Doc. No. TMDA/DMC/MRE/G/003
Revision No. 1

TANZANIA MEDICINES AND MEDICAL DEVICES AUTHORITY

GUIDELINES ON SUBMISSION OF DOCUMENTATION FOR RENEWAL OF REGISTRATION OF HUMAN AND VETERINARY PHARMACEUTICAL PRODUCTS

(Made under section 17 of the Tanzania Medicines and Medical Devices (Registration of Medicinal Products) Regulations,2015)

March 2020

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Acknowledgements

These Guidelines on Submission of Documentation for Renewal of Registration of Human and Veterinary Pharmaceutical Products have been crafted in order to define a more systematic and better way of handling renewal applications of registered pharmaceutical products received by the Authority.

Since the beginning of registration system in Tanzania, renewal of registration has been administratively handled based on general requirements present in the then main Guidelines on Submission of Documentation for Registration of Human Pharmaceutical Products for human medicines and Guidelines on Submission of Documentation for Registration of Veterinary Pharmaceutical Products for veterinary medicines. Despite the success in handling and providing responses to customers in timely manner, challenges remained in the way applications for renewal of registration of medicinal products are compiled and submitted by applicants. This has necessitated development of this first version of the guidelines in order to properly guide applicants when filing applications for renewal of registration. This in turn will improve transparency and predictability of applications for renewal of registration.

The Guidelines have been drafted and finalized by a team of TMDA staff namely Mr. Felchism Apolnary, Dr. Rukia S. Mng'ombe and Dr. Athanas Mseki who essentially reviewed guidelines from other countries and came up with these guidelines.

The Authority would therefore wish to thank the above-mentioned TMDA experts for their dedication, time and commitment during preparation of the Guidelines.

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Acting Director, Medical Products Control
Tanzania Medicines and Medical Devices Authority

Abbreviations

API	-	Active Pharmaceutical Ingredient
BP	-	British Pharmacopoeia
BSE	-	Bovine Spongiform Encephalopathy
CE	-	"Conformite Europeene"
CEP	-	European Certificate of Suitability
CPP	-	Certificate of a Pharmaceutical Product
DMF	-	Drug Master File
DRA	-	Drug Regulatory Authority
FPP	-	Finished Pharmaceutical Product
GMP	-	Good Manufacturing Practice
ICH	-	International Conference on Harmonization of Technical Requirements for Registration of Human Medicines
INN	-	International Non-proprietary Name
JP	-	Japanese Pharmacopoeia
'N'	-	Notification
NDRA	-	National Drug Regulatory Authority
PhEur	-	EuropeanPharmacopoeia
PhInt	-	International Pharmacopoeia
OoS	-	Out of Specification (Outside Specification)
SPC	-	Summary of Product Characteristics
TMDA	-	Tanzania Medicine and Medical Devices Authority
TMDA	-	Tanzania Medicine and Medical Devices Act
TSE	-	Transmissible Spongiform Encephalopathy
USP	-	United States Pharmacopoeia

Foreword

The Tanzania Medicine and Medical Devices Authority (TMDA) was established under the Tanzania Food, Drugs and Cosmetics Act, Cap. 219 with the mission of protecting and promoting public health by ensuring quality, safety and effectiveness of food, medicines, 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 being allowed to circulate in the market. This is a fundamental requirement for authorization of medicinal products in Tanzania. In order to have consistent and uniform submissions, TMDA on regular basis issues application guidelines to provide guidance to applicants on content and format of minimum information required for new and renewal of registration of medicinal products.

Keeping in mind that during the life cycle of a medicinal product, there are current and emerging technical requirements which need to be met at all times. Therefore, it had been considered necessary to craft these guidelines to address existing gaps in terms of technical requirements during approval of applications for re-registration.

This is the first edition of the guidelines for handling applications for renewal of registration of medicinal products developed by TMDA. The requirements specified in the guidelines have been developed taking into consideration the best practices gathered from other countries.

All applicants are encouraged to familiarize with the guidelines and follow them when preparing and submitting applications for renewal of registration 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 these guidelines will ensure that all relevant information is provided in registration dossiers submitted for renewal of registration and hence facilitate efficient and effective evaluation. It will also help to avoid queries which results in unnecessary delays in authorizing re-registration thereby improving access to medicines of proven quality, safety and efficacy in the shortest time possible.

