South African Health Products
Regulatory Authority
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30 September 2022

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, 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.
This guideline will be available from the office of the Chief Executive Officer and the website after consolidation of all comments

Document History

Final Version	Reason for Amendment	Effective Date
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 IAin 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 quality variation fees. Update of templates regarding SAHPRA address change and removal of CD/USB submissions.	[29 September 2020]
5	Inclusion of variation timelines in section 3. Modifies addendum item 4.1.14 to include procedural exceptions regarding Type IAin veterinary applications.	[01 February 2022]

	Introduces document requirements in section 5.2. Update on interpretation of variation fees. Amendment of calendar days to working days.	
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]

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CHIEF EXECUTIVE OFFICER

Contents

List of abbreviations and definitions

Amendments	Used interchangeably with the term 'variations'
APIMF	Active Pharmaceutical Ingredient Master File Equivalent to ASMF: Active Substance Master File (EU terminology)[1]
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
CTD	Common Technical Document Equivalent to: EU-CTD (EU terminology)[1]
DDPS	Detailed Description of the Pharmacovigilance System
DHCP	Dear Healthcare Professional (letter)
DVP	Dear Veterinarian Professional (letter)
EC	European Commission
eCTD	Electronic Common Technical Document
EMA	European Medicines Agency. This translates to SAHPRA where the national authority is referenced
EU	European Union
HCR	Holder of the Certificate of Registration Equivalent to MAH: Market Authorisation Holder (EU terminology)[1]
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)
Medicine	Equivalent to Medicinal Product (EU terminology)[1]
Package Leaflet	Equivalent to PIL: Patient Information Leaflet
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
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 manufacture is carried out outside South Arica, the qualified person as defined by EMA may be applied
QPPV	Qualified person responsible for pharmacovigilance
RMP	Risk Management Plan
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 Equivalent to EU: European Union (EU terminology)[1]

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

1. Note that the EU terminology is not being adopted for use in South Africa. The equivalent EU terms are simply included here to aid interpretation of the EU variations classification guideline and EU variations regulation. Where the relevant EU guidelines / regulations refer to this terminology, applicants should apply and interpret the equivalent SA wording.

To clarify the term 'EU' itself: Where this term is referred to geographically, applicants / HCRs should interpret 'South Africa' instead (e.g., reference to manufacturing sites outside of the EU should be interpreted as manufacturing sites outside of SA)

Note that where the relevant EU guidelines / regulations reference EU-specific databases, e.g., EudraGMP, applicants should apply and interpret equivalent SA databases, or ignore these references.

1. INTRODUCTION

The South African Health Products Regulatory Authority (SAHPRA) has decided to harmonise certain SAHPRA human and veterinary medicine policies and procedures with those of the European Medicines Agency (EMA). These in turn 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). By doing so, SAHPRA will reflect global best practices in terms of the safety, quality and efficacy of health product regulation.

SAHPRA will adopt the EU variation classification guidelines for human and veterinary medicines[1] in full (link to relevant EU variations guidelines). This yields ongoing benefits as any updates to the EU guidelines will simultaneously be updates for SAHPRA. However, there will be specific exceptions for SAHPRA including:

- Alterations: EU codes/procedures adopted by SAHPRA with an adjustment for implementation in South Africa
- Exclusions: EU codes/procedures that will not be adopted by SAHPRA
- Additions: Additional codes created by SAHPRA

To facilitate a smooth transition to the EU variation classification guidelines, SAHPRA has clarified the interpretation of selected EU codes. These are termed 'clarifications.' Note that clarified codes are still adopted by SAHPRA in full.

This guideline details the *exceptions* to the adoption, and must be read in conjunction with the EU variation classification guidelines. Any guidance in the EU variation classification guidelines that is neither altered nor excluded in this guideline is implicitly adopted in full by SAHPRA.

Please note: Unless mentioned otherwise, where EMA guidelines adopted in South Africa include references to European Union (EU) legislation, the requirements contained in the referenced EU legislation are not applicable to the evaluation of medicines by SAHPRA. South African legislation will apply wherever relevant and current.

Applicants should consult the BAU Variations Communication for guidance on the submission procedure for variations applications.

2. IMPLEMENTATION

SAHPRA's adoption of the EU variation classification guidelines was implemented from 15 November 2019 for all Type IA and Type IB applications. Any variation applications re-submitted for evaluation should be classified according to newly adopted EU codes, regardless of former classification under MCC guidelines.

Applicants need to notify SAHPRA of the Type IA and Type IB variations through an online portal. Applicants must comply with new data requirements as per EU guideline and the SAHPRA variation addendum.

SAHPRA will adopt / follow the same timelines as the EU for the implementation of any future changes to the EU variation classification guidelines (e.g., if the EU implements a 3-month transition period associated with a new requirement, the same timelines will apply in South Africa).

1 Any guidance regarding complementary and biological medicines referenced in the EU variations guidelines does not apply to SAHPRA – existing guidelines will apply.

The BAU Variations Communication explains the process and timelines for variation resubmissions, notifications, and new submissions.

3. DEFINITIONS

SAHPRA adopts the definitions of extensions and Type IA, Type IB and Type II variations detailed in the EU variations regulation (link to regulation). Note that 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 do not require any prior approval but must be notified by the HCR immediately following implementation

It must be noted that upon submission of notification of Type IA or Type IA_{IN} to SAHPRA, the agency may review the Type IA or Type IA_{IN} notification within 30 working days.

For Type IA and Type IA_{IN} variations, if SAHPRA has not sent the HCR its opinion on the application within 37 working days the application will be deemed implementable.

Type IB variations are changes that may have minimal effects on the overall safety, efficacy and quality of the FPP. Applicants must satisfy themselves that they meet all of the prescribed conditions for the change and submit all required documentation with the variation application.

