South African Health Products
Regulatory Authority
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30 September 2025

GUIDELINE FOR VARIATIONS ADDENDUM FOR HUMAN AND VETERINARY MEDICINES

This document provides recommendations to applicants wishing to submit applications for the variation of human and veterinary medicines. In addition to this guideline, the South African Health Products Regulatory Authority (SAHPRA) reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine in keeping with the knowledge current at the time of evaluation. SAHPRA is committed to ensure that all registered medicines will be of the required quality, safety and efficacy.

Document History

Final Version	Reason for Amendment	Effective Date [dd Month yyyy]
1	Publication for comment	[10 May 2019]
2	Adds alterations to codes B.IV.1.a.1 (changes procedure type to Type IB) and B.IV.a.2 (eliminates restriction of the code to be for veterinary products only); Excludes code A.2.a based on non-applicability.	[15 November 2019]
3	Modifies addendum items 4.1.3 and 4.1.7 to include the addition of contraindication as a Type IB. Amends the documentation requirements in tables 5.2.1 & 5.2.2. Introduces the following quality sections to allow SAHPRA an additional review period prior to implementation (4.3.1 - 4.3.4; 4.3.7; 4.3.10 - 4.3.12; 4.3.15) Introduces additional document requirements in 5.4. Provides the requirement of a resolution letter in sections 4.3.8 and 4.3.9	[June 2020]
4	Update to remove additional review period and include alignment of certain quality codes to EMA classification. Alignment with EMA guidelines on Type IA and IA_{IN} in terms of SAHPRA response timelines from date of notification. Update includes revisit of Inspectorate timelines and commitment. Inclusion of documentation for submission of quality and administrative changes are defined. Inclusion of administrative change in proprietary name on certificate. Update on interpretation of	[29 September 2020]

	quality variation fees. Update of templates regarding SAHPRA address change and removal of CD/USB submissions.	
5	Inclusion of variation timelines in section 3. Modifies addendum item 4.1.14 to include procedural exceptions regarding Type IA_{IN} veterinary applications. Introduces document requirements in section 5.2. Update on interpretation of variation fees. Amendment of calendar days to working days.	[01 February 2022]
6	More details added to 4.4.2. Included Types of variations under 5.1. General Included the email address for PEM Quality variation application related queries under 5.3. Quality Additional information included for Points 3, 11, 12 & 14 in Table 5.3.1	[30 September 2022]
7	Consolidation of all variation communications and guidelines for units within SAHPRA. Creating new codes for some variations which were not previously included. Moving from adoption of EMA codes to adaptation of EMA variation classifications and integration of SAHPRA specific requirements.	[30 June 2025]

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Contents

Glossary

Abbreviation/ Term	Meaning
Amendments	Used interchangeably with the term 'variations.'
APIMF	Active Pharmaceutical Ingredient Master File Equivalent to ASMF: Active Substance Master File (EU terminology)
BSE	Bovine Spongiform Encephalopathy
BTIF	Bioequivalence Trial Information Form (OF-PEM-PRE-01J)
CCDS	Company Core Data Sheet
Clone	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.
CP	Comparability Protocol
CTD	Common Technical Document Equivalent to: EU-CTD (EU terminology)
DDPS	Detailed Description of the Pharmacovigilance System
DHCPL	Dear Healthcare Professional Letter
DNA	Deoxyribonucleic Acid
DVPL	Dear Veterinarian Professional Letter
EC	European Commission
eCTD	Electronic Common Technical Document
EMA	European Medicines Agency
EU	European Union
HCR	Holder of the Certificate of Registration Equivalent to MAH: Market Authorisation Holder (EU terminology)[1]
HPLC	High-Performance Liquid Chromatography
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use

ICSR	Individual Case Safety Report
Label	Equivalent to: Labelling (EU terminology)[1]
Legal Status	Includes, but is not limited to, Scheduling Status in South Africa
MAH: Market Authorisation Holder	Equivalent to HCR: Holder of the Certificate of Registration
MCC	Medicines Control Council (now SAHPRA)
MCB	Master Cell Bank
Medicine	Equivalent to Medicinal Product (EU terminology)[1N&S]
N&S	Names and Scheduling
PASS	Post-Authorisation Safety Studies
PBRER	Periodic Benefit-Risk Evaluation Report
PEM	Pharmaceutical Evaluation Management (PEM)
PI	Professional Information Equivalent to SmPC: Summary of Product Characteristics (EU terminology)[1]
PIL	Patient Information Leaflet Equivalent to Package Leaflet (EU terminology)[1]
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance
QC	Quality Control
QIS	Quality Information Summary
QOS	Quality Overall Summary
QP	Qualified person: where reference is made to the qualified person, if the manufacturer is in South Africa, this refers to the Responsible Pharmacist. Where the manufacturing is conducted outside of South Arica, the qualified person as defined by EMA may be applied.
QPPV	Qualified person responsible for pharmacovigilance

RMP	Risk Management Plan
RP	Responsible Pharmacist
RRA	Recognised Regulatory Authority – a term used to refer to the list of regulatory authorities with which SAHPRA aligns itself.
RSA	Republic of South Africa
TOA	Transfer of Applicancy
The Authority	Relevant regulatory authority, in this case SAHPRA
ToHCR	Transfer of the Holder of Certificate of Registration
USRN	Urgent Safety Restriction Notice
VICH	International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products
WCB	Working Cell Bank
WHO	World Health Organization

Definitions of Terms

TERM	MEANING
Adjuvant	A substance or combination of substances used in conjunction with a biological medicine to achieve (for example, increase, accelerate, prolong and/or target) or modulate a specific physiological or immune response to the biological in order to enhance the clinical effectiveness of the biological medicine.

Antigen (vaccine)	**The following definitions apply in this document:** • The active ingredient in a vaccine against which the immune response is raised. It may be a live attenuated preparation of bacteria, viruses or parasites; inactivated (killed) whole organisms; crude cellular fractions or purified active biological ingredients, including recombinant proteins (i.e., those derived from recombinant DNA expressed in a host cell); polysaccharides and conjugates formed by covalent linkage of polysaccharides to components such as mutated or inactivated proteins and/or toxoids; synthetic active biological ingredients; polynucleotides (such as plasmid DNA vaccines); or living vectored cells expressing specific heterologous immunogens. It may also be a combination of the antigens or immunogens listed above. • Intermediate or component that may undergo chemical change or processing in the manufacture of the final product (drug product) and is present in the final product in a modified form intended to furnish the specified activity or effect. Also referred to as Drug Substance, Active Ingredient, or Active Substance in other documents.
Biological Medicine	All medicines that contain a living organism or are derived from a living organism or biological processes. **They include, but are not limited to the following:** i. Plasma-derived and animal products e.g. Clotting factors, immunosera, antivenoms ii. Vaccines iii. Biotechnology-derived medicines (recombinant DNA products), for e.g., rHu-anti-haemophilic factors, hormones, cytokines, enzymes, monoclonal antibodies, erythropoietins, nucleic acids iv. Products developed for Human Gene therapy. Well-characterised, low-molecular mass, medicinal biological compounds, may be excluded by specific regulatory decisions from the biological medicine status,

