Australian Government
Department of Health
Therapeutic Goods Administration

Consultation paper: Risk management plans for medicines and biologicals

Australian requirements and recommendations

A proposed new version of current guidance

Version 3.0, October 2016

TGA Health Safety Regulation

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Risk management plans for medicines and biologicals

Where stated, "RMP" refers to the RMP format requested by the TGA. This typically comprises both the EU RMP and an Australian Specific Annex (ASA). For more information, see *RMP format*.

Since April 2009, the TGA has required Risk Management Plans (RMP) be submitted for all:

- new chemical entities (i.e. a substance / product not currently entered in the ARTG)
- registered products:
  - when there is a major change in the way in which the product is used or
  - if a new safety concern is identified with an existing product.

The requirements are set out in the Mandatory requirements for an effective application - CTD module 1: Administrative information and prescribing information for Australia.

For biologicals, the TGA has required RMP to be submitted since May 2011 for applications for inclusion in the ARTG of all class 3 and 4 biologicals and selected class 2 biologicals.

Please note

All sponsors must comply with the requirements set out in the Australian pharmacovigilance requirements and recommendations for medicines sponsors and Biovigilance responsibilities of sponsors of biologicals - Australian requirements and recommendations.

For submissions involving biosimilars, refer to the TGA guideline Evaluation of biosimilars.

What is an RMP?

An RMP is a detailed description of a risk management system. The RMP essentially contains:

- A description and analysis of the safety profile of the medicine or biological including a summary of the safety concerns; and
- A set of product vigilance and risk minimisation activities designed to identify, characterise and manage risks relating to the medicine or biological including the assessment of the effectiveness of these activities and interventions.

The RMP covers the entire life cycle of the product. Therefore, it will need to be periodically updated to reflect new knowledge and understanding of the products' safety profile and benefit-risk balance.

Why have RMPs been introduced?

Limited safety information for new medicines

At the time of authorisation, information on the safety of a medicine or biological is relatively limited. This is due to the limitations of clinical trials, including:

- relatively small numbers of subjects in clinical trials compared with the intended treatment population
- restricted population in terms of age, gender or ethnicity
- restricted co-morbidity
- restricted co-medication
- restricted conditions of use
- relatively short duration of exposure and follow-up
- statistical problems associated with assessing many different outcomes.

As a result, not all safety issues related to a medicine or biological will have been identified during pre-marketing studies, particularly in the case of new chemical entities, biologicals, and where a sponsor applies for use in a new population, such as in children.

Maintaining the benefit-risk balance

A medicine or biological is authorised on the basis that in the specified indication(s), at the time of authorisation, the benefit-risk balance is favourable for the target population. However, not all benefits or risks will apply equally to all patients.

When considering how to maximise or assess the benefit-risk balance, risks need to be understood in the context of benefit. An RMP identifies how safety concerns will be identified and mitigated once the product is supplied, to help ensure the benefit-risk balance remains favourable.

When an RMP is required

An RMP must be submitted with applications for registration or inclusion of all:

- new chemical entities
- biosimilars
- vaccines
- class 3 and 4 biologicals in accordance with the TGA biological framework.

An RMP may be requested with applications for inclusion of selected class 2 biologicals when the TGA identifies a safety concern for which additional biovigilance or risk minimisation may be required.

An RMP (or RMP update) will normally be expected with applications involving a significant change to an existing registration, such as a:

- significantly different population

- paediatric indication
- new dosage form or route of administration with inherently higher risk (e.g. oral tablets vs iv injection)
- new manufacturing process of a biotechnologically-derived product
- other significant change in indication.

What constitutes a significant change in indication?

A significant change in indication occurs when the new (proposed) treatment target population differs materially from the previously approved target population for a medicine. This may include (but is not limited to) a:

- new disease area
- new age group (e.g. paediatric indication)
- change from treatment of severe disease to treatment of a less severely affected population
- change from 2nd line to 1st line treatment
- change to a combination treatment regimen (particularly for oncology indications, or where there is a significant safety concern with one or more of the included medicines).

Is an RMP required for generics?

An RMP is not required for generic medicines unless:

- there is an RMP for the reference product **and** a safety concern has been identified for which additional risk minimisation activities are being conducted; or
- there is no RMP for the reference product, but there are safety concerns with the reference product that have required specific risk minimisation activities. This includes, but is not limited to, thalidomide, leflunomide, clozapine, lenalidomide, isotretinoin and zoledronic acid and derivatives of these products.
- we request one (requested by the Delegate).

