

COMMUNICATION TO STAKEHOLDERS

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BAU Variations Communication

This document is intended to provide communication to applicants wishing to submit variations to existing registrations. This will be a “living document” and will be updated. Kindly note that this is an interim document and that the information will be incorporated into a General Information Guideline for Variations. It is important that applicants adhere to the administrative requirements to avoid delays in the processing and evaluation of applications. This document should be read in conjunction with SAHPRA’s revised guidelines and templates, available from SAHPRA’s website.

Document History

Final Version	Reason for Amendment	Effective Date
1	First publication released for implementation	[01 February 2021]
2	Amended section 3.5 to specify that all eCTD (Type I/II) variations are submitted via the FTP. Provided clarity in section 3.7 on how to proceed with “z” code submission requests. Included section 4.6, the process of submitting a TOA in eCTD format. Addition of a dedicated email address for the submission of medicine deregistration and application withdrawals, sections 4.3 and 4.4 respectively.	[June 2022]
3	Amended section 3.8 Submission requirements for Priority Review Applications (Type I and Type II), and 4.1 Submitting an application that requires review by both units, Quality and Inspectorate. Amended section 4.2 Submitting an application for the re-scheduling of a registered medicine or scheduled substance. Updated section 3.5 Submitting a Type I eCTD and all Type II Variation. Included section 4.6, the process of submitting a TOA in eSubmission format. Amendment of calendar days to working days	[February 2022]
4	Removed section 4.5 – Submitting a TOA application in eCTD format - since TOA applications may be submitted in a follow up sequence	[30 September 2022]

	<p>Removed section 4.6 – Submitting a TOA application in eSubmission format- since TOA applications may be submitted in a follow up sequence</p> <p>Updated section 2 – included a dedicated mailbox for Inspectorate variation queries</p> <p>Updated 3.4 – Included information on amendments to the Quality sections of the PI/PIL</p> <p>Updated section 3.14 – provided more information on the Certification process</p> <p>Updated section 3.19 – Included link to updated payment guideline and included Inspectorate fees</p>	
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ABBREVIATIONS AND ACRONYMS

API	Active Pharmaceutical Ingredient (also known as Drug Substance)
ASMF	Active Substance Master File
BAU	Business As Usual
DMF	Drug Master File
DVP	Digital Variations Portal
eCTD	Electronic Common Technical Document
eSubmission	Electronic Submission
EMA	European Medicines Agency
EU	European Union
FPRC	Finished Product Release Control
FPRR	Finished Product Release Responsibility
FTP	File Transfer Protocol
GMP	Good Manufacturing Practice
HCR	Holder of the Certificate of Registration
HIV	Human Immunodeficiency Virus
HPA	Health Products Authorisation
INN	International non-proprietary name (INN)
PEM	Pharmaceutical Evaluation & Management
PI	Professional Information
PIL	Patient Information Leaflet
RP	Responsible Pharmacist
RRA	Recognised Regulatory Authority
SAHPRA	South African Health Products Regulatory Authority
SCoRE	Summary of Critical Regulatory Elements
SmPC	Summary of Product Characteristics
ToA	Transfer of Applicancy

1. INTRODUCTION

The purpose of this document is to inform applicants on how to submit variation applications to the South African Health Products Regulatory Authority (SAHPRA) for Category A and C medicines as well as what to expect during variation evaluation.

Applicants should start by reading through this document with reference to the General Information Guideline [2.01] [https://www.sahpra.org.za/wp-content/uploads/2020/01/2.01_General-information_-Jul19_v10.pdf], the General Information Guideline for veterinary medicines [3.01] and the Submission of Business as Usual (BAU) registration and variation applications communication, issued by SAHPRA in July 2019 [[Submission of BAU Registration And Variation Applications - SAHPRA](#)]. Thereafter applicants should familiarise themselves with the latest/revised guidelines and templates. Appendix A contains a list of the most relevant guidelines and templates.

This is a living document and will be updated frequently as experience is gained through the processing of variations.

2. GENERAL INFORMATION

Type I eSubmission variation applications and eSubmission response submissions should be submitted via the Digital Variations Portal (DVP), refer to section 3.4.

Exception: All eSubmission responses for quality applications should be submitted via the FTP.

The DVP is not applicable to the Biological medicines (refer to exception note, point 3.4.3).

The DVP is not applicable to veterinary medicines. All veterinary variations applications should be submitted via the File Transfer Protocol (FTP) in eSubmission format only.

Type I eCTD, eCTD response submissions and all Type II variation applications should be submitted via the File Transfer Protocol (FTP), refer to section 3.5.

Applicants are to note that Quality and Clinical variations should be submitted separately, but simultaneously. The relevant Quality and Clinical variation fees will be applicable (refer to section 3.19)

Please note that SAHPRA timelines are calculated in working days, however the DVP system is programmed to calculate calendar days.

This is being rectified and will be corrected on the DVP.

Applicants are advised NOT to combine either Proprietary Name Change or Transfer of HCR variation applications with any Type I or II variations in same application to streamline the evaluation process.

For applications submitted for replacement or addition of a manufacturer/ packer/ laboratory the Inspectorate Approval Letter and/or Summary Report generated by the DVP effectively serves as an addendum to the registration certificate.

