Navigating Risk Management Plans (RMPs) in the Evolving Regulatory Landscape

Pharmacovigilance (PV) is a vital part of healthcare and for monitoring the benefit-risk profile of medicinal products. The purpose of the European Medicines Agency's (EMA's) risk management plan (RMP) is to "document the risk management system considered necessary to identify, characterise and minimise the important risks of a medicinal product" and thus to help sponsors plan their PV and risk minimisation strategy. The plan is based on the frequency and severity of the risks identified during product development (including a new indication for a previously approved product), and during the post-marketing setting.

Regulations and procedures in PV are continually evolving and changing worldwide. On 30 March 2017, the EMA published Revision 2 to the RMP template, requiring that all EU-RMP submissions post 31 Mar 2018 use the new template. Significant changes have been introduced in the revised template[2], which has been used by some since its announcement and is the subject of much discussion in the industry. The complexity of the new RMP template has introduced significant challenges to preparing high-quality and compliant documents that meet all of the requirements. This article discusses the different challenges posed by the new RMP template, and how to navigate them successfully.

Background

The EU RMP consists of seven parts, including the product overview, safety specification, PV plan, plans for post-authorisation efficacy studies, risk minimisation measures, summary and annexes. It is a standalone scientific synopsis which includes relevant parts of the dossier and emphasises the important, clinically relevant facts.

Certain aspects of the RMP, in particular the safety specification, are subdivided into modules so the content can be tailored to the type of the medicinal product (innovator products, generics, biosimilars, etc). This design helps in reusing modules across different safety documents which in turn improves consistency and prevents discrepancies.[1]

If several medicinal products have the same active substance, the differences between indications, formulations and target population can be accommodated by dividing the relevant parts of the RMP into modules and/or sections. This structure also means that the RMPs can be simply updated. As the product matures, some RMP modules or sections may cease changing, for example, non-clinical studies and clinical trials. These RMP modules can be locked in place until new data needs to be added. This modular structure also simplifies the process for the RMPs of established products or biosimilars, as they do not require all the information, such as reference medicinal products.

Key Changes in the EU RMP Template

The updated EU RMP template is following an industry trend towards large, repetitive documents being streamlined to accompany submission documents.

The revised template intends to achieve –

- Better representation of safety concerns – identification, presentation and focus areas
- Removal of duplication within the RMP and across other submission documents
- Additional guidance on the expected changes during the lifecycle of the product
- Updated requirements for different types of initial MA applications to create risk-proportionate RMPs
- More succinct document

Other additions include a public summary for lay people that will form a part of the European Public Assessment Report (EPAR) and a section for information on plans for post-authorisation efficacy studies. The key changes for each part are presented in Table 1, below:

Part	Key Changes
Part I: Product Overview	• No significant differences.
Part II: Safety Specification	• Module SI: Epidemiology of the indication (S) and target population (S) ◦ Only data relevant for identification of the safety concerns required. ◦ Brief summary of epidemiology, including an interpretive, high level overview of the information. ◦ May not be applicable for generics, fixed combination medicinal products, and biosimilars which do not contain a new active substance. ◦ Risk proportionality principle to be followed. ◦ Differences in specification with the "originator" product to be justified for generic products. • Module SII: Non-clinical part of the safety specification ◦ Data requirements for clinical and non-clinical sections have changed. More details are to be provided. ◦ Detailed patient exposure data is required and must be stratified by demographics, special populations and regions, wherever possible. Important to note this data may not be available for mature products as it was not required previously.

	• Module SIII-IV: Clinical trials
	  • More details are required with regard to duration of exposure, age group – gender, dose, ethnic origin, etc.
	  • Module SVI: Additional EU requirements for safety specification
	  • Only potential for misuse for illegal purposes is retained.
	• Module SVII: Identified and potential risks
	  • Several sub-modules have been added.
	  • Risk-proportionate approach and detailed justifications are required for inclusion as well as exclusion of risks from the categories of 'important' identified or potential risks.
	  • Risk-benefit impact assessment is required for individual risks.

