Table of Contents

SCOPE 2

GENERAL INFORMATION FOR CEM POST REGISTRATION 2

Classification of clinical variations 2

SAHPRA VARIATIONS CLASSIFICATIONS AND CODES 3

Clinical, Pharmacovigilance and Veterinary (C.I) 3

SCOPE

This annexure contains details on the specific categories and codes for variations specific to the safety and efficacy of registered medicines and any amendments made on the professional information (PI) and patient information leaflet (PIL) of such registered medicines for the South African Health Products Regulatory Authority (SAHPRA). This annexure is relevant only to submissions made for variations affecting the safety and efficacy of orthodox human medicines. For other units, e.g. veterinary, biological refer to the relevant annexures.

GENERAL INFORMATION FOR CLINICAL EVALUATION MANAGEMENT (CEM) POST REGISTRATION

Classification of clinical variations

SAHPRA has classified its variations application for human and veterinary medicines according to the consolidated variations guideline.

The variations classifications for Type I and Type II amendments are detailed below.

Type IAIN Minor Variations

Type IAIN variations must be notified to SAHPRA by the HCR at least 47 working days prior to implementation. Within 47 working days of receiving a valid Type IAIN variation, SAHPRA will notify the HCR of its decision. If no outcome is communicated within this timeframe, the variation will be considered acceptable and implementable by default. However, SAHPRA reserves the right to review the variation post-implementation and issue a formal outcome.

Note: that this is only applicable to the Type IAIN codes requiring Clinical evaluation of human medicines:

Type IB variations that must be notified by the HCR at least 87 working days prior to implementation. If 87 working days have elapsed from the time the notification was submitted, and no communication is received by the Holder of a Certificate of Registration (HCR) from SAHPRA, the HCR may implement the variation. However, the Authority reserves the right to still review the variation after it was self-implemented and issue an outcome.

The HCR may not implement Type II variations until the Authority has completed its review. The review timeline for Type II variations is 200 working days, in addition to 30 working days for technical screening.

If one or more conditions are not met, the applicant must classify the change using a higher code, e.g. If a condition of type IA is not met, the variation is upgraded to a Type IB. The Authority reserves the right to upgrade or downgrade a classification based on internal risk assessment of the variation/s applied for and the references submitted.

SAHPRA VARIATIONS CLASSIFICATIONS AND CODES

Clinical, Pharmacovigilance and Veterinary (C.I)

a) Summary of SAHPRA codes and variation classifications

Table 4.1.1 below summarises the C.I codes used by SAHPRA.

SAHPRA code	Code description
C.I.0.1	Format updates to the PI/PIL in accordance with relevant changes to the Act, general regulations and guidelines
C.I.0.2a – C.I.0.2b	Implementation of editorial changes to the PI/PIL
C.I.0.3	Safety or safety-related change(s) in the PI/PIL of an innovator medicine, which has been approved by an 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
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
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 an RRA
C.I.4	Change(s) in the PI, PIL or Label due to new quality, preclinical, clinical or pharmacovigilance data
C.I.5a – C.I.5b	Change in the legal/scheduling status of a medicine
C.I.6a – C.I.6c	Change(s) to therapeutic indications
C.I.7a – C.I.7b	Deletion of a pharmaceutical form / strength
C.I.8a	Introduction of, or changes to, a summary of pharmacovigilance system for medicines for human use

C.I.10	Change in the frequency and/or date of submission of periodic safety update reports (PSUR) for human medicines
C.I.11a – C.I.11b	Introduction of, or change(s) to, the obligations and conditions of a registration / HCR, including the RMP
C.I.12	Inclusion or deletion of black symbols and explanatory statements for medicines in the list of human and veterinary medicines that are subject to additional monitoring as prescribed by SAHPRA
C.I.13a – C.I.13b-C.I.13c	Other variations not specifically covered elsewhere in the EU variation classification guidelines

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

b) Code-related exception

SAHPRA code	C.I.0.2a – C.I.0.2b	**SAHPRA classification**	Type IA_{IN} (a); Type IB (b)
Code description	**Implementation of editorial changes to the PI and PIL** b) 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 applicants to make editorial changes to the PI/PIL and notify SAHPRA.		

SAHPRA code	C.I.0.3	**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 an RRA. T**his 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 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 RRAs. (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.

	Clarification		
SAHPRA code	C.I.2a – C.I.2b	**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:**		

	2) 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 under this code may NOT contradict existing contraindications approved by SAHPRA.

	Clarification		
SAHPRA code	C.I.3a – C.I.3b	**SAHPRA classification**	Type IB (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 an 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**		
SAHPRA code	C.I.4	**SAHPRA classification**	Type II
Code description	a. Change(s) in the PI, PIL or Label due to new quality, preclinical, clinical or pharmacovigilance data b. Amendments to the PI / PIL that requires review of the risk management plan (RMP)		

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.

SAHPRA code	C.I.5a – C.I.5b	**SAHPRA classification**	Type IA_{IN} (a); Type II (b)
Code description	**Change in the legal/scheduling status of a medicine** b) 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		

SAHPRA Code	C.I.6a – C.I.6c	**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.

	SAHPRA Code	C.I.7a - C.I.7b	**SAHPRA classification**	Type IB (a); Type II (b)
Code description		a) Deletion of a pharmaceutical form/strength without data b) Deletion of a pharmaceutical form/strength with data		
Details				

	SAHPRA Code	C.I.8	**SAHPRA classification**	Type II Safety

Code description	Introduction of, or changes to, a summary of pharmacovigilance system for medicines for human use
Details	

SAHPRA Code	C.I.10	**SAHPRA classification**	Type II safety
Code description	Change in the frequency and/or date of submission of periodic safety update reports (PSUR) for human medicines		
Details			

SAHPRA Code	C.I.11a - C.I.11b, C.I.11c	**SAHPRA classification**	Type IB (a), Type II; (b, c)
Code description	**Introduction of, or change(s) to, the obligations and conditions of a registration / HCR, including the RMP:** 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 safety data to be submitted by the HCR		

	c) Implementation of change(s) of clinical data for safety and efficacy on products to be submitted by the HCR
Details	The code can be used for conditional medicine registrations that require additional data to be furnished to the Authority at a specified period.

SAHPRA code	C.I.12	**SAHPRA classification**	Type IA_{IN}
Code description	Inclusion or deletion of black symbols 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.		

SAHPRA code	C.I.13a – C.I.13b, C.I.13c	**SAHPRA classification**	Type IB (a); Type II (b), (c)
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, e.g. submission of PIL for the first time. b) Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the HCR. c) Submission of clinical data for safety and efficacy on products with conditional registration.		

	d) Submission of Bioequivalence studies for safety and efficacy to Clinical Post Registration unit.
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 there is uncertainty, 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)

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.

	Exception type	Alteration	**Affected procedure(s)**	All Type IB Clinical variations
Exception description	Within 60 working days after online submission to SAHPRA of a valid Type IB variation, SAHPRA will notify the HCR of the application's outcome. If SAHPRA has not sent the HCR its opinion on the application within *60 working days* following the online submission to SAHPRA 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.

	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, special warning and precaution for use, 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 five (5) working days of receipt of response from the Authority (or if no response is received from the Authority within five (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.

[1] Code adopted as-is, without exceptions