DEVELOPMENT OF A PHARMACOVIGILANCE SYSTEM

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ABSTRACT

Pharmacovigilance (PV) is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicnal products. The well established and adequately maintained PV system allows early detection of potential adverse events signals which is essential in order to ensure patient safety. PV activities are currently subject of intense legislative changes.

The aim of the current publication is to propose a methodological approach to establish a PV system for marketing authorisation holder, according to the relevant Bulgarian and EU legislation related to PV.

The current Bulgarian legislative documents related to PV (1 law, 1 regulation, 4 instructions prepared by Bulgarian Drug Agency (BDA)) and applicable EU PV legislation (2 Regulations, 1 Directive and 2 guidelines) were analyzed.

We have identified 17 basic process of monitoring of drug safety, which are needed to be managed and supervised by the marketing authorisation holder with regard to the pharmacovigilance.

Based on the ISO requirements for quality management systems, we have developed guidelines for the marketing authorization holders (MAH) which are intended to be used in ensuring patient safety, in clarifying the safety profile of medicinal products, when assessing the risk/benefit ratio, in ensuring the safe and rational use of medicines, and in fulfilling the MAH obligations required by regulatory authorities.

The developed guidelines are intended to support marketing authorization holders operating in Bulgaria to implement the legislative updates related to pharmacovigilance.

Key words: *quality management, pharmacovigilance, medicinal products, marketing authorization holder*

INTRODUCTION

Once a medicinal product is marketed, new information will be generated, which can have an impact on the benefits and/or risks of the product. Pharmacovigilance (PV) is the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long term and short term side effects of medicnal products. [14]

Evaluation of this information should be a continuing process, in consultation with regulatory authorities. Detailed evaluation of the information generated through pharmacovigilance activities is important for all products to ensure their safe use. The benefit-risk balance can be improved by reducing risks to patients through effective pharmacovigilance. The well established and adequately maintained PV system allows early detection of potential adverse events signals which is essential for patient safety. PV activities are currently subject of intense legislative changes. The PV effort in the European Union (EU) is coordinated by the European Medicines Agency (EMA) and conducted by the national competent authorities (NCAs). The main responsibility of the EMA is to maintain and develop the PV database consisting of all suspected serious adverse reactions to medicinal products observed in the European Community. The system is called EudraVigilance and contains separate but similar databases of human and veterinary reactions.[6] EMA requires the individual marketing authorisation holders, to submit all received adverse reactions in electronic form (save in exceptional circumstances). The reporting obligations of the various stakeholders are defined in the Community legislation. [5, 12,15]

The aim of the current publication is to propose a methodological approach to establish a PV system for marketing authorisation holder, according to the relevant Bulgarian and EU legislation related to PV.

MATERIALS AND METHODS

The current Bulgarian legislative documents related to PV (1 law, 1 regulation, 4 instructions prepared by Bulgarian Drug Agency (BDA)) and applicable EU PV legislation (2 Regulations, 1 Directive and 2 guidelines) were analyzed. A 4 step methodology was applied to establish the PV system. GAP analysis technique was applied in order to identify the level of compliance and as a first step of the PV system establishment. Second step was preparation of the standard operating procedures (SOPs), while the third step was implementation of written procedures, including distribution of SOPs and training activities. System audit was the 4th step which aimed to the verification of the level of compliance achieved.

RESULTS AND DISCUSSION

I. Review of applicable PV legislation

The relevant EU and Bulgarian local PV legislation is presented in Table 1.

Directive 2001/83 [4] concerns all medicinal products, although for pharmacovigilance it is most relevant to products authorised by the national, mutual recognition and decentralised procedures. It requires Member States to take all appropriate measures to encourage the health

care professionals to report suspected adverse reactions to the competent authorities and to have a PV system in place. The directive contain specific requirements regarding the PV Qualified Person (QP), exchange of PV information between the Member States etc.

Regulation (EC) No 726/2004 of the European Parliament and of the Council of 31 March 2004 [12] regulates the supervision and pharmacovigilance of centrally authorized medicinal products. It expands the criteria for reporting adverse reactions and increases the frequency of the periodic safety update reports (PSUR) following the initial placing of the product on the Community market and sets up a network for the electronic transmission of information to the authorities in the event of an alert relating to faulty manufacture or serious adverse reactions.

Volume 9A [15] has been prepared by the European Commission in close consultation with EMA, Member States and interested parties and is specifically related to pharmacovigilance of medicinal products for human use. It brings together general guidance on the requirements, procedures, roles and activities in this field, for both MAHs and Competent Authorities of medicinal products for human use and it incorporates international agreements reached within the framework of the International Conference on Harmonisation (ICH).

These 3 basic PV legislative texts are supplemented by Commission Regulation (EEC) 540/95 [3], which regulates the procedures concerning "suspected unexpected non-serious adverse reactions".

