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Guidelines on good pharmacovigilance practices (GVP)

Introductory cover note, last updated with new Addendum II to Module VI on masking of personal data in individual case safety reports submitted to EudraVigilance

Background to GVP

Amended legislation for pharmacovigilance applies in the European Union (EU) since July 2012. To support its implementation, a set of guidelines for the conduct of pharmacovigilance in the EU was developed which replaced the previous set in Volume 9A of the Rules Governing Medicinal Products in the EU.

This guidance on good pharmacovigilance practices (GVP) is organised into two types of chapters, namely Modules on pharmacovigilance processes and Product- or Population-Specific Considerations.

History of the GVP development process and latest updates

The first seven Modules (I, II, IV, V, VII, VIII and IX) on prioritised processes were consulted between 21 February and 18 April 2012 and revised, taking into account the comments received from stakeholders. They were available in their first final versions which came into force on 2 July 2012.

Module III on pharmacovigilance inspections and Module X on processes for additional monitoring of medicinal products were released on 27 June 2012 for public consultation until 24 August 2012, and Module IV on pharmacovigilance audits and Module XV on safety communication were released on 26 July 2012 for public consultation until 21 September 2012. Modules III and IV were published in their final versions, together with the updated GVP Annex I on definitions, on 13 December 2012. The final Module XV was published on 24 January 2013, together with a Template for Direct Healthcare Professional Letters in the GVP Annex II. On 25 April 2013, the final Module X on additional monitoring was published as final, taking into account latest additional legislation.

Since their first release as final, some Modules have been revised as final, and further Modules and Product- or Population-Specific Considerations chapters have been issued:

On 12 April 2013, Module II was published in its first revision, mainly to provide clarifications for herbal medicinal products.

On 25 April 2013, Module VIII Revision 1 and its Addendum Revision 1 as well as in Annex II – Template for the PSUR Cover Page Revision 1 were published.

On 7 June 2013, the draft revision 1 of Module VI on the management and reporting of adverse reactions was released for public consultation, in order to provide more guidance on the clock state for reporting of valid case reports, reporting from post-authorisation safety studies as well as the handling of languages. Also on 7 June 2013, draft Module XVI on risk minimisation measures was released for public consultation. Both consultations closed on 5 August 2013. Module XVI was published in its final version on 28 February 2014; and revision 1 of Module VI was published as final on 15 September 2014.

On 12 December 2013, the first Product- or Population-Specific Considerations, i.e. the Considerations P.I on vaccines, was provided in its final version, following its public consultation launched on 12 April 2013. Also on 12 December 2013, revision 1 of Module VII on periodic safety update reports was provided in its final version following public consultation launched on 25 April 2013. This revision included updates for consistency with the recently finalised ICH-E2C(R2) guideline and on the operations in the EU.

On 8 January 2014, the definitions relating to vaccine pharmacovigilance, launched for public consultation on 12 April 2013, were published without any change post-consultation, together with other amendments to definitions and explanatory notes as detailed on page 2 of the GVP Annex I on definitions in its revision 2.

On 25 April 2014, revision 1 of Module V on risk management system was published, mainly to amend the requirements of part VI of the RMP as published already in the updated RMP templates, to introduce amendments in line with the new requirements for variation applications and to align the definitions of Missing information and Safety concern and their explanatory notes with legal requirements, as well as to amend the definition for Risk minimisation activity. Annex I on definitions was updated accordingly and published as revision 3, and likewise Module XVI on risk minimisation measures was published as revision 1.

On 15 September 2014, revision 1 of Module III was published with a reference to the new Union procedures for pharmacovigilance inspections.

On 27 April 2015, Addendum I to Module XVI on educational materials was published as a draft for public consultation and published as final on 15 December 2015.

On 11 August 2015, revision 1 of the Module IV was published with a clarifying note what does not constitute an audit, and a public consultation was launched for revision 2 of Module VIII and its Addendum, in particular to clarify the link between the legislation on non-interventional post-authorisation safety studies (PASS) and categories 1-4 of non-interventional PASS for risk management planning and to update procedural and transmission requirements. These documents, having been amended in the light of their public consultations, were published as final on 8 August 2016.

On 15 December 2015, revision 1 of Module XV on safety communication, with revision 1 of the Template for Direct Healthcare Professional Letters (DHPCs) and a new Template for DHPC-Communication Plans in GVP Annex II, and the second Product- or Population-Specific Considerations, namely P.II on biological medicinal products, were released for public consultation until 29 February 2016. The Considerations P.II were published as final, having been amended in the light of the public consultation, on 15 August 2016. The final revision 1 of Module XV on safety communication and the Templates were published on 12 October 2017, taking into account comments received during the public consultation.