Part III: Pharma-covigilance Plan	• Detailed description of PV activities/studies intended to identify and/or further characterise safety concerns. • Studies measuring the effectiveness of risk minimisation measures where such studies are required. • Detailed instructions and guidance have been added on inclusion of various annexes pertaining to post-authorisation safety studies (PASS).
Part IV: Plans for Post-authorisation Efficacy Studies	• A list of post-authorisation efficacy studies (PAES) imposed depending upon specific obligations to be included. Examples of such specific requirements are provided in the guidance. • If no such studies are required, RMP Part IV may be left empty.
Part V: Risk Minimisation Measures	• No significant changes. • The revision clarifies initial marketing authorisation applications for generic, hybrid medicinal products and fixed combination products with no new active substance, noting that if the medicinal product does not have additional risk minimisation activities, sections V.1 – V.3 may not be applicable and a statement regarding alignment with reference medicinal product is sufficient. • The new template explains routine and additional risk minimisation activities in greater detail.
Part VI: Summary of the RMP	• A separate RMP Part VI should be provided for each product in the RMP. As it is a stand-alone document, any references to other parts of eCTD dossier or other medicinal products' published RMP summaries should not be included.
Part VII: Annexes	• The number of annexes has been reduced from 12 to 8.

Lifecycle Management of RMPs

Benefit-risk assessment for all marketed drugs is an ongoing activity and needs to continue throughout the lifecycle of the product. A new or revised RMP may need to be submitted to the EMA at various points during a product's lifecycle. An update is expected to be submitted when:

- There is a change in the list of the safety concerns
- There is a new or significant change in the existing additional PV or risk minimisation activities.

This would include a change in study objectives, population, due date of final results, due date for protocol submission for an imposed study, addition of a new safety concern in the key messages of the educational materials, with the procedure triggering those changes.

The RMP update can be submitted either as part of a procedure driven by another main change defining the procedure classification (e.g. extension of indication, new formulation, etc.) or as a stand-alone variation exclusively, including the RMP. Irrespective of whether the RMP update is consequential to another change or a stand-alone update, the RMP document follows the electronics common technical document (eCTD) lifecycle management and should be provided in Module 1.8.1 of the eCTD structure.

Revision 2 of the guidance on format of the risk-management plan in the EU should be used for all products, including generics.

Best Practices for Developing RMPs

The new template includes additional expectations in many parts and modules, along with several new sections. The overall objective is to create a risk-proportionate and concise document which should not include duplication. Therefore, based on either the need to develop a new RMP or to create/update a region-specific RMP, an effective strategy needs to be developed; collation and review of all the available data in the form of previous RMPs, aggregate reports, reference safety information (RSI) including core & regional labels, and regulatory commitments.

By reviewing the existing data, applicants will gain a better understanding of the additional data required and the sources that should be explored. This is particularly important for generics or biosimilars, which may not have substantial clinical data as compared to the reference medicinal product. This could be due to exemptions from certain requirements on toxicology and clinical studies. In order to maintain consistency, data from the reference medicinal product has to be referred to for creating many sections of the RMPs for generics or biosimilars. Labels of reference medicinal product (RFP) available from regulatory websites, the European public assessment reports (EPARs) and the summary provided by the Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) can be very useful starting points.

Epidemiology Data

Epidemiological databases like the GLOBOCAN and SEER Programme of the National Cancer Institute, United States provide data on major types of cancers. Publicly available databases such as US FDA (Food and Drug Administration) AERS (Adverse Event Reporting System), the Drug Analysis

Prints (DAP) available from The Medicines and Healthcare products Regulatory Agency (MHRA) of the United Kingdom, EudraVigilance and the World Health Organisation (WHO) ADR database provide a number of reports and insights into the types of reactions that have been reported for drugs. However, they do not provide exposure, nor are they useful for determining background rates.

Effective Use of Published Literature
Literature should be screened using widely recognised reference databases (e.g. Medline, PubMed, Embase Excerpta Medica). It is important to check authenticity of all reference literatures along with their latest updates, so that the most recent and relevant information can be extracted. Examples of some commonly used websites/online sources include:

- Medical textbooks, information on human diseases: Merck Manual, Medscape.
- Clinical guidelines: The National Institute for Health and Care Excellence (NICE) guidelines (UK); The National Comprehensive Cancer Network (NCCN) guidelines (US).

