descriptive statistics)
*…

(a) List number and concentration of calibration standards used
*…

(b) State number of curves run during the study
*…

(c) Summarize descriptive data including slope, intercept, correlation coefficients
*…

(d) Describe the regression model used including any weighting
*…

(e) State the limit of quantitation (LOQ)
(Summarize inter-day and intra-day precision and accuracy at the LOQ)
*…

8.3 Quality Control Samples
*…

(a) Identify the concentrations of the QC samples, their date of preparation and the storage conditions employed prior to their analysis
*…

(b) State the number of QC samples in each analytical run per concentration
*…

8.4 Precision and Accuracy
*…

(a) Summarize inter-day and intra-day precision and accuracy of QC samples analysed during subject sample analysis and inter-day precision of back-calculated standards
*…

8.5 Repeat Analysis

(a) List repeats by sample identification and include the following information for each repeat: initial value; reason for repeat; repeat value(s); accepted value; and reason for acceptance
*…

(b) Report the number of repeats as a percentage of the total number samples assayed
*…

8.6 Chromatograms
(State the location in the submission where the sample chromatograms can be found. The chromatograms should be obtained from a minimum of two analytical batches and include at least 20% of the subjects, up to a maximum of five. A complete set includes standards, QC samples, pre-dose and post-dose subject samples for both phases. Each chromatogram should be clearly labelled with respect to the following: date of analysis; subject ID number; study period; sampling time; analyte; standard or QC, with concentration; analyte and internal standard peaks; peak heights and/or areas)
*…

8.7 Comments from review of Section 8.0 – *TFDA use only*

9.0 ANALYTICAL VALIDATION REPORT

9.1 Precision and Accuracy
*…

(a) Summarize inter-day and intra-day accuracy and precision during assay validation
*…

(b) Summarize inter-day and intra-day accuracy and precision during assay re-validation

(If applicable)
*…

9.2 Stability
(For each section provide the location of the raw data, a description of the methodology employed and a summary of the data)
(a) Summarize data on long-term storage stability
*…

(b) Summarize data on freeze-thaw stability
*…

(c) Summarize data on bench top stability
*…

(d) Summarize data on autosampler storage stability
*…

(e) Summarize data from any other stability studies conducted
(e.g., stock solution stability)
*…

9.3 Specificity
(Methods to verify specificity against endogenous/exogenous compounds & results)
*…

9.4 Recovery
(Method and results of assessment for analyte and internal standard including mean and CV %)
*…

9.5 Comments from review of Section 9.0 – *TFDA use only*

10.0 QUALITY ASSURANCE

10.1 Internal quality assurance methods
(State locations in the submission where internal quality assurance methods and results are described for each of study sites (see 3.2 b-d)
*…

10.2 Monitoring, Auditing, Inspections
(Provide a list of all monitoring and auditing reports of the study, and of recent inspections of study sites by other regulatory agencies. State locations in the submission of the respective reports for each of study sites (see 3.2 b-d)
*…

10.3 Comments from review of Section 10 – *TFDA use only*

CONCLUSIONS AND RECOMMENDATIONS – *TFDA use only*

11. Declaration of the 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:-

11. The current edition of the Tanzania "Good Manufacturing Practices Guidelines for Pharmaceuticals Products" or equivalent guideline is applied in full in all premises involved in the manufacture of this medicine.

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

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

11.4. 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.

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

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

11.7Each 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.

11.8 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.

11.9 T he person releasing the product is an authorized person as defined by the Tanzania "Good Manufacturing Practices Guidelines for pharmaceuticals.

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

11.11 All the documentation referred to in this application is available for review during GMP inspection.

11.12 Clinical trials (where applicable) were conducted in accordance with ICH , WHO or Tanzanian Guidelines for Good Clinical Practice,

I also agree that:

1113. As a holder of marketing authorization/registration of the product I will adhere to Tanzanian requirements for handling adverse reactions.

11.14. As holder of registration I will adhere to Tanzanian requirements for handling batch recalls of the products.

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

QUERIES TO BE COMMUNICATED TO THE MANUFACTURER

A. General remark, if applicable

B. Overall conclusion

Please fill in the relevant conclusion, based on the review of the data on efficacy and safety, in the first part of the document.
Please copy all relevant information to be communicated to the manufacturer in the query letter and save it accordingly.

