SAHPRA
South African
Health Products
Regulatory Authority

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COMMUNICATION TO INDUSTRY

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Quality Variations

INTRODUCTION

This document is intended to provide a communication to industry on post registration quality variation general announcements and submission of exception codes.

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SAHPRA Chief Executive Officer (CEO)

Definition of abbreviations and terms

APIs	Active Pharmaceutical Ingredients
CE	European Conformity
CTD	Common Technical Document
EC	European Commission
EMA	European Medicines Agency
FPP	Finished Pharmaceutical Products
ICH	The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
MBR	Medisyne Beheer Raad
MRF	Medicine Registration Form
RRA	Recognised Regulatory Authority
SAHPRA	South African Health Products Regulatory Authority
USFDA	United States of America Food and Drug Administration
USP	United States Pharmacopeia

1. General

All queries relating to status updates, z-codes and extension requests should be emailed to postregqualityvariations@sahpra.org.za.

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

1.1 Status updates

Include a screenshot of the Variations Status Checker Portal (www.sahpra.org.za/variations-status-checker-portal/) available online with the query and indicate the sequence you are querying.

1.2 Z-code requests

Submit a copy of the cover letter with justification **(GLF-HPA-06A)**.

1.3 Extension requests

- Only extension up to 90 days will be granted, unless otherwise justified.

1.4 Common Issues

- Addition of a manufacturer and primary packer must be applied for separately with fees for each change using code Type IB, B.II.b.1.e and Type IA_{IN} B.II.b.1.b respectively, both codes must be evaluated and approved by Quality and Inspectorate before implementation.

1.5 General Information

- The timeline for evaluation of Type IB variations has been extended to 67 working days and will no longer follow the previous 37 working day timeline. Please note that SAHPRA timelines are calculated in working days.

- Applicants are to note that Quality and Clinical variations should be submitted separately, but simultaneously. The relevant Quality and Clinical variation fees will be applicable.

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

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

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

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

2. Exception codes for quality variations

The following codes are to be submitted pertaining to the details section of each code and **please note that Nitrosamines Assessment Reports should be submitted as a variation as of 01 October 2024.**

	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.		

	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.			

	Exception type	Alteration	**EMA code**	B.II.a.1.a, B.II.a.1.b; B.II.a.2
EMA/ SAHPRA classification	Type IA_{IN} B.II.b.1.a Type IB B.II.b.1.b Type IAin. B.II.a.2.a Type IB, B.II.a.2.b			
Code description	Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking.			

	Change in the shape or dimensions of the pharmaceutical form
Details	In lieu of samples of finished product, provide pictures/ photographs of the final product described in 3.2.P.1. These snapshots can be included in 3.2.P.1.

	Exception type	Alteration	**EMA code**	B.II.c.1.g
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.		

	Exception type	Alteration	**EMA code**	B.II.d.2.e 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.		

	Exception type	Alteration	**EMA code**	B.II.e.1.b.1, B.II.e.1.b.2
EMA/ SAHPRA classification		Type IB, B.II.e.1.b.1 Type II, B.II.e.1.b.2		
Code description		Change in type of container or addition of a new container		
Details		In lieu of samples of the new container/ closure, provide pictures/ photographs in Module 3.2.P.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".		

	Exception type	Alteration	**EMA code**	B.II.CTD
EMA/ SAHPRA classification		Type IA		
Code description		Full update from MBR/ MRF to CTD.		
Details		Applicant must include CTD checklist in their submission (GLF-HPA-06B).		

	Exception type	Addition	**SAHPRA code**	B.r.a
EMA/ SAHPRA classification		Type IA		
Code description		Submission of Type IA variation for products registered through reliance only.		
Details		Applicable to Type IA/Type IAin variations These Type IA variations submitted to the RRA must be classified as Type IA and may be grouped as a single variation provided the following conditions and documentation requirements are met: **Conditions:** • For Type IA & IAin variations submitted to and implementable in the RRA through which product was registered. • Sameness has been maintained since the time of product registration except for regional specific differences agreed upon at the time of registration. • The list of variations must be clearly reflected on the covering letter submitted to the RRA and these must concur with covering letter submitted to SAHPRA. **Documentation:** • Provide proof of submission to RRA and if available an acknowledgement or approval communication from the RRA. Any rejection/ query letter issued by the RRA regarding these Type IA variations must be provided. • Provide Sameness Declaration **(GLF-PEM-02L)** stating that information provided to the RRA and SAHPRA are the same. • All supporting documents and amended sections of dossier pertaining to the variation must be submitted to SAHPRA regardless of evaluation pathway. If proof of submission and/ or approval communication from RRA are not available, the change will remain a Type IA variation and must be submitted under applicable code as per EMA variations guideline.		

	Exception type	Addition	**SAHPRA code**	B.r.b
EMA/ SAHPRA classification		Type IA		

Code description	Submission of Type IB variation for products registered through reliance only.
Details	Applicable to Type IB variations These IB variations may be classified as Type IA and may be grouped as a single variation provided the following conditions and documentation requirements are met: **Conditions:** • Type IB variation(s) has been approved by the RRA through which product was registered. • Sameness has been maintained since the time of product registration except for regional specific differences agreed upon at the time of registration. • The list of variations must be clearly reflected on the covering letter submitted to the RRA and these must align with the covering letter submitted to SAHPRA. **Documentation:** • Assessment report and approval letter/ communication from RRA. Any rejection/ query letter issued by the RRA regarding these Type IB variations must be provided. • Provide Sameness Declaration **(GLF-PEM-02L)** stating that information provided to the RRA and SAHPRA are the same. • All supporting documents and amended sections of dossier pertaining to the variation must be submitted to SAHPRA regardless of evaluation pathway. If assessment reports and approval communication from RRA are not available, the change will remain a Type IB variation and must be submitted under applicable code as per EMA variations guideline.

	Exception type	Addition	**SAHPRA code**	B.r.II
EMA/SAHPRA classification		Type IB		
Code description		Submission of Type II variation for products registered through reliance only		
Details		Applicable to Type II variations. Each Type II variation may be classified as a (separate) Type IB variation provided the following condition and documentation requirements are met: **Conditions:** • Type II variations has been approved by the RRA through which product was registered. • Sameness has been maintained since the time of product registration except for regional specific differences agreed upon at the time of registration. • The list of variations must be clearly reflected on the covering letter submitted to the RRA and these must concur with the covering letter submitted to SAHPRA.		

	Documentation: • Assessment report and approval letter/ communication from RRA. Any rejection/query letter issued by the RRA regarding these Type II variations must be provided. • Provide a Sameness Declaration stating that information provided to the RRA and SAHPRA are the same. • All supporting documents and amended sections of dossier pertaining to the variation must be submitted to SAHPRA regardless of evaluation pathway. If assessment reports and approval communication are not available, the change will remain a Type II variation and may only be implemented once approval letter is issued by SAHPRA.

	Exception type	Addition	**SAHPRA code**	B.I.rc
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 OR commitments made upon submission and approval of previous variations (e.g. follow-up stability data, batch analysis data etc.).		

	Exception type	Addition	**SAHPRA code**	B.II.rc
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 OR commitments made upon submission and approval of previous variations (e.g. follow-up stability data, batch analysis data etc.).		

	Exception type	Addition	**SAHPRA code**	B.I.n
EMA/ SAHPRA classification		Type IA		
Code description		Provision of nitrosamine risk assessment report as requested in Nitrosamine Communication.		
Details		This code is to be used when providing a nitrosamine risk assessment report as requested in the Nitrosamine Communication issued by SAHPRA. • Addition of specification for nitrosamine impurities to API manufacturer specification should be classified as Type IB, B.I.b.1.h. • Addition of specification for nitrosamine impurities to finished product specification should be classified as Type IB, B.II.d.1.g.		

	Exception type	Alteration	**SAHPRA code**	B.II.PV
EMA/ SAHPRA classification		Type IB		
Code description		Amendment of the product labelling in response to a Pharmacovigilance recommendation.		
Details		This code is to be used when updating the label due to a Pharmacovigilance recommendation. • Attach all communications from PV to the cover letter. • Updated label. Additional information specified in the PV recommendation.		