Risk Management Plan Guideline

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About the Therapeutic Goods Administration

- The Therapeutic Goods Administration (TGA) is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.

- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.

- The work of the TGA is based on applying scientific and clinical expertise to decision-making to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.

- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.

- To report a problem with a medicine or medical device, please see the information on the TGA website.
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Risk Management Plan

Purpose of the guideline

On 1 April 2009 the Therapeutic Goods Administration (TGA) introduced an initiative in which Sponsors of prescription medicine products may be required to submit a Risk Management Plan (RMP). This document has been prepared to provide the prescription medicine industry with information and guidance on this initiative.

Overview of Risk Management Plans

Why have Risk Management Plans been introduced?

It is recognised that not all safety issues related to a medicine will be identified during pre-marketing trials. This can occur for new chemical entities, biological products and where a Sponsor applies for use in a new population, such as children. A Risk Management Plan (RMP) identifies how safety concerns will be identified and mitigated.

Risk Management Plan

What is a Risk Management Plan?

A Risk Management Plan is a set of pharmacovigilance activities and interventions designed to identify, characterise and manage risks relating to a medicine. It consists of an overview of the safety profile of the medicine, a pharmacovigilance plan and a risk minimisation plan. The RMP covers the entire life cycle of the product. Therefore, the RMP will need to be periodically updated to reflect new knowledge and understanding of the safety profile of the product.


Guidance on RMPs is included in the Module 1 - Administrative Information and Prescribing Information for Australia guideline in Module 1.13 Information relating to Pharmacovigilance.

RMP Requirements in Australia

When is a Risk Management Plan required?

A RMP may need to be submitted at any time of a product’s life-cycle – i.e. during both the pre-authorisation and post-authorisation phases.

A RMP should be submitted:

- with an application for:
  - any product containing a new active substance;
  - a similar biological medicinal product;
– a generic/hybrid medicinal product where a safety concern requiring additional risk minimisation activities has been identified with the reference medicinal product;

- with an application for paediatric use;
- with an application involving a significant change in marketing approval (e.g. new dosage form, new route of administration, new manufacturing process of a biotechnologically-derived product, significant change in indication, including a new paediatric indication) unless it has been agreed with the TGA that submission is not required;
- on request from the TGA (both pre- and post-authorisation); and
- on the initiative of an Applicant/Marketing Authorisation Holder when they identify a safety concern with a medicinal product at any stage of its life cycle.

In some circumstances, products which are not in the above categories which are seeking a new authorisation may require a RMP:

- Known active substances;
- Hybrid medicinal products where the changes compared with the reference medicinal product suggest different risks;
- Bibliographical applications; and
- Fixed combination applications.

The TGA can request a RMP be submitted for drugs which are already approved and on the Australian Register of Therapeutic Goods (ARTG) when a safety issue arises. Sponsors are encouraged to review the EU Guideline on Risk Management Systems for Medicinal Products for Human Use (EMEA/CHMP/96268/2005), which outlines when a RMP is required.

A Sponsor should consult with the TGA on any questions it may have about their responsibilities relating to these criteria. Contact details are provided at the end of this document.

How should the intention to submit an RMP be identified in the Streamlined Submission Project

As part of the streamlined submission process, a Sponsor will be required to indicate whether they will be submitting an RMP. If after reviewing the guidelines sponsors remain uncertain if an RMP should be submitted, they can discuss requirements with the TGA. Contact details are provided at the end of this document.

The intention to submit a RMP must be indicated accurately in the Pre-submission Planning Form (PPF) by completion of the information relating to CTD Section 1.13. If it is indicated that an RMP will be submitted in the PPF, an RMP will be expected by the TGA. Further information on the streamlined submission process and requirements for completion of the PPF is available from the TGA website.

If an RMP will not be submitted either a copy of an RMP waiver (see 4.3) must be attached to the PPF or a justification provided as to why a RMP is not required, specifically addressing the requirements. If the justification for not requiring an RMP is deemed to be inadequate then an RMP will be required for the submission to be accepted for evaluation.

