



Pharmacovigilance Legislation in the European Union: AN OVERVIEW OF LEGAL FRAMEWORK AND DEVELOPMENTS

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INTRODUCTION - PHARMACOVIGILANCE SYSTEMS IN THE EUROPEAN UNION (EU)

Pharmacovigilance (PHV) is the science of drug safety. In practice, it is the collection, detection, assessment, monitoring, and prevention of adverse or undesired side effects, also known as adverse drug reactions (ADRs) associated with the use of marketed pharmaceutical products. The main aim of PHV is to treat patients safely and effectively by preventing harm and also by evaluating and minimizing the risk that may come from taking a particular medicine.

Some of the key PHV activities are:

- Data collection, evaluation, monitoring, and audit(s) on safety of medicines;
- Assessment of data for so-called ‘signals’—data which may indicate a possible change in the safety profile of drug(s);
- Proactive assessment of potential risk of drugs—expected or unexpected—as well as any actions and measures to minimize such risk(s) through so-called “risk management”;

- Timely and transparent information and communication to patients, health care professionals, the public, and pharmaceutical companies—for instance, by issuing advice or recommendations to modify, restrict, or even stop a treatment or medicine when the risk of taking it outweighs the benefit. This is then referred to as the “benefit-risk profile of a product which is no longer positive.”
- Timely and transparent information and communication to regulators in order to inform specific regulatory actions, such as requirements for additional monitoring of certain medicines.

In the EU, PHV is a key public health function.¹ PHV activities are shared between the individual Member States’ (MSs) National Competent Authorities (NCAs), the European Commission (EC)² and the European Medicines Agency (EMA).³ EMA has a key role in coordinating these activities through its expert committee on PHV, the Pharmacovigilance Risk Assessment Committee (PRAC).⁴ EMA is also responsible for managing any interactions with individual Marketing

Authorization Holders (MAHs), which, according to the EU legislation, have separate, specific obligations and responsibilities in terms of PHV.

LEGAL BASIS AND SCOPE OF PHV

The legal basis for PHV for medicines for human use in the EU is laid down in Regulation (EC) No 726/2004⁵ and its 2010 amendment through Regulation (EU) No 1235/2010,⁶ including advanced therapy medicinal products (ATMPs).⁷ They specifically cover the procedures for authorization of centrally authorized medicinal products, such as submission and granting of marketing authorization (MA), as well as their supervision once on the market; Directive 2001/83/EC⁸ deals specifically with provisions for nationally authorized medicines. Directive 2010/84/EU⁹ further increased patient protection and streamlined operational PHV processes by providing legal framework on how to produce, distribute, and use medicines, as well as for the submission of data on medicines by MAHs.

In fact, the legal requirement for data submission on medicines by MAHs, maintenance of submitted medicinal product information and notification to EMA of any new information or variation is a key concept of the 2010 pharmacovigilance legislation,¹⁰ following the so called “Article 57 requirement (Article 57(2) of Regulation (EC) No 726/2004.”¹¹

In 2012, the EU PHV legislation underwent a major overhaul through Directive 2012/26/EU,¹² applicable since October 2013, which provides guidance on notification and assessment of safety issues, and Regulation (EU) No 1027/2012.¹³ On March 7, 2013, the EU Commission adopted the Commission Implementing Regulation (EU) No 520/2012,¹⁴ which describes how to practically implement the PHV legislation. It also allowed, for the first time, the direct reporting of ADRs to NCAs by patients. It also covers, for instance, medication errors and overdose(s). It is probably best known for the introduction of the so-called “Black Symbol,” a black inverted triangle (▼)¹⁵ together with a short sentence explaining that the medicine is under additional monitoring (see Figure 1). The additional monitoring requirement applies to:

- All products authorized in the EU after Jan. 1, 2011, including biosimilar medicines;
- Products of biological origin—for instance vaccines or those derived from human blood or plasma, and which are authorized in the EU after Jan. 1, 2011;
- Provisionally licensed products, whereby the MAH for the medicine is required to submit additional data or studies.

The medicine remains on the ‘list of medicines under additional monitoring’¹⁶ for five years or until the PRAC decides to remove it. The entire list is reviewed monthly; at the time of writing this article the most recent list is from March 29, 2017.¹⁷

The 2010/12 Legislation and the Implementing Regulation is often referred to as the “New pharmacovigilance

legislation in the EU.” It is regarded by many as the biggest development and change to the regulation of human medicines in the EU since 1995.

GOOD PHARMACOVIGILANCE PRACTICES (GVP) AND GUIDELINE ON GVP

Guidance and instructions for MAHs, EMA, and NCAs on how to apply the new PHV legislation is given in the “Guideline on Good Pharmacovigilance Practices (GVP).” It describes a set of practical measures for PHV processes on how, when, and what to report and includes details on monitoring and surveillance—for instance through inspections and audits—as well as how to manage and minimize risk for patients.

