South African Health Products
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Risk Management Plans for Medicines for Human Use

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This document has been prepared to serve as a guideline to the holders of certificate of registration/applicants on the Authority's requirements regarding risk management plans for medicines, including biological medicines, in South Africa. It represents SAHPRA's current thinking on the safety, quality and efficacy of medicines. SAHPRA reserves the right to request any additional information to establish the safety, quality and efficacy of a medicine and may make amendments in keeping with the knowledge which is current at the time of consideration of safety data.

Document History

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1. Definitions, Descriptions and Acronyms

1.1 Holder of Certificate of Registration

The holder of the certificate of registration (HCR) is the person, natural or juristic, in whose name the certificate of registration for a product has been granted and who is responsible for compliance with the conditions of registration. The terms “holder of certificate of registration” (holder) and “applicant” are used interchangeably.

1.2 Risk Management Plan (RMP)

A risk management plan (RMP) is a dynamic, stand-alone document reflecting both known and emerging safety data (i.e., non-clinical and clinical) that is updated throughout the medicine’s life cycle. It describes a 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. Medicines for which an RMP has been imposed as a condition of registration need to comply with this section. The RMP is an integral part of the electronic Common Technical Document (eCTD) submitted as an application for registration of a medicine (as module 1.13).

1.3 Pharmacovigilance and Risk Minimisation Activities

Pharmacovigilance is defined by the World Health Organization (WHO) as the science and activities relating to the detection, assessment, understanding and prevention of adverse events or any other drug-related problems. Risk minimisation activities are interventions intended to prevent or reduce the occurrence of adverse reactions associated with exposure to a medicine, or to reduce their severity or impact on the patient. Pharmacovigilance and risk minimization activities are classified as routine or additional. Risk minimisation is also referred to as risk mitigation.

1.3.1 Routine pharmacovigilance and risk minimisation activities

Routine pharmacovigilance activities are the minimum set of activities required for all medicines as per the obligations set out in the registration certificate. Routine risk minimisation activities apply to all medicines and relate to standard activities such as product labelling, the wording of the professional information and patient information leaflet, and scheduling status. Scheduling status may also be linked to the indications, strength, dosage, duration of use and pack size. Routine pharmacovigilance and risk minimisation activities apply to medicines for which no specific safety concerns have arisen.

1.3.2 Additional pharmacovigilance and risk minimisation activities

Where specific concerns have arisen, additional pharmacovigilance and risk minimisation activities 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, the provision of educational materials to patients and healthcare providers, controlled access programmes, and additional risk communication through Dear Healthcare Professional letters. Examples of routine and additional pharmacovigilance and risk minimisation activities are provided in Table 1.

Table 1: Example of routine and additional pharmacovigilance activities

	Routine	Additional
Pharmacovigilance activities	• Collection, follow-up and reporting of adverse events • Continuous monitoring of the benefit-risk profile	• Post-marketing clinical trial obligations • Patient registries
Risk minimisation activities	• Professional Information • Patient Information Leaflet • Packaging and labelling • Scheduling status	• Educational programmes or tools for healthcare providers and/or patients • Controlled access programmes • Dear Healthcare Professional communication

1.4 Reports prepared by other medicines regulatory authorities or institutions

In terms of section 2B (2) of the Medicines and Related Substances Act, SAHPRA may liaise with any other medicines regulatory authority or institution and may exchange information with and receive information from any such authority or institution. SAHPRA may also enter into agreements to co-operate with any medicine's regulatory authority or institution. Reports on the safety, efficacy and quality of a medicine, prepared by other regulatory authorities or institutions, may be relied upon by SAHPRA.

1.5 International Council for Harmonisation

The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) is a joint regulatory-industry harmonisation initiative for medicines. SAHPRA has observer status at ICH. The ICH Guidance on Pharmacovigilance Planning (ICH E2E) is intended to aid in the planning of pharmacovigilance activities, especially in preparation for the early post-marketing period of a new medicine.