	and in that case, will not be reviewed through the biological medicines review process.
Change	Refers to any change made to an approved marketing authorisation in product composition, active and non-active ingredients, manufacturing process, quality controls, equipment, containers, shelf life, storage conditions, facilities, or product labelling information by the marketing authorisation holder. This is also referred to as a variation in other documents.
Certificate Variation	Transfer of Applicant and Proprietary Name Change Variation
Comparability Exercise	The activities, including study design, conduct of studies, and evaluation of data, which are designed to investigate whether the products are comparable. In addition to routine analyses performed during production and control of the active biological ingredient or final product, these evaluations typically include further characterisation studies. In some cases, non-clinical or clinical data might contribute to the conclusion.
Comparability Protocol (CP)	The CP establishes the tests to be done and acceptable limits to be achieved to demonstrate comparability of the pre-amendment and post-amendment products following specific quality change(s). A CP is a highly specific, a well-defined plan for the future implementation of a quality (e.g., manufacturing-related changes, change of analytical method and site transfer change. It is also referred to as Post Approval Change Management Protocol in other documents.
Container Closure System	**This system refers to the following components:** • A primary container closure system is a packaging component that is or may be in direct contact with the final product dosage form (e.g., vial, pre-filled syringe). *(Container closure systems for the active biological ingredients or intermediates of medicines normally only include primary container closure systems.)* • A secondary container closure system is a packaging component that is not and will not be in direct contact with the dosage form (e.g., carton, tray).
Dosage Form	This is the pharmaceutical form in which the active ingredients, excipients and physical formulation of a medicine is presented.
Final Lot	A collection of sealed final containers that are homogeneous with respect to the composition of the product. A final lot must therefore have been filled in one continuous working session.

Final Product	A finished dosage form (e.g., tablet or solution) that contains an active ingredient, but not necessarily, in association with inactive ingredients. It is also referred to as a Finished Product or Drug Product in other documents.
Formulated bulk	An intermediate in the drug product manufacturing process, consisting of the final formulation of drug substance and excipients at the concentration to be filled into primary containers.
Holder of the Certificate of Registration (HCR)	An HCR refers to a person or legal entity in whose name a registration certificate has been granted and who is responsible for all aspects of the medicine, including quality, safety, and compliance with conditions of registration.
Intermediate	A material produced during steps in the manufacturing of a medicine that must undergo further processing before it becomes a final product.
Manufacturer	This refers to a person manufacturing a medicine and includes a manufacturing pharmacy.
Master cell bank (MCB)	An MCB is an aliquot of a single pool of cells, which generally has been prepared from the selected cell clone under defined conditions, dispensed into multiple containers and stored under defined conditions.
Prior approval amendment (PAA)	A PAA is an amendment requiring approval from SAHPRA prior to implementation of the amendment. Also, referred to as change application dossier or Type II variation in other documents.
Product Labelling Information	Printed materials that accompany a prescription medicine and refer to all labelling items as per the Medicines and Related Substances Act, 101 of 1965, General Regulations # 10, #11 and # 12): • Professional Information (PI), including prescribing information, which provides product information on indication, dosage and administration, safety and efficacy results, contraindications, warnings, and a description of the product for health care providers. • Inner label or container label • Outer label or carton • Patient Information Leaflet (PIL)
Quality attribute	A physical, chemical, biological or microbiological property or characteristic.
Quality change	In the context of this document, quality change refers to a change in the manufacturing process, product composition, quality control testing, equipment, or facility.

Raw materials	A general term used to denote the culture media components, reagents or solvents intended for use in the production of starting material, drug substance, intermediates, or drug products.
Registration Application	A formal application to SAHPRA for approval to register and market a new medicine. The purpose of the Registration Application is to determine whether the medicine meets the statutory standards for safety, effectiveness, product labelling information and manufacturing.
Source material/starting material	Material from a biological source that marks the beginning of the manufacturing process of a drug as described in a marketing authorisation or licence application and from which the active ingredient is derived either directly (e.g., plasma derivatives, ascitic fluid, bovine lung, etc.) or indirectly (e.g., cell substrates, host/vector production cells, eggs, viral strains, etc.).
Specification	A list of tests, references to analytical procedures, and appropriate acceptance criteria which are numerical limits, ranges or other criteria for the tests described. Specifications are critical quality standards that are proposed and justified by the manufacturer and approved by the regulatory authorities.
Vaccine	Preparations containing antigens capable of inducing a specific and active immunity in humans against an infectious agent or toxin.
Vaccine Efficacy	Relative reduction in disease incidence in vaccinated people compared to unvaccinated people measured in a randomised, placebo-controlled clinical trial. In the context of this guidance document, medicine efficacy relates to all clinical data obtained to ensure medicine efficacy, immunogenicity, or its effectiveness.
Working Cell Bank (WCB)	The WCB is prepared from aliquots of a homogeneous suspension of cells obtained from culturing the master cell bank under defined culture conditions.

1. INTRODUCTION

1.1 Purpose

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 a variation evaluation.

1.2 Scope

SAHPRA has established specific requirements for the submission of amendments/variations to registered products, for human and veterinary medicines, as well as biologicals. This guideline should be read in conjunction with the relevant annexures and SAHPRA guidelines for each specific unit, as well as the latest/revised relevant guidelines and templates listed in Appendix A.

The requirements specified in this guideline and its annexures, are aligned to the framework of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), as well as the International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH). In doing so, SAHPRA will reflect global best practices in terms of the safety, quality and efficacy of health product regulations.

2. LEGAL PROVISION

In accordance with the Medicines and related substances Act (Act 101 of 1965, as amended), Section 15. (3) (a) (i) - (iii), specifies registration of medicines, medical devices or IVDs, which should comply with the prescribed requirements and should be safe, efficacious and of good quality. General regulations regarding the act, regulation 53 (1) and (2) specifies that any changes to accepted standards or specifications of the registered product should be submitted to the Authority for prior approval and approval should be granted before these changes are implemented.

3. Classification of Amendments/Variations

3.1 Sub-heading 1

Type IA variations (notifications):

Minor changes that have minimal or no impact on quality, safety, or efficacy of the product.

Type IA variations are split into two categories with differing procedural treatment:

a) Type IA: Minor variations that do not require any prior approval but must be notified by the HCR within 12 months following implementation (‘Do and Tell’ procedure).

b) Type IA_{IN}: Minor variations that must be notified by the HCR at least 47 working days prior to implementation. If 47 working days have elapsed from the time the notification was submitted, and no communication is received by the HCR from SAHPRA, the HCR may implement the variation.

