Risk management plans in the EU: Managing safety concerns

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Abstract
The preparation of pharmacovigilance documents is related to ongoing activities during the life cycle of a medicinal product and encompasses crucial processes beyond writing: strategic planning and interdisciplinary work in the context of submissions, definition of the safety concerns of a medicinal product, alignment with the key messages in marketing authorisation application dossiers, and interactions with health authorities during assessment.

Safety concerns are a set of important risks and missing information that are defined during clinical development and carried forward into the post-marketing phase. The risk management plan (RMP) describes the system managing the safety concerns. Although safety concerns are well defined in the EU Good Pharmacovigilance Practice (GVP) guidance, in practice, they are nonetheless frequently the subject of interactions with health authorities. For the RMP, the revised definition of safety concerns in GVP Module V revision 2 has implications not only for other pharmacovigilance documents, but also for the management of safety concerns worldwide.

In the world of pharmacovigilance (PV), the concept of safety concerns is not new. Safety concerns, defined as important identified risks, important potential risks, and missing information (see Table 1), had already played a significant role in Volume 9a of The Rules Governing Medicinal Products[1] in the European Union, the guideline preceding the current European legislation, the Guidelines on Good Pharmacovigilance Practice (GVP).[2] However, before 2012, the impact of safety concerns on the writing and management of pharmacovigilance documents was very low.

This changed in 2011 with the introduction of the Development Safety Update Report (DSUR)[3] and the implementation of the GVP modules on the Risk Management Plan (RMP)[4] and the Periodic Safety Update Report[5] (PSUR, also: Periodic Benefit Risk Evaluation Report, PBRER) in 2012.

In all three reports, safety concerns play a central role and have become major drivers of the content and resources associated with writing these documents. If the DSUR, RMP, and PSUR are seen as three chapters in the life cycle of a medicinal product, one could consider the safety concerns as the "main characters" of the story told in these PV documents (Figure 1).

Once the first investigational clinical trial of a clinical development programme is approved anywhere in the world, clinical trial sponsors are obliged to write an annual DSUR, the "first chapter" in the life cycle of a medicinal product. The objective of the DSUR is to provide a single concise common report on the periodic analysis of clinical trial safety for an investigational drug. Focusing on significant safety findings, the DSUR introduces the concept of important identified and potential risks defined as "an identified risk or potential risk that could have an impact on the benefit-risk balance of the product or have implications for public health".[3] In the DSUR, particular emphasis is placed each year on interpretation of data related to newly identified safety concerns, or significant new information related to previously identified safety concerns. As more and more safety data are produced and evaluated over time, some safety concerns may be excluded and others might be added to the DSUR, so that there will likely be a set of important identified and potential risks at the time when the company is starting to prepare the marketing authorisation application.

The "second chapter" in the life cycle of a medicinal product is the RMP, which is a mandatory part of the application for marketing

Table 1. Definition of safety concerns

Identified risk	An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest
Potential risk	An untoward occurrence for which there is some basis for suspicion of an association with the medicinal product of interest but where this association has not been confirmed
Important identified risk and important potential risk	An identified risk or potential risk that could have an impact on the benefit-risk balance of the product or have implications for public health
Missing information	Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant
Safety concern	An important identified risk, an important potential risk, or missing information