Other times an RMP is required

In addition to the evaluation process, an RMP may be submitted or requested at any stage of a product's life-cycle, during both the pre-authorisation and post-authorisation phases.

Ensure you submit an updated RMP if:

- there is a significant change to the benefit-risk balance of one or more medicinal or biological products included in the RMP and/or
- we request one when there is a concern about a risk affecting the benefit-risk balance (see also Submitting RMP updates after regulatory approval).

Medicines and biologicals already on the Australian Register of Therapeutic Goods (ARTG)

If a safety concern is identified, we may request an RMP (on a case-by-case basis) for medicines and biologicals that are already on the ARTG. We will notify the sponsor in writing, and provide our reason(s) for the request.

If a sponsor identifies a safety concern requiring amendments to the approved product vigilance or risk minimisation activities, then they should submit an updated RMP (see Submitting Risk Management Plans after regulatory approval).

Any updated RMP submission requires a:

- summary table of changes between the updated RMP and the last RMP submitted to us
- cover letter stating the reason for submission.

If an RMP is not required

This **does not exempt** sponsors from routine product vigilance and risk minimisation requirements. Routine product vigilance (called pharmacovigilance for medicines and biovigilance for biologicals) includes:

- collecting and collating in an accessible manner all suspected adverse reactions that are reported to the personnel of the company
- reporting to regulatory authorities
- continuous monitoring of the safety profiles of approved products, including signal detection and updating of labelling
- preparation of PSURs for submission as specified in the approval letter, or when requested by the TGA
- meeting other TGA requirements.

If you're not sure an RMP is required

If you are uncertain whether an RMP is required for a particular application, please seek our advice as early as possible.

- See How to tell us whether you'll be submitting an RMP with an application

Who is responsible for the RMP?

The sponsor is responsible for the RMP, which will include the following:

- developing an 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; and
- communicating this information to the TGA in a timely manner.

How to tell us whether you'll be submitting an RMP with an application

Medicines

Ensure you accurately indicate whether you will be submitting an RMP by completing the information relating to CTD Section 1.13 in the Pre-submission Planning Form (PPF).

If an RMP is not mandatory

If it is not mandatory to submit an RMP, and you think an RMP is unnecessary, ensure you provide a brief justification.

Assessing the requirement for an RMP

We will assess the requirement to submit an RMP at the Pre-submission Planning stage of the application process. This applies to applications for:

- a new combination of well-known active ingredients commonly used together
- low-risk changes to indication, population, form, strength, dose and route of administration.

Where we conclude that the change to the registration of a medicine does not demonstrate a new or increased level of risk to the consumer, we will advise the sponsor that they do not need to submit an RMP for evaluation with their application. However, we expect that the sponsor will continue to maintain any existing RMP relating to the product(s).

If we conclude that the change to registration may result in a new risk or heightened level of risk, and the sponsor has indicated that an RMP will not be submitted in the PPF, we will notify the sponsor that an RMP must be submitted for evaluation.

Biologicals

We will assess the requirement for an RMP during any pre-submission process or during the screening of an application following receipt.

If you are uncertain whether to submit an RMP

Contact the RMP coordinator to discuss **as early as possible** prior to completing the Pre-submission Planning Form (for medicines) or submitting your application (for biologicals).

We will assess the requirement for an RMP, taking into account any justification provided by the sponsor, and then notify the sponsor in writing, usually by email.

RMP format

Risk management plans submitted to the TGA should follow:

- European Medicines Agency (EMA) Guideline on good pharmacovigilance practices: Module V - Risk management systems (EMA/838713/2011 Rev 1*) with the exception of section V.C.3.1-*Requirements in specific situations*, and
- *Guidance on format of the risk management plan (RMP) in the EU-integrated format*.

Risk management plans for biologicals should include additional sections about possible risks specific to a biological. Refer to 'Additional requirements for RMPs for biologicals' for further information.

You should provide an unadapted EU RMP (if one exists), including V.B.8.6 RMP Module SVI: *Additional EU requirements for the* safety *specification*.

If no EU RMP exists, and you submit an alternative RMP (for example, a global or core RMP):

- ensure it covers all the modules of the EU RMP, and
- it is (preferably) presented in the current EU RMP format.

Include an Australian-specific Annex (ASA) to document all differences between the plan for Australia and the submitted EU, global or core RMP (See Australian-specific Annex to the EU RMP).