On 29 February 2016, revision 2 of Module V on risk management system was released for public consultation until 31 May 2016 and published as final, taking into account the consultation comments, on 30 March 2017. At the same time, Module XVI was published in its revision 2 to delete the description of routine risk minimisation tools, as these had been detailed in GVP Module V, and to give further clarifications on some aspects on risk minimisation.

On 8 August 2016, draft revision 2 of Module VI on management and reporting of adverse reactions and draft revision 1 of Module IX on signal management with its Addendum were released for public consultation until 14 October 2016. Revision 2 of Module VI was finalised with amendments in the light of the public consultation and published on 2 August 2017. Its Addendum on the duplicate management of suspected adverse reaction reports was likewise published on 2 August 2017 as new guidance in GVP, based on a previous guideline published before GVP came into existence. Revision 1 of Module IX on signal management and its Addendum on methods were published as final on 12 October 2017, taking into account comments received during the public consultation. All these documents, i.e. revised Modules VI and IX and their Addenda, came into effect on 22 November 2017, together with the new EudraVigilance functionalities and application of the ICH-E2B(R3) guideline.

On 30 March 2017, Module II was published as revision 2 with updates in relation to outdated transitionary guidance, the new Article 57 database and a few aspects to be clarified regarding the pharmacovigilance systems master file (PMSF).

On 12 October 2017, revision 3 of Module VIII on PASS was published in order to align this Module with the recently published revision 2 of Module VI. Revision 4 of the Annex I on definitions was

published, mainly with terms introduced by Regulation (EU) No 536/2014 Art 2(2)(1) on clinical trials and other terms relevant to recently developed or revised GVP documents. An updated Annex V on abbreviations was published too.

On 2 August 2017, a public consultation was launched until 13 October 2017 for new Product- or Population-Specific Considerations, namely on the paediatric population. This Considerations chapter P.IV was based on a guideline published before GVP came into existence and was the first GVP Considerations focussing on a specific population group. Taking into account the comments received during the public consultation, it was finalised and published on 7 November 2018.

On 11 December 2019, the Considerations chapter P.III focussing on pharmacovigilance for the use of medicines by pregnant and breastfeeding women was released for public consultation until 28 February 2020.

On 23 June 2020, an update of Addendum I of Module VIII on requirements and recommendations for the submission of information on non-interventional post-authorisation safety studies was published as revision 3. The finalisation of this document is foreseen for 2025/6.

On 3 February 2021, a public consultation was launched until 28 April 2021 for revision 3 of Module XVI on risk minimisation measures and its new Addendum II on methods for effectiveness evaluation of risk minimisation measures. Together, these two GVP documents clarify and enhance tools for risk minimisation and strengthen methods for studying the effectiveness of the implementation of risk minimisation measures and the possible need for adjusting measures in the interest of patient safety. Guidance on the important collaboration with patient and healthcare representatives in the related regulatory processes was included too. On 5 August 2024, both documents were published in their final versions, taking into account the comments received from the public consultation, recent experiences and research on risk minimisation measures and the overall advances in the field drawing from the implementation science. Given new terminology in GVP Module XVI and the recent coming into application of Regulation (EU) No 536/2014, revision 5 of GVP Annex I on definitions was published too

On 14 March 2022, a public consultation was launched for Addendum III of Module XVI on pregnancy prevention programmes and other pregnancy-specific risk minimisation measures. This draft guidance defined the elements of a pregnancy prevention programme and provides for deciding when such programme is needed or other risk minimisation measures are considered appropriate to avoid adverse pregnancy outcomes due to use of medicines and to preserve health of both the mother and the child. The finalisation of this document is foreseen for 2025.

Today, the new Addendum II to Module VI on the masking of personal data in individual case safety reports submitted to EudraVigilance is published. As part of its finalisation, this document was consulted with the EudraVigilance Expert Working Group.

Objectives of pharmacovigilance

Pharmacovigilance has been defined by the World Health Organization (WHO) as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem.

In line with this general definition, underlying objectives of the applicable EU legislation for pharmacovigilance are:

- Preventing harm from adverse reactions in humans arising from the use of authorised medicinal products within or outside the terms of marketing authorisation or from occupational exposure; and

- Promoting the safe and effective use of medicinal products, in particular through providing timely information about the safety of medicinal products to patients, healthcare professionals and the public.

Pharmacovigilance is therefore an activity contributing to the protection of patients' and public health.

