

SCOPE Work Package 8 Lifecycle Pharmacovigilance

Practical Guide on Risk Management Plan Assessment

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Assessment



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Contents

Acknowledgments	3
1. Introduction	4
1.1 Purpose of the document	4
1.2 Relevant guidelines	5
1.3 Definitions and abbreviations	5
2. Practical guidance	7
2.1 Practical approach	7
2.2 Support for overcoming challenges during evaluation of different parts of the RMP	9
2.3 Support for drafting requests for supplementary information	14
2.4 Support for better delivery of procedure recommendations and final outcomes	15
2.5 Updates of RMP	16

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1. Introduction

1.1 Purpose of the document

The purpose of this document is to provide a practical guide on the RMP assessment that results of the work in SCOPE Joint Action, WP8 Lifecycle Pharmacovigilance, Risk Management Plan (RMP) assessment. A survey, based on a questionnaire to National Competent Authorities (NCAs) concerning their experience and practice in assessing RMPs, is the main source for the practical guide given in this document.

The following aspects should be considered:

- This document is intended to give practical guidance on some aspects of RMP assessment and on the drafting of assessment reports. It is not intended in any sense to replace RMP guidance and requirements detailed by regulatory agencies or legal obligations. It is not intended to advise on procedural aspects or to influence templates and guiding text provided by the EMA. Assessors need to be familiar with legislation and guidelines and refer to these as appropriate throughout the assessment process.
- During the SCOPE project period there has been an ongoing revision of the guideline on Good Pharmacovigilance Practices (GVP) Module V. Major changes are proposed in the version that has been on public consultation. Parts of the new proposals are already included in templates and are therefore also included in this Practical guide. Other parts are more challenging and need more guidance, which will be mentioned in this document. The final revision of GVP Volume V is expected December 2016.,
- Part of the RMP assessment procedure for Centrally Authorised Products (CAPs) has changed since the survey was performed, influencing the way the Safety Specification is assessed. As the practical guide documents should be living documents, the present version of the document presents a high level overview of the new changes in relevant sections (4.1 and 4.2.1).
- Due to the multifactorial nature of the assessment process, it is not feasible to cover all aspects and each assessment must be completed on a case-by-case basis.

1.2 Relevant guidelines

- [EMA web-portal for relevant GVP modules](#)
- Guideline on good pharmacovigilance practice (GVP): Module V -Risk Management Systems
- Guideline on good pharmacovigilance practice (GVP): Module XVI – Risk minimisation measures – Selection of tools and effectiveness indicators
- CMDh recommendation on the summary of the pharmacovigilance system and risk management plan in the mutual recognition and centralised procedures
http://www.hma.eu/fileadmin/dateien/Human_Medicines/CMD_h_/procedural_guidance/01_General_Info/CMDh_066_2006_Rev01_2014_09_clean.pdf
- Guidelines on PV in relation to specific products and specific patient populations:
 - Guideline on good pharmacovigilance practices (GVP): Product- or Population-Specific Considerations I: Vaccines for prophylaxis against infectious diseases
 - Guideline on good pharmacovigilance practices (GVP): Product- or Population-Specific Considerations II: Biological medicinal products (under development)
 - Concept paper on guidelines on good pharmacovigilance practice (GVP) Product- or Population specific considerations III: pregnancy and breastfeeding (under development)
 - Guideline on conduct of pharmacovigilance for medicines used by the paediatric population (under revision)
 - [Guidance on safety and efficacy follow-up – risk management of advanced therapy medicinal products](#)

1.3 Definitions and abbreviations

Terminology	Description
ADR	Adverse Drug Reaction
ADS	Alternative Data Source
B/R	Benefit/risk
CP	Centralised Procedure
CAPs	Centrally Authorised Products
CHMP	Committee for Medicinal Products for Human Use
CRPS	Complex Regional Pain Syndrome
DSUR	Development Safety Updated Report
EM	Educational Materials

Terminology	Description
EMA	European Medicines Agency
EU	European Union
GVP	Guideline on Good Pharmacovigilance Practices
HPV	Human Papilloma Virus
LoQs	List of Questions
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MS	Member State
NCA	National Competent Authority
OV	Overview Assessor
PAES	Post-Authorisation Efficacy Study
PAS	Post-Authorisation Study
PASS	Post-Authorisation Safety Studies
PIL	Patient Information Leaflet
PK	Pharmacokinetics
PRAC	Pharmacovigilance Risk Assessment Committee
PRIME	Priority Medicines
PSUR	Periodic Safety Update Report
PSUSA	Single assessment of Periodic Safety Update Reports
PV	Pharmacovigilance
RMM	Risk Minimisation Measure
RMP	Risk Management Plan
RMS	Reference Member State
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
WHO	World Health Organisation
WP	Work Package

2. Practical guidance



2.1 Practical approach

(better planning, organisation and pre-assessment preparatory work)

2.1.1 Plan what resources you need during the assessment

- a) Check the **timetable** and consider if other work plans within your responsibility will make it difficult for you. If difficulties adhering to the timetable are foreseen, contact your manager and discuss how to reallocate other assessment work that may need to be completed during that time. If work sharing within a team of assessors is possible, this will ensure adherence to the timetable.
- b) If it is a RMP for a new application for a new substance, you may need to **collaborate with the Committee for Medicinal Products for Human Use (CHMP) pre-clinical and clinical assessor**, as both pre-clinical data and safety data from the clinical trial program are important for determining what should be included in the safety specification. In case of medication error, it may also be useful to collaborate with a quality assessor. In some member states (MSs) it is the pharmacovigilance (PV) assessors performing the RMP assessment, in other MSs this will be the clinical assessors.

According to the new timelines and responsibilities for assessment of new applications in centralised procedure, the assessment of the safety specification is now the responsibilities of the CHMP Rapporteurs (usually from another MS than the Pharmacovigilance Risk Assessment Committee (PRAC) rapporteur). They are to ensure that the safety specification is an accurate representation of the non-clinical and clinical dossier and to flag any key safety findings relevant to the RMP. The PRAC rapporteur has to assess the Pharmacovigilance Plan and Risk Minimisation Plan based on the RMP provided by the Applicant and the CHMP Rapporteurs' assessment of the Safety specification. At the end of the procedure, the PRAC assessment report is to be merged with the CHMP assessment report. To clarify any questions during the procedure, it would be useful to speak with the CHMP Rapporteurs by participating in teleconferences usually held during the assessment procedure. External **expert(s)** in the field might also be useful to consult. The expert(s) should be informed as early as possible about the product under assessment and the timelines in place.

For new medicines of major public health interests (high medical need) accelerated assessment has recently been introduced. This procedure reduces the timeframe for review of an application for a marketing authorisation from a maximum of 210 days to 150 days. For this procedure the collaboration between PRAC Rapporteur and CHMP Rapporteurs are critical for the best assessment of the RMP.

If the application is part of a national procedure, the whole RMP document is to be assessed within the Reference Member State (RMS) /National Competent Authority (NCA).

- c) **Interim meetings.** Depending on the product and whether more than one assessor is required, it may be helpful for interim meetings with the assessment team to be held before the deadline set for the PRAC preliminary assessment report. You must also plan time to check the quality of the preliminary report. Make agreements with a senior assessor or your manager or find the time slot for discussing the preliminary report in a quality meeting. For generics, if the RMP is being assessed by an Overview Assessor (OV), a discussion/meeting with the **quality/clinical assessors** may be useful to find out if there are any concerns that might impact the RMP.



2.1.2 Assessment report templates

Make sure you have the correct **template** for the assessment report, according to both the stage of the assessment you are at and the kind of medicinal product that is being assessed. If the product is going through a Centralised Procedure (CP), there are templates provided by the EMA. Otherwise a range of templates are published by the EMA (see link below) or your NCA may provide templates in local SOPs/guidance. The guiding text in the template and the [GVP module V](#) will be helpful.

2.1.3 Consistency with other RMPs

Make sure you are aware of any relevant previous or ongoing procedures (e.g. RMP assessment for substances from the same class). If products with substances in the same pharmacological class have been approved, check how to obtain RMP documents for these, e.g. EMA website/EPAR (<http://www.ema.europa.eu>)

If the RMP under assessment is for a generic product, you should check if the originator (e.g. EMA website/EPAR) or another generic already has an RMP and how to this can be obtained, e.g. CMDh website (<http://www.hma.eu.464.html>).

While RMPs for medicines within the same class should act as a general guide, certain risks may differ between products in the class and so each application should be considered on a case-by-case basis, taking into consideration all the supporting evidence and any differences in formulation, dose, routes of administration, patient population, etc.

2.1.4 PRIME

EMA has recently launched the PRIME scheme to support development of medicinal products of major public health interest through early and enhanced scientific and regular dialogue. More guidance is needed on how this will influence what kind of studies need to be included in the Pharmacovigilance Plan of the RMP and how the PRAC Rapporteur should be involved.