Risk Management Plan waiver

What is a “RMP waiver” and when can a sponsor consider this option?

An RMP Waiver is issued by the TGA in response to a request from a Sponsor. The waiver documents the agency agreement that submission of a RMP is not required in a particular situation on a case by case basis. Sponsors are encouraged to apply for a RMP waiver as early as possible in
order to allow time to develop a RMP if a waiver is not agreed to. The waiver application is submitted to the RMP coordinator (see contact details at the end of this document), and must include a scientific justification that clearly outlines why a RMP is not required, including the safety specifications and current safety profile.

**What medicines that are already on the ARTG require a Risk Management Plan?**

The TGA may request a RMP for medicines that are already on the ARTG if a safety concern is identified. This will be done on a case by case basis. The TGA will notify the sponsor in writing and provide a reason for requesting a RMP.

**Do generic medicines require a Risk Management Plan?**

A RMP is required for any generic product where a safety concern requiring additional risk minimisation activities has been identified with the reference medicinal product.

In practice this means a RMP will be required if:

- There is a RMP for the reference product and a safety concern is identified for which additional risk minimisation activities are being conducted; or
- There is no RMP for the reference product, but there are ongoing safety concerns with the reference product which have required specific risk minimisation activities prior to the introduction of the requirements for a RMP. Examples of these are thalidomide, leflunomide, clozapine, lenalidomide, isotretinoin and zoledronic acid.

A Sponsor should initially check whether the innovator has a RMP, which can be done by reviewing whether there is an AusPAR for the product. If the Sponsor still has questions regarding the need for a RMP they should contact the TGA. Contact details are provided at the end of this document.

**Who is responsible for the Risk Management Plan?**

The Sponsor is responsible for the RMP, which will include:

- Developing a RMP;
- Updating the RMP as new safety information emerges;
- Implementing the activities and interventions outlined in the RMP;
- Collecting information and performing an analysis regarding the efficacy of these activities and interventions;
- Communicating this information to the TGA in a timely manner.

**Risk Management Plan format**


The TGA recommends that where an existing global or European Union (EU) RMP is submitted that an Australian Specific Annex (ASA, see Section 5) is included with the RMP. The Annex should identify any differences between the EU-RMP and the local implementation of risk management activities, for example any differences between the EU Summary of Product Characteristics (SmPC) and the proposed Australian Product Information (PI), and the reasons for the difference. This will allow the TGA to assess the appropriateness of the proposed RMP in the Australian environment.
What must be included in the Risk Management Plan?


Particular attention should be paid to ensuring:

- Study protocols (or current drafts) are included for all studies referred to in the pharmacovigilance or risk minimisation plans - the aims, methodology, limitations and practical applications must be available;
- All attachments, annexes and appendices referred to in the RMP are included in full. This excludes the Eudravigilance Annex 1;
- Plans for all communication and/or education programmes proposed as risk minimisation activities, including aims of the programme, methods, evaluation or monitoring, timeline for the provision of relevant documents (e.g. health care provider and consumer letters, educational materials) to the TGA;
- Specific timelines are provided for planned activities (e.g. estimated start, end and reporting dates for planned studies, communication programme milestones) and
- Details on how planned activities will be monitored and/or evaluated for effectiveness.

This is necessary to allow the TGA to assess the appropriateness and value of the planned activities.

What are examples of activities or interventions that may be included in a Risk Management Plan?

There are a variety of activities that may be considered. One example of an additional pharmacovigilance activity may include an observational cohort study to further identify the occurrence of adverse events that were equivocal or not seen during pre-marketing trials. Although not detected during product development, they may be associated with the class of medicine and therefore represent a potential safety concern.

