

Pharmacovigilance in the Russian Federation: Construction, Development and Reforms of PV System

Gildeeva GN* and Belostotsky AV

Pharmaceutical Science Department, I.M. Sechenov First Moscow State Medical University, Russia

*Corresponding author: Gildeeva GN, Pharmaceutical Science Department, Chair of Organization and Management in the Field of Drugs Circulation, I.M. Sechenov First Moscow State Medical University, Russia, Tel: +7495656 2717; E-mail: gilgeln@gmail.com

Received date: Apr 14, 2017; Accepted date: Apr 25, 2017; Publish date: May 04, 2017

Copyright: © 2017 Gildeeva GN, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Abstract

The review outlines the current issues of Pharmacovigilance System in the Russian Federation, namely present state of regulatory aspects of PV system in Russia, regulatory requirements in Russia and in Eurasian Economic Union, review of the causes of under-reporting of ADRs. Specific focus has been made on topical issues such as a harmonization of the requirements to the Pharmacovigilance System, currently underway in Russia, the issue of Guidelines on Good Pharmacovigilance Practice (GVP) in the Eurasian Economic Union. These actions are aimed at improving and harmonizing the rules governing the main aspects of the Pharmacovigilance System in the Russian Federation. Also the review analyses one of the most important aspects in development of a new Pharmacovigilance System-the attitude towards pharmacovigilance in patients and healthcare professionals.

Keywords: Pharmacovigilance; Adverse reactions; Drugs' safety monitoring; Eurasian Economic Union; Roszdravnadzor

Introduction

Currently, the use of modern medicines can significantly improve the quality of life of patients, improve the prognosis and reduce mortality in many diseases.

On the other hand, the introduction of innovative drugs with high biological activity into clinical practice, growing sensitization of the population to biologically active and chemical substances, irrational use of drugs, polypharmacy, medical errors, the presence on the pharmaceutical market of a large number of generics, some of which do not meet the quality criteria, increased the risk of development of undesirable Adverse Drug Reactions (ADR).

The available data show that ADRs are a frequent cause of hospitalization, require additional treatment and can even lead to a death of patients.

Today, the use of medicines in clinical practice is based on the mandatory assessment of the benefit/risk ratio, when the likely benefits of using medicines significantly outweigh the potential risk.

This requires not only convincing evidence of the effectiveness of medicines, but also the studying of their safety. Monitoring of drug's safety is carried out within the framework of the pharmacovigilance system.

The World Health Organization (WHO) describes "pharmacovigilance" as "the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem" and defines it "as an obligatory investment in the future public health of the territory."

Pharmacovigilance is an important tool for determining the potential risks and benefits of the medicines.

Establishment and Evolution of the State Russian System for Monitoring of Safety and Effectiveness of Medicines

Pharmacovigilance (PV) is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects (definition of World Health Organization, 2002).

Before the marketing authorization of a medicine, data of its safety and efficacy is limited to the results from pre-clinical and clinical trials due to a small number of patients and a limited period of time.

Some Adverse Drug Reactions (ADRs) may not be seen until it has been used on a larger population and on patients with different concomitant diseases and medications. That is why it is extremely important that the safety and efficacy of all medicines is carefully tracked throughout their life cycle.

Therefore PV is a vital tool which allows health authorities to proceed with assessment of benefit/risk ratio of a medicine, after it has been put on the market and potentially detect infrequent and serious ADRs that were not detected during clinical trials. PV can also identify new safety signals related to product quality and/or changes in the use of a medicine, when it is shown to work well in different groups of patients or for different conditions. To achieve this goal it is necessary to set a strong national PV system. Therefore, it is extremely necessary to implement PV system in all periods of medicines lifecycle-before authorization and, more significantly, at the post-authorization stage.

As stated by experts in the field of PV-"in Russia until recently the problem of drugs safety although not entirely ignored, was obviously doomed to take the back seat" [1]. PV system was destroyed in the 1990s and could not gain momentum to ensure effective functioning until now, which is why it was pointless to talk about drugs safety in Russia at that time [2].

