RWANDA FDA
Rwanda Food and Drugs Authority

# GUIDELINES FOR RENEWAL OF PHARMACEUTICAL PRODUCTS MARKETING AUTHORIZATION

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**FOREWORD**

Rwanda Food and Drugs Authority is a regulatory body established by the Law N° 003/2018 of 09/02/2018. One of the functions of Rwanda FDA is to regulate matters related to quality, safety, and efficacy of medical products to protect public health and improve access to medical products in Rwanda.
Considering the provisions of the technical regulations governing the registration of human medicinal products, the Authority has to issue this Guidelines for Renewal of Pharmaceutical Products Marketing Authorization.

Keep in mind that during the lifecycle of a medical product, there are current and emerging technical requirements which need to be met at all times. Therefore, it had been considered necessary to develop these guidelines to address existing gaps in terms of technical requirements during the approval of applications for renewal.

Applicants are requested to adhere to these guidelines by providing all relevant information for the renewal of registration of pharmaceutical products. This will prevent queries that result in unnecessary delays and facilitate an efficient and effective evaluation and approval process.

The Authority acknowledges all the efforts and contributions from our stakeholders that participated in the development and validation of these guidelines.

**Prof. Emile BIENVENU**
**Director General**

Digitally signed by Rwanda FDA (Director General)
Date: 2024.08.15 18:56:13 +02'00'

## DOCUMENT DEVELOPMENT HISTORY

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## DOCUMENT REVISION HISTORY

| Version number | Changes made and/or reasons for revision |
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| 1 | First Issue |
| 2 | 1. Adoption of the new template for guidelines<br>2. Adoption of the new document number format<br>3. Change of mode of application submission by considering the IRIMS<br>4. Change of the document title to make it clear and concise<br>5. Editorial changes |

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## ACRONYMS AND ABBREVIATIONS

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|---|---|
| **FPPs** | Final Pharmaceutical Products |
| **GMP** | Good Manufacturing Practice |
| **MA** | Marketing Authorisation |
| **MAA** | Marketing Authorisation Application |
| **MAH** | Marketing Authorisation Holder |
| **PIL** | Package Information Leaflet |
| **Rwanda FDA** | Rwanda Food and Drugs Authority |
| **SmPC** | Summary of Product Characteristics |

## GLOSSARY / DEFINITIONS

The definitions provided below apply to the words and phrases used in these guidelines. The following definitions are provided to facilitate the interpretation of these guidelines. Other terminologies can be found in the Rwanda FDA Glossary of terms

**Active pharmaceutical ingredient (API)** means any component that provides pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or animals.

**Applicant** means a person who applies for registration of a human pharmaceutical product to Rwanda FDA, who must be the owner of the product. He may be a manufacturer or a person to whose order and specifications, the product is manufactured. After the product is registered, the applicant shall be the Marketing Authorisation Holder.

**Authority** refers to the Rwanda Food and Drugs Authority, or its acronym "Rwanda FDA" established under Article 2 of Law Nº 003/2018 of 09/02/2018

**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 medical 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 of such as a carton.

**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 a medicine that is developed to be the same as a medicine that has already been authorised. Its authorisation is based on efficacy and safety data from studies on the authorised medicine

**Label** means any tag, brand, mark, pictorial or other descriptive matter, written, printed, stencilled, marked, embossed or impressed on or attached to a container of any medical product.

**Marketing authorization (product license, registration certificate)** is a legal document issued by the competent authority for the purposes of marketing or free distribution of a product which has been approved after evaluation for safety, efficacy and quality.

**Manufacturer** means a person or a firm that is engaged in the manufacture of pharmaceutical products. It involves operations such as production, packaging, repackaging, labelling and relabelling of pharmaceuticals.

**Manufacturing site** means the location where the manufacturing process of a pharmaceutical products is undertaken.

**Manufacture** means all operations that involve preparation, processing, filling transforming, packaging, and repackaging and labelling of pharmaceutical products.

**Master formula** A document or set of documents specifying the starting materials with their quantities and the packaging materials, together with a description of the procedures and precautions required to produce a specified quantity of a finished product as well as the processing instructions, including the in-process controls.

**Mock-up** is a copy of the flat artwork design in full colour, providing a replica of both the outer and immediate packaging, providing a two-dimensional presentation of the packaging/ labelling of the medicine. It is also referred to as a paper copy or computer-generated version**.**

**On-going stability study** is the study carried out by the manufacturer on production batches according to a predetermined schedule in order to monitor, confirm and extend the projected retest period (or shelf-life) of the API, or confirm or extend the shelf-life of the FPP.

**Pharmaceutical product** is any substance capable of preventing, treating human or animal diseases and any other substance intended for administration to a human being or an animal in order to diagnose diseases, restore, correct or carry out modification of organic or mental functions. It also means products used in disinfecting premises in which food and drugs are manufactured, prepared or stored, cleaning hospitals, equipment and farm houses.