Examples of risk minimisation activities beyond routine may include communication programmes such as providing educational material to prescribers or performing routine tests. For instance, where a drug is suspected to be teratogenic there may be a requirement to perform a pregnancy test prior to prescription and to ensure adequate contraception. Any additional risk minimisation activity needs to include a detailed outline of how the effectiveness of the activity to minimise the risk will be evaluated for effectiveness.

Is it possible that routine pharmacovigilance activities will be the only proposed pharmacovigilance activity?

Yes. After each safety issue has been appropriately identified and characterised the Sponsor must propose a plan on how they will manage this risk. In some cases, routine pharmacovigilance will be sufficient.

Is it possible that routine risk minimisation activities i.e. label maintenance as defined in Volume 9A will be the only proposed risk minimisation activity?

Yes. After each safety issue has been appropriately identified and characterised the Sponsor must propose a plan on how they will manage this risk. In some cases, routine risk minimisation will be sufficient.
Can a Risk Management Plan be considered a substitute for routine pharmacovigilance activities?

No. All Sponsors are required to comply with the requirements set out in the Australian Guidelines for Pharmacovigilance Responsibilities of Sponsors of Medicines. Any interventions or activities proposed in the RMP may be additional to routine pharmacovigilance.

Australian Specific Annex (ASA) to the EU-RMP

Purpose of the ASA

The ASA should provide Australian specific information that is important in assessing the 'risk' in Australia (and therefore appropriateness of proposed plans/activities), the relevance of pharmacovigilance and risk management activities in Australia, and identify and explain the reasons for any differences with activities planned overseas.

When is an Australian Specific Annex required?

An ASA is required in all cases when an EU-RMP is submitted. An ASA is not required when a full Australian RMP is submitted.

ASA content

This should include:

- Differences in indications between the EU and Australia
- Australian specific epidemiological information on the population to be treated (information relating to the size of the target population or any specifics that need to be known in assessing use in this population in Australia). Refer to Section 1.7.1 in the Safety Specifications section of a EU-RMP for reference
- Australian information on potential for medication errors or other risks if an extension of indication or new dosage form is proposed
- Applicability of global activities to the Australian environment if no specific Australian data will be collected

Format of Australian Specific Annex (ASA) to the EU-RMP

The ASA should be referenced as an Annex in the EU RMP - this can be after the last annex referred to in the EU-RMP.

A recommended format for the ASA is outlined below.

1. Introduction
   a. Purpose of Australian Annex for this RMP
   b. Background to product's registration history, e.g. Orphan status, NCE, Line extension, include dates and ARTG number as appropriate.

2. Pharmacovigilance Practice
   2.1 Pharmacovigilance Organization in Australia
   2.2 Studies referenced in the RMP
Describe involvement of Australia in and applicability of global studies to the Australian environment, or if not applicable or relevant to the Australian environment include a justification.

3. Risk Minimization Plan
   a. Address how Risk minimisation activities will be implemented and evaluated in Australia. If surveys or studies are referenced in the ASA, copies of outlines and protocols should be provided.
   b. Provide a justification if activities overseas are not to be implemented in Australia.
   c. Indicate how evaluation of risk minimisation activities – including educational activities will be undertaken. Sponsors are responsible for showing that the measures they are using to mitigate risk are working and if not what actions they will take to ensure effectiveness.

4. Contact Person for RMP
   This should be the person responsible for the activities in the RMP within the Sponsor company and will usually be the Australian pharmacovigilance contact person.

Evaluation of RMP for registration of prescription medicines

Who is responsible for evaluating the Risk Management Plan?
Evaluation of the RMP will be undertaken by the Office of Product Review (OPR) within the TGA. In some cases advice will be sought from the Advisory Committee on the Safety of Medicines (AC SOM). In evaluating the RMP consideration will be given to the following:

- Safety specifications provided by the Sponsor at the time of application; and
- The identification of additional safety concerns during the course of TGA’s evaluation of other modules included in the application (which may result in amendments to the safety specifications submitted by the Sponsor).

Once the evaluation process is complete it is recommended to submit a final version of the ASA confirming the risk management activities for monitoring purposes.

