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## **GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR REGISTRATION OF F HUMAN MEDICINAL PRODUCTS**

***(Made under section 53 (1) of Zanzibar Food, Drugs and Cosmetics Act, 2006)***

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**To Protect and Enhance Health Care of Public Health**

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**Burhan O. Simai**  
**Registrar**  
**Zanzibar Food and Drugs Board.**

## Abbreviations

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

## Foreword

The Zanzibar Food and Drugs Board (ZFDA) was established under the Zanzibar Food, Drugs and Cosmetics Act No. 2 of 2006 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-market 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 order to have consistent and uniform submissions, ZFDA provides application guidelines to give guidance to applicants on content and format of minimum information required for registration of medicinal products.

Development in pharmaceutical research broadens knowledge of medicines and therapy which also calls for new demands on standards of medicines. In the like manner, standards of obtaining scientific evidence on quality, safety and efficacy of medicines and presenting it to national medicines regulatory authorities for obtaining registration must be updated to match the new demands. Such evidence is gathered during drug and formulation development and compiled into a drug dossier.

All applicants are encouraged to familiarize with the guidelines and follow them strictly when preparing and submitting applications for marketing authorization of medicinal products. However, the guidelines are not intended to inhibit innovation and they only provide for minimum requirements thereby giving room for applicants to submit additional data.

Adherence to guidelines will ensure that all relevant information is provided in registration dossiers submitted for marketing authorization. This will facilitate efficient and effective evaluation as well as approval process. It will also help to avoid queries which results in unnecessary delays in giving approvals to new medicines thereby improving access to medicines of proven quality, safety and efficacy in the shortest time possible.

**Burhan O. Simai**  
**Registrar**  
**Zanzibar Food and Drugs Board.**

## Introduction

**Section 53 (1)** of the Zanzibar Food, Drugs and Cosmetics Act, 2006 provides conditions under which a medicinal product may be registered in Zanzibar. These conditions include:

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

Furthermore, **Section 56 (1)** of the Act prohibits the sell, supply or importation of any drug unless it is registered under the provisions of the Act.

This guidelines gives details on requirements for active pharmaceutical ingredients (APIs) as well as finished pharmaceutical products (FPPs). In addition, requirements on bioequivalence and bio-waver(s). This addition is 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 two main parts: the main guidelines and six annexes as follows:

The main guidelines are divided into seven sections:

- a) General Application Requirements
- b) Summary of Product Characteristics
- c) Active Pharmaceutical Ingredient(s)
- d) Finished Pharmaceutical Product(s)
- e) Interchangeability
- f) Pharmacology, Toxicology and Efficacy of New Drugs
- g) Fixed-Dose Combination Medicinal Products

The annexes are:

- i. Application Form: Quality Data
- ii. Application Form: Bioequivalence Data
- 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
- vi. Anatomic Therapeutic Chemical (ATC) Classification System

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 defined in the current 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 and herbal drugs, separate guidelines are available and these can be accessed online from the Ministry of Health website under [ZFDB](http://ZFDB); [www.zanhealth.info](http://www.zanhealth.info)

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 and Bioequivalence parts, 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 and as far as possible evaluation of dossiers submitted will 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, [ZFDB](http://ZFDB) will in the interest of patient safety and well being not accept outdated methods and techniques and will evaluate products based on the current state of scientific knowledge and standards. Applicants are therefore encouraged to keep abreast with scientific developments and use current scientific information to develop and test their products.

Applicants are also requested to read these guidelines together with the [Zanzibar Food, Drugs and Cosmetics Act, 2006](http://Zanzibar Food, Drugs and Cosmetics Act, 2006) and Regulations made there under ([www.zanhealth.info](http://www.zanhealth.info)).

## 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).

### *Board*

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

### *Bio-equivalence*

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

### *Composition*

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

### *Container*

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

### *Container labelling*

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

### *Drug, medicine or pharmaceutical product*

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

- (a) The diagnosis, treatment, mitigation or prevention of a disease, disorder, abnormal physical or mental state, or the symptoms thereof, in man;
- (b) Restoring, correcting or beneficial modification of organic or mental functions in man;
- (c) Disinfection in premises in which drugs are manufactured, prepared or kept, hospitals and equipment;
- (d) Articles intended for use as a component of any articles specified in clause (a), (b) or (c); but does not include medical devices or their components, parts or accessories.

### *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 (multisource) 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).

*Interchangeability*

An interchangeable pharmaceutical product is one that is therapeutically equivalent to an innovator (reference) product.

*Label*

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

*Manufacture (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).

*Marketing authorization (registration)*

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

*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 pharmaceutical product*

A pharmaceutical 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.

*Applicant*

A person who owns a formula or trademark of a product, who may be a manufacturer or a person to whose order and specifications the product is manufactured and who shall be the registration holder and have the primary responsibility of the product on the Tanzanian market.

*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 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 drugs*

APIs (not products) which:

- have been marketed for at least five years in countries that undertake active post-marketing surveillance;
- 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.

### *Well-established drug products*

Pharmaceutical products which contain well established drugs 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.