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INTRODUCTION

Section 51 of the Tanzania Medicines and Medical Devices Act Cap. 219 prescribes that a medicinal product shall be registered only if:

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

Furthermore, Section 22 (1) of the Act prohibits the sell, supply or importation of any drug unless it is registered in accordance with the provisions of the Act. According to section 13 of the Tanzania Medicines and Medical Devices (Registration of Medicinal Products) Regulations, 2015, certificate of registration of a medicinal product shall unless earlier suspended or revoked, and subject to payment of prescribed annual retention fees is valid for a period of five (5) years from the date of issuance.

It is acknowledged that in the course of five years several aspects of the registered medicinal product may change significantly as a result of notified variations and other un-notified changes in manufacturing and control of the products. These may have significant impact on the respective product and therefore, the objective of renewal of registration is to ensure that the product continues to conform to the above mentioned requirements.

Section 17 of the regulations further provides for requirements for application for renewal of registration of a medicinal product.

The guidelines cover the steps that are followed from the submission of a dossier to the final outcome, the timeframe and procedure for the Authority to amend, where necessary the conditions of renewal of registration of a particular product.

The guidelines are divided into three major parts covering general requirements and application procedures for human and veterinary pharmaceutical products, processing of applications and technical requirements for application for renewal of medicinal products.

Applicants are requested to read carefully these guidelines, fill in application forms, prepare dossiers and other required documents and submit them in hard-copy as well as in electronic forms on a CD-ROM.

The guidelines present current thinking on technical requirements necessary to facilitate renewal of registration of medicinal products. Evaluation of the applications will as far as possible be based on the principles laid down in these guidelines. It is worth noting that TMDA will in the interest of patient safety and well being not accept outdated methods and techniques and will evaluate products based on up to date scientific knowledge and standards known or existing at the time of evaluation. Applicants are therefore encouraged to keep abreast with scientific developments and apply the most up to date scientific information and technology to develop and test their products.

Applicants are also requested to read these guidelines together with the Tanzania Medicines and Medical Devices Act, Cap. 219 and other relevant Regulations made there under.

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 medicinal product as a therapeutically active compound (ingredient).

Authority
Means the Tanzania Medicines and Medical Devices Authority, or its acronym —TMDA established under Section 4 of the Tanzania Medicines and Medical Devices Act, Cap. 219.

Drug Master File
A drug master file (DMF) is a master file that provides a full set of data on an API.

Finished Pharmaceutical Product (FPP)
Means a product that has undergone all stages of production, including packaging in its final container and labeling

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

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

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

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

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

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

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

Registration of a medicine or Marketing authorization (registration)
Means an official authorization or registration of a product by TMDA for the purpose of marketing or free distribution in Tanzania after evaluation for safety, efficacy and quality.

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 labeling and product information.

SCOPE
These guidelines will be applicable for application for renewal of registration of both human and veterinary medicinal products.

POST RENEWAL VARIATION TO PHARMACEUTICAL PRODUCTS

All variations to a registered pharmaceutical product shall be made according to requirements stipulated in the Application Guidelines for Variation of Registered Medicinal Products. No variation will be accepted during submission of renewal of registration.

1.0 GENERAL REQUIREMENTS AND APPLICATION PROCEDURES

Applications should be made to the Authority at least ninety (90) days before expiry of validity of registration of a particular pharmaceutical product;

1.1 All applications and supporting documents shall be in English. All submitted documents which are in any language other than English must be accompanied by a certified or notarized English translation;

2.1 The responsibility of applying for product renewal of registration rests with the company responsible for the introduction of the product into the Tanzanian market, i.e.: the Marketing Authorization Holder (MAH);

3.1 Applications must be duly completed and supported by all of the required documents as stipulated in these guidelines and where appropriate in line with Guidelines on Submission of Documentation for Registration of Human and Veterinary Pharmaceutical Products;

4.1 The covering letter and application form shall be submitted in hard copy and the entire dossier on a CD-ROM or the entire application be electronically submitted to the Authority;

5.1 Data shall be presented on A4 and $80g/m^2$ paper with 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.

6.1 Two samples of the smallest commercial pack(s) from one batch with batch certificates of analysis;

7.1 Non refundable Product renewal fees as stipulated in the Tanzania Food and Drugs (Fees and Charges) Regulations in force. Evidence of payment of the fees must be presented at the time of submission of the application;

8.1 Evidence of conformance of the finished product manufacturing facility with current good manufacturing practice (GMP) requirements as prescribed in GMP guidelines of TMDA;

9.1 List of all countries where the product has been reviewed and approved over the registration period of the product and registration numbers. If available, copies of registration certificates should be provided.