Pharmacovigilance in the EU: roles of different actors

In the EU, a regulatory network consisting of the competent authorities in Member States, the European Commission and the European Medicines Agency (in GVP referred to as "the Agency") is responsible for granting marketing authorisations and supervising medicinal products, including the conduct of pharmacovigilance. The Agency has a core role in coordinating these activities for the network.

In addition to the network's responsibilities, EU legislation imposes responsibility for pharmacovigilance, together with specific obligations (i.e. in terms of tasks and responsibilities), on marketing authorisation holders.

In the past, the role of healthcare professionals was mainly seen as contributing to pharmacovigilance through spontaneous reporting of suspected adverse reaction cases and as receiving, together with the patients, advice on minimising risks through updated product information or other information materials. However over time, participation of patients and healthcare professionals in EU regulatory processes, including those for pharmacovigilance, has steadily increased. Member States have established schemes for reporting of suspected adverse reactions by patients themselves. This was supported by an EU legal framework for patient reporting in all Member States introduced through the pharmacovigilance legislation in force since 2012. Also, this legislation has further increased public participation by including patient and healthcare professional representatives in the Pharmacovigilance and Risk Assessment Committee (PRAC) and through public hearings on pharmacovigilance and benefit-risk matters at the Agency, involving all stakeholders. Other options for engaging patient and healthcare professional representatives to inform regulatory decisions and support their implementation in healthcare have been established too and are used regularly.

Legal basis, scope and development process of GVP

The legal framework for pharmacovigilance of medicinal products for human use in the EU is given in Regulation (EC) No 726/2004 and Directive 2001/83/EC on the Community code relating to medicinal products for human use, as amended in 2010 by Regulation (EU) No 1235/2010 and Directives 2010/84/EU and 2012/26/EU respectively, as well as by the Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC. It should be noted that Chapter 3 of the Regulation (EC) No 726/2004 as amended, Title IX of the Directive 2001/83/EC as amended and the Implementing Regulation contain the majority of pharmacovigilance provisions in the legislation, however, other measures directly relevant to the conduct of pharmacovigilance are found in other Chapters and Titles of this Regulation and Directive.

The aforementioned amending legislation of 2010 which came into force in 2012, together with the related Implementing Regulation of 2012, was commonly referred to as the 'new pharmacovigilance legislation in the EU'. It was the outcome of a major review of the current pharmacovigilance system in the EU conducted by the European Commission, followed by a formal law-making process in the Council and European Parliament. The legislation has the primary aim to strengthen and rationalise pharmacovigilance and increase patient safety.

GVP is drawn up based on Article 108a(a) of Directive 2001/83/EC as amended, by the Agency in cooperation with competent authorities in Member States and interested parties.

The pharmacovigilance legal requirements and GVP apply to all medicinal products authorised in the EU, whether centrally or nationally authorised. While risk proportionality underpins the new legislation, the requirements are generally the same for different types of product unless specific provision or exemptions apply as indicated in the GVP chapters.

GVP is drawn up to facilitate the performance of pharmacovigilance activities within the EU and applies to marketing authorisation holders in the EU, the Agency and competent authorities in Member States. Where in GVP reference is made to Member States of the EU, this should be read to include Iceland, Liechtenstein and Norway. These countries have, through the Agreement of the European Economic Area (EEA), adopted the complete Union acquis (i.e. the legislation at EU level, guidelines and judgements) on medicinal products, and are consequently parties to the EU procedures. The pharmacovigilance Regulation (EU) No 1235/2010 and Directive 2010/84/EU have likewise been implemented in these countries[1].

GVP is developed within a governance structure set up by the Agency and national competent authorities specifically for the implementation of pharmacovigilance legislation. This structure allows for the close collaboration of Member States, the Agency and the European Commission services, with regular stakeholder meetings as an integral part of the implementation process.

Each draft document of GVP is prepared by an author team consisting of experts from Member States and the Agency, taking into account comments collected during stakeholder interactions, and agreed by the EU regulatory network for public consultation. After public consultation, the GVP document is finalised within the governance structure, addressing the comments from the public consultation, and then issued by the Agency and the Heads of Medicines Agency as final on the Agency's website.

Proposals for corrections, revision/addition of guidance or new GVP documents can be made by any member of the EU regulatory network as well as any other stakeholder. Members of the public and non-regulatory stakeholder organisations can send proposals via:

https://www.ema.europa.eu/en/about-us/contacts-european-medicines-agency/send-question-european-medicines-agency.

There might not be an immediate, individual response, but all proposals will be reviewed regularly and prioritised within the governance structure for further development of GVP.