The success of drugs' safety monitoring depends on the ability to design an efficient system of monitoring, registration and analysis of data on ADRs. Considering experience of the Russian Federation in

this area, it has all preconditions to achieve effective operation of PV system; however, certain issues are to be improved, which will be considered in details further in this article.

PV system in the USSR was created after the thalidomide disaster detection (1956-1962) [3,4]. Approximately at the same time International Program on Drug Safety was initiated by WHO. In 1967 World Health Assembly Resolution (WHA 20.51) was adopted.

It marked the beginning of International Drug Safety Monitoring System. Meanwhile in 1969 in USSR ministerial department for registration, classification, and information on ADRs was created, carrying all functions of the Federal PV Centre [5].

This centre in general was performing all the functions, which are assigned to the drug safety monitoring system nowadays-the identification and registration of ADRs, analysis and systematization of ADRs data on domestic and foreign drugs, submission of this information to Health authorities for urgent measures (changing a product information or prohibition of the use of certain medicines), prevention of ADRs occurrence, wide education of a medical community with the issues of ADRs and increasing of physicians' qualification in this area [6]. Further, after the abolition of this centre in 1991, necessity for the monitoring of ADRs was considered legislatively.

Russia was the only country in Europe that for nearly 7 years had not centre for the medicines' safety and effectiveness monitoring; the International Foundation for Safe and Efficient Drugs decided to set up such a centre [7].

In 1997 the Federal Centre for Drugs Adverse Effects Studying of the Ministry of Healthcare of the Russian Federation and a few regional centres were founded for collecting and registering ADRs.

In 1998 according to the Federal Law "On Medicines" No. 86 dated 22.06.1998, the duty of ADRs monitoring was assigned to the medical staff [8].

During this time, owing to the initiative of Vladimir Lepakhin, the head of the Federal Monitoring Centre for Drug Safety, the network of regional centres for Drug's Safety supervision began to form in the Russian Federation. Nevertheless, the system of collecting information on ADRs was imperfect, and its biggest drawback in the Russian Federation, as well as around the world, was a low awareness and activity of HCPs (doctors, pharmacists, healthcare officials).

In 2008 the Federal Service on Surveillance and Control in the field of healthcare of the Russian Federation (Roszdravnadzor) issued a few recommendation letters. These letters regulated the establishment of Regional Monitoring Centres for Drug's Safety (letter dated 29.01.08 No. 01I-29A/08), organization and functions of these centres (letter dated 07.10.08 No. 01I-653/08), the detailed procedure for collecting and processing of information about ADRs with a focus on the regions (letter dated 22.07.08 No. 01I-455/08).

A template to report ADRs in routine practice of medical and prophylactic treatment facilities was also proposed (letter dated 15.08.08 No. 01I-518/08).

Simultaneously a direct mechanism of ADRs reporting was set up, avoiding the stage of territorial analysis and decision making in regional centres, by directly reporting to national Roszdravnadzor database (letter dated 02.12.08 No. 01I-752/08).

This letter also recommended providing availability of basic tool of PV-notification about ADR in every inpatient and outpatient medical card. Unfortunately, this method was not put into practice fully, and at present time only not numerous healthcare centres abide by these recommendations.

Besides, despite rather successful operation of Regional Centres for Drug's Safety Supervision, capable to detect issues of drug's safety, to educate, to carry out its own expertise of the received messages, actually activities of such centres were withdrawn from the existing PV system of the Russian Federation by the Roszdravnadzor letter, dated 28.11.11 No. 04-1192/11, about the revocation of the previous letters with the exception of the last (from 02.12.08 No. 01I-752/08). Monitoring and expertise of drugs safety acquired strictly centralized nature [9].