2.0 PROCESSING OF APPLICATIONS (MANAGEMENT OF APPLICATIONS)

2.1 Upon receipt, an acknowledgement letter for the receipt of the application will be issued and a reference number will be allocated to the application. The reference number assigned should be used in all subsequent correspondences relating to the application.

2.2 Evaluation of the application shall be carried out within the timelines stipulated in the Clients Service Charter implemented by the Authority and outcomes communicated to the applicant.

2.3 In the course of evaluation, the Authority may request for further information and additional supporting documents from the applicant. Required information should be made available within 60 days from the date of the request so as to facilitate timely renewal of the applied product;

2.4 Notification for renewal of registration of the product shall be followed by issuance of new registration certificate. Applicants should read carefully the conditions under which the medicine is registered overleaf the certificate and adhere to them throughout the life cycle of the product.

3.0 TECHNICAL REQUIREMENTS FOR APPLICATIONS FOR RENEWAL OF MEDICINAL PRODUCTS

All applications for renewal of registration of human and veterinary pharmaceutical products shall be accompanied by the following documentation/requirements:

3.1 ACTIVE PHARMACEUTICAL INGREDIENT(s) [API(s)]

3.1.1 Names and complete addresses of all current suppliers of active pharmaceutical ingredient(s) along with manufacturing and GMP certificates of the active pharmaceutical ingredient(s) manufacturing facilities issued by competent regulatory authorities;

3.1.2 Copy of current signed, dated and numbered specifications and analytical procedures used for testing of the active pharmaceutical ingredient(s) by the finished product manufacturer;

3.1.3 Information on container-closure system used for storage of the API in FPP manufacturer's storage facilities, storage conditions specified for the API and re-test period/shelf life implemented for the respective API;

3.2 FINISHED PHARMACEUTICAL PRODUCT (FPP)

3.2.1 Detailed description of qualitative and quantitative composition of the unit dosage form and of the commercial batch size(s) approved including colourants, coating agents in a manner provided for in section 3.2.P.1 of the main registration guidelines for human and veterinary pharmaceutical products;

3.2.2 A copy of batch manufacturing record (BMR) for the largest production batch manufactured within six months before the date of submission of the renewal application;

3.2.3 Report on annual product quality review for all batches of the finished product manufactured in the past 36 months before the date of application of the renewal. At minimum the report should include the following:

a) A review of starting and primary packaging materials used in the FPP, especially those from new sources;
b) A tabulated review of quality control and in-process control results;
c) A review of all batches that failed to meet established specification(s) ; ;
d) A review of all changes carried out to the processes or analytical methods;
e) A review of the results of the stability monitoring programme and
f) A list of validated analytical and manufacturing procedures and their revalidation dates.

3.2.4 A copy of current signed, dated and version numbered release and shelf life specifications of the finished products along with standard testing procedures;

3.2.5 Information on container/closure system(s). Data should be submitted according to the requirements stipulated under section 3.2.P.7 of the main registration guideline for human pharmaceutical products and 3.2.P.7 of the main Guidelines for Registration Veterinary Pharmaceutical products;

3.2.6 Data on stability study. For pharmaceutical products previously registered with long term stability data which do not support stability of the product under zone IV B, data should be provided to demonstrate stability of the product under storage conditions of 30°C 2°C/75% ± 5% relative humidity. Studies should be conducted according to requirements stipulated under section 3.2.P.8 of the main Guidelines on Submission of Documentation for Registration of Veterinary pharmaceutical products and specific guidelines on Stability Testing Requirements for Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products for human pharmaceutical products;

3.2.7 List of all variations submitted to and accepted by TMDA over the registration period of the product.

Reference number	**Description of change**	**Date submitted**	**Approval/Rejection date and reference number of the letter**	**Implementation status**

3.3 PRODUCT INFORMATION

3.3.1 Specimen of current package insert and copies of colored mock up labels of the product as per current requirements prescribed in section 1.5.4 of the main Registration Guidelines for Human Pharmaceutical Products and

section 1.5 of the main Registration Guidelines for Veterinary Pharmaceutical Products.

3.3.2 All prescription medicines should be accompanied by SmPC. Refer Guidelines on Format and Content of Summary of Product Characteristics for Human Pharmaceutical Products and section 1.5.1 of the main Registration Guidelines for Veterinary Pharmaceutical Products.

3.3.3 All Pharmaceutical preparations with potential for long-term use and self-administered injections and Over the Counter (OTC) medicines must contain a patient information leaflet. Languages used for PIL and labelling should be clearly expressed in English and/or Kiswahili. *Refer* Guidelines on Format and Content of Patient Information Leaflet for Human Pharmaceutical Products.