Upon submission of notification of Type IA or Type IA_{IN} to SAHPRA, the Authority may review the Type IA or Type IA_{IN} notification within 47 working days.

If SAHPRA has not sent the HCR its opinion on the application within 47 working days, the application will be deemed implementable. Applicants must satisfy themselves that they meet all the prescribed conditions for the change and submit all required documentation with the variation submission.

Note: In the case of notifications of Type IA and minor variations of Type IB, failure to meet the specified conditions or provide all necessary documentation in the application, as applicable, may lead to the immediate rejection of the variation, even if the review time has elapsed.

Exceptions: The timeline for Type IA Certificate Variations, for propriety name change and TOA (CV.0.1 and CV.0.2), is 30 working days and can only be implemented once the revised registration certificate is issued.

3.2 Type IB variations (minor variations)

Type IB variations are changes that may have minor impact on the overall safety, efficacy and quality of the product. Applicants must submit all required documentation with the variation submission.

Upon submission of minor variation of Type IB to SAHPRA, the Authority may review the Type IB submission within 87 working days, unless otherwise indicated. If SAHPRA has not sent the HCR its opinion on the application within 87 working days, the application will be deemed implementable (as applicable depending on the variation code).

Note: All Type IA and IB variation applications submitted via the SAHPRA ENGAGEMENT PORTAL and/or FTP require seven (7) working days in addition to the evaluation period, for administrative processes, which is already included in the respective 47 or 87 working days mentioned elsewhere in this guideline.

In the case of notifications of Type IA and minor variations of Type IB, failure to meet the specified conditions or provide all necessary documentation in the application, as applicable, may lead to the immediate rejection of the variation, even if the review time has elapsed.

The timeline for evaluation of Type IB variations is 87 working days. If no response has been received from SAHPRA within this time, changes may be implemented, however SAHPRA may still reject, request reversal of

implementation or request further data after the time has elapsed. Please note that SAHPRA timelines are calculated in working days.

Exceptions: All Type IB applications applicable to Names and Scheduling will require prior approval by SAHPRA before the changes can be implemented, i.e. Proprietary names change applications. The timeline for Names and Scheduling Type IB proprietary name change applications is 100 working days.

3.3 Type II variations

Type II variations are changes that could have major impact on the overall safety, efficacy and quality of the product. The documentation required for the changes included in this reporting type must be submitted for review and prior approval by SAHPRA is required before the changes can be implemented.

To facilitate timeous evaluation and approval of Type II variations, SAHPRA has included the Type II variations classification in this guideline (refer to the relevant annexures as referenced below).

Upon submission of Type II variations to SAHPRA, the Authority will review the Type II submission within 220 working days for all variations.

NOTE: This guideline lists only the minimum technical data requirements for Type II variations. Applicants are advised to include additional data in support of the Type II variation if available. SAHPRA reserves the right to request further data if deemed necessary.

Exceptions

The timeline for Rescheduling Type II variation applications, is 250 working days.
The timeline for Authorised Prescribers Amendment Type II variation applications, which serve as a request made to SAHPRA, is 250 working days.

Note: All Type II variations applications submitted via the FTP require up to 20 working days in addition to the evaluation period, for administrative processes, which is already included in the respective 220 working days mentioned elsewhere in this guideline.

3.4 Classification Codes

For SAHPRA classifications and codes for each of the above-mentioned types of variations, refer to the following annexures per unit:

a. Annexure A: Health Products Authorisation (HPA)

b. Annexure B: Quality (PEM)
c. Annexure C: Clinical (CEM)
d. Annexure D: Names and Scheduling (N&S)
e. Annexure E: Inspectorate (INS)
f. Annexure F: Biological Medicines (PEM)
g. Annexure G: Veterinary Medicines (PEM)

3.5 Where to submit applications

The SAHPRA Engagement Portal is an online platform designed to facilitate interactions between applicants and SAHPRA. The portal enables users to submit and track applications, manage their profiles and ensure compliance with regulatory requirements. File Transfer Protocol (FTP) details must be set under the Organisation Details before attempting to create applications that require eCTD uploads to the SAHPRA FTP Server. A request for the FTP User Guide for Files/Dossier Submission and access to the FTP should be sent to variationsuploadqueries@sahpra.org.za. When requesting access to the FTP, applicants should include the company name and license number.

3.6 Submitting variations for duplicates and 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.

Refer to SAHPRA eCTD Specification 3.1 for additional information.

For 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.

Note: The PI/PIL may need to be separated for variations for different strengths on the advice of the Regulator.

For clinical variation applications of masters/duplicates and clones the applicant should ensure that the proposed **clean** PIs and PILs have the **specific product** name(s) throughout the document (PI/PIL) instead of using 'PRODUCT NAME'.

Note: All clean proposed PI and PIL must be dated, initialled, paginated as page X of Y.

3.7 Submitting grouped variations

3.8 Submission of multiple variations in a single application (grouped variation)

A grouped variation refers to a single application submitted for multiple changes to a marketing authorisation for a medicinal product. These changes can involve different types of variations, but they must be linked to the same marketing authorisation and can be grouped together under specific conditions. While grouping of different types of variations (Type Ia, Type Ib and Type II) is acceptable, variations for different units should not be grouped in a single submission. For information on the acceptable number of variations to be grouped in a single submission, please refer to SAHPRA's Engagement Portal communications or contact HPA at variationsuploadqueries@sahpra.org.za.

There should be a clear link or relationship between the grouped variations. For example, a Type II variation for a new indication might be grouped with Type IA variations for PI/PIL updates.

A common scenario is grouping a major variation (e.g., Type II for a new indication) with consequential variations (e.g., Type IB for new pack sizes or changes to the product information).

Type I variations may be submitted with Type II variations; however, the Type I variations are not implementable until the entire variation submission is approved. Applicants found to have implemented Type I variations prior to the approval of Type II variations within the same submission will have all variations related to the specific submission rejected.

For fees applicable to grouped variations refer to Regulations Regarding Fees Payable in terms of the provisions of the Medicines and Related Substances Act, 1965 (Act No. 101 Of 1965, as amended) related to quality.

For clinical variations, each variation in the grouped submission will be charged as per classification code in accordance with the type of variation submitted. Each variation must be clearly identified as outlined in annexure C and will be charged individually based on its classification. For PV recommendations added to the PI, each recommendation must be accompanied by the corresponding payment. A fee will be charged per PV recommendation submitted.

In general, it is recommended that all identified changes related to the product dossier must be submitted as individual variations in separate submissions with the applicable fees. There should be no grouping of variations related to the same module in the dossier, unless the changes are related. The exception to this is PI/PIL amendments and the annual notifications (Type IA only) for changes made to the dossier in compliance with the pharmaceutical quality system of the manufacturer.

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

3.9 Submitting Quality and Clinical variations together

Quality and clinical variations, that require review by both units, should be submitted separately and sequentially. The relevant Quality and Clinical variation fees will be applicable (follows the same principle for when the applicant applies for new FPP, except the clinical variation is submitted separately from the quality variation).