**Release specifications** 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.

**Specifications** is defined as a list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges, or other criteria for the tests described. It establishes the set of criteria to which a new drug substance or new drug product should conform to be considered acceptable for its intended use.

**Shelf life specifications** 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.

**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.

## INTRODUCTION

Rwanda Food and Drugs Authority (Rwanda FDA) is established by the Law N° 003/2018 of 09/02/2018, especially in its article 8 and 9;
Considering the provisions of the technical regulations governing the registration of human medicinal products, the Authority has issued *Guidelines for Renewal of Pharmaceutical Products Marketing Authorization.*

These guidelines provide guidance to applicants on the format and content of minimum documents and information required for renewal of registration of pharmaceutical products. It also guides the Authority in managing applications for Renewal of Pharmaceutical Products Marketing Authorization.

Applicants and users are encouraged to familiarize with the guidelines when preparing and submitting/reviewing applications for Renewal of Registered Human and Veterinary Medicinal Products.

Renewal of registration is required as specified in the regulation to ensure all changes made with respect to the manufacture and quality control of Human and Veterinary Pharmaceutical Products are updated, reported, and evaluated to ensure safety and quality. Changes include variations, both those notified and those not notified to Rwanda FDA.

These guidelines provide requirements to be fulfilled by applicants, including specific documents to be submitted for evaluation prior to renewal of Pharmaceutical Products registration.
Applicants are required to read carefully these guidelines together with relevant regulations and guidelines for registration along with other references provided in this document.
It should be noted that the Authority has the right to request any further information or documents, with a commitment that such requests are justifiable, and will be for the purpose of ensuring the quality, safety, and efficacy of the submitted product.

## SCOPE

These guidelines shall apply to applications for Registered Human and Veterinary Pharmaceutical Products, submitted to the Authority for renewal of registration.

## SUBMISSION REQUIREMENTS AND ASSESSMENT

### 1. Mode of submission

An application for renew of product registration for either locally manufactured or imported, shall be made in writing via a cover letter and application form dated and signed by the applicant addressed to the following address:

An application for renew of product registration being either locally manufactured or imported, shall be made through Rwanda FDA Online Portal
If the applicant is a foreign company, he/she shall appoint a local technical representative.

A reference number is automatically assigned to the application and it will be used in all subsequent correspondences relating to the application. An acknowledgement receipt will be automatically issued by the system. Product samples should be submitted to Rwanda FDA Head Office. The samples should be accompanied with a printed notification email clearly stating the application reference number generated from the portal at the time of submission.

### 2. General Requirements

2.1. In accordance with laws and regulations in place, marketing authorisation holders should apply for renewal of registration to the Authority at least ninety (90) calendar days before its expiry. The Authority foresees a grace period for renewal of ninety (90) days after the specified expiry date. Failure to renew the marketing authorization within the grace period, the application shall be considered as new.

2.2. It is the responsibility of the MAH to apply for renewal of the registration of the pharmaceutical product.

2.3. The application should be submitted in **English, French or Kinyarwanda**. Any document which is in any language other than English, French, or Kinyarwanda must be accompanied by **a certified or notarized translation**.

2.4. Data should be presented in a readable format, font size 12, style Times New Roman. Every page shall be numbered sequentially (x of y). Extension sheets, tables, diagrams, and other supporting documents shall, where possible, be of the same size, clear, well-annotated, numbered, and appropriately cross-referenced.

2.5. Proof of payment of the non-refundable renewal fee at the time of submission should be submitted with the application for renewal. Applicable fees are defined in the regulation related to regulations governing tariff/fees and charges on services rendered by Rwanda Food and Drugs Authority. Any application not accompanied by the relevant proof of payment will not be considered. Note that the Authority reserves the right to determine the correct interpretation of the fee payable based on the published schedule.

2.6. Evidence of compliance of the pharmaceutical product manufacturing facility with current Good Manufacturing Practices (GMP) requirements as prescribed in Rwanda FDA GMP guidelines should be provided. If a valid Rwanda FDA GMP certificate is not available a proof of GMP inspection application to Rwanda FDA should be submitted.

2.7. The MAH should provide a list of all countries where the product has been reviewed and approved over the registration period of the product, the registration numbers, and copies of registration certificates, if available.

2.8. At renewal, the Authority will perform a new check of the samples across all marketed product presentations. Two (2) commercial samples with batch certificates of analysis should be provided to the Authority as part of the renewal application, for each strength, dosage form, and container type in the smallest marketed pack size. In case the MAH plans to change the overall design and readability of the labelling and/or package leaflet at the time of renewal, submission of specimens of the previous product design will not be necessary.