### *WHO-type certificate*

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

## **SECTION 1: GENERAL INFORMATION**

### **PART I: GENERAL REQUIREMENTS**

#### ***1.1 Language***

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

#### ***1.2 Local Responsible Person***

Every applicant who is not resident in Tanzania shall appoint a local responsible person who must reside in Zanzibar. The person who must be a person residing or a company incorporated in Zanzibar and authorized by ZFDB to deal in medicinal products. Evidence shall be made by submitting a power of attorney that complies with Zanzibarian Law.

The local responsible person shall be responsible for facilitating communication with the applicant and when the product is registered he shall assume all legal responsibilities regarding the product on the Tanzanian market.

### **1.3 Data presentation**

Data shall be presented on A4 and 80g/m<sup>2</sup> 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 dossier.

All sections of the dossier must be bound separately and 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. Two or more sections separated by clearly marked dividers may be bound in a single file provided that the total number of pages does not exceed 500. The papers must unless otherwise justified be printed on both sides.

The binding shall be in such a manner as to allow sections to be detached for evaluation by different experts and also to allow convenient up-dating by addition of new documents such as supplementary information, evaluation reports, query letters and query 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 Trade/Brand and generic names of the product in capital letters at the centre of the top cover

For generic medicines data on quality and therapeutic equivalence (clinical-interchangeability) shall be presented in separate files.

In the case of new drugs, in addition to quality data, separate files will be required for safety and efficacy data.

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**

For purposes of submission to ZFDB, 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 and Bioequivalent parts 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 ZFDB
- viii. Non refundable application fee for registration of human medicines in Tanzania and GMP inspection fees for facilities not yet inspected and approved by ZFDB

#### **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 ZFDB Application Guidelines for Variation of Registered Human Medicinal Products also available on ZFDB website; ([www.zanhealth.info](http://www.zanhealth.info)).

#### **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 and GMP inspection fees for facilities not inspected and approved by ZFDB 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 ZFDB or by bank transfer to:

**Account No. 021103000579 at the people's bank of Zanzibar, Forodhani 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 Receiving of new 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 ZFDB head office located at Mnazimmoja Kaunda Road, Zanzibar, Tanzania.

An application may only be received by ZFDB upon payment of the application fees.

#### **1.6.2 Evaluation**

### **1.6.2.1 Evaluation of scientific data**

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

An application may be fast tracked and be evaluated within three (3) months of its submission if 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.

Assessment of product dossiers involves evaluators from within or outside **ZFDB**. The evaluation report produced by the evaluator is 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 is done against the requirements of these guidelines in accordance with the Standard Operating Procedures for Evaluation. However, the Authority reserves the right to request any additional information to establish the quality, safety and efficacy of a medicine in keeping with the level of knowledge current at the time of evaluation.

Decisions on registration of a medicinal product will be made based on data made available in the submitted dossier. Non compliance to the requirements prescribed in the guidelines in content and format will lead to refusal of registration of the product.

The **Board** 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 process stops until when **ZFDB** receives a written response to the query. All queries issued in the same letter must be submitted together in one set 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.

### **1.6.2.2 Laboratory analyses of product sample**

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

### **1.6.2.3 Verification of compliance to Good Manufacturing Practices (GMP)**

If the new application is from a new manufacturing site, **ZFDB** may conduct inspection of the site or use other means to verify whether the facility complies with **Zanzibar's** Good Manufacturing Practices (GMP) Regulations and/or guidelines. After the inspection, inspection observation memorandum that details issues to be addressed will be signed by both the inspectee and **ZFDB**

GMP inspectors and a full report will be sent to the applicant within **60 days** of conducting the inspection.

When the facility is found not to comply with current GMP, the applicant will be required to rectify the observed deficiencies and submit a compliance report within a time frame agreed during the inspection. Based on the report, the Authority may either approve the facility or conduct re-inspection. If the applicant does not rectify and request for re-inspection within the 12 months or if after re-inspection the facility is found not to comply with GMP, it will be deemed that the applicant has failed to rectify the deficiencies and has therefore withdrawn the respective application(s). The application will be closed and thereafter registration of the product will only be considered upon submission of a new application.

Inspection of a facility for the purposes of considering applications for renewal of registration shall be done only once and if the facility is found not to comply with GMP, registration of all products manufactured by the facility shall be withdrawn.

### **1.6.3 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. A product is tabled before the Committee if it has complied with all the minimum requirements outlined in these guidelines or is grossly deficient such that it cannot be granted registration (disqualified).

Registration will be granted subject to the product complying with criteria prescribed under **Section 53** of the **Zanzibar Food, Drugs and Cosmetics Act, 2006** as explained elsewhere in these guidelines.

If the Committee is satisfied that a product has complied with all the prescribed registration requirements, granting of marketing authorization will be recommended. A certificate of marketing authorization together with applicable conditions shall be issued. However, if there are unresolved safety, quality or efficacy issues the Committee may defer approval pending resolution of the issues. Should the applicant fail to provide the required data within **180 days**, the product will be disqualified and the application will be closed.

### **1.6.4. Timelines**

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

#### **1.6.4.1 Fast-tracked registration**

Complete applications will be processed within **90days** working days of receiving the application including evaluation of documentation and consideration by a technical committee.