Since September 2010 the circulation of medicines has been regulated by Federal Law No. 61-FZ "On Circulation of Medicines". In this law a safety of medicines is referred as the cause for rejection / termination of drugs registration. In addition, articles 64-66 of chapter 13 are devoted directly to "Monitoring of the medicine's safety in circulation in the Russian Federation" [10].

It was followed by the Order No. 757n, dated 26.08.10, which approved the centralized procedure for the registration and expertise of ADRs [11].

According to accepted legislative acts, all parties of medicine circulation (health care professionals, patients, manufacturers of medicines and Marketing Authorization Holders (MAHs)) have been entrusted with an commitment to report to the Roszdravnadzor on all cases of ADRs (included and not included into the instructions for medical use), as well as on serious adverse reactions, unexpected serious adverse reactions, cases of drug interactions with other agents encountered during clinical use of the drugs.

For this purpose in 2008 centralized unified database of ADRs, Automated Information System (AIS-Roszdravnadzor) was launched.

PV in pharmaceuticals companies and marketing authorization holders was governed by the most harmonized with international law "Guidelines for the organization of the Drug's Safety Monitoring System (PV) in drug manufacturers or MAHs (approved by Roszdravnadzor from 05.10.2009).

Despite the fact that the requirements for the provision of documents on drug's safety monitoring are absent in Federal Law No. 61, this manual describes the necessary organization principles of PV system in MAH.

There registered the duty of drug manufacturers to provide a detailed description of PV system: the presence of the qualified person responsible for

PV (QPPV), the organizational structure of the PV department, computerized systems and databases, information on trainings on PV, risk management plans, Periodic Safety Update Reports that should be provided within strict deadlines.

This manual is a direct reflection of the existing European system. In such an organization of PV system, can be observed the features of harmonization of the Russian legislation with the European one.

Moreover on the 23th of December, 2014 at the meeting of the Supreme Eurasian Economic Council an "Agreement on Common

Principles and Rules for The Circulation of Drugs within Eurasian Economic Union (EAEC)” was signed by the Member States of EAEC.

On the 3 days of November, 2016 by the decision #87 of the Council of the Eurasian Economic Commission, “Guidelines on good PV practice in Eurasian Economic Union” was approved.

The new provisions not only tighten the requirements for submission of both immediate and periodic reports, but also introduce requirements for pharmaceutical companies to provide documents such as risk management plan, which will largely ensure safety of medicinal products, registered and outstanding on territory of the EAEC.

The regulation also requires pharmaceutical companies to assign a Qualified Person in one of the countries to be responsible for all the other relevant EAEC countries, in which the company operates.

But despite the active efforts of government in the field of development of the national PV system, the elaboration of legal regulation and practical implementation of modern methods of PV, the system has challenges and shortcomings and requires further improvement.

On April 1, 2017, the Order #1071 "On Approval of the Procedure for the Implementation of Pharmacovigilance" dated February 15, 2017 came into force, which:

1. Harmonized with the Guidelines on Good Pharmacovigilance Practice of the Eurasian Economic Union;
2. Describes the organization of the ADRs data expertise incoming to Roszdravnadzor;
3. Describes the detailed requirements for MAHs, clinical research organizations and medical organizations to the urgent reporting of certain types of ADRs;
4. Describes the requirements for submitting of PSUR and DSUR;
5. Describes the requirements for MAHs for submitting of RMP at detection new drug safety problems;
6. Contains the templates of the main documents (notification of ADR, PSUR, DSUR), harmonized with the ICH and GVP of the EAEC.

