Australian Government
Department of Health
Therapeutic Goods Administration

Risk management plans for medicines and biologicals

Australian requirements and recommendations

Version 3.1, November 2017

TGA Health Safety Regulation

Contents

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.

This guidance is for sponsors of prescription medicines and biologicals making applications to enter or vary ARTG entries.

A risk management plan (RMP) documents the risk management system required to identify, characterise and minimise a product's important risks. The TGA requires RMPs to be submitted for evaluation with certain higher-risk applications to enter a medicine or biological in the Australian Register of Therapeutic Goods (ARTG) or to vary an ARTG entry (see When an RMP is required).

RMPs must be maintained throughout the lifecycle of the product and important updates submitted to the TGA for evaluation (see Submitting RMP updates after regulatory approval).

As a sponsor, you are responsible for the RMP, including:

- developing the RMP
- updating the RMP as new safety information emerges
- implementing the activities and interventions outlined in the RMP
- collecting and analysing information to monitor the effectiveness of these activities and interventions
- communicating RMP changes to the TGA in a timely manner

About this guidance

This guidance:

- explains when you must submit an RMP with an application for registration, inclusion or variation in the ARTG
- describes what to include in an RMP and the required format for RMPs
- details special requirements for RMPs for biologicals
- outlines how the TGA evaluates RMPs
- explains when to submit RMP updates after regulatory approval
- describes how the TGA monitors sponsor compliance with RMP commitments

As part of the Australian Government MMDR reforms, TGA will be consulting on version 4.0 of this guidance in early 2018.

Further information

For further information about risk management plans, see the following TGA guidance:

- Pharmacovigilance responsibilities of medicines sponsors: Australian recommendations and requirements
- Biovigilance responsibilities of biologicals sponsors: Australian recommendations and requirements
- Mandatory requirements for an effective application
- CTD module 1: Administrative information and prescribing information for Australia
- Regulation of biosimilar medicines

The following TGA-adopted EU guidelines are relevant:

- EMA/838713/2011 Guideline on good pharmacovigilance practices (GVP) Module V - Risk management systems
- EMA/488220/2012 Guideline on good pharmacovigilance practices (GVP) Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases
- EMEA/359381/2009 CHMP Recommendations for the Pharmacovigilance Plan as part of the Risk Management Plan to be submitted with the Marketing Authorisation Application for a Pandemic Influenza Vaccine

Useful publication:

- Practical approaches to risk minimisation for medicinal products: Report of CIOMS Working Group IX

The following EU guidelines have not been adopted by the TGA at the moment, but are also relevant to RMPs:

- EMEA/149995/2008 Guideline on safety and efficacy follow-up - risk management of advanced therapy medicinal products
- EMA/204715 Guideline on good pharmacovigilance practices - *Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators*
- EMA/PRAC/613102 Guidance on the format of the risk management plan (RMP) in the EU - in integrated format
- EMA/PRAC/222346 Interim guidance on enhanced safety surveillance for seasonal influenza vaccines in the EU

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, you will need to update it periodically to reflect new knowledge and understanding of the products' safety profile and benefit-risk balance.

Why RMPs are required

A medicine or biological is approved for registration or inclusion on the basis that in the specified indication(s), at the time of approval, the benefit–risk balance is favourable for the target population.

All products have possible safety concerns, with varying degrees of severity, likelihood of occurrence and impact on the individual patient and public health. Some adverse reactions and risks are unknown at the time of approval (because of the limited duration, size and diversity of the patient population included in clinical trials) and will only be identified and/or characterised during post-approval use.

An RMP describes 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

You must submit an RMP with applications for registration or inclusion of all:

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

We may request that you submit an RMP with applications for inclusion of selected class 2 biologicals when we identify a safety concern for which additional biovigilance or risk minimisation may be required.

Biological medicines (for example, vaccines, plasma derivatives and products of the fermentation of recombinant cell lines) are regulated as prescription medicines and are distinct from biologicals, which are living human or animal cells or tissues.

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 or biological. 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)

When an RMP is required for biosimilars

An RMP is required for a biosimilar unless:

- there is an RMP for the reference product and there are neither additional pharmacovigilance activities nor additional risk minimisation activities being conducted, **and**
- the biosimilar will have identical indications and equivalent presentations to the reference product.

When an RMP is 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

OR

- 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 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 Australian Register of Therapeutic Goods (ARTG). We will notify you in writing, and provide our reason(s) for the request.

If you identify a safety concern requiring amendments to the approved product vigilance or risk minimisation activities, then you 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** you from routine product vigilance and risk minimisation requirements. Routine product vigilance (called pharmacovigilance for medicines and biovigilance for biologicals) requirements are set out in:

- Pharmacovigilance responsibilities of medicines sponsors: Australian recommendations and requirements
- Biovigilance responsibilities of biologicals sponsors: Australian recommendations and requirements (under development)

These requirements include, but are not limited to:

- collecting and collating in an accessible manner all suspected adverse reactions that are reported to the personnel of the company
- reporting serious adverse reactions to regulatory authorities
- continuous monitoring of the safety profiles of approved products, including signal detection and updating of labelling
- preparation of Periodic Safety Update Reports (PSURs), where applicable, 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 not sure whether you should submit an RMP with an application, contact us for advice **as early as possible** before you complete the Pre-submission Planning Form (for medicines) or submit your application (for biologicals).