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

For clinical variations - where amendments have been made on the Quality section of the PI/PIL, the applicant is required to submit the Quality unit approval letter as part of the supporting documents. Applicants to note that amendments to any quality aspects of the medicine within the PI/PIL are subject to Quality Unit approval and may only be implemented in the PI/PIL if approved by the Quality Unit. Where the applicant is just bringing the PI/PIL in line with current PI/PIL guidelines and the Quality aspects were approved at registration the applicant may submit a declaration to confirm that the Quality aspects were approved at registration, and no unsolicited changes have been made.

3.10 Submitting Quality and Inspectorate variations together

Quality and Inspectorate variations that require review by both units should be submitted separately and sequentially.

Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product and/or addition/replacement of a primary packaging site of the finished product will require evaluation by Quality Unit as well as Inspectorate Unit.

The evaluation of Quality and Inspectorate variations are evaluated sequentially. The Quality Unit will do the evaluations first. Once approval is received by the Quality Unit, submit the inspectorate variation and ensure that the Quality approval letter is included. Thereafter the Inspectorate Unit will conduct the evaluation and communicate the final outcome.

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

NOTE: This change is not implementable unless approval is received from both the Quality and Inspectorate Units.

3.11 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.

- In order to encourage the maintenance of reliance throughout the lifecycle of the product, different units in SAHPRA have established reliance mechanisms. Refer to the unit specific sections of this guideline or the relevant annexures for details on applying reliance to registered products.
- 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 (SAHPGL-HPA-07) and Reliance Guideline (SAHGL-BAU-01) contain 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 (SAHPGL-CEM-01), and Quality and Bioequivalence Guideline (SAHPGL-PEM-02).

3.12 Fees

The fees applicable to variations are published in the Government Gazette, Regulations Regarding Fees Payable in terms of the provisions of the Medicines and Related Substances Act, 1965 (Act No. 101 Of 1965, as amended).

Refer to SAHPGL-FIN-01 SAHPRA Payment Guideline for the details of the payment of fees to SAHPRA.

If a bulk payment is made, the breakdown should be clear on the Applications Cover Page. The Proof of Payment and Applications Cover Page should be included in module 1.2.2.1.

Please note that the fees payable for each unit are independently charged as these variations are reviewed independently.

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

3.13 Submission requirements for priority review applications (TYPE II applications only)

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

3.14 Variations status checker

SAHPRA has implemented a Variations Status Checker. This new tool is listed under "Online Services" on the SAHPRA website. The purpose of this tool is to enable applicants to check the status of their new variation(s) submissions.

- Kindly note that the search function is case sensitive and ensure that the application number is typed correctly.
- The status of the submissions is as they appear on the Variations Status Checker.
- For submissions that are not on the Variations Status Checker after seven (7) days from receiving a passed technical validation email notification, the applicant should send an email to **variationsuploadqueries@sahpra.org.za** and not to the Technical Units.

All queries relating to specific unit status updates should be directed to the relevant unit query mailbox.

All queries relating to status updates, z-codes and extension requests for the PEM Post Registration Unit should be emailed to **postregqualityvariations@sahpra.org.za**.

NOTE: Please refrain from directing emails to individual staff members.

Applicants are requested to refrain from sending unnecessary status update queries. An applicant may follow up on the status of a Type II submission if they have not received feedback from the relevant variations' unit, 220 working days after the date of submission.

3.15 Applying for a withdrawal of a variation submission

If a withdrawal of a variation submission is necessary, submit the withdrawal of a variation submission in a follow-up sequence via the SAHPRA Engagement Portal in line with the current eCTD specifications.

The following relevant supporting documentation should be submitted:

- The letter includes the motivation for the withdrawal of the variation submission, signed by the RP.
- Proof of submission of the variation application.

3.16 Submitting the QIS/QOS

The QIS (Quality Information Summary) document is a product lifecycle management document, and it is important that it is updated with each variation made to the product, which affects the QIS.

It is required that an updated and complete QIS be submitted with all quality variation submissions, if affected by the change. 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 e.g.~~,(strike)~~. Once the variation is approved, the applicant can replace the stuck through information on the QIS document with the newly approved data.

A QOS (Quality Overall Summary) is only required for Type II API source change variations. Only the sections of the QOS pertaining to the new source (3.2.S) should be completed.

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

Note: The QIS/QOS is not a requirement for Certification, Clinical, Veterinary and Biological Medicines (Quality and Clinical) Variations.

3.17 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 submission. 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 submission according to the requirements.

Applicants are advised to include a completed validation template in their submission. A PDF and word version of this document should be included in Module 1.2.5.

For z-code applications: All conditions and all documentation requirements are applicable as far as is relevant. Alternatively, the applicant may populate Z-code information in Type II section of the validation template (Section C).

3.18 Format change to the PI and PIL

The format for Professional Information and Patient Information Leaflets is reflected in the updated SAHPRA guidelines SAHPGL-CEM-02 and SAHPGL-CEM-03.

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

Repository of PIs and PILs

SAHPRA has published a repository of PIs and PILs on its website for the benefit of healthcare 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 generic and innovator PI/PIL 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 within five (5) working days. Non-compliance may result in withdrawal of variation approval. For Schedule 0-2, the applicant must upload the approved PI/PIL onto the SAHPRA OTC repository within 10 working days, for uploading onto the PI and PIL repository. Non-compliance may result in withdrawal of the variation approval.

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

Note: For veterinary medicines, all the PIs are attached to the vet medicines database as well.

For quality variations affecting the PI/PIL (e.g., change in appearance of FPP, change in container, storage conditions etc.), include a revised PI/PIL in your submission (in Module 1.5.5).

Once variations affecting the PI/PIL are approved by the Quality Unit, applicants must submit the amended PI/PIL as well as PEM approval letter to the Clinical Unit (refer to Annexure C for clinical codes).

3.19 CERTIFICATE VARIATIONS

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.

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.

Only selected variation applications require the issuing of an amended registration certificate:

- Changes in the proprietary name of a product.
- Transfer of the Holder of Certificate of Registration.

The approval letters issued by the relevant units for all other changes (i.e., amendment to dosage form, changes in the manufacturer, change in formulation), that are reflected on registration certificate must be appended to the current registration certificate.

For transfer of applicant and proprietary name change variations, a separate sequence to issue the revised registration certificate must be submitted and must include the approval letter issued by the naming and scheduling unit and/or approval letter issued by Inspectorate.

Applicants must submit these applications separately, without any technical variations, e.g., adding a new/additional manufacturer and/or a primary packer. This will allow for a streamlined process for certification.

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.

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

3.20 De-linking of dossiers

Refer to the SAHPRA eCTD Specification 3.1 for more information.