The chronology of legislative changes in the Russian pharmacovigilance system is presented in Table 1.

| The main changes in the Russian PV system | Period |
|---|------------|
| Creation of ministerial department for registration, classification and information on ADRs which was performing all functions of the Federal PV Centre | 1969 |
| Abolition of ministerial department for registration, classification and information on ADRs | 1991 |
| Foundation of the Federal Centre for Drugs Adverse Effects Studying of the Ministry of Healthcare of the Russian Federation and a few regional centres | 1997 |
| According to the Federal Law "On Medicines" No. 86 dated 22.06.1998, the duty of ADRs monitoring was assigned to the medical staff. | 22.06.1998 |
| Roszdravnadzor issued the recommendation letter dated 29.01.08 No. 011-29A/08, which regulated the establishment of Regional Monitoring Centres for Drug's Safety | 29.01.2008 |
| Roszdravnadzor issued the recommendation letter dated 22.07.08 No. 011-455/08, which described the detailed procedure for | 22.07.2008 |

| | |
|---|------------|
| collecting and processing of information about ADRs with a focus on the regions | |
| Roszdravnadzor issued the recommendation letter dated 15.08.08 No. 011-518/08, which proposed a template to report ADRs in routine practice of medical and prophylactic treatment facilities | 15.08.2008 |
| Roszdravnadzor issued the recommendation letter dated 07.10.08 No. 011-653/08, which regulated the organization and functions of the regional centres | 07.10.2008 |
| Roszdravnadzor issued the recommendation letter dated 02.12.08 No. 011-752/08, which described the direct mechanism of ADRs reporting national Roszdravnadzor database avoiding regional centres | 02.12.2008 |
| Launching of centralized unified database of ADRs-Automated Information System of Roszdravnadzor (AIS-Roszdravnadzor) | 2008 |
| "Guidelines for the organization of the Drug's Safety Monitoring System (PV) in drug manufacturers" or MAHs was approved by Roszdravnadzor on 05.10.2009. This manual describes the necessary organization principles of PV system in MAH | 05.10.2009 |
| Roszdravnadzor issued the letter, dated 28.11.11 No. 04-1192/11, about the revocation of the previous letters with the exception of the last (from 02.12.08 No. 011-752/08) | 28.11.2011 |
| In 2010 circulation of medicines has been regulated by The Federal Law of the Russian Federation No. 61-FZ, enacted on 12.04.2010 "On circulation of drugs". Articles 64-66 of chapter 13 are describe the responsibilities of MAHs, HCPs and regulatory authorities in monitoring of the medicine's safety | 12.04.2010 |
| Roszdravnadzor issued the Order No. 757n, dated 26.08.10, which approved the centralized procedure for the registration and expertise of ADRs | 26.08.2010 |
| "Agreement on Common Principles and Rules for The Circulation of Drugs within Eurasian Economic Union (EAEC)" was signed by the Member States of EAEC. Article 12 of this document is devoted to Pharmacovigilance system in the territory of the Member States | 23.12.2014 |
| The decision #87 of the Council of the Eurasian Economic Commission approved "Guidelines on good PV practice in Eurasian Economic Union" | 03.11.2016 |
| Roszdravnadzor issued the Order #1071 "On Approval of the Procedure for the Implementation of Pharmacovigilance" dated February 15, 2017 | 01.04.2017 |

Table 1: Chronology of legislative changes in the Russian pharmacovigilance system.

The Main Problems of the Functioning of the PV System in the Russian Federation and Solutions

The development and authorization of the medicine aims to make effective and safe medicines available for their use as quickly as possible. Thus, regulatory authorities and pharmaceutical companies are continuously searching for more risk-based methods that allow faster access while still ensuring adequate efficacy and safety. Such methods rely upon supplementary data, being collected after post-marketing authorization approval, to study the issues that were not clear before the marketing approval and to confirm the benefit/risk profile. [12].

The Spontaneous Reporting System (SRS) is the most globally used tool for detecting the signals from post-marketing supervision of drugs' safety and efficacy. But deficiencies of SRS include

underreporting, incomplete information on ADRs, low activity of Russian pharmaceutical companies in respect of the identification, registration and submission of ADRs information, low activity of medical staff in providing spontaneous reports, extremely low public awareness in the matters of drugs safety and sensitivity to external factors, poor quality of Periodic Safety Update Reports and Risk Management plans [13].

According to Roszdravnadzor report, approximately 30% of the reports on ADRs do not meet all requirements, necessary to conduct comprehensive analysis of causal relationship between use of a drug and appearance of an adverse reaction, as well as to evaluate the severity of ADRs.