It must be noted that upon submission of notification of Type IB to SAHPRA, the agency may review the Type IB notification within 30 working days for quality, and/or inspectorate and within 60 working days for clinical variations.

For Type IB variations, If SAHPRA has not sent the HCR its opinion on the application within 37 or 67 working days (as applicable depending on the variation code) the application will be deemed implementable.

Note: All Type I variations applications submitted via the DVP and/or FTP require 7 working days in addition to the evaluation period, for administrative processes.
While in the case of minor variations of Type IA and Type IB, failure to provide all necessary documentation in the application will not necessarily lead to the immediate rejection of the variation if the holder provides any missing documentation immediately on request of SAHPRA,

However, a minor variation of Type IA and Type IB may be rejected in specific circumstances with the consequence that the holder of the registration certificate must immediately undo the already implemented variations concerned.

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

It must be noted that upon submission of Type II variations to SAHPRA, the agency may review the Type II within 120 working days for all variations.

Note: All Type II variations applications submitted via the FTP require 7 - 15 working days in addition to the evaluation period, for administrative processes.

4. EXCEPTIONS TO THE EU VARIATION CLASSIFICATION GUIDELINE

4.1 Clinical, Pharmacovigilance and Veterinary (C.I)

a) Summary of SAHPRA codes and variation classifications

Table 4.1.1 below summarises the C.I codes adopted by SAHPRA, along with any exceptions. Sections (b) and (c) that follow provide the details of all code-related and procedural exceptions.

Table 4.1.1 – summary of codes adopted/excluded for Clinical, Veterinary and Pharmacovigilance

SAHPRA/EMA code	Code description	Exception type	Exception number
C.I.0.1	Format updates to the PI/PIL in accordance with relevant changes to the Act, general regulations and guidelines	Addition	4.1.1
C.I.0.2a – C.I.0.2b	Implementation of editorial changes to the PI/PIL	Addition	4.1.2
C.I.0.3	Safety or safety-related change(s) in the PI/PIL of an innovator medicine, which has been approved by a RRA, and which does NOT alter the clinical benefit-risk profile for the use of the medicine, or does NOT soften any safety or safety related information	Addition	4.1.3
C.I.1a – C.I.1c	Change(s) in the PI, PIL or Label intended to implement the outcome of a Union referral procedure	Exclusion	4.1.4
C.I.2a – C.I.2b	Change(s) in the PI or PIL of a generic/biosimilar medicine following assessment of the same change for the reference product	Adopted with clarification	4.1.5
C.I.3a – C.I.3b	Change(s) in the PI, PIL or Label of human medicines intended to implement a recommendation from the Authority arising from a USRN, PSUR, PASS, PBRER, or RMP, including those approved by a RRA.	Adopted with clarification	4.1.6
C.I.4	Change(s) in the PI, PIL or Label due to new quality, preclinical, clinical or pharmacovigilance data	Adopted with clarification	4.1.7
C.I.5a – C.I.5b	Change in the legal/scheduling status of a medicine	Alteration	4.1.8
C.I.6a – C.I.6c	Change(s) to therapeutic indications	Alteration	4.1.9
C.I.7a – C.I.7b	Deletion of a pharmaceutical form / strength	None[2]	N/A
C.I.8a	Introduction of, or changes to, a summary of	Exclusion	4.1.10

2 Code adopted as-is, without exceptions

	pharmacovigilance system for medicines for human use		
C.I.9a – C.I.9d	Change(s) to an existing pharmacovigilance system as described in the detailed description of the pharmacovigilance system (DDPS)	Exclusion	4.1.11
C.I.10	Change in the frequency and/or date of submission of periodic safety update reports (PSUR) for human medicines	None[3]	N/A
C.I.11a – C.I.11b	Introduction of, or change(s) to, the obligations and conditions of a registration / HCR, including the RMP	None[3]	N/A
C.I.12	Inclusion or deletion of black symbol and explanatory statements for medicines in the list of human and veterinary medicines that are subject to additional monitoring as prescribed by SAHPRA	Adopted with clarification	4.1.12
C.I.13a – C.I.13b	Other variations not specifically covered elsewhere in the EU variation classification guidelines	Alteration	4.1.13

b) Code-related exceptions

4.1.1	**Exception type**	Addition	**SAHPRA code**	C.I.0.1
EMA classification		NA	**SAHPRA classification**	Type IA_{IN}
Code description		Format updates to the PI/PIL in accordance with relevant changes to the Act, general regulations and guidelines		
Details		Enables applicants to update the PI/PIL to the most recent EMA format (according to SAHPRA's PI and PIL guidelines) and notify SAHPRA. This code is strictly limited to format changes and may not be used to align other content of the PI/PIL with changes to the Act, general regulations and guidelines. Note: Changes made to the PI shall apply to the PIL and are simultaneously incorporated into the PIL. There is no PIL requirement for veterinary medicines.		

4.1.2	**Exception type**	Addition	**SAHPRA code**	C.I.0.2a – C.I.0.2b
EMA classification		NA	**SAHPRA classification**	Type IA_{IN} (a); Type IB (b)
Code description		Implementation of editorial changes to the PI and PIL a) Changes that do not have an impact on the safe use of medicines (e.g. deleting obsolete information, improving the flow of information, harmonising or combining of PIs within a range in line with recent approvals)		

	b) Changes that have an impact on the safe use of medicines
Details	Allows applicant to make editorial changes to the PI/PIL and notify SAHPRA.