The only situation in which an ASA is not required is if:

- the RMP submitted to us will be applied in its entirety to Australia, **and**
- there are no differences to its implementation (i.e., the pharmacovigilance and risk minimisation activities proposed for Australia are identical to those proposed in the submitted RMP, including product information statements).

In these cases, ensure this is specifically stated.

Additional requirements for RMPs for biologicals

Risk management plans for biologicals should include discussion of possible risks specific to biologicals that may not apply to other therapeutic products. Sponsors should refer to the EMA Guideline on good pharmacovigilance practices: Module V - Risk management systems (EMA/838713/2011 Rev 1*) and the EMA Guideline on safety and efficacy follow-up - risk management of advanced therapy medicinal products (EMEA/149995/2008), which contain guidance about:

- the possible risks specific to biologicals
- biovigilance, efficacy follow-up and risk minimisation activities of particular relevance to biologicals.

While the EMA guidelines are focused on medicines and advanced therapy medicinal products (ATMPs) — which include a narrower group of products than those regulated under the Australian biologicals framework — the concepts and information are applicable to biologicals.

The additions described below are required for RMPs for biologicals. If an RMP section is not applicable to a particular product, state this in the RMP and provide a justification rather than omitting the section.

1. RMP Part II module SVI *Additional EU requirements for the safety specification* should contain an additional section '*Specific risks of biological products*' that includes discussion of risks that would not fit into other parts of the safety specifications in the EU RMP. The discussion should be structured as follows:
    a. Flow chart of the logistics of the therapy (for instance, harvesting, transport, controls, manipulation, conditioning, administration, clinical follow-up…)
    b. Risks to living donors (where applicable)

c. Risks to patients in relation to quality characteristics, storage and distribution of the product

d. Risks to patients related to administration procedures

e. Risks related to the interaction of the product and the patient

f. Risks related to scaffolds, matrices and biomaterials

g. Risks related to the persistence of the product in the patient

h. Risks to healthcare professionals, care givers, offspring and other close contacts with the product or its components, or with patients, presented in a summary fashion and based on the environmental risk assessment

2. RMP Part II module SVII *Identified and potential risks* should be replaced with RMP module SVII *Identified and potential risks (ATMP version).* The ATMP version of module SVII requires sponsors to consider risks that may relate to biological products but not to other products.

3. RMP Part II should include an additional section *'Evaluation of the need for efficacy follow-up'*. When a need for efficacy follow-up is identified, the efficacy follow-up plan should be described in Annex 9 of the RMP, as described in 8.4 *Evaluation of the need for efficacy follow-up* of the EMA Guideline on safety and efficacy follow-up — risk management of advanced therapy medicinal products (EMEA/149995/2008).

4. A detailed description of the sponsor's biovigilance system in Australia should be provided either in the Australian-specific Annex (where an EU, global or core RMP is provided) or in RMP Part III *Pharmacovigilance plan* (when an Australian RMP is provided). Sponsors should refer to *Biovigilance responsibilities of sponsors of biologicals: Australian requirements and recommendations* for further guidance about fulfilling their biovigilance responsibilities.

   The description of the biovigilance system should include:

   a. a summary of the sponsor's routine biovigilance activities,

   b. details of the elements of the biovigilance system needed to support the additional biovigilance activities included in the RMP, and

   c. details of procedures for traceability of products from donor to recipient, and recipient to donor, to investigate and act on possible disease transmission.

5. The biovigilance plan described in RMP Part III should include consideration of safety follow-up issues relevant to biological products, as set out in 8.3 *Pharmacovigilance plan (incorporating safety follow-up)* of the EMA Guideline on safety and efficacy follow-up — risk management of advanced therapy medicinal products (EMEA/149995/2008).

6. When developing the risk minimisation plan to include in RMP Part V sponsors should consider the guidance provided on reducing particular risks of a biologicals product provided in 8.5 *Risk Minimisation plan* of the EMA Guideline on safety and efficacy follow-up - risk management of advanced therapy medicinal products (EMEA/149995/2008).