Note:

- All variations applications submitted via the DVP and/or FTP require 7 working days in addition to the evaluation period, for administrative processes.
- Inspectorate Variations queries for both Type I and II variations should be emailed to the designated email address: variations.inspectorate@sahpra.org.za

SAHPRA reserves the right to request any additional information or withdrawal of a variation implementation in keeping with the quality and safety of a medicine.

3. VARIATIONS

3.1 EU Variation Classification

SAHPRA has adopted the European Union (EU) variation classification guideline, with the full details (including the associated exceptions) published in the Variations Addendum for Human and Veterinary Medicines [2.08].

3.2 The Digital Variations Portal (DVP)

The purpose of the Digital Variations Portal is two-fold:

- Facilitate the submission and processing of Type I variation applications
- Provide an electronic database of implemented variations for use by Port Health, without the need for industry to wait for amended registration certificates

SAHPRA will not tolerate fraudulent and/or dishonest notifications via the portal and will communicate clear consequences for any offenders.

3.3 Creating a User Profile for the DVP

Before creating a variation application on the Digital Variations Portal (DVP), applicants will need to register a user account on the DVP. A company's Responsible Pharmacist (RP) will create the initial user profile and account on the DVP. The primary user of the Digital Variations Portal is the applicant's Responsible Pharmacist. The Responsible Pharmacist (RP) will submit details of the applicant company along with their South African Pharmacy Council registration certificate. SAHPRA will then approve or deny the account creation.

Once the registration profile is created and approved, the RP can add secondary users from within the applicant company. There are two options for secondary user permissions: 1) secondary users can submit and modify only their own variations; or 2) secondary users can view and modify all submitted variations from the primary user profile. The primary user (the applicant's RP) determines the rights of each secondary user from the "Users" tab once they are logged into the Portal.

Please note: the username is the applicant's company email address. All secondary users should have the same company's email address domain as the RP.

3.4 Submitting a Type I eSubmission Variation

As of 01st June 2021, all Type I eSubmission variations should only be submitted through the Digital Variations Portal (DVP), provided that the documentation file size does not exceed 2 GB

If the documentation file size exceeds 2 GB, refer to section 3.5 on how to submit the variation.

All Type I eCTD variations should be submitted through the File Transfer Protocol (FTP), provided that the documentation file size does not exceed 5 GB.

Refer to section 3.5 on how to submit the variation.

Refer to section 3.6 on how to name the folder for Type I submission via the FTP.

The applicant is to ensure that the proof of payment (POP) is included in the submission for all Type I variation applications submitted on the DVP and that the fee paid is correct as per Government Gazette dated 22 December 2020, [http://www.gpwnline.co.za/Gazettes/Gazettes/44026_22-12_Health.pdf] and the Explanatory note on fees payable for technical amendments related to Quality,

[<https://www.sahpra.org.za/wp-content/uploads/2021/03/Explanatory-Notes-for-Technical-Amendments-related-to-Quality-1.pdf>].

Should the application not comply with this requirement, the application will be rejected.

Applicants will first enter information identifying the product for which variation applications are being submitted. Applicants will subsequently select the EU variation codes relevant to the selected product. Note that certain variation codes will require the applicant to provide additional information. Applicants are required to explain the full variation in free-text fields.

Applicants can save variation applications that are in progress before submitting if the user does not complete the full application in one sitting. Upon submission through the DVP, variation applications will be dealt with in 1 of 2 ways:

1. Type IA and IA_{IN} evaluation period: SAHPRA will review Type IA and IA_{IN} variations within 30 working days following receipt. The regulator will check the correctness of the submission, presence of the required documentation and compliance with required conditions in accordance with the EMA classification guideline and relevant SAHPRA guidelines.
2. Type IB evaluation period exception codes (B.II.b.1.a, B.II.b.1.b, B.II.b.1.e and B.II.b.1.f): Requires additional supporting documents to be submitted via the DVP; the evaluation date commences upon online submission to SAHPRA. Applicants should refer to the Variations Addendum for Human and Veterinary Medicines [2.08] for further information regarding Type IB evaluation period.
3. For Inspectorate-Biological variations, that involves replacement or addition of a manufacturing site/packaging site/ batch control or testing site, the applicant is required to submit the Biological Unit Approval letter as part of the supporting documents.
4. For clinical-where amendments have been made on the Quality section of the PI and PIL, the applicant is required to submit P&A unit approval letter as part of the supporting documents. Applicant to note that Amendments to any quality aspects of the medicine within the PI/PIL are subject to P&A unit approval and may only be implemented in the PI/PIL if approved by the P&A unit. Where the applicant is just bringing the PI and PIL in line with current PI/PIL guidelines and the quality aspects were approved long time ago (at registration) the applicant may submit a declaration to confirm that the quality aspects were approved at registration.

Note: Type I eCTD variations should be submitted through the File Transfer Protocol (FTP). The Applicant is to notify Variations@sahpra.org.za of the FTP submission by providing a screenshot of the successful upload. The proof of submission, the application letter and the proof of payment should also be uploaded on the DVP for Inspectorate **ONLY** and Inspectorate-Biological variations.