Structure of GVP

Pharmacovigilance activities are organised by distinct but connected processes, and each GVP Module presents one major pharmacovigilance process. In addition, GVP provides guidance on the conduct of pharmacovigilance for specific product types or specific populations in which medicines are used. These GVP Considerations apply in conjunction with the process-related guidance in the Modules.

Some guidelines developed under the previous legislation remain valid in principle (unless any aspect is not compatible with the 2010 legislation) until they are revised at a later point in time for inclusion in GVP. They are published on the Agency's GVP webpage in GVP Annex III.

Within each GVP chapter, Section A provides the legal, technical and scientific context of the respective process. Section B gives guidance which, while based on EU legislation, reflects scientific and regulatory approaches, formats and standards agreed internationally in various forums; or, where such

[1] The only exemption from this is that legally binding acts from the EU (e.g. Commission Decisions) do not directly confer rights and obligations but have first to be transposed into legally binding acts in Iceland, Liechtenstein and Norway.

formal agreements or expert consensus do not exist, Section B describes approaches which are considered in line with general current thinking in the field. Section C focusses on the specifics of applying the approaches, formats and standards in the EU and other aspects of operating the respective process in the EU.

In particular in Sections B, the term "competent authority" is to be understood in its generic meaning of an authority regulating medicinal products and/or an authority appointed at national level for being in charge of all or individual pharmacovigilance processes. For the purpose of applying GVP in the EU, the term "competent authority" covers the competent authorities in Member States and the Agency.

A table of contents of GVP is kept up to date on the GVP webpage, accessible under

https://www.ema.europa.eu/en/human-regulatory-overview/post-authorisation/pharmacovigilance-post-authorisation/good-pharmacovigilance-practices-gvp.

The overall structure of GVP was reviewed on 17 November 2015 by the Implementation Group, then in place as part of above mentioned governance structure, and the following planned GVP Modules were considered not necessary anymore, given that other guidance had been made available since the initial planning of GVP: Module XI on public participation, Module XII on safety-related action, Module XIII on incident management and information exchange within the EU regulatory network and Module XIV on international collaboration. Should GVP chapters still refer to Module XI, one should consult the Agency's webpage on https://www.ema.europa.eu/en/partners-networks/patients-consumers and https://www.ema.europa.eu/en/partners-networks/healthcare-professionals. Should GVP chapters still refer to Module XII, one should consult the Agency's website on https://www.ema.europa.eu/en/human-regulatory/post-authorisation. Should GVP chapters still refer to Module XIII, one should consult the Agency's webpage on https://www.ema.europa.eu/human-regulatory/post-authorisation/pharmacovigilance/incident-management-plan. Should GVP chapters still refer to Module XIV, one should consult the Agency's webpage on https://www.ema.europa.eu/en/partners-networks/international-activities.

Referencing of legal requirements in GVP

In GVP, any reference to Regulation (EC) No 726/2004 and Directive 2001/83/EC always refers to the Regulation and Directive respectively in their latest amended versions. Where reference is made to specific Articles in square brackets, "REG" means Regulation (EC) No 726/2004 as amended and "DIR" means Directive 2001/83/EC as amended. If reference is provided to any other Regulation or Directive, its full reference is provided.

Reference to specific Articles of the Commission Implementing Regulation (EU) No 520/2012 on the Performance of Pharmacovigilance Activities Provided for in Regulation (EC) No 726/2004 and Directive 2001/83/EC is provided in square brackets with the indication "IR".

Text in GVP describing legal requirements makes reference to the specific article in the legislation and uses the same modal verb as used in the article, which is usually "shall". Guidance for the implementation of legal requirements is presented with the modal verb "should".

Practical advice for the public consultation

Those participating in the public consultation of a GVP document are asked to submit comments via the link to the EU survey tool provided on the GVP document released for public consultation.

The public consultations relate to guidance in GVP proposed for the practical implementation of the applicable legislation. Participants are therefore asked not to comment on the underlying legal

requirements (identified in the draft GVP documents by reference to the respective legal Articles), as these cannot be altered through the GVP consultation process.

Participants should note that their comments will be published on the Agency's website, identifying the sender's organisation. However, where a sender does not represent an organisation but submits comments as an individual, the name of the individual will be published unless the participants objects to the publication. In the absence of a legitimate interest to oppose the publication of the name, the contribution will not be published nor will, in principle, its content be taken into account for finalising the GVP document. Please consult the Agency's Privacy Policy (https://www.ema.europa.eu/en/documents/other/european-medicines-agencys-privacy-statement-public-targeted-consultations_en.pdf).

The European Medicines Agency thanks all those participating in the public consultations for their contributions.