Regulatory Matters

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EMA guidance meets reality: An evolving story

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One key point in 2012 to the Good Pharmacovigilance Practices (GVP) guidelines was mandatory consultation of all stakeholders before the first publication of GVP and after its implementation. Execution of these guidelines was influenced by public participation through means such as online forums. In addition, stakeholders such as patients and healthcare professional representatives now provide opinions to the European Medicines Agency (EMA) on pharmacovigilance matters through public hearings. Many modules – components of the GVP guidelines – underwent intensive revisions based on the discussions triggered by the stakeholders' feedback before their final publishing.

Revised Modules

The GVP modules that underwent significant revision to address stakeholders' feedback, collected experience, and evolving processes are briefly presented in the table below. The history of revisions is regularly updated by EMA;[1] the individual guidance documents (final or draft currently under public consultation) can be accessed from the EMA webpage on GVP guidance.[2]

From a regulatory pharmacovigilance writing perspective, the most significant revisions were applied to the documents as shown on the following page. (See Table 1 for an overview of all revisions.)

Conclusion

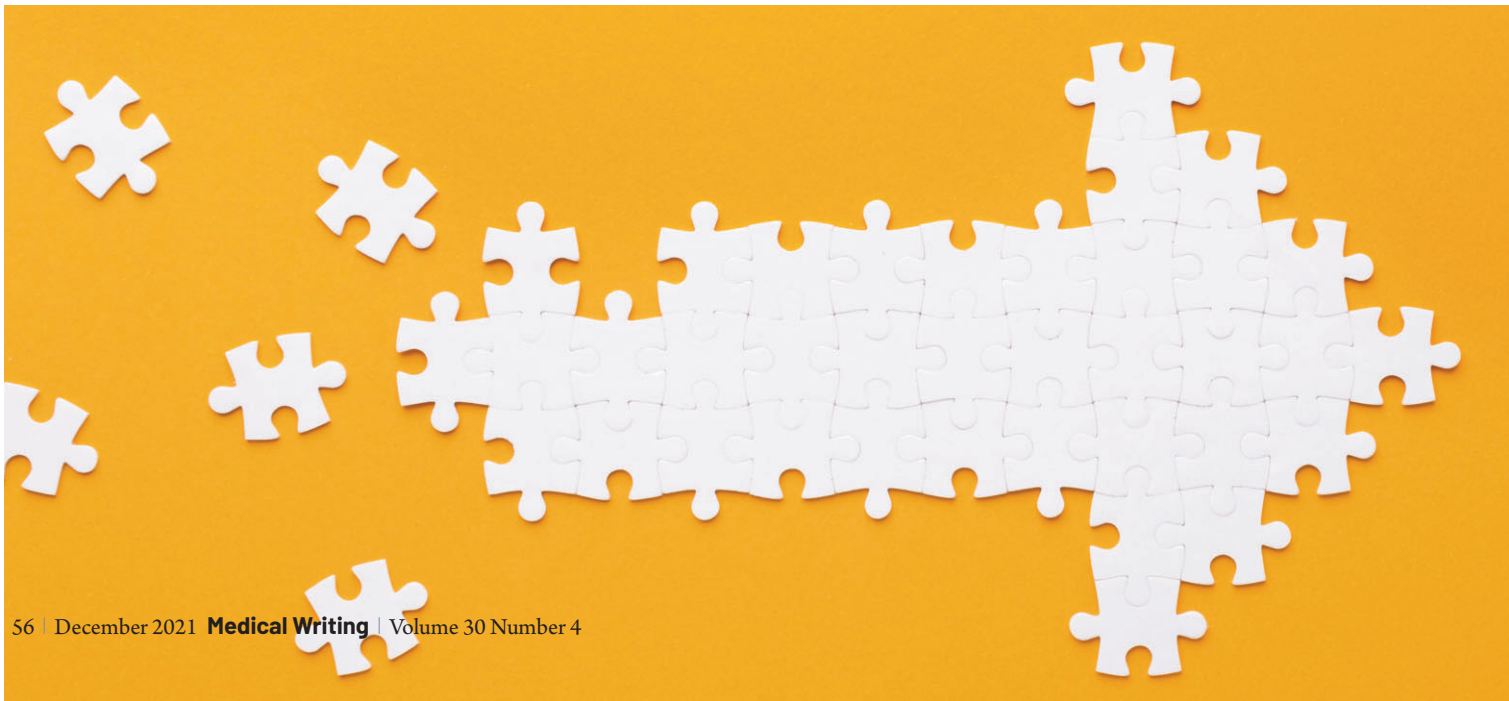
In the effort to streamline pharmacovigilance activities in the EU, the EMA has consistently sought stakeholders' feedback on the implementation of the GVP guidance. Discussions, proposals, and public consultations have led to either major updates or fine-tuning of the guidance. The increasing experience with pharmacovigilance processes and the dialogue between the EMA and all stakeholders contribute to a constant adjustment of the guidance. Further evolution is to be expected in the near future to account for a changing regulatory environment and the integration of digital tools in pharmacovigilance.

