Research Article

Main Challenges of the Development of Pharmacovigilance in the Republic of Kazakhstan

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Accepted on: 05-04-2016; **Finalized on:** 30-04-2016.

ABSTRACT

This article determines the key stages in the development of pharmacovigilance in the Republic of Kazakhstan (RK). Particular attention is paid to the functional challenges of the drug safety monitoring system at the present stage: regulatory procedures in the field of pharmacovigilance in the RK, reporting of domestic pharmaceutical manufacturers and health-care professionals, poor understanding of the involvement of patients, consumer reporting and the need to use information technology in the pharmacovigilance system.

Keywords: pharmacovigilance, drug safety monitoring, domestic/foreign pharmaceutical manufacturers, patients, consumers, monitoring of adverse effects, "yellow card".

INTRODUCTION

Drug safety and pharmacovigilance is a dynamic clinical and scientific discipline. The World Health Organization (WHO) defines pharmacovigilance as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem"[1]. It plays a key role in ensuring that doctors and patients have enough information to make a right decision when it comes to choosing a drug for treatment[2]. According to the WHO, an improper and uncontrolled use of drugs in self-medication is the cause of mortality among the population and ranks fifth in the world after injuries, diseases of the circulatory system, oncology and respiratory diseases. The most common causes of death are poisoning, overdose, adverse effects, incompatibility with other drugs. In order to prevent or reduce harm to patients and thus improve public health, there are mechanisms to evaluate and monitor the safety of medicines[3]. While major achievements of pharmacovigilance discipline have taken place in the West, not much has been achieved in Kazakhstan. However, more and more clinical trials and clinical activities are being conducted in Kazakhstan, and there is a great need to understand and implement the pharmacovigilance system. Currently, the pharmacovigilance system progresses from year to year.

MATHERIALS AND METHODS

The authors have analyzed the most important foreign and national standard acts, which regulate the pharmacovigilance in the Kazakh Republic. There were also examined the sources, which highlight the main aspects of pharmacovigilance policy in Kazakhstan.

RESULTS AND DISCUSSION

Main historical stages of the pharmacovigilance system formation

Pharmacovigilance was officially presented in December 1961 with the publication of a letter (report) in the Lancet by the Australian doctor William McBride, who first suggested a causal link between serious fetal deformities (phocomelia) and the thalidomide product, used during pregnancy as an antiemetic and sedative agent[4]. In 1968, the WHO implemented a pilot project "Programme for International Drug Monitoring", aimed at pooling data on adverse drug reactions (ADRs) from around the world. In particular, the main objective of the WHO Programme was and is to identify warning signals as soon as possible. The term "pharmacovigilance" was proposed in the mid-70s by the French group of pharmacology and toxicology to determine the activities contributing to "Assessment of risks and side effects potentially associated with drug treatment"[5].

When Kazakhstan was part of the Union of Soviet Socialist Republics (USSR), the pioneer in the field of drug efficacy and safety monitoring was the Department of Accounting, Systemization and Express Information about Adverse Drug Effects (1969), which in 1973 was transformed into the All-Union Organizational and Methodological Center for Study of Adverse Drug Reactions. This organization was focused on identifying, recording, analyzing ADRs, informing health-care professionals about ADRs and methods of their prevention, and participated in international pharmacovigilance activities. After the collapse of the USSR, this organization was abolished in 1991 along with the Ministry of Health of the USSR, which completely stopped the work on monitoring the effectiveness and

safety of drugs in the country and for a long time there was no monitoring center of drug safety[6].

The Government Decision No. 790 of June 25, 1996 approved the list of republican state enterprises which included the "National Center for Expertise of Drugs, Medical Devices and Medical Equipment". Its main subject is the implementation of industrial and economic activities in the health field on ensuring drug safety, efficiency, and quality, as well as research into the development of new original drugs, pharmacy and pharmacology[7].

On October 2, 2002, in order to improve work in the field of drug safety, efficacy and quality, the Government Decision of the Republic of Kazakhstan No. 108 made a decision to reorganize the Republican state enterprise "The medicines center "Dari-Darmek" of the Ministry of Health of the Republic of Kazakhstan by its conversion to the Republican state enterprise "National Center for Expertise of Drugs, Medical Devices and Medical Equipment" of the Ministry of Health of the Republic of Kazakhstan (RSE NCED MD and ME)[8].

The period from 2005 to 2008 is considered to be a period of the formation and development of the system of ADRs monitoring in the country. During this period a regulatory framework for public pharmacovigilance system has been established, seminars-trainings for medical and pharmaceutical workers have been conducted in order to implement the spontaneous method of collecting information about ADRs. In 2008, Kazakhstan was accepted as a full member of the WHO Program for International Drug Monitoring.

