

Pharmacovigilance

SECTION EDITOR



Tiziana von Bruchhausen, PhD
tiziana.von_bruchhausen@
boehringer-ingenheim.com

Editorial

Dear members,

I am delighted to launch the Pharmacovigilance (PV) section in this journal issue! Those of you who have been around for a while may know that, in the past, PV-related articles were published either as feature articles or as guest topics in the Communication section (and with this, I would like to thank Lisa Chamberlain James for making this possible over the past six years!) It is now time for a dedicated PV section to explore and highlight hot topics in the PV area or potential common interests

between the PV-Special Interest Group (PV-SIG) and other EMWA SIGs.

In this brand-new PV section, Sam Ramsden from Boehringer Ingelheim provides very interesting heads-up about the forthcoming revision of the EU guideline on additional risk minimisation. Sam recently coordinated the review of the draft good pharmacovigilance practices (GVP) Module XVI rev.3 guideline by the European Federation of Pharmaceutical Industries and Associations (EFPIA). While guiding medical writers through such a complex topic, he shows how national guidelines integrate growing experience and knowledge with the ultimate goal

to protect patients.

A further PV topic is included in this journal issue in the Regulatory Matters section (see p. 56): Joan D'souza, active supporting member of the PV-SIG, prepared with me an overview of the evolution of the GVP guidance since first publication in 2012.

This is another example of how public consultations and interaction with stakeholders contribute to improve implementation of the guidance.

I wish our members happy reading!

Tiziana

What to expect from the revision to GVP Module XVI

Within the European Union (EU), the Good Pharmacovigilance Practices (GVP) guidelines define the regulatory expectations related to pharmacovigilance (PV), including the risk management system of a Marketing Authorisation Holder (MAH). Risk minimisation is essential to ensure safe and optimal patient care. Respective activities are used as barriers in medical practice to prevent or mitigate risks to the patient, healthcare provider, or public health. In general, there are two types of risk minimisation recognised in the EU regulatory framework: (1) routine risk minimisation that includes the product information (e.g. Summary of Product's Characteristics [SmPCs]) and legal status (e.g. over-the-counter or prescription-only medicine); and (2) additional risk minimisation that includes activities such as educational programmes, restricted access, and pregnancy prevention. GVP Module XVI¹ deals exclusively with what is known as additional risk minimisation measures and the measurement of their effectiveness.

Within the Risk Management Plan (RMP)² and the Periodic Safety Update Report (PSUR),³

the evaluation of important risks provides a conclusion of their impact on the authorised patient population and the appropriate strategy to manage the risks in the post-marketing environment. Most of the time, routine risk minimisation is considered sufficient to manage

The evaluation of important risks provides a conclusion of their impact on the authorised patient population and the appropriate strategy to manage the risks in the post-marketing environment.

risks; however, in situations where the seriousness and/or likelihood of occurrence is not sufficiently managed by routine activities, additional risk minimisation may be necessary as described in the applicable GVP Module XVI.¹ Furthermore, when additional risk minimisation is required, a detailed plan and periodic evaluation for measuring the effectiveness of the risk minimisation activity is required to ensure they meet the defined goals and objectives, and are not causing an unacceptable

burden on patients and healthcare providers. Therefore, GVP Module XVI¹ also details the requirements and approach to generate metrics to assess the effectiveness of additional risk minimisation.

On February 1, 2021, EMA issued a draft of the 3rd revision of GVP Module XVI⁴ for public

Samuel Ramsden, MSc, BSc, CAS
Head, Risk Management Office
Boehringer-Ingelheim
Ingelheim am Rhein, Germany
samuel_david.ramsden@boehringer-ingenheim.com

consultation and this article will contextualise the proposed changes.

Regulatory history

The history of GVP Module XVI and supporting addenda is presented in Table 1.

Important changes with draft revision (Rev) 3

GVP Module XVI Rev 3⁴ went through a round of public consultation and is currently under finalisation, anticipated coming into effect in Q4 2021/Q1 2022. Therefore, the changes that are described below could be modified in the final version.

Dissemination Plan

In the draft Rev 3 guideline, there is a clear description of the need to prepare a risk minimisation dissemination plan. This plan complements the information, such as root cause, risk factors, and proposed measures to prevent



and mitigate important risks, which are included in the RMP Part II module VII and Part V.² The plan should provide in-depth details about the objectives, target audience, implementation strategy, and milestones. Plans for additional risk minimisation should be submitted to National Competent Authorities (NCAs) as part of the national negotiation prior to the launch of the product.^{1,4}

What does this mean for medical writers?