What to include in the RMP

A submission that is acceptable for evaluation will contain the following:

- Study protocols (or current drafts) for all studies referred to in the product vigilance or risk minimisation plans—the aims, methodology, limitations and practical applications
- All attachments, annexes and appendices referred to in the RMP, in full (see Mandatory requirements for an effective application)
- Plans for all communication and/or education programs proposed as risk minimisation activities, including aims of the program, methods, evaluation or monitoring of the effectiveness of the program, and timelines for the provision of relevant documents (for example: health professional and consumer letters, educational materials) to the TGA
- Timelines for planned activities, for example estimated start, end and reporting dates for planned studies, or communication program milestones.

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

Examples of activities or interventions that may be included

Various activities may be considered, for example:

- ***Additional pharmacovigilance activity*** - an observational cohort study to further identify the occurrence of adverse events that were equivocal or not observed 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.

- ***Risk minimisation activities*** - beyond the routine, these may include communication programs, such as providing educational material to prescribers or performing specific tests. For instance, where a medicine 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. Examples of measures to assess this include:

  – cross sectional surveys with results evaluated against established criteria

  – post-authorisation studies.

  If an educational program is accredited with a learned college, this usually includes/provides an acceptable measure of effectiveness of risk minimisation activity.

  Guidance on the measurement of the effectiveness of additional risk minimisation activities is in the Guideline on good pharmacovigilance practices - *Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators*.

Australian-specific annex to the EU RMP

The Australian-specific annex (ASA) enables the EU RMP (or, if no current EU RMP exists, then a core or global RMP) to be adapted to the Australian context.

The ASA is required because global activities proposed in the EU RMP may differ from those planned for Australia. For example, the sponsor may propose different wording for the Australian PI than what is proposed in the EU RMP for the SmPC.

Information needed in 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 product vigilance and risk minimisation activities to Australia, and identify and explain the reasons for any differences from activities planned overseas (this includes product information statements).

If an RMP activity to be conducted overseas will not include Australian data, the ASA should address the applicability of that activity to the Australian context.

When is an ASA required?

Ensure you submit an ASA with the EU RMP (or alternative RMP where no current EU RMP exists).

Are there any exceptions to this requirement?

The only situation where an ASA is not routinely required is if:

- the RMP submitted will be applied in its entirety to Australia

  and

- there are **no** differences to its implementation

  (i.e. the pharmacovigilance and risk minimisation activities proposed for Australia are **identical** to that proposed in the RMP, including product information statements).

If this is the case, ensure this is specifically stated.

Format and content of the ASA

An ASA template is available to provide guidance when drafting ASAs (see ASA template).

Evaluation process for risk management plans

The process used to evaluate the RMP (as a component of the application) is in accordance with the prescription medicines registration and biological inclusion processes.

Who is responsible for evaluating the RMP?

Several areas of the TGA will undertake evaluation of the RMP, including the Risk Management Plan Evaluation section.

What is considered in the evaluation?

In evaluating the RMP, we will consider:

- safety specifications identified (by the sponsor) at the time of application
- identification of additional safety concerns during the course of our evaluation of other modules included in the application (which may result in amendments to the safety specifications originally submitted)
- adequacy and appropriateness of the proposed product vigilance and risk minimisation plans for the specified safety concerns.

RMP Evaluation process for medicines

Step	Description
Evaluation Round 1 (Milestone 3)	Recommendations for amendments: · Table of ongoing safety concerns · Consumer Medicine Information document · Product Information document · Risk minimisation · Pharmacovigilance
Round 1 report	Response to request for information (s31)
Evaluation Round 2 (Milestone 5)	Reconciliation of s31 response to issues raised in Round 1 report. Incorporation of advice: · ACSOV · ACSOM · ACSMD · Clinical · Non-clinical
Round 2 (Final) reconciliation	
Committee advice (Milestone 6) *(if required)*	Advisory Committee for Prescription Medicines (ACPM)
Final PI/CMI/RMP negotiation	Incorporation of advice: ACPM

Decision to approve (Milestone 7)	Delegate
Post-approval	Ongoing pharmacovigilance and risk-minimisation: · Periodic Safety Update Report (PSUR) submission for a specified period of time · RMP updates submitted as per guidelines for the life cycle of the product.

RMP Evaluation process for biologicals

Step	Description
Evaluation Round 1	Recommendations for amendments: · Table of ongoing safety concerns · Consumer Medicine Information document · Product Information document · Risk minimisation · Biovigilance
Round 1 report	Response to request for information (s32JA)
Evaluation Round 2	Reconciliation of s32JA response to issues raised in Round 1 report. Incorporation of advice: · ACSOM · ACSMD · ACB · Clinical · Non-clinical
Round 2 (Final) reconciliation	
Committee advice *(if required)*	Advisory Committee for Biologicals (ACB)
Final PI/CMI/RMP negotiation	Incorporation of advice: ACB
Decision to approve	Delegate

Step	Description
Post-approval	Ongoing biovigilance and risk-minimisation: · Periodic Safety Update Report (PSUR) submission for a specified period of time · RMP updates submitted as per guidelines for the life cycle of the product.