Disclaimers

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

References

1. Guidelines on good pharmacovigilance practices (GVP). Introductory cover note, last updated with revision 3 of Module XVI on risk minimisation measures and its Addendum II on methods for their effectiveness evaluation for public consultation. European Medicines Agency and Heads of Medicines Agencies. 2021 [cited 2021 Sept. 4]. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guidelines-good-pharmacovigilance-practices-gvp-introductory-cover-note-last-updated-revision-3_en-0.pdf
2. Good pharmacovigilance practices. European Medicines Agency. 2021 [cited 2021 Sept. 1]. Available from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices
3. Explanatory note to GVP Module VII. European Medicines Agency and Heads of Medicines Agencies. 2021 [cited 2021 Sept. 9]. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vii-periodic-safety-update-report-explanatory_en.pdf



Module V-Risk management systems

Soon after the implementation of GVP Module V, it became clear that the definitions of safety concerns (i.e., important identified risks, important potential risks, and missing information) needed further clarification and pragmatic guidance. In many cases, based on the initial guidance, the Risk Management Plans (RMPs) included long lists of safety concerns and related pharmacovigilance and risk minimisation activities, leading to a significant burden on the risk management system of medicinal products and on the marketing authorisation holders. The second revision of GVP Module V was a long-awaited, major revision that provided guidance to critically review the list of safety concerns. The "importance" of identified and potential risks is now linked not only to the impact of the safety concerns on the benefit-risk balance of the product, but also on the need for further characterisation and management. Updated guidance was given to tailor RMPs to different types of initial marketing authorisation applications. Along with Module V Rev. 2, a major update of the related RMP template was published. The RMP is now a more risk-proportionate document that focuses only on those safety concerns that need further characterisation and management. Furthermore, following feedback from all concerned stakeholders, the public summary of the RMP underwent a major revision; the related template is now more structured, the content is rather technical, the language is plain but scientific, and definitions of the RMP terminology are provided.

Module VII-Periodic safety update report

A new revision was announced for this module shortly after publication of Rev. 1. The need for a major update of the guidance is based on the challenges encountered since its first implementation, the experience collected with preparation and assessment of Periodic Safety Update Reports (PSURs), and the feedback received from the stakeholders. In particular, there appeared to be diverging expectations and guidance interpretations among stakeholders, including individual national competent authorities. For example, the appropriate presentation, level of detail, and discussion of safety data, monitoring topics, signals, and safety concerns in PSURs needed clarification and training. Furthermore, since publication of GVP Module V Rev. 2, there were outstanding questions related to the expected evolution of safety concerns in PSURs, such as, when these are revised in, or removed from, RMPs. To temporarily address the still unmet need of a major update of Module VII, the "Explanatory Note to GVP Module VII"[3] was issued and has undergone three updates to further clarify the guidance expectations to the industry. Currently, this explanatory note must be read in conjunction with GVP Module VII, but will be replaced by a future, major update of the module.

Module XVI- Risk minimisation measures: selection of tools and effectiveness indicators

Since the first publication of this module, there were outstanding questions among the stakeholders related to guidance implementation. Particularly, the development of risk minimisation measures revealed unclear areas (e.g., design, target audience, objectives, and effectiveness measurements of risk minimisation tools). Module XVI Rev. 2 was issued along with GVP Module V Rev. 2. Since the latter included the description of routine risk minimisation tools, Module XVI Rev. 2 focused on additional risk minimisation measures. Therefore, the second revisions of Modules V and XVI complement each other and must be read together. However, Rev. 2 revealed a need for further practical guidance and clarifications. The third revision of Module XVI, which is still under finalisation, clarifies the role of risk minimisation for risk management planning and for the impact on the benefit-risk balance of medicinal products, as well as the role of the related effectiveness evaluation. Rev. 3 also includes further clarifications on the role of risk communication, dissemination, and implementation, and on the role of healthcare professionals and patients in risk minimisation. Furthermore, Addendum II to GVP Module XVI provides guidance to stakeholders to monitor outcomes of risk minimisation measures. Rev. 3 of this Addendum is currently under finalisation along with Module XVI Rev. 3.