Data source: GVP Annex I Rev 4

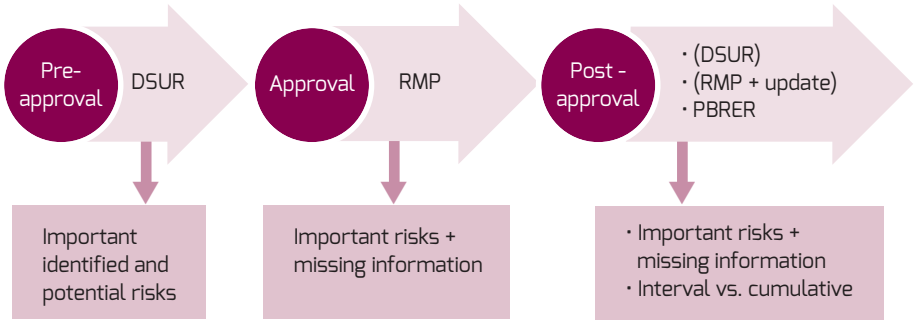

Figure 1. Life cycle of the safety concerns

Abbreviations: DSUR, Development Safety Update Report; RMP, Risk Management Plan; PBRER, Periodic Benefit-Risk Evaluation Report.

authorisation in the EU and serves as a detailed description of the risk management system. GVP dedicates Module V to the topic of the RMP[4] and describes the risk management system as "a set of pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to medicinal products including the assessment of the effectiveness of those activities and interventions". In its first version (revision 1),[6] GVP Module V introduces the RMP in a modular structure, with Module SVII focusing exclusively on the evaluation of the safety concerns. Unless new important identified or potential risks are defined based on the analysis of pooled clinical trial data during preparation of the first RMP, they will likely be copied from the DSUR, probably adding "missing information" to the list of safety concerns, based on the current definition. In addition to the evaluation of the safety concerns, authors of the RMP are asked to present detailed PV activities to further evaluate the safety concerns and to minimise these risks, as well as to provide measures to evaluate the effectiveness of additional risk minimisation. As part of the RMP, Part VI is prepared, presenting the safety concerns in plain language so that the public can later understand the medicinal product's safety concerns and the associated risk management system.

Once the submission package is ready and submitted to the EMA, the RMP is thoroughly reviewed by assessors who take a critical look at the safety concerns and associated PV activities and risk minimisation measures. The assessors commonly request changes to the list of the safety concerns or other sections. As a result, there can be multiple updates to the RMP before the medicinal product is finally approved.

After successful registration in the EU, it is

time for the "third chapter" in the life cycle of a medicinal product to begin. The PSUR, newly designed with the implementation of GVP Module VII,[5] presents the post-marketing evaluation of the safety concerns in section 16. When the RMP and PSUR GVP modules were introduced in 2012, the modular structure of the RMP allowed for an easy transfer of RMP Module SVII to PSUR section 16, since the list of safety concerns was identical. For many products, this list grew over time, often with each PSUR assessment, leading to products with more than 20 safety concerns. Many of these important risks were managed by routine activities, e.g., a warning statement in the product information with no additional pharmacovigilance activities. Over the years, when there was no reason to update the RMP, RMPs were left with outdated data, because only the PSUR presents periodic and cumulative up-to date evaluations of the safety concerns.

Revision 2 of GVP Module V,[4] implemented in 2017, introduced a new RMP template and updated definitions for safety concerns, aimed at reducing the "laundry list" of safety concerns. The new RMP should be designed to focus on those risks that have an impact on the benefit-risk balance of the product and would usually warrant further evaluation as part of the PV plan and/or additional risk minimisation activities. A scientific rationale is now needed for inclusion of missing information in the RMP (Figure 2). As of March 2018, the use of the revised RMP format became mandatory for all RMP submissions. The guidance on the format was updated in October 2018.[7]

As can be expected, revision 2 of GVP Module V led to a well-received reduction of safety concerns presented in the RMP, also reducing the workload of writing, updating, and assessing RMPs. Some marketing authorisation holders (MAHs) were asked by assessors to revise the list of safety concerns in accordance with revision 2, others proactively proposed to remove safety concerns, e.g., when submitting the PSUR. Currently, the feedback received from the EMA is inconsistent: sometimes safety concerns are removed without hesitation, whereas it is requested that others remain in the RMP, although there are no additional PV or risk minimisation activities.