4.1.3	**Exception type**	Addition	**SAHPRA code**	C.I.0.3
EMA classification		NA	**SAHPRA classification**	Type IB
Code description		Safety or safety-related change(s) in the PI/PIL of an innovator medicine, which has been approved by a RRA, and which does NOT negatively alter the clinical benefit-risk profile for the use of the medicine, or does NOT soften any safety or safety related information (e.g. addition of post-marketing side effects / special warnings and precautions for use / interactions / addition of contraindications)		
Details		Code introduced to expedite updates which strengthen the safety profile of an innovator medicine, where the updates have been approved by a RRA. This code is NOT to be used for the following (non-exhaustive) variation applications: • Changes to indications • Changes to posology and method of administration • Changes to the composition/formulation • Deletion / modification of contraindications Any additions to special warnings and precautions for use applied for under this code may NOT contradict existing contraindications approved by SAHPRA. Contraindications already approved by SAHPRA may not be deleted or modified to align with RRA. (The existing contraindications on PIs were based on clinical data reviewed by SAHPRA, and any changes made to the contraindications should be substantiated by data, which SAHPRA will need to review) For the addition of special warnings and precautions for use / contraindications applied for under this code, applicants are required to submit any new data in support of the application to SAHPRA, primarily for record-keeping purposes. However, SAHPRA may review the data as part of the evaluation where necessary on a case-by-case basis. Where a safety restriction regarding special warnings and precautions for use is deemed urgent, applicants must follow the USRN procedure instead and use code C.I.3.		

4.1.4	**Exception type**	Exclusion	**EMA code**	C.I.1a – C.I.1.c
EMA classification		Type IA_{IN} (a); Type IB (b); Type II (c)	**SAHPRA classification**	N/A

Code description	Change(s) in the PI, PIL or Label intended to implement the outcome of a Union referral procedure
Details	This code is excluded as it is specific to EMA referral procedures – SAHPRA additions will cover any variations relevant to South Africa that fall under C.I.1.

4.1.5	**Clarification**		
EMA/SAHPRA code	C.I.2a – C.I.2b	**EMA/SAHPRA classification**	Type IB (a); Type II (b)
Code description	Change(s) in the PI or PIL of a generic/biosimilar/clone medicine following assessment of the same change for the reference product		
Details	The term 'reference product' refers to the associated local South African innovator product. There are, however, two exceptions: 1) The latest SAHPRA-approved generic medicine may be used as a reference where the local South African innovator is no longer marketed / is de-registered / is materially outdated 2) The most recently approved PI of a RRA may be used as a reference for safety updates in instances where the local South African innovator is outdated Note that any changes to contraindications and special warnings and precautions for use applied for under this code may NOT contradict existing contraindications approved by SAHPRA.		

4.1.6	**Clarification**		
EMA/SAHPRA code	C.I.3a – C.I.3b	**EMA/SAHPRA classification**	Type IA_{IN} (a); Type II (b)
Code description	Change(s) in the PI, PIL or Label of human medicines intended to implement a recommendation from the Authority arising from a USRN, PSUR, PASS, PBRER, or RMP, including those approved by a RRA.		
Details	Code description clarified for implementation in South Africa. Note that the implementation of conditions for registrations fall under code C.I.11a – C.I.11b. For urgent safety restrictions, code C.I.3 should be used together with the USRN procedure initiated by the HCR. In these instances, code C.I.3 takes preference over other codes which may result in similar changes to the PI/PIL, but where the variation application is not deemed urgent (e.g., the addition of a warning / contraindication may also arise through codes C.I.0.3 and C.I.4 where no USRN procedure is required).		

4.1.7	Clarification		
EMA/SAHPRA code	C.I.4	**EMA/SAHPRA classification**	Type II
Code description	Change(s) in the PI, PIL or Label due to new quality, preclinical, clinical or pharmacovigilance data		
Details	SAHPRA adopts this code in full, but wishes to clarify example variations that fall under this code. See non-exhaustive list below: • Amendment to approved dosage instruction/information • Modification / deletion of a contraindication • Changes to the benefit-risk profile of the medicine • Safety-related changes that stem from significant public health concern, food safety or environmental changes Where a safety restriction is deemed urgent, applicants must follow the USRN procedure instead and use code C.I.3. For a generic / biosimilar / clone medicine code C.I.2 will apply instead when the same change has already been implemented for the associated reference product.		

4.1.8	Exception type	Alteration	**EMA/SAHPRA code**	C.I.5a – C.I.5b
EMA classification		Type IB (a); Type II (b)	**SAHPRA classification**	Type IA_{IN} (a); Type II (b)
Code description		Change in the legal / scheduling status of a medicine a) For generic / biosimilar/ clone medicines following an approved legal status change of the reference medicine / product b) All other legal / scheduling status changes		
Details		Legal / scheduling changes for generic, clone and biosimilar products have been re-classified as Type IA_{IN} variations where the same change has already been effected for the reference medicine. Note that the reference medicine may not necessarily be the associated South African innovator and could be another South African generic medicine. For C.I.5a to qualify as a Type IA_{IN} variation, any conditions applicable to re-scheduling of the local reference product must also be adhered to by the applicant. Where indications change as a result of re-scheduling, the associated codes (e.g., C.I.2a, C.I.6c) will apply and the overall application will no longer be treated as a Type IA_{IN} variation. Applicants are advised that C.I.5.b changes are alignments of the PI to a scheduling change as published in a gazette and does not refer to an amendment to the schedule of a product		

4.1.9	**Exception type**	Alteration	**EMA/SAHPRA code**	C.I.6a – C.I.6c
EMA classification		Type II (a); Type IB (b)	**SAHPRA classification**	Type II (a, b); Type IB (c)
Code description		Change(s) to therapeutic indications a) Addition of a new therapeutic indication or modification of an approved one b) Deletion of a therapeutic indication due to safety and efficacy reasons c) Deletion of a therapeutic indication due to non-safety/efficacy reasons		
Details		Where the applicant applies for the deletion of therapeutic indications for safety and efficacy reasons, the variation shall be treated as a Type II. All other deletions of a therapeutic indication shall be treated as a Type IB (e.g., due to marketing / commercial reasons). Note that the code description applicable to SAHPRA has been altered and is reflected above. Where the deletion of a therapeutic indication is deemed urgent for safety and efficacy reasons, applicants must follow the USRN procedure instead and use code C.I.3. Code C.I.2a applies to generic / biosimilar/ clone products aligning their therapeutic indications with those of the local innovator products (see the note regarding C.I.6 in the EU variations classification guideline).		

