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Guidelines on good pharmacovigilance practices (GVP)

Introductory cover note, last updated with 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 for public consultation, and final revision 2 of module VIII on post-authorisation studies with its addendum

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Background to GVP

New legislation for pharmacovigilance applies in the European Union (EU) since July 2012, and to support its implementation, a set of guidelines for the conduct of pharmacovigilance in the EU has been developed which, as they have been adopted, replaced the previous set in Volume 9A of the Rules Governing Medicinal Products in the EU.

This new 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 on prioritised processes were consulted between 21 February and 18 April 2012 and revised, taking into account the comments received from stakeholders. They are available in their 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: Module II was published in its first revision, mainly to provide clarifications for herbal medicinal products, on 12 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 25 April 2013.

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 chapter with Product- or Population-Specific Considerations was provided in its final version, i.e. the chapter P.I on vaccines, following its public consultation launched on 12 April 2013. Also, 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 is published with a clarifying note what does not constitute an audit, and a public consultation, over two months, is 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.

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 on biological medicinal products, were released for public consultation until 29 February 2016.

On 29 February 2016, revision 2 of Module V on risk management system was released for public consultation until 31 May 2016.

Today, 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 are released for public consultation over a period of ten weeks. Further, revision 2 of Module VIII on post-authorisation studies and its Addendum are published as final, having been amended in the light of their public consultations.

For timelines when the remaining new Considerations will be published for public consultation, please see the GVP webpage of the Agency's website:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c.

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. A large number of Member States have established, over the last years, schemes for reporting of suspected adverse reactions by patients themselves. An EU legal framework for patient reporting in all Member States has now been introduced through the new pharmacovigilance legislation. The new legislation further increases public participation by including patient and healthcare professional representatives in the new Pharmacovigilance and Risk Assessment Committee (PRAC) and through public hearings on pharmacovigilance and benefit-risk matters at the Agency, involving all stakeholders.

Legal basis, scope and process for 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 2010/12, together with the related Implementing Regulation, is 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.

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. Iceland, Liechtenstein and Norway have so far, 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 new pharmacovigilance Regulation (EU) No 1235/2010 and Directive 2010/84/EU will however only formally apply to these countries once they have been incorporated into the EEA Agreement. In the meantime and thereafter, where in GVP reference is made to Member States of the EU, this should be read to include Norway, Iceland and Liechtenstein¹.

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

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

Each draft chapter of GVP is prepared by a project team (Modules) or author team (Considerations) consisting of experts from Member States and the Agency, taking into account comments collected during the stakeholder meetings. The draft chapters are agreed by the Heads of Medicines Agencies' European Risk Management Strategy Facilitation Group (ERMS FG) and are released for public consultation on behalf of the EU regulatory network. After public consultation, the chapters are finalised within the governance structure, addressing the comments from stakeholders, and then published by the Agency.

Maintenance and further development of GVP

Proposals for corrections, revision/addition of guidance or new GVP chapters 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 http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/landing/ask_ema_landing_page.jsp&mid. There might not be an immediate, individual response, but all proposals will be reviewed regularly and prioritised within the governance structure set up by the Agency and national competent authorities for the implementation of the new pharmacovigilance legislation.

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.

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

Within each chapters, 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 for a; or, where such 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

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 Norway, Iceland and Liechtenstein.

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:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c.

The overall structure of GVP was reviewed by the Implementation Group of above mentioned governance structure on 17 November 2015 and the following planned GVP Modules are not necessary anymore, given that other guidance has 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 exchange of information exchange within the EU regulatory network and Module XIV on international collaboration. Where GVP chapters refer to Modules XI or XIV, one should now consult the Agency’s webpage on Partners & Networks

(http://www.ema.europa.eu/ema/index.jsp?curl=pages/partners_and_networks/general/general_content_00212.jsp&mid), and where GVP chapters refer to Module XII, one should now consult the post-

authorisation section for human medicinal products of the Agency’s website

(http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000090.jsp&mid). Where GVP chapters refer to Module XIII, one should now consult the Agency’s webpage

on incident management

(http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000544.jsp&mid=WC0b01ac05805b713e).

Referencing of legal requirements in GVP

In GVP, any reference to Regulation (EC) No 726/2004 and Directive 2001/83/EC refers to the Regulation and Directive respectively, always including their latest amendments. 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 are asked to please submit comments by using the specific templates for each chapter (see page 1 of each draft chapter) and the Definition or Template Annex, when these are under consultation too. Comments will only be processed if submitted as **completed templates in open word format**. Participants may additionally submit pdf-files of their comments, if they wish to do so, if they accompany them by a statement that the open and pdf-files are identical in content.

The public consultation relates to the guidance 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 chapters by reference to the respective 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 (but not the sender's name). Where a sender does not represent an organisation but submits comments as an individual, the sender's name will be published unless the sender objects against 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. Please consult the Agency's Privacy Policy

(http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/general/general_content_000516.jsp&mid)

and the specific privacy statement for this consultation

(http://www.ema.europa.eu/docs/en_GB/document_library/Other/2012/02/WC500123144.pdf).

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