The roles of the Advisory Committees

In some cases, we will seek advice from one (or more) of our advisory committees on the adequacy and appropriateness of the safety specifications, and product vigilance and risk minimisation activities, detailed in the RMP:

- Advisory Committee on the Safety of Medicines (ACSOM)
- Advisory Committee on the Safety of Vaccines (ACSOV)
- Advisory Committee on the Safety of Medical Devices (ACSMD)
- Advisory Committee on Biologicals (ACB)

We notify the sponsor in the RMP report when a product is to be referred to one or more of these committees.

If advice is required

We will usually seek advice between Milestone 3 and Milestone 4 of the prescription medicines registration process, and between the first and second rounds of RMP evaluation for biologicals. This allows the evaluator to combine the s31 or s32JA responses and the committee advice into the final RMP advice, which is made available to the Delegate and the sponsor.

It is not always possible to refer products to the committees during this time (e.g. if the TGA or international regulators identify new safety concerns later in the submission cycle).

We will endeavour to provide the questions to the sponsor prior to the committee meeting. However, in accordance with the prescription medicines registration process, there is no opportunity to submit additional or supplementary data at this stage prior to committee review.

When does the TGA provide feedback on the evaluation of an RMP?

Medicines

We will issue a full RMP evaluation report, and any recommendations and/or questions on the RMP, via the single round s31 information requests at Milestone 3.

The relevant recommendations from the clinical and non-clinical evaluation reports, and the sponsor's response to the RMP evaluation report, will be incorporated into the final RMP advice document after Milestone 5 for medicines.

This advice will be provided to the Delegate, and then sent to the sponsor with the Delegate's overview (if there is no Delegate's overview, this will happen soon after Milestone 5).

The RMP may be subject to review or consideration by the TGA's advisory committees and, in this case, the relevant minutes from the ACSOM, ACSOV and/or ACSMD meeting(s) will be provided to the sponsor.

Biologicals

We will issue a full RMP evaluation report, and any recommendations and/or questions on the RMP, via the s32JA information request after the first round of RMP evaluation.

The relevant recommendations from the clinical and non-clinical evaluation reports, and the sponsor's response to the RMP evaluation report, will be incorporated into the final RMP advice document after the second round of RMP evaluation.

This final report will be provided to the Delegate, and then sent to the sponsor before any regulatory decision.

The RMP may be subject to review or consideration by the TGA's advisory committees and, in this case, the relevant minutes from the ACSOM, ACB and/or ACSMD meeting(s) will be provided to the sponsor.

RMP updates during the evaluation process

You may submit an updated RMP with your response to the consolidated s31 questions or s32JA request and the RMP evaluation report. If you anticipate an updated RMP will be available during the evaluation process, please identify this in the RMP documentation (for example, by including the due date for the updated RMP).

Summary table

Any updated RMP submission requires a:

- summary table of changes between the updated RMP and the last RMP submitted to the TGA
- cover letter stating the reason for submission.

Maintaining records

Ensure you maintain records of when RMPs were submitted to us, **and** the significant changes between each version of the RMP.

Other requirements

- Ensure you reflect any updates to the Product Information (PI) and/or Consumer Medicine Information (CMI) documents (that result from the evaluation process) in the subsequent version of the ASA.
- For changes that have no impact on the EU RMP, but impact the ASA, providing an updated ASA is sufficient, with a reference to the current EU RMP version (for example: changes to Australian PI/CMI documents).
- We recommend that, on completion of the evaluation process, sponsors submit a final version of the RMP confirming the risk management activities for monitoring purposes.

Submitting RMP updates after regulatory approval

The updated RMP or PSUR are not replacements for normal mechanisms of informing us about safety related issues.

Whenever you submit an updated RMP, ensure you:

- clearly indicate all changes from previous RMPs in the documents (preferably in a summary table), **and**
- include a cover letter stating the reason for submission.

This will allow for a more efficient evaluation of the updated RMP.