4.1.10	**Exception type**	Exclusion	**EMA code**	C.I.8a
EMA classification		Type IA_{IN} (a)	**SAHPRA classification**	N/A
Code description		Introduction of, or changes to, a summary of pharmacovigilance system for medicines for human use		
Details		Code currently excluded as the underlying requirements (e.g., QPPV) are not applicable in South Africa. This code may be adopted in future, with related guidance to be provided in SAHPRA's pharmacovigilance guidelines.		

4.1.11	**Exception type**	Exclusion	**EMA code**	C.I.9a – C.I.9d
EMA classification		Type IA_{IN} (a, b, d); Type IA (c)	**SAHPRA classification**	N/A
Code description		Change(s) to an existing pharmacovigilance system as described in the detailed description of the pharmacovigilance system (DDPS)		
Details		Code currently excluded as the underlying requirements (e.g. QPPV) are not applicable in South Africa. This code may be adopted in future, with related guidance to be provided in SAHPRA's pharmacovigilance guidelines.		

4.1.12	**Exception type**	Alteration	**EMA/SAHPRA code**	C.I.12
EMA classification		Type IA_{IN}	**SAHPRA classification**	Type IA_{IN}
Code description		Inclusion or deletion of black symbol and explanatory statements for medicines in the list of human and veterinary medicines that are subject to additional monitoring as prescribed by SAHPRA		
Details		SAHPRA is adopting the black symbol used by EMA and will publish a list of human and veterinary medicines which are subject to additional monitoring. This list will be based on EMA's list and adjusted to fit the South African context. The list will be monitored and updated by SAHPRA's Pharmacovigilance directorate on an on-going basis. Code C.I.12 will only become effective once SAHPRA's list of human and veterinary medicines which are subject to additional monitoring is finalised and published. The Pharmacovigilance directorate will publish separate timelines for implementation and guidance for SAHPRA's industry partners.		

4.1.13	**Exception type**	Alteration	**EMA/SAHPRA code**	C.I.13a – C.I.13b
EMA classification		Type II	**SAHPRA classification**	Type IB (a); Type II (b)
Code description		Other variations not specifically covered elsewhere in the EU variation classification guidelines a) Implementation of change(s) for which no new additional data is required to be submitted by the HCR b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the HCR		
Details		Additional Type IB introduced to accommodate changes not covered elsewhere in the addendum, which do not require additional information from the applicant. Code C.1.13 is intended for changes which the HCR believes are not covered appropriately by any of the other variations codes contained in this addendum / guideline. Where unsure, the HCR may request SAHPRA to provide a recommendation on the classification of the variation. The letter of application should clearly reflect this request, with reference made to code C.1.13. Note that the code description applicable to SAHPRA has been altered and is reflected above.		

c) Procedural exceptions (applicable to Clinical evaluation of human medicines only)

4.1.14	**Exception type**	Alteration	**Affected procedure(s)**	All Type IA_{IN} Clinical variations

Exception description	Within *30 working days* following the acknowledgement of receipt of a valid Type IA_{IN} variation, SAHPRA will notify the HCR of the outcome of the application. If SAHPRA has not sent the HCR its opinion on the application within *30 working days* following the acknowledgement of receipt of a valid Type IA_{IN} variation, the application will be deemed acceptable and implementable. Note that this alteration only applies to the following Type IA_{IN} codes requiring Clinical evaluation of human medicines: • C.I.0.1 • C.I.0.2a • C.I.3a • C.I.5a • C.I.11a

Note:

For veterinary medicines, within *60 working days* following the acknowledgement of receipt of a valid Type IA_{IN} variation, SAHPRA will notify the HCR of the outcome of the application. If SAHPRA has not sent the HCR its opinion on the application within *60 working days* following the acknowledgement of receipt of a valid Type IA_{IN} variation, the application will be deemed acceptable and implementable.

4.1.15	**Exception type**	Alteration	**Affected procedure(s)**	All Type IB Clinical variations
Exception description		Within *60 working days* following the acknowledgement of receipt of a valid Type IB variation, SAHPRA will notify the HCR of the outcome of the application. If SAHPRA has not sent the HCR its opinion on the application within *60 working days* following the acknowledgement of receipt of a valid Type IB variation, the application will be deemed acceptable and implementable. Note that this alteration only applies to the following Type IB codes requiring Clinical evaluation of human medicines: • C.I.0.2b • C.I.0.3 • C.I.2a • C.I.6c • C.I.7a • C.I.7b • C.I.13a		

	This is an alteration to the 30 days stipulated by EMA, to accommodate Clinical's current application absorption capacity.

4.1.16	**Exception type**	Exclusion	**Affected procedure(s)**	All Type II Clinical variations
Exception description		SAHPRA's Clinical unit will not be adopting EMA's procedures for handling Type II variations. These variations will be handled as per SAHPRA's internal procedures, which will be communicated once new processes have been implemented.		