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1.6 Periodic Benefit Risk Evaluation Report

A Periodic Benefit Risk Evaluation Report (PBRER) is a pharmacovigilance document intended to provide a comprehensive, concise, and critical analysis of new or emerging information on the risks of a medicine, and on its benefits in approved indications, to enable an appraisal of the product's overall benefit-risk profile. The format of the PBRER is outlined in the ICH guideline Clinical Safety Data Management Periodic Benefit-Risk Evaluation Report (PBRER) for Marketed Drugs (ICH E2C (R2)).

1.7 Periodic Safety Update Report

A Periodic Safety Update Report (PSUR) is a report prepared by the holder of certificate of registration describing the worldwide safety experience with a medicine at a defined time after its registration.

1.8 Data lock point for RMPs

Data Lock Point (DLP) is the designated cut-off date for data to be included in a risk management plan. It is recommended that a DLP date must be stated on the RMP document and should not be more than 6 months before the RMP sign-off date. RMP for initial registration applications should reflect the DLP of the Clinical Safety Summary.

2. Introduction

2.1 Purpose of the guideline

2.1.1 SAHPRA has adopted and integrated the ICH) E2E Guideline (into the regulatory review of medicines in South Africa to:

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

2.1.2 This guidance:

a) describes what an RMP is;
b) explains when an RMP must be submitted;
c) describes what to include in the RMP and the required format for RMPs;
d) details special requirements for RMPs for biological medicines, biosimilars and generic medicines;
e) explains when to submit RMP updates following regulatory approval.

2.2 Legal Basis

2.2.1 This guideline is based on the requirements of General Regulation 40 issued in terms of the Medicines and Related Substances Act, (Act 101 of 1965), as amended (Government Notice No. 859, Government Gazette No. 41064, 25 August 2017).

2.3 Scope and application

2.3.1 This guideline provides guidance to HCRs and applicants on the submission of a South African RMP, the expected structure of the RMP, and the requirements for updates to be provided to the Authority. The guideline applies to medicines, as defined in the Medicines and Related Substances Act (Act 101 of 1965). The guideline applies only to Category A medicines, defined in General Regulation 9 as "medicines which are intended for use in humans and which are, without manipulation, ready for administration, including packaged preparations where only a vehicle is added to the effective medicine".

2.3.2 The guideline does not apply to Category B medicines ("medicines intended for use in humans which cannot normally be administered without further manipulation"), category C medicines ("medicines intended for veterinary use which are, without further manipulation, ready for administration, including packaged preparations where only a vehicle is added to the effective medicine") or Category D medicines ("complementary medicines intended for use in humans and animals which are, without further manipulation, ready for administration, including packaged preparations where only a vehicle is added to the effective medicine").

2.3.3 The submission of RMPs will not be required for medical devices, unless submitted as a combination product.

2.4 Overview of Risk Management Plans

2.4.1 The decision to register a medicine relies on a satisfactory balance of benefits and risks, based on the information available at the time. The safety profile of a medicine may change over time. In particular, during the early post-marketing period, a medicine might be used in settings different from those studied in clinical trials and a much larger population might be exposed in a relatively short timeframe. Adverse reactions and risks which were unknown at the time of registration may be identified.

2.4.2 The known safety concerns and emerging safety signals require active strategies to mitigate risks during the post-registration phase and to ensure that the assessed benefit-risk profile of a medicine remains favourable. The ICH E2E Guideline provides instructions with respect to the characterisation of important identified risks of medicines, important potential risks and important missing information. ICH E2E defines two basic parts of an RMP: the safety specification section and the pharmacovigilance plan. It does not include risk minimisation. However, it was acknowledged at the time of development of ICH E2E that risk minimisation is an integral part of risk management planning.

3. RMP Requirements in South Africa

3.1 When to submit a Risk Management Plan to SAHPRA

3.1.1 SAHPRA requires that all new applications for medicine registration and some Clinical Type II variations applications as detailed below (refer to section 3.4) must be accompanied by an RMP. 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.

3.1.2 RMP should be submitted:

a) with all **new** registrations of:
   i) new chemical entities;
   ii) new biological entities;
   iii) generic medicines where clinical data (including extensions) are provided unless these extensions have been approved by an authority SAHPRA aligns with and no RMP has been required;
   iv) generic medicines where a safety concern requiring additional risk minimisation activities has been identified with the originator medicine;
   v) biosimilar medicines;
   vi) radiopharmaceuticals

vii) any medicine returning to the market after being previously withdrawn due to a serious safety issue.

b) on request by the Authority;

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).