Since the beginning of 2009, a new stage has started in the development of pharmacovigilance, which is aimed at improving and harmonizing the requirements of regulatory documents in drug safety control. Previously, according to the Decree of the Ministry of Health of the Republic of Kazakhstan No. 52 of February 14, 2005 "On approval of the Instruction on monitoring adverse drug reactions" only medical or pharmaceutical workers could report on ADRs. Since November 2009, in accordance with the Decree of the Ministry of Health of the Republic of Kazakhstan No. 647 "On Approval of Rules for monitoring adverse drug reactions in medical and pharmaceutical organizations", the monitoring of ADRs is conducted:

- in medical and pharmaceutical establishments;
- during the conduct of clinical investigations;
- by holders of registration certificates.

The Decree of the Minister of Health and Social Development of the Republic of Kazakhstan No. 421 of May 29, 2015 approved the rules for the performance of pharmacovigilance of medicinal products and monitoring of ADRs, medical devices and medical equipment.

In 2016, in connection with the start of operation of the overall pharmaceutical market of the Eurasian Economic Union (EEU) it is planned to adopt common Rules of good pharmacovigilance practices (GVP), elaborated by an international working group of experts of the Union member states.

There has been no such document in the member countries of the EEU before. National pharmacovigilance systems were functioning on the basis of different legal acts and guidelines. The organization and effectiveness of these activities varied considerably depending on cultural characteristics, the degree of elaboration of the legislation, the level of staff training, access to and development of communication channels, etc. After joining the EEU, the domestic legislation of the member states should be harmonized with international treaties and other supranational legal acts, hence the rules and requirements of GVP will be used by all members of the Union, which leads to the unification of pharmacovigilance systems.

Main functional problems of the pharmacovigilance system in the Republic of Kazakhstan

Despite the existence of legislative acts in the field of pharmacovigilance in the Republic of Kazakhstan, *the first-priority problem today is the low activity of manufacturers, related to the identification, registration and transmission of information about ADRs*.

According to the RSE NCED MD and ME, the following data have been identified for the three reporting years (2013-2015): 1916 cases in 2015, 1669 – in 2014, and 1784 – in 2013, of them from the manufacturers: 488 cases – in 2015, 320 cases – in 2014 (data for 2013 and 2012 are not available) (see Figure 1).

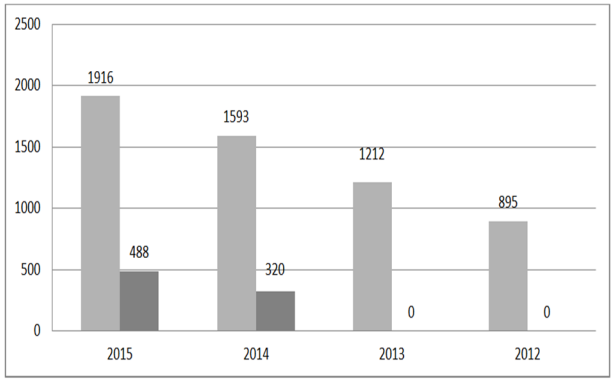

Figure 1: Total number of registered reports for 2012-2015

As reported by the RSE NCED MD and ME, the majority of reports on ADRs comes from large foreign companies with representation in the Republic of Kazakhstan: "Sanofi-Aventis Group", "F. Hoffmann-La Roche Ltd.", "GlaxoSmithKline", "Aegis", "Bayer". The activity for drug safety monitoring of the majority of domestic manufacturers is still in its infancy, but one can already identify a number of companies which were able to form a pharmacovigilance system within a short time: "Santo

Polpharma Group", "VIVA", "Nobel". In general, the activity of domestic manufacturers for providing spontaneous reports on ADRs remains at a low level.

In addition to supplying information about ADRs, manufacturers are required to submit periodic drug safety reports - periodic safety update reports (PSURs) which contain the information on the safety of a specific medicine, derived from spontaneous reports, the literature data and clinical investigations within a certain period. Periodic reports should include a scientifically based evaluation of the benefit-risk balance of a medicine[9].

The PSUR is provided by RSE NCED MD and ME in accordance with the following standard periodicity:

- every six months over two years after registration;
- annually - over the next three years;
- thereafter - every three years;
- or after receiving a report from the central office (if applicable);
- in the future - in the subsequent re-registration of the medicine - every five years; immediately upon request of the authorized organization.