In general, the implementation of variation applications grouped as a single submission will move at the pace of the most restrictive / slowest individual variation type. Applicants are thus advised to consolidate all Type I variations for a single registered product in a single application, and all Type II variations for a single registered product in a separate application. If Type I and Type II variations are consolidated in a single application, the applicant cannot implement the Type I variation/s until the Type II variation/s have been approved.

Type I applications in eSubmission format submitted and approved on the DVP should be listed in the amendment schedule of the next Type II variation application. The SAHPRA generated DVP code or the variations summary obtained on the DVP should be included in the Type II variation application.

3.5 Submitting a Type I eCTD and all Type II Variation

SAHPRA has established a File Transfer Protocol (FTP) system for large electronic submissions of eCTDs and eSubmissions. To gain access to the FTP system applicants are to contact SAHPRA at variations@sahpra.org.za.

For variations submitted in eCTD format for the first time, applicants will be required to include a baseline as part of the dossier. For variations submitted in eSubmission format, applicants may opt to include a baseline where relevant and practical (see guidelines [2.23] and [2.58]).

All Type I eCTD, eCTD response submissions and all Type II variations should be submitted through the File Transfer Protocol (FTP).

The applicant is to notify Variations@sahpra.org.za of the FTP submission by providing a screenshot of the successful upload.

FTP proof of submission, the application letter and the proof of payment should be uploaded on the DVP for Inspectorate **ONLY** and Inspectorate-Biological variations.

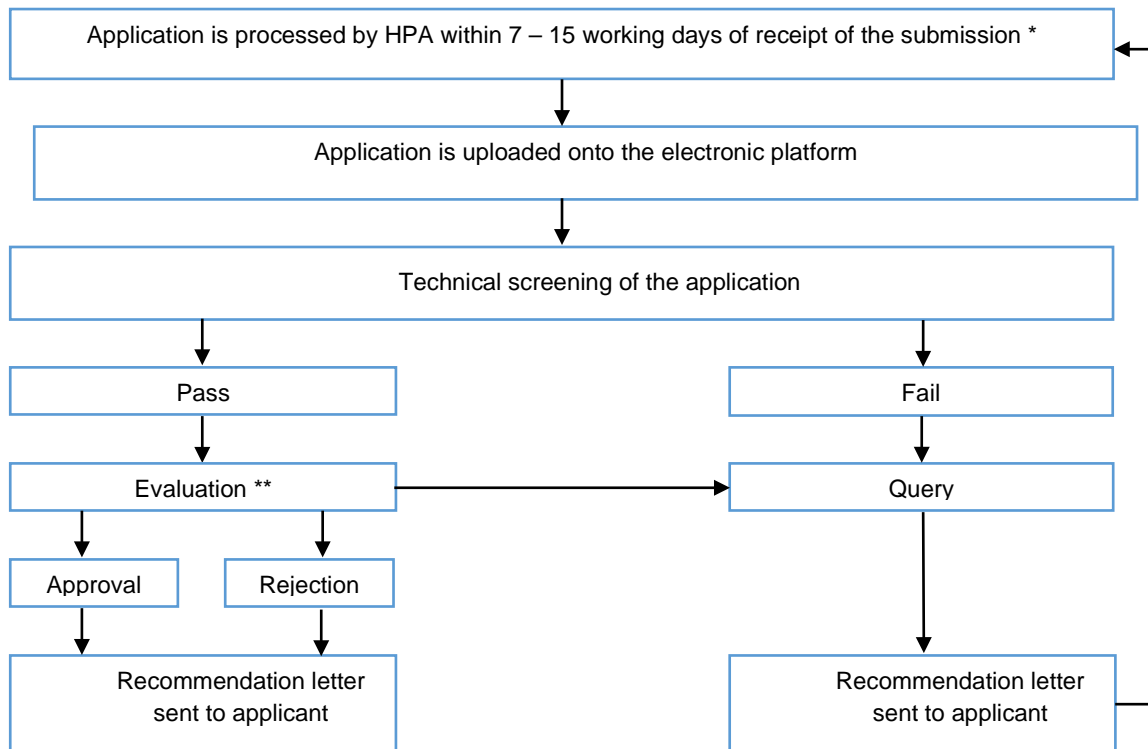
Note: FTP Proof of Submission should **not** be uploaded on the DVP for Clinical and Quality Type I eCTD variations.

The applicant is to ensure that the POP is included in the submission for all Type I and Type II variation applications submitted on the FTP and that the fee paid is correct as per Government Gazette dated 22 December 2020, [http://www.gpwonline.co.za/Gazettes/Gazettes/44026_22-12_Health.pdf] and the Explanatory note on fees payable for technical amendments related to Quality, [<https://www.sahpra.org.za/wp-content/uploads/2021/03/Explanatory-Notes-for-Technical-Amendments-related-to-Quality-1.pdf>].

Should the application not comply with this requirement, the application will not proceed to the next stage and ultimately evaluation will be delayed.

Please note: If the proof of payment has not been included in the application, a new application and new sequence would be required by the regulator.

3.5.1 Process flow for all TYPE I/II variation applications submitted via the (FTP)



* A Type I variation submitted via the FTP is prioritized to be uploaded within 7 working days, provided that the submission follows the correct FTP file naming convention (refer to section 3.6).