A great deal of submitted reports does not provide information about diagnosis that reasoned drug prescription, no information about concomitant medication. In many cases following primary report delivery there is no information about outcomes of the ADR. Quite often reporters fail to correctly assess the seriousness of ADRs.

Under-reporting and low quality of ADRs reports are a major drawback of the PV system for several reasons, including [14,15]:

- Complacency (i.e., the belief that very serious ADRs are well documented by the time a drug is marketed);
- Insecurity (i.e., the belief that it is nearly impossible to determine whether a drug is responsible for a particular adverse reaction);
- Diffidence (i.e., the belief that reporting an ADR should only be done if there is certainty that it is related to the use of a particular drug);
- Indifference (i.e., the belief that a single case that an individual physician might observe could not contribute to medical knowledge);
- Ignorance (i.e., the belief that it is only necessary to report serious or unexpected ADRs);
- Lack of awareness of the requirements for reporting;
- Difficulty in accessing reporting forms;
- Fear of medico-legal consequences.

Large-scale pharmacoepidemiological study on the awareness of doctors and pharmacists on PV issues showed an insufficient level of their knowledge [16].

Less than half of the 600 respondents correctly formulated the term "PV" as control and supervision activities on the quality, efficiency and safety of drugs. Every third healthcare professional thought that it is executive authority that controls the production and turnover of medicines. The rest did not know the definition nor had difficulties with answer. The term "adverse reaction" was correctly interpreted only by 13% of doctors and 46% of pharmacists.

Almost all respondents encountered with cases of ADRs. But only 24% of doctors and 5% pharmacy workers submitted ADR reporting form to regulatory authorities. Most of the doctors, when handling issues with ADRs, tried found out the cause-and-effect relationship, built only upon their personal opinion, and cancelled the drug, sometimes making a record in the medical card. And only 14% of physicians had appealed for Clinical Pharmacologist advice.

The study also showed that the majority of doctors and pharmacists were showing interest in the problem of pharmacotherapy safety. They noted that at congresses at various levels only isolated reports reflected these problems, the rest are devoted to the results of clinical trials, the

benefits of some drugs and other disadvantages, as well as schemes and treatment standards.

The necessity of special training programs on safety of drug therapy indicated 91% of pharmacists and 79% of physicians. The rest found it sufficient to listen to lectures in postgraduate education programs.

In the recent years, also the role of patients as an element of PV system has been considerably accentuated [17,18].

It is essential that every physician and pharmacist consider the work to identify ADRs, its proper registration and informing the regulatory authorities as a professional responsibility. They does not have to decide whether exactly this medication caused some adverse reaction, it is enough just to assume the existence of possible causal relationship.

In Russia barriers preventing patients' active participation in PV system include immensely low awareness of the drug consumers with safety issues. Consequently, an ordinary consumer facing a problem of ADRs reports this issue only to its physician, who often prescribes suspension of suspected medicine without further reporting on the ADR [19].

To solve these problems significant amount of work is needed not only in engaging HCPs and patients in understanding their role in ADRs reporting, but also to explain the purpose of a risk management [20].

Experience, gained by some countries, shows the need to create databases on ADRs for consumers to report ADRs and for HCPs for verification and analysis of data, also development of training and educational programs for patients [21].

Patients should understand that they are responsible to comply with the treatment schemes and recommendations in the instructions for medicinal use and to be aware of important risks. A good realization by patients of the potential benefits and risks of a medicine is apparently should have a positive effect on quality of ADR reports.

For HCPs, the emphasis should be on education and training, both at the undergraduate and graduate level, to recognize ADRs and knowing what, how and where to report them, e.g. by practicing how to fill out a Report form. Healthcare professionals also have to stay informed about changing regulations and evolving procedures and/or techniques. Hence, continuous education of HCPs is needed, with the aim of improving their awareness of the importance of ADRs and the risk factors that lead to them, in order to reduce the incidence of ADRs and to increase the number of reported suspected ADRs.