The second problem of the monitoring system of drug safety in Kazakhstan – the low activity of health practitioners in providing spontaneous reports. The reasons for this, according to experts, are: the fear of persecution, a lack of knowledge in the field of pharmacovigilance, the low interest of doctors, a lack of time for filling in the forms and sending reports[10,11].

The number of maps-reports by regions (regional health departments) (numerical and percentage value) for the period from 2012 to 2014 is presented in Table 1.

Table 1: Number of region-wise maps-reports

Names of cities and regional centers	Total	%
	For 3 years	For 3 years
Almaty	1516	40,97
Pavlodar	761	20,57
Kostanay	315	8,51
Astana	292	7,89
Taraz	276	7,46
Petropavlovsk	121	3,27
Kyzylorda	104	2,81
Shymkent	86	2,32
Kokshetau	82	2,22
Aktobe	69	1,86
Karagandy	30	0,81
Uralsk	12	0,32
Taldykorgan	10	0,27
Semey	3	0,08
Aktau	2	0,06
Atyrau	*1*	0,03
Total	**3700**	**100 %**

The workers of pharmaceutical care (pharmaceutical chemists, pharmacists) who have a direct contact with both drugs and consumers are also an important link in the system of pharmacovigilance. It should be taken into consideration that the country has a large level of self-treatment of the population. According to the results of the survey of different target groups in Kazakhstan, 92% of respondents resort to self-treatment[12].

The third problem is the lack of understanding of the role of patients and consumers of drugs (the absence of consumer reports).

In recent years, in a number of developed countries the role of patients as a link of the pharmacovigilance system has significantly increased[13,14]. In 2008 at the 31th meeting of representatives of the national pharmacovigilance centers of the member countries of the WHO Program for International Drug Monitoring (Uppsala, Sweden) a working group was established to discuss the training of patients in informing appropriate safety control bodies about ADRs[15]. The experience of some countries with respect to consumer participation in the work of pharmacovigilance has shown that the quality of reports derived from the population depends on awareness on the safety of drugs and the level of organization of the work of this structure in each country. The experts indicated the need to create the information databases on ADRs, received from consumers, as well as the handling system of such reports (verification and analysis of data); to run educational programs and to collaborate with patient organizations. In 2012, the WHO published Guidelines for the creation of "consumer reporting" system[16]. The WHO stresses that consumer reports are an additional source of information on adverse reactions, especially on the previously unknown ones and cannot be considered as an alternative to reports of health-care professionals.

In some countries an extensive information campaign contributes to the activity of patients in terms of providing reports on ADRs - leaflets in pharmacies, journal articles for patients and consumers, Internet resources. Websites of health agencies have special pages for patients and consumers, which in an intelligible form provide the information on topics of medicine, drugs, drug safety, news in the field of health law.

Finally, the fourth problem is the lack of an integrated information system for all participants in the monitoring of adverse effects.

Analysis of the current situation in health care indicates the need to improve the system of collection and identification of ADRs in the pharmacovigilance system and the lack of an integrated information system for all participants in the monitoring of adverse effects[17]. In accordance with the State Program for Health Development of the Republic of Kazakhstan "Densaulyk", approved by the Decree of the President, the development of informatization of the healthcare

industry will be continued in 2016-2019. This confirms the relevance of the implementation of IT-technologies in health care in general and in pharmacovigilance in particular, the active use of which will systematize the data and allow an in-depth analysis by the incidence of adverse effects, gender, age and other characteristics to be conducted in a given period of time. The results of analytical reports will allow to make decisions on the improvement of ADRs management and the development of appropriate recommendations.

The global trend in health development is closely connected with the development of IT-technologies. In the Organization for Economic Cooperation and Development an active process of introducing new information and communication technologies is under way to greatly simplify the relationship between doctor and patient. The development of smart medicine is becoming a major trend in the industry.

In Kazakhstan, despite the remarkable progress in the implementation of modern information technology in the health field, the creation of a number of portals and the improvement of computer technology supply, the developed and implemented web applications are aimed at solving specific issues of financing and management of the health system. All the existing portals and sites should be structured.

CONCLUSION

Thus, at the present time there is a number of problems in the pharmacovigilance system of the Republic of Kazakhstan which need to be solved. The successful development of pharmacovigilance in the short term depends on the improvement of the normative legal regulation, the practical implementation of modern methods of pharmacovigilance, including the use of IT-technologies, and the formation of a responsible attitude to drug safety in all the subjects of drug circulation. An integrated approach to pharmacovigilance issues at the present stage is an important development goal in the field of drug safety.

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Source of Support: Nil, **Conflict of Interest:** None.