ZAMBIA MEDICINES REGULATORY AUTHORITY

APPLICATION FOR RENEWAL OF MARKETING AUTHORISATION OF MEDICINES REGISTERED BEFORE 2015

Draft Zero	December 2019
Version 1 draft	December 2019
Version 2	
Date of implementation	December 2019

Abbreviations

API	Active Pharmaceutical Ingredient
CTD	Common Technical Document
CRO	Clinical Research Organisation
FPP	Finished Pharmaceutical Product
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
PIL	Patient Information Leaflet
QOS	Quality Overall Summary
SmPC	Summary of Product Characteristics
ZAMRA	Zambia Medicines Regulatory Authority

1. INTRODUCTION

In accordance with the provisions set out in Section 39 of the Medicines and Allied Substances Act (No 3) of 2013 and the Statutory Instrument No. 79 of 2019 (The Medicines and Allied Substances (Marketing Authorisation of Medicines) Regulations, 2019), a Marketing Authorisation Holder (MAH) should submit an application for Renewal of Marketing Authorisation (MA) to the Authority 5 years from the date of grant of MA or when requested to do so by the Authority (whichever date is earlier).

These guidelines are intended to assist MAH to prepare applications for renewal of marketing authorisations which were issued before 2015. The applicants are required to demonstrate conformity of the product to the current standards and norms, and consistency of product quality over the MA validity period.

The Authority will issue an additional guideline for products registered from 1st January 2015 and onwards.

2. Interpretations

In these guidelines, unless the context otherwise requires -

"Active substance" means a biologically or chemically active substance or compound that is used or intended to be used in the manufacture of a product as an active compound (ingredient);

"Applicant" means a person who submits an application for renewal of marketing authorisation; who may be a manufacturer, patent holder or a person responsible for placing the product on the market with Power of Attorney from, or in contract with, the manufacturer or patent holder;

"Authority" means the Zambia Medicines Regulatory Authority;

"Marketing Authorisation" means the authorisation granted under section thirty-nine of the Medicines and Allied Substances Act No. 3 of 2013, for the placement of a medicine or allied substance on the market. Synonymous to product registration;

"**Market Authorisation Holder**" means any person who may either be the trademark owner or authorized person, who has rights to sell the product and is responsible for placing the product on the Zambian market;

SECTION 1: GENERAL REQUIREMENTS

1.1 An application for Renewal of Marketing Authorisation (MA) of a medicine or an allied substance shall be submitted by a Marketing Authorisation Holder (MAH) for quality review 5 years from the date of grant of marketing authorisation or when requested to do so by the Authority.

1.2 The MAH shall submit an application to the Authority before 30th June 2020.

1.3 The application should be sent to the following address:

The Director General
Zambia Medicines Regulatory Authority
P.O. Box 31890
Plot 6903, Tuleteka Road
Off Makishi Road Rhodes Park
Zambia

SECTION 2: HOW TO SUBMIT AN APPLICATION FOR RENEWAL

1.4 Payment of Renewal Fees should be done before the deadline of 31st March 2020.

1.5 A separate application and payment of fees shall be required for each marketing authorisation (MA). Both hard and electronic copies of the application will be required.

1.6 Hard copies of the application should be filed in a spring A4 size file with collapsible edge made of biodegradable material. Data shall be presented on A4 and 80g/m^2 paper with readily readable letters of at least Times New Roman 12 font size. 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.

SECTION 3: TECHNICAL REQUIREMENTS FOR RENEWAL OF MARKETING AUTHORISATION

1.7 The MAH shall submit hard as well as electronic copies (in PDF or WinWord format, on CD-ROM or Flash Drive) of the following documents, where specified:

(i) A covering letter, which should contain a clear statement by the responsible person submitting the quality review, indicating that the information submitted is true and correct;

(ii) A duly completed application form for renewal of MA, in searchable PDF format (as per Annex 1);

(iii) Proof of payment of the prescribed fees;

(iv) Summary of key product information, in Microsoft Word format (as per Annex 2);

(v) Two (2) samples of smallest commercial pack of the product;

(vi) Approved product information i.e. Summary of Product Characteristics (SmPC) and/or Patient Information Leaflet (PIL), in PDF and Microsoft Word format;

(vii) Attestation notifying the Authority that no further amendments have occurred to information provided in the initial application, other than those already submitted to ZAMRA as applications for amendments. A consolidated report of all amendments made to the product should be submitted, in PDF format (as per Annex 3);

(viii) A pharmacovigilance plan and a consolidated report on adverse drug reaction reports, as well as other safety updates, in PDF format; and

(ix) Product quality review report, in PDF format.