The revised definition of safety concerns introduced in revision 2 does not apply to the PSUR. Safety concerns in the PSUR are still defined according to GVP – Annex I,[8] i.e., risks

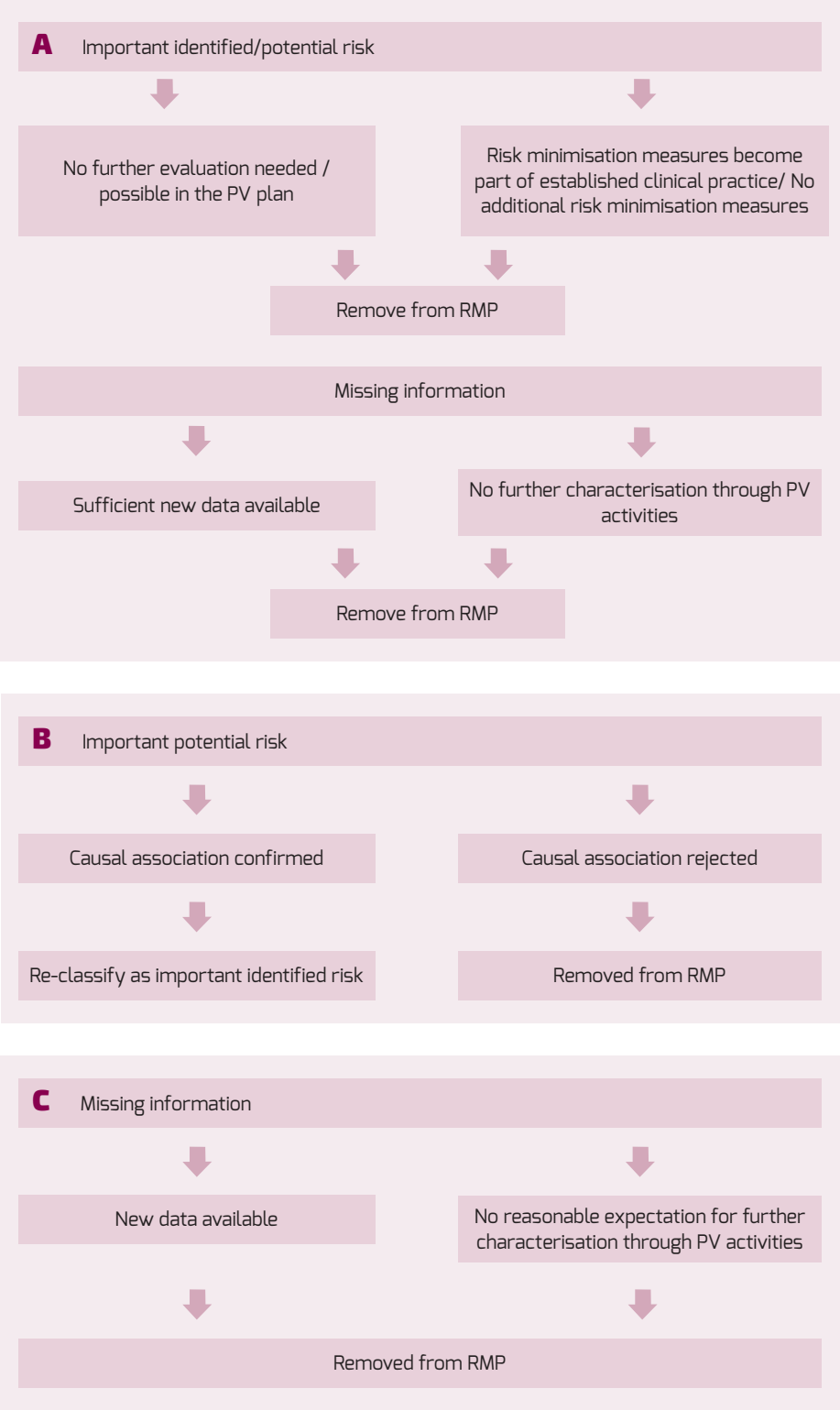

Figure 2. Changes over time in the list of safety concerns according to GVP Module V revision 2. When knowledge on the product's safety increases, and PV activities or additional risk minimisation measures are no longer needed, safety concerns might be removed or re-classified in the RMP. Lack of data over time might be a reason for removal of important potential risks and missing information topics.
Abbreviations: PV, pharmacovigilance; RMP, Risk Management Plan.

that affect the benefit-risk balance. Simply removing an important risk from the RMP does not justify removing it from the PSUR.

