

A shot at demystifying the risk management plan for medical writers

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Abstract

A risk management plan (RMP) is a complex regulatory document which is now required in the European Union as part of a medicine's approval process. This article offers practical guidance for medical writers who are interested in writing an RMP. In a step-by-step approach, the medical writer is led through the RMP template with the aim of taming this mystical beast.

Keywords: Risk Management Plan, European Medicines Agency, Medical writing, Pharmacovigilance

Writing a risk management plan (RMP) for the first time can be a daunting prospect. This article aims to provide some tips for medical writers who are new to preparing RMPs. Most of you will know that the RMP is a legally binding regulatory document submitted to health authorities. It is now mandatory for all new marketing authorisation applications in the European Union (EU), except for those for homoeopathic medicinal products registered via the simplified registration procedure and traditional herbal medicinal products. Once an RMP is accepted by the health authorities, the Marketing Authorisation Holder (MAH) has a legal obligation to perform the activities described in the RMP.

Objectives of the RMP

The RMP gives a detailed description of pharmacovigilance activities and interventions designed to identify, characterise, and manage risks relating to a medicinal product (MP).¹ The ultimate goal of the RMP is to improve the benefit-risk balance by combining risk assessment and risk minimisation.

First, the RMP describes what is known and not known about the safety profile of the MP. Once that has been established, the RMP outlines measures to prevent or minimise the risks and how the effectiveness of those measures will be

assessed and monitored. In addition, the RMP proposes pharmacovigilance activities to study further safety concerns during use of the drug in the real-life setting and documents the need for efficacy studies in the post-authorisation phase.

Structure of the RMP

The RMP is structured in a modular format and consists of seven parts, where part II ('Safety specification') is further divided into eight modules (see Table 1 for an overview of the parts and modules of the RMP alongside their respective aims). Normally, all parts of an EU-RMP should be submitted. In certain circumstances, some parts or modules may be omitted unless they are requested by the competent authority. For example, generic applications based on Article 10(1) of Directive 2001/83/EC do not require RMP part II modules SI-SVII.

Check reference RMPs

Before you start writing the RMP for your product, always consider whether RMPs are available for products with the same active substance or within the same pharmacotherapeutic group. These should be taken into account even if they are approved for a different indication and posology. Also, reference to other products with similar indications and/or risks can be useful.²

In the case of a generic drug, check if RMPs exist for the innovator, the reference product, or a generic. The RMP for a generic should comply with the RMP for the reference product, unless some safety concerns are clearly no longer relevant. Addition of further safety concerns in a generic RMP (in relation to the reference product) has to be thoroughly justified. Provided that the reference MP has no additional pharmacovigilance studies or stipulated efficacy studies imposed as a condition of the marketing authorisation, RMP parts III and IV may be

Table 1: EU-RMP structure and objectives of the respective parts

RMP structure		Objectives
Part I	Product overview	Provide administrative and active substance information
Part II	Safety specification	Identify what is known and not known about the medicinal product
	Module SI: Epidemiology of indication(s) and target population(s) Module SII: Non-clinical part of the safety specification Module SIII: Clinical trial exposure Module SIV: Populations not studied in clinical trials Module SV: Post-authorisation experience Module SVI: Additional EU requirements for the safety specification Module SVII: Identified and potential risks Module SVIII: Summary of the safety concerns	
Part III	Pharmacovigilance plan	Plan a programme to identify new safety concerns and characterise known ones
Part IV	Plans for post-authorisation efficacy studies	Investigate effectiveness in everyday medical practice
Part V	Risk minimisation measures	Take steps to prevent or minimise known or suspected risks and evaluate the effectiveness of risk minimisation measures
Part VI	Summary of the risk minimisation plan	Provide a public summary of the RMP written in lay language
Part VII	Annexes	

omitted for generics. Part VI should be based on an appropriately modified version of the public summary for the reference MP.¹

How to write an RMP – A step-by-step approach

First of all, get yourself acquainted with the formal requirements for content and submission of EU-RMPs as outlined in Good Pharmacovigilance Practices (GVP) Module V published by the European Medicines Agency (EMA).¹ Use the guidance on format of the RMP which is available for download on the EMA website as either an integrated template with all modules in one document, an abridged format suitable for generic medicines, or the complete set of individual modules.³ Don't be surprised to find that this template is very repetitive and tables will have to be copied again and again in different parts.

Due to the complexity of the RMP, you will most probably work together with a multidisciplinary team (e.g. toxicologists, pharmacologists, pharmacovigilance, clinical and regulatory experts), who will advise on the evaluation of risks and the proposed measures for prevention and risk minimisation.⁴ Note that the RMP is a stand-alone document and cross references to other parts of the dossier should therefore be avoided. Table 2 indicates the location of information in the

common technical document (CTD) according to GVP guideline Module V.¹

Part I - Product overview

This section is straightforward to prepare. It provides administrative information on the RMP and an overview of the product it covers. It also includes active substance information, pharmacotherapeutic group (Anatomical Therapeutic Chemical [ATC] Classification System), mode of action, indication, posology, and pharmaceutical forms/strengths.

Part II - Safety specification

Part II is organised in eight modules. Apart from module SVI, which includes additional elements required to be submitted in the EU, all other modules correspond to safety specification headings in ICH-E2E.⁵ The purpose of the safety specifications is to provide a synopsis of the safety profile of the MP and should include what is known and not known about the MP.

Module SI: Epidemiology of the indication(s) and target population(s)

This module provides background information on the proposed indication(s), explaining what events occur as part of the disease and what events can be expected in the target population. The following issues have to be discussed:

Table 2: Mapping between RMP modules and CTD according to GVP guideline Module V

RMP	CTD
Part I - Product overview	Module 2.3: Quality overall summary Module 3: Quality Module 2.5: Clinical overview
Module SI: Epidemiology of the indication(s) and target population(s)	
Module SII: Non-clinical part of the safety specification	Module 2.4: Non-clinical overview Module 2.6: Non-clinical written and tabulated summaries Module 4: Non-clinical study reports Module 2.7: Clinical summary – briefly Module 5: Clinical study reports Module 2.5: Clinical overview Module 2.5: Clinical overview – briefly Module 2.5: Clinical overview (including benefit-risk conclusion) Module 2.7: Clinical summary SmPC
Module SIII: Clinical trial exposure	
Module SIV: Populations not studied in clinical trials	Module 2.5: Clinical overview
Module SV: Post-authorisation experience	Module 2.5: Clinical overview (including benefit-risk conclusion)
Module SVII: Identified and potential risks	Module 2.7: Clinical summary SmPC
Module SVIII: Summary of the safety concerns	Module 2.5: Clinical overview Module 2.7: Clinical summary
Part III - Pharmacovigilance activities	Module 2.5: Clinical overview Module 2.7: Clinical summary
Part IV - Plans for post-authorisation efficacy studies	Module 2.5: Clinical overview Module 2.7: Clinical summary
Part V - Risk minimisation measures	Module 2.5: Clinical overview Module 2.7: Clinical summary

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- epidemiology of the indication(s), including
 - incidence and prevalence
 - demographics of the target population(s)
 - risk factors for the disease
 - main treatment options
 - mortality and morbidity
- concomitant medications in the target population(s)
- important co-morbidities found in the target population(s)

Preparing this part of the RMP will provide no real challenge for medical writers, especially if they have some experience in writing clinical overviews.

Module SII: Non-clinical part of the safety specification

This module is basically a summary of the non-clinical parts of the CTD, so any experience with preparing non-clinical overviews will be very helpful. You are asked to present a summary of the important non-clinical safety findings, such as toxicity, general pharmacology, drug interactions, and other toxicity-related information or data. Justify inclusion or exclusion of non-clinical findings as important risks depending on their relevance for humans and also note missing information. Safety concerns arising from non-clinical data should be carried forward to module SVIII.

Module SIII: Clinical trial exposure

Again, this is a pretty straightforward section, where meticulous work is required to provide a tabulated and/or graphical summary of a variety of exposure

measures from clinical trials, such as duration of exposure, dose levels, or age groups.

Module SIV: Populations not studied in clinical trials

In this module, you should discuss which subpopulations within the expected target population have not been studied in clinical trials (e.g. pregnant women or patients with severe renal impairment). The relevance of inclusion and exclusion criteria should also be explained, especially when exclusion criteria from study protocols are not proposed as contraindications in the Summary of Product Characteristics (SmPC). Typical populations to be discussed in this section are children, the elderly, pregnant or lactating women, and patients with hepatic or renal impairment.

Only safety concerns which are still outstanding should be carried through to module SVIII.

Module SV: Post-authorisation experience

Post-authorisation experience is only required for updates of the RMP and is therefore not further discussed here.

Module SVI: Additional EU requirements for the safety specification

This module is special insofar as it contains some safety topics not included in ICH-E2E:

- harm from overdose (either intentional or accidental)
- transmission of infectious agents
- misuse for illegal purposes (e.g. use as a recreational drug)

- medication errors
- off-label use
- specific paediatric issues (including potential for paediatric off-label use, safety and efficacy issues identified in the Paediatric Investigation Plan)

Safety concerns from this module have to be carried through to module SVIII.

Module SVII: Identified and potential risks

This module should provide more information on the important identified and potential risks. Note that this should be a concise chapter and not a collection of adverse events from clinical studies or lists of adverse reactions from section 4.8 of the SmPC ('Undesirable effects'). Make sure it only contains important adverse reactions, important interactions, and important pharmacological class effects.

For each important identified risk and important potential risk, a variety of information has to be provided, such as frequency, severity, and nature of risk, risk factors, and preventability.

Module SVIII: Summary of the safety concerns

A safety concern may be:

- an important identified risk (confirmed by clinical data);
- an important potential risk (not refuted by clinical data or of unknown significance); or
- missing information (e.g. high likelihood of off-label use or populations not studied such as pregnant and lactating women, children, or patients with severe hepatic/renal impairment).

Safety concerns identified in modules SII, SIV, SVI, and SVII are included here. Also, each risk listed in SmPC sections 4.3 ('Contraindications') and 4.4 ('Special warnings and precautions for use') should be regarded as an 'important risk'. However, do not include adverse drug reactions mentioned in SmPC section 4.8 ('Undesirable effects') as important identified risks if they are currently considered unlikely to affect the benefit-risk assessment of the product. Carefully check the SmPC for evidence of missing information.⁶

Part III - Pharmacovigilance plan

The Pharmacovigilance plan (PhV Plan) describes how the MAH identifies and characterises safety concerns by proactive monitoring. It does NOT include actions intended to reduce, prevent, or mitigate risks.¹

For each safety concern summarised in module SVIII, the planned PhV activities have to be listed and can be divided into routine and additional PhV activities. If safety concerns are well characterised, routine post-authorisation PhV will suffice. Additional PhV activities may be non-clinical studies, clinical trials, or non-interventional studies.¹ For safety concerns with additional PhV activities, provide an action plan and a summary table including expected dates of milestones.

Part IV - Plans for post-authorisation efficacy studies

Whereas parts II, III, and V are concerned with drug safety, part IV deals with the efficacy of the MP. The PhV legislation provides the legal basis for requiring post-authorisation efficacy studies for products

- where there are concerns about efficacy in everyday medical practice; or
- when knowledge about the disease or the clinical methodology used to investigate efficacy indicates that previous efficacy evaluations may need significant revision.

For paediatric medicines and advanced therapy medicinal products (ATMPs), long-term follow up of efficacy is required. This section may be omitted for generics if the reference MP does not have any efficacy studies imposed as a condition of the marketing authorisation.¹

Part V - Risk minimisation measures

Risk minimisation measures (covered in more detail in another article in this issue – see page 62) fall into two categories: routine and additional activities. No general guidance is possible on which activities are to be used as this is a case-by-case decision. However, the proposed activities should always be proportional to the risks.

It is possible that routine risk minimisation activities will be the only proposed risk minimisation activities. They include appropriate information and warnings in the product information (SmPC, package leaflet, and labelling), and may also relate to package size and legal status of the product (i.e. prescription status). Additional risk minimisation activities are all measures which go beyond the above and should be confined to the most serious risks. An action plan needs to be provided on how the effectiveness of additional activities will be evaluated. Further information on additional risk minimisation activities can be found in GVP Module XVI.⁷

Part VI - Summary of the RMP

Part VI is split into two sections. Section VI.1 ('Elements for summary tables in the European public assessment report (EPAR)') contains summary tables from parts I, III, IV, and V.

Section VI.2 ('Elements for a Public Summary') is the publicly available scientific summary of the RMP written for the lay reader. This section has several subsections to summarise all the key aspects of the RMP, including a short chapter about disease epidemiology, treatment benefits of the drug, unknowns relating to treatment benefits, and a summary of safety concerns. Furthermore, a summary of the risk minimisation measures, which puts the MP's risks in the context of the treatment benefits,⁸ has to be provided, along with the planned post-authorisation development plan (if applicable). Section VI.2 can be regarded as one of the key challenges for the medical writer as it represents the 'public face' of the RMP and should be a useful resource for patients and physicians.⁶

Part VII - Annexes

This part consists of 12 annexes, including the current or proposed product information, worldwide marketing authorisation, and other supporting data such as referenced material.

Conclusion

The RMP is a complex document, but it is structured in a clear manner and can be mastered by following a step-by-step approach. Medical writers, with their attention to detail, writing expertise, and communication skills, are a valuable part of the authoring team. For someone with experience in regulatory writing, preparing an RMP can be a rewarding challenge.

Author information

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