#### ***1.6.4.2 Evaluation of new applications***

Complete new applications will be processed (evaluation and consideration by a technical committee) **within 3 months** of receipt. The applicant will be required to provide any requested additional data within **180** days of such a request. Should additional time be required a formal request must be submitted and approved by the **Board** within the **180** working days period.

#### ***1.6.4.3 Closure of applications***

When the applicant fails to submit written responses to queries within 180 days from the date of their issuance, it will be deemed that he has withdrawn the application or if the queries have been reissued for a second time, provides unsatisfactory responses, the product will be disqualified and the application will be closed.

#### ***1.7. Validity of registration***

The registration of a human medicinal product subject to payment of annual retention fees shall be valid for five (5) years unless earlier suspended or revoked by **ZFDB** or withdrawn by applicant. The **Board** 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. Appeals for review***

**Any applicant whose product has been refused registration may within 60 days of being given a notice to that effect, submit a written petition to the Registrar pleading for revision of the decision". The petition shall be supported with evidence based reasons. However, any new data that was not in the product's dossier shall be considered only if it is submitted as part of a fresh application.**

## **SECTION 2: SUMMARY OF PRODUCT CHARACTERISTICS**

Real size copy 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 ZFDB.

### **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 Anatomic Therapeutic and Chemical (ATC) Classification and Distribution Category**

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

### **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 1st 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/Marketing authorization holder/applicant**

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 first registration/renewal of the registration**

To be included after obtaining first registration or renewal of registration. The date should correspond to the initial registration of the medicinal product concerned. It should not reflect individual strength/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**

To be stated at the time of printing once a change to the SPC has been approved.

## **SECTION 3: ACTIVE PHARMACEUTICAL INGREDIENT(s) [API(s)]**

The information on the API 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 under **Section 3**, or
- By completing **Section 3**. 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 **ZFDB**.

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.jserv?@\\_ID=430&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_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.jserv?@\\_ID=422&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_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.jserv?@\\_ID=423&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_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.jserv?@\\_ID=417&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_ID=417&@_MODE=GLB)
- ICH-Q2B Validation of Analytical Procedures: Methodology  
[http://www.ich.org/MediaServer.jserv?@\\_ID=418&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_ID=418&@_MODE=GLB)
- WHO Expert Committee on Specifications for Pharmaceutical Preparations. 32<sup>nd</sup> 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 to 10 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-compensial 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 <sub>2</sub> O <sub>2</sub>
Photolytic	Metal halide, Hg , Xe lamp, or UV-B/fluorescent
Metal ions (optional)	0.05 M Fe <sup>2+</sup> or Cu <sup>2+</sup>

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 **ZFDB**.

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 **ZFDB**.

Reference:

ICH-Q1A (R2) Stability Testing of New Drug Substances and Products  
[http://www.ich.org/MediaServer.jserv?@\\_ID=419&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_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.jserv?@\\_ID=419&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_ID=419&@_MODE=GLB)
- Q1B Stability Testing: Photostability Testing of New Drug Substances and Products  
[http://www.ich.org/MediaServer.jserv?@\\_ID=412&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_ID=412&@_MODE=GLB)
- Q1E Evaluation for Stability Data  
[http://www.ich.org/MediaServer.jserv?@\\_ID=415&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_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 4: FINISHED PHARMACEUTICAL PRODUCT(s) [FPP(s)]**

### **4.1 Manufacturing and Marketing authorization**

Submit a valid Manufacturing Authorization for pharmaceutical production. Submit a Marketing Authorization to demonstrate that the product is registered or licensed in the country of origin.

### **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.jserv?@\\_ID=1707&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_ID=1707&@_MODE=GLB)
- ICH Q9 guidelines: Quality Risk Management  
[http://www.ich.org/MediaServer.jserv?@\\_ID=1957&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_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](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, 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. Submit a valid GMP Certificate.

#### **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.

Stages of manufacture at which sampling is carried out for in-process control tests should be indicated. 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](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:

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, **ZFDB** need to be informed immediately. In such cases corrective actions should be proposed and any changes proposed in the manufacturing process should receive prior **ZFDB** 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, 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 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  $\pm 5\%$  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. 32<sup>nd</sup> 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.jserv?@\\_ID=417&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_ID=417&@_MODE=GLB)
- ICH-Q2B Validation of Analytical Procedures: Methodology
- [http://www.ich.org/MediaServer.jserv?@\\_ID=418&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_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 pharmaceuticals (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.jserv?@\\_ID=412&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_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 **ZFDB** 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 **Zanzibar**.

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,  $30 \pm 2^{\circ}\text{C}$  and  $75 \pm 5\%$  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  $40 \pm 2^{\circ}\text{C}$  and NMT  $25 \pm 5\%$  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.jserv?@\\_ID=415&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_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  $30 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$  (2 years) and  $40 \pm 2^{\circ}\text{C}/75 \pm 5\% \text{ RH}$  (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.jserv?@\\_ID=415&@\\_MODE=GLB](http://www.ich.org/MediaServer.jserv?@_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 packaging and where applicable secondary packaging label**

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 leaflet**

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 5: INTERCHANGEABILITY**

Bio-equivalence study report for multi-source (generic) preparations should be submitted. Studies should be conducted based on the WHO guidelines on registration requirements to establish interchangeability.

