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# “A Guide to the Implementation of South Africa Specific Risk Management Plans for Medicines”.

04 August 2022 - Florah Matlala

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# Vigilance Legal Basis

Medicines and Related Substances Act, Act 101 of 1965, as amended, changed from pharmacovigilance to vigilance to incorporate all health products regulated by the Authority.

- **Vigilance** is defined as the **continuous monitoring and evaluation** of safety, efficacy, performance profile and management of any risk **throughout the life cycle of a health product**.
- The Authority must, among others, in order to achieve its objects:
  - Ensure that evidence of existing and new adverse events and reactions, interactions, and signals emerging from post-marketing surveillance and vigilance activities are investigated, monitored, analysed and acted upon; and this is achieved through vigilance
- **In terms of safety this includes:**
  - Looking for signals of new or previously understood adverse effects
  - **Monitoring the risk-benefit profile of the health products over its life cycle as we build experience with the products**
  - Looking for new risk factors for known adverse effects
  - Reviewing reporting rates

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# Vigilance Legal Basis

According to **Regulation 40** of Medicines Related Substances Act, 1965 (Act 101 of 1965) as amended,

(1) A **Holder of Certificate of Registration (HCR)/applicant** and licence holder **must** inform the Authority of any:

(a) new or existing quality, safety or effectiveness concerns related to any medicine, including but not limited to adverse drug reactions; and

(b) **risk management activities** associated with paragraph (a).

(2) An HCR/applicant and licence holder, must maintain or have access to records of the reports and case reports referred to in subregulation (1).

(3) A healthcare provider, veterinarian or any other person should inform the Authority, of any:

(a) suspected adverse drug reactions; or

(b) new or existing safety, quality or effectiveness concerns, occurring as a result of the use of any medicine or scheduled substance.

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# Risk Management Plan (RMP)

- Dynamic, stand-alone document reflecting both **known** and **emerging** safety data (i.e., non-clinical and clinical)
- Updated throughout the medicine's life cycle
- Set of **pharmacovigilance activities** and **interventions** designed to **identify**, **characterise**, **prevent**, or **minimise** risks related to a specific medicine
- and the **assessment** of the **effectiveness** of those interventions.

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# Risk Management Plan (RMP)

- **Routine pharmacovigilance activities**
  - minimum set of activities required for all medicines as per the obligations set out in the registration certificate.
  - Apply to all medicines, irrespective of specific safety concerns identified.
  - Relate to standard activities e.g.,
    - collection, follow-up and reporting of adverse events,
    - product labelling,
    - scheduling status

- **Additional pharmacovigilance and risk minimisation activities**
  - Applicable where specific safety concerns have arisen,
  - Designed to address these safety concerns & may be imposed as a condition of registration of a medicine.
  - Examples include:
    - training on the administration of a medicine,
    - educational programmes and tools
    - controlled access programmes,
    - additional risk communication through Dear Healthcare Professional letters
    - Patient registers and
    - Post-marketing studies

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# Purpose of the RMP guideline

- To support a **life cycle** of medicines in pharmacovigilance,
- To **enhance** the quality of SAHPRA's regulatory assessments,
- To support **ongoing evaluation of safety information** that could have an impact on the benefit-risk profile of medicines,
- To **align** local health products vigilance with international best practices; and
- To support South Africans' **timely access** to safe, efficacious, and high-quality medicines.

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# Proposed RMP Requirements in SA

a) SAHPRA requires RMP submission for applications of medicine registration and some Clinical Type II variations applications as follows:
   - New chemical entities including biologicals
   - New generic medicines where clinical data is provided
   - Generic medicine where a safety concern requiring additional risk minimization activities has been identified with the originator medicine
   - Biosimilars
   - Radiopharmaceuticals
   - Any medicine returning to the market after being previously withdrawn due to a serious safety issue

b) RMPs can also **be requested by the Authority** as part of an ongoing review or other situations in order to support informed regulatory decision making about a medicine.

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# Proposed RMP Requirements in SA

c) when a **serious safety concern is identified** with a medicine at any stage in its life cycle, that **may lead to a significant change in the benefit-risk profile**, in the South African context;

d) when the **results of post-marketing safety studies warrant reconsideration of the benefit-risk profile**; and

e) for any medicine where a **significant change in the therapeutic indication is to be considered** (e.g. when the proposed target population differs, a new disease area is involved, the target age group is changed).