The GVP consist of Modules (Modules I-XVI), Annexes (I-III) and population-specific considerations.¹⁸ The first seven modules came into force on July 2, 2012, following a public consultation between February and April 2012. As of April 2017, there are twelve modules and two addendums (I, II, III, IV, V, VI, VII, VIII, VIII Addendum I, IX, X, XV, XVI, XVII Addendum I), with three more modules planned for 2017.

The population-specific considerations include vaccines (I) and biological medicinal products (II) with three more population-specific considerations to be developed in 2017 (pregnancy and breastfeeding, pediatric population, and geriatric population). Additional information, such as definitions, templates, and additional guidance is covered in three Annexes (I; IIa; IIb; IIIa; IIIb; IIIc; IIId; IIIe, IIIf).

MOST RECENT UPDATES TO PHV AND GVP

In 2014, the EU Commission adopted a Commission Delegated Regulation (EU)¹⁹ on post-authorization efficacy studies (PAES). These are specific studies which are conducted in order to add additional or complementary efficacy data on an authorized medicine. This may be due to improve the scientific understanding of the medicine, such as real-life situations, or because some data can only be gathered post-authorization, such as the long-term effect(s) of a certain drug.

Since the initial publication of the first seven modules of GVP in June 2012, additional modules were released and revised following public consultation. The most recent revisions include Module V to amend requirements of risk management plans, Module IV to clarify the definition of a PHV audit, Module VI on reporting of adverse reactions, and Module IX on signal management.

On March 30, 2017, the EMA published the latest revision (Revision 2) of Module V and Revision 2 to Module II, which includes the new Article 57 database²⁰ and pharmacovigilance systems master file.

The timelines of all GVP public consultations and release of final documents can be found on EMA’s GVP webpage.

SUMMARY/CONCLUSIONS AND FUTURE CHALLENGES



Figure 1: Introduction of the "Black Symbol"

The Commission Implementing Regulation (EU) No 520/2012 was adopted March 2013 and is probably best known for the introduction of the so-called "Black Symbol," a black inverted triangle (▼)¹⁵, together with a short sentence explaining that the medicine is under additional monitoring.

PHV systems in the EU have developed considerably since its inception through Regulation (EC) No 726/2004 and Directive 2001/83/EC; with more developments to follow in the coming years with the advancement of research and science and an increasing number of newly developed and more complex medicines—medicines designed for specific patient populations or specific situations. These may have unknown and unpredictable adverse effects on human health.

PPTA member companies recognize that minimizing the potential harm that may arise from medicines is essential and take proactive actions such as transparency, communication, and patient involvement, and through providing timely, high quality safety data and proactive risk-management. ●

References:

1. http://ec.europa.eu/health/human-use/pharmacovigilance_en
2. http://ec.europa.eu/health/human-use/safe_pharma/index_en.htm
3. http://www.ema.europa.eu/ema/index.jsp?curl=pages/home/Home_Page.jsp&mid=
4. http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000537.jsp&mid=WC0b01ac058058cb18
5. Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency.
6. REGULATION (EU) No 1235/2010 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 15 December 2010 amending, as regards pharmacovigilance of medicinal products for human use, Regulation (EC) No 726/2004 laying down Community procedures for the authorisation and supervision of medicinal products for human and veterinary use and establishing a European Medicines Agency, and Regulation (EC) No 1394/2007 on advanced therapy medicinal products.
7. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000294.jsp&mid=WC0b01ac05800241e0
8. Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use.
9. DIRECTIVE 2010/84/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use.
10. http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000491.jsp
11. http://www.ema.europa.eu/docs/en_GB/document_library/Other/2014/12/WC500179265.pdf
12. DIRECTIVE 2012/26/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 25 October 2012 amending Directive 2001/83/EC as regards pharmacovigilance.
13. REGULATION (EU) No 1027/2012 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 25 October 2012 amending Regulation (EC) No 726/2004 as regards pharmacovigilance.
14. COMMISSION IMPLEMENTING REGULATION (EU) No 520/2012 of 19 June 2012 on the performance of pharmacovigilance activities provided for in Regulation (EC) No 726/2004 of the European Parliament and of the Council and Directive 2001/83/EC of the European Parliament and of the Council.
15. http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/document_listing/document_listing_000365.jsp&mid=WC0b01ac058067bfff
16. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000366.jsp&mid=WC0b01ac058067c852
17. http://www.ema.europa.eu/docs/en_GB/document_library/Medicines_under_additional_monitoring/2013/04/WC500142453.pdf
18. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/document_listing/document_listing_000345.jsp&mid=WC0b01ac058058f32c
19. Commission Delegated Regulation (EU) No 357/2014 of 3 February 2014 supplementing Directive 2001/83/EC of the European Parliament and of the Council and Regulation (EC) No 726/2004 of the European Parliament and of the Council as regards situations in which post-authorisation efficacy studies may be required.
20. http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fregulation%2Fgeneral%2Fgeneral_content_000496.jsp