SAHPRA
South African
Health Products
Regulatory Authority

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COMMUNICATION TO STAKEHOLDERS

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Variations Communication

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Normal submission of Type IA & IAIN, IB, II

The South African Health Products Regulatory Authority (SAHPRA) allows for variation submissions as follows:

- **Type IA variations (inclusive of Type IAIN):** a maximum of three (3) type IA variation changes (unrelated or related) is applicable for a product submission PER RESPONSIBLE UNIT.
- **Type IB variations:** a maximum of two (2) type IB variation changes (unrelated or related) are applicable for a product submission PER RESPONSIBLE UNIT.
- **Type II variations:** a maximum of one (1) variation is applicable for a product submission related variations criteria PER RESPONSIBLE UNIT.

RELATED CHANGES Bundled submission of Type IA & IAIN, IB, II

Related Changes in a bundled submission, as defined by SAHPRA, is a regulatory mechanism that allows marketing authorisation holders (MAHs) to submit multiple changes to a medicinal product in a single submission. This streamlines the review process and reduces administrative burden.

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There are a few key points to understand:

- Types of variations that can be grouped include Type IA & IA_{IN}, IB and Type II changes, provided they are logically connected or impact the product in a related way.
- RELATED Changes bundled submissions may **ONLY** be used when changes are interdependent – like a formulation change that also affects the product's labelling.
- A justification must be provided in the application form explaining why the variations are to be considered a RELATED CHANGE bundled submission.

A related change submission for a variation refers to the practice of submitting multiple changes to a medicinal product in a single submission when these changes are logically connected or interdependent.

For example, if you are changing the manufacturing site and updating the product labelling to reflect that change, those would be considered related and could be submitted together. They key is that the changes must affect the product in a connected way – either technically, procedurally or in terms of regulatory impact.

According to SAHPRA's guidance, when submitting grouped or related variations:

- Justify the relationship between the changes.
- The submission must clearly indicate how changes are consequential and/or related, i.e., meaningful to be reviewed simultaneously. Applicants are encouraged to group related variations wherever possible. Exceptional justifications will be considered for groupings of variations that SAHPRA would not in principle consider acceptable.
- Some types (like type IA) can be grouped more freely, while others (like Type II) may require prior approval or additional documentation. MAHs are advised to request approval from SAHPRA at least two (2) months in advance of the submission of a group of variations, together with the justification as to why the holder believes that the proposed group should be acceptable.
- It must note however that when submitting Type IA/IA_{IN} variations as part of a group, the legal deadlines for submission of each variation should be respected, i.e., a type IA_{IN} should always be submitted immediately, whether it is grouped with other variations, and any Type IA variation should always be submitted within 12 months following its implementation.

Grouped variations applications should be presented in accordance with the headings and numberings of the 2.21 ZA-SAHPRA eCTD Specifications v3.1. The submission requirements

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as set out in the *Variations Addendum for Human and Veterinary Medicines (SAHPGL-HPA-06)* will also apply to grouped variations, but the application should be provided as one integrated submission package (i.e., one eCTD sequence) covering all changes resulting from the variations.

- One cover letter, clearly indicating that the application concerns a related changed bundled submission of variations as well as which type of variation is the highest in the related change bundled submission. Indicate whether the grouping has been agreed with SAHPRA.
- Grouping of related change bundled submission variations must follow the process on the portal. The selection of codes within the respective Grouped variation type is unlimited but costs will apply accordingly.
- The 1.5.2.1 Tabulated Schedule of Amendments should clearly identify the relevant CTD sections in support of each variation.
- Supportive documentation for all variations concerned, submitted as one integrated package.
- If applicable, one revised Professional Information, Patient Information Leaflet and/or Labelling including all changes applied for.

A related change bundled submission application will follow the review procedure of the "highest" variation in the group.

For example:

- A group of a Type II and 2 Type IB variations will follow the timetable of a Type II variation.
- A new indication and a Type II variation will follow the timetable of the new indication.

In the case of related change bundled submissions of Type IA/IA_{IN} variations, SAHPRA will issue a letter reflecting which variations are accepted or rejected. The MAH shall immediately cease to apply the rejected variation(s) concerned and resubmit the variations under a new sequence.

Upon finalisation of the review of the related changes bundled submission variations, SAHPRA will issue a letter reflecting the outcome of the related changes bundled submission variations. The letter will also list any variations not considered approved.

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Timelines:

Type II variations including the related changes bundled submission variation applications: 220 working days from date of receipt at SAHPRA.

Unforeseen changes

An unforeseen variation refers to a change to a medicinal product that is not explicitly listed in the European Commission's variation classification guidelines or SAHPRA's Variations Addendum. In other words, it is a regulatory grey area – when an MAH wants to make a change that does not clearly fall under the defined Type IA, IB or II categories, and there is no existing guidance on how to classify it.

The MAH is to request a classification recommendation to SAHPRA at least two (2) months prior to planned submission date via email to the relevant technical unit managers. SAHPRA will then assess the change and issue a recommendation on how the unforeseen change should be classified. The MAH is to include SAHPRA's issued classification in the justification for a proposed grouping of variations submission and the applicable fee.

Pilot Implementation of Submission Windows for Type II Variations

SAHPRA is launching a pilot initiative introducing predefined submission windows exclusively for **Type II variation applications**, including **related changes bundled variation submissions**, within the following periods:

- 01 October 2025 – 14 October 2025
- 02 January 2026 – 15 January 2026
- 01 April 2026 – 14 April 2026

This structured approach aims to enhance regulatory efficiency by enabling better planning and management of timelines for SAHPRA.

Expected outcomes to be communicated to MAHs at each milestone:

- **Strategic Resource Allocation**: Concentrating Type II submissions within defined windows allows SAHPRA to optimise the use of scientific reviewers and improve workload distribution for complex assessments.
- **Predictable Review Timelines**: The window-based model supports consistent review cycles, enabling SAHPRA to maintain target timelines—220 working days for Type II

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variations. It also ensures timely technical screening, evaluator availability, and communication with applicants.

Kind regards,

Christelna Reynecke

Chief Operating Officer

SAHPRA

Date: 30 June 2025