** A Type I variation is evaluated as per the stipulated timelines (refer to section 3.4).

** A Type II variation is evaluated within 120 working days of the application being received by the technical unit, subject to the availability of evaluators.

Exception

A Type I eSubmission variation may be submitted via the FTP only if the documentation file size exceeds 2 GB.

As this is a time sensitive application, the applicants are to email variations@sahpra.org.za informing SAHPRA of this Type I variation submission through the FTP.

Applicants are to include a justification statement stating the reason for submitting a Type I eSubmission variation through the FTP (e.g., Type I variation is submitted via the FTP due to the file size being 4 GB, therefore the 2 GB DVP file size limit has been exceeded). This statement must appear in the Letter of Application (Applicants are **strongly urged** to adhere to the Letter of application format and structure as seen in point 4.7 below).

Submitting eCTD Type I variations for Inspectorate

All Type I eCTD variations for Inspectorate should be submitted through the File Transfer Protocol (FTP).

The Applicant is to notify Variations@sahpra.org.za of the FTP submission by providing a screenshot of the successful upload. The FTP proof of submission, the application letter and the proof of payment should also be uploaded on the DVP. The Type IA_{IN} variations will be dealt with as mentioned above, section 3.4.

Applicants are to note:

- Submission of a Type I eSubmission variation via the FTP (documentation file size **not** exceeding 2 GB), will lead to the rejection of the application.
- Applicants should not submit the same application on both platforms (FTP and DVP). Submission of a Type I variation on both platforms (FTP and DVP), will lead to the rejection of the application. This does not apply to eCTD Type I variations for Inspectorate (refer to paragraph above).
- As mentioned above for inspectorate **ONLY** and Inspectorate-Biological applications, the proof of FTP submission, the application letter and proof of payment should also be uploaded on the DVP, the variation summary from the DVP would serve as the recommendation letter.
- SAHPRA will issue a recommendation letter within the application review period for all Type I/II variation applications submitted via the FTP in lieu of the variation summary issued on the DVP.
 - For Type IA and Type IA_{IN} variations, if SAHPRA has not sent the HCR its opinion on the application within 37 working days the application will be deemed implementable provided that the submission follows the correct FTP file naming convention (refer to section 3.6).
 - For Type IB variations, If SAHPRA has not sent the HCR its opinion on the application within 37 or 67 working days (as applicable depending on the variation code) the application will be deemed implementable provided that the submission follows the correct FTP file naming convention (refer to section 3.6).

3.6 FTP file naming convention

Applicants are requested to adhere to the below file naming convention when submitting variation applications on the FTP. This will aid SAHPRA to route the application to the relevant technical unit.

The applicant is to ensure that the file is correctly named. Incorrect file names or files that do not conform to the below naming convention, may lead to a delay in the evaluation or rejection of the application.

Note: Implementation timelines will be affected and the review period will commence once the application is received at the correct technical unit.

<u>Variation unit</u>	<u>FTP file naming convention</u>	<u>Example</u>
• Inspectorate	Application number-BAU(V- i)-Sequence	50000-BAU(V- i)-0000
• Clinical	Application number-BAU(V- c)-Sequence	50000-BAU(V- c)-0000
• Quality	Application number-BAU(V- q)-Sequence	50000-BAU(V- q)-0000
• Biological	Application number-BAU(V- b)-Sequence	50000-BAU(V- b)-0000
• Names & Scheduling	Application number-BAU(V- n)-Sequence	50000-BAU(V- n)-0000
• Veterinary	Application number-BAU(V- v)-Sequence	50000-BAU(V- v)-0000
• Multi-unit	Application number-BAU(V- i-b-c-q-n)-Sequence	50000-BAU(V- i-b-c-q-n)-0000

- Type I submissions via the FTP, must adhere to the below FTP file naming convention for multi-unit and single unit applications:
Eg: Multi-unit application
Application number-BAU(V-i-n)-Sequence-Type I

Eg: Single unit application
Application number-BAU(V-i)-Sequence-Type I
- Response submissions via the FTP, must adhere to the below FTP file naming convention:
Application number-BAU(V-i-b-c-q-n)-Sequence-VR
- Priority application submissions via the FTP, must adhere to the below FTP file naming convention:
Priority review reference number-BAU(V-i-b-c-q-n)-Sequence
See section 3.8 Submission requirements for Priority Review Applications (Type I and Type II)

3.7 Unforeseen changes (z-codes)

Applicants can submit "z" code variations to SAHPRA for unforeseen changes not accounted for in the EMA guidelines under the same classification codes as evaluated under EMA. Any codes that have not been detailed in the SAHPRA variations addendum should be submitted as a "z" code.

Applicants are to submit "z" code variation requests to the relevant technical unit (Unit Manager & Variations email addresses) and wait for confirmation from SAHPRA. The relevant unit will inform the applicant within 5 working days of the correct application classification and the application fee required, via email. "z" code submissions cannot be made without obtaining and / or receiving confirmation from SAHPRA.

Applicants must include the confirmation received from the technical unit as an annex to the application letter.

Please note for clinical variations where applicants are submitting a PIL for the first time for review, these have no code in the variations addendum and should be submitted as Type IB on the DVP for eSubmission applications. Applications in eCTD format should be submitted via the FTP.