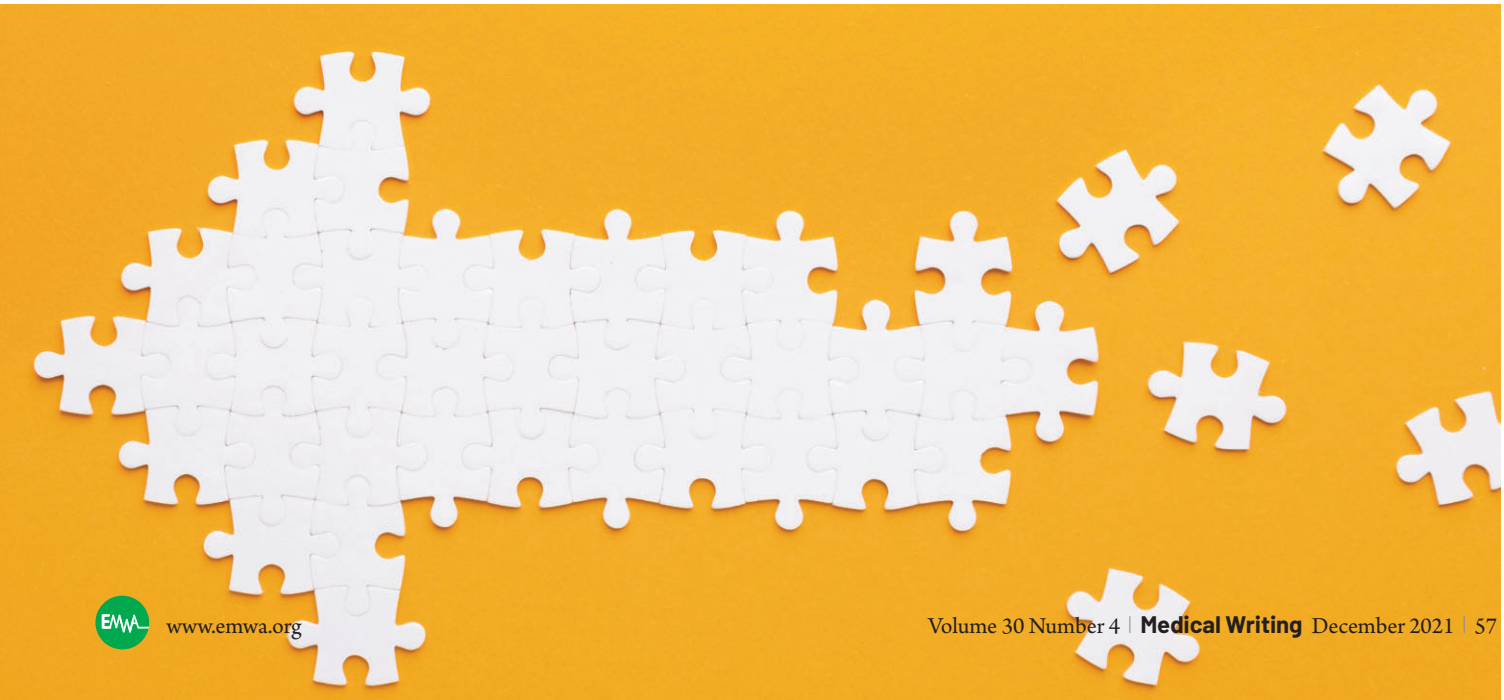


Table 1. Overview of the revisions made to GVP modules to address stakeholders' feedback, collected experience, and evolving processes

GVP module / Topic	Overall no. of revisions	Contents of selected significant updates
V Risk management systems	3	Rev. 2: • Explanation of the definitions of safety concerns and practical guidance on how to apply them • Guidance on the expected changes in the Risk Management Plan (RMP) during the lifecycle of the product • Updated requirements for different types of initial marketing authorisation applications, with the aim to create risk-proportionate RMPs • Major template update to reflect risk-proportionality, including major revision of the public summary of RMP • Parallel alignment revision of Module XVI
VI Reports of suspected adverse reactions to medicinal products	2	Rev. 2: • Updated guidance on individual case safety reports (ICSRs) submission, follow-up, duplicate detection, validation, data quality management • New guidance on electronic submission modalities of ICSRs and on management of reports on off-label use and from Post-Authorisation Safety Studies (PASS) • Transfer of the guidance on emerging safety issues to Good Pharmacovigilance Practice (GVP) Module IX • Parallel alignment revision of Module VIII
VII Periodic Safety Update Report	1	• Major update pending based on experience in preparation and assessment of Periodic Safety Update Reports (PSURs). "Explanatory Note to GVP Module VII" published to complement Module VII until the next major update
VIII Post-Authorisation Safety Studies (PASS)	2	Rev. 2 of module and its Addendum: • Clarification of link between legislation on non-interventional PASS and categories 1 to 4 • Alignment with GVP module VI Rev. 2
IX Signal management	1	• Clarifications of terminology, roles, responsibilities, and processes for signal management • Updated guidance on the monitoring of EudraVigilance data • Revised definition and process for emerging safety issues (transferred from Module VI Rev. 2)
XV Safety communication	1	• Revision of guidance on safety communication, along with revision of the template for Direct Healthcare Professional Letters (DHPCs) • Alignment with outcome of work package 2 on communication and dissemination of the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action of the Member States
XVI Risk minimisation measures	3	• Rev. 2: Alignment with GVP Module V Rev. 2 • Rev. 3 + Addendum: Recommendations, clarifications, and details about additional risk minimisation measures and risk communication, dissemination, and implementation