EMA releases the revised Good Pharmacovigilance Practices Module V

updated guidance on risk management plans

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Abstract

Recently, the EMA released the revised Module V – Risk Management Systems (Rev 2) of Good Pharmacovigilance Practices (GVP) accompanied by a revised version of the guidance on the format of the risk management plan (RMP) in the EU – in integrated format. The revision will result in concise, scientifically focussed and risk-proportionate documents and is applicable to all sections of the RMP, especially sections that have become overly lengthy over time and often duplicate information presented elsewhere in the dossier or in other documents, such as the periodic safety update report.

A changing environment

Since its beginning, pharmacovigilance (PV) has undergone continuous transformation. Legislation, guidelines, and processes have evolved over time to better ensure patient safety and improve monitoring of the safety of medicinal products. After releasing the Good Pharmacovigilance Practices (GVP) guideline[1] in 2012, the European Medicines Agency (EMA) committed to continuously improve the PV guidance based on stakeholder feedback and experience. Some GVP modules were revised to include clarifications or improvement of definitions and processes.[2] In parallel, a platform for regular dialogue with industry, the EMA-Industry stakeholder platform,[3] was established, with regular meetings to provide updates and discuss specific topics, including risk management plans (RMPs). After publishing an initial revision in 2013, the EMA released a draft of Revision 2 of GVP module V[4] on risk management systems and a draft version of the related RMP template[5] for public consultation in February 2016. The guidance and template consultation resulted in a wide variety of stakeholder feedback from marketing authorisation holders, industry associations, national healthcare system representatives, and individuals, among many others. The main topics raised during the consultation phase included the definition and life cycle of safety concerns (important identified risk, important potential risk, and missing information), issues regarding inconsistencies between the different parts and modules of the RMP, and other technical issues and questions surrounding duplication of information provided in the RMP and other safety summary documents.

The final guidance,[6] released at the end of March 2017, set a new milestone in the process of continuous improvement of the RMP guidance. The new RMP template[7] is a straightforward, well-structured document that medical writers can easily use to prepare RMPs, and the concepts behind risk management have been clarified and adjusted to better reflect the stages of the life cycle of a medicinal product. Understanding these principles and the expectations of the revised guidance is crucial to prepare and manage RMPs that effectively identify the risks of a medicinal product and lead to appropriate safety decisions, thus, better ensuring patient safety.

Revision 2: What has changed?

Besides streamlining the guidance text by removing duplications within the RMP modules and with other guidance documents, Revision 2 of GVP module V addresses most of the areas for improvement that had been identified during previous consultations with industry.[6,8] An intrinsic challenge of RMPs was to determine the safety concerns: important identified risks, important potential risks, and missing information. In addition, the role of the RMP as a planning document was not clearly linked to the

Table 1. Clarifications of terminology in GVP module V Revision 1 and Revision 2

Term	GVP module V Revision 1[8]	GVP module V Revision 2[6]
Identified risk	An untoward occurrence for which there is adequate evidence of an association with the medicinal product of interest	Undesirable clinical outcomes for which there is sufficient scientific evidence that they are caused by the medicinal product
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	Undesirable clinical outcomes for which there is scientific evidence to suspect the possibility of a causal relationship with the medicinal product, but where there is currently insufficient evidence to conclude that this association is causal
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	The RMP should focus on the important identified risks that are likely to have an impact on the risk-benefit balance of the product. An important identified risk to be included in the RMP would usually warrant: ● Further evaluation as part of the pharmacovigilance plan (e.g. to investigate frequency, severity, seriousness and outcome of this risk under normal conditions of use, which populations are particularly at risk); ● Risk minimisation activities: product information advising on specific clinical actions to be taken to minimise the risk, or additional risk minimisation activities. The important potential risks to be included in the RMP are those important potential risks that, when further characterised and if confirmed, would have an impact on the risk-benefit balance of the medicinal product
Missing information	Gaps in knowledge about a medicinal product, related to safety or use in particular patient populations, which could be clinically significant	Gaps in knowledge about the safety of a medicinal product for certain anticipated utilisation (e.g. long-term use) or for use in particular patient populations, for which there is insufficient knowledge to determine whether the safety profile differs from that characterised so far