4.1.17	**Exception type**	Alteration	**Affected procedure(s)**	USRN procedure
Exception description		SAHPRA has defined its own procedures for Urgent Safety Restriction Notices (USRNs), replacing those outlined in the EMA guidelines. Note that SAHPRA's veterinary medicines unit will adopt the VICH procedure for urgent safety restrictions. The guidance provided below replaces SAHPRA's 9.13 Package Inserts Concerning Urgent Safety Restrictions: USRN communication document, which is no longer valid. The following amendments relating to safety will be allowed as USRNs. An USRN may only be used for an amendment which has a **more restrictive effect** on the safe use of the medicines than has been previously approved by SAHPRA, such as: • Modification/deletion of therapeutic indication • Limiting the population in which the product may be used • Adding a contraindication, warning and special precaution, interaction or adverse reaction • Adding an instruction on posology that is intended to improve the safe use of the medicine Changes not allowed include: • Additional headings • Changes which in any way may relax the way in which the medicine is used. • Any wording or information to further qualify ("soften") or elaborate on the new safety-related information, such as "unknown clinical significance", "only occurs at higher dose", "occurs rarely", etc. • Comparative statements • Class statements, e.g., "as with other betablockers"		

- Additional information on lack of interaction with other substances
- Additional information on treatment of overdose

The procedures for USRNs in South Africa are as follows:

1. The applicant should immediately notify the Authority of the restrictions to be introduced.
2. The Authority will respond to the applicant within 5 working days confirming whether the request qualifies as an USRN or not. If no response and/or objections are received from the Authority within the 5 working days, the application is deemed accepted as an USRN.
3. The applicant must within 5 working days of receipt of response from the Authority (or if no response is received from the Authority within 5 working days) submit the USRN variation application accompanied by a Dear Healthcare Professional (DHCP) letter for urgent review.
4. In instances where the Authority has imposed the USRN, the applicant must within 15 working days of initial notification from the Authority submit the USRN and DHCP letter for urgent review.
5. USRN applications will typically be handled through variation code C.I.3 (the document requirements for a USRN application are those associated with code C.I.3 – see section 5 of this addendum). In instances where there is no implementation of wording agreed by the Authority, and where the USRN-related amendments have yet to be approved for the local innovator PI, generics may submit the DHCP letter separately from the USRN application. The DHCP letter should be submitted immediately upfront, with the USRN application following as a code C.I.2a once the associated innovator PI has been finalised.
6. The review of the USRN application may run in parallel with the issuing of a DHCP letter. The draft DHCP letter will be reviewed according to internal SAHPRA procedures. The DHCP letter review should be finalised within a time period of no longer than 30 working days (includes interaction with the applicant/HCR).
7. The HCR should distribute the DHCP letter to the relevant healthcare professionals within 10 working days of receipt of the finalised DHCP letter (see the Process for handling “Dear Healthcare Professional” letters relating to safety and medicines safety alerts guideline).
8. Unless the applicant receives a written objection from SAHPRA within 30 working days of receipt of the submission for an USRN, the applicant shall commence implementation of the USRN to the PI.
9. The USRN and the variations which are related to the safety issues shall be implemented within the time frame agreed by the applicant and the Authority and submission of the revised PI/PIL for the Authority’s records.

	10. The amended PI must be made publicly available (either in hard copy or electronically) within 120 working days of commencement of the implementation of the USRN. 11. If an applicant is found to have implemented an USRN to the PI without complying with the process, the applicant will be required to resubmit full documentation with repayment of the required fee.

4.2. Veterinary (C.II)

a) Summary of SAHPRA codes and variation classifications

All relevant C.I codes will apply to veterinary medicines as they do for human medicines – see section 4.1 of this addendum for the details of these exceptions. Note that any reference to a PIL for veterinary medicines is not applicable to SAHPRA – relevant codes should be interpreted with respect to the Label and PI only.

The adoption of C.II codes specific to veterinary medicines is explicitly covered below.

Table 4.2.1 – summary of codes adopted/excluded for Veterinary

SAHPRA/EMA code	Code description	Exception type	Exception number
All C.I codes	C.I codes relevant to veterinary medicines are adopted with the same exceptions detailed in section 4.1 of this addendum document	Various	4.1.1 – 4.1.13
C.II.1	Variations concerning a change to or addition of a non-food producing target species	None[3]	N/A
C.II.2a – C.II.2b	Deletion of a food producing or non-food producing target species a) Deletion as a result of a safety and/or efficacy issue b) Deletion not resulting from a safety and/or efficacy issue	Adopted with clarification	4.2.1
C.II.3	Changes to the withdrawal period for a veterinary medicine	None[4]	N/A
C.II.4	Variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for veterinary vaccine relevant diseases listed on the "Controlled and Notifiable diseases list"	Alteration	4.2.2

3 Code adopted as-is, without exceptions.

C.II.5	Variations concerning the replacement of a strain for a veterinary vaccine against equine influenza	Exclusion – combined with code C.II.4 above	4.2.2
C.II.6	Changes to the label which are not connected with the PI	None[4]	N/A
C.II.7a – C.II.7b	Introduction of a new Pharmacovigilance system	Exclusion	4.2.3
C.II.8	Change in the frequency and/or date of submission of period safety update reports (PSUR)	None[4]	N/A

b) Code-related exceptions

4.2.1	**Clarification**		
EMA/SAHPRA code	C.II.2a – C.II.2b	**EMA/SAHPRA classification**	Type II (a); Type IB (b)
Code description	Deletion of a food producing or non-food producing target species a) Deletion as a result of a safety and/or efficacy issue b) Deletion not resulting from a safety and/or efficacy issue		
Details	Code clarified to include deletions related to safety and efficacy issues.		

4.2.2	**Exception type**	Alteration	**EMA code**	C.II.4
EMA classification		Type II	**SAHPRA classification**	Type II
Code description		Variations concerning the replacement or addition of a serotype, strain, antigen or combination of serotypes, strains or antigens for veterinary vaccine relevant diseases listed on the “Controlled and Notifiable diseases list”		
Details		SAHPRA has expanded the scope of diseases relevant to this code. Note that code C.II.5 falls away with an exclusion, as the content is now incorporated into code C.II.4 (i.e. there is no longer a need for a separate code for equine influenza).		