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# Proposed RMP Requirements in SA

**New fixed-dose combinations will require an RMP when:**

- one or more of the active ingredients is a new chemical entity; or
- one or more of the active ingredients requires additional risk minimisation activities.

**For generic applications**

An RMP is **not routinely required,** however, it is required in the following circumstances:

- where a safety concern requiring additional risk minimisation activities has been identified with the originator medicine;
- if the HCRs/applicants identifies a significant change in the benefit-risk profile, or uncertainties associated with the medicine;
- if the introduction of the generic may lead to a new safety concern, such as an enhanced risk of medication error or off-label use.

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# Proposed RMP Requirements in SA - Variations

An RMP **must** be submitted with an application **for a major variation (Type II) if the variation results in a new or heightened risk**, such as when:

- the proposed target population differs significantly from the previously approved target population;
- a new route of administration with inherently higher risk (e.g., intravenous vs subcutaneous) is proposed;
- a change in the therapeutic indication is proposed.

For Type 1A and 1B variations, an RMP is not required unless:

- the Authority requests it,
- the HCR/applicant determines that changes in the medicine requires an RMP.

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# Proposed RMP Format

The European Union (EU) RMP format represents an acceptable approach to fulfilling the Authority's requirements for RMPs. As per the European Medicines Agency (EMA) requirements, the EU RMP includes the following sections:

- product overview; safety specifications (epidemiology of the indication(s) and target population(s)
- significant non-clinical safety findings (e.g., toxicity), clinical trial exposure, populations not studied in clinical trials, post-authorisation experience, additional requirements for the safety specification, and identified and potential risks);
- pharmacovigilance plans (routine pharmacovigilance activities and additional pharmacovigilance activities);
- plans for post-authorisation studies;
- risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities); and
- summary of the risk management plan.

The Authority requires that HCRs/Applicants:

- Either develop a South African specific RMP or
- Submit EU RMP together with an SA-specific Annex (SASA)

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# Proposed SA-Specific Annex (SASA)

The following are examples of special considerations related to medical practice or populations in South Africa that should be considered in the SA RMP or SA-specific Annex:

- SA-specific epidemiology of the medical condition(s) or risk factors that reflect the registered indication(s) in South Africa;
- genetic or extrinsic factors that are specific to the South African population;
- SA data on patient exposure;
- post-registration experience in SA, if the medicine is already marketed;
- routine and additional pharmacovigilance or risk minimisation activities planned to be conducted in SA, considering the Authority's regulations and guidelines and the SA context;
- appropriate milestones and timelines for reporting on additional pharmacovigilance and risk minimisation activities to be implemented in SA.

Where an existing global or EU RMP is submitted together with an SA-specific Annex, the Annex should **specify any differences** between the global/EU-RMP and the local implementation of risk management activities (i.e., routine and additional pharmacovigilance or risk minimisation activities).

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# Proposed RMP Submission Requirements

- eSubmission/eCTD
- Cover letter/note to the reviewer
  - reason for submission/submission type (e.g., RMP update)
  - If the RMP is included with a new application (as module 1.13), the new application cover letter should make reference to the RMP.
- Version number and date
  - A new RMP version number should be assigned each time any parts/modules are updated
  - Summary table of changes between the updated and latest RMPs, detailing the changes since the last submitted version.
  - Revision date reflected as “Last Revised Date”
- Declaration to be signed by the QPPV/local Pharmacovigilance Officer
- Any RMPs requested by the Authority must be submitted within **90 calendar days**.

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# Conclusion

- Risk management in pharmacovigilance is undertaken to promote safe use of medicines and safeguard health of the patients.
- The role of HCRs/applicants in monitoring the risk-benefit profile of medicines post-registration through RMPs is fundamental in safeguarding health of the SA public.
- Medicine safety is a collaborative effort by all stakeholders


**Disclaimer:**

*The contents of this presentation does not constitutes the final requirements of RMP guideline*

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# SAHPRA Pharmacovigilance Contact Details

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|---|---|
| Adverse Event reporting: | adr@sahpra.org.za |
| E2B submissions: | e2b@sahpra.org.za |
| Pharmacovigilance related queries: | pvqueries@sahpra.org.za |
| Pharmacovigilance Submissions: | pvsubmissions@sahpra.org.za |
| Support for MedSafety App and Vigilance Hub: | medsafetysupport@sahpra.org.za |
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