SECTION 4: REQUIREMENT FOR LOCAL RESPONSIBLE PERSON FOR FOREIGN-BASED MARKETING AUTHORISATION HOLDERS

1.8 Pursuant to Section 17 of S.I. No. 79 of 2019, all foreign-based MAH are also required to submit copies of letter of appointment of a Local Responsible together with Power of Attorney, stating that the appointee shall be responsible for submitting the application on behalf of the MAH, receive the decision of the Authority on behalf of the MAH and shall implement the pharmacovigilance plan on behalf of the MAH.

SECTION 5: HOW TO MAKE PAYMENTS

1.9 The Renewal of Marketing Authorisation Fees for each may be paid to one of the following account:-

Name of Account holder:	Zambia Medicines Regulatory Authority
Name of Bank:	Standard Chartered Bank, North-End Branch, Cairo Road, Lusaka, Zambia
ZMK Bank Account No.	0100122033800
US Dollar Account No.	8700211468100
Swift Code:	SCBLZMLX

Payment of any applicable bank transfer charges shall be borne by the MAH. The MAH shall ensure that an advice note is sent to the Authority giving details of the payment, in particular the name of the applicant, the products paid for and amount paid.

SECTION 6: PROCESSING OF APPLICATIONS

1.10 The Authority may during assessment of applications request for additional samples, documents, information or clarifications. The application may be rejected, resulting in lapse of MA, if the MAH fails to satisfactorily address the issues within thirty (30) days from the date of request.

1.11 Notwithstanding Section 1.9, the Authority may reject an application for renewal if:

(i) It is found that a product and/or specified manufacturing site no longer complies with the our recommended standards;

(ii) The MAH fails to submit an application for renewal of MA; or

(iii) Any fraud or omissions by the applicant, manufacturer(s) of a finished pharmaceutical

product (FPP) or active pharmaceutical ingredient (API) or clinical research organisation (CROs) in the initial application, becomes evident; and

(iv) The Authority considers that a batch (or batches) of the supplied approved product is (were) not in compliance with the approved specifications.

1.12 Where the Authority refuses to renew the marketing authorisation, it shall notify the MAH in writing of such a decision and the reason(s) thereof.

Annex 1: Application form for Renewal of Marketing Authorisation

FORM I
(Regulations 3 (1) and 14 (5))
(To be completed in triplicate)

The Medicines and Allied Substances Act, 2013
(Act No. 3 of 2013)

The Medicines and Allied Substances
(Marketing Authorisation of Medicines) Regulations, 2019

APPLICATION FOR A MARKETING AUTHORISATION				
Please complete in block letters		Shaded fields for official use only	Application No.	
			Date and Time	
Information required		*Information Provided*		✓
PART 1 **PARTICULARS OF APPLICANT**				
A	**PARTICULARS OF COMPANY**			
1.	(a) Name of business entity			
	(b) Tax Payer Identification Number (where applicable)			
2.	Type of business entity			
3.	Business premises			
	a) Plot No:			
	b) Street:			
	c) Telephone No:			
	d) Fax No:			
	e) Mobile No:			
	f) Email address			
	g) Postal address			
	h) Town			
	i) District			
	j) Province			
	k) Country			
B	**CONTACT PERSON**			
	a) Name			
	b) Designation			
	c) Physical address			
	d) Postal address			
	e) Phone No.			
	f) Fax No.			
	g) Email address			
C	**LOCAL RESPONSIBLE PERSON (Applicable to foreign based applicants)**			
	Name			
	Designation			
	Physical address			
	Postal address			
	Phone No.			
	Fax No.			

	Email address						
PART II PARTICULARS OF THE PRODUCT							
1.	Name of the medicine						
2.	International non-proprietary names of the active pharmaceutical ingredient, including form (salt, hydrate, polymorph) and strength (in case of a herbal medicine, specify the botanical, English or any other name and the quantities of each ingredient)						
3.	ATC code						
4.	Dosage form						
5.	Route of administration						
6.	Name and site address of source of the active raw material (in case of herbal medicine)						
7.	Container, closure and administration system						
8.	Proposed indication (specify target species in case of veterinary medicine)						
9.	Package size						
10.	Shelf life (months)						
11.	Storage conditions/ instructions						
12.	Proposed category of distribution						
13.	Marketing authorisation status in other countries						
	PART III PARTICULARS OF MANUFACTURER						
	Name, address and responsibility (e.g. fabrication, packaging, labelling, testing etc.) of each manufacturer, including contractors and each proposed production site or facility involved in manufacturing and testing of the product:						
1.	Name:						
2.	Physical address (include block(s)/unit(s) if applicable						
3.	Responsibility:						
	If more than one site is involved (e.g. manufacturing of dosage form, primary packaging, release etc.), clearly identify the site for each stage.						
	Include copies of the latest GMP certificate for manufacturer and packers or a copy of the appropriate manufacturing licence						
PART IV COMPOSITION							
	List of all components of the finished pharmaceutical product and their amounts on a per unit, batch and percentage basis including individual components of mixtures prepared in-house (e.g. coatings) and overages, if any						
	Ingredients and quality standard (in case of a herbal medicine, specify the	**Function (reason for inclusion)**	**Strength (Label Claim)**				
			Quantity per unit dosage form (e.g.	**% per unit dosage**	**Quantity per batch**	**% per batch**	

	botanical, English or any other name		**mg/Tablet)**	**form**			
	<complete with appropriate title e.g. core tablet, contents of capsule, powder for injection>						
	Subtotal 1						
	<complete with appropriate title e.g. film-coating>						
	Subtotal 2						
	Total						