Please mark on the top of the cover page in capital word RECOMMEDED if the product is recommended for registration or QUERIED if it is not recommended pending resolution of queries or REFUSED if it is recommended not to be granted registration.

RECOMMENDATIONS FOR INSPECTION

ANNEX 3: Application Form for Renewal of Registration of Human Medicinal Product

APPLICATION FORM FOR RENEWAL OF REGISTRATION OF HUMAN MEDICINAL PRODUCT

General Instructions:

Please read all the instructions carefully prior to completing this Application form.

Provide accurate, concise, but as far as possible complete summary of all necessary data and relevant particulars in all areas of the form. Note that all areas are to be filled out by the applicant EXCEPT where indicated by GREY COLOURS which are for TFDA Official Use Only.

Please state the exact location (Annex number) of any appended documents in the relevant sections of the form.

Before submitting the completed form, please countercheck to confirm whether you have provided all requested information.

This application form should be accompanied by a Batch Manufacturing Record (BMR) of a real batch manufactured within the last six months from the date of submission of this application.

Should you have any questions regarding this form, please contact the Tanzania Food and Drugs Authority (TFDA).

A properly filled out and signed original copy of the form with all its annexes (including a hard copy and an electronic copy in MS Word on a CD-ROM) must be submitted. A complete application should be sent to the following address:

Director General
Tanzania Food and Drugs Authority
P.O. Box 77150
EPI Mabibo
Off Mandela Road
Dar-es-Salaam
Tanzania

1. For official use only

1.1 Application Number		
1.2 Date of submission of the dossier		
1.3 Evaluator	Name	Signature
1.4 Auditor	Name	Signature
1.5 Date of evaluation		
1.6 Date of auditing		
1.7 Number of files		
1.8 Conclusion of the assessment *If the dossier is* **RECOMMENDED** *specify:* • *Primary packaging and shelf-life of product,* • *Storage condition of product and special precautions.* • *Distribution category*	**RECOMMENDED (no outstanding issues)** **QUERY RAISED** **REJECTED** **(*Please delete which does not apply*)**	

2. To be filled in by the applicant

2.1Registration number	
2.2Date of expiry of current registration	
2.3Proprietary Name of the Product	
2.4International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API), strength, pharmaceutical form.	
2.5 Anatomic Therapeutic Classification (ATC) Code	
2.6 Name and address of applicant (who must be the holder of the marketing authorization) Name: Physical Address: Postal Address: City:	

District: Region/State: Country: Email: Fax: Phone Name of contact person in the company:	
2.7 Name and address(es) of the manufacturer(s) of the active pharmaceutical ingredient(s). *(Add as many rows as necessary)* Name: Physical Address: Postal Address: City: District: Region/State: Country: Email: Fax: Phone: Name of contact person in the company:	
2.8 site/location of manufacture of API (s)	
2.9 Name(s) and complete address (es) of the manufacturer(s) of the finished product(s), including the final product release if different from applicant. *(Add as many rows as necessary)* Name: Physical Address: Postal Address: City: District: Region/State:	

Country: Email: Fax: Phone: Name of contact person in the company:	
2.10. Site/location of manufacture FPP	
2.11 Local Agent: Name: Physical Address: Postal Address: City: District: Region/State: Country: Email: Fax: Phone Name of contact person in the company:	
2.12 Visual description of the FPP	
2.13 Visual description of the packaging	
2.14 Sample	
2.15 Current registration status in other countries including East African community (EAC) and the Southern African Development Community (SADC) countries	

3. FINISHED PHARMACEUTICAL PRODUCT(s) [FPP(s)]
3.1 Manufacturing and Marketing authorization
3.2 Additional pharmaceutical development studies (if any)

3.3 Formulation

Strength (label claim)	
Master Production Document Reference Number and/or Version	
Batch Size (number of dosage units)	

Ingredients (APIs and excipients) starting with APIs	Quality standard	Specifi-cation	Dosage per unit composition		Batch quantities	
			mg	%	kg	%
Film coating/Hard capsule						

Composition of all *components that are mixtures* (e.g., colourants, coatings, capsule shells, imprinting inks):

Description of accompanying reconstitution diluent(s), if applicable:

3.4 Quality Control of the FPP

4.9.1 Specifications for the FPP

Standard Claimed (e.g., In-house, BP, PhEur, PhInt, USP)		
Specification Reference Number and/or Version		
Test	Analytical Procedure (Type/Source/Version)	Acceptance Criteria

