South African Health Products
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RENEWAL OF REGISTRATION OF HUMAN AND VETERINARY MEDICINES

This document is intended to provide guidance on the renewal of registration of human and veterinary medicines.

Document History

Final Version	Reason for Amendment	Effective Date
1	New	22 June 2022
2	Extensive amendments in line with stakeholder comments after implementation pilot study	31 May 2023
3	Amended in line with the updated document number for eCTD validation and technical screening for renewals Edited section 4.1 point 6 to clarify that if no formal notification nor renewal is received, the medicines register will be changed to "Cancelled"	06 July 2023
4	Amended in line with stakeholder comments Edited 4.1 point 5 to include further information on the submission process Edited 4.1 point 10 to now point 11 to provide clarity on Clones/replicas of a parent application, as well as different strengths Edited 4.3 • Module 1, PQR and Pharmacovigilance requirements	22 August 2023

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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"
BMCT(s)	Border Medicines Control Technicians These are SAHPRA-employed medicines control officials stationed at the ports of entry for medicines
Clone	Is defined as an application submitted by the Innovator as a copy of its own product under a different proprietary name at any stage during the product life cycle (of the registered product)
CPP	Certificate of Pharmaceutical Product (WHO Certification Scheme)
Drug Master File	A drug master file (DMF) is a master file that provides a full set of data on an API
DVP	Digital Variations Portal
eCTD	Electronic Common Technical Document It is the standard dossier format for submitting applications and variations to the majority of global medicines regulators, including SAHPRA
Finished Pharmaceutical Product (FPP)	Means a product that has undergone all stages of production, including packaging in its final container and labeling
FTP	File Transfer Protocol
GMP	Good Manufacturing Practice
HCR	The Holder of the Certificate of Registration
HPA	Health Products Authorisation
IVD	*In-Vitro* Diagnostics
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 includes any veterinary medicine
PBRER	Periodic Benefit-Risk Evaluation Report

Abbreviation/ Term	Meaning
Pharmacopoeia	Means a current edition of the British Pharmacopoeia, European Pharmacopoeia, United States Pharmacopoeia, International Pharmacopoeia and Japanese Pharmacopoeia
PI	Professional Information
PIC/S	Pharmaceutical Inspection Convention & Pharmaceutical Inspection Co-operation Scheme
PIL	Patient Information Leaflet
PQR	Product Quality Review
PSUR	Periodic Safety Update Report
QIS	Quality Information Summary
QOS	Quality Overall Summary
Registration of a medicine	Means the registration of a product by SAHPRA for the purpose of selling in South Africa after evaluation for safety, efficacy and quality, and whereby the product is included in the register referred to in Section 13 of the Medicines and Related Substances Act (Act 101 of 1965, as amended)
Replica	Is defined as a copy of an already registered generic product, submitted by the same or by another applicant at any stage during the product life cycle (of the registered product).
RRAs	Recognised Regulatory Authorities A term used to refer to the regulatory authorities with which SAHPRA aligns itself
SAHPRA	The South African Health Products Regulatory Authority
SAPC	The South African Pharmacy Council
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
WHO	The World Health Organization

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, In-Vitro Diagnostics (IVDs) for human and animal use and related matters in the public interest.

It is acknowledged that during 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, including reviews of annual reports of registered medicines.

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

The guideline presents SAHPRA's 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 this guideline. It is worth noting that conditions of registration specify that current GMP is to be maintained, which includes the expectation for the latest technological and scientific methods to be used in the manufacture and control of products. SAHPRA will, at the time of a renewal of a registration, expect variations to have been submitted separately for evaluation, to ensure that the dossier is in line with current GMP, as well as with the latest international scientific requirements. Applicants are also requested to read this guideline together with the Medicines and Related Substances Act (Act 101 of 1965), as amended, and other relevant Regulations made thereunder.

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 and submit the renewal application via the FTP system.

The following file name convention to be used for the renewal submissions:

Application number-REN-Sequence number

Example:

(i) When converting to eCTD the following naming convention should be used:

540000-REN-0000 (for the baseline) and 540000-REN-0001 (for the renewal information)

(ii) When the renewal application is submitted as a follow-up sequence, the following naming convention should be used:

540000-REN-00XX where XX is the relevant follow-up sequence number

1.1 Purpose

To provide guidance on the submission of renewals for medicine registrations.

1.2 Scope

This guideline is relevant to applications for renewal of registration of both human and veterinary medicinal products. This guideline does not extend to medical devices, IVDs and complementary medicines as SAHPRA does not currently register these types of products.