PART V
TYPE OF APPLICATION

	Indicate the type of medicine, the type of data included as proof of efficacy, and the review procedure using a check mark (√) or a cross (X)						
	Human Medicine:		NCE		**Data as proof of efficacy:**		
	Chemical		Multisource		Preclinical		
	Biological		Biosimilar		Clinical		
	Veterinary Medicine:				Bio-study		
	Chemical				BCS biowaiver		
	Biological				Bibliography		
	Herbal:						
	Review Procedure:						
	Routine		Abridged		Fast Track (Expedited)		

DECLARATION AND SIGNATURE:

I declare that all the information I have stated in this application is correct and truthful to the best of my knowledge and belief. I understand that submission of false information shall render the application void and that if approval is granted, the market authorisation may be revoked.

Particulars of the Person signing on behalf of the Applicant

…… …….
Name Designation

…… ……
Signature Date

FOR OFFICIAL USE ONLY

Date of Submission: ……...……

Application Number: ……

Payments Receipt Number: ……..……

Application complete (proceed to evaluation): ……

Application incomplete (refer to applicant for additional information): ……

……

OFFICIAL
STAMP

Annex 2: Summary of Key Product Information

ZAMBIA MEDICINES REGULATORY AUTHORITY

Summary of Product Information

1.0 INTRODUCTION

Non-proprietary name(s) of the finished pharmaceutical product(s) (FPP)			
Proprietary name(s) of the finished pharmaceutical product(s) (FPP)			
International non-proprietary name(s) of the active pharmaceutical ingredient(s) (API(s)), including form (salt, hydrate, polymorph)			
Strength, (indicate strengths of each API if more than one)			
Date of Submission <for official use only>			
Date of Evaluation <for official use only>			
Receipt Number <for official use only>			
Application Number <for official use only>			
Dosage form			
Route of administration			
Proposed indication(s)			
Name and address of Holder of Marketing Authorisation			
Name(s) and address(es) of the manufacturer(s) of the drug substance manufacturer(s)			

2. DRUG SUBSTANCE (or ACTIVE PHARMACEUTICAL INGREDIENT (API))

2.1 Name and site address of Manufacturer(s) of the API(s)

2.1.1 Name, address and responsibility (e.g. fabrication, packaging, labelling, testing, storage) of each manufacturer, including contractors and each proposed production site or facility involved in these activities:

Name and address (including block(s)/unit(s))	**Responsibility** (e.g. bulk manufacture, quality testing, release)	**API-PQ number /APIMF/CEP number** (if applicable)	**Letter of access provided?**

2.1.2 Certificates of manufacturing authorisation and Good Manufacturing Practice (GMP)

(Valid copies of manufacturing authorisation and Good Manufacturing Practice (GMP) certificates, for inspections conducted in the last 3 years)

2.2 Control of the API(s)

2.2.1 Quality Specifications of the API(s) from the FPP manufacturer:

(Signed, dated, version controlled and implemented quality specifications)

Standard (e.g. Ph.Int., Ph.Eur., BP, USP, in-house)		
Specification reference number and version		
Test	**Acceptance criteria**	**Analytical procedure** (Type/Source/Version)
Description		
Identification		
Impurities		
Assay		
etc.		

2.2.2 Methods of Analysis of the API(s) from the FPP manufacturer:

(Signed, dated, version controlled and implemented methods of analysis for the API(s))

2.3 Container Closure System of the API

(Technical description of the container closure system(s) for the storage and shipment of the API, including the nature of materials of construction and artworks showing the dimensions of the container)

2.4 Stability of the API

(The recommended storage conditions and re-test period (or shelf-life, as appropriate))

Container closure system	**Storage statement**	**Re-test period***

3. DRUG PRODUCT (or FINISHED PHARMACEUTICAL PRODUCT (FPP))

3.1 Description and Composition of the FPP

3.1.1 Description of the FPP

(Detailed technical description of the finished product)

3.1.2 Composition of the FPP:

(Composition, i.e. list of all components of the FPP and their amounts on a per unit basis and percentage basis (including individual components of mixtures prepared in-house (e.g. coatings) and overages, if any)