Another guideline which is relevant for marketing authorization holders in Bulgaria is **ICH Harmonized Tripartite Guideline on Pharmacovigilance Planning E2E** [8]. This guideline does not cover the entire scope of pharmacovigilance. It describes a method for summarising the important identified risks of a medicinal product, important potential risks, and important missing information, including the potentially at-risk populations and situations where the product is likely to be used that have not been studied pre-approval. It proposes a structure for a Pharmacovigilance Plan and sets out principles of good practice for the design and conduct of observational studies. The guideline was prepared by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH process and it is recommended for adoption by the regulatory bodies of the EU, USA and Japan.

Bulgarian local legislation consists of 2 legislative documents, the Law on medicinal products for human use and Regulation on adverse events reporting. They are harmonized with EU

legislation in general and contain some country specific requirements. [1,2] Besides there are 4 local instructions available on BDA website concerning reporting of adverse events from medical professionals, approval of public safety information, PSUR preparation etc. [7]

A new legislation on pharmacovigilance was published on 31 December 2010 in the Official Journal of the EU, consisting of a new Regulation [13] and a New directive [5]. It will become effective as of July 2012 and are not subject of this publication.

Table 1. Pharmacovigilance legislation in EU and Bulgaria

Type of documentation	Document identification	Basic requirements
EU legislation	**Commission Regulation (EC) No 540/95** [3]	Regulates the procedures concerning "suspected unexpected non-serious adverse reactions".
	Regulation (EC) No 726/2004 [12]	Regulates the PV activities for centrally authorized medicinal products.
	Directive 2001/83/EC [4]	Title IX Pharmacovigilance regulates PV activities with regard to adverse events reporting for medicinal products authorized through national, mutual recognition and decentralised procedures.
	VOLUME 9A, of The Rules Governing Medicinal Products in the European Union, Guidelines on Pharmacovigilance for Medicinal Products for Human Use [15]	Describes the legal basis of MAHs' obligations for PV, role and responsibilities of the MAH and the qualified person, requirements for PV system, submission of safety variations, inspections etc.
	ICH Harmonized Tripartite Guideline. Pharmacovigilance Planning E2E [8]	Intended to aid in planning pharmacovigilance activities, especially in preparation for the early postmarketing period of a new medicinal product. The main focus of this guideline is on a Safety Specification and Pharmacovigilance Plan that might be submitted at the time of licence application.
Bulgarian local legislation	**Law on medicinal products for human use** [1]	Harmonized with Regulation (EC) No 726/2004 and Directive 2001/83. Requires local contact person for PV activities.
	Regulation on adverse events reporting and PSURs [2]	Regulates the specific requirements concerning the adverse events reporting and PSUR preparation and submission.
Bulgarian Drug Agency instructions	**Instruction concerning paragraph 192 of the Law on medicinal products in human medicine** [7]	Dissemination of public information related to safety of medicinal products and BDA approval procedures.
	Additional guidelines concerning PSUR submission [7]	Advices on PSUR preparation, submission incl. covering letter template.
	Guidelines concerning reporting of adverse events from medical professionals [7]	Contains the most used PV terms, some practical advises, most frequently asked questions and answers, information evaluation, brief PV history etc.
	Guidelines concerning submission of urgent adverse events reporting according to article184 and article189 of the Law on medicinal products for human use [7]	Contains specific requirements concerning the PV system from the perspective of adverse events reporting.

II. Basic elements of PV system

As a result of the performed GAP analysis and review of applicable legislation, we have identified **17 basic processes for monitoring of drug safety**, which are needed to be managed and supervised by the marketing authorisation holder with regard to the pharmacovigilance.

Based on the ISO requirements for quality management systems [9-10], we have developed guidelines for the marketing authorization holders (MAH) which are intended to be used in ensuring patient safety, in clarifying the safety profile of medicinal products, when assessing the risk/benefit ratio, in ensuring the safe and rational use of medicines, and in fulfilling the MAH obligations required by regulatory authorities.

These guidelines cover the following processes:

- Adverse events reporting.

- Literature screening.
- Responsibilities of PV Qualified Person.
- Organization, performance and feedback of/from PV trainings.
- External communications (BDA, Ministry of health etc.)\
- PSUR writing.
- Third party agreements which may affect PV system.
- Signal detection and risk-benefit analysis.
- Archiving of PV documents
- Labelling changes.
- Crisis management.
- Compliance monitoring,
- Risk Management Plans.
- PV Audit
- Product complaints.
- Medical information.
- Post-marketing studies.

For each of the above processes a SOP is needed and process is audited at least once annually to check the compliance.

CONCLUSIONS

Pharmacovigilance is important part of marketing authorization holders' activities and is very important tools to ensure patient safety. The developed guidelines are intended to support the marketing authorization holders operating in Bulgaria to implement the legislative updates related to pharmacovigilance thus increasing the level of protection of human health.

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