		Batch release	Shelf life

3.5 Container/closure system(s) and other packaging

(e) Description of the container closure systems, including unit count or fill size, container size or volume:

(f) Materials of construction of each primary packaging component:

(g) Summary of specifications of each primary and functional secondary (e.g., foil pouches) packaging components:

3.6 Completed Real time stability testing:

Applicable only if registration was based on accelerated and partial real time stability data

Stability protocol for continuing (i.e., ongoing) batches:

Protocol Parameter	Description
Storage conditions (including tolerances)	
Testing frequency	
Number of batches per strength and batch sizes	
Container closure system(s)	
Stability-indicating quality parameters	
Photostability testing	
Tests and acceptance criteria	
Other	

FPPs packaged in impermeable containers

FPPs packaged in semi-permeable containers

Evaluation of results of stability studies

(a) Summary of stress testing and results (e.g., photostability studies, cyclic studies for semi-solids, freeze-thaw studies):

(b) Summary of real time testing (e.g., studies conducted, protocols used, results obtained):

(i) Description of stability study details:

Storage Conditions (°C, % RH)	Batch Number	Batch Size	Container Closure System	Completed (and Proposed) Test Intervals (in months)

(ii) Summary and discussion of stability study results:

(c) Proposed storage conditions and shelf life (and in-use storage conditions and in-use period, if applicable):

Extrapolation of data

Core storage statements

3.7. Container labelling

3.7.1 Packaging or, where there is no outer packaging, on the immediate packaging

3.7.2 Blisters and strips

3.8 Current package insert and if available patient information leaflet

4. Summary of all approved variations made before submission of this application.

5. Variations intended to made in this application (Follow Variation guidelines for submission of required data)

6. Declaration of the 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:-

6.1 The current edition of the Tanzania "Good Manufacturing Practices Guidelines for Pharmaceuticals Products**"** or equivalent guideline is applied in full in all premises involved in the manufacture of this medicine.

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

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

6.4. 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.

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

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

6.7 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.

6.8 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.

6.9 The person releasing the product is an authorized person as defined by the Tanzania **"**Good Manufacturing Practices Guidelines for pharmaceuticals".

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

6.11 All the documentation referred to in this application is available for review during GMP inspection.

6.12 Clinical trials (where applicable) were conducted in accordance with Good Clinical Practice,

I also agree that:

6.13 As a holder of marketing authorization/registration of the product I will adhere to Tanzanian requirements for handling adverse reactions.

6.14 As holder of registration I will adhere to Tanzanian requirements for handling batch recalls of the products.

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

This product assessment report should be written in clear unambiguous language referring to deficiencies or lack of data submitted, as communication with the manufacturer may result from the assessment.

The report should be completed by an evaluator and auditor

The assessment report should be typed with "Bookman Old Style 11" fonts. The format of tables must not be changed.

QUERIES TO BE COMMUNICATED TO THE MANUFACTURER

Please copy all relevant observation and information to be communicated to the manufacturer in the query letter (format to be provided) and save it accordingly

A. General remark, if applicable

B. Observations, queries

ACTIVE PHARMACEUTICAL INGREDIENT(s) (INN)

FINISHED PHARMACEUTICAL PRODUCT (INN .mg PHARMACEUTICAL FORM)

C. Overall conclusion

Please fill in the relevant conclusion, based on the review of the data on quality, in the first part of the document.

Please mark on the top of the cover page the in capital word RECOMMEDED if the product is recommended for registration or QUERIED if it is not recommended pending resolution of queries or REFUSED if it is recommended not to be granted registration.

The dossier can be recommended for registration only, if minor issues are pending.

D. Outstanding commitments

Please list the outstanding commitments, which should be answered before the product can be authorized for marketing.

RECOMMENDATIONS FOR INSPECTION

ANNEX 4: Model Stability Report for Active Pharmaceutical Ingredients (APIs)

Prepared by: .....
Approved by: .....
Date: .....

Model Stability Report of ..... Active Pharmaceutical Ingredient

Approved INN name:

1. BATCHES TESTED

Batch number			
Date of manufacture			
Site of manufacture			
Batch size (kg)			
Primary packing materials			
Date of initial analysis			

Note: The batches to be sampled should be representative of the manufacturing synthesis process and should be manufactured from different batches of key intermediates.