Revision 2 of GVP Module V introduced a new way to categorise and evaluate important risks: having defined the important risks as those that (could) have an impact on the benefit-risk profile of a medicinal product, there may now be a subset that is considered "more important". For example, "more important" risks are those that need further characterisation through additional PV activities or management by additional risk minimisation measures.

The PSUR guidance has not been updated since GVP Module V revision 2. Therefore, there is an apparent disconnect between the criteria that apply to either document and no clear guidance on how to manage safety concerns between the PSUR and RMP.

If an important identified risk is removed from the RMP, the EMA might request to keep this risk in the PSUR, either as a monitoring topic or in section 16 as an important risk. In some cases, it could be sufficient to monitor removed risks through routine PV activities, without including them in the PSUR. Should any new relevant safety findings emerge over time, which would trigger re-evaluation and re-categorisation of these risks, the RMP would subsequently be updated. Currently, there is no clear guidance on how to proceed with the PSUR when safety concerns are removed from the RMP.

The situation becomes more complex when a MAH markets a medicinal product also outside the EU. While the RMP is considered as a regional (EU) document, the PSUR is a global report, accepted by health authorities around the world. The RMP refers to the safety concerns approved by a health authority and describes the risk minimisation measures included in the local product information (the Summary of Product Characteristics). For this reason, it is not sufficient to transfer information from Module SVII of the RMP to section 16 of the PSUR. The PSUR should also include safety concerns defined by health authorities outside the EU. In some situations, various countries or regions may have a certain risk in the list of the safety concerns, but the categorisation might differ (e.g., identified vs potential). Such deviations need to be taken into consideration and appropriately described in the PSUR. To add a further layer of complexity, MAHs might have their own list of safety concerns that represents their view of the product's benefit-risk profile worldwide. Companies need to create strategies on how to manage the safety concerns across regional and global PV documents.

There is some ICH[9] and EU[10] guidance on how to present regional deviations in the list of safety concerns in PSURs. However, there is no unambiguous guidance on how to categorise safety concerns in the PSUR that have been removed from the RMP: these could be handled as monitoring topics, risks not considered important, or as important risks. What is the correct perspective of data presentation and risk categorisation for global PSURs: should the EU list of safety concerns really be used as a minimum for PSURs, as indicated in the explanatory notes to the PSUR guidance GVP Module VII?[10]

All of these questions are not just theoretical, almost philosophical brainstorming, but represent real situations the MAHs face in post-marketing based on their interactions with health authorities, subsequent PSUR submissions, and possible RMP updates.

Many RMPs still include safety concerns that do not strictly meet the approach presented in GPV Module V revision 2. This poses issues in particular for companies that have to create RMPs for generic products. MAHs and assessors might need further training to ensure that only risks with additional PV or risk minimisation activities are included.

When revision 2 of GVP Module V was issued, the EMA announced an upcoming update of the PSUR guidance (GVP Module VII). Unfortunately, this update was put on hold. In the meantime, MAHs and regulatory agencies have been in active dialogue regarding the re-categorisation of safety concerns and the interactions between RMPs and PSURs. The experience gained so far after revision 2 of GVP Module V should provide a good basis for a revision of the PSUR guidance, which would be helpful for all those involved in preparing and assessing safety documents.

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Disclaimers

The opinions expressed in this article are the authors' own and are not necessarily shared by their employer or EMWA.

Conflicts of interest

The authors declare no conflicts of interest.

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