South African Health Products
Regulatory Authority
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Renewal of Human and Veterinary Medicines Requirements and Process

This document is intended to provide guidance on implementation of renewals for medicine registration. This will be a "living document" and will be updated as required.

Document History

Final Version	Reason for Amendment	Effective Date
1	New	22 June 2022
2		

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Contents

Glossary

Abbreviation/ Term	Meaning
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 South African Health Products Regulatory Authority or its acronym "SAHPRA".
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	Medicine a) Means any substance or mixture of substances used or purporting to be suitable for use or manufactured or sold for use in: i) the diagnosis, treatment, mitigation, modification or prevention of disease, abnormal physical or mental state or the symptoms thereof in humans; or ii) restoring, correcting or modifying any somatic or psychic or organic function in humans; and iii) includes any veterinary medicine
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	Means an official authorization or registration of a product by SAHPRA for the purpose of marketing or free distribution in South Africa after evaluation for safety, efficacy and quality.
Variation	Means a change to any aspect of a medicinal product, including but not limited to a change to formulation, method and site of manufacture, specifications for the finished product and ingredients, container closure type or specifications and container labeling, indications and product information.

1. INTRODUCTION

The registration of medicines in South Africa is governed by the provisions and requirements of the Medicines and Related Substances Act, 1965 (Act 101 of 1965), (hereinafter "the Act"), as amended, and its subordinate Regulations and Guidelines. The South African Health Products Regulatory Authority ("SAHPRA" or "the Authority") is a statutory body established in terms of the Act to provide for the monitoring, evaluation, regulation, investigation, inspection, registration and control of medicines, Scheduled substances, clinical trials and medical devices, IVDs for human and animal use and related matters in the public interest.

It is acknowledged that in the course of five (5) years, several aspects of the registered medicinal product may change significantly as a result of notified variations. These collective changes may significantly impact on the quality, safety and efficacy of the product and therefore, the objective of renewal of registration is to ensure that the product continues to be safe, effective and of good quality for ongoing public use.
There are benefit risk assessments performed throughout product life cycle, reviews of annual reports of registered medicines.

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

This guideline is divided into three major parts stipulating the general requirements and application procedures for human and veterinary medicinal products; processing of applications; and technical requirements for application for renewal of medicinal products.

Applicants are requested to carefully read these guidelines, fill in Renewal application form, and submit the relevant sections of the dossier in the SAHPRA online application portal which will be introduced during July 2022 The application form, eCTD folder and related attachments will be submitted via the online portal.

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 SAHPRA will not accept outdated methods and techniques in the interest of patient safety and well-being. Furthermore, the Authority 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 current scientific information and technology to develop and test their products.

Applicants are also requested to read these guidelines together with the Medicines and Related Substances Act, 1965 (Act 101 of 1965) as amended, and other relevant Regulations made there under.

1.1 PURPOSE

To provide guidance on implementation of renewals for medicine registration or marketing authorisation.

1.2 SCOPE

These guidelines are relevant for application for renewal of registration or marketing authorization of both human and veterinary medicinal products.

2. LEGAL PROVISION

The legal provision for implementation of renewals is covered in the Medicines and Related Substance Act No. 101 of 1965, as amended. Section 2B(1) (c) provides for the periodic re-evaluation or re-assessment and monitoring of medicines, medical devices and IVDs. Section 15(6)(a)(b) provides for the Registration of medicines, medical devices or IVDs. It further states that any registration under this section may be made subject to such conditions as may be determined by the Authority; and shall in the case of medicines, be valid for a period of five years. Section 2B(c) provides for the periodic re-evaluation or re-assessment and monitoring of medicines, medical devices and IVDs.

3. POST RENEWAL VARIATION TO MEDICINAL PRODUCTS

All variations to a registered pharmaceutical product shall be made according to requirements stipulated in the Variations Addendum and relevant Variation guidelines. This process will not be interrupted.

No variations will be accepted as part the renewal of registration as this will impact the processing and swift turn-around of renewals. The dedicated workstream will only review the renewal applications.

4. REQUIREMENTS FOR RENEWAL APPLICATIONS

4.1 GENERAL REQUIREMENTS AND APPLICATION PROCEDURES

Applications should be made to the Authority at least six (6) months before expiry of validity of registration of a particular medicinal product. The current certificates do not contain an expiry date and therefor the due date for submissions will be initially communicated by means of an applicant specific renewal schedule. Changes to the current registration certificate in Q3 of 2022 will introduce an expiry date to facilitate tracking on the applicant's side, moving forward.

Please make note of the following:

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

2. The responsibility of applying for renewal of product registration remains with the company responsible for the introduction of the product into the South African market, i.e., Holder of Certificate of Registration

3. Applications must be duly completed and supported by all of the required documents as stipulated in these guidelines and where appropriate in line with the current edition of the General Information guideline.

4. The application should be submitted online along with a non-refundable product renewal fees as stipulated in the Fees gazette and the General Information guideline. The renewal fees will be published for public comments and submitted for gazetting in Q4 2022. The evidence of payment of the fees must be presented at the time of submission of the application.

5. After receipt of the full and complete application that meets the criteria and payment of the fees, the status of the application will be changed from “active” to “renewal in progress”. This will allow the applicant to continue to supply the market with the product whilst the renewal is being completed. Failure to submit the application and completing payment will result in the status of the product being changed from “active” to “expired” upon expiry date.

NB: **Incomplete and incorrect applications cannot be processed, and the admin** status cannot be changed to “renewal in progress”. This potentially may affect supply. Kindly ensure that submissions are correct.