2. GENERAL INFORMATION

- Structure
- Chemical name(s)
- Other non-proprietary name(s), e.g., national name, United States Adopted Name (USAN), Japanese Accepted Name (JAN); British Approved Name (BAN)
- Chemical Abstracts Service (CAS) registry number

3. CONTAINER/CLOSURE SYSTEM

A description of the container/closure system(s) should be provided, including the identity of materials of construction of each primary packaging component, and their specifications. The specifications should include description and identification.

4. LITERATURE AND SUPPORTING DATA

Before stability studies are initiated, information on the stability of the active pharmaceutical ingredient (API) should be sought, collected and analyzed. Published decomposition process and degradability of the API and the finished pharmaceutical products (FPP) should be referred to.

Stability data can be presented on laboratory- and pilot-scale batches and on synthesis routes other than those proposed for marketing.

Note: Literature data, if available, should be scrutinized, sometimes experimentally verified, and completed with information on polymorphism, particle size, hygroscopicity, etc., if applicable.

5. STABILITY-INDICATING ANALYTICAL METHODS

Make reference to the release specification number containing the description of validated, stability-indicating methods. The accuracy as well as the precision (standard deviations) of the methods should be recorded. The tests for impurities and degradants should be validated to demonstrate that they are specific to the API being examined and are of adequate sensitivity

6. TESTING PLAN

Storage condition	Storage time (months)								
	0	3	6	12	18	24	36	48	60
Accelerated: 40±2°C/75±5 % RH	X	X	X						
Long term*: 30±2°C/75±5 % RH	X	X	X	X	X	X	X	X	X
Long term (2): 25±2°C/60±5 % RH	To be conducted only if the API is not stable at 30°C								

***** The long term studies should cover the whole retest period, which is not necessarily five (5) years.

A significant change is considered to have occurred if:

- The assay value shows a 5% decrease as compared with the initial assay value of a batch;
- Any specified degradation product is present in amounts greater than its specification limit;
- The specifications for appearance and physical properties, e.g. color, are no longer met.

7. TEST PARAMETERS

7.1 Chemical characteristics [assay, contents of impurities and degradants].

7.2 Physical characteristics [e.g. appearance including possible change in color, moisture content as well as polymorphs if applicable].

7.3 Photostability testing should be conducted on at least one primary batch of the API.

7.4 Microbiological attributes (total microbial count and absence of pathogens, every year) when the API is intended to be used in a parenteral dosage form.

8. OTHER REQUIREMENTS

8.1 A stability report must be prepared giving details of the study results and conclusions. The results should be presented as both a table and a graph.

8.2 The stability of a given API, and therefore the proposed retest period and storage conditions, must be proposed on the basis of these results.

8.3 Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested retest period will be granted, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

8.4 An approach for analyzing data of a quantitative attribute that is expected to change with time is to determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate.

8.5 Storage conditions recommended on the basis of stability studies should be prominently indicated on the label.

8.6 Once the API supplier has been approved, additional stability studies are required whenever major modifications are made to the manufacturing synthesis process, packaging materials or methods.

9. CONCLUSIONS

The obtained stability data support a proposed retest date of ... months.
Storage conditions and retest date approved by the national Drug Regulatory Authority on the basis of stability studies should be prominently indicated on the label.

Contact person in Applicant Company

Name:
Position in the company:
Postal address:
Physical address:
Telephone number:
Fax number:
E-mail address:
Website:

ANNEX 5: Model Stability Report for Capsules/Tablets

Prepared by: .....
Approved by: .....
Date: .....

Model Stability Report of .....mg Capsules/Tablets

Approved generic name, if different from the name in the title above:

1. BATCHES TESTED

Batch number			
Date of manufacture			
Site of manufacture			
Batch size (kg)			
Batch size (number of units)			
Primary packing materials			
Date of initial analysis			
Batch number of the active pharmaceutical ingredient (API)			

2. UNIT COMPOSITION OF A CAPSULE/TABLET

3. CONTAINER/CLOSURE SYSTEM

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.

4. LITERATURE AND SUPPORTING DATA

Published decomposition process and degradability of the API and the finished pharmaceutical products (FPP) revealed that.....

Development formulations and stress tests in open systems (in particular, 100% RH and light) showed that .....