Ensure you maintain records of when RMPs were submitted to the TGA, and the significant changes between each version of the RMP.

When to submit an updated RMP

An updated RMP should be submitted:

- when we request it
- whenever there is a significant (material) change to the RMP, including but not limited to:
  - when the RMP is modified as a result of new information that may lead to a change to the benefit-risk profile
  - when an important (product vigilance or risk minimisation) milestone is reached, or an activity is terminated, added, or substantially altered
  - when changes to the summary of ongoing safety concerns are made.

In addition, we may require an updated RMP after registration to incorporate the changes agreed prior to approval.

If the date for the submission of a Periodic Safety Update Report (PSUR) and the need to update an RMP coincide, both can be submitted at the same time.

Note

There is no requirement to send the clinical delegate a copy of updated RMPs.

If you are uncertain whether an updated RMP should be submitted

Contact the RMP coordinator for advice.

What to include with an updated RMP

Ensure you include:

- an updated ASA with any updated EU RMP submitted
- a summary of all changes since the previous version.

If no change or update to the ASA is required, identify this at the start of the ASA by including a statement that all Australian specific information is unchanged.

Where RMPs are not required

Where RMPs are not required, but voluntarily submitted by sponsors (no RMP evaluated in Australia for that product), ensure you summarise the reasons for:

- an updated RMP being required in the EU, **and**
- the change (if any) in the safety information.

Periodic safety update reports (PSUR)

The TGA has adopted the EU PSUR guidelines with annotations:

- Guideline on good pharmacovigilance practices (GVP) Module VII – Periodic safety update report (Rev 1).

Where we have identified additional safety concerns, and these have been included in the ASA, ensure you report these in an attachment to the PSUR.

Other requirements

- A formal notification or variation (Category 3) application is not required if the RMP is updated. However, the submission of an RMP update and/or PSUR does not mean that other required regulatory processes, such as a Safety Related Requests (SRRs), do not need to occur.
- For Product Information (PI)/Consumer Medicine Information (CMI) changes with no impact on the RMP, include a sentence in the updated document package for PI/CMIs justifying why an RMP change is not required.

Acknowledgement, evaluation and feedback of the updated RMP

Where updated RMPs are required, we will:

- acknowledge receipt
- conduct the review
- contact the sponsor if there is a query or an issue that needs to be discussed.

Contact information

Please direct any questions and advice relating to Risk Management Plans (RMPs) to:

Post: RMP Coordinator
Pharmacovigilance and Special Access Branch
PO Box 100
WODEN ACT 2606
AUSTRALIA

Phone: 02 6232 8841

Email: rmp.coordinator@tga.gov.au

Frequently asked questions

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

Yes.

Once 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, the sponsor may propose that routine pharmacovigilance will be sufficient.

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

Yes.

Once 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, the sponsor may propose that routine risk minimisation, as defined in *Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators*, will be sufficient.

Can an RMP be considered a substitute for routine pharmacovigilance activities?

No.

Sponsors are required to comply with the requirements set out in the Australian Guidelines for Pharmacovigilance Responsibilities of Sponsors of Medicines or Biovigilance responsibilities of sponsors of biologicals: Australian requirements and recommendations.

Any interventions or activities proposed in the RMP may be additional to routine pharmacovigilance or biovigilance.

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 additional risk minimisation activities.

The proposed 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.

Guidance on the measurement of additional risk minimisation activities is in the Guideline on good pharmacovigilance practices - *Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators.*

What elements of an RMP are required when ad hoc safety issues are identified, and the TGA requests an RMP?

Both an EU RMP and ASA should be submitted.

If no EU RMP exists, ensure you submit an alternative RMP covering all modules in the EU RMP, and preferably in the EU format. (See RMP format)

If you have a registered medicine or included biological, but it has not yet been marketed, do you need to update the RMP?

If you have a TGA-approved RMP, it should be maintained and updated (in accordance with relevant guidance) regardless of its marketing status.

Who is responsible for monitoring compliance with the RMP commitments?

The sponsor is responsible for ensuring compliance with RMP commitments, and should notify us as soon as possible if (for whatever reason) RMP commitments are unable to be met as stated.

Once an RMP has been evaluated, we will undertake periodic audits and monitoring to assess whether post-marketing commitments contained in the RMP are met.

Will the evaluation of the RMP be included in the Australian Public Assessment Report (AusPAR)?