At the clinical level, one of the ways to improve medication safety is to develop a culture of safety in the healthcare organization. For example, the organization's leadership should maintain a clear commitment to safety by emphasizing that safety takes priority over production or efficiency; employee job descriptions and performance evaluations should include a component for participation in safety initiatives that are supported by recourses, rewards and incentives.

Doctors, nurses, pharmacists and other HCPs should communicate more with patients about the risks, contraindications and possible ADRs from medications and instruct on steps that should be taken when they experience an ADE.

But all initiatives are meaningless without the contributions of all stakeholders-also regulators and MAHs.

Along with the collection and analysis of spontaneous reports of ADRs another important element in ensuring the safe use of drugs is active actions of MAHs aimed at preventing of known risks.

MAHs must continuously monitor the safety and efficacy of its medicines; inform the authorities of any changes that might have an impact on the marketing authorization, and to ensure that the product information is up-to-date. MAHs' responsibilities also should include providing all the available information, such as the results of clinical trials and post-authorization studies, as well as reporting changes in the use of a medicine. It is also appropriate to ensure that all relevant information collected on the safety of a medicine is taken into consideration when the licence is being renewed [22].

Regulatory authorities may also require additional monitoring for specific medicines, for example an obligation to conduct a post-authorization safety study or to conditions or restrictions with regard to the safe and effective use of the medicinal product that will be specified in the Risk Management Plan (RMP). RMP is usually required for new active substances, biosimilars and medicines for paediatric use and for medicines involving a significant change in the marketing authorization, including a new manufacturing process of a biotechnologically-derived medicinal product [23].

MAHs are responsible for:

- Continuous monitoring and evaluation of PV data and information on the risks of the medicine;
- Submission of data on ADRs to the regulatory authorities;
- Communication with the regulatory authorities on any information that may impact the benefit/risk ratio;
- Update of the product information and provide the relevant safety information to HCPs and patients.

According to the Order No. 757n from August 26, 2010 of Ministry of Health of Russia Marketing Authorization Holders must submit to the regulatory authorities Periodic Safety Update Reports (PSURs).

The PSUR allows a periodical but exhaustive evaluation of the worldwide safety data of a marketed drug or biological product. The PSUR can be a significant source for the identification of new safety signals, changes in the benefit-risk profile, an indicator for the need for risk management activities, as well as a tracing mechanism to monitor the effectiveness of such activities [24].

Review of received by Roszdravnadzor PSURs made possible to identify common defects in them such as absence of review of scientific publications related to safety issues; failure to trace resolutions of foreign regulatory agencies operating in the field of healthcare, taken into account of changes introduced to the drug safety profile on account of received reports on associated ADRs.

In this regard, in assistance to MAHs in 2013 Roszdravnadzor published "Guidelines for the preparation of Periodic Safety Update Reports of Medicines".

The proposed new methodological recommendations of PSUR format is adapted to the version, which described in the Manual of the International Conference on Harmonization (ICH) E2C (R1) ICH Topic E2C (R1) "Clinical Safety Data Management: Periodic Safety Update Reports for Marketed Drugs".

It is important to note some of the key features of these recommendations:

PSUR should include information about all adverse reactions, regardless of whether MAH considers these reactions associated with the use of this drug or not.

MAH may decide not to include into PSUR those ADRs on which a causal relationship with the drug is denied by both the sender of the spontaneous reports and MAH.

At the same time in PSUR must be given details of the alleged amount of drug intake (exposure) that will quantify the risks of adverse reactions or safety concerns.

It is important to note that a detailed assessment of the safety profile of medicines is not possible without the use of the entire spectrum of PV methods, including post marketing interventional or observational clinical studies, epidemiological studies, maintenance of the application registers of the drug.

In addition, the responsibility of manufacturers related to PV must be ensured with lawsuits about harm compensation, reputation risks and financial sanctions.