3.1.3 An RMP may be submitted at any time in a product's life-cycle. The RMP should be updated to reflect new knowledge and understanding of the safety profile of a medicine, as required.

3.2 When is an RMP required for a new fixed-dose combination?

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

a) one or more of the active ingredients is a new chemical entity; or

b) one or more of the active ingredients requires additional risk minimisation activities.

3.3 When is an RMP required for a generic?

3.3.1 An RMP is not routinely required for generic medicine applications. However, RMP is required in the following circumstances:

a) where a safety concern requiring additional risk minimisation activities has been identified with the originator medicine;

b) if the HCRs/applicants identifies that there has been a significant change to what is known about the benefits, harms, or uncertainties associated with the medicine;

c) 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.

3.3.2 The Authority may request a generic manufacturer to revise or submit an RMP.

3.4 When is an RMP required for a variation?

3.4.1 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:

a) the proposed target population differs significantly from the previously approved target population;

b) a new route of administration with inherently higher risk (e.g., intravenous vs subcutaneous) is proposed;

c) a change in the therapeutic indication is proposed.

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

a) the Authority requests it,

b) the HCR/applicant determines that changes in the medicine result in the need for an RMP.

3.5 When is a RMP not required?

3.5.1 In cases where a medicine does not meet the requirement for an RMP submission, the applicant/HCR must still comply with routine pharmacovigilance requirements. Routine pharmacovigilance requirements are set out in SAHPRA Guideline 2.33 Post-Marketing Reporting of Adverse Drug Reactions to Human Medicines in South Africa.

3.5.2 Routine pharmacovigilance requirements include, but are not limited to the following:

a) collecting and collating all suspected adverse reactions relating to a medicine that are reported to the applicant/HCR;
b) reporting all serious adverse reactions associated with the medicines to the Authority;
c) continuous monitoring of the safety profiles of approved products, including signal detection and updating of labelling;
d) preparation of Periodic Safety Update Reports (PSURs)/ Periodic Benefit Risk Evaluation Report (PBRER), for submission as specified in the guideline, or when requested by SAHPRA.

4. Acceptable Risk Management Plan Format

4.1 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:

a) product overview; safety specifications (epidemiology of the indication(s) and target population(s)
b) 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);
c) pharmacovigilance plans (routine pharmacovigilance activities and additional pharmacovigilance activities);
d) plans for post-authorisation studies;
e) risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities); and
f) summary of the risk management plan.

4.2 Notwithstanding the general acceptability of the EU RMP format, the Authority requires that additional information specific to the South African context must be submitted. Applicants / HCRs can therefore either develop a South African specific RMP or can submit an already-prepared EU RMP together with an SA-specific Annex (SASA) (refer to section 6 for more detail).

4.3 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:

a) SA-specific epidemiology of the medical condition(s) or risk factors that reflect the registered indication(s) in South Africa;

b) genetic or extrinsic factors that are specific to the South African population;
c) SA data on patient exposure;
d) post-registration experience in SA, if the medicine is already marketed;
e) 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;
f) appropriate milestones and timelines for reporting on additional pharmacovigilance and risk minimisation activities to be implemented in SA.

4.4 Where an existing global or EU RMP is submitted together with an SA-specific Annex, the Annex should identify 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). For example, any differences between the EU Summary of Product Characteristics (SmPC) and the SAHPRA-approved Professional Information (PI), and the reasons for the difference should be provided. This will allow the Authority to assess the appropriateness of the proposed RMP in the SA environment.

4.5 To allow the Authority to assess the appropriateness and value of planned pharmacovigilance or risk minimisation activities, the following details should be included:
a) study protocols (or current drafts) for all studies referred to in the pharmacovigilance or risk minimisation plans (including aims, methodology, limitations and practical applications);
b) plans for any proposed communication and/or education programmes (including aims, methods, evaluation or monitoring of effectiveness, timelines for the provision of relevant documents);
c) timelines for planned activities (such as estimated start, end and reporting dates for planned studies,
d) monitoring and/or evaluation plans to assess the effectiveness of any pharmacovigilance or risk minimisation interventions.

