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. 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.

First publication released for implementation	v1 February 2021
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.	v2 May 2021

TABLE OF CONTENTS

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 SAHPRA for Category A 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]. 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 should be submitted via the Digital Variations Portal (DVP), refer to section 3.4.
However, the Digital Variations Portal is not yet applicable to the Biological medicines (refer to exception note, point 3.4.3).

Type I eCTD 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.

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.

3. VARIATIONS

3.1. EU Variation Classification

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

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 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 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.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 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 calendar 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.

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.

   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 and the application letter 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.

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.

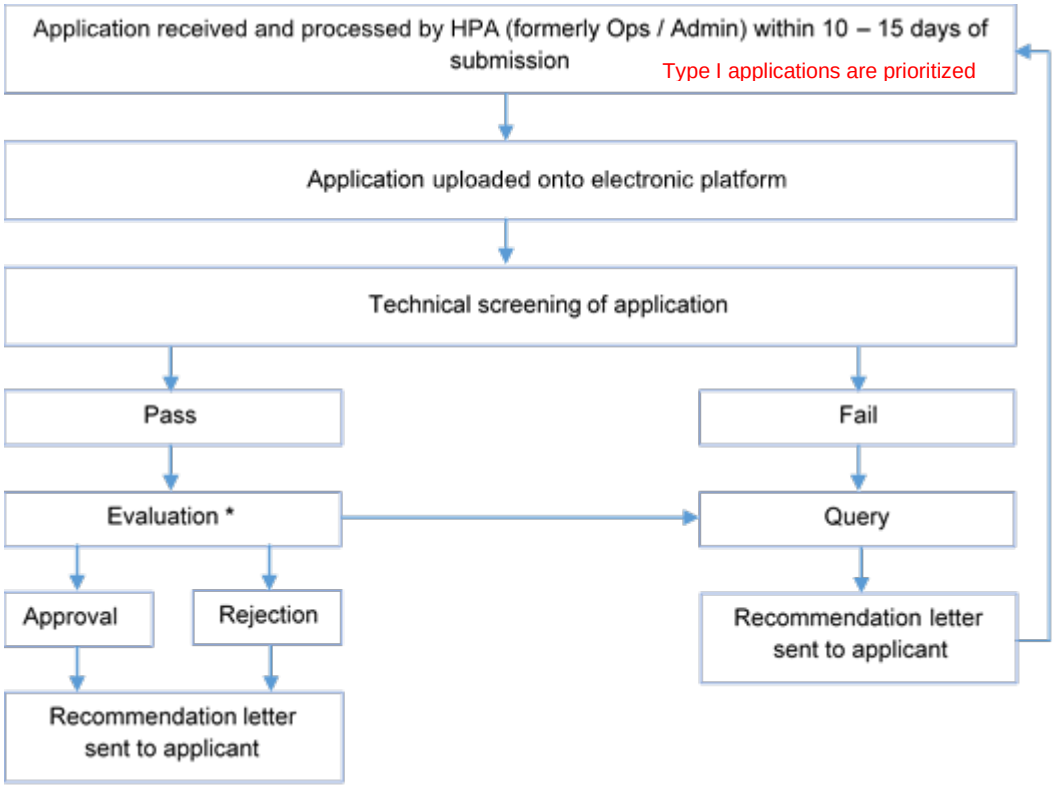
For variations submitted in eCTD format for the first time, applicants will be required to include a baseline as part of the dossier. For variations submitted in eSubmission format, applicants may opt to include a baseline where relevant and practical (see guidelines [2.23] and [2.58]).

All Type I eCTD 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.
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 and uploaded within 7 working days.
* A Type I variation is evaluated as per the stipulated timelines (refer to section 3.4), subject to the availability of evaluators.
***** 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 the template appended below, refer to 4.6).

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 proof of submission and the application letter 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).
- 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.
- As mentioned above for inspectorate **ONLY** and Inspectorate-Biological applications, the proof of FTP submission and the application letter should also be uploaded on the DVP, the variation summary from the DVP would serve as the recommendation letter.

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 new file naming convention will be implemented after the implementation date of this guideline.
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 of the application.

Applicants to note that the application number should be used in the FTP file naming convention for both, BAU new medicines and variations applications.

Variation unit	**FTP file naming convention**	**Example**
• 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

Exception

- Type I submissions via the FTP, must adhere to the below FTP file naming convention:
  Application number-BAU(V-i-b-c-q-n)-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 confimation 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)

Applicants are reminded that products subject to stock outs, products that have been successful in obtaining a tender or products used in the management of Cancer, HIV, TB, or products for emergency-use are considered priority and must follow the priority review approval process defined below.

Priority review approval should be applied for prior to submission of the application.
The following relevant supporting documentation should be submitted:

- Applicants are required to provide a printout of stockholding should a product be subject to stock out
- Applicants to provide supporting documentation of **approved** tenders which SAHPRA will cross-check with the National Department of Health.

