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Patient Health Protection

Guidelines on good pharmacovigilance practices (GVP)

Introductory cover note, last updated with finalisation of module XV

Background to GVP

New legislation for pharmacovigilance applies in the European Union (EU) since July 2012, and to support its implementation, a new set of guidelines for the conduct of pharmacovigilance in the EU is under development which, as they are adopted, replace the current set in Volume 9A of the Rules Governing Medicinal Products in the EU.

This new guidance on good pharmacovigilance practices (GVP) is organised into Modules. The first seven Modules on prioritised topics 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 and 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. Two further Modules, i.e. 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 on definitions, on 13 December 2012.

The final Module XV is published now, together with a template for Direct Healthcare Professional Letters in Annex II, while the final Module X will be published later in 2013, to implement latest additional legislation.

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

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:

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- 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 Directive 2010/84/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, 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 Modules.

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 Liechtenstein[1].

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 Module of GVP has been prepared by a project team consisting of experts from Member States and the Agency, taking into account comments collected during the stakeholder meetings. The draft Modules were 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 Modules are finalised within the governance structure, addressing the comments from stakeholders, and then published by the Agency.

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".

[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.

Structure of GVP

Pharmacovigilance activities are organised by distinct but connected processes, and each GVP Module presents one major pharmacovigilance process.

A draft list of GVP Modules (see Annex 1) identifies the finalised Modules and the other Modules currently under public consultation or under development for future public consultations. Currently some guidelines dedicated to product- or population-specific aspects of pharmacovigilance are published on the Agency's website. They 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.

Within the Modules, Sections A provide the legal, technical and scientific context of the respective process. Sections B give guidance which, while based on EU legislation, reflects scientific and regulatory approaches, formats and standards agreed internationally in various fora, or where such formal agreements or expert consensus do not exist, Sections B describe approaches which are considered in line with general current thinking in the field. Sections C focus 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.

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 Module (see page 1 of each draft Module) and the Definition Annex, when this is 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 Modules 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).

Timelines for finalisation of GVP

Modules I, II, V, VI, VII, VIII and IX were finalised and published on 25 June 2012 for coming into force on 2 July 2012. Modules III and IV were published as final on 13 December 2012, and Module XV on 24 January 2013. The remaining Modules will be finalised in the course of 2013.

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

Annex: Draft list of GVP Modules[2]

GUIDANCE ON GOOD PHARMACOVIGILANCE PRACTICES (GVP)

INTRODUCTION	Legal Basis and Structure of Pharmacovigilance Guidance
MODULE I	**Pharmacovigilance Systems and their Quality Systems**
MODULE II	**Pharmacovigilance System Master File**
MODULE III	**Pharmacovigilance Inspections**
MODULE IV	**Pharmacovigilance Audits**
MODULE V	**Risk Management Systems**
MODULE VI	**Management and Reporting of Adverse Reactions to Medicinal Products**
MODULE VII	**Periodic Safety Update Report**
MODULE VIII	**Post-Authorisation Safety Studies**
MODULE IX	**Signal Management**
MODULE X	*Additional Monitoring*
MODULE XI	Public Participation in Pharmacovigilance
MODULE XII	Continuous Pharmacovigilance, Ongoing Benefit-Risk Evaluation, Regulatory Action and Planning of Public Communication
MODULE XIII	For references to incident management, see Module XII
MODULE XIV	International Collaboration
MODULE XV	**Safety Communication**
MODULE XVI	Tools, Educational Materials and Effectiveness Measurement for Risk Minimisation

PRODUCT- AND POPULATION-SPECIFIC CONSIDERATIONS

ANNEX I	**DEFINITIONS**[3]
ANNEX II	TERMINOLOGIES
ANNEX III	TEMPLATES
ANNEX IV	LIST OF INTERNATIONAL PHARMACOVIGILANCE GUIDANCE DOCUMENTS
ANNEX V	LIST OF OTHER GUIDANCE DOCUMENTS

[2] Modules in bold font type have been published as final, those in italics are subject to finalisation following public consultation.
[3] The Annex on definitions published as final will be a revised to include further definitions subject to ongoing or future public consultation.