In Russia domestic MAHs currently have a relatively "passive" role in terms of PV. Their PV obligations are limited to reporting on certain events that have become known to the MAH and submitting regular reports to the regulatory authorities.

The new Regulation requirements will motivate MAHs to proactively identify and validate safety signals, submit additional safety information to the regulatory authorities and audit PV systems on a regular basis.

Current Indicators, Reflecting Activities of Pharmacovigilance in Russia

Till now, the method of SRS stands for the principal model of PV system in Russia, the same way in most world countries. This method provides for collecting of data on all medicines circulating in the market in the real-life conditions without limitations over observation period with all groups of patients. To ensure successful functioning of SRS method, all stake-holders of the process should be active and database should have an adequate capacity. The minimum level providing for viability of the SRS method is measured to be 100 reports per 1 million citizens. Average number of the reports submitted to AIS-Roszdravnadzor system per 1 million Russian citizens reached 162 in 2015. It should be noted, since 2008 the number of annual reports submitted to AIS-Roszdravnadzor system was constantly growing (107 reports on the average), but this amount is still much lower comparing to the number of reports send in the European Community or in the USA (the norm of WHO-600 reports per million). However, Russia is a leader in CIS countries in terms of the number of reports submitted to WHO (in 2014 Uppsala Monitoring Centre-UMC-published in *VigiBase* 1,442 reports received from Russia). In addition to that, in the period 22.07.2012-10.05.2016 AIS-Roszdravnadzor system was annually supplied with 3571 drugs Periodic Safety Update Reports (PSUR), that is approximately 900 per year given the number of registration certificates(32 000), <10% of MAHs report PSUR.

Discussion and Conclusion

In the Order from 13.02.2013 No. 66 (edition dated 07.04.2016) "On approval of the Strategy of drug provision of the population of the Russian Federation for the period up to 2025 and its implementation plan" developed Ministry of Health of Russia, presents the main

directions of development of PV service, which in particular includes further improvement nationwide database of undesirable ADRs, the introduction of procedures of operative change of drug status (suspension/revocation of the registration certificate), and changes in standards of medical care in the identification of serious and/or unexpected adverse events; organization of constant monitoring of clinical trials in the Russian Federation in order to identify any ADRs; promptly informing healthcare professionals about the identified side effects of drugs and changes in the profile of drug safety (through online resources, medical periodicals and so on).

These provisions are particularly relevant in the conditions of ongoing reform of the domestic pharmaceutical industry, which provides for the replacement of imported drugs by native analogues for development their own original products. Assessment of the risks, associated with their use, safety, and benefit/risk ratio will be possible only with the effective functioning of the Russian national PV system at all levels, including a motivated and active in this area of MAHs, regulatory authorities, healthcare professionals and patients [25,26].

An integrated approach to PV issues at the present stage is an important vector of development of innovative models of the domestic pharmaceutical industry.

Also from April 1, 2017, the procedure for the realization of pharmacovigilance by Roszdravnadzor has come into effect.

Approved Order No. 1071, dated 15.02.17 "On Approval of the Procedure for the Implementation of Pharmacovigilance", not simply defines the pharmacovigilance procedures, but describes as detailed as possible the procedure for conducting pharmacovigilance. Among the ways and mechanisms used by Roszdravnadzor in this area: Analysis of information on the side effects of drugs provided by subjects of drug circulation, adverse reactions, serious adverse reactions, unforeseen adverse reactions in the use of medicines, individual intolerance, lack of efficacy, and also on other facts and circumstances that pose a threat to human life or health in the use of medicines.

The order lists all cases when the subject of drug circulation should provide information on the ADR or lack of therapeutic effect of the medicinal product, as well as about the serious ADR to the drug which is studied in the clinical trial.

Undoubtedly, time, experience and close cooperation of the government bodies with all stakeholders are the main components of success in the implementation of the robust Pharmacovigilance System in the Russian Federation.