3.21 Responding to Queries

If applicable, queries will be communicated to the applicant. The applicant will be requested to submit the correct information in a follow-up sequence. The applicant should also provide proof of upload of the response to the certification mailbox: certificationvariations@sahpra.org.za.

The proprietary name change variation application for the de-linked medicine must be submitted as a follow-up sequence and the applicant should amend the eCTD envelope to remove the details of the master.

3.22 Request for extension

Applicants may submit a written request for one extension of timeline for a response per response round, which may not exceed a further 30 working days.

A written request should be submitted, with a motivation letter attached. Such motivation should be addressed to postregqualityvariations@sahpra.org.za, biological.variations@sahpra.org.za or clinical.variations@sahpra.org.za , and namesandscheduling.variations@sahpra.org.za within 30 working days from the date of the recommendation. The motivation letter should include the product name(s), application number(s) and be submitted along with a copy of the recommendation letter.

Consult the fees guideline for appropriate fees for second response round. Submissions that do not address all queries by the second response round will be rejected.

Note: If an applicant does not respond to the query in the stipulated time and does not communicate any request for extension, this application will be tabled for rejection.

Note: Applicants are reminded that new variations/changes may not be included in response submissions. These new variations should be applied for, in a separate submission. If new variations are of high priority, e.g., variations related to the implementation of pharmacovigilance recommendations, the response-variation application should have proof of payment for the additional variation attached.

The latest SAHPRA fees gazette should be consulted for the appropriate fees payable.

3.23 Period for response submissions and number of query rounds for Clinical Variations Unit

If an applicant does not respond to the query in the stipulated time and does not communicate any request for an extension, the fee paid for the application will be recognised and the applicant will have to make a new payment upon response.

3.24 Inspectorate Permittable Query Rounds

For Inspectorate Type I and II variations, only one query response round will be permitted. If the applicant fails to address the queries within 10 working days, the variation application will be rejected, and the applicant shall re-submit the variation application, with the applicable Type I and Type II Inspectorate fees.

3.25 Quality (PEM Post-registration)

3.26 Quality requirements for baseline submissions and CTD conversions

The CTD checklist **(GLF-HPA-06B)** for quality requirements for baseline submissions has been included (also accessible on the SAHPRA website. Applicants are requested to append the completed checklist to the cover letter (module 1.0) of the baseline submission, only for applications which contain a CTD conversion

variation, (B.II.CTD). In instances where a document specified on the list has not been included in the submission, a justification for the omission must be provided.

3.27 Editorial changes to the quality sections of the dossier

If changes to the dossier only concern editorial changes, such changes need not be submitted as a separate variation but can be included as a notification together with a subsequent variation concerning that part of the dossier. In such a case, a declaration should be provided that the contents of the associated sections of the dossier have not been changed by the editorial changes beyond the substance of the variation submitted.

Editorial changes should always be clearly identified in the cover letter as follows: A brief description of the editorial changes should be provided in the tabulated schedule of amendments. All the editorial changes should be listed in the present/proposed table, and a justification as to why the holder considers them 'editorial' (i.e., why they should not trigger a specific variation) should be provided for each change.

3.28 Unforeseen changes (z-codes)

Any unforeseen changes that have not been detailed in Annexure B of this guideline should be submitted as a "z" code request.

Applicants are to submit "z" code variation requests, for unforeseen changes to the relevant technical unit (Unit Manager and dedicated query email addresses) and wait for confirmation from SAHPRA. The relevant unit will inform the applicant within 10 working days of the correct classification, and the submission fee required, via email. "z" Code submissions, will not be accepted, without prior approval from SAHPRA. The confirmation received from the technical unit should be included in Module 1.0.3, Correspondence from SAHPRA.

The confirmed z-code must be uploaded to the SAHPRA Engagement Portal. To initiate this, the applicant should email portal.data@sahpra.org.za requesting the inclusion of the z-code using the specified table format. The email must also include a copy of the approved z-code letter issued by the technical unit:

variation_code	variation_type	submission_type	risk_level	Implementation_time	description	clinical	Quality	n_s	inspectorate	pv	initial_sequence_fee	initial_sequence_priority_fee	response_fee	response_2_fee	notification_to_hpa_required	document_fee
C.I.6.a	II	sub-type-25	L1	120	Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	1	0	0	0	0	32800	44900		7200	1	850

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.

3.29 The process for Z-code request to the PEM post registration unit is defined below

This process is specific to quality variations, for human allopathic medicines. Prior to submitting a Z-Code request to SAHPRA, the applicant must first confirm that a relevant code for such a variation does not exist in Annexure B of this guideline.

A Z-code request should be submitted to the PEM post-registration unit mailbox, postregqualityvariations@sahpra.org.za, using the Z-code Request Form **(GLF-HPA-06A).** This form is accessible on the SAHPRA website and must accompany the Z-code request email. The applicant must ensure that the Z-code request form and email are included in the submission. Z-code requests are product and sequence specific and may not be re-used for other submissions.

All queries related to PEM quality variation submissions must be submitted via the dedicated email address: postregqualityvariations@sahpra.org.za.

Table 1 – list of key documentation/data required for quality variation applications

1. Letter of application with (M1.0): • Purpose of the variation(s) • Description, Classification and Code of the Variation(s) (e.g., Type IB – B.II.b.3a) • Where a variation involves other products, the applicant must indicate/highlight on the letter of application.
2. Application form (M1.2.1)
3. Proof of payment for the variation application and fees breakdown for bulk payments (M1.2.2.1)
4. Letter of authorisation for communication on behalf of the applicant/PHCR (M1.2.2.2)
5. Dossier product information (M1.2.2.3) (If applicable)
6. API change control (M1.2.2.6) (If applicable)
7. The current approved PI and PIL (M1.3.1.1 & M1.3.2) (if applicable)
8. Amendment/variation schedule (M1.5.2.1)
9. GMP certificates (M1.7.3) (if applicable)
10. SAPC registration (M1.7.7)
11. Responsible pharmacist declaration (M1.7.7) when required.
12. Completed validation template for variation applications indicating whether conditions are met and supporting documents are included as per EMA variation guideline (M1.2.5)
13. Batch Manufacturing Records (M3.2.R.7) for changes to the FP formulation, FP manufacturer, batch size, manufacturing process & equipment, in process control specification (if applicable)
14. Amended QIS (and QOS where applicable) document (M3.2.R.8)
15. BTIF (MS Word format), where variations include a Biostudy (Working documents folder)
Reliance documentation – to be supplied for abridged and verified reviews
16. Unredacted rapporteur assessment reports from RRAs, if available (M1.10)

17. Letter of access granting SAHPRA permission to obtain un-redacted reports from RRAs (attached to the letter of application – M1.0) [Not required in instances where the applicant supplies the unredacted reports of RRAs to SAHPRA directly]

*The submitted specifications and analytical procedures must be signed, dated and version controlled.
*For addition of API, the FPP manufacturer data must be submitted (3.2.S.4 & 3.2.S.5)
* The QIS (and QOS where applicable) 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.