Medical writers involved in the preparation of RMPs and risk minimisation proposals should be aware of the need to submit the proposal to

NCAs. No standard template has been included by the EMA in the draft guideline for the dissemination plan. Therefore, MAHs can develop a company-customised template to support a harmonised approach for implementation of risk minimisation plans that acknowledges the company's situation and way of working. Furthermore, the information included in the RMP and Annex II of the European Public Assessment Report (EPAR) should be aligned with what is detailed in the risk minimisation plan in terms of root causes of risks, stakeholders that should receive the interventions, implementation strategy, and milestones.

Additional risk minimisation tools

The draft Rev 3 guideline⁴ further improves the clarification of types, objectives, and target audience of the different additional risk minimisation measures. Activities such as educational programmes, Direct Healthcare Professional Communication (DHPC), controlled access, and pregnancy prevention programmes, are addressed in detailed sections outlining considerations for the target audience, such as specific types of information relevant for physicians or patients. Situations where each risk minimisation measure should be considered are also described. This is helpful because it provides guidance on

Table 1: History of GVP Module XVI and supporting addenda

| GVP module / Addendum | First publication | Revisions | Comments |
|--|--|--|--|
| GVP XVI risk minimisation measures: Selection of tools and effectiveness indicators ¹ | Feb 28, 2014 | Rev 1: Apr 25, 2014 Rev 2: Mar 30, 2017 Rev 3 ⁴ released for public consultation: Feb 3, 2021 | Planned date for Rev 3 coming into effect: Q4 2021/Q1 2022 |
| Addendum I – Educational materials | Dec 15, 2015 | Not applicable | No revisions |
| Addendum II – Methods for effectiveness evaluation ⁵ | First released for consultation: Feb 3, 2021 | Not applicable | Planned date for coming into effect: Q4 2021/Q1 2022 |



how objectives of risk minimisation need to be aligned with the choice of tools. Educational materials are further stratified, and specific reference is made to guides, check lists, risk awareness forms, demonstration kits, patient diaries, and patient cards. Although the tools are not “new”, the specific mention of them and individualised considerations for each type is a welcome addition to help clarify the appropriate use of the different interventions. Controlled access programmes have also been stratified and include controlled prescription and supply systems, and centre accredited systems.

What does this mean for medical writers?

Medical writers working on respective materials (e.g., educational guides or check lists) should consider the objectives of the various tools defined in the guideline to ensure the inclusion of appropriate information. In terms of project management, they need to prompt project team members to provide their respective expertise to design the risk minimisation tool. Furthermore, the development of templates for use within the organisation can improve internal and external communication when creating and implementing the interventions.

Effectiveness measurements

The requirement of the evaluation of effectiveness of risk minimisation measures has been expanded and clarified. The Rev 3 draft guideline⁴ specifies that effectiveness evaluations should be focused, i.e. the approach to assess the effectiveness should be aligned with the objectives, target audience, and milestones of the risk minimisation activity. Furthermore, emphasis has been given on how and when risk minimisation evaluation should occur, which includes a close interaction between prospective planning in the RMP, targeted endpoints in the Post Authorisation Safety Study (PASS), and appropriate regulatory follow-up. The evaluation of effectiveness and regulatory follow-up also benefits from patient and healthcare provider input, which is also emphasised for the design and evaluation of risk minimisation.

Timelines for consideration are described, and the evaluation should take place at defined intervals of 1, 3, and 5 years after initial im-

plementation of the risk minimisation activity. These timeframes will be defined based on the type of intervention and agreed with the EMA and NCAs. The timelines will also have to be reflected in the RMP² and aligned with PASS⁶ activities. A detailed timeline for the measurement of effectiveness will also help support the appropriate approach to risk minimisation over the lifecycle.

Planned timelines for evaluation will help establish the relevance of risk minimisation measures through a timely demonstration if important risks and risk minimisation become routine knowledge and integrated into clinical practice.

The draft guideline includes a new section detailing the need to evaluate both the intended and the unintended outcomes of a risk minimisation activity.

The draft guideline includes a new section detailing the need to evaluate both the intended and the unintended outcomes of a risk minimisation activity.

of a risk minimisation activity. MAHs must understand if the risk minimisation activity is having the desired effect, for example, if an appropriate change in clinical knowledge has been achieved about how to mitigate a risk. This desired outcome should be evaluated against any

unintended consequence of the risk minimisation. Evaluating intended and unintended consequences aims to ensure that risk minimisation is fit-for-purpose and does not lead to an unacceptable burden on the intended stakeholders. For example, patients might stop taking the medicine because it is too difficult to follow the requirement of the risk minimisation activity.