### Reference:

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

Instead of bio-equivalence trial, comparative clinical trial using clinical or pharmacodynamic endpoints can be presented. These endpoints should be justified and validated for the compound and trial should be designed to show equivalence. Trial showing the absence of significant difference cannot be accepted.

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. Reference preparation in bio-equivalence study should be innovator preparation or product registered by TFDA, ICH and associated countries or from WHO list of international comparator products if listed.

### Reference:

Guidance on the selection of comparator pharmaceutical products for equivalence assessment of interchangeable multisource (generic) products. In: *WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-sixth report*. Geneva, World Health Organization, 2002 (WHO Technical Report Series, No. 902):161–180.

- 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, 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 6: 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 defined in current ICH guidelines.

## **Section 7: 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-ninth report. Geneva, World Health Organization, 2005: Annex 5, (WHO Technical Report Series, No.929).

**ANNEX 1: Application Form For Marketing Authorization Of  
A Human Medicinal Product: Quality Part**

**General Instructions:**

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

Provide as much detailed, accurate and final information as possible. Note that all areas are to be filled out by the applicant EXCEPT where indicated by grey areas which are for ZFDB 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.

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

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 pharmaceutical quality part of the dossier. The entire dossier should be submitted both as hard-copy and on CD-ROM. The application should be sent to the following address:

Registrar  
Zanzibar Food and Drugs Board  
P.O. Box 3595  
Mnazimmoja  
Kaunda Road  
Zanzibar,  
Tanzania

Application Number		
Date of submission of the dossier		
Evaluator	Name	Signature
Auditor	Name	Signature
Date of evaluation		
Date of auditing		
Number of files		
Anatomic Therapeutic Classification (ATC) Code		
Proprietary Product Name (if relevant)		
International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API), strength, pharmaceutical form.		
<p>Conclusion of the assessment  <i>If the dossier is <b>RECOMMENDED</b> specify:</i></p> <ul style="list-style-type: none"> <li>- Primary packaging and shelf-life of product,</li> <li>- Storage condition of product and special precautions.</li> <li>- Distribution category</li> </ul>	<p><b>RECOMMENDED (no outstanding issues)</b>  <b>QUERY RAISED</b>  <b>REJECTED</b>  <i>(Please delete which does not apply)</i></p>	
Name and complete address of the Applicant		
Name(s) and complete address(es) of the manufacturer(s) of the finished product(s), including the final product release if different from the manufacturer. <i>(Add as many rows as necessary)</i>		
Name and address(es) of the manufacturer(s) of the active pharmaceutical ingredient(s). <i>(Add as many rows as necessary)</i>		
Name and complete address of the Local Agent		
Visual description of the FPP		
Visual description of the packaging		
Sample		
Registration status in other countries (e.g. SADC and EAC)		



<b>3. ACTIVE PHARMACEUTICAL INGREDIENT(s) [API(s)]</b>
<b>3.1 Nomenclature</b>
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
<b>3.2 Properties of API(s)</b>
3.2.1 API not described in BP, PhInt, PhEur, or USP
<p>(a) List of studies performed (e.g., IR, UV, NMR, MS, elemental analysis) and summary of the interpretation of evidence of structure:</p> <p>(b) Discussion on the potential for isomerism and identification of stereochemistry (e.g., geometric isomerism, number of chiral centres and configurations):</p> <p>(c) Summary of studies performed to identify potential polymorphic forms (including solvates):</p> <p>(d) Summary of studies performed to identify the particle size distribution of the API:</p> <p>(e) Potentially critical, additional characteristics:</p> <ul style="list-style-type: none"> <li>▪ Physical description (e.g., appearance, colour, physical state):</li> <li>▪ Physical form (e.g., polymorphic form, solvate, hydrate):</li> <li>▪ Solubilities (e.g., in common solvents, aqueous/nonaqueous solubility profile):</li> <li>▪ Partition coefficient</li> <li>▪ Hygroscopicity</li> <li>▪ Others (e.g., pH and pKa values, melting or boiling points, optical rotation, refractive index (for a liquid), UV absorption maxima and molar absorptivity):</li> </ul>

3.2.2 API described in BP, PhInt, PhEur, or USP
<p>(a) Summary of studies performed to identify potential polymorphic forms (including solvates):</p> <p>(b) Summary of studies performed to identify the particle size distribution of the API:</p> <p>(c) Potentially critical, additional characteristics:</p> <ul style="list-style-type: none"> <li>▪ Physical description (e.g., appearance, colour, physical state):</li> <li>▪ Physical form (e.g., polymorphic form, solvate, hydrate):</li> <li>▪ Solubilities (e.g., in common solvents, aqueous/nonaqueous solubility profile):</li> <li>▪ Partition coefficient</li> <li>▪ Hygroscopicity</li> <li>▪ Others (e.g., pH and pKa values, melting or boiling points, optical rotation, refractive index (for a liquid), UV absorption maxima and molar absorptivity):</li> </ul>
3.2.3 Information from literature
<b>3.3 Site(s) of manufacture</b>
List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF letters of access), if applicable):
<b>3.4 Route(s) of synthesis</b>
3.4.1 API not described in BP, PhInt, PhEur, or USP
<p><b>Controls of Critical Steps and Intermediates</b></p> <p>Summary of the controls performed at critical steps of the manufacturing process and on intermediates:</p> <p>Process Validation and/or Evaluation</p> <p>Description of process validation and/or evaluation studies (e.g., for aseptic processing and sterilization):</p> <p><i>Manufacturing Process Development</i></p> <p>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:</p> <p><i>Impurities</i></p> <p>(a) Identification of potential and actual impurities arising from the synthesis, manufacture and/or degradation:</p> <p>List of impurities (e.g., starting materials, by-products, intermediates, chiral impurities, degradation products), including chemical name, structure, and</p>