The AusPAR will contain a section on *Pharmacovigilance findings*, which may include the following information:

- **Pharmacovigilance system** – a summary of the safety concerns and evaluation of the pharmacovigilance and risk minimisation activities described in the RMP. If additional risk minimisation activities are required, these will be included.

  We will supplement this information with a table containing the proposed pharmacovigilance activities and proposed risk minimisation activities for each identified safety concern.

  The AusPAR may include timelines for planned activities, such as reporting dates for planned studies, communication program milestones, any differences between the risk minimisation activities undertaken in Australia compared to the EU.

- **RMP Evaluation** – important issues raised in the RMP Evaluation Report and the RMP Advice document.

Note: AusPARs are not currently published for biologicals.

How is the RMP referred to in the conditions of registration or inclusion?

The latest version of the RMP and ASA reviewed will be included in the conditions of registration or inclusion (taking into account any updates provided during the evaluation process).

In addition, the sponsors' written agreements to the RMP evaluator's recommendations during the s31 process or s32JA process (which are not explicitly stated in the RMP document), as well as any further requirements determined by the Delegate, may be included in the conditions of registration or inclusion.

Australian-specific annex template

1. Introduction

1.1 Purpose of Australian specific annex for this risk management plan

The Australian-specific annex (ASA) should:

- provide Australian-specific information that is important in assessing and managing the risk in Australia (and therefore appropriateness of proposed plans/activities) and the relevance of pharmacovigilance and risk management activities in Australia
- identify and explain the reasons for any differences from activities planned overseas
- address the applicability of global activities to the Australian environment, if no specific Australian data will be collected.

1.2 Registration history

Provide the Australian registration history including:

- current and previous application types (e.g. New Chemical Entity, line-extension etc.)
- orphan status
- pertinent dates
- ARTG number(s) as appropriate.

Include:

- a summary of previously submitted and approved, withdrawn or rejected Australian applications
- a summary of any submissions currently under evaluation (include relevant application numbers)
- a table comparing the approved and/or proposed indications in Australia and the EU, identifying and explaining the reasons for any differences.

1.3 History of RMPs submitted in Australia

Provide information on the RMPs previously submitted for evaluation in Australia for the product.

Include a tabulated history of all RMPs submitted in Australia pertaining to the product (with summary of changes between versions, unless this is clearly included in the EU RMP).

1.4 Epidemiology of the population to be treated in Australia

Provide Australian 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 Australia.

For each indication, discuss:

- incidence and prevalence
- demographics of the target population (age, sex, race/ethnic origin)
- risk factors for the disease
- main treatment options
- mortality and morbidity (natural history).

2. Pharmacovigilance plan

For biologicals, replace 'pharmacovigilance' with 'biovigilance'.

2.1 Pharmacovigilance organisation in Australia

Include confirmation that the local pharmacovigilance organisation is operating in accordance with current TGA guidelines for responsibilities of sponsors.

2.2 Routine pharmacovigilance activities

Describe routine activities carried out in Australia (including targeted questionnaires).

Include justifications for any routine activities included in the EU RMP that are not to be implemented in Australia.

For biologicals, a detailed description of the biovigilance system in Australia should be provided, including:

- a summary of the sponsor's routine biovigilance activities,
- details of the elements of the biovigilance system needed to support the additional biovigilance activities included in the RMP, and
- details of procedures for traceability of products from donor to recipient, and recipient to donor, to investigate and act on possible disease transmission.

2.3 Pharmacovigilance activities for safety concerns specific to Australia

This section should include details of any safety concerns for Australia that are additional to those proposed in the EU RMP.

Relevant information should include:

- why the additional safety concern is included in the ASA (e.g. TGA requirement)
- the Australian pharmacovigilance plan for each additional safety concern.

If the pharmacovigilance plan for the specific safety concern includes additional activities then details of these should be provided.

If there are no additional safety concerns for Australia then this can be simply stated.

2.4 Studies referenced in the pharmacovigilance plan of the RMP

Outline the differences, if any, between the additional pharmacovigilance activities proposed in the EU RMP and those proposed for Australia.

Ensure you consider the following when completing this section:

- Whether Australia is involved in each pharmacovigilance study outlined in the EU RMP. If not, provide a brief justification for how each study is still considered applicable and/or relevant to Australia. If an EU RMP pharmacovigilance activity is not considered applicable or relevant to the Australian environment, provide a justification for this also.
- Include details of any Australian-specific studies that are not detailed in the EU RMP, but are part of the pharmacovigilance plan for Australia. Such activities should be clearly assigned to an existing safety concern (suggested table format below). If Australian-specific studies are referenced in the ASA, provide (as a minimum) copies of draft protocols for these studies.
- If dates for submission of study results in Australia differ from the dates proposed in the EU RMP, provide a summary table setting out the anticipated dates for their submission in Australia.