4.6 All attachments, annexes and appendices referred to in the RMP must be provided in full.

5. RMP submission requirements

5.1 Submission presentation requirements

5.1.1 Each RMP update should have a distinct version number and date. When any part of the RMP is revised, the revision date should be reflected as the "Last Revised" date, which is when the RMP is considered final. A new RMP version number should be assigned each time any parts/modules are updated. Additionally, a clean version should be submitted to the Authority, including a summary table of changes between the updated and latest RMPs, detailing the changes since the last submitted version.

5.1.2 All RMPs /updates to RMP should be accompanied by a cover letter or a note to reviewer stating the reason for submission. If the RMP is included with a new application (as module 1.13), the new application cover letter should make reference to the RMP. The cover letter should indicate the

submission type (e.g., RMP update). Reference to scientific information related to the reason for submission or summary of changes that have been made to the RMP should be provided. All RMPs or follow-up commitments should be submitted in eCTD or eSubmission format.

5.1.3 All RMPs submitted shall be accompanied by a declaration to be signed by the QPPV/local Pharmacovigilance Officer.

5.2 Timelines for the submission of RMPs

5.2.1 Any RMPs requested by the Authority must be submitted within 90 calendar days.

5.3 Foreign Reviews

5.3.1 RMP reviews issued by medicines regulatory authorities with which SAHPRA aligns itself (US FDA, EMA, Health Canada, TGA, MHRA) should be provided, if available at the time of the initial submission to SAHPRA. Where more than one such RMP review is available, all reviews should be submitted.

5.3.2 Any RMP review that becomes available at a later stage can be submitted as unsolicited information.

6. South Africa Specific Annexure (SASA)

6.1 Introduction

6.1.1 Purpose of South Africa Specific Annexure for the Risk Management Plan

6.1.1.1 The SASA should:

a) provide SA-specific information that is important in assessing and managing the risk locally (and therefore appropriateness of proposed plans/activities) and the relevance of pharmacovigilance and risk management activities to be implemented in SA;
b) identify and explain the reasons for any differences from activities planned in other countries; and
c) address the applicability of global activities to the SA environment, if no specific SA data will be collected.

6.1.2 Registration history

6.1.2.1 The SASA should provide the SA registration history including:

a) current and previous application types as depicted in module 1.2.1 amendment history (including the status of the submission);
b) medicine usage status;
c) pertinent dates (e.g. Registration dates, amendments);
d) registration number(s), as appropriate.

6.1.2.2 The SASA should include:

a) a summary of previously submitted and approved, withdrawn or rejected SAHPRA applications;
b) a summary of any submissions currently under evaluation (including relevant application numbers);

c) a table comparing the approved and/or proposed indications in SA and other regulators that SAHPRA aligns itself with, identifying and explaining the reasons for any differences.

6.1.3 History of RMPs submitted in SA

6.1.3.1 A tabulated history of all RMPs submitted in SA pertaining to the product (with summary of changes between versions) should be provided.

6.1.4 Epidemiology of the population to be treated in SA

6.1.4.1 The SASA should provide SA-specific epidemiological information on the population to be treated, regarding the size of the target population or any specific data that are relevant to assessing potential use of the medicine in SA.

6.1.4.2 For each indication, data are required on:

a) incidence and prevalence of the condition;
b) demographics of the target population (age, sex, ethnicity);
c) risk factors for the condition;
d) current treatment options;
e) estimates of mortality and morbidity

6.2 Pharmacovigilance Plan

6.2.1 Pharmacovigilance organisation in SA

6.2.1.1 The applicant/HCR must confirm that local pharmacovigilance activities will be conducted in accordance with the current SAHPRA guideline (“2.33 Post-marketing reporting of adverse drug reactions to human medicines in South Africa”).

6.2.2 Routine Pharmacovigilance Activities

6.2.2.1 Routine pharmacovigilance activities to be carried out in SA should be described. Justification for not implementing any routine activities included in the EU RMP in SA is required.

6.2.2.2 Where appropriate, details of procedures that will enable the traceability of biological products, allowing for the investigation of possible disease transmission, between donor and recipient, are to be described in any biovigilance system to be implemented in SA should be provided.

6.2.3 Pharmacovigilance activities for safety concerns specific to SA

6.2.3.1 When a safety concern specific to SA is identified, and additional pharmacovigilance or risk minimisation activities are proposed, beyond those included in the EU/global RMP, justification for the additional safety concern must be provided. If the pharmacovigilance plan for the specific safety concern includes additional activities, then details must be provided.

6.2.4 Studies Referenced in the Pharmacovigilance Plan of the RMP

6.2.4.1 Any differences between the additional studies listed in the EU/global RMP and those proposed for SA must be justified and tabulated. Where SA data is to be collected in relation to a pharmacovigilance study outlined in the EU/global RMP or any SA-specific study is proposed, the (draft) protocols for these studies must be provided, and anticipated dates for submission of study results in SA must be tabulated.

6.3 Risk minimisation activities for generic medicines

In circumstances where risk minimisation activities are required for generics (refer to section 3.3), the RMP should describe the proposed additional risk minimisation activities for the generic, and justify any difference with existing additional risk minimisation activities for the originator medicine. Additional risk minimisation materials for a generic medicine should cover the same key safety messages as those for the originator medicine, and any safety concerns specific to the generic.

6.3.1 How risk minimisation activities will be implemented

6.3.1.1 In a tabular form, the proposed wording relating to the specified safety concerns and missing information items in the proposed SA PI and PIL, should be provided as follows:

Safety concerns	Risk minimisation activities (routine & additional) proposed in EU	Risk minimisation activities (routine & additional) proposed in SA	Comments
Item 1	**Routine activities:** include exact wording for EU SmPC statements proposed for this safety element **Additional activities:** include details of additional activities to be undertaken for this safety concern in the EU	**Routine activities:** include exact wording for SA PI statements proposed for this safety **Additional activities: i**nclude details of additional activities to be undertaken for this safety concern in the SA	If routine and/or additional activities differ for SA from those proposed in EU RMP, provide justification for the differences

6.3.2 Potential for medication errors or other risks, if applicable

6.3.2.1 SA-specific information (if available) on the potential for medication errors or other risks (e.g. if an extension of indication or new dosage form is proposed) should be provided.

6.3.3 How risk minimisation activities will be evaluated in SA

6.3.3.1 Details about how and when evaluation of additional risk minimisation activities, including educational activities, will be undertaken in SA and reported to the Authority, should be provided. How the measures used to mitigate risk are expected to work and what actions will

be taken to ensure product effectiveness, if risk mitigation measures do not work, need to be detailed.

6.4 Summary of the RMP

6.4.1 A table briefly summarising the pharmacovigilance and risk minimisation activities proposed for SA should be provided, as follows:

Safety concerns/missing information	Pharmacovigilance activities (routine & additional) proposed for SA	Risk minimisation activities (routine and additional for SA)
Item 1	**Routine activities:** e.g. Routine pharmacovigilance targeted questionnaire **Additional activities:** include study title or identifier [summary only]	**Routine activities:** e.g. Section of the PI/PIL **Additional activities:** e.g. Educational programme [summary only]

6.5 Person responsible for the RMP and contact details

6.5.1 The person responsible for the implementation of activities in the RMP will usually be the QPPV/local pharmacovigilance officer in South Africa.

7. Role and responsibilities of the Holder of Certificate of Registration/Applicants

7.1 The HCR/applicant is responsible for the RMP, which will include:

a) developing the RMP;
b) updating the RMP as new safety information emerges; to reflect new knowledge and understanding of the medicines' safety profile and benefit-risk balance.
c) implementing the activities and interventions outlined in the RMP;
d) collecting information and performing an analysis regarding the efficacy of these activities and interventions; and
e) communicating this information to the Authority in a timely manner.

8. References

8.1 Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev 2), 2017.

8.2 Risk management plans for medicines and biologicals. Australian requirements and recommendations. Therapeutic Goods Administration. Version 3.3, March 2019.

9. Validity

15.1 This guideline is valid for a period of 5 years from the effective date of revision. It will be reviewed on this timeframe or as and when required.