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:																																				
<b>3.5 Specifications</b>																																				
3.5.1 API not described in BP, PhInt, PhEur, or USP																																				
<table border="1" style="width: 100%; border-collapse: collapse;"> <tr> <td style="width: 60%; padding: 5px;">Standard Claimed (e.g., In-house, BP, PhEur, PhInt, USP)</td> <td style="width: 40%;"></td> </tr> <tr> <td style="padding: 5px;">Specification Reference Number and/or Version</td> <td></td> </tr> <tr> <td style="padding: 5px;"> <table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 30%; padding: 5px;">Test</th> <th style="width: 30%; padding: 5px;">Analytical Procedure (Type/Source/Version)</th> <th style="width: 40%; padding: 5px;">Acceptance Criteria</th> </tr> </thead> <tbody> <tr><td style="height: 20px;"></td><td></td><td></td></tr> </tbody> </table> </td> <td></td> </tr> </table>	Standard Claimed (e.g., In-house, BP, PhEur, PhInt, USP)		Specification Reference Number and/or Version		<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 30%; padding: 5px;">Test</th> <th style="width: 30%; padding: 5px;">Analytical Procedure (Type/Source/Version)</th> <th style="width: 40%; padding: 5px;">Acceptance Criteria</th> </tr> </thead> <tbody> <tr><td style="height: 20px;"></td><td></td><td></td></tr> </tbody> </table>	Test	Analytical Procedure (Type/Source/Version)	Acceptance Criteria																												
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Test	Analytical Procedure (Type/Source/Version)	Acceptance Criteria																																		
Batch Analyses																																				
(a) Description of the batches:																																				
<table border="1" style="width: 100%; border-collapse: collapse;"> <thead> <tr> <th style="width: 25%; padding: 5px;">Batch Number</th> <th style="width: 25%; padding: 5px;">Batch Size</th> <th style="width: 25%; padding: 5px;">Date and Site of Production</th> <th style="width: 25%; padding: 5px;">Use (e.g., clinical, comparative)</th> </tr> </thead> <tbody> <tr><td style="height: 20px;"></td><td></td><td></td><td></td></tr> <tr><td style="height: 20px;"></td><td></td><td></td><td></td></tr> <tr><td style="height: 20px;"></td><td></td><td></td><td></td></tr> <tr><td style="height: 20px;"></td><td></td><td></td><td></td></tr> </tbody> </table>	Batch Number	Batch Size	Date and Site of Production	Use (e.g., clinical, comparative)																																
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:

<b>4.4 Sites of manufacture</b>	
..... +	
List of referenced Drug Master Files (DMFs) and DMF Numbers (copies of DMF letters of access are attached to <b>Section 4.4 Sites of manufacture</b> in the dossier submitted for registration).	
<b>4.5 Manufacturing process</b>	
<b>4.6 Manufacturing Process Controls of Critical Steps and Intermediates</b>	
Summary of controls performed at the critical steps of the manufacturing process and on isolated intermediates:	
<b>4.7 Process Validation and Evaluation</b>	
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	
<b>4.8 Specifications for excipients</b>	
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 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

<p><i>Reference Standards or Materials</i></p> <p>(a) Source of reference standards or reference materials (e.g., In-House, USP, BP, PhEur, PhInt):</p> <p>(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):</p>	
4.9.3 Validation of analytical procedures	
4.9.4 Batch analyses	
<b>4.10 Container/closure system(s) and other packaging</b>	
<p>(a) Description of the container closure systems, including unit count or fill size, container size or volume:</p> <p>(b) Materials of construction of each primary packaging component:</p> <p>(c) Summary of specifications of each primary and functional secondary (e.g., foil pouches) packaging components:</p> <p>(d) List of referenced Drug Master Files (DMFs) and DMF Numbers, if applicable:</p>	
<b>4.11 Stability testing</b>	
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				
<b>4.12 Container labelling</b>				
4.12.1 Outer packaging or, where there is no outer packaging, on the immediate packaging				
4.12.2 Blisters and strips				
<b>4.13 Patient information and package inserts</b>				

## 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”** or equivalent guideline is applied in full in all premises involved in the manufacture of this medicine.
- 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 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.

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 RECOMMENDED 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 A Human  
Medicinal Product: Bioequivalence Part**

**General Instructions:**

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

Provide as much detailed, accurate and final information as possible. Note that all areas are to be filled out by the applicant EXCEPT where indicated by grey areas which are for ZFDB 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 (ZFDB).