Studies Referenced in the Pharmacovigilance Plan of the RMP – suggested format

Additional activity	Assigned safety concerns or missing information	Actions/outcome proposed	Australian involvement	Planned submission of data in Australia
Additional activity (with unique title and protocol ID) *[Hyperlink to study protocol]*	List of assigned safety concerns or missing information	Summary of proposed actions and/or outcomes	Yes/No	Include interim and final dates
…	…	…	…	…

3. Risk minimisation plan

3.1 How risk minimisation activities will be implemented in Australia

If relevant, describe and provide detail about any additional risk minimisation activities to be undertaken in Australia. If applicable, provide (as a minimum) copies of draft Australian educational materials.

Ensure you identify and justify the differences between risk minimisation activities in the EU (as detailed in the EU RMP) compared to those proposed for Australia.

Provide a table comparing all planned risk minimisation measures for Australia with those proposed in the EU (suggested format below). Wording relating to all the specified *Safety Concerns* and *Missing Information* items in the proposed Australian PI and CMI should be included in the table.

How risk minimisation activities will be implemented in Australia – suggested format

Safety concerns or missing information	Risk minimisation activities (routine and additional) proposed in the EU RMP	Risk minimisation activities (routine and additional) proposed for Australia	Differences between EU and Australian activities with justification
Item 1	**Routine activities** *Include exact wording for EU SmPC statements proposed for this safety concern* **Additional activities** *Include details of additional activities to be undertaken for this safety concern in the EU*	**Routine activities** *Include exact wording for Australian PI statements proposed for this safety concern* **Additional activities** *Include details of additional activities to be undertaken for this safety concern in Australia.*	*If routine and/or additional activities differ for Australia from that proposed in the EU RMP, provide justification for these differences.*
Item 2	…	…	…

3.2 Potential for medication errors or other risks if applicable

Ensure you include Australian information (if available) on the potential for medication errors or other risks, for example: if an extension of indication or new dosage form is proposed.

3.3 How risk minimisation activities will be evaluated in Australia.

Provide detail about how and when evaluation of additional risk minimisation activities, including educational activities, will be undertaken and reported to the TGA.

You must demonstrate that the measures used to mitigate risk are working and, if not, what actions will be taken to ensure effectiveness.

4. Summary of the RMP

Provide a table briefly summarising the pharmacovigilance and risk minimisation activities proposed for Australia. (suggested format below)

Safety concerns or missing information	Pharmacovigilance activities (routine and additional) proposed for Australia	Risk minimisation activities (routine and additional) proposed for Australia
Item 1	**Routine activities** *e.g. Routine pharmacovigilance Targeted questionnaire* **Additional activities** *Include study title/identifier* [Less detail than the previous tables; summary only]	**Routine activities** *e.g. Section of the PI/CMI* **Additional activities** *e.g. Educational programme* [Less detail than the previous tables; summary only]
Item 2	…	…

5. Person responsible for this RMP and contact details

This should be the person responsible for the implementation of activities in the RMP within the sponsor company, and will usually be the Australian Contact Person for Pharmacovigilance ('the nominated contact person').

6. References

Provide a reference list, if required.

7. Appendices

This section allows for flexibility of submitting additional (relevant) documents as appendices to the RMP (e.g. Australian-specific educational materials).

Version history

Version	Description of change	Author	Effective date
V1.0	Original Publication	Risk Management Plans Section/Office of Product Review	03/09/2012
V1.1	Updated Template	Risk Management Plans Section/Office of Product Review	05/09/2012
V1.2	Updated content	Risk Management Plans Section/Office of Product Review	14/09/2012
V1.3	Updated content	Risk Management Plans Section/Office of Product Review	03/10/2012
V2.0	Updated content, added Australian-specific annex as attachment	Risk Management Plan Evaluation Section/Post-market Surveillance Branch	May 2015
V3.0	Published for consultation – updated content to include reference to biologicals	Risk Management Plan Evaluation Section/Post-market Surveillance Branch	October 2016

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 1605
https://www.tga.gov.au