While developing a search strategy, filters should be applied with due consideration to the specific purpose of the literature search.

When using literature as a major source for identification and characterisation of risks, the selection should focus on articles that provide the most recent data with the maximum strength of evidence. For example, if clinical trial data are being used to cite the frequency of an identified/potential risk, articles involving meta-analysis or systematic reviews in the indications will gain precedence over those concerning individual clinical trials.

Monitoring of Regulatory Websites
Marketing authorisation holders (MAHs) are required to take into account monitoring requirements and recommendations by health authorities (HA). This information from HA websites is crucial for discussion in the RMP and specific requirements to be addressed for designing risk minimisation measures. Examples for the EMA include cumulative list of signals evaluated by PRAC, list of products under additional monitoring, EPAR and CMDh list of safety concerns and outcomes of PSUSA procedures.

Identification of Risks
The new RMP template provides detailed guidance for selection of important risks for inclusion in the RMP. For innovators, this activity is comparatively easier due to availability of adequate non-clinical and clinical data. For generic products and biosimilars, extensive literature search may be required to find relevant information for characterisation of safety concerns. Product information, and public assessment reports of the reference product, and in the EU, the EPAR and CMDh list may be used as reference material. While the overall approach should be to align the reference and the generic products, it is possible that the safety concerns for a generic product may not exactly match those of the reference product.

For products marketed/intended for marketing in different countries, it is not unusual for safety concerns to differ. A local regulatory authority may request for certain additional safety concerns to be addressed or, what is considered an important potential risk by the regulator in one region may be considered an important identified risk by the regulator in another region.

Use of footnotes to document regional differences in safety concerns, separate tables for each region, or including information indicating the varying status of each of the risks can help in representing such discrepancies and ensuring regional compliance. In addition, the MAH may also indicate the company's core position on the categorisation of various risks.

Characterisation of Risks
For assessment of benefit-risk impact for individual risks, two components are essential in determining the impact on an individual patient. These include impact on health and impact on quality of life.

Regarding public health, one should assess the overall impact of that risk at the population level, such as incidence rate in exposed population, course of the disease, and the consequences (including consideration of seriousness, preventability, and reversibility).

Quantitative measures, such as the ratio of number needed to treat (NNT) to number needed to harm (NNH), relative risk or risk ratio (RR) and odds ratio (OR), are also useful in assessing the public health impact. However, a careful interpretation of these measures is required. For example, an RR of 2 can be a difference between a 10% rate and a 20% rate of occurrence of an adverse event (AE), or between a 1% and 2% rate of occurrence. Thus, both absolute and relative risk should be considered for determining public health impact.

Routine risk minimisation activities are those which apply to every medicinal product. These relate to the product labelling, packaging and the legal status of the product. The majority of safety concerns are addressed by routine risk minimisation measures. Additional risk minimisation activities are introduced for certain important risks for which routine risk minimisation is considered insufficient. In determining if additional risk minimisation activities are needed, safety concerns should be prioritised in terms of impact on public health, treatment and preventability. Focus should be on selecting the most appropriate measure for the most important and preventable risk. Additional PV activities, such as pre-clinical, clinical, epidemiological or non-interventional studies, are not considered routine. When any doubt exists about whether, or which, additional PV activities are needed, competent authorities may be consulted.

Summary
The EMA has published a second revision of the RMP template aligned with Guideline on GVP Module V Revision 2, meaning that all EU RMPs submitted to the EMA on or after March 31, 2018 must be submitted using the updated EMA template. This updated EU RMP template is designed to streamline the documentation to accompany submission documents.

This is a continuously evolving landscape and it will take time for applicants to get used to using the new template. Updating older RMPs to the new RMP template is not a simple task and demands a good understanding of drug safety and regulatory expectations. Companies need to ensure they have the relevant knowledge and expertise in place (whether it be in-house or from a speciality service provider) for implementing these new requirements.

For more information about how Sciformix can assist with risk management plans, please visit: https://www.sciformix.com/our-expertise/safety-risk-management/.

REFERENCES

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