When will TGA provide feedback on the evaluation of a Risk Management Plan?
The process by which the RMP will be evaluated is outlined in Figure 1 as follows:
1. **Evaluation.** TGA evaluates the RMP in parallel with other modules;

2. **Requests for information.** Where applicable, TGA information requests relating to the RMP are directed to a Sponsor via the single round of Section 31 requests for information (Milestone 3 – Milestone 4 above);

3. **Referral to expert advisory group.** Where applicable, the RMP evaluation is reviewed by ACSOM;

4. **Sponsor review (1).** Sponsor review of the completed RMP evaluation;

5. **Delegate overview.** TGA delegate prepares a delegate overview based on the completed RMP evaluation and other evaluation reports/summaries;

6. **Sponsor review (2).** Opportunity provided for Sponsor to review the delegate overview and provide a pre-Advisory Committee on Prescription Medicines (ACPM) response;

7. **ACPM review.** ACPM review of documentation and provision of advice;

8. **Final RMP changes.** Where applicable, the delegate and Sponsor negotiate changes and/or additional commitments to be made within the RMP;

9. **Decision.** Delegate consideration and decision regarding registration of the medicine.
The version of the RMP and ASA reviewed will be included as a condition of registration. Also included in this condition may be written agreements by sponsors to OPR recommendations during the s31 process that are not explicit in the RMP document, and any further requirements determined by the delegate.

**RMP updates during the evaluation process**

An updated RMP can be submitted along with the sponsors’ response to the consolidated s31 queries. If an updated RMP is anticipated to be available during the evaluation process, it is requested that the sponsor identify this in the RMP documentation, e.g. due date for next update RMP, so this can be anticipated and planned for by the evaluator.

Any updates to the Product Information and/or Consumer Medicine Information documents that occur during the evaluation process should be reflected in the next version of the ASA.

For changes that have no impact to the EU-RMP but impact the ASA, submission of an updated ASA is sufficient, with a reference to the current EU-RMP version, for example changes to Australian approved PI/CMI.

**Will the evaluation of the Risk Management Plan be included in the AusPAR?**

The AusPAR will contain a section titled Pharmacovigilance that will contain the following information:

- **Pharmacovigilance system** – comprising a statement as to whether or not the pharmacovigilance systems described by an applicant meet the standards adopted by TGA;

- **Risk management plan** – comprising a general statement about whether risk minimisation activities are required. This will be supplemented with a table containing proposed pharmacovigilance activities and proposed risk minimisation activities for each identified safety issue.

**How is the RMP referred to in the conditions of registration?**

The condition of registration will refer to the specific RMP version (and any updates in the future), any response by the sponsor that agrees to additions or clarifications not explicit in the RMP, and any further conditions relevant to the post market period.

**ACSOM**

ACSOM’s main role in RMPs is to provide advice to OPR on pharmacovigilance and risk management activities. ACSOM advice, if necessary, will be sought in the period between last month of round 1 evaluation (Milestone 3 in Figure 1) and the sponsor response to questions (Milestone 4 in Figure 1). This will allow the evaluator to combine the s31 responses and ACSOM advice into the final evaluation report – which is then made available to the delegate and the sponsor.

**RMPs in the post-marketing period**

**What is the process for submitting RMP updates after regulatory approval?**

Updates to RMPs should be provided as outlined in the relevant EU guidelines. If there is still uncertainty about whether an update is required, the RMP coordinator can be emailed for advice.
An updated ASA should accompany any updated EU-RMPs when submitted and include a summary of all changes since the previous version. If no change or update to the ASA is required, then this should be identified at the start of the ASA by inclusion of a statement that all AU specific information is unchanged. There is no requirement for the delegate to be sent a copy of updated RMPs.

The updated EU-RMP should be submitted at the same time as the next PSUR unless other requirements have been made as a registration condition.