Component and quality standard (and grade, if applicable)	**Function**	**Strength (label claim)**					
		Quant. per unit or per mL	**%**	**Quant. per unit or per mL**	**%**	**Quantity per unit or per mL**	**%**
<complete with appropriate titles e.g. Core tablet (Layer 1, Layer 2, etc. as applicable), Contents of capsule, Powder for injection>							
Subtotal 1							
<complete with appropriate title e.g. Film-coating >							
Subtotal 2							
Total							

3.1.3 Composition of all *components purchased as mixtures* (e.g. colorants, coatings, capsule shells, imprinting inks)

(Qualitative and quantitative list of excipients which are purchased as mixtures and used as such in the finished product, including the standards for the individual components).

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

(Detailed description of the diluent co-packaged with the finished product, including its standard).

3.2 *Name and site address of Manufacturer(s) of the FPP*

3.2.1 Name, address and responsibility (e.g. fabrication, packaging, labelling, testing) of each manufacturer, including contractors and each proposed production site or facility involved in manufacturing and testing:

Name and address (include block(s)/unit(s))	**Responsibility** (e.g. bulk manufacture, quality testing, release)

3.2.2 Certificates of manufacturing authorisation and Good Manufacturing Practice (GMP)

(Valid copies of manufacturing authorisation and Good Manufacturing Practice (GMP) certificates, for inspections conducted in the last 3 years)

3.3 *Batch Formula*

(Information on all the approved commercial batch sizes)

Largest commercial batch size:

Other commercial batch sizes:

3.3.1 *List* of all components of the FPP used in the manufacturing process and their amounts on a per batch basis (including components of mixtures prepared in-house (e.g. coatings) and overages, if any):

Strength (label claim)			
Master production document reference number and/or version			
Proposed commercial batch size(s) (e.g. number of dosage units)			
Component and quality standard (and grade, if applicable)	**Quantity per batch (e.g. kg/batch)**	**Quantity per batch (e.g. kg/batch)**	**Quantity per batch (e.g. kg/batch)**
<complete with appropriate titles e.g. Core tablet (Layer 1, Layer 2, etc. as applicable), Contents of capsule, Powder for injection>			
Subtotal 1			
<complete with appropriate title e.g. Film-coating >			
Subtotal 2			
Total			

3.4 *Description of Manufacturing Process and Process Controls*

3.4.1 Flow diagram of the manufacturing process

3.4.2 *Controls of Critical Steps and Intermediates*

(Summary of controls performed at the critical steps of the manufacturing process and on isolated intermediates)

Step (e.g. granulation, compression, coating)	**Controls (parameters/limits/frequency of testing)**

(Discussion of validated holding periods for intermediates (including bulk product))

3.4.3 *Process Validation and/or Evaluation*

(Summary of the process validation and/or evaluation studies conducted and/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))

(Document code(s) for the process validation protocol(s) and/or report(s) (including reference number/version/date))

3.5 Control of the FPP

3.5.1 Quality Specification(s) for the FPP

(Signed, dated, version controlled and implemented quality specifications)

Standard (e.g. Ph.Int., BP, USP, in-house)			
Specification reference number and version			
Test	**Acceptance criteria (release)**	**Acceptance criteria (shelf-life)**	**Analytical procedure (type/source/version)**
Description			
Identification			
Impurities			
Assay			
etc.			

3.5.2 Methods of Analysis of the FPP

(Signed, dated, version controlled and implemented methods of analysis for the FPP)

3.6 Container Closure System

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

Description (including materials of construction)	**Strength**	**Unit count or fill size** (e.g. 60s, 100s etc.)	**Container size** (e.g. 5 ml, 100 ml etc.)

3.7 Stability of the FPP

(The recommended storage conditions and shelf-life, as appropriate))

Container closure system	**Storage statement**	**Shelf-life**

3.7.1 *Post-approval on-going stability data*

(Summary of post-approval on-going stability data and discussions)

Parameter	**Details**	
Storage condition(s) (◦C, % RH)		
Batch number(s) / batch size(s)	*<primary batches>*	
Tests and acceptance criteria	Description	
	Moisture	

Parameter	Details	
	Impurities	
	Assay	
	etc.	
Testing frequency		
Container closure system(s)		

Annex 3: <u>Consolidated report of all amendments to the product from initial approval</u>

The MAH shall submit a summary, in tabular format, of any minor and/or major changes (including those pending) to the initially registered product as per format given below:

Description	**Date of Submission to ZAMRA**	**Date of Approval/ Rejection**	**Date of Implementation**
Major Amendments			
<list of all amendments>			
Minor Amendments			
<list of all amendments>			

(NOTE: For all approved amendments, copies of letters of approval should be attached)