5. STABILITY-INDICATING ANALYTICAL METHODS

Make reference to release and at-the-end of shelf life specification numbers containing the description of validated, stability-indicating methods.
The accuracy as well as the precision of the method is ... standard deviations.
The tests for impurities and degradants have been validated (validation report is attached).

6. TEST RESULTS

Batch No.:
Container:

Chemical data

Initial values			
Storage condition	**Assay (mg)**	**Degradant 1 (%)**	**Degradant 2 (%)**
3 months, 40±2 °C / 75±5 %RH 3 months, 30±2°C / 75±5 %RH			
6 months, 40±2 °C / 75±5 %RH 6 months, 30±2°C / 75±5 %RH			
12 months, 30±2°C / 75±5 %RH			
18 months, 30±2°C / 75±5 % RH			
24 months, 30±2°C / 75±5 % RH			
36 months, 30±2°C / 75±5 % RH			
48 months, 30±2°C / 75±5 % RH			
60 months, 30±2°C / 75±5 % RH			

Batch No.:
Container:
Physical data

Initial values			
Storage condition	**Appearance**	**Dissolution rate,...min., %**	**LOD**
3 months, 40±2 °C / 75±5 %RH 3 months, 30±2°C / 75±5 % RH			
6 months, 40±2 °C / 75±5 %RH 6 months, 30±2°C / 75±5 % RH			
12 months, 30±2°C / 75±5 % RH			
18 months, 30±2°C / 75±5 % RH			
24 months, 30±2°C / 75±5 % RH			
36 months, 30±2°C / 75±5 % RH			
48 months, 30±2°C / 75±5 % RH			
60 months, 30±2°C / 75±5 % RH			

Note: change headings and add tables, as necessary.

Batch No.:
Container:
Microbiological attributes

Initial values		
Storage condition	Total microbial count	Pathogen microbes
3 months, 40±2 °C / 75±5 %RH 3 months, 30±2°C / 75±5 % RH		
6 months, 40±2 °C / 75±5 %RH 6 months, 30±2°C / 75±5 % RH		
12 months, 30±2°C / 75±5 % RH		
18 months, 30±2°C / 75±5 % RH		
24 months, 30±2°C / 75±5 % RH		
36 months, 30±2°C / 75±5 % RH		
48 months, 30±2°C / 75±5 % RH		
60 months, 30±2°C / 75±5 % RH		

7. ANALYSIS OF RESULTS

7.1 Where the data show so little degradation and so little variability that it is apparent from looking at the data that the requested shelf life will be granted, it is normally unnecessary to go through the formal statistical analysis; providing a justification for the omission should be sufficient.

7.2 If data of a quantitative attribute that have changed significantly during the stability tests, present them in a graph and determine the time at which the 95% one-sided confidence limit for the mean curve intersects the acceptance criterion. If analysis shows that the batch-to-batch variability is small, it is advantageous to combine the data into one overall estimate.

8. CONCLUSIONS

The obtained stability data support a proposed shelf life of ..... months.

Note: Storage conditions approved by the Tanzania Food and Drugs Authority on the basis of stability studies should be prominently indicated on the label.

Contact person in Applicant Company

Name:
Position in company:
Postal address:
Telephone number: Fax number:
E-mail address.

Revision History

Revision number	Date	Author	Description of Change	Section(s) Modified	Authorized by
1st Edition (Revision 0)	December 1995	HDR	New	All new	Registrar Pharmacy Board
2nd Edition (Revision 1)	November 1999	HDR	Wide-ranging	Wide-ranging	Registrar Pharmacy Board
3rd Edition (Revision 2)	June 2004	DPER	Wide-ranging	Wide-ranging	Director General
4th Edition (Revision 3)	November 2008	DMC	Wide-ranging	Wide-ranging	Director General
Revision 4	August 2012	DMC	Minor corrections and minor additions: i) Defining roles of an applicant who becomes a MAH ii) Specification of file cover and requirement for separate files and CDs for each section. iii) Appeal replaced with "application for review of decision". iv) ATC referenced to WHO publication and corresponding annex removed v) Embossing of Batch number, manufacturing and expiry dates on container labels vi) Addition of declaration by the applicant on the application forms vii) Harmonization of relative humidity during stability studies throughout the guidelines to 75±5 %RH)	 Section 1.2 Section 1.3.1 Section 1.8 Section 2.2 and annex 6 Section 4.12 Annexes 1,2 and 3 Annexes 4 and 5	Director General