An updated EU-RMP should also be submitted when:

- New information is received that may impact on current SS, PV plan or RM activities
- Within 60 days of an important milestone being reached (PV or RM) or results of a study becoming available
- At request of TGA

All updated documents should be provided with a cover letter stating the reason and rationale behind the updated RMP, and key considerations or issues.

Where RMPs are not required but sent in by sponsors spontaneously (no RMP evaluated in Australia for that product) the sponsor is requested to summarise the reasons for an updated RMP being required in the EU and the change, if any, in the safety information.

**How should the effectiveness of risk minimisation activities be measured and who is responsible?**

The sponsor is responsible for monitoring and evaluating the effectiveness of risk minimising activities. The proposed risk minimisation activities should be dependent on an assessment of the risk, the population, and how the risk changes during the course of the post-market period.

**What elements of a RMP are required when ad hoc safety issues are concerned and TGA requests a RMP?**

A full Australian RMP or the EU-RMP, and ASA, should be submitted.

**If you have a registered product, but not marketed, do you need to update RMP?**

If you have a TGA approved RMP regardless of marketing status, the RMP should be maintained and updated in accordance with relevant guidance.

**Is a formal Notification or Category 3 application required if the RMP is updated?**

No, however, submission of an RMP update does not mean that other required processes, such as a Safety Related Notification, do not need to occur. That is, the updated RMP is not a replacement for normal mechanisms of informing the TGA about safety related and other issues.

All updated documents should be provided with a cover letter stating the reason and rationale behind the update, and key considerations or issues.
If there are changes to safety information e.g. requested by the agency or based on changes to the Core Data Sheet or local safety update to the PI, will the RMP need to be updated?

Yes, an RMP update is required for those products that have implementation of RMP as a condition of registration. The TGA can request a RMP (or updated RMP) at any time to address changes to safety information.

For PI/CMI changes with no impact on the RMP, include in the updated document package for PI/CMIs a sentence justifying why an RMP change isn’t required.

Acknowledgement, evaluation and feedback of updated RMP

Where updated RMPs are required (that is an RMP was evaluated as part of the submission process, and is therefore a requirement that it be implemented in Australia):

- Receipt will be acknowledged
- Review will be conducted by the OPR
- The sponsor will only be contacted further if there is a query or issue that needs to be discussed.

Responsibilities for monitoring compliance with the risk management plan commitments?

The sponsor is responsible for monitoring and ensuring compliance with RMP commitments. Once a RMP has been evaluated, the TGA will ensure that post-marketing commitments contained in the RMP are complied with. If necessary the TGA will follow up with sponsors to confirm compliance.

Contact information

Any questions and advice relating to risk management plans should be directed to the following:

RMP Coordinator
Office of Product Review
Email: rmp.coordinator@tga.gov.au
Telephone: 02 6232 8841

References


Annex 1

Recommended format of Australian Specific Annex to the EU-RMP

1. Introduction

a. Purpose of Australian Annex for this RMP

b. Background to product’s registration history, e.g. Orphan status, NCE, Line extension, include dates and ARTG number as appropriate.

2. Pharmacovigilance Practice

a. Pharmacovigilance Organization in Australia

b. Studies referenced in the RMP

Describe involvement of Australia in and applicability of global studies to the Australian environment, or if not applicable or relevant to the Australian environment include all information on how appropriate safety information will be collected to address the Australian context.

3. Risk Minimization Plan

a. Address how Risk minimisation activities will be implemented and evaluated in Australia. If surveys or studies are referenced in the ASA, copies of outlines and protocols should be provided.

b. Provide a justification if activities overseas are not to be implemented in Australia.

c. Indicate how evaluation of risk minimisation activities – including educational activities will be undertaken. Sponsors are responsible for showing that the measures they are using to mitigate risk are working and if not what actions they will take to ensure effectiveness.

4. Contact Person for RMP

This should be the person responsible for the activities in the RMP within the Sponsor company, and will usually be the Australian pharmacovigilance contact person.