References

1. Astakhova AV, Lepakhin VK (2008) Adverse Reactions and Safety monitoring (2nd edn.). EKSMO Publishing, Moscow.
2. Khoseva EN, Norozova TE (2013) Problematic aspects of pharmacovigilance systems in the Russian Federation at the present stage. *Good Clinical Practice*.
3. Lenz W, Knapp K (1962) Thalidomide embryopathy. *Dtsch Med Wochenschr* 15: 1232-1242.
4. McBride WG (1961) Thalidomide and congenital abnormalities. *The Lancet* 278: 1358.
5. Babayan EA (1976) Some aspects of the Adverse Drug Reaction. *Side Effects of Drugs* 6: 7-10.
6. Astakhova AV, Lepakhin VK (2004) Adverse reactions and drug's safety monitoring: Guidelines for pharmacovigilance.
7. Ovchinnikova EA (2003) Role of drug's safety monitoring in resolving the issue of drugs rational use. *Good Clinical Practice* 4: 88-95.
8. Federal Law on Medicines (1998) Russian Federation.
9. Kolbin AS, Zagorodnikova KA, Burbello AT (2012) PV in The Russian Federation and in the European Union in the light of new EU directives. Are there any changes, waiting for us?
10. Federal Law on circulation of medicine (2010) Russian Federation.
11. On approval of the of medicines safety monitoring procedure (2012) Ministry of Health Care of The Russian Federation.
12. Good Pharmacovigilance Principles and Considerations for Biotherapeutic Safety (2015) International Federation of Pharmaceutical Manufacturers and Associations.
13. Tandon VR, Mahajan V, Khajuria V, Gillani Z (2015) Under-reporting of adverse drug reactions: A challenge for Pharmacovigilance in India. *Indian J Pharmacol* 47: 65-71.
14. Biagi C, Montanaro N, Buccellato E, Roberto G, Vaccheri A, et al. (2013) Underreporting in PV: An intervention for ItalianGPs (Emilia-Romagna region). *Eur J Clin Pharmacol* 69: 237-44.
15. Inman WH (1996) Attitudes to adverse drug reaction reporting. *Br J Clin Pharmacol* 41: 434-435.
16. Khoseva EN, Morozova TE, Ermakov DA, Oshorova SD (2013) Issues on control of medication safety in clinical practice: position of patients and medical staff. *The doctor-postgraduate* 2: 203-212.
17. Van GK, Berg DV (2004) Patients' Role in Reporting Adverse Drug Reactions. *Expert Opin Drug Saf* 3: 363-368.
18. Foster JM, van der Molen T, de Jong-van den Berg L (2007) Patient Reporting of Side Effects may provide an Important Source of Information in Clinical Practice. *Eur J Clin Pharmacol* 63: 979-980.
19. Khoseva EN, Morozova TE, Andrushishina TB (2012) Safety and Efficacy of Today's Remedies from Patients' Viewpoint. *Clin Pharmacol Ther* 21: 30-34.
20. Edwards IR, Lindquist M (2009) Understanding and Communicating Key Concepts in Risk Management: What do we mean by Benefit and Risk? *Drug Saf* 32: 449-452.
21. Meeting of representatives of national centres for Pharmacovigilance of the countries participating in WHO program for drugs safety international monitoring: review data (2009) *Drugs Safety and Pharmacovigilance*.
22. Directive 2010/84/EU of the European Parliament and of the Council (2010) *Official J European Union*.
23. Regulation (EU) No 1235/2010 of the European Parliament (2010) *Official J European Union*.
24. Klepper MJ (2004) The periodic safety update report as a Pharmacovigilance tool. *Drug Saf* 27: 569-578.
25. On approval of the Strategy of drug provision of the population of the Russian Federation for the period up to 2025 and its implementation plan (2013) Ministry of Health of Russia.
26. Gildeeva GN, Yurkov VI (2016) Pharmacovigilance in Russia: Challenges, Prospects and Current State of Affairs. *J Pharmacovigil* 4: 1-5.