Source: GVP module V Revision 1 and GVP module V Revision 2[6,8] Abbreviations: GVP, good pharmacovigilance practices; PV, pharmacovigilance; RMP, risk management plan

life cycle of the medicinal product. The main questions asked in stakeholder meetings and consultations between the EMA and industry can be summarised as follows:

- What should be considered relevant for inclusion in the safety specification (Part II) of the RMP? (What is "important"? When is missing information relevant for inclusion in the RMP?)
- How should important risks be defined and characterised? (For example, can "off-label use in children" be defined as an important potential risk? Should an adverse clinical outcome be defined?)
- How should the safety concerns evolve through the life cycle of the medicinal product? (What is the expectation of the EMA and the national authorities?)

Clear premises

GVP module V Revision 2 provides some more specific wording and clarifications for the definition of identified and potential risks, missing information, and important risk. Further guidance was added to provide a pragmatic approach while applying definitions.

As already specified in Revision 1,[8] the RMP should still focus on those risks that are relevant for the risk-benefit balance of the medicinal product. Revision 2 clarifies that risks should be identified through adverse clinical outcomes that are caused by the use of a medicinal product (identified risks) or that might be caused by the use of a medicinal product (potential risks). For example, if off-label use in children is considered an important potential risk for a medicinal product, the potentially associated adverse clinical event should be defined. With regard to missing information, the focus is on a potential different safety profile in certain situations or populations as compared to the known safety profile.

The definition of important risk is still based on the impact on the risk-benefit balance of the medicinal product, but it is now also linked to the need for further evaluation through PV activities (important identified and potential risks) or to the need for management through risk minimisation measures (important identified risks).

A key aspect of GVP module V Revision 2 is the evidence supporting identification of important (identified and potential) risks and missing information. In line with this, Module SVII now includes sections to discuss the evidence for defining, re-classifying, or removing safety concerns.

Table 1 compares the definitions provided in GVP module V Revision 1 and Revision 2.

Less is more

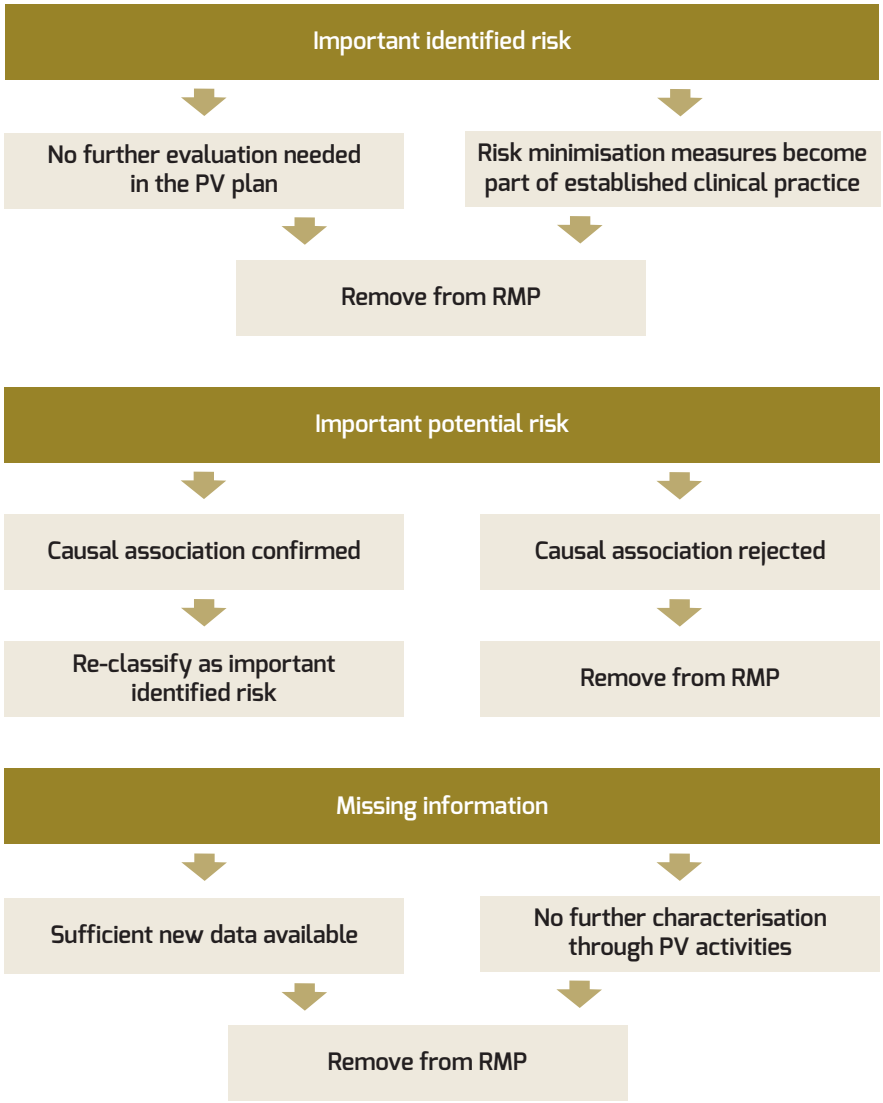
Another challenge when preparing RMPs was how to integrate safety information gathered over time, what to focus on, and how increasing knowledge should support changes in the RMP. In GVP module V Revision 2, the purpose of the RMP is redefined to strengthen the concept of risk proportionality. The amount of information expected to be provided in the safety specification of the RMP varies depending on the stage