3.30 Clinical Post Registration

3.31 Submission of Type I and II variation(s) application(s)

For variation applications affecting the PI and PIL, approval from the Names and Scheduling Unit must first be obtained before submission of the variation application to the Clinical Unit. For variations affecting the PI and PIL from the PEM Unit, applicants must provide proof of submission.

The submission of Type I and II variation application(s) for evaluation should be classified according to SAHPRA CODES AND VARIATION CLASSIFICATIONS.

Types of submissions that are prohibited:

1. Parallel submissions of variation application(s) are not acceptable, i.e., 1. simultaneous submissions of separate variation application(s) of the same product, 2. submission of variation(s) whilst there is a variation application in progress.

2. Combined variation applications codes for different Units, i.e., Quality and Clinical.

In case of a negative outcome of a Type IAin or Type IB application because the conditions for the variation(s) are not met or because documentation is deficient, the applicant may not use a PI/PIL that was self-implemented but subsequently rejected by the Authority as the currently approved version, as it is not considered fully compliant.

Submitting a new or updated risk management plan (RMP) post-registration

New and updated RMPs should be submitted in a follow-up sequence via the SAHPRA Engagement Portal.

3.32 Period for response submissions and number of query rounds

For Type I and II responses to technical screening queries, only 2 (two) query response rounds will be permitted. If the applicant fails to address the queries adequately by the 2nd (second) query round, the application will be rejected, and the applicant shall submit a new application(s), and the applicable fee shall be payable.

For responses to Type I and II clinical evaluation recommendations, only 2 (two) query response rounds will be permitted. If the applicant fails to address the queries adequately by the 2nd (second) query round, the variation application will be rejected, and the applicant shall re-submit the variation application, with the applicable Type II fees.

3.33 NAMES AND SCHEDULING

Variations applications are categorised as below:

- Proprietary name change: Type IB - Code N.S.1 a-d
- Rescheduling application: Type II – Code N.S.2 a-d
- Authorised Prescribers Amendment: Type II – Code N.S.3. a

3.34 *N.B. All Names and Scheduling Type IB and Type II applications require regulatory approval prior to implementation.* Proprietary Name Change Variation Applications

A guidance on the criteria applied by SAHPRA when evaluating the suitability of a proposed proprietary name for a medicine intended for human or veterinary use is stipulated in the SAHPGL-CEM-NS-03 Guideline for Proprietary Names for Medicines.

The variation application to request a proprietary name change (Type IB) 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 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 proposed, then only one name may appear on all modules.

It is recommended that three (3) proposed proprietary names are submitted for evaluation by application. Where more than three (3) proposed proprietary names are submitted per application, only the first three (3) proposed proprietary names will be evaluated per submission. The timeline for Type IB proprietary name changes is 100 working days.

3.35 Rescheduling Variation Applications

A guide on the criteria for rescheduling of registered medicine or substances is stipulated in the SAHPGL-CEM-NS-02 Guideline Scheduling of Substances and Medicines and SAHPGL-CEM-NS-01 Guideline for the Rescheduling of Substances and Medicines.

Variation applications for the rescheduling of a registered medicine or substance (Type II) for evaluation by the Names and Scheduling Unit, must be submitted via the SAHPRA Engagement Portal. Refer to the SAHPRA eCTD Specification 3.1 for more information.

In the event of a rescheduling application for a product moving to a lower schedule, a unique proprietary name and a separate registration dossier is required.

For rescheduling of an existing registered product to a lower schedule which is part of an existing dossier, a delinking from the master dossier will be required.

The proprietary name change variation application for the de-linked medicine, should be submitted as the next follow-up sequence and the applicant should amend the eCTD envelope to remove the details of the master.

Scheduling of medicines as approved and gazetted by the Minister of Health

Rescheduling recommendations that SAHPRA has approved will be submitted as an amendment to the published Schedules, for consideration by the Minister of Health and publication in the Government *Gazette.*

Applicants are required to update their PI/PIL and all relevant sections of the dossier for the registered product to align with the new requirements as published and gazetted by the Minister of Health.

For Rescheduling Type II variation applications made to SAHPRA, the timeline will be 250 working days.

3.36 Authorised Prescribers Amendment

A guidance on the criteria and policies applied by SAHPRA when evaluating applications for amendments to the Schedules with the objective of specifying substances to be made available for prescription by designated categories of health professionals, other than medical practitioners or dentists, as provided for by section 22A of the Medicines and Related Substances Act, 1965 (Act 101 of 1965) refer to SAHPGL-CEM-NS-04 Scheduling of Substances for Prescribing by Authorised Prescribers other than Medical Practitioners or Dentists.

Authorised Prescribers Amendment applications are requests made to SAHPRA and follow a 250 working day timeline.

3.37 N&S Permittable Query Rounds

The review process for proprietary name changes and rescheduling variation applications will permit for a maximum number of two response rounds. If the applicant fails to address the queries adequately by the second query round, the application will be tabled for rejection.

The applicant will be required to submit a new application, and the applicable fee shall be payable.

Each response timeframe should be within 20 working days of receipt and notification of recommendation variations@sahpra.org.za. Applicants may submit a written request for extension, addressed to variations@sahpra.org.za and namesandscheduling.variations@sahpra.org.za.

3.38 Inspectorate

All queries related to Inspectorate variation applications must be submitted via the dedicated email address: variations.inspectorate@sahpra.org.za.

For Proprietary Name Change, the Inspectorate Unit should verify the GMP status of the manufacturing site listed in the medicines register prior to an updated registration certificate being issued. Therefore, applicants must apply for GMP Site verification to the Inspectorate Unit using an Inspectorate code simultaneously when applying for Proprietary name change. Applicants are reminded to include valid GMP certificates/Licence/Resolution letter when applying for GMP Site verification for proprietary name change.

For Transfer of Applicancy, applicants are advised not to include Proprietary Name Change when applying for Transfer of Applicancy. The applicant is requested to apply for TOA first and after receiving approval from Inspectorate they can then apply for PNC. Certification will only begin processing the revised registration certificate once the approval letter from both the Inspectorate and N&S is received.

3.39 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:

Inspectorate reserves the right to reject or approve the inspection outcome from the inspection conducted by an Authority in which a GMP MRA with SAHPRA exists. Refer to the Guideline SAHPGL-INSP-02_v8-Guideline-on-Good-Manufacturing-Practice-for-Medicines, Section 3.2.

Standard documentation for Inspectorate variation applications (Refer eCTD Validation and Technical screening for Variation).

3.40 Documentation/ data requirements

3.41 General

All variation submission should include an application form, available on the SAHPRA website, the cover letter and tabulated schedule of amendments (see appendix).

3.42 Clinical and Pharmacovigilance

Table 2 below covers all the *potential* documentation/data requirements for a given submission (to be read in conjunction with both the SAHPGL-CEM-01 Clinical Guideline and 2.24 Guidance for the Submission of the South Africa CTD / eCTD – General & Module 1). This represents the key requirements for variations applications – applicants may submit other relevant documentation not listed in Table 2 as needed. **Note** that the MRF4 form is no longer required.

This is followed by Table 3, which provides the requirements for each code applicable to Clinical and Pharmacovigilance.

Table 2 – list of key documentation/data required for clinical variation applications

Standard documentation for variation applications

18. Letter of application with a company letter head (M1.0):
    - Purpose of the variation(s)
    - Description, Classification and Code of the Variation(s) (e.g. Type II – C.I.4)
    - Where a variation leads to or is the consequence of other variations to the term of the same registered medicine, a description of the relation between these variations should be provided in the appropriate section of the application
    - Where a variation is considered 'unforeseen' (i.e. C.I.13), a brief explanation/justification is required
    - Where a variation is the implementation of wording requested by SAHPRA, reference to the associated agreement/assessment/decision should be attached to the letter of application
19. Application form (M1.2.1)
20. Proof of payment for the Variation application (M1.2.2.1)
21. The current approved dated PI and PIL (M1.3.1.1 & M1.3.2)
22. Annotated/revised proposed PI and PIL as well as the clean versions (M1.3). The annotated/revised proposed PI and PIL should be dated, initialled, paginated as page X of Y.
23. Validation template for variation applications (M1.2.5)

24. For generic applications, the latest approved South African innovator PI, and if the medicine is no longer marketed in South Africa, the most recently updated SAHPRA approved generic medicine PI (M1.3.1.2)

Additional requirements for selected variation applications

25. Dear Healthcare Professional (DHCP) Letter (attached to the letter of application – M1.0)
26. PBRER/PSUR (M5.3.6)
27. RMP (M1.8.2
28. Peer-reviewed literature-based studies in support of the proposed variation(s) (M5)

Clinical data [where applicable for relevant Type II variations]

29. Overview of clinical data supporting the proposed variation(s) (M2.5)
30. Synopsis of each clinical study supporting the proposed variation(s) (M2.7)
31. Clinical expert reports with data/information relevant to the proposed variation(s) of the PI (M2.5)
32. Clinical study data relevant to the proposed variation(s) of the PI (M5)
33. Studies demonstrating additional pharmacokinetic properties in special populations, if not studied previously (M5)

Reliance documentation – to be supplied for both abridged and verified reviews

34. Latest approved SmPC/ PI approved by a RRA, where applicable (M1.10.3)

Reliance documentation – to be supplied for abridged reviews of Type II variations only

35. Unredacted rapporteur assessment reports from RRAs, if available (M1.10)
36. Letter of access granting SAHPRA permission to obtain unredacted reports from RRAs (attached to the letter of application – M1.0) [Not required in instances where the applicant supplies the un-redacted reports of RRAs to SAHPRA directly]

37. Correspondence between the applicant and other RRAs, concerning queries relating to safety, efficacy, risk/benefit and RMP issues. Detailed explanation/reasons if registration/approval was refused by a Regulator with which SAHPRA aligns itself (M1.10.1)
a. For variations submitted in eCTD format: • When clinical data is required, the data submitted should be limited to the proposed variation – data in support of the initial registration alone is not required. • b. Refer to the SAHGL-BAU-01 Reliance Guideline, which defines the evaluation pathways for variations, along with the requirements for the letter of access.

Table 3 – documentation/data requirements for the codes implemented by SAHPRA

EMA/SAHPRA variation code	SAHPRA classification	Document/data requirements
C.I.0.1	Type IA_{IN}	1 – 6
C.I.0.2a - C.I.0.2b	Type IA_{IN} - Type IB	1 – 6 - 1 – 6
C.I.0.3	Type IB	1 – 6, (11 – 16)*, 17
C.I.2a - C.I.2b	Type IB - Type II	1 – 7; 17^{+} - 1 – 7; (11 – 16)*; $(17 – 20)^{+}$
C.I.3a - C.I.3b	Type IA_{IN} - Type II	1 – 6; 8* - 1 – 7, (8 – 16)*; $(17– 20)^{+}$
C.I.4	Type II	1 – 7; (9 – 16)*; $(17 – 20)^{+}$
C.I.5a - C.I.5b	Type IA_{IN} - Type II	1 – 7 - 1 – 7;
C.I.6a -	Type II -	1 – 7; (11 – 16)*; $(17 – 20)^{+}$ -

C.I.6b - C.I.6c	Type II - Type IB	1 – 7; (11 – 16)*; (17 – 20)+ - 1 – 7
C.I.7a - C.I.7b	Type IB - Type IB	1 – 7, - 1 – 7,
C.I.10	Type IA_{IN}	1 – 6
C.I.11a - C.I.11b	Type IA_{IN} - Type II	1 – 6 - 1 – 7; (9 – 16)*; (17 – 20)+
C.I.12	Type IA_{IN}	1 – 6
C.I.13a - C.I.13b	Type IB - Type II	1 – 7 - 1 – 7; (9 – 16)*; (17 – 20)+
C.I.13c	Type II	1-6; (12-16)
* Where applicable + where an abridged or verified review is applicable (i.e. where the variation has been approved by either SAHPRA or an RRA)		

3.43 Work-sharing and extension applications

3.44 Work-sharing

SAHPRA will not be adopting the EU procedures related to work-sharing. For information on SAHPRA's reliance pathways, consult the Reliance guideline.

3.45 Extension applications

SAHPRA will adopt the EU classification of extension applications for human and veterinary medicines, outlined in Annex I of the EU variations regulation (EC Regulation No. 1234/2008). These applications fundamentally alter the terms of the initial registration and thus cannot be evaluated according to a variation's procedure. Extension applications will typically be accompanied by a new registration certificate.

The following classifications in Annex I are excluded, as biologicals and complementary medicines are currently out of the scope of the adoption of EU variations guidelines:

- 1(c)
- 1(d)
- 1(f)

In terms of procedure, extension applications will be treated as new registrations by SAHPRA. Note the following exceptions in terms of documentation requirements:

- Data submitted in support of such applications should be limited to the extension (i.e., there is no need to submit data / references in support of the initial registration)
- Applicants should include the latest approved PI and PIL of the initial registered product.

3.46 Appendix

The following must be included as part of the submission of a variation application to SAHPRA:

a) Letter of application – M1.0
b) Tabulated Schedule of Amendments – M1.5.2.1
c) Medicine Register Details – M1.5.2.2
d) Affidavit by the HCR / Applicant – M1.5.2.3
e) Relevant documents

4. REFERENCES

The following related documents are referenced: Appendix A.

5. VALIDITY

This guideline is valid for a period of five (5) years from the effective date of revision and replaces the old revision (v6). It will be reviewed on this timeframe or as and when required.

APPENDIX A: RELEVANT DOCUMENTS

Appendix A1: Guidelines

[SAHPGL-HPA-07]	**General information guideline**
[SAHPGL-PEM-02]	**Quality and Bioequivalence Guideline**
[SAHPGL-HPA-06]	**Variations Addendum for Human and Veterinary Medicine**
[SAHPGL-CEM-01]	**Clinical guideline**
[SAHPGL-CEM-03]	**Guideline for Patient Information Leaflet for Human Medicines**
[SAHPGL-CEM-02]	**Guideline for Professional Information for Human Medicines**
[2.23]	**Submission in eCTD format**
[2.58]	**Submission in eSubmission format**
[SAHPGL-PEM-BIO-05]	**Biological medicines amendment guideline**

[SAHPGL-PEM-VET-04]	**General Information Guideline for Veterinary Medicines**
[SAHPGL-PEM-VET-02]	**Veterinary Medicines Clinical Guideline**
[SAHPGL-INSP-02]	**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**
[SAHGL-BAU-015.08]	**Reliance Guideline**

Appendix A2: Templates

[GLF-HPA-03A]	**SAHPRA Variation Validation Template for eCTD**
[6.42]	**SAHPRA Variation Validation Template for eSubmission**
[GLF-PEM-02C]	**Template for Module 2.3_Quality Information Summary (QIS)**
[GLF-PEM-02D]	**Template for Module 2.3_Quality Overall Summary (QOS)**

Appendix A3: LETTER OF APPLICATION

Instructions for applicant in grey (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

2nd Floor Loftus Park

Kirkness Rd

Arcadia

Pretoria

0083

{Letter Date}

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 has been 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.

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:

Tabulated Schedule of Amendments

Note: Landscape format is recommended for this table. A column headed "Effect of amendment" is only applicable to Module 3.2.P.1 and should NOT be included for the whole table. Only those variations / amendments listed in the table below may be reflected in the dossier.

The amended Modules are as follows:

Modules	**Comparison between Modules**		**Reason for amendment**	**Reviewer's comment**
	Existing	Amended		
Example 1 is **not acceptable** – it will take longer to evaluate as the changes have not been identified for easy reference. The format of example 2 is recommended as evaluation is facilitated by the identification of the specific items.				
Example 1 3.2.P.8	Stability report: XXX	Stability report YYY replaces report XXX	Includes stability data on 2 batches stored for 36 months	
Example 2 3.2.P.8.3	Stability data on two production batches stored for 24 months	Stability data on the same two production batches	Extension of the shelf- life to 36	

	(about 2 years) at 25 ºC/60 % RH and for 3 months at 40 ºC/75 % RH submitted.	stored for 36 months at 25 ºC/60 % RH included.	months applied for.	
	No index attached data only referred to.	Detailed index included	Administrative update to facilitate review.	
3.2.P.8.1	Shelf-life of 24 months approved.	A discussion of the results is included, and a 36-month shelf-life is inferred.	Extension of the shelf- life to 36 months applied for.	

Note: Stability specification limits should be reflected in the stability report. Out-of-specification results should be addressed.

Medicine Register Details

The following information should be included in Module 1.5.2.2.

1. **Product to which this application refers**

Proprietary name of medicine	Registration/Reference number	Registered medicine (R) / Old Medicine (OM)

2. **Details** (if there is no change to the "Current", indicate as such under "Proposed", do not state N/A)

	Details on Current registration certificate/old medicine letter	Details on Proposed registration certificate/old medicine letter
Proprietary Name		
HCR/Applicant		
Name of Address		

Contact person:		
Name		
Designation		
Telephone no.		
Manufacturer		
Name and Address		
SAHPRA License No.		
SMF Reference No.		
Packer		
Name and Address		
SAHPRA License No.		
SMF Reference No.		
FPRC		
Name and Address		

SAHPRA License No.		
SMF Reference No.		
FPRR		
Name and Address		
SAHPRA License No.		
SMF Reference No.		
Formulation	If the formulation is the same, confirmation of this effect will suffice.	

Affidavit by the HCR / Applicant

The following affidavit should be included in Module 1.5.2.3. The affidavit should be on company letterhead and include only those statements relevant to the application. In the case of a Transfer of the Certificate of Registration (ToHCR), this must be done by the proposed HCR.

AFFIDAVIT BY THE HCR / APPLICANT

PRODUCT NAME: { } REGISTRATION NUMBER: { }

I, {insert full name and surname} Responsible Pharmacist [as defined in Section 22C(1)(b) of Act 101 of 1965] of {insert Company name} confirm that:

1. I am in possession of the master documentation pertaining to the above-mentioned medicine.
2. This master documentation is the same as that which was in existence when the medicine was initially registered or which has been updated in accordance with amendments of the medicine registration form (MRF1/CTD) in accordance with the provisions of the regulations under the Medicines and Related Substances Control Act, 1965 (Act 101of 1965).
3. The master documentation conforms with the Registration dossier;
4. The master documentation is properly authorised (i.e., signed and dated by at least the responsible pharmacist), *and* the quality assurance or production manager as applicable;
5. The master documentation has been supplied to the new manufacturer/packer or laboratory {state company and role} and that applicable control records have been compiled. I confirm further that I have signed these to indicate my approval that they contain all the requirements listed in the relevant

master documents; namely

- formulation and method of manufacture and packaging in-process control procedures
- specifications pharmaceutical ingredients specifications for the final product specifications for the packaging material specifications for the label
- specifications for the package insert
- testing procedures for the pharmaceutical ingredients testing procedures for the final product
- testing procedures for the packaging materials.

6. I confirm that a technical agreement and/or signed contract(s) exist(s) with all third-party manufacturer(s)/packer(s)/laboratory(ies) involved in manufacturing of this product.

7. For an alternative/additional manufacturer:

- I confirm that the manufacturing procedure (including equipment) is identical to the manufacturing procedure currently used or
- I confirm that the manufacturing procedure (including equipment) differs, but falls within the <Type IA><Type IA_{IN}>< and><Type IB> amendments or
- I confirm that the manufacturing procedure (or equipment) is different from the manufacturing procedure (or equipment) currently on file outside of the <Type IA><Type IA_{IN}>< and><Type IB> amendments and that comparative data (efficacy), stability data or protocol (as applicable), and a validation protocol for the first three production batches, are submitted.

8. <I confirm that the PI will be updated to reflect the new HCR details and will submit the amended PI with the first update of the dossier after authorisation of this amendment. (for ToHCRs only)>

9. <I confirm that the Registration dossier will be fully updated to the current statutory format and current scientific standards within 12 months of transfer of the certificate of registration, or approval of additional, or change of manufacturer.>

OR

<I confirm that the Registration dossier will be fully updated to the current statutory format and current

scientific standards by (stipulate date) in accordance with the programme as approved by the Inspectorate.>

Signed on {DD/MM/YYYY}: