



# The 360° approach to authoring risk management plans

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## Abstract

Amidst the dynamic landscape of pharmacovigilance legislation, medical writers have been gaining increased visibility and importance beyond what had been their traditional role of coordinating and facilitating the development of risk management plans. Over the past couple of years, medical writers have been contributing extensively in driving the seamless integration of the recent Good Pharmacovigilance Practices guidance version 2.0 into companies' global pharmacovigilance systems, quality assurance systems, and relevant standard operating procedures. A comprehensive "360°" approach adapted by medical writers ensures efficient authoring of high-quality RMPs.

During the drug development process, the top priority at any stage for every stakeholder is patient safety. While there are numerous regulations by different health authorities (HAs), the Risk Management Plan (RMP) introduced by European Medicines Agency (EMA) in 2007 is considered to be one of the best examples of "good pharmacovigilance practices" (GVP) to ensure patients' safety. Since then, this pharmacovigilance (PV) system has mandated the development of an effective safety plan for every marketed product right from the first marketing authorisation application (MAA) to as long as it available in the market. An RMP has been demonstrated as one of the most effective PV tools and a key turning point for global PV regulatory practices. The GVP Module V switched the entire perspective of risk management approach from "spontaneous reactive" to "continuous proactive" in dealing with patients' safety.

Unlike other regulatory documents, the process of RMP development is unique and elaborate, and the medical writer (MW) plays a significant role in efficient authoring of RMP. This article highlights key approaches for authoring RMPs to help MWs to avoid errors or prevent unnecessary health

authority questions. This article is meant to serve an overview of the topic, designed to provide insights about a holistic, "360°" approach for RMP development rather than serving as detailed template training.

## Essence of a risk management plan

### Not just a regulatory document!

An RMP is a comprehensive document that details the safety profile of a product, a PV plan for collecting additional safety and efficacy data, and measures to mitigate safety concerns associated with the product's use.

The GVP Module V switched the entire perspective of risk management approach from "spontaneous reactive" to "continuous proactive" in dealing with patients' safety.

Additionally, it provides all the commitments of a marketing authorisation holder (MAH) on further plans to evaluate the effectiveness of risk-minimisation measures for managing patients' safety.<sup>1</sup>

It forms a part of the Common Technical Document (CTD) Module 1.8.2. It is not just a regulatory document or a regular safety report but also a legally binding administrative document with monetary implications. Since 2014, the key RMP elements have become a part of the European public assessment report as a lay summary with transparency implications and a

big impact on the MAH's market position – legally, financially, and in terms of reputation.<sup>2</sup>

### A global reference

EMA's RMP has been adapted worldwide and deemed a reference for other HAs of Rest of the World (ROW) countries (other than EMA or FDA) either to develop their own RMP guidance or to accept EMA's GVP guidelines. An RMP has been gaining increased importance for newer products especially those approved via regulatory procedures that enable earlier patient access (for example, conditional approval for orphan drugs) without compromising an efficient preliminary assessment of the product's safety. Nevertheless, such regulatory procedures often need more robust reviews by the HAs and a stringent risk management strategy with additional PV activities or risk-minimisation measures beyond those considered to be routine. This results in an increase in global cost of RMP implementation for the MAH.

### Risk-based approach

A single product requires a single RMP regardless of the indications, formulations, or dosage forms, etc., unless otherwise justified by a scientific rationale and agreed with the HA. It is a living document that is updated continually throughout the lifecycle of a product in the market but, unlike other safety reports, not necessarily at regular intervals. The RMP submission requirements follow a "risk-based approach". The first RMP version starts with the first MAA and triggers for subsequent updates include any significant changes to the marketing authorisation, significant changes to the benefit-risk profile, the completion of important milestones for PV activities or risk-minimisation measures, or at the request of a HA when new information is available from the literature.

## Trends in GVP Module V

### Journey over a decade

The RMP guidance has been undergoing continuous transformation since its inception in 2007 and has taken a logical shape over the last 12 years in terms of data flow, consistency, and transparency in a submission-friendly modular format. Over time, the focus of an RMP has transitioned significantly from *drug* safety to *patient* safety. The evolution represents a paradigm shift from "safety" to "benefit-risk balance", and introduced the requirement to evaluate effectiveness of risk-minimisation mea-

asures. The concept of "additional monitoring" was introduced in 2013 for all new medicines approved after 2011 to reiterate the importance of reporting suspected adverse drug reactions by the physicians and patients.<sup>3</sup>

### Two years of GVP 2.0: The impact and trade-off

It has been a couple of years since the industry experienced a major overhaul to the RMP template in parallel with the revised GVP guidance, version 2.0 in 2017. The extent of revisions was substantial but with a more risk-proportionate approach crucial to risk-benefit evaluation. With major revision to the definitions of identified and potential risks, MAHs are now clearer about categorising the risks while ensuring alignment with the adverse drug reactions defined in the product label. This led to re-evaluation of risk management strategies and development of more appropriate PV plans for each risk in the RMP. Because of these changes, MAHs required additional efforts and resources to submit all their revised RMPs within the regulatory deadline before Q2 2018. Moreover, this had a direct impact on the existing periodic benefit-risk evaluation reports (PBREs) for most of the marketed products. Nonetheless, the key focus is now streamlined to the information relevant to risk-benefit assessment. On the other hand, EMA has significantly eliminated redundant, non-value added requirements or integrated sections into more relevant RMP modules and removed duplication of information across other safety documents; for example, the section on post-marketing experience is now limited to exposure data rather than a duplication of overall periodic safety update report findings. Additionally, changes to the administrative sections and annexes have eased the job of an MW to a great extent, especially reducing the time required to ensure consistency across modules. However, the overall concept of mapping, which explains the similarity of specific sections between RMP modules with the other CTD modules and PBRE, remained the same in this revision.

The challenge for MAHs was not only to meet the regulatory deadline for submission of all revised RMPs but also to update their internal standard operating procedures and working guidance documents for regulatory compliance. Apart from these challenges, MAHs had to handle the administrative requirement of creating a "track change version" for existing RMPs and

since the new template had major changes, this posed an impossible task. However, this could be waived off for some of the RMP updates after HA agreement. Despite these challenges, collaboration amongst the project teams and constant HA interactions have been vital in dealing with the changes and in meeting the submission deadlines for RMP updates.

So far, most HAs of ROW countries with or without their own RMP requirements have been accepting RMP submissions in the older format, but it is anticipated that they will soon adopt this new RMP format. MAHs hope to implement a global risk management approach with minimal variations across countries to ensure efficient monitoring of patient safety.

## Importance of medical writer's role

### The template expert

Excelling in the art of RMP authoring is not as complex as it may seem, provided a logical and scientific approach is followed in applying the guidance in any scenario of an RMP development. Until the recent revision, MWs interpreted the GVP template to be too bureaucratic and a bit ambiguous especially when the rationale behind the requirements was either unclear or unexplained. One needs to be aware of the nuances of each RMP module and understand the interdependencies across the modules for optimal and chronological data flow between the modules. Stakeholders involved in developing regulatory guidance are aware that these are living documents, dependent on the dynamic regulatory landscape with the advent of wide range of new therapeutics. Hence, MWs should invest extra time in understanding the GVP guidance and template, religiously follow them, and learn to tackle the flaws on a case-by-case basis. Over time, MWs gain further knowledge and experience on the template requirements based on rapporteurs' comments, Pharmacovigilance Risk Assessment Committee's assessment reports, and health authority questions received at different time points after the CTD submission (e.g. Day 120, Day 180, etc).

### The collaborator

As with the development of any other regulatory document, it is not the sole responsibility of an MW to develop an RMP. It requires a team of authors from various departments, not confined to safety, clinical, pre-clinical, epidemiology, regulatory, biostatistics, data management,

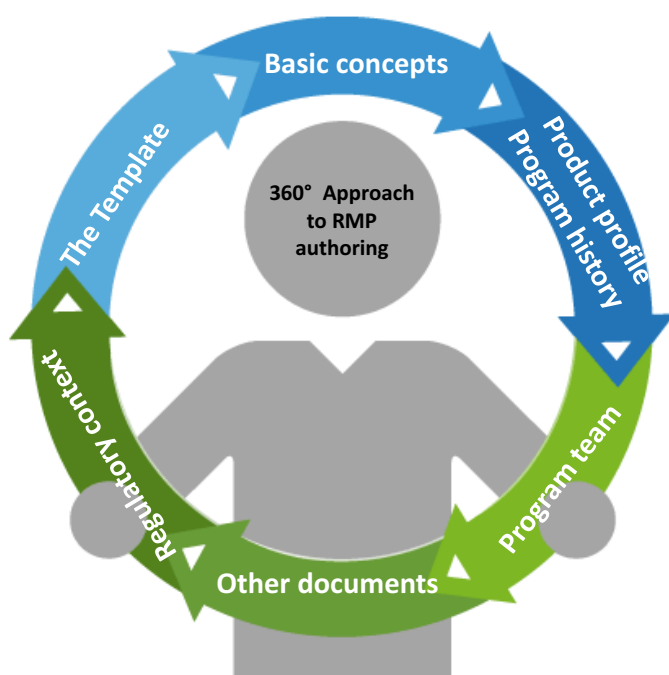


Figure 1. The 360° approach to authoring a Risk Management Plan.

pharmacokinetics, formulation development, etc. Based on the conventional organisational framework in the industry, the contributors are often dedicated to specific products but the MW may not be. An MW is deemed to be the template expert and a key driver of RMP development process since he or she gains a broader experience on RMP authoring for multiple products compared to any other RMP contributor in the project team. Therefore, an MW

should take the lead in guiding the team on RMP template requirements. Furthermore, an MW is a key collaborator in communicating with other regulatory MWs on the submission to ensure consistency of key messages in the RMP with various CTD documents (for example, Modules 2.7.4, 2.5).

Likewise, it is the team who has broader knowledge of a product's profile and its regulatory lifecycle rather than an MW. Therefore, an

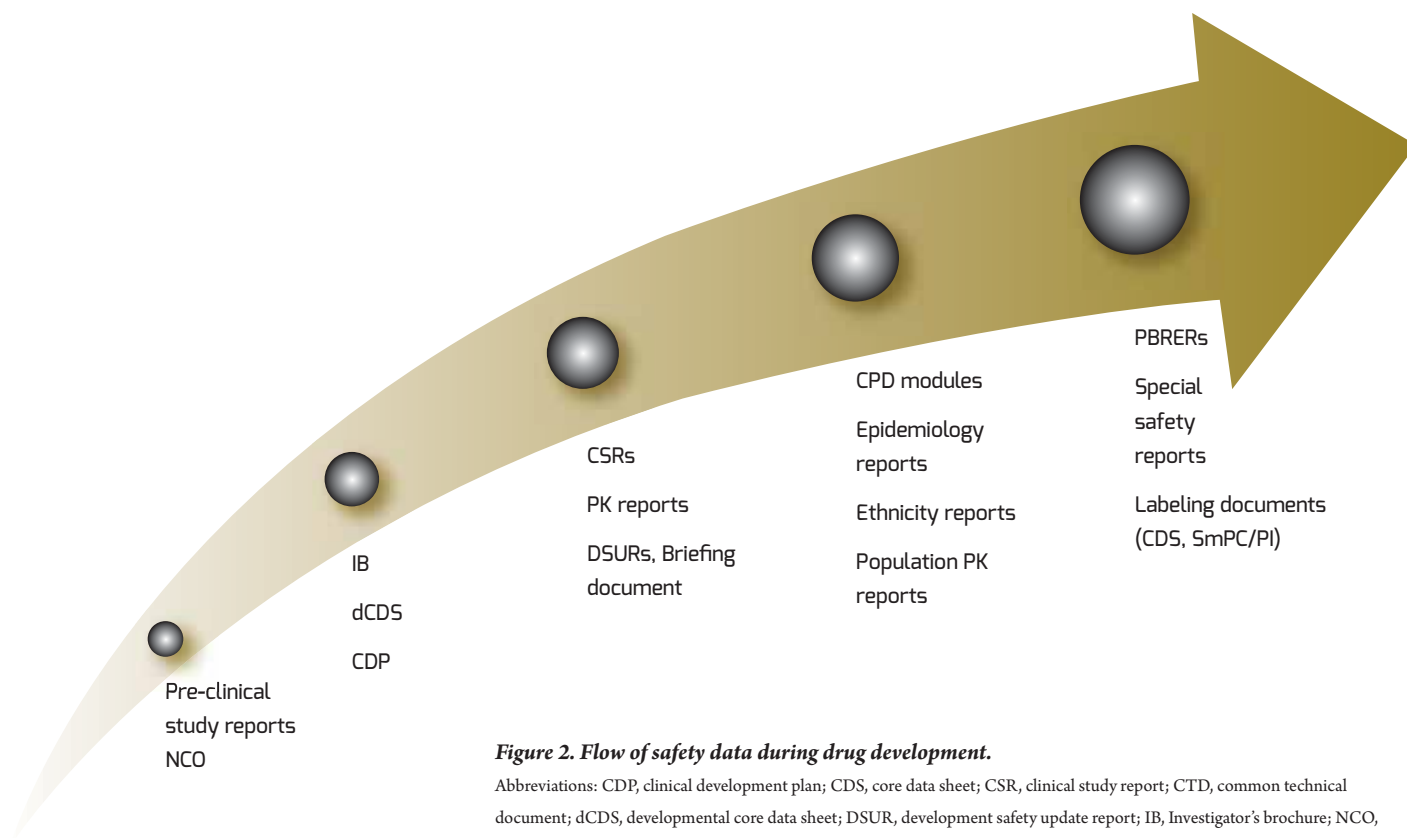
MW should seek relevant contributions on the scientific aspects of the product from the team. Eventually, it is the team's responsibility to collaborate and integrate with each other to develop a high quality RMP with minimal or no health authority questions at least in terms of template compliance.

### The 360° approach

An MW could adapt a holistic approach for seamless authoring of high quality RMPs and the concepts detailed below may provide a basic guidance on a 360° approach towards RMP authoring (Figure 1).

#### Basic concepts

Whilst authoring any document, an MW is expected to have sufficient knowledge on the disease or therapeutic areas pertaining to the product. Beyond this, extensive knowledge and understanding of PV domain is an additional prerequisite for authoring RMPs. Probably this is one of the reasons why RMP MWs are usually titled as "safety" MWs and not "regulatory" MWs. The GVP guidance covers all the possible definitions that are required in the context of an RMP, and an MW should understand their clear meaning and differences, if any. An MW should also be well aware of the different categories of PV activities and to which category the proposed activities belong to. Beyond the RMP guidance, an MW can also refer EMA's guidance on lay summaries, which can be applied to develop the RMP lay summary for European public assessment report.<sup>4</sup>



**Figure 2. Flow of safety data during drug development.**

Abbreviations: CDP, clinical development plan; CDS, core data sheet; CSR, clinical study report; CTD, common technical document; dCDS, developmental core data sheet; DSUR, development safety update report; IB, Investigator's brochure; NCO, non-clinical overview; PBRER, periodic benefit-risk evaluation report; PI, prescribing information; PK, pharmacokinetics; SmPC, summary of product characteristics.

### The template

The framework of an RMP template essentially follows a typical risk management cycle with three key elements:<sup>1</sup>

1. What is known and unknown about the safety profile of the product?
2. Which activities are undertaken to collect additional data to fill the knowledge gap about the product's profile?
3. What measures are implemented to mitigate the risks?

Information related to these three elements flow chronologically within the modular framework of the RMP template. Safety specification module of the RMP covers all the aspects required to define, categorise, and justify the safety concerns of a product; which includes epidemiology, pre-clinical and clinical data covering relevant safety, efficacy, and pharmacokinetics, limitations of the clinical programme, and post marketing data, where applicable. This comprehensive assessment is paramount to be able to strategise the remaining elements of an RMP, i.e., PV plan and risk-minimisation measures while justifying the proposed strategy. Where necessary, MAH may need to develop additional PV activities or risk-minimisation measures. Therefore, the MW

should be aware of the interdependencies between the modules and ensure consistency across them and also with other documents within the CTD or other safety reports within the regulatory procedure of the submission.

### Product profile

Since an RMP covers key safety concerns of a product, an MW should understand its overall safety profile before beginning to draft an RMP. As a starting point, the class of the drug itself provides a clear picture of its pharmacological class effects to understand the preliminary safety profile of the product. Safety data start to be generated from the pre-clinical setting and as the molecule progresses in its lifecycle through the clinical development, more in-depth and reliable safety data become available for adequate safety assessment. So, the first comprehensive document to refer to would be an investigator's brochure followed by the developmental core data sheet (dCDS) or the current approved label, if applicable. Understanding the chronological flow of safety data from one document to another and realising the differences in purpose behind each document within the clinical programme helps the MW to refer the right document for precise information needed for the RMP (Figure 2).

### Programme history

As a single RMP exists for a single product, understanding the overall plan for the clinical development programme and leveraging prior submission experience eases the process of RMP authoring. For example, awareness of the history of approvals, indications, formulations, triggers for RMP updates, regulatory actions taken for safety reasons, Pharmacovigilance Risk Assessment Committee assessment reports, etc. This knowledge helps an MW to identify specific modules or sections of an RMP impacted and the extent of update required.

### Regulatory context

The extent of an RMP update highly depends on the trigger for the update and the regulatory procedure it falls under (for example, Type I, Type II variations, renewals, article referrals etc.).<sup>5</sup> So, awareness on the context of these regulatory procedures helps in understanding the scope of an RMP update. Further, it is necessary to understand the context of disease or therapeutic area of an RMP submission (e.g. paediatric indications, advanced therapy medicinal products, biosimilars, generics, associated medical devices). The template requirements depend primarily on the scope of the submission



and not all sections of the RMP might be applicable. Understanding the trigger helps in identifying sections or modules impacted during an RMP update (for example, reaching PV or risk-minimisation milestones, demotion or upgradation of a risk etc.). Fundamentally, the knowledge of current regulatory landscape helps in evaluating the impact on RMP updates.

**Relevance of other documents**

The modular format has an obligation to ensure

consistency with the source documents and other documents in the overall programme. This does not mean we have a compelling reason to literally ensure verbatim alignment but only ensure message-led alignment. The major documents within the clinical programme that could be referred as a source include CTD modules (2.7), investigator’s brochure, safety reports, labelling documents (CDS or summary of product characteristics), clinical study report, PBRER, development safety update report etc.,

depending on the regulatory procedure. The GVP guidance provides a mapping between the RMP and CTD modules and with the PBRER as a recommendation. Table 1 and Table 2

**The programme team**

RMP authoring is beyond collating content; it is a strategy in itself that is legally binding. Therefore, collaborating with the right stakeholders at the right time apart from regular project meetings is imperative in implementing the risk-manage-

**Table 1. Mapping between RMP and eCTD modules**

RMP Module	eCTD
Part I Product(s) Overview	Module 2.3 Quality overall summary Module 3 Quality
Module SI Epidemiology of the indication(s) and target population(s)	Module 2.5 Clinical overview
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 SIII Clinical trial exposure	Module 2.7 Clinical summary Module 5 Clinical study reports
Module IV Populations not studied in clinical trials	Module 2.5 Clinical overview
Module SV Post-authorisation experience	Module 2.5 Clinical overview
Module SVI Additional EU requirements for the safety specification	Data not presented elsewhere in eCTD
Module SVII Identified and potential risks	Module 2.5 Clinical overview (including benefit-risk conclusion) Module 2.7 Clinical summary (SmPC)
Module SVIII Summary of safety concerns	Module 2.5 Clinical overview Module 2.7 Clinical summary
Part III Pharmacovigilance plan (including post-authorisation safety studies)	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 (including evaluation of the effectiveness of risk-minimisation activities)	Module 2.5 Clinical overview Module 2.7 Clinical summary

Abbreviations: eCTD, electronic common technical document; RMP, risk management plan; SmPC, summary of product characteristics.

Source: Guideline on Good Pharmacovigilance practices (GVP), Module V –Risk management system, Revision 2, European Medicines Agency. March 28, 2017.

**Table 2. Mapping between RMP and PSUR sections**

RMP section	PSUR section
Part II Module SIII Clinical trial exposure	Sub-section 5.1 Cumulative subject exposure in clinical trials
Part II Module SV Post-authorisation experience	Sub-section 5.2 Cumulative and interval patient exposure from marketing experience
Module SVII Identified and potential risks and Module SVIII Summary of the safety concerns	Sub-sections 16.1 Summaries of safety concerns and 16.2 Characterisation of risks
Part V Risk-minimisation measures (including evaluation of the effectiveness of risk-minimisation activities)	Sub-section 16.5 Effectiveness of risk-minimisation (if applicable)

Abbreviations: PSUR, periodic safety update report; RMP, risk management plan.

Source: Guideline on Good Pharmacovigilance practices (GVP), Module V –Risk management system, Revision 2, European Medicines Agency. March 28, 2017.



RMP authoring is beyond collating content; it is a strategy in itself that is legally binding.

ment strategy. For example, consider the following opportunities to keep the RMP development process moving forward smoothly:

- Collaborate with statistician and statistical programmer during the planning phase to review the requirements for mock statistical outputs for each safety concern.
- Communicate regularly with the safety lead to get an update regarding any changes to the safety profile since he/she is the official responsible author of an RMP and answerable to the qualified person for pharmacovigilance.
- Collaborate with the regulatory affairs representative during the planning phase and after HA meetings or labelling review committee meetings to be sure you are aware of any changes to the scope of submission requirements.
- Gather relevant inputs/contributions from the epidemiologist and pre-clinical expert before data availability.

Similarly, the MW should provide review comments to the statistician and the programmer on the mock statistical outputs and identify any data discrepancies in draft statistical outputs to avoid major rework and potential delays in the submission timelines. Collating clinical inputs including administrative information on the PV milestones for clinical studies and the risk-benefit information before and during the content draft stage helps in avoiding last-minute follow-ups. Throughout the RMP development stages, an MW should ensure that inputs received from each contributor are compliant with the template requirements.

In conclusion, implementing a comprehensive approach eases the overall process of RMP

authoring within the constant, dynamic regulatory landscape of the GVP legislation. An MW acts as a “cog in the wheel” throughout the RMP development process and has been gaining increased importance not only as an active contributor but also as an expert and a collaborator in developing high quality RMPs.

### Acknowledgements

The author would like to thank Gogula K for review feedback.

### Disclaimers

The opinions expressed in this article are the author’s own and not necessarily shared by her employer or EMWA.

### Conflicts of interest

The author declares no conflicts of interest.

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