4.2 PROCESSING OF APPLICATIONS (MANAGEMENT OF APPLICATIONS

The following stages are involved for renewal applications from the time of application submission to the outcome:

1. Upon receipt of an application, an application number will be auto generated for the applicants noting and reference.

2. Evaluation of the application shall be carried out within the timelines stipulated and the respective outcomes will be communicated to the applicant(s);

3. During evaluation, the Authority may request for further information and additional supporting documents from the applicant in line with the guideline requirements. Required information should be made available within thirty (30) days from the date of the request so as to facilitate timely renewal of the applied product;

4. Notification for renewal of registration of the product shall be communicated followed by an issuance of new registration certificate. Applicants should carefully read the conditions under which the medicine is registered – attached to the certificate - and adhere to them throughout the product lifecycle.

4.3 TECHNICAL REQUIREMENTS FOR APPLICATION FOR RENEWAL OF MEDICINAL PRODUCTS

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

MODULE 1: ADMINISTRATIVE & PRESCRIBING INFORMATION

Section	Requirement
1.0	Letter of Application for Renewal
	Notarised Declaration:
	A notarised declaration by the HCR regarding the correctness, completeness and accuracy of all the documents submitted during the renewal procedure.
1.2.1	Application Form, inclusive of *Amendment History* :
	Tabular summary of the types of variations notified to, approved by and still pending with SAHPRA for the product during the preceding 5 years, together with the respective dates of approval, if applicable.
	NB: For clinical, a tabular summary will only be required for pending variations.
1.2.2.1	Proof of Payment
1.3	**ZA Labelling and Packaging Labelling:**
	The Professional Information (PI)/Patient Information Leaflet (PIL) approved 5 years prior and the current SAHPRA-approved PI/PIL(the latter if applicable), indicating labelling amendments made in the preceding 5 years by means of underlining, as well as coloured mock-up packaging labels of the product.
1.5.2.2	Copy of Current Registration Certificate(s) for Product(s)
1.7.3	**Good Manufacturing Practice (GMP):**
	1. Certificates of GMP of the Active Pharmaceutical Ingredient(s) manufacturing facilities, issued by Recognised Regulatory Authorities (RRAs);
	2. Certificates of GMP of the Final Pharmaceutical Product(s) manufacturing facilities**, issued by Recognised Regulatory Authorities (RRAs).
	** Includes all sites involved in the testing, manufacturing and packaging of the FPP
1.7.6	**Certificate of Pharmaceutical Product (CoPP – WHO Format):**
	Issued by the relevant Health/Regulatory body in the country of manufacture of the product.
1.7.7.	**Licensing of South African Holder of Certificate of Registration (HCR):**
	1. Premises License, as issued by the National Department of Health;
	2. Registration of Pharmacy and Responsible Pharmacist with the South African Pharmacy Council (SAPC).
	3. Section 22C(1)(b) License issued by SAHPRA

Note: CoPP as referenced in section 1.7.6 does not apply to products manufactured in South Africa

1. **For Products first registered from the year 2018 onwards, where an CTD or eCTD has already been submitted – in addition to the above, the following will be required:**

SECTION A

ANNUAL PRODUCT QUALITY REVIEW (PQR):

A Product Quality Review should be submitted with the objective of verifying the consistency of the quality of the FPP and its manufacturing process, applying the current format.

Rejected batches should not be included in the analysis but must be reported separately together with the reports of failure investigations, as indicated below.

Reviews should be conducted with no fewer than 10 consecutive batches manufactured over the period of the past 12 months or, where 10 batches were not manufactured in the past 12 months, no fewer than 25 consecutive batches manufactured over the period of the past 36 months* and should include at least:

1. A review of starting and primary packaging materials used in the FPP, especially those from new sources;
2. A review critical in-process controls and finished product results;
3. A review of all batches that failed to meet established specification(s) and their investigations;
4. A review of all significant deviations or non-conformances and related investigations;
5. A review of all changes carried out to the processes or analytical methods;
6. A review of the results of the stability-monitoring programme;
7. A review of all quality-related returns, complaints and recalls, including export-only medicinal products;
8. A review of the adequacy of previous corrective actions;
9. A list of validated analytical and manufacturing procedures and their revalidation dates;
10. A declaration that the risk assessment for applications registered without nitrosamine risk assessment has been done and the necessary updates have been submitted
11. A summary report of Post-Marketing Surveillance activities in the preceding 5 years;

* **Batches manufactured at a lower scale than that stated above will be handled on a case-by-case**

basis and more extensive documentation may be required in such cases.

SECTION B

A risk-benefit assessment report of the preceding 5 years

The report should consist of the following sections:

1. A summary report of all adverse drug reactions observed in the preceding 5 years and actions taken;
2. A summary review of Periodic Risk-Benefit Evaluation Reports (PBRERs) in the preceding 5 years;
3. Risk-benefit conclusions by the Holder of the Certificate of Registration;

Further Notes:

1. Reviews must include data from all batches manufactured during the review.
2. Data should be presented in tabular or graphical form, where applicable.
3. PQRs should not be summaries without data.

SECTION C

1. Completed QOS and QIS must be submitted. The SAHPRA templates will be used.
2. A declaration that data related to any commitments/compliance with conditions which the product was registered under, must be submitted.

2. **For Old Medicines and Products registered in the year 2017 and dating further back – an full eCTD baseline submission in line with the General Guidelines for registration will be required – the schedule of these products will be shared applicant by applicant as a roadmap has been devised for each applicant based on the number of active product registrations they have to allow adequate time for these baseline submissions to be prepared and submitted as per each applicant's schedule – which will be shared individually.**

5. REFERENCES

N/A

6. VALIDITY

This guideline is valid for a period of 5 years from the effective date of revision. It will be reviewed on this timeframe or as and when required.