2. LEGAL PROVISION

The legal provision for implementation of a renewal procedure 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.

3. POST-REGISTRATION 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 Renewals workstream will only review renewal applications.

For applications that have a renewal query that warrants variation, the applicant shall submit the variation to relevant post-registration unit and share the proof of submission with HPA for the renewal to be finalised. Proof of submission should be sent to the dedicated renewals email address: renewals@sahpra.org.za.

4. REQUIREMENTS AND PROCEDURE FOR RENEWAL APPLICATIONS

4.1 GENERAL REQUIREMENTS

For Old Medicines and products registered in the year 2017 and dating further back, a full eCTD baseline submission, in line with the General Information guideline for registration should be submitted (only if the dossier has not yet been converted to eCTD). 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.

Renewal applications should be made to the Authority at least six (6) months before expiry of validity of registration of a particular medicinal product. Registration certificates issued from the 1st of October 2022

contain an expiry date; however, older products' registration certificates do not, and in these cases renewal dates will be via the applicant-specific renewal schedule.

Please take note of the following:

1. A screening checklist, with specific reference to renewal applications, to be completed by applicants and included in Module 1.8 (eCTD Validation and Technical Screening for Renewals: GLF-HPA-04A) .

2. All applications and supporting documents shall be in English. Any submitted documents which are in a language other than English must be accompanied by an English translation.

3. 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., the Holder of Certificate of Registration (HCR), or the new HCR if there was a transfer of the registration certificate since the initial registration or last renewal of registration. SAHPRA will only liaise with the current HCR listed for the product and not with any proposed HCRs, as a result of a pending transfer of registration certificate. No transfer of registration certificate may be submitted while a renewal application is still being reviewed. When applications are transferred to a new HCR, it remains the previous HCR's responsibility to inform the new HCR of the renewal due date, as per the renewal roadmap. The roadmap will not be amended by SAHPRA to reflect transfers of applicancy.

4. Applications must be duly completed and supported by all the required documents, as stipulated in this guideline and supplementary documents, and where appropriate in line with the current edition of the General Information guideline.

5. The application should be submitted online via the SAHPRA FTP in line with the General Information guideline. The application should be logged on the SAHPRA service desk (https://service.sahpra.org.za) and proof of submission should be uploaded onto the service desk. More information on how to use the service desk is available on the SAHPRA website under the menu tab about us > digital transformation

6. Renewal fees will be invoiced and payable at the end of the renewal process, at the point of renewal outcome decision.

7. Applicants not wishing to renew their registrations, should cancel these formally, in writing, six (6) months before the application is due for renewal, either according to the submission date in the Renewals Roadmap (for older products) or the expiry date on the registration certificate (for newer products). This notification is to be sent to both cancellations@sahpra.org.za **and** renewals@sahpra.org.za. Upon receipt by SAHPRA of the applicant's official cancellation notification, the registration status of the affected product will change from "Registered" to "Cancelled" on the medicines register (https://medapps.sahpra.org.za). If the applicant has not formally cancelled the application nor has they submitted the renewal of the application, it is of the opinion of the authority that the holder of the registration certificate has failed to comply with the condition to which medicine was registered. The applicant will be informed via the medicines register as the status will be changed to "Cancelled" if no renewal application is received.

8. Should an applicant opt not to renew a product registration, while still having product in the market after expiry thereof due to a lengthier shelf-life, SAHPRA will issue a temporary registration renewal certificate for this product, valid for one (1) year (product status will be reflected as "Registered" on the register during this time). The applicant will be allowed to continue sale of the current batches in the

market for one (1) further year, after which the product status will change to "Expired". However, the applicant would be required to submit a declaration to the Renewals Team detailing the batch number(s) of product still in the market and the remaining shelf-lives of these batches. No further batches of the expired product will be allowed to be sold in the South African market, only those indicated in the declaration.

9. Upon receipt of the complete renewal application that meets all criteria, and the proof of fee payment, the status of the product on the medicines register will be changed from "Registered" 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 associated payment by the due date (i.e., the submission date indicated in the Renewals Roadmap (for older products) or six (6) months prior to the expiry date of the product as reflected on the registration certificate (for newer products), whichever is applicable, will result in the status of the product being changed from "Registered" to "Expired" upon expiry date.

10. Should the product expire while still under renewal, as a result of delays by SAHPRA, the regulator will issue a temporary registration renewal certificate with a one (1) year validity. This document will prevent disruptions in patients' access to medicines occurring at Port of Entry due to expired registration certificates. SAHPRA's border medicines control technicians (BMCTs) will accept the temporary registration renewal certificate. This certificate will also enable submission of pricing applications and tenders during this period. The status of the affected product on the register will be "Renewal in progress".

11. Clones/replicas of a parent application, as well as different strengths (of same product range) registered at different times, could be submitted at the same time for renewal as one renewal application provided the relevant strengths and clones/replicas are due for renewal, i.e., registered in 2018 and before. This will be done on case-by-case bases and should be done at the time the first application is due for renewal.

4.2 PROCESSING OF APPLICATIONS

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

1. Upon receipt of an application, a reference number will be auto-generated via the Quantum system for applicants' noting and reference.

2. All renewal applications will be screened for completeness and the status will be updated to reflect "Review" upon passing screening. If an application is found to be incomplete upon screening, the applicant will be notified by SAHPRA and will be requested to amend and resubmit the application or to supply the outstanding information/documentation.

3. Evaluation of the application shall be carried out within the timelines stipulated (please refer to the attached renewal process flow diagram in **Annexure 1**) and the respective outcomes will be communicated to the applicant(s) via the Quantum system. Critical process milestones, such as receipt, screening, review and certification will be relayed to applicants via this system.

4. During evaluation, SAHPRA may request further information and additional supporting documents from the applicant in line with the guideline requirements. The required information should be made available within thirty (30) working days from the date of the request so as to facilitate timely renewal of the relevant product.

5. Notification of the renewal of registration of the product shall be communicated via the Quantum system, followed by the issuance of new registration certificate. Applicants should carefully read the conditions under which the medicine is registered (appended to the certificate) and adhere to them throughout the product lifecycle.

6. The full renewal review timeframe is 120 working days (six (6) months), from the time of submission of a renewal application by an applicant to the issuance of the renewed registration certificate by SAHPRA.

4.3 TECHNICAL REQUIREMENTS

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	Requirements
Working folder	Copies of the current approved PI and PIL in MS Word format Proof of approval of the PI/PIL (if applicable) 1.8 eCTD VALIDATION and TECHNICAL SCREENING FOR RENEWALS in MS Word format QIS and / or QOS in MS Word format
1.0	Letter of Application
1.2.1	Application Form (inclusive of up-to-date ***f) Variation History***)
1.3	**South African Labelling and Packaging:** 1. Copies of the current SAHPRA-approved Professional Information (PI) and Patient Information Leaflet (PIL) 2. The Professional Information (PI) and Patient Information Leaflet (PIL) from 5 years prior to the renewal application 3. The Professional Information (PI) and Patient Information Leaflet (PIL) variation approval 4. Coloured mock-ups of packaging of the product, i.e., blister, label and unit carton in PDF format. Facsimile labels will be accepted for dormant dossiers.
1.5.2.2	A copy of current registration certificate(s) for the product(s), as well as copies of DVP Variation Summaries regarding site variations received in the preceding 5 years
1.7.2	**Inspection Reports or Equivalent Document** A Product Quality Review (PQR) should be submitted with the objective of verifying the consistency of the quality of the FPP and its manufacturing process. *Please refer below for details.*
1.7.3	**Latest GMP Certificate or a Copy of the Appropriate Licence:** 1. Certificates of GMP Compliance of the Active Pharmaceutical Ingredient(s) manufacturing facilities, issued by Recognised Regulatory Authorities (RRAs) or by the National Competent Authority of the country of manufacture 2. Certificates of GMP Compliance of the Finished Pharmaceutical Product(s) (FPP) manufacturing facilities, issued by Recognised Regulatory Authorities (RRAs). Certificates should be provided for all sites involved in the testing, manufacturing and packaging of

Section	Requirements
	the FPP 3. Section 22C(1)(b) Licence(s) issued by SAHPRA for local sites
1.7.6	**Certificate of Pharmaceutical Product (CPP) (WHO Certification Scheme):**
	A CPP issued by the relevant Health/Regulatory body in the country of manufacture of the product or, if not registered in the country of origin, a CPP from a Health Authority of a country where the product is registered and marketed (legalisation/notarisation not required). *This requirement is not applicable to products manufactured in South Africa.*
1.7.7	**South African Pharmacy Council (SAPC) Registration:**
	Registration of Pharmacy, pharmacist responsible/authorised to communicate with the Authority and Responsible Pharmacist with the SAPC
1.13	**Risk Management Plan**
	A copy of the risk-benefit assessment report of the preceding 5 years. *Please refer below for details.*

PRODUCT QUALITY REVIEW (PQR)

A copy of the latest available Product Quality Review, containing the information stipulated in the PIC/S GMP Guide and following the guidance provided therein, should be submitted with the objective of verifying the consistency of the quality of the FPP and its manufacturing process.

Rejected batches should not be included in the analysis but should be reported separately together with the reports of failure investigations, as indicated below. Batches produced for other markets may be included but are required to have the same formulation and manufacturing process of the product registered in South Africa.

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:

i. A review of starting materials including packaging materials used in the product, especially those from new sources and in particular the review of supply chain traceability of active substances;
ii. A review of critical in-process controls and finished product results;
iii. A review of all batches that failed to meet established specification(s) and their investigation;
iv. A review of all significant deviations or non-conformances, their related investigations, and the effectiveness of resultant corrective and preventive actions taken;
v. A review of all changes carried out to the processes or analytical methods;
vi. A review of variations submitted, granted or refused, including those for third country (export only) dossiers;
vii. A review of the results of the stability monitoring programme and any adverse trends;
viii. A review of all quality-related returns, complaints and recalls and the investigations performed at the time; including export-only medicinal products.
ix. A review of adequacy of any other previous product process or equipment corrective actions;
x. For new registration applications and variations to registered dossiers, a review of post-marketing commitments;

xi. The qualification status of relevant equipment and utilities, e.g. HVAC, water, compressed gases, etc;
xii. A review of any contractual arrangements, as defined in Chapter 7 of the PIC/S GMP Guide Part I, to ensure that they are up to date.
xiii. 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.

Notes:
1. Product Quality Review to be included in Module 1.7.2 Inspection reports or equivalent document, only to be updated for registration renewal applications, not routinely.
2. Reviews should include data from all batches manufactured during the review.
3. Data should be presented in tabular or graphical form, where applicable.
4. PQRs should not be summaries of the outcome of review without data.

PHARMACOVIGILANCE

In order to support the renewal of the product, the following should be submitted:

i. An executive summary report of the latest Periodic Risk-Benefit Evaluation Reports (PBRERs) or Periodic Safety Update Reports (PSURs) (included in Section 1.13 Risk Management Plan).
ii. Risk-benefit conclusions by the Holder of the Certificate of Registration, namely by the Clinical Expert or the HCR Responsible Pharmacist. The conclusion/statement should:
    - Confirm that the product can be safely renewed for a 5-year period, or any action recommended or initiated should be specified and justified.
    - Confirm that the authorities have been kept informed of any additional data significant for the assessment of the benefit-risk balance of the product concerned.
    - Confirm that the product information is up to date with the current scientific knowledge including the conclusions of the assessments and the recommendations made.

QUALITY OVERALL SUMMARY (QOS) AND QUALITY INFORMATION SUMMARY (QIS)

1. Completed SAHPRA-specific QOS and QIS to be submitted in Module 3.2.R.8 – Other and the working documents. Refer to the SAHPRA QOS (GLF-PEM-02D) and QIS (GLF-PEM-02C) templates. Both the QOS and QIS are required for the first registration renewal, whereupon only the updated QIS will be required for subsequent renewal applications. If the product was registered with a SCoRE document and a complete, updated SCoRE document is available in Module 3.2.R.8, then a QOS will not be required.
2. A declaration that data related to any commitments/compliance with conditions which the product was registered under, must be submitted.
3. A declaration that the risk assessment for applications registered without nitrosamine risk assessment has been done and the necessary updates

5. REFERENCES

The following related documents are referenced:

1. PIC/S Good Manufacturing Practice (GMP) Guide Part I (https://picscheme.org/)
2. Medicines and Related Substances Act (Act 101 of 1965), as amended, together with relevant Regulations
3. Variations Addendum for Human and Veterinary Medicines: SAHPGL-HPA-06
4. General Information: SAHPGL-HPA-07
5. eCTD Validation and Technical Screening for Renewals: GLF-HPA-04A
6. QOS Template: GLF-PEM-02D

7. QIS Template: GLF-PEM-02C

6. VALIDITY

This guideline is valid for a period of 5 years from the effective date of revision and replaces **Renewal of Human and Veterinary Medicines Requirements and Process Guideline, SAHPGL-HPA-04-v1 dated 22 June 2022.** It will be reviewed on this timeframe or as and when required.

7. ANNEXURES

7.1 Annexure 1: Renewals Process Flow Diagram