2.2 Support for overcoming challenges during evaluation of different parts of the RMP



2.2.1 Safety specification

The purpose of the safety specification is to provide an adequate discussion on the safety profile of the medicinal product, as identified during its development or others in the class, with a focus on those aspects that need further characterisation and/or risk management activities. Ensuring that the safety specifications comprehensively capture the most important concerns requires a particular emphasis on incorporating both non-clinical and clinical data. Does the safety specification provide a true reflection of the safety profile, including what is known or unknown in the targeted patient groups?

- a) The list of safety concerns should be limited and strictly focused on risks considered important to **benefit/risk (B/R)**. Keep in mind that the list of safety concerns will be used for future reporting in PSURs and should not be an exhaustive list of all risks associated with the product (as listed in the SmPC 4.8). To decide what risks are considered important and need to be included in the RMP:
 - Ask yourself if the risk is potentially so serious and so frequent that it could impact on the B/R of the product, or that specific guidance/tools are needed to ensure correct use of the medicine. A risk may not be “important” if it is infrequent, non-serious, reversible and readily managed with no significant impact on the individual patients or public health. A common ADR may not constitute an important risk if it is not linked to clinically significant adverse sequelae.
 - In assessing the public health impact of individual risks, one should consider the following points, which are intended to be illustrative rather than comprehensive: extent of product use (size of treated populations), frequency and health consequences (including consideration of seriousness, preventability and reversibility).
- b) Once you have agreed which are the “important” risks, you must decide if they should be categorised as an **identified** risk or a **potential** risk. In general, in the case of RMPs for new initial applications:
 - If the risk is seen in the clinical trials and there is either a plausible mechanism or the incidence is greater than placebo or background rates in the targeted population, this should be considered an identified risk. If the background rate is higher or about the same as seen in the clinical trials, it might not be an identified risk. If the background rate is lower than that seen in the clinical trials, it is more probable that this is an identified risk.
 - If the risk is seen only in pre-clinical studies it should be considered a potential risk.
 - If this is a known class effect, but not seen in the clinical trials etc., it should be considered a potential risk (see GVP Module V).

c) Assessment of risk in **specific populations** in situations where exposure has been limited, as commonly occurs in the clinical development program, is a particular challenge. Ask yourself what the limitations of the safety database are and what reassurance it provides regarding the safety profile of the medicinal product, as well as whether these groups are likely to use the medicine in real world clinical practice:



- How many individual patients have been exposed to the medicine, at what doses, in clinical trials and in post-marketing experience worldwide? How long have they been exposed for? Kaplan-Meier curves are a useful way to illustrate these aspects. What are the age and gender characteristics of exposed patients? Is there any evidence that the safety profile may differ in patients of different ethnicities? What are the exclusion criteria in the clinical trials (these considerations are also relevant for deciding areas of missing information) – do any of these reflect patients who are likely to receive the drug in its everyday use?
 - Consideration should be given to the indication for which the medicinal product is proposed. For example, if it is indicated for children or elderly (special populations), is the population exposed in clinical trial representative of the post-marketing clinical practice?
 - Has all appropriate data been reviewed when compiling the safety specification, or are there important (outstanding) issues from other sections of the dossier that have not been discussed in the safety specification?
 - Are there specific risks, e.g. particular safety concerns associated with likely off-label use, misuse and abuse, overdose, transmission of infectious disease, medication error, or a lack of efficacy?
- d) To decide on **missing information**:
- Usually we only want to specify something as missing information if we want to study exposure in those patient groups further.
 - Subgroups of the targeted populations that are expected to frequently use the product and are not included in the clinical development program can be considered as missing information, e.g. patients with impaired renal and hepatic function, children, elderly, pregnant and lactating women, off-label use. Exclusion criteria should not automatically translate into missing information. The assessor should rather consider clinical relevance and likely real-world use to be of importance for the missing information. It can be useful to confer guidance on PV in specific populations (e.g. pregnant and lactating women, paediatric population) when considering whether any specific populations are to be listed as missing information in the Safety specification.
 - If the indication implies chronic use, long-term use should be considered as missing information if not studied.



- If studies of relevant drug-drug interaction have not been done, this should be considered as possible missing information. It might be relevant to bear in mind whether a different safety profile might be expected in some patient groups, e.g. different ethnicities might have differences in PK that would impact safety.
- e) **List of Questions (LoQs)** related to safety specifications in the new procedure will be part of the CHMP assessment report. If you, as PRAC rapporteur/PV assessor, find additional questions justified, these should be highlighted in comments on the CHMP preliminary assessment report. It might be useful to discuss this with the CHMP assessor.
- f) **RMPs for advance therapy medicinal products (ATMPs)** – be aware there are specific risks that are to be considered for these products, see Guidance on Safety and Efficacy Follow-up – Risk Management of Advanced Therapy Medical Products)
- g) **RMPs for generic/biosimilar products/ fixed dose combinations** – the expectation is that the safety specification is essentially the same as for the reference product or other generic products for which an RMP is in place, however, this should not preclude an RMP from being improved if the comparator RMP is of poor quality. In general, the following questions should be considered:
- Have relevant safety concerns from the reference medicinal product been included in the safety specification?
 - What is included in the RMP summary of other products with the same substance?
 - Are there any recommendations from other procedures, e.g. referral procedures on key elements to be included in RMPs for the specific substance or for the class?
 - Have any important new signals been identified during Periodic Safety Update Report (PSUR)/ Single assessment of Periodic Safety Update Reports (PSUSA) procedures of the same substance, if available?
 - Are there any important risks with the substance discussed in literature?

2.2.2 Pharmacovigilance Plan



The purpose of the Pharmacovigilance plan is to present an overview of how to further characterise the risks identified in the safety specification, investigate any potential risks, seek missing information and measure the effectiveness of any additional risk minimisation measures. One challenge is to decide whether additional PV activities are needed and the how the study would be useful and feasible..

For new substances:

- a) Consider whether **routine PV** activities would be able to address important uncertainties (generate information that is needed) within a reasonable timescale. If the question is to explore whether a safety concern occurs or not, routine PV is suitable, i.e. signal detection.
- b) Questionnaires to collect follow-up information on specific individual case safety reports are considered routine PV. Look into the questionnaires as proposed by the MAH - they should be short and to the point, otherwise they will be a burden for the reporter to respond to. Ask for proposals of the questionnaires.

Identify important potential/identified risks/missing information that needs further characterisation, for example:

- The risk is new, potentially serious or disabling and may not easily be recognised, e.g. the relation between Pandemrix and narcolepsy.
- The incidence is not known – background incidence in the target population should be discussed.
- Are there changes in frequency over time for an adverse event?
- A plausible mechanism is not known.
- More information on how to minimise the risk is needed, e.g. identifying specific risk groups, identifying the degree of off-label use.
- In the case of orphan treatments, or products authorised under exceptional circumstances, the safety database may be very limited and robust measures to collect further safety data are needed (e.g. via a registry).

The above situations may justify additional PV activities, such as non-clinical studies, clinical trials or non-interventional studies such as Post-Authorisation Safety Studies (PASS).

- c) Consider which studies are actually feasible and discuss the likelihood that results of additional studies will lead to regulatory changes, e.g. refinement of recommendations for safe and effective use.
- d) Determine the feasibility of a PASS by considering in how many MSs the product is intended to be marketed and how many patients are expected to be prescribed and if it is feasible a PASS can be performed.

- e) Assess the potential and consequences for misuse, abuse, off-label use, immunogenicity for biologicals, for malignancy and identify any need for additional monitoring or studies.
- f) In case of **accelerated assessment** the safety database is usually small and clinical trials in phase II and III are still ongoing to collect more information on both efficacy and safety. You should consider if it will be useful to include these clinical trials in the Pharmacovigilance Plan.
- g) **Consistency with other related products:** It may be relevant to consult PV plans for other substances in the same therapeutic class. Is there uncertainty over the degree of risk of class effects associated with a new active substance (which is not first in class)? In the case of biosimilars or generics, consistency with the innovator product is usually required concerning additional risk minimisation, but usually not concerning additional PV activities.
- h) For **generic products:** consider if any of the additional PV activities will also be reasonable to require also for a generic product. If PASS are imposed on the innovator product, it should be discussed as to whether similar studies should also be imposed on the generic product and how this might happen. Consider if an ongoing registry study may already be collecting information on the generic product(s). Joint PASS should be discussed as an alternative.



2.2.3 Plan for Post-Authorisation Pharmacovigilance Plan Efficacy Studies (PAES)

If PAES are imposed as conditions of the marketing authorisation or as specific obligations in the context of conditional marketing authorisation, a list of these should be part of the RMP. Collaboration with the CHMP Rapporteurs and follow-up of the CHMP opinion is important to allow relevant amendments to the RMP at the end of the procedure.

2.2.4 Risk minimisation plan

For each safety concern, it is necessary to assess the risk minimisation measures needed to prevent or reduce the severity of ADRs associated with exposure. The choice of measure depends on different factors, such as the severity of risk, the healthcare setting, the indication, the pharmaceutical form and the target population.

The challenge is to differentiate between risks that can be efficiently managed by routine Risk Minimisation Measures (RMMs) (information in the Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and the product label) and risks that require additional RMMs. If additional RMMs are necessary, it must also be considered what kind of RMMs are most appropriate to minimise the individual risks. Consideration should also be given to whether any of the potential risks need RMMs for the safe and effective use of the product.

When considering the need for **additional RMMs**, ask yourself:



- a) Have any specific risk minimisation tools been used in the clinical trials? If yes, is it possible that similar tools are needed in daily clinical practice based on the experiences from the clinical trial program?
- b) If additional RMMs have been suggested, are they risk proportionate, justified and adequate? Ask yourself if any specific recommendations are needed for the prescriber or the patient/care givers to manage the risk, e.g. any specific dose recommendations, monitoring recommendations, contraindications or specific warnings. Liaise with the CHMP rapporteur or other assessors for this if necessary.
- c) If the RMMs concern children, is there any benefit in asking PDCO for some advice?
- d) Will the proposed additional RMMs have any impact on the design of or wording on the package material?
- e) If educational material is proposed, consider if it is in line with the GVP module XVI Addendum I – Educational material. Ask yourself if it adds anything to the information already in the product information?
- f) Are the methodologies for measuring and assessing the effectiveness of additional RMMs well described and appropriate? Have criteria for evaluating the success of additional RMMs been defined? Are the proposed measures appropriate and feasible? Is there previous experience with other drugs in this setting? See [GVP XVI](#).
- g) How and to whom will the RMMs be communicated?

2.3 Support for drafting requests for supplementary information

The request for supplementary information to companies needs to be clear, relevant, precise and focused on concerns that need to be assessed. Ensure requests are realistic and proportionate. Avoid wording that is open to misinterpretation and requests for information that is only “nice to know”.

2.3.1 Safety specification

- If important risks are seen in (non)-clinical trials are not included, recommend this to be included and request the Applicant/Marketing Authorisation Holder (MAH) to include this.

2.3.2 Pharmacovigilance Plan



- If the evaluation concludes that there is a need for more knowledge about safety in specific patient groups or about specific safety concerns discussed in the RMP, the Applicant/MAH should be requested to propose appropriate studies.
- Recommend that the Applicant/MAH includes timetables of studies, if these are not provided.
- Ask for a synopsis of study protocols, or study protocols if these are not provided.
- Ask for studies on the effectiveness of RMMs in case of additional RMMs, if appropriate (consider whether it is possible for the MAHs to carry out such a study).

2.3.3 Risk Minimisation Plan

- If Educational Material (EM) or other RMM tools are proposed, request drafts, descriptions or illustrations if appropriate.

2.4 Support for better delivery of procedure recommendations and final outcomes

2.4.1 General considerations

When drafting recommendations, bear in mind that they should describe what to do, without lengthy explanations of the reasons (this has been already explained in the previous sections of the assessment report). Wording should be clear and concise. Work closely with a PRAC member, especially with respect to the text to be used for recommendations. If possible, become familiar with the wording that has been used in previous procedures for drafting of recommendations for similar safety concerns.

If you work within a team, when editing the proposed text between meetings/TCs/e-working, make a new text available and highlight changes in the document before the next step/appointment, to allow the team members to examine them and comment.

2.4.2 Management of imposed conditions

If imposed conditions to the Marketing Authorisation (MA) are proposed (e.g. studies in the PV plan or additional RMMs) these conditions must be reflected in Annex IIB to the MA for CAPs and the appropriate documents for national procedures (e.g. the final assessment report). Make sure the conditions are clearly stated and key elements for successful development of RMMs are included.

2.5 Updates of RMP



When new information is available either through routine or additional pharmacovigilance it is important to consider if the different parts of the RMP need to be updated. Ask yourself:

- Are identified risks sufficiently characterised? Is the management of the risks integrated in the routine clinical practice, e.g. NICE or national clinical guidance? If so, you should consider removing the risk(s) from the safety specification unless specific RMMs are still needed.
- Are potential risks real or not? You should consider if they should be upgraded to identified risks or can be deleted.
- Is missing information sufficiently characterised? You should assess if any can be deleted.
- Are updates on status of studies in the Pharmacovigilance Plan needed?
- Are additional RMMs still needed, e.g. if management of the specific risk is integrated in clinical practice (see above) or should new additional RMMs be added if new risks have been identified?

More guidance is expected on when to remove a safety concern or stopping implementation of an additional RMM.