

Monitoring of adverse drug reactions – the new regulations in Poland

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ABSTRACT

The results of analyses carried out all over the world clearly indicate that drug-induced side effects are the cause of 10 to 15% of all hospital admissions. The effectiveness of pharmacovigilance in the country depends mainly on the availability of information about the risks associated with the use of drugs in patients. Collecting data on adverse drug reactions depends largely on the type of system used in the country. Continuous monitoring of suspected adverse drug reactions is very important in detecting new or investigating changing risks and then their management. That process plays an essential role in the management

of risks that are already known. In view of the above, the aim of this article is to present the functioning of pharmacovigilance system in Poland, according to the latest amendment of the Pharmaceutical Law. The authors pointed out the definition of adverse drug reaction, characterised the system of pharmacovigilance in the European Union. There are also presented the rules of adverse drug reactions reporting in Poland, taking into account both existing so far, and new legislation.

Key words: medicinal product, adverse drug reaction, monitoring of adverse drug reactions

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INTRODUCTION

Continuous reporting of suspected adverse drug reactions in the European Economic Area helps to monitor the benefits and risks associated with the use of drugs and allows to detect emerging safety signals. The safety signal can be defined as new information related to adverse events or any other problems associated with the drug, which requires further studies. In the European Union these signals are detected through a regular analysis of adverse events report in the EudraVigilance system.

According to the Act of 6 September 2001, the Pharmaceutical Law, each application of a medicinal product for marketing authorisation should specify the description of the adverse event monitoring system, which will be implemented by the marketing authorisation holder and the statement confirming that the entity has at its disposal the services of the person who will be responsible for ongoing monitoring of the medicinal product safety, and that has a system that provides the possibility of immediate reporting of suspected adverse reactions in the territory of the Member States of the European Union or the Member States of the European Free Trade Association (EFTA) - parties of the European Economic Area or other countries. The description of possible side effects should also be provided in the Summary of Product Characteristics.

1. Adverse drug reaction - the definition

The World Health Organization (WHO) defines the adverse drug reaction (ADR) as harmful and unintended consequence of the drug application observed in doses used for the prevention, diagnosis or treatment [1]. A similar definition is given by the Polish Pharmaceutical Law, according to which the adverse effect of a medicinal product is any unfavourable and unintended effect of the drug.

There are highlighted two main types of side effects, so-called reactions of type A and type B. The probability of the occurrence of A-type reaction enhances with increasing doses of the drug, so that it can be minimised, while B-type reactions do not depend on the pharmacological properties of the drug or dose, so in order to remove these reactions, there is a need to discontinue treatment with that substance [2].

It is worth to pay attention to the definition of the serious adverse drug reaction and unexpected serious adverse drug reaction, stated in the Pharmaceutical Law. The serious adverse drug reaction is defined as an action that irrespective of the drug dose causes death of a patient, life threatening, the necessity of hospitalisation or its

prolongation, persistent or significant injury, illness, congenital anomaly, birth defects, or other action of the medicinal product that will be recognised as a serious event by the doctor. Unexpected serious adverse drug reaction is, however, any adverse reaction, which the nature or severity is not consistent with the data included in the Summary of Product Characteristics [3].

2. The monitoring of adverse drug reactions in the European Union

The European Union (EU) has implemented a rigorous safety evaluation system of the drug after its marketing authorisation. The system of pharmacovigilance in the EU includes:

1. National drug registration offices in the Member States,
2. The European Commission as the competent authority for medicinal products authorised through the centralised procedure in the European Union,
3. European Medicines Agency in charge of the medicinal products authorised through the centralised procedure and the coordination of the whole system.

The pharmacovigilance system in the European Union operates with the management and involvement of regulatory authorities in Member States, the European Commission and the European Medicines Agency. In some Member States, regional centres are in place under the coordination of the national competent authority [4].

Within this system, the Agency's role is to coordinate the EU pharmacovigilance system and to ensure the provision of advice for the safe and effective use of medicines.

The drug monitoring system in the European Union deals with the following tasks:

- collecting data from all available sources, including case reports on individual patients, epidemiological studies and clinical trials,
- data analysis and detection of possible signals involving new or changing risks,
- evaluation of risk management plans, case reports, test reports, periodic safety reports and review of benefits and risks presented by marketing authorisation holders,
- control of the marketing authorisation holders,
- risk assessment in terms of its probability, magnitude and risk factors,
- risk management, often through further research and efforts aimed at the limitation of the drug usage.

In addition, a marketing authorisation holder has a legal obligation to collect data continuously and carry out activities in the field of pharmacovigilance. Data must be transmitted to the competent authorities within a certain

timeframe, and emerging concerns about the risk-benefit ratio must be reported immediately. If it is necessary, the competent authorities may require further investigation. There are various official procedures for updating product information and implementation other security measures with varying degrees of urgency.

The European Medicines Agency plays a key role in the safety-monitoring of medicines in the EU. The main role of the Agency in this area is to support the coordination of the European pharmacovigilance system, providing information on the safe and effective use of medicines and management of the EudraVigilance system [5].

EudraVigilance is a web-based information system designed to manage information on safety reports. The European Medicines Agency launched EudraVigilance in December 2001. Since then, the system has extended to allow commercial and non-commercial sponsors to report suspected unexpected serious adverse reactions (SUSARs) occurring during clinical trials electronically.

The system is in full compliance with the specifications of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). It includes a fully automated safety and message processing mechanism using XML-based messaging and a large reference pharmacovigilance database incorporating an extensive query and tracking and tracing capability. Data from EudraVigilance are published in the European database of suspected adverse drug reaction reports.

This website allows users to view the total number of individual suspected side effect reports submitted to EudraVigilance for each centrally authorised medicine. Users can sort these reports by age group, sex, type of suspected side effect and outcome. EudraVigilance data are analysed at least every month. For some medicines it is done more frequently, at least every two weeks [4].

3. The adverse drug reactions monitoring system in Poland

3.1. The former situation

Pharmacovigilance in Poland bases on the following regulations:

- the Act of 6 September 2001 Pharmaceutical Law (Journal of Laws of 2001 No. 126, item 1381, as amended);
- the Act of 5 December 1996 on the professions of doctor and dental practitioner (Journal of Laws of 1997 No.28, item 152, as amended);
- the Regulation of the Minister of Health of 17 February 2003 on the monitoring of the

medicines safety (Journal of Laws 2003 No. 47, item 405).

The system of pharmacovigilance of medicinal products in Poland involved six basic functions:

1. collection, evaluation and processing of data on adverse drug effects, including information derived from spontaneous reports (spontaneous declaration is a declaration made by a health care professional), the information provided by the pharmaceutical companies and other sources (eg. World Health Organization);
2. cooperation with medical professionals in order to ensure the effective, proper and fair reporting of adverse effects;
3. receiving, cataloging and evaluation of spontaneous reports;
4. forwarding copies of spontaneous reports on the serious side effects to a marketing authorisation holder;
5. collecting data on the sale of medicinal products on the whole territory of Poland, sent by the marketing authorisation holder;
6. cooperation with other national and international institutions involved in the oversight of the medicinal products safety [6].

According to the Pharmaceutical Law, the marketing authorisation holder is required to indicate a person, whose duties include supervision of the medicinal product safety monitoring, keeping records of reported adverse reactions, and presenting to the President of The Office for Registration of Medicinal Products, Medical Devices and Biocidal Products specified reports:

- reports on individual cases of adverse drug reactions reported by a physician, dentist, veterinarian, pharmacist, medical representative, bearing in mind that the reports of serious adverse reactions should be presented immediately, no later than within 15 days after the date of being informed of that case,
- periodic reports on the safety of medicinal products, in accordance with the data included in the register of reported adverse reactions (every 6 months from the date of the first drug marketing authorisation in the world, every 6 months for 2 years from the date when the product was launched on the market, every 12 months for the next two years from the third year after the product was introduced on the market, and then every three years and, in special cases, at the request of the President of the Office),
- reports on security research, conducted after obtaining the marketing authorisation [7].

Under the former rules, reporting of adverse drug reactions should be made by doctors and pharmacists. Information on medicinal products are collected by the Department of Adverse Drug Reaction Monitoring of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. The adverse drug reaction registration form should include four key information:

- name of the medicinal product,
- description of the reaction (at least one side effect),
- data of the patient,
- data of the person reporting the event (personal data and contact) [8].

3.2. The introduced changes

The purpose of the Act amending the Pharmaceutical Law and some other acts [9], signed by the Polish president in October 2013, which entered into force on 25 November 2013, is to adapt the existing legal regulations in Poland to the provisions of the Directive 210/84/UE 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] and 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 [11]. The overall objective of the proposed changes was to increase the ability to detect adverse drug reaction.

The amendment of the Pharmaceutical Law involves change of adverse drug reaction definition. The drug will be considered as a health-threatening if patient's health deteriorates after taking the product, regardless of whether he will take the drug according to the label or he will take the wrong product or he will apply too high dose of the medicine [12].

In order to allow reporting of adverse drug reactions by patients and their guardians, the definition of the so-called a single case of adverse reaction is included in the Act. This facility will allow reporting of adverse reactions by them both to the persons performing medical profession and to the President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. The amendment of the Act also includes an obligation to report adverse drug reactions by emergency medical technicians, nurses, midwives, paramedics, laboratory diagnosticians, and pharmaceutical technicians who have been authorised to perform professional activities in the pharmacy. Similar responsibilities will be imposed on parallel importers.

Medical practitioners will be required to report adverse drug reactions to marketing authorization holders or to the President of the

Office, with particular reference to the adverse events of:

- medicinal products containing a new active substance authorised in any states during the five years preceding the application,
- complex medicinal products containing a new combination of active substances,
- medicinal products containing known active substance, but administered by the other way,
- treatment with a new pharmaceutical form of medicinal products,
- medicinal products which have gained a new indication,
- medicinal products which adverse reaction became the reason for the use of another medicinal product, medical procedure or method of treatment practised in patient,
- occurring during pregnancy or at birth.

Reporting a single adverse reaction should include:

1. initials, sex or age of the patient,
2. name of the person making the notification,
3. address of the workplace - in the case of medical professionals,
4. signature of the person making the application - if it is not transmitted by electronic means,
5. information on the reported medicinal product (at least the name of the product and a description of its adverse reaction).

A significant change will be the requirement to put the information on medicinal products in the European EudraVigilance database by certain institutions (the President of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products, marketing authorisation holders). The European EudraVigilance is intended to exchange the information on medicinal products and the potential negative consequences of their use, both between EU countries and other countries. Deadline for application of that information into the database will be 90 days since the President of the Office or manufacturer learned about the negative effects of the drug on the human body. In the case of severe adverse reactions that period will be shortened to 15 days.

Attention should also be paid to the principle resulting from amendments to the Pharmaceutical Law, indicating the absence of the obligation imposed on marketing authorisation holders to submit periodic reports on the safety of drugs in the case of reference medicinal products, homeopathic medicines, traditional herbal medicinal products or medicinal products containing substances with well-established medicinal. The President of the Office will be able to waive that requirement in the event of a shortage of information on the medicinal product safety.

The amendments to the Pharmaceutical Law, however, imposes some obligations on marketing authorisation holders, involving among others, the need to implement a risk management system concerning the use of medicinal products. That interventions should include treatment with the products, which for various reasons are not fully known, and prevention of their possible adverse reactions. The negligence of that obligation will result in an administrative penalty, which will replace the applicable criminal penalty.

CONCLUSIONS

The audit of the pharmacovigilance system in the Member States of the European Union carried out in 2010 showed that the supervision over the medicinal products safety was not effective enough.

Both in Poland and in other countries, notifications of side effects of the drugs are reported mainly by pharmaceutical companies (under so called “the safety reports”). Spontaneous reports represent only 30% of all notifications registered by the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products. It is particularly important while considering the fact that adverse drug reactions are one of the causes of death in the European Union and constitute up to 15% of all hospital admissions [13]. The fact that averagely 20% of all countries’ funds spent on health care financing is destined to treatment of drug-induced adverse reactions, confirms the importance of that problem.

Many adverse drug effects can be prevented. In this regard, the effective reporting of adverse drug reactions conditioned by the creation of an appropriate safety monitoring system involved all medicinal products used in patients, is particularly important. An effective solution seems to be pharmacovigilance using a computer system in which doctors, nurses, and pharmacists would have access to the patient's medical history. Such a system may help to identify potential risks related to their therapy. The great emphasis should also be paid to medical professionals as well as patients education. The quantity and quality of reported adverse reactions will depend on their awareness and sensitivity to disturbing symptoms [14, 15, 16].

Moreover, it is important not only to monitor the existing adverse effects, but also to prevent their occurring, including the use of “precautionary principle” according to which if there is probable, although poorly known, risk of adverse effects of new technology (in this case – drug), it is better not to implement it rather than risk uncertain but potentially very harmful consequences [17], which was suggested by

Sienkiewicz D., Kułak W., Okurowska-Zawada B. and Paszko-Patej G. in the article concerning adverse events of vaccination.

Conflicts of interest

The authors have declared no conflicts of interest.

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