2.9. All information on the safety, quality, and efficacy of the product (where applicable).

## 3. Technical Documentation Requirements

All applications for renewal of pharmaceutical products marketing authorization 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 the 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 colorants, coating agents in a manner provided for in section 3.2.P.1 of the main registration guidelines for human 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 guidelines for human pharmaceutical products and 3.2.P.7 of the main Guidelines for Registration of Veterinary Medicinal 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 IVA, 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 guidelines for registration of pharmaceutical products and specific guidelines on Stability Testing Requirements for Active Pharmaceutical Ingredients (APIs) and Finished Pharmaceutical Products;

3.2.7. List of all variations submitted to and accepted by the Authority 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** |
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### 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 the Guidelines for Registration of Human Pharmaceutical Products and Registration Guidelines for Veterinary Medicinal Products.

3.3.2. All prescription medicines should be accompanied by SmPC. Refer to Guidelines on Format and Content of Summary of Product Characteristics for Human Pharmaceutical Products.

3.3.3. All pharmaceutical products with exception of medicines for hospital use only must contain a patient information leaflet as prescribed in the Guidance on Format and Content of Patient Information Leaflets for Pharmaceutical Products

3.3.4. Submission of periodic post-marketing surveillance and safety studies

**3.4.Evaluation Process**

3.4.1. After receiving the product renewal application, the application will be scheduled for evaluation according to the first-in-first-out (FIFO) rules. Priority assessment may be granted where the product is intended for treatment of rare disease conditions or in the case of emergency situations.

3.4.2. A product dossier is assessed by two assessors to provide scientific and regulatory oversight regarding the quality, safety, and efficacy of the product under assessment.

3.4.3. During the evaluation, additional data and/or samples may be requested through an official communication letter. Once a query has been issued to the applicant, the assessment process stops until the Authority receives a written response to the raised queries. Further processing of the application may only be undertaken if responses to queries issued in the official communication letter contain all outstanding information requested in one submission. Failure to comply with this condition, or if the queries have been reissued for a **second** time and the applicant provides unsatisfactory responses, will result in the MA suspension.

3.4.4. In the event that the responses to the queries are not submitted within **thirty (30) calendar days** from the date they were issued, the application will be considered withdrawn unless the applicant has requested for an extension of the deadline from the Authority. Thereafter, renewal for registration of the product may only be considered upon new submission of renewal application.

3.4.5. A final dossier assessment report shall be presented to Peer Review Committee (PRC) before making a final decision for granting or rejecting the renewal of the registered product. The renewal processes should be completed in maximum period of **Ninety (90) days from the application date.**

3.4.6. The assessment will consist of a benefit-risk balance re-evaluation, on the basis of a consolidated version of the file in respect of quality, safety, and efficacy, including evaluation of data contained in suspected adverse reactions reports, the Periodic Safety Update Report (PSUR) data, and any relevant new information affecting the benefit-risk

balance for the product. A full re-evaluation of the whole dossier normally should not take place. Serious public health concerns should be addressed as part of the renewal process, and the product will not be renewed if serious public health issues remain at the end of the procedure, or if an existing suspension on the marketing authorisation cannot be lifted.

3.4.7. Inspection status, particularly regarding the pharmacovigilance system, as well as GMP compliance status of the manufacturer(s), and the potential impact of the findings on the benefit-risk balance of the medicinal product, will be reviewed during the assessment of the renewal application.

3.4.8. At the time of renewal, compliance by the MAH with the conditions imposed on the medicinal product will be evaluated. As a result, these conditions may be modified and/or new conditions may be imposed.

3.4.9. Review of whether the marketing authorisation holder complies or not, with their obligation to maintain up-to-date product information.

3.4.10. Where there are adequate and objective reasons not to renew the marketing authorisation in its existing terms, and changes are necessary to the SmPC, labelling, and/or PIL arising from the renewal evaluation, the marketing authorisation holder may submit additional information and/or change the product information as part of the renewal process to address the concerns raised. Such changes will not require a separate variation procedure.

3.4.11. Other issues arising from assessment and changes due to the revision of the SmPC guidelines, and/or other relevant guidelines impacting on the product information should be considered within the renewal process. Proposed changes to the SmPC, labelling, and PIL must be indicated on the renewal application form.

3.4.12. None of the changes introduced at renewal can substitute for the marketing authorisation holder's obligation to update the marketing authorisation throughout the life of the product by variation application as data emerge, provided that the implemented changes fall within the scope of application of the Authority regulations governing registration of medicinal products, concerning the application for variation of a registered medical product.

3.4.13. Major changes to the product, such as the introduction of new indications, and quality changes, such as an extension of shelf life, shall not be modified through the renewal procedure and must be assessed through the appropriate variation procedure.

3.4.14. Accordingly, no new studies should be submitted within the renewal unless this impact the benefit-risk balance of the medicinal product. However, any new data should be discussed in the addendum to the relevant overview.

**ENDORSEMENT OF THE GUIDELINES**

| | **Prepared by** | **Checked by** | | **Approved by** |
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