The approach to effectiveness evaluation has also been expanded. In the initial guideline, effectiveness evaluation could be categorised as either a process indicator (e.g. dissemination, changes in knowledge or behaviour) or an outcome indicator (e.g., actual change in the incidence of the risk). In the draft guideline, the concept of effectiveness evaluation is addressed in more depth, and the following hierarchy is used: dissemination and risk awareness, behavioural change, and health outcomes. The draft guideline includes relevant considerations and expectation with regards to the necessary data to be collected for qualitative and quantitative assessments of the three levels of effectiveness.

The measurement of effectiveness of risk minimisation can be considered a PASS and therefore, the respective expectations need to be fulfilled.⁶ In Addendum II⁵ of the draft guideline, a detailed consideration for study design and protocol preparation is provided.

What does this mean for medical writers?

Medical writers involved in writing protocols and study reports should be aware of the added requirements for studies used to measure the effectiveness of risk minimisation.^{4,5,6} The endpoints in study protocols should be focused and aligned with the objectives of the risk minimisation activity and any interim and final study reports should clearly describe if the objectives of the risk minimisation measure were met. This calls for close cooperation of medical writers and epidemiologists when developing the study-relevant documents, to ensure appropriate considerations. Different methodology is recommended within the guideline,^{4,5} which should be considered when a protocol is prepared.

Finally, the evaluation of effectiveness should be accurately and appropriately documented in the RMP² and assessed in the PSUR.³ The necessary milestones documented in the RMP should be carried into the organisation's lifecycle management plan. The key focus in the description of effectiveness in the RMP should be on how the outcome informs on risk minimisation and PV planning.⁴ In the PSUR, the effectiveness of risk minimisation should

focus on how the implemented measures impact the safety and benefit-risk balance of the product.⁴ The medical writer should ensure that there is a continuity between the objectives of the risk minimisation measures and the endpoints in the protocol, the conclusions in the study report, further planning in the RMP, and communication in the PSUR.

Conclusion

Rev 3 of GVP Module XVI is a welcome evolution of the regulations defining additional risk minimisation and measurement of effectiveness and reflects the experience gained since the coming into effect of the first version in 2014. Clarification through the inclusion of greater detail has helped resolve some of the outstanding questions MAHs faced with previous versions of the guideline. The additional information included about target audience and objectives for risk minimisation tools, and the expansion of consideration for effectiveness measurements should help teams design focused and relevant risk minimisation. Moving forward, it would be helpful to have more guidance on digital intervention and dissemination to acknowledge the important role these platforms now play in society. Overall, it is appreciated that the accumulation of knowledge and experience is being included in national guidelines for risk minimisation with the ultimate goal to protect patients and the public health.

Acknowledgements

The author would like to thank Dr Tiziana von Bruchhausen and Dr. Sabine Jeck-Thole for their valuable feedback during the writing of this article.

Disclaimers

Samuel Ramsden is an employee of Boehringer Ingelheim. The views and opinions represented in this article are solely those of the author and are not endorsed by or necessarily representative of those of Boehringer Ingelheim or EMWA.

Conflicts of interest

The author declares no conflicts of interest.

Data availability statement

For inquiries about data and other supplemental information, please contact the corresponding author.

References

1. The European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module XVI – Risk minimisation

measures: selection of tools and effectiveness indicators (Rev 2). 2017. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xvi-risk-minimisation-measures-selection-tools_en-3.pdf

2. The European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module V – Risk management systems (Rev 2). 2017. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf
3. The European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VII – Periodic safety update report (Rev 1). 2013. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-vii-periodic-safety-update-report_en.pdf
4. The European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 3). Draft for public consultation. 2021. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-risk-minimisation-measures-selection-tools_en.pdf
5. The European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module XVI Addendum II – Methods for effectiveness evaluation. Draft for public consultation. 2021. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/guideline-good-pharmacovigilance-practices-gvp-module-xvi-addendum-ii-methods-effectiveness_en.pdf
6. The European Medicines Agency. Guideline on good pharmacovigilance practices (GVP). Module VIII – Post-authorisation safety studies (Rev 3). 2017. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-gvp-module-viii-post-authorisation-safety-studies-rev-3_en.pdf