3.8 Submission requirements for Priority Review Applications (Type I and Type II)

Kindly refer to the current version of the communication regarding priority review requests published on the SAHPRA website.

3.9 Submitting Type II Variations with Type I Variations

According to EMA Guidelines as adopted by SAHPRA, Type I variations may be submitted with Type II variations; however, the Type I variations are not implementable until the entire variation application, including Type II variations, are approved.

If an Applicant submits a Type I variation with a Type II variation, then the Type I variation must not be submitted on the Digital Variations Portal. Applicants found to have implemented Type I variations prior to the approval of a Type II variations within the same dossier will have all variations related to the specific dossier rejected.

For the purpose of dossier completeness, when the applicant wishes to submit a Type II variation, the applicant should ensure that their Type I variations on the DVP/ FTP are finalized prior to submitting the Type II variation and that the Type I variations that were deemed implementable or approved on the DVP are included in the Type II variation application.

For Type I variations that have not been finalized and there is an urgent Type II that needs to be submitted, applicants can notify the regulator through variations@sahpra.org.za of such an application and review will be expedited.

3.10 Submitting the SCoRE document

The SCoRE document is a product lifecycle document and it is important that it is updated with each variation made to the product.

For applications where a SCoRE document has been submitted at the time of registration, it will be required that an updated SCoRE document be submitted with the variation application. Only the sections that have been amended should be highlighted in yellow and the sections that have been replaced should have a strike through for eg. (strike). Once the variation is approved, the applicant can replace the struck through information on the SCoRE document with the newly approved data.

For applications that did not have a SCoRE document at the time of registration, the Applicant may either:

- submit a partial SCoRE document with the sections that have been amended. Note it is the intent that ultimately each product should have a SCoRE document and that it reflects the status of approved information of the dossier.
- submit a full SCoRE document, this will however require that the dossier be submitted as per current eCTD/eSubmission requirements such that the full SCoRE is verified by SAHPRA as a reflection of the approved information.

Note that it is the intent that ultimately each product should have a SCoRE document and that it reflects the status of approved information in the dossier.

The SCoRE document is a requirement and this should not change the prescribed review timelines of 30 working days for Type I and 120 working days for Type II.

Applications submitted without a SCoRE document will be rejected and the applicant will be requested to resubmit the application according to the requirements.

Note: The SCoRE document is not a requirement for Clinical, Veterinary and Biological Medicines (Quality and Clinical) Variations.

3.11 Submitting the Variation Validation Template

The purpose of the Variation Validation Template is to verify that all the required information has been supplied to SAHPRA to evaluate the variation application. It is also used for follow-up sequences that may be required for the variation.

Applications submitted without the Variation Validation Template will be rejected and the applicant will be requested to resubmit the application according to the requirements.

3.12 Format change to PI and PIL

SAHPRA has adopted the EMA format for Professional Information and Patient Information Leaflets. This

format is reflected in the updated SAHPRA guidelines [2.14] and [2.16].

The format change requires amendments to General Regulations 10 and 11 of the Medicines and Related Substances Act, 1965 (Act 101 of 1965, as amended). The comment period for these amendments closed on 31 August 2019, with SAHPRA expecting the final changes to be published in the Government Gazette.

The fees gazette of 22 December 2020 and the SAHPRA payment guide of November 2020 should be consulted for applicable fees.

Note: PI changes to the EMA format is also applicable to veterinary medicines.

3.13 Repository of PIs and PILs

SAHPRA has published a repository of PIs and PILs on its website for the benefit of health care providers and patients, as well as to enable streamlined Clinical evaluations of applications for generic medicines. Where available for a given molecule, applications for generic medicines are required to reference the latest published SAHPRA-approved innovator PI in the application. Clinical screening queries will be immediately flagged for applications referencing an outdated / illegible PI where the latest version has been published on SAHPRA's website at the time of submission.

Note that the published PIs on SAHPRA's website may also be applicable to selected variation applications (e.g., safety update of a generic medicine where the same change has already been approved for the reference local innovator medicine).

The final dated versions of the generics and innovator PI/PIL for all variations deemed implementable on the DVP or for which an approval letter has been sent to the HCR/MAH, should be sent in PDF format to pipilrepository@sahpra.org.za for uploading onto the PI and PIL repository. Non-compliance may result in withdrawal of the variation approval.

All PI/PILs not yet submitted should be sent to the above address as soon as possible.

Note: PI/PIL repository for veterinary medicines is under discussion.

3.14 Certification

Please note: Throughout the communication, whenever the terms registration certificate(s) or certificate(s) appear and the term old medicine letter has not been included, the assumption should be that the same applies for old medicine letters as well. Hence if the variation application submitted is for an unregistered product (old medicine), then the term old medicine letter is applicable, except in distinctly specific circumstances wherein the term old medicine letter cannot be practically applicable.

Considering the Digital Variations Portal and associated database, only selected variation applications require the issuing of an amended registration certificate:

- Changes in the proprietary name of a product (A.2.b in the EU Variation Classification Guideline)
- Transfer of the Holder of Certificate of Registration (A.0.1 in the Variations addendum)

Both variations are considered to be Type II, as stipulated in the Variations Addendum for Human and Veterinary Medicines [2.08].

Applicants must submit these applications separately to any technical changes e.g. adding a

new/additional manufacturer. This will allow for a streamlined process for certification.

Valid GMP certificates/resolution letters/manufacturing licences for all the sites listed in the Module 1.2.1 and 1.5.2.2.1 must be submitted for each certification variation application. (Valid GMP certificates are required even for re-submissions).

Please note: On submission of transfer of Holder of Certificate of Registration/proprietary name change applications there should be no pending variations that affect the information on the registration certificate.

For transfer of Holder of certificate of registration or proprietary name change variations, a variation is only considered approved once a revised Old medicine approval letter/ registration certificate is issued.

The above-mentioned Type II variations require 120 working days for review, subject to the availability of evaluators.

The timeline includes review of the application by the names and scheduling unit, inspectorate unit and processing of an amended certificate by HPA.

Certification will only begin processing the revised registration certificate once the unit has received the Inspectorate and/or naming approval letter.

Certification require 20-30 working days to finalise the revised registration certificate, barring no query(ies) on the application.

Should an application not require a revised registration certificate, the applicant can create a variation summary within the Digital Variations Portal, which effectively serves as an addendum to the registration certificate. The updated variation summary can be obtained on the Digital Variations Portal within 24 hours of approval of the variation application.

A read-only database with variation summaries for each product is available to Port Health to act as a primary source of approved variations.

Queries:

Applicants are to note that; to streamline the process in the Certification Unit, responses to queries will take the queue to ensure that applications are processed on a first in first out basis. Queries should be addressed within 5 working days. Applications with delayed responses will be placed at the back of the certification queue.

3.14.1 Information required when applying for an amendment to the registration certificate

Standard documentation for certification variation applications

1. Letter of application with (M1.0):
 - Purpose of the variation(s)

- Internal SAHPRA Code as per General Information guideline to aid routing
- Description, Classification and Code of the Variation(s) (e.g., Type II – A.0.1)
- SAHPRA name change approval letter*
- SAHPRA Transfer of HCR inspectorate approval letter*

2. Application form (M1.2.1)

3. Proof of payment for the variation application (M1.2.2.1)

A payment breakdown for bulk payments (M1.2.2.1)

4. Electronic copy of the letter of cession from the current registered HCR signed by the RP

5. Electronic copy of the letter of acceptance from the proposed HCR signed by the RP of the proposed applicant

6. The current approved PI and PIL (M1.3.1.1 & M1.3.2)

7. Amendment schedule (M1.5.2.1)

8. Medicine register details (M1.5.2.2.1)

9. Variations summary (appended to the registration certificate/old medicine letter in M1.5.2.2.2)#

10. Copy of current approved registration certificate or old medicine letter (M1.5.2.2.2)

11. Valid SAHPRA licence to manufacture, import or export medicines for the proposed HCR (M1.7.3)

12. Current, valid GMP certificates, resolution letter or manufacturing licences for all approved sites performing a function related to the product - manufacture, packer, FPRC, FPRR/Applicant (M1.7.3)

* Applicable when an application is re-submitted with a prior approval letter

Where applicable

3.15 Submitting Certificate Variation Applications

- If the variation application applied for is a Type II variation inclusive of Type I variations e.g.
 - Adding a packer or laboratory (FPRC)
 - Changing the name of a manufacturer
 - Changing the name or address of a packer or laboratory (FPRC)
 - Deletion of a site (i.e. manufacturer, packer, laboratory (FPRC) or additional FPRR), the applicant can combine variations in one application at the time of submission
- However, if a Type I variation application has previously been applied for through the Digital

Variations Portal (DVP), then a variations summary must be attached to the Type II variation application as an appendix in module 1.5.2.2.2 (appended to the registration certificate/old medicine letter)

The Type I information that has been applied for through the DVP and approved through the variations summary must be added onto module 1.5.2.2.1 medicine register details under the “proposed column” and NOT the “current column”. Only information appearing on the current registration certificate/old medicine letter must be included under the “current column”.

All certification queries and query responses must be emailed to certificationvariations@sahpra.org.za. Do not submit certification query responses via the FTP unless specifically requested to do so.

3.16 Proprietary name change variation application

- The variation application to request a proprietary name change from the Names and Scheduling unit should be made at the same time as the application to amend the proprietary name on the current registration certificate.
- The fees payable for a Type II variation are as per the latest government gazette.
- The proposed proprietary names should be included in all the relevant modules, i.e. if the applicant has proposed multiple names for the product, then all proposed names should appear in the variation application.

However, if only one name is suggested then only one name may appear on all modules.

- Proprietary name variation applications will proceed to the certification unit only when all other approvals have been received from the relevant units, i.e. Names and Scheduling unit and Inspectorate unit and/or any other unit in the case of a combined variation application.
- Valid GMP certificates/resolution letters/manufacturing licences for all the sites listed in the Module 1.2.1 and 1.5.2.2.1 must be submitted.