4.2.3	**Exception type**	Exclusion	**EMA code**	C.II.7a – C.II.7b
EMA classification		Type II (a); Type IB (b)	**SAHPRA classification**	N/A
Code description		Introduction of a new Pharmacovigilance system		
Details		SAHPRA will only adopt this code once the PV function for Veterinary medicines has		

	been formalised.

4.3 Quality (B)

a) Applicants are reminded that this document does not apply to variation applications for Biological products. Should an application require the evaluation of a biological product as well as changes to manufacturer, packer and laboratory, applicants must first obtain approval from the Biological unit and provide all supporting documentation of this approval to support the application for the GMP related changes. Failure to provide this information will result in the immediate rejection of the application.

b) Summary of SAHPRA codes and variation classifications

SAHPRA/EMA code	Code description	Exception type	Exception number
B.I.a.1 – 5 B.I.b.2 B.I.c.1 – 3 B.I.d.1 B.I.e.1 – 5 B.II.a.1 – 6 B.II.b.1c, d B.II.b.3 – 5 B.II.c.1 – 4 B.II.d.1 – 3 B.II.e.1 – 7 B.II.f.1 B.II.g.1 – 5 B.II.h.1 B.III.1 – 2 B.IV.1.a.3 B.IV.1.b, c	Various	None[4]	N/A
B.I.b.1a – B.I.b.1i	Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance	Adopted with clarification	4.3.1
B.I.b.1i	Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance	Alteration	4.3.2
B.II.b.1a, b, e, f	Replacement or addition of a FPP manufacturing site for part or all of the manufacturing process of the finished product	Alteration	4.3.3
B.II.b.2	Change to importer, batch release arrangements and quality control testing of the finished product	Alteration	4.3.4

4 Code adopted as-is, without exceptions

B.II.c.1g	Change in the specification parameters and/or limits of an excipient	Alteration	4.3.5
B.II.d.2e – f	Change in test procedure for the finished product	Alteration	4.3.6
B.IV.1.a.2	Removes restriction to veterinary products only	Alteration	4.3.7
B.I.z	Registration condition for API	Addition	4.3.8
B.II.z	Registration condition for FPP	Addition	4.3.9

b) Code-related exceptions

4.3.1	**Clarification**		
EMA/SAHPRA code	B.I.b.1a – B.I.b.1i	**EMA/SAHPRA classification**	Type IA_{IN} (a); Type IA (b, c, d); Type IB (h, i); Type II (e, f, g)
Code description	Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance		
Details	When changes to specifications parameters and/or limits result from adoption of a new monograph or a monograph from a different pharmacopeia, the variations codes in B.I.b.1 would also apply.		

4.3.2	**Exception type**	Alteration	**EMA code**	B.I.b.1i
EMA/SAHPRA classification		Type IB		
Code description		Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance		
Details		Newly adopted monographs do not need to be from the European Pharmacopoeia or the national pharmacopoeia of a European Union member state. SAHPRA will be accepting monographs from all Recognised Regulatory Authorities as stipulated in the General Information and Quality and Bioequivalence guidelines.		

4.3.3	**Exception type**	Alteration	**EMA code**	B.II.b.1a, b, e, f
EMA/SAHPRA classification		Type IA_{IN} (a, b); Type IB (e, f)		
Code description		Replacement or addition of a FPP manufacturing site for part or all of the manufacturing process of the finished product		
Details		For a site to be deemed GMP compliant: • SAHPRA requires that conditions 2, 4, 5 and the revised condition 1 (revision found below) be fulfilled in order for sites indicated in B.II.b.1 a, b, e and f to be deemed to be GMP compliant • Applicants are to provide the revised version of document 1 (revision found below) <u>Please note the revision to condition 1</u>: Satisfactory inspection in the last 3 years must have been conducted by a member of PIC/S or a country with a GMP MRA between said country's regulatory authority and SAHPRA		

	Please note the revision to document 1: Proof that the proposed site is appropriately authorised for the pharmaceutical form of the product concerned. Applicants are to submit a resolution letter (for local sites), certificate of GMP compliance and, a manufacturing license issued within the last 3 years by SAHPRA or an authority in which a GMP MRA with SAHPRA exists (i.e., a PIC/S member state, Zazibona work-sharing agreement or WHO PQ). Please note that SAHPRA 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. Within *60 working days* following the receipt of a valid Type IB (B.II.b.1.e and B.II.b.f) and Type 1Ain (B.II.b.1.b) variation by Inspectorate Unit, SAHPRA will notify the HCR of the outcome of the application. If SAHPRA has not sent the HCR its opinion on the application within *60 working days* following the receipt of a valid Type IB (B.II.b.1.e and B.II.b.f) and Type IAin (B.II.b.1.b) variation, the application will be deemed acceptable and implementable. This is an alteration to the 30 days stipulated by EMA, to accommodate Inspectorate's current application absorption capacity (i.e it is a temporary alteration). Applicants are advised that the alteration for the above-mentioned codes is a temporary alteration which SAHPRA commits to revisit within 12 months.

4.3.4	**Exception type**	Alteration	**EMA code**	B.II.b.2a – B.II.b.2c.3
EMA classification		Type IA_{IN} (c1, c2); Type IA (a); Type II (b, c3)	**SAHPRA classification**	Type IA_{IN} (a, c1, c2); Type II (b, c3)
Code description		Change to importer, batch release arrangements and quality control testing of the finished product		
Details		For a site to be deemed GMP compliant: • Conditions 1 and 5 do not apply • Applicants are to fulfil conditions 3 and 4 as well as the revised condition 2 (revision found below) • Applicants are to provide the revised version of document 1 (revision found below) Note that code B.II.B.2a is now classified as a Type IA_{IN}. Please note the revision to condition 2: An appropriate authorisation refers to a satisfactory inspection conducted in the last 3 years by a member of PIC/S or a country with a GMP MRA between said country's regulatory authority and SAHPRA Please note the revision to document 1: Applicants are to submit a resolution letter (for local sites), a certificate of GMP compliance and a manufacturing license issued within the last 3 years by SAHPRA or an authority in which a GMP MRA with SAHPRA exists (i.e., a PIC/S member state, Zazibona work-sharing agreement or WHO PQ).		