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 pharmaceutical quality part of the dossier. The entire dossier should be submitted both as hard-copy and on CD-ROM. The application should be sent to the following address:

Registrar  
Zanzibar Food and Drugs Board  
P.O. Box 3595  
Mnazimmoja  
Kaunda Road  
Zanzibar,  
Tanzania

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		
Proprietary Product Name (if relevant)		
International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API), strength, pharmaceutical form.		
Conclusion of the assessment	<b>RECOMMENDED (no outstanding issues)</b> <b>QUERY RAISED</b> <b>REJECTED</b> <i>(Please delete which does not apply)</i>	
SPC , PIL submitted	(state location in submission)	
SPC, PIL, Package Labelling acceptable	Yes:_____// No:_____	
Name and complete address of the Applicant		
Name and address of the Contract Research Organisation(s) where the clinical studies proving efficacy and safety of the product were conducted. <i>(Add as much rows as necessary)</i>		

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.

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 part 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

<b>Composition of the batches used for clinical, bioequivalence or dissolution studies</b>				
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 (%)

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.

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 (C<sub>max</sub> 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**

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 – <i>ZFDB use only</i>
-----	--

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  $\pm$  SD of subjects

\*...

(e) Range and mean height and weight  $\pm$  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 – <i>ZFDB use only</i>
-----	--

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 – <i>ZFDB use only</i>

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 – <i>ZFDB use only</i>

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

Parameter	Test			Reference		
	Arithmetic Mean	Standard deviation	Inter-individual coefficient of variation (%)	Arithmetic Mean	Standard deviation	Inter-individual coefficient of variation (%)
AUC <sub>T</sub> (units)						
AUC <sub>I</sub> (units)						
C <sub>max</sub> (units)						
T <sub>max</sub> (units)						
T <sub>½</sub> (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,  $AUC_t$ ,  $C_{MAX}$ , 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 – ZFDB 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 – *ZFDB 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 – *ZFDB 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 – <i>ZFDB use only</i>
--

CONCLUSIONS AND RECOMMENDATIONS – <i>ZFDB use only</i>
--

### 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.
- 11.7 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.
- 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 The 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 Good Clinical Practice,

I also agree that:

- 11.13. 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 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.

### **RECOMMENDATIONS FOR INSPECTION**

### **ANNEX 3: 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 as much details, accurate and complete information as possible. Note that all areas are to be filled out by the applicant EXCEPT where indicated by GREY COLOURS which are for ZFDB 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 (ZFDB).

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 together with the pharmaceutical quality part of the dossier. The entire dossier should be submitted both in hard-copy and on a CD-ROM. A complete application should be sent to the following address:

Registrar  
Zanzibar Food and Drugs Board  
P.O. Box 3595  
Mnazimmoja  
Kaunda Road  
Zanzibar,  
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 <i>If the dossier is <b>RECOMMENDED</b> specify:</i> <ul style="list-style-type: none"> <li>• <i>Primary packaging and shelf-life of product,</i></li> <li>• <i>Storage condition of product and special precautions.</i></li> <li>• <i>Distribution category</i></li> </ul>	<b>RECOMMENDED (no outstanding issues)</b> <b>QUERY RAISED</b> <b>REJECTED</b> <i>(Please delete which does not apply)</i>	
<b>2. To be filled in by the applicant</b>		
2.1 Registration number		
2.2 Date of expiry of current registration		
2.3 Proprietary Name of the Product		
2.4 International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API), strength, pharmaceutical form.		
2.5 Anatomic Therapeutic Classification (ATC) Code		
2.6 Name and complete address of the Applicant		
2.7 Name and address(es) of the manufacturer(s) of the active pharmaceutical ingredient(s). <i>(Add as many rows as necessary)</i>		
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 manufacturer. <i>(Add as many rows as necessary)</i>	
2.10. Site/location of manufacture FPP	
2.11 Name and complete address of the Local Responsible Person ( who must be resident in Tanzania and in case of company be incorporated in Tanzania)	
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	

<b>3. FINISHED PHARMACEUTICAL PRODUCT(s) [FPP(s)]</b>				
<b>3.1 Manufacturing and Marketing authorization</b>				
<b>3.3 Formulation</b>				
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 composi tion	Batch quantities

			m g	%	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 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**

- (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**

<b>Initial values</b>			
<b>Storage condition</b>	<b>Assay (mg)</b>	<b>Degradant 1 (%)</b>	<b>Degradant 2 (%)</b>
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**

<b>Initial values</b>			
<b>Storage condition</b>	<b>Appearance</b>	<b>Dissolution rate,...min., %</b>	<b>LOD</b>
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**

<b>Initial values</b>		
<b>Storage condition</b>	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.

## **ANNEX 6: Anatomic Therapeutic Chemical (Atc) Classification System**

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

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

### **The main groups of the ATC classification system are:-**

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

**A ALIMENTARY TRACT AND METABOLISM**

- A01 Stomatologicals, mouth preparations
  - A Stomatologicals, mouth preparations
- A02 Antacids, antiflatulents and antipeptic ulcerants
  - A Antacids and antiflatulents
  - B Antipeptic ulcerants
  - C Others
- A03 Gastrointestinal antispasmodics and anticholinergics
  - A Synthetics, incl. Papaverine
  - B Belladonna and derivatives, pain
  - C Antispasmodics in combination with psycholeptics
  - D Antispasmodics in combination with analgesics
  - E Other combinations
- A04 Antiemetics and antinauseants
  - A Anti-emetics and antinauseants
- A05 Cholagogues and hepatic protectors
  - A Bile therapy, cholagogues and choleretics
  - B Hepatic protectors, lipotropics
  - C Cholagogues and lipotropics in combination
- A06 Laxatives
  - A Laxative
- A07 Antidiarrhoeals, intestinal antiinflammatory/antiinfective agents
  - A Intestinal anti-infectives
  - B Intestinal adsorbents
  - C Electrolytes with carbohydrates
  - D Antipropulsives
  - E Intestinal anti-inflammatory agents
  - F Antidiarrhoeal microorganisms
  - X Various antidiarrhoeals
- A08 Antiobesity preparations excl. diet products
  - A Antiobesity preparations, excl. diet products
- A09 Digestives, incl. Enzymes
  - A Digestives, incl. Enzymes
- A10 Antidiabetic therapy
  - A Insulins and other parenterals
  - B Oral antidiabetics
- A11 Vitamins
  - A Multivitamins, combinations
  - B Multivitamins, plain

- C Vitamin A and D, incl. combinations of the two
  - D Vitamin B<sub>1</sub>, plain and in combination with Vitamin B<sub>6</sub> and B<sub>12</sub>
  - E Vitamin B – Complex incl. combinations
  - G Ascorbic acid (Vitamin C), incl. combinations
  - H Other plain vitamin preparations
  - J Other vitamin products, combination
- AB12 Mineral Supplements
- A Calcium
  - B Potassium
  - C Other Mineral supplements
- A13 Tonics
- A Tonics
- A14 Anabolics, systemic
- A Anabolic steroids
  - B Other anabolic agents
- A15 Appetite stimulants
- A16 Other alimentary tract and metabolism products
- B BLOOD AND BLOOD FORMING ORGANS**
- B01 Anticoagulants
- A Anticoagulants
- B02 Antihæmorrhagics
- A Antifibrinolytics
  - B Vitamin K and Others
- B03 Antianaemic preparations
- A Haematinics, iron and all combinations
  - B Vitamin B<sub>12</sub> and folic acid
- B04 Cholesterol reducers, antiatheroma preparation
- A Cholesterol reducers, antiatheroma preparations
- B05 Plasma substitutes and perfusion solutions
- A Blood and related products
  - B I.V. solutions
  - C Irrigating solutions
  - D Peritoneal dialytics
  - X I.V. solution additives
  - Z Haemodialytics
- B06 Other hæmatological agents, incl. Fibrinolytics and hyaluronidase
- A Other hæmatological agents, incl. Fibrinolytics and hyaluronidase

## **C      **CARDIOVASCULAR SYSTEM****

- C01 Cardiac therapy
  - A Cardiac glycosides
  - B Antiarrhythmics
  - C Antiadrenergic agents, ganglion – blocking
  - D Arteriolar smooth muscle, agents acting on
  - E Renin – angiotensin system, agents acting on
  - K Other hypotensives
  - L Hypotensives and diuretics in combination
  
- C02 Diuretics
  - A Low – ceiling diuretics, thiazides
  - B Low – ceiling diuretics, excl. thiazides
  - C High – ceiling diuretics
  - D Potassium – sparing drugs
  - E Diuretics and potassium – sparing drugs in combination
  
- C03 Peripheral vasodilators
  - A Peripheral vasodilators
  
- C04 Vasoprotectives
  - A Antihaemorrhoidals, topical preparations
  - B Antivaricose therapy
  - C Capillary stabilizing agents
  
- C05 Beta blocking agents
  - A Beta blocking agents, plain

## **D      **DERMATOLOGICALS****

- D01 Antifungals, dermatological
  - A Antifungals, topical preparations
  - B Antifungals, systemic preparations
  
- D02 Emollients and protectives
  - A Emollients and protectives
  
- D03 Cicatrizants, excl. medicated dressings
  
- D04 Antipruritics, incl. Antihistamines, Anaesthetics, etc.
  - A Antipruritics, incl. Antihistamines, Anaesthetics, etc.
  
- D05 Coal tar, sulphur and resorcinol products
  - A Coal tar, sulphur and resorcinol products
  
- D06 Antibiotics and chemotherapeutics, dermatologicals
  - A Antibiotics, topical preparations
  - B Chemotherapeutics, topical preparations
  - C Antibiotics and chemotherapeutics, combinations

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

D08 Antiseptics and disinfectants  
A Antiseptics and disinfectants

D09 Medicated dressings  
A Medicated dressings

D10 Antiacne preparations  
A Anti – acne preparations

D11 Other dermatological preparations

## **G GENITO-URINARY SYSTEM AND SEX HORMONES**

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

G02 Other gynaecologicals  
A Oxytocics  
B Topical contraceptives  
C Other gynaecologicals