3.17 Submitting Variations for Duplicates or Different Strengths

In circumstances whereby identical variations are being submitted for duplicate products or different strengths of the same product, SAHPRA encourages the applicant to submit a combined dossier rather than multiple/separate dossiers. This reduces the workload burden for SAHPRA and should result in faster overall turnaround time as well as ensuring document completeness. Please refer to “Guidance for the Submission in eCTD Format or Guidance for the Submission eSubmission Format” and the guideline on “Multiple Submissions of the Same Application for Registration with Different Proprietary Names” (May 2019) for additional information.

For DVP submissions of PI/PIL variation applications where there are different strengths of the same product on one PI/PIL, only one application should be submitted.

3.18 Documentation for Reliance

SAHPRA has developed reliance pathways to streamline the application approval process. To facilitate this process, Applicants are reminded of the reliance requirements below.

- Unredacted reports are required should the application have received approval from Recognised Regulatory Authorities (RRAs)

- SAHPRA will be implementing reliance models for qualifying applications. The General Information Guideline [2.01] contains the latest information regarding SAHPRA's evaluation pathways as well as SAHPRA's Recognised Regulatory Authorities (RRAs) and collaborative / work sharing procedures
- To apply for a verified review, applicants are encouraged to leverage SAHPRA's repository of PI/PILs
- Additional information is provided in the Clinical Guideline [2.09], Variation addendum for Human and Veterinary Medicines [2.08] and Quality and Bioequivalence Guideline [2.02]

3.19 Fees

Normal text The fees applicable to variations are published in the Government Gazette dated 22 December 2020 [http://www.gpwonline.co.za/Gazettes/Gazettes/44026_22-12_Health.pdf].

To provide clarity for the submission of fee payments and categorization, SAHPRA has published a guideline [SAHPRA Payment Guideline_May 2021, https://www.sahpra.org.za/wp-content/uploads/2021/06/SAHPRA_Payment_Guideline.pdf].

If a bulk payment is made, the breakdown should be clear on the Applications Cover Page [<https://www.sahpra.org.za/wp-content/uploads/2020/11/Applications-Cover-Page.docx>]. The Proof of payment and Applications Cover Page should be included in module 1.2.2.1.

Quality fees:

A separate communication providing an Explanatory note on fees payable for technical amendments related to Quality has been published on the SAHPRA website, [<https://www.sahpra.org.za/wp-content/uploads/2021/03/Explanatory-Notes-for-Technical-Amendments-related-to-Quality-1.pdf>].

This communication is to provide clarity on fees payable for technical variations related to quality as indicated in the current SAHPRA fees on the Government Gazette, dated 22 December 2020.

Please note that the fees payable for Quality are independently charged as these variations are reviewed independently of Inspectorate.

For veterinary medicines, the fees for quality variations are under discussion.

Clinical fees:

1. Evaluation of request to amend PI and PIL in respect of which data relating to safety must be evaluated has a fee of R15 600.
2. Evaluation of request to amend PI and PIL in respect of which clinical data relating to safety and efficacy must be evaluated (i.e. submission of a new product indication), has a fee of R15 600.
3. Evaluation of request to amend the Generic medicine PI and PIL where clinical data are not required, has a fee of R2 600 (i.e. Type I variations).
4. For veterinary medicines, a fee of R4000 is requested for all variations where clinical data and biostudies are included.

Applicants to note that the above fees apply for both, Generic **and** Innovator medicines, for all amendments of the PI and PIL.

Inspectorate fees:

All Inspectorate Type IA, IA_{IN} & IB variation applications submitted on the DVP/ FTP must be accompanied by the relevant proof of payment, R800 per application number (per product/ per strength).

Please note that the fees payable for Inspectorate are independently charged as these variations are reviewed independently of Quality.

4. MISCELLANEOUS

4.1 Submitting an application that requires review by both units, Quality and Inspectorate.

As per the SAHPRA variation addendum (includes EMA variations guideline), replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product (B.II.b.1.b and B.II.b.1.e-f). Replacement or addition of a manufacturer/primary packer/laboratory requires evaluation by Quality as well as Inspectorate.

As of the 01st of February 2022, the evaluation of Quality and Inspectorate variations (B.II.b.1.b and B.II.b.1.e-f), will no longer be evaluated in parallel but sequentially. The application will still be submitted simultaneously, Quality will do the evaluations first and then transfer to Inspectorate for further evaluation by the unit and finalization

Please note that the respective fees applicable for both the Quality and Inspectorate variations must accompany the submission.

4.2 Submitting an application for the re-scheduling of a registered medicine or scheduled substance

Re-scheduling applications are not regarded as variations. The fees applicable to re-scheduling applications are published in the Government Gazette dated 22 December 2020, [http://www.gpwonline.co.za/Gazettes/Gazettes/44026_22-12_Health.pdf]

Applications for the re-scheduling of a registered medicine or scheduled substance for evaluation by the naming and scheduling unit, must be submitted via the FTP.

The format and content of the applications are as per the current SAHPRA Guideline to the Scheduling of Medicines and SAHPRA Application for Rescheduling of Substances and Medicines.

Applicants are requested to adhere to the below file naming convention. This will assist SAHPRA to route the application to the technical unit.

The applicant is to ensure that the file is correctly named. Incorrectly named files may lead to a delay in the evaluation of the application.