	Please note that SAHPRA 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.

4.3.5	**Exception type**	Alteration	**EMA code**	B.II.c.1g
EMA/SAHPRA classification		Type IB		
Code description		Change in the specification parameters and/or limits of an excipient		
Details		Newly adopted monographs do not need to be from the European Pharmacopoeia or the national pharmacopoeia of a European Union member state. SAHPRA will be accepting monographs from all Recognised Regulatory Authorities as stipulated in the General Information and Quality and Bioequivalence guidelines.		

4.3.6	**Exception type**	Alteration	**EMA code**	B.II.d.2e and f
EMA/SAHPRA classification		Type IA		
Code description		Change in test procedure for the finished product		
Details		The monograph should be compliant with a monograph from one of SAHPRA's Recognised Regulatory Authorities as stipulated in the General Information and Quality and Bioequivalence guidelines.		

4.3.7	**Exception type**	Alteration	**EMA code**	B.IV.1.a.2
EMA/SAHPRA classification		Type IB		
Code description		Change of a measuring or administration device • Addition or replacement of a device which is not an integrated part of the primary packaging • Device without CE marking for veterinary products only		
Details		Eliminates the restriction of the code to be "for veterinary products only". Edits language to be "Device without CE marking"		

4.3.8	**Exception type**	Addition	**SAHPRA code**	B.I.z
EMA/SAHPRA classification		Type IA		
Code description		Registration condition for API		
Details		This code is to be used when providing data related to the API to comply with the commitments made at the time of registration. Example: Nitrosamine Risk Assessment M3.2.S.4 and M3.2.S.5 from the FPP manufacturer		

4.3.9	Exception type	Addition	SAHPRA code	B.II.z
EMA/SAHPRA classification		Type IA		
Code description		Registration condition for FPP		
Details		This code is to be used when providing data related to the FPP to comply with the commitments made at the time of product registration. Example: Nitrosamine Risk Assessment Process validation on 3 consecutive batches		

4.4 Names and Scheduling (A)

a) Code-related exceptions

4.4.1	Exception type	Exclusion	EMA code	A.2.a
EMA classification		Type IA_{IN}		
Code description		Change in the proprietary name of the authorised medicine		
Details		Excluding A.2.a as it refers to Centrally Authorised products, which is not relevant for applications to SAHPRA in this case		

4.4.2	Exception type	Alteration	EMA code	A.2.b
EMA classification		Type IB	SAHPRA classification	Type II
Code description		Change in the proprietary name of the authorised medicine		
Details		Elevating a change in the product name of an authorized product to a high-risk variation to ensure that any changes are in line with current naming and scheduling policies. The application letter of the proprietary name change applications should be addressed to the name and scheduling unit. Applicants are to submit a resolution letter (for local sites), certificate of GMP compliance and, a manufacturing license issued within the last 3 years by SAHPRA or an authority in which a GMP MRA with SAHPRA exists (i.e., a PIC/S member state, Zazibona work-sharing agreement or WHO PQ) If there has been a transfer of applicancy, the new applicant must provide proof that they hold all the rights pertaining to that particular dossier which must include a signed letter from the responsible pharmacist acknowledging that all rights to the dossier has been ceded to the new applicant.		

4.5 Health Products Authorisation (A)

For Administrative code, A.4, SAHPRA wishes to emphasise the condition to be fulfilled: The manufacturing site and all manufacturing operations must remain the same. Variations which materially alter the site may not be treated as notifications.

a) Code-related exceptions

4.5.1	**Exception type**	Addition	**SAHPRA code**	A.0.1
EMA classification		NA	**SAHPRA classification**	Type II
Code description		Application for a Transfer of Holder of Certificate of Registration (ToHCR) for a registered medicine		
Details		New code introduced allowing applicants to effect changes in the Holder of Certificate of Registration (i.e., change in product ownership). Note that ToHCRs do not apply for medicines that have yet to be registered. Applications will be assessed on a case–by-case basis to confirm where such changes are warranted.		

4.5.2	**Exception type**	Alteration	**EMA code**	A.2.b
EMA classification		Type IB	**SAHPRA classification**	Type II
Code description		Change in the proprietary name of the authorised medicine - certification		
Details		Elevating a change in the product name of an authorized product to a high-risk variation to ensure that any changes are in line with current naming and scheduling policies Applicants are to submit the SAHPRA name change approval letter, a resolution letter (for local sites), certificate of GMP compliance and a manufacturing license issued within the last 3 years by SAHPRA or an authority in which a GMP MRA with SAHPRA exists (i.e., a PIC/S member state, Zazibona work-sharing agreement or WHO PQ)		

5. DOCUMENTATION/ DATA REQUIREMENTS

In this first step towards harmonisation, not all of SAHPRA's directorates will fully adopt the documentation/data submission requirements provided in the EMA variation classification guidelines. This section outlines the associated exceptions and clarifications for selected directorates. SAHPRA implicitly adopts the document requirements stipulated in the EU variations classification guideline in full where no mention is made of any exceptions in this addendum / guideline.

5.1 General

Any reference to the "variation application form" in the EU guidelines should be read as the SAHPRA

application form (available on SAHPRA's website) and amendments schedule (see appendix).