Priority review requests should be addressed to the below:

Type of Variation	Email Address	
Quality	PriorityQvariations@sahpra.org.za	For all priority Quality variations
Clinical	PriorityCvariations@sahpra.org.za	For all priority Clinical variations
Inspectorate	PriorityIvariations@sahpra.org.za	For all priority Inspectorate variations excluding: • Transfer of Applicant and Proprietary name change applications
Certification	PriorityRCvariations@sahpra.org.za	For priority Transfer of Applicant and Proprietary name change applications only.

If approved, a priority review reference number will be issued to the applicant. This reference number should be:

- included in FTP file name.
- reflected clearly and in bold **red text** on the cover letter.
- quoted in all communication relating to the application.

Applications approved for priority review will be prioritized at the time of submission. It must be noted that the priority applications jump the normal BAU queue and follow the priority applications queue. Therefore, the timeline is dependent on the number of priority applications received and/or complexity of variations applied for.

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 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 striked 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 current 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 current status of approved information in the dossier.

The SCoRE document is a requirement and this should not change the prescribed timelines of 30 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.

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 in order 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.

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 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.

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 of these variations are considered to be Type II, as stipulated in the Interim Variations Addendum for Human and Veterinary Medicines [2.08a].
Applicants are advised to submit these applications separately to any content changes to 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.

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 inspectorate unit and processing of an amended certificate by HPA.

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.

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)
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 and changing a manufacturer, the applicant can combine variations in one application at the time of submission (also see heading: 3.9 Submitting Type II Variations with Type I Variations)
- 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], Interim Variation addendum for Human and Veterinary Medicines [2.08a] and Quality and Bioequivalence Guideline [2.02]

3.19. Fees

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_Nov 2020, https://www.sahpra.org.za/wp-content/uploads/2020/11/SAHPRA-Payment-Guideline-Nov-2020.pdf].

All proof of payment must be submitted in PDF format and not as a scanned copy.

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 clarify the Type II levels as indicated in the current SAHPRA fees on the Government Gazette, dated 22 December 2020.

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).

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.

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). Replacement or addition of a manufacturer/primary packer/laboratory requires evaluation by Quality as well as Inspectorate. Therefore, applicants are to indicate on their covering letters that this variation (B.II.b.1) must be routed to both Quality and Inspectorate variations.
Please note that the respective fees applicable for both the Quality and Inspectorate variations must accompany this 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.

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	Example
Application number-BAU(V-n&s)-RSCH-Sequence	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.
- Proof of submission of the variation application

4.5. Submitting a TOA application in eCTD format

A baseline (sequence 0000) must be prepared and submitted by the proposed HCR for Transfer of Applicancy applications in eCTD format. The baseline submission should reflect the status of the most recently approved dossier.

eCTD baseline submissions for a TOA application submitted via the FTP, must adhere to the below FTP file naming convention:
Application number-BAU(V-i)-Sequence-TOA

The Transfer of Applicancy variation application (sequence 0001) must be referenced to the baseline submitted by the proposed HCR.

Kindly note that this is an interim measure for the submission of eCTD TOA applications. SAHPRA is currently working on a solution with the service provider.

4.6. 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 the application appropriately. The table is intended to be a relatively high-level summary, with more information on the exact nature of the variations provided in the amendment schedule.

Variations/changes included in this application			
Code	Procedure	Code description	Summary
E.g., C.I.2a	Type IB	Change(s) in the PI or PIL of a generic/biosimilar medicine following assessment of the same change for the reference product	Special warnings and precautions updated to reflect content of published local innovator PI [product name X, published 2018/05/21]
E.g., C.I.6a	Type II	Addition of a new therapeutic indication or modification of an approved one	Application for an additional indication for Myelofibrosis, supported by new clinical trial data. Indication has been approved by the EMA and FDA.

Amendment history

Module 1.2.1 f) Amendment history reflects the particulars of the previous pharmaceutical amendments (if applicable). Include this history here for amendments

Contact for validation errors:

Should there be validation errors, please contact:

{Name and Surname}

{Designation}

{Email address}

{Contact number}

I declare that:

- the variations are in line with the relevant, current guidelines and/or a motivation for any deviation has been submitted
- no variations other than those stated in the list of changes/amendments have been made

Yours faithfully,

{Name}
{Designation and contact details}

Signed:

_____

APPENDIX A: RELEVANT DOCUMENTS

Guidelines

[2.01]	General information guideline
[2.02]	Quality and Bioequivalence Guideline
[2.08a]	Interim 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
[4.01]	SA Guide to Good Manufacturing Practice
[2.36]	Guideline to the Scheduling of Medicines
[17.05]	SAHPRA Payment Guideline

Templates

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