FTP file naming convention

Application number-BAU(V-n&s)-RSCH-Sequence

Example

50000-BAU(V-n&s)-RSCH-Sequence

The amendment of the PI/PIL in line with the inscription of the re-scheduled substance in the Government Gazette is not regarded as a re-scheduling application. This must follow the Evaluation of request to amend the medicine PI and PIL where clinical data is not required, as outlined above.

4.3 Submitting an application for the deregistration of a registered medicine or substance

Applications for the deregistration of a registered medicine or substance must be submitted via the dedicated email address, cancellations@sahpra.org.za.

The following relevant supporting documentation should be submitted:

- Motivational letter for the deregistration of the registered medicine or substance, signed by the RP
- Copy of the original medicine registration certificate / Affidavit

4.4 Submitting an application for the withdrawal of a variation submission

Applications for the withdrawal of a variation must be submitted via the dedicated email address, variations@sahpra.org.za.

The following relevant supporting documentation should be submitted:

- Motivational letter for the withdrawal of the variation submission, signed by the RP.
- Proof of submission of the variation application

4.5 Letter of Application

Applicants are requested to adhere to the template below upon submission of a variation application to SAHPRA

Instructions for applicant in gray (delete once read): Copy and paste the text in this document into your official company letterhead. Fill in all relevant information in the letter template, indicated by { }. Delete { } once information has been filled in.

The Chief Executive Officer

SAHPRA
 Loftus Park
 2nd Floor Kirkness Rd
 Arcadia
 Pretoria
 0083

{Letter Date}

{Working code e.g. eCTD-VPA /eSubmission VPA/, (Clinical, Quality, N&S, Inspectorate, Certification)}

Dear Madam,

APPLICATION FOR A VARIATION / AMENDMENT TO A REGISTERED PRODUCT

Registration Number(s)	
Product Proprietary name(s)	
API(s)	
Dosage strength (and Dosage form)	
Type of submission	<Type IA _{IN} ><Type IA><Type IB><Type II><Response to recommendations> This refers to the overall submission, which is classified according to the most extensive procedure (e.g., if a Type IB and Type II are submitted together, the overall submission will be treated as a Type II)
Sequence number	

Description of the submission
 {Brief product description}

Format of the submission
 We confirm that the submission is checked with an up-to-date and state-of-the-art anti-virus software: {Name of the antivirus software and version of the checker} and is virus-free.
 Application format: <eCTD><eSubmission>
 If eCTD, state the name of the eCTD validation tool used to check compliance
 If eSubmission, state briefly (2 lines max) why eSubmission was used instead of the SAHPRA preferred eCTD format

Summary of the variations / amendments applied for

Applicants are to list and describe all of the variations applied for, in order to aid SAHPRA with routing
 Instructions for applicant in gray (delete once read): Copy and paste the text in this document into your official company letterhead. Fill in all relevant information in the letter template, indicated by { }. Delete { } once information has been filled in.

The Chief Executive Officer

SAHPRA

Loftus Park

2nd Floor Kirkness Rd

Arcadia

Pretoria

0083

{Letter Date}

{Working code e.g. eCTD-VPA /eSubmission VPA/, (Clinical, Quality, N&S, Inspectorate, Certification)}

Dear Madam,

APPLICATION FOR A VARIATION / AMENDMENT TO A REGISTERED PRODUCT

Registration Number(s)	
Product Proprietary name(s)	
API(s)	
Dosage strength (and Dosage form)	
Type of submission	<Type IA _{IN} ><Type IA><Type IB><Type II><Response to recommendations> This refers to the overall submission, which is classified according to the most extensive procedure (e.g., if a Type IB and Type II are submitted together, the overall submission will be treated as a Type II)
Sequence number	

Description of the submission
 {Brief product description}

Format of the submission
 We confirm that the submission is checked with an up-to-date and state-of-the-art anti-virus software: {Name of the antivirus software and version of the checker} and is virus-free.
 Application format: <eCTD><eSubmission>
 If eCTD, state the name of the eCTD validation tool used to check compliance
 If eSubmission, state briefly (2 lines max) why eSubmission was used instead of the SAHPRA preferred eCTD format

Signed:

APPENDIX A: RELEVANT DOCUMENTS

Guidelines

[2.01]	General information guideline
[2.02]	Quality and Bioequivalence Guideline
[2.08]	Variations for Human and Veterinary Medicine
[2.09]	Clinical guideline
[2.14]	Guideline for Patient Information Leaflet for Human Medicines
[2.16]	Guideline for Professional Information for Human Medicines
[2.23]	Submission in eCTD format
[2.58]	Submission in eSubmission format
[2.61]	Biological medicines amendment guideline
[3.01]	General Information Guideline for Veterinary Medicines
[3.14]	Veterinary Clinical Guideline
[4.01]	SA Guide to Good Manufacturing Practice
[SAHPGL-CEM-NS-02]	Guideline to the Scheduling of Medicines
SAHPGL-CEM-NS-01	Application for rescheduling of a substance or medicine
[17.05]	SAHPRA Payment Guideline

Templates

[6.31]	Summary of Critical Regulatory Elements
[6.41]	SAHPRA Variation Validation Template for eCTD
[6.42]	SAHPRA Variation Validation Template for eSubmission