3.3.4 Submission of periodic post-marketing surveillance and safety studies

4. Revision History

Revision No.	Date	Description of Change
1	16 March, 2020	Change in a name of the Authority from *Tanzania Food and Drugs Authority* to *Tanzania Medicine and Medical Devices Authority.*
2	16 March, 2020	Change of the Act from *Tanzania Food, Drugs and Cosmetics Act* to *Tanzania Medical Devices Act*
3	16 March, 2020	Change of the control number of the guidelines from *TFDA/DMC/HVR/G/003 to TMDA/DMC/MRE/G/003*

ANNEX 1: APPLICATION FORM FOR RENEWAL OF REGISTRATION OF HUMAN AND VETERINARY PHARMACEUTICAL PRODUCTS

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 TMDA 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 all commercial batches 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 Medicines and Medical Devices Authority (TMDA).

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:

Director General
Tanzania Medicines and Medical Devices Authority
P.O. Box 77150
EPI Mabibo
Off Mandela Road
Dar-es-Salaam
Tanzania

1. **For official use only**

1.1 Application Number		
1.2 Date of submission of the dossier		
1.3 Evaluator	Name	Signature
1.4 Auditor	Name	Signature
1.5 Date of evaluation		
1.6 Date of auditing		
1.7 Number of files		
1.8 Conclusion of the assessment *If the dossier is* **RECOMMENDED***specify:* • *Primary packaging and shelf-life of product,* • *Storage condition of product and special precautions.* • *Distribution category*	**RECOMMENDED (no outstanding issues)** **QUERY RAISED** **REJECTED** **(*Please delete which does not apply*)**	
2. To be filled in by the applicant		
Type of the pharmaceutical product Human Veterinary		
2.1Registration number		

2.2Date of expiry of current registration	
2.3Proprietary Name of the Product	
2.4International Non-proprietary Name (INN) of the Active Pharmaceutical Ingredient (API), strength,	
2.5 Pharmaceutical Dosage form	
2.6 Route of administration	
2.7 Anatomic Therapeutic Classification (ATC) Code	
2.8Name and address (physical and postal) of Applicant	
2.9 Name and address(es) of the manufacturer(s) of the active pharmaceutical ingredient(s). *(Add as many rows as necessary)*	
2.10 site/location of manufacture of API (s)	
2.11 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. *(Add as many rows as necessary)*	
2.12. Site/location of manufacture FPP	
2.13 Name and complete address of the Local Responsible Person (who must be resident in Tanzania and in case of company be incorporated in Tanzania)	
2.14 Visual physical description of the FPP	
2.15 Packing/pack size	
2.16 Proposed shelf life (in months)	
2.17 Proposed shelf life (after reconstitution or dilution)	
2.18 Proposed shelf life (after first opening container)	

2.19 Proposed storage conditions	
2.20 Proposed storage conditions after first opening	
2.21 Distribution category: eg Controlled Drug ☐ POM ☐ Pharmacy Only ☐ OTC ☐ General sale ☐ (Applicants are invited to indicate which categories they are requesting, however, the NMRAs reserve the right to change and/or apply only those categories provided for in their national legislation)	
2.22 Country of origin	
2.23 Current registration status in other countries including East African community (EAC) and the Southern African Development Community (SADC) countries	

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

3.1 Manufacturing and Marketing authorization

3.3 Formulation

Strength (label claim)						
Master Production Document Reference Number and/or Version						
Batch Size (number of dosage units)						
Ingredients (APIs and excipients) starting with APIs	Quality standard	Specifi-cation	Dosage per unit compositi on		Batch quantities	
			mg	%	kg	%

Film coating/Hard capsule						

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

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

3.4 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

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

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

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

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

4.0 DECLARATION BY AN APPLICANT
I, the undersigned certify that all the information in this form and accompanying documentation is correct, complete and true to the best of my knowledge. I further confirm that the information referred to in my application dossier is available for verification during GMP inspection. I also agree that I shall carry out pharmacovigilance to monitor the safety of the product in the market and provide safety update reports to the National Medicines Regulatory Authority of the EAC Partners States. I further agree that I am obliged to follow the requirements of the Partner States Legislations and Regulations, which are applicable to medicinal products. I also consent to the processing of information provided by the EAC Partner States. It is hereby confirmed that fees will be paid/have been paid according to the National/Community rules* Name: ……..…….. Position in the company ……

Signature: ……..……

Date:……...

Official stamp:……...

* Note: If fees have been paid, attach proof of payment