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

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

## **H SYSTEMIC HORMONAL PREPARATIONS, EXCL. SEX HORMONES**

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

H02 Systemic corticosteroids

- A Systemic corticosteroids, plain
  - B Systemic corticosteroids, combinations
  - C Antiadrenal preparations
- H03 Thyroid therapy
- A Thyroid preparations
  - B Antithyroid preparations
  - C Iodine therapy
- H04 Pancreatic hormones
- A Glycogenolytic hormones
- H05 Calcium homeostasis
- A Parathyroid hormones
  - B Antiparathyroid hormones
- J GENERAL ANTIINFECTIVES, SYSTEMIC**
- J01 Systemic antibiotics
- A Tetracyclines
  - B Chloramphenicol
  - C Penicillins with increases effect on Gram – negative bacilli
  - D Cephalosporins
  - E Trimethoprim, excl. combinations with sulphonamides
  - F Macrolides
  - G Streptomycins
  - H Penicillins
  - J Penicillin and streptomycin in combination
  - K All other antibiotics
- J02 Systemic antimycotics, excl. griseofulvin
- A Systemic antimycotics, excl. griseofulvin
- J03 Systemic chemotherapeutics
- A Sulfonamides
  - B Sulfonamides and antiinfectives in combination
  - C Other chemotherapeutics
- J04 Tuberculostatics, excl. streptomycin
- A Tuberculostatics, excl. streptomycin
- J05 Systemic antivirals
- A Agents affecting the virus directly
  - B Immunostimulating agents
  - C Agents with immunostimulants and antiviral activity
- J06 Immune sera and immunoglobulins
- A Immune sera
  - B Immunoglobulins
- J07 Vaccines

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

**L ANTI-NEOPLASTIC AND IMMUNOSUPPRESSIVE DRUGS**

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

- L02 Hormone therapy
  - A Hormones
  - B Anti-hormones

**M MUSCULO – SKELETAL SYSTEM**

- M01 Anti-inflammatory and anti-rheumatic products
  - A Anti-inflammatory and anti-rheumatic products pre – steroids
  - B Combinations with corticosteroids
- M02 Topical products for joint and muscular pain
  - A Topical products for joint and muscular pain
- M03 Muscle relaxants
  - A Peripherally acting agents
  - B Centrally acting agents
  - C Directly acting agents
- M04 Antigout preparations
  - A Antigout preparations
- M05 Other drugs for disorders of the musculo – skeletal system
  - A Other drugs for disorders of the musculo – skeletal system

**N CENTRAL NERVOUS SYSTEM**

- N01 Anaesthetics
  - A Anaesthetics, general
  - B Local anaesthetics, excl. dermatologicals
- N02 Analgesics
  - A Narcotics
  - B Other analgesics and antipyretics
  - C Anti-migraine preparations
- N03 Anti-epileptics
  - A Anti – Parkinson drugs

- N04 Psycholeptics
  - A Neuroleptics
  - B Tranquilizers
  - C Hypnotics and sedatives
- N05 Psychoanaleptics
  - A Antidepressants
  - B Psychostimulants
  - C Psycholeptics and psychoanaleptics in combination
- N06 Other CNS drugs, incl. Parasympathomimetics
  - A Parasympathomimetics

**P ANTI-PARASITIC PRODUCTS**

- P01 Antiprotozoals
  - A Amoebicides and similar
  - B Antimalarials
  - X Other antiprotozoals
- P02 Anthelmintics
  - A Schistosomicides
  - X Other anthelmintics
- P03 Ectoparasiticides, incl. Scarbicides
  - A Ectoparasiticides, incl. Scarbicides

**R RESPIRATORY SYSTEM**

- R01 Nasal preparations
  - A Nasal decongestants, topical preparations
- R02 Throat preparations
  - A Throat preparations
- R03 Anti-asthmatics
  - A Bronchodilators and other anti – asthmatics, excl. R03B
  - B Respiratory stimulants
- R04 Chest rubs and other inhalants
  - A Chest rubs and other inhalants
- R05 Cough and cold preparations
  - A Cold preparations without antiinfectives
  - B Cold preparations with antiinfectives
  - C Expectorants, excl. combinations with antitussives
  - D Antitussives, excl. combinations with expectorants
  - E Systemic nasal decongestants
  - F Antitussives and expectorants, combination

- R06 Antihistamines for Systemic use
  - A Antihistamines for systemic use

**S      SENSORY ORGANS**

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

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

- S03 Ophthalmological and otological preparations
  - A Antiinfectives
  - B Corticosteroids
  - C Corticosteroids and antiinfectives in combination
  - D Other ophthalmological preparations

**V      VARIOUS**

- V01 Allergens
  - A Allergens

- V02 Immunosuppressive drugs
  - C Immunosuppressive drugs

- V03 All other therapeutic products
  - A All other therapeutic products

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

- V05 Surgical antiseptics

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

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

## Revision History

Revision number	Date	Author	Description of Change	Section(s) Modified	Approvals
1 <sup>st</sup> Edition	December 1995	HDR	New	All new	Registrar Pharmacy Board
2 <sup>nd</sup> Edition	November 1999	HDR	Wide-ranging	Wide-ranging	Registrar Pharmacy Board
3 <sup>rd</sup> Edition	June 2004	DPER	Wide-ranging	Wide-ranging	Director General
4 <sup>th</sup> Edition	November 2008	DMC	Minor corrections and minor additions: -Specification of file cover -Embossing of Batch number, manufacturing and expiry dates -Harmonization in the relative humidity stability studies conditions	-Section 1 -Section 3 -Section 4	Director General