Email the RMP coordinator describing the proposed application. We will assess the requirement for an RMP, taking into account the information you provide, and notify you in writing. If no RMP is required, you can include our advice in Module 1.8.2 of your submission, as described in CTD Module 1: Administrative information and prescribing information for Australia.

Even if submission of an RMP is not required, we expect that you will continue to maintain any existing RMP relating to the product(s).

- See Submitting RMP updates

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 you that you do not need to submit an RMP for evaluation with your application. However, we expect that the you 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 you have indicated that an RMP will not be submitted in the PPF, we will notify you 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.

RMP format

Risk management plans should comply with all of the following:

- EMA/838713/2011 Guideline on good pharmacovigilance practices (GVP) Module V — Risk management systems (with the exception of section V.C.3.1-*Requirements in specific situations)*
- EMA/PRAC/613102 Guidance on the format of the risk management plan (RMP) in the EU — in integrated 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).

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

Provide an EU RMP

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
- preferably, present it in the current EU RMP format

Additional requirements for RMPs for biologicals

In a Risk Management Plan for biologicals, include discussion of possible risks specific to biologicals that may not apply to other therapeutic products. Refer to:

- EMA/838713/2011 Guideline on good pharmacovigilance practices (GVP) Module V — Risk management systems (with the exception of section V.C.3.1-*Requirements in specific situations)*
- EMEA/149995/2008 Guideline on safety and efficacy follow-up - risk management of advanced therapy medicinal products, which contains guidance about:
  - the possible risks specific to biologicals
  - biovigilance, efficacy follow-up and risk minimisation activities of particular relevance to biologicals

The concepts and information in these EMA guidelines are applicable to biologicals, despite the EMA guidelines being 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 following information is required for RMPs for biologicals. These additions may be included in the EU RMP or included as an attachment to the Australian-specific annex.

If an RMP section is not applicable to a particular product, do not omit the section, but instead state this in the RMP and provide a justification.

1. Consider the specific risks of biologicals. This can be in the safety specification in the EU RMP or in a separate attachment to the Australian-specific annex. For guidance on risks to address refer to:

· EMEA/149995/2008 Guideline on safety and efficacy follow-up - risk management of advanced therapy medicinal products, Section 8.1 *Safety specifications.*

2. Include a section *'Evaluation of the need for efficacy follow-up'* in either RMP Part II or attached to the Australian-specific annex. When a need for efficacy follow-up is identified, the efficacy follow-up plan should be included in Annex 9 of the RMP or as an attachment to the Australian-specific Annex. Refer to:

· EMEA/149995/2008 Guideline on safety and efficacy follow-up – risk management of advanced therapy medicinal products, Section 8.4 *Evaluation of the need for efficacy follow-up*.

3. Provide a detailed description of the sponsor's biovigilance system in Australia 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). Refer to:

· *Biovigilance responsibilities of sponsors of biologicals: Australian requirements and recommendations* (under development).

   The description of the biovigilance system should include:

   – 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

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

4. In the biovigilance plan described in RMP Part III or in the Australian-specific annex, include consideration of safety follow-up issues relevant to biologicals. Refer to:

· EMEA/149995/2008 Guideline on safety and efficacy follow-up – risk management of advanced therapy medicinal products, Section 8.3 *Pharmacovigilance plan (incorporating safety follow-up)*

5. When developing the risk minimisation plan, consider the guidance provided on reducing particular risks of a biological product. Refer to:

· EMEA/149995/2008 Guideline on safety and efficacy follow-up – risk management of advanced therapy medicinal products, Section 8.5 *Risk Minimisation plan*

What to include in the RMP

An RMP 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 to the TGA of relevant documents (for example: health professional and consumer letters, educational materials)

- timelines for planned activities, for example estimated start, end and reporting dates for planned studies, or communication program milestones

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

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).

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 EMA/204715 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 that 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?

Submit an ASA with the EU RMP, or an alternative RMP if no current EU RMP exists.

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

The ASA template provides guidance when drafting ASAs.

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
- additional safety concerns identified 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
Round 1 evaluation (Milestone 3)	Recommendations for amendments: Summary of safety concerns Consumer Medicine Information document Product Information document Risk minimisation plan Pharmacovigilance plan If available, advice from the clinical and nonclinical evaluations will be incorporated at this stage
Round 1 report	Response to request for information (s31)
Round 2 evaluation (Milestone 5)	Reconciliation of s31 response to issues raised in Round 1 report. Incorporation of further advice from: ACM/ACV (if sought after milestone 3) Clinical Nonclinical
Post-Round 2 evaluation	Consider pre-ACM/ACV response
Expert advisory review (Milestone 6) *(if required)*	Advisory Committee on Medicines (ACM) or Advisory Committee on Vaccines (ACV)
Final reconciliation	Final RMP negotiation, considering any ACM/ACV advice, the post-ACM/ACV response and final PI and CMI modifications
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
Round 1 Evaluation	Recommendations for amendments: Table of ongoing safety concerns Patient information leaflet Product Information document Risk minimisation Biovigilance
Round 1 report	Response to request for information (s32JA)
Round 2 Evaluation	Reconciliation of s32JA response to issues raised in Round 1 report. Incorporation of advice: ACB (if sought after round 1 evaluation) Clinical Nonclinical
Post-Round 2 evaluation	Consider pre-ACB response
Expert advisory review (Milestone 6) *(if required)*	Advisory Committee on Biologicals (ACB)
Final reconciliation	Final RMP negotiation, considering any ACB advice, the post-ACB response and final PI and CMI modifications
Post-Round 2 evaluation	Delegate
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 role 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, product vigilance and risk minimisation activities, detailed in the RMP:

- Advisory Committee on Medicines (ACM)

- Advisory Committee on Vaccines (ACV)
- 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 may seek expert advice on the risk management plan either:

- between Milestone 3 and Milestone 4 of the prescription medicines registration process, and between the first and second rounds of RMP evaluation for biologicals

OR

- at the committee advice phase (Milestone 6 of the prescription medicines registration process)

We will endeavour to provide the questions to the sponsor prior to the committee meeting. However, in accordance with the prescription medicines registration process and the biologicals inclusion 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 RMP evaluation?

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 nonclinical evaluation reports and the sponsor's response to the RMP evaluation report will be incorporated into the RMP advice document after Milestone 5.

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 advisory committees and, in this case, the relevant minutes from the ACM or ACV meeting(s) will be provided to the sponsor.

If there are outstanding issues after the round 2 RMP evaluation, we will conduct further rounds of RMP evaluation. After each round of evaluation, we will send the updated RMP evaluation report 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 nonclinical evaluation reports and the sponsor's response to the RMP evaluation report will be incorporated into the RMP advice document after the second round of RMP evaluation.

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

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

If there are outstanding issues after the round 2 RMP evaluation, we will conduct further rounds of RMP evaluation. After each round of evaluation, we will send the updated RMP evaluation report 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 in the RMP any updates to the Product Information (PI),Consumer Medicine Information (CMI) or Patient Information Leaflet (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)
- 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

Submit an updated RMP:

- 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.

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 (that is, 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:

- EMA/816292 Guideline on good pharmacovigilance practices (GVP) Module VII - Periodic safety update report

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

- An RMP update or PSUR does not necessarily require a minor variation request or notification. However, other regulatory processes may need to occur, such as a safety-related request (a type of minor variation).
- For Product Information (PI), Consumer Medicine Information (CMI) or Patient Information Leaflet changes with no impact on the RMP, include a sentence in the updated document package for the PI or CMI change 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@health.gov.au

Frequently asked questions

1. Is it possible that routine product vigilance activities will be the only proposed product vigilance 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 product vigilance will be sufficient.

2. 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 is sufficient, as defined in

- EMA/204715 Guideline on good pharmacovigilance practices - *Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators*

3. Can an RMP be considered a substitute for routine product vigilance activities?

No.

Sponsors are required to comply with the requirements set out in:

- Pharmacovigilance responsibilities of medicines sponsors: Australian recommendations and requirements
- Biovigilance responsibilities of biologicals sponsors: Australian recommendations and requirements (under development)

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

4. 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:

- EMA/204715 Guideline on good pharmacovigilance practices - *Module XVI– Risk minimisation measures: selection of tools and effectiveness indicators*

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

Submit both an EU RMP and ASA.

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

6. 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, you should maintain and update it (in accordance with relevant guidance) regardless of its marketing status.

7. 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.

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

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

- **Safety specification** – 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.

AusPARs are not currently published for biologicals.

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

Conditions of registration or inclusion:

- will include the latest reviewed version of the RMP and ASA (taking into account any updates provided during the evaluation process)
- may include the sponsor's written agreements to the RMP evaluator's recommendations during the s31 process or s32JA process (those not explicitly stated in the RMP document)
- will include any further requirements determined by the Delegate

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
- 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 includes:

- 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 provide details.

If there are no additional safety concerns for Australia then state this.

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.
- 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.

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). Include in the table wording relating to all the specified *Safety Concerns* and *Missing Information* items in the proposed Australian PI and CMI.

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 **<u>Additional activities</u>** 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

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).

Summary of the RMP

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 or identifier [Less detail than the previous tables: summary only]	Routine activities e.g. Section of the PI and/or 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

Version	Description of change	Author	Effective date
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
V3.1	Revised with biologicals content following consultation	Risk Management Plan Evaluation Section, Pharmacovigilance and Special Access Branch	November 2017

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