of the medicinal product life cycle and the need for post-authorisation data. For initial marketing authorisation applications, a full RMP needs to be submitted, whereas for products with an established safety profile and post-marketing knowledge (e.g. generic drugs, fixed-drug combinations with no active substance, and well-established products), most modules of the safety specification can be omitted.

Similarly, according to the principle of risk proportionality, knowledge regarding a medicinal product's safety profile are expected to increase and safety concerns are expected to evolve as a product proceeds through its life cycle. GVP module V Revision 2 provides guidance on the post-authorisation removal of safety concerns and encourages marketing authorisation holders to critically revise the list of safety concerns and the associated PV activities and risk minimisation measures during the post-marketing phase. In particular, the list of safety concerns will change over time as knowledge regarding the product's safety profile increases, thus confirming or refuting a causal association with the medicinal product (see Figure 1). In addition, PV activities and risk minimisation measures can also change over time (e.g. when studies are either newly planned or completed or when risk minimisation measures are either integrated in clinical practice or shown to be ineffective). Therefore, the requirement for submission of RMP updates is linked to significant changes in the list of safety concerns, the PV plan, and/or the risk minimisation plan.

Moving forward: What's next?

The RMP prepared according to GVP module V Revision 2 is more focussed on those risks that are relevant to the risk-benefit balance of the medicinal product, and which need further evaluation (PV activities) and/or management (risk minimisation activities). The amount of information provided should be risk-proportionate, and the RMP is expected to evolve during the life cycle of the medicinal product. Although general understanding of the revised guidance, as well as individual opinions shared by members of the Pharmacovigilance Risk Assessment Committee (unpublished), clearly point towards the need for critical review of the list of safety concerns during the life cycle of a medicinal product, the question remains as to whether marketing authorisation holders will deem the available evidence sufficient for a critical review, and whether the assessors will agree on the proposed changes. The next phase of the life cycle of the RMP guidance has started, and we can expect further clarifications and adjustments in the future, based on increasing experience with Revision 2 and continuing dialogue between the EMA and industry stakeholders.



Abbreviations: PV, pharmacovigilance; RMP, risk management plan

Figure 1. Expected changes over time in the list of safety concerns according to GVP module V Revision 2.[6]

Conclusion

Revision 2 of GVP module V will result in shorter RMPs. Most sections on risks that are not classified as "important" have been removed, and the section on post-marketing experience has been reduced to the presentation of post-authorisation exposure to avoid redundancies with the periodic safety update report. Once implemented, the clarifications about safety concerns will hopefully lead to a smoother RMP update process and, in the long run, fewer important risks that have to be managed in the RMP. This can be the actual breakthrough of the revision, if it leads to RMPs that do not overwhelm the reader with information and data on risks that are already provided in many other documents, but that instead focus on the issues of their original intent. These issues are identifying or characterising the safety profile of

the medicinal product, indicating how to further characterise its safety profile, and documenting measures to prevent or minimise the risks associated with the medicinal product, including an assessment of the effectiveness of those measures.

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Conflicts of Interest and Disclaimers

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