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

Replacement or addition of a manufacturing site for part or all of the manufacturing process of the finished product (B.II.b.1.b and B.II.b.1.e-f). Replacement or addition of a manufacturer/primary packer/laboratory requires evaluation by Quality as well as Inspectorate.

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

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

5.2 Clinical and Pharmacovigilance

Table 5.2.1 below covers all the *potential* documentation/data requirements for a given submission (to be read in conjunction with both the 2.09 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 5.2.1 as needed. Note that the MRF4 form is no longer required.

This is followed by Table 5.2.2, which provides the requirements for each code applicable to Clinical and Pharmacovigilance.

Table 5.2.1 – list of key documentation/data required for clinical variation applications

Standard documentation for 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 – 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
2. Application form (M1.2.1)
3. Proof of payment for the Variation application (M1.2.2.1)
4. The current approved PI and PIL (M1.3.1.1 & M1.3.2)[a]
5. Annotated/revised proposed PI and PIL as well as the clean versions (M1.5)[a]
6. Validation template for variation applications (M1.8)
7. For generic applications, the latest approved South African innovator PI, and if 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

8. Dear Healthcare Professional (DHCP) Letter (attached to the letter of application – M1.0)
9. PBRER/PSUR (M5.3.6)
10. RMP (M1.13)
11. Peer-reviewed literature-based studies in support of the proposed variation(s) (M5)

Clinical data[b] [where applicable for relevant Type II variations]

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

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

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

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

18. Un-redacted rapporteur assessment reports from RRAs, if available (M1.10)
19. 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]
20. 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:

There is no need to resubmit the currently approved versions of the PI and PIL, as they will already be contained in the previous sequence. Where relevant, a reference/hyperlink to the approved versions in the previous sequence is sufficient. Furthermore, the clean versions of the new, amended PI and PIL replace the latest-approved versions contained in modules 1.3.1.1 and 1.3.2 respectively.

b. 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.

c. Refer to the 2.09 Clinical Guideline, which defines the evaluation pathways for variations, along with the requirements for the letter of access.

Table 5.2.2 – 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 - C.I.6b - C.I.6c	Type II - Type II - Type IB	1 – 7; (11 – 16)*; (17 – 20)$^{+}$ - 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)$^{+}$
* where applicable $^{+}$ where an abridged or verified review is applicable (i.e. where the variation has been approved by either SAHPRA or a RRA)		

5.3 Quality

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

Wherever "ICH/VICH" guidelines are referred to for stability, in terms of limits, conditions, and/or parameters, this should be read in line with SAHPRA and SADC stability guidelines. Whenever reference is made to EU regulations this is to be read in terms of requirements outlined in the SAHPRA Quality and BE guidelines.

Table 5.3.1 – list of key documentation/data required for quality 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 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)
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. Completed validation template for variation applications indicating whether conditions are met and supporting documents are included as per EMA variation guideline (M1.8)
12. 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)
13. Amended SCoRE document (M3.2.R.8)
14. BTIF (MS Word format), where variations include a Biostudy (Working documents folder)

Reliance documentation – to be supplied for abridged and verified reviews

15. Unredacted rapporteur assessment reports from RRAs, if available (M1.10)
16. 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 SCoRE document is a requirement, and this should not change the prescribed review timelines of 30 working days for Type I and 120 working days for Type II.

5.4 Health Product Authorisation

In addition to any requirements set out in 2.24 Guidance for the Submission of the South Africa CTD / eCTD – General & Module 1, Transfers of the Holder of Certificate of Registration (ToHCR – code A.0.1) require the following key documents:

Table 5.4.1: List of key documentation/data required for administrative variation applications

Standard documentation for 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*
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
5. Electronic copy of the letter of acceptance from the proposed HCR
6. The current approved PI and PIL (M1.3.1.1 & M1.3.2)*
7. Amendment/variation schedule (M1.5.2.1)
8. Medicine register details (M1.5.2.2.1)
9. Variations summary (M1.5.2.2.2)*
10. 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 GMP certificates or manufacturing licences for all approved sites performing a function related to the product's manufacture, packer, FPRC, FPRR/Applicant (M1.7.3)

* *Where applicable*

6. WORK-SHARING AND EXTENSION APPLICATIONS

6.1 Work-sharing

SAHPRA will not be adopting the EU procedures related to work-sharing. For information on SAHPRA's reliance pathways consult the Clinical, and Quality and Bioequivalence guidelines.

6.2 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 variations 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

7. 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_May 2021, https://www.sahpra.org.za/wp-content/uploads/2021/06/SAHPRA_Payment_Guideline.pdf].

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

Quality fees:
A separate communication providing an Explanatory note on fees payable for technical amendments related to Quality has been published on the SAHPRA website,

[https://www.sahpra.org.za/wp-content/uploads/2021/03/Explanatory-Notes-for-Technical-Amendments-related-to-Quality-1.pdf]. This communication provides clarity on fees payable for technical variations related to quality as indicated in the current SAHPRA fees on the Government Gazette, dated 22 December 2020.

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 must be accompanied by the relevant proof of payment, R800 per application. Please note that the fees payable for Inspectorate changes are independently charged and are reviewed independently of Quality

8. APPENDIX

The following templates 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

8.1 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}

{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 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:

8.2 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 at 25 ºC/60 % RH and for 3 months at 40ºC/75 % RH submitted.	Stability data on the same two production batches stored for 36 months at 25 ºC/60 % RH included.	Extension of the shelf- life to 36 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 months 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.

8.3 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 to this effect will suffice.	

8.4 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:

a) I am in possession of the master documentation pertaining to the above-mentioned medicine.

b) 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).

c) The master documentation conforms with the Registration dossier;

d) 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;

e) 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.

f) 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.

g) 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.

h) <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)>

i) <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}: