

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

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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 related to functioning of the system designed to monitor drugs safety nowadays, reporting and accountability of pharmaceutical products manufacturers and medical staff, the role played by regional centers for drugs safety monitoring, insufficient understanding of the part taken by patients in the system of Pharmacovigilance. Further to the foregoing, appropriate consideration has been given to the prospects of Russian Pharmacovigilance System and its harmonization with global practice.

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." Pharmacovigilance systems are widely recognized as important tools in the regulatory process for medicines, for protecting public health and an integral component of patient health-care. The WHO describes a national Pharmacovigilance system "as an obligatory investment in the future public health of the territory".

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Today in Russia, the new pharmacovigilance system is a big step forward in ensuring a new quality of knowledge about medicines and the possibilities of their safe use. It is expected that the new system will be seriously different from the one that existed for the last 10 - 15 years. The level and quality of pharmacovigilance will significantly increase, and the approach to analysis of drug safety profile will change, as well as the attitude towards monitoring of side effects of drugs of all participants in the process - medical staff, pharmaceutical companies, regulators and patients. And also, it is expected that there will be a new technical component of pharmacovigilance, without which it is impossible to obtain reliable information about side effects.

One of the most important aspects in development of a new system is to change the attitude towards pharmacovigilance, both in patients and physicians: reporting on ADRs is not a sign of a physician's mistake, but, on the contrary, it is a physician's concern about a patient. Therefore, there should be no fear of administrative responsibility and punishment. Reports on ADRs help make the use of medicines safer by making appropriate changes to the INSTRUCTION on medical use of medicinal products. Time, experience and close cooperation of the government bodies with all stakeholders are the main components of success in the implementation of the new pharmacovigilance system in the Russian Federation.

Overview of Main Historical Stages of Pharmacovigilance System in the Russian Federation.

In accordance with the definition of World Health Organization, Pharmacovigilance (PV) is defined as the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or (WHO, 2002).

Before a medicine is authorized for use, evidence of its safety and efficacy is limited to the results from clinical trials. This means that at the time of a medicine's authorization, it will only have been tested in a relatively small number of patients for a limited length of time.

Some side effects or adverse reactions (ADRs) may not be seen until a very large number of people have received the medicine and used it over longer time periods. This only happens once healthcare professionals (HCPs) begin prescribing. It is therefore vital that the safety of all medicines is monitored throughout their use in healthcare practice.

PV is necessary as it allows health authorities to continue to assess benefit/risk throughout the life-cycle of a medicine and potentially detect rare and serious ADRs that were not detected before marketing authorization. PV can also identify new safety signals related to product quality and/or changes in use and prescription patterns. In order to do so it is important that a robust national PV system is established. 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 is not worth talking about drugs safety in Russia at present [2].

The future of drugs safety to a greater extent depends on the ability to design an efficient system of monitoring, registration and analysis of data on adverse reactions. Considering historical experience, Russia has any and all premises and prerequisites to warrant effective operation of PV system created; however, certain topical aspects need to be resolved, which issues would be discussed in more detail further in this review.

PV system in the USSR was created after the thalidomide disaster detection [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 Center [5].

This center 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 center in 1991, necessity for the monitoring of ADRs was considered legislatively.

Russia was the only European country that for almost 7 years had no centre for drugs safety monitoring; the initiative to set up such a centre has been also launched by the International Foundation for Safe and Efficient Drugs [7].

In 1997 the Federal Center for Drugs Adverse Effects Studying of the Ministry of Healthcare of the Russian Federation was founded along with a few regional centers for filing of 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 Center for Drug Safety, the network of regional centers 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 related to the subject matter of organization of PV system in the Russian Federation.

They regulated the establishment of Regional Monitoring Centers for Drug's Safety (letter dated 29.01.08 No 01И-29А / 08), organization and functions of these centers (letter dated 07.10.08 No 01И-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 01И-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 01И-518/08).

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

This letter also recommended to provide availability of basic tool of PV – notification about ADR in every inpatient and outpatient medical card. Regretfully, this mechanism was not put into practice in its entirety, and presently only isolated healthcare centers adhere to these recommendations.

Besides, despite rather successful operation of Regional Centers 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 centers 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 01И-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 drugs circulation (physicians, pharmacists, patients and drugs consumers, manufacturers of medicines and marketing authorization holders (MAHs)) have been charged with an obligation to report to the Federal Service on Surveillance and Control in the field of healthcare of the Russian Federation on any and all instances of adverse effects not included into the prescribing information, as well as on serious adverse reactions, unexpected undesired effects observed at the background of drugs use, particulars of interactions with other agents encountered in the scope of clinical studies conducting and clinical use of the drugs.

To succeed in attaining the goals set, Automated Information System (AIS-Roszdravnadzor) was launched in 2008, to become unified centralized database of ADRs in Russia.

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 2015 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 3rd of November 2016 by the decision # 87 of the Council of the Eurasian Economic Commission, "Guideline on good PV practices 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 appoint a QPPV in one of the countries, in which they operate within the EAEC, to be responsible for all the other relevant EAEC countries.

It will also make certain products subject to additional safety monitoring and will expect manufacturers to take a more active role in the area of PV (for example Biotherapeutic Medicines).

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.

The main problems of the functioning of the PV system in the Russian Federation and ways of solutions.

As described previously, the ability to conduct PV is an important tool for health authorities to continuously assess the benefit/risk throughout the lifecycle of a medicine. Product development and subsequent authorization aims at making medicinal products available that have been demonstrated to be effective and safe. At the same time, however, it is important to ensure that medicines are made available as quickly as possible to patients that need them. Thus, national regulatory agencies and pharmaceutical industry are constantly looking for more risk-based approaches that allow earlier access while still ensuring adequate efficacy and safety. Such approaches rely on

additional data, being generated after post-marketing authorization approval, to clarify the issues that were unclear at the time of marketing approval and to confirm the benefit/risk profile, based on the results of application in clinical practice [12].

Among various PV systems, the spontaneous reporting system (SRS) plays a central role to detect signals from post-marketing surveillance of drugs. SRS is the most widely and globally used. But drawbacks of spontaneous reporting include underreporting, incomplete information, 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, somewhat 30% of the reports with information about observed ADRs does not contain data necessary to conduct adequate and comprehensive analysis of cause and effect relationship between administration of a drug and development of an adverse reaction, as well as required to evaluate the severity of ADRs.

Many submitted reports provide no information about indications for therapeutic use that reasoned drug prescription, no data on diagnosis identified for a patient, and no information about concurrent medication treatment. In many instances following primary report delivery, Roszdravnadzor remains uninformed about outcomes of the adverse reaction occurred. Quite often applicants fail to perform own evaluation of causal relationship between drug use and development of an adverse reaction, or fail to correctly assess the severity of such an adverse effect.

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 or 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 regulator 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 canceled 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, obstacles impeding patients' active participation in PV system include extremely low familiarization of the public with drugs safety issues and unavailability of omnipresent opportunities to use computer-based and internet technologies. Consequently, an ordinary consumer facing a problem of drugs adverse reaction is capable to report this issue only to its attending physician, who often dictates discontinuation of suspected drug without further reporting on the ADR [19].

In order to address these problems considerable effort is needed in not only engaging HCPs and patients in understanding their role in ADRs reporting, but also to explain why risk management is needed and how these safety risks should be considered in the context of their treatment [20].

Experience, gained by some countries in regards to participation of consumers in the functioning of PV system, has shown that quality of reports submitted by the public depends upon its awareness of drugs safety issues and particular level of operations arrangement of PV in the given country. Experts have stressed the need to generate databases on ADRs submitted by consumers along with setting up of a system of handling such a feedback (stipulating for verification and analysis of data), implementation of training and educational programs and collaboration with patient societies [21].

PV reporting systems should be easy to use to allow reporting by any party including patients and HCPs and well-structured to facilitate the meaningful analysis of ADR data.

Patients also have the responsibility to comply with the treatment schedules and recommendations in the label and to be aware of important risks. Although much of the focus for ADR reporting has been centered on the regulatory authorities, the manufacturers responsible for the medicines themselves and the reporting healthcare practitioner, PV systems are opening up to more direct input from patients themselves as well as other representative bodies. A good understanding by patients of the potential benefits and risks of a medicine is likely to have a positive effect on reporting of ADRs and compliance with suggested risk minimization activities.

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.

Even the best designed PV system and all initiatives to encourage HCPs and patients for assistance in reporting of ADRs 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 should be responsible for continuously monitoring the safety of its medicinal products for human use, for informing the authorities of any changes that might have an impact on the marketing authorization, and for ensuring that the product information is kept up-to-date. As medicinal products for human use could be used outside the terms of the marketing authorization, the MAHs' responsibilities should include providing all the available information, including the results of clinical trials or other studies, as well as reporting any use of the medicinal product which is outside the terms of the marketing authorization. It is also appropriate to ensure that all relevant information collected on the safety of the medicinal product for human use is taken into account when the marketing authorization is being renewed [22].

Competent authorities may also require additional monitoring for specific medicinal products for human use that are subject to the 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. Risk management plans are normally required for new active substances, biosimilars and medicinal products for pediatric use and for medicinal products for human use involving a significant change in the marketing authorization, including a new manufacturing process of a biotechnologically-derived medicinal product [23].

MAHs record all suspected adverse reactions occurring in EAEC, and which are brought to their attention spontaneously by the patients or HCP, or occurring in the context of post-authorization study. MAHs take in consideration any reporting of suspected adverse reaction carried out by electronic means or by any other appropriate means, to patients and healthcare professionals.

With the exception of reports of suspected adverse reactions contained in the national network of PV, the MAH should submit electronically to the EAEC database information on all suspected serious adverse reactions occurring in the EAEC, within 15 days following the day on which the holder concerned gained knowledge of the event.

In summary, MAHs are responsible for:

- Continuous monitoring of PV data and scientific evaluation of all information on the risks of the medicinal product.
- Submission of accurate and verifiable data on ADRs to the competent authority.
- Effective communication with the competent authority on any information that may impact the benefit/risk balance.
- Update of the product information to reflect all scientific knowledge and communication of relevant safety information to HCPs and patients.

According to the Order No757n dated August 26, 2010 of Ministry of Health of Russia MAH must submit to the competent authorities the information on suspected adverse reactions of a medicinal product, in form of a periodic safety update reports (PSURs).

The PSUR was designed to be a stand-alone document that allows a periodic but comprehensive assessment of the worldwide safety data of a marketed drug or biological product. The PSUR can be an important source for the identification of new safety signals, a means of determining changes in the benefit-risk profile, an effective means of risk communication to regulatory authorities and an indicator for the need for risk management initiatives, as well as a tracking mechanism monitoring the effectiveness of such initiatives. For these reasons, the PSUR can be an important PV tool [24].

Review of received by Roszdravnadzor PSURs made possible to identify common defects in them.

In the scope of PSUR preparation, the concerned parties sometimes ignore analysis of scientific publications related to safety issues of the active pharmaceutical ingredient of the drug; there are instances of failure to trace resolutions of foreign regulatory agencies operating in the field of healthcare, taken in consideration 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 E 2 C (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 will urge MAHs to proactively identify, validate and action product safety signals, submit additional safety information (obtained from international and national sources) to the regulatory authorities and audit PV systems on a regular basis.

Since the new Regulation appears to be generally harmonized with the EU regulations, multinational companies should be able to apply their PV standards and procedures used in the EU to the EAEC market, subject to making only minor amendments to reflect the distinct local requirements. Previously Russian national legislation provided for different standards of reportable events, thus creating an additional burden for multinational companies.

Another issue deals with participation of Regional Centers for Drugs Safety Monitoring in the process of State PV System development. One of the possible options to involve regional centers into the process, considered by specialists of Roszdravnadzor, is to accredit them as experts’ facilities conducting primary evaluation of data on adverse reactions. The primary experts’ assessment referred above can contribute to improvement of the quality of information provided in respect to drugs safety. Besides, regional centers for safety supervision are capable to render consulting assistance to medical staff with respect to the issues of safe and rational pharmacotherapy.

For effective PV, global standards and guidelines are needed as well as free exchange of information regarding ADRs on a local, regional or global level. Such exchange has been made easier by the standardization of the minimum criteria for a meaningful adverse reaction report.

Current indicators, reflecting activities of Pharmacovigilance in Russia.

So far, the method of spontaneous reports stands for the principal layout of PV in Russia, similarly to the approach in place in most world countries. This pattern provides for gathering of data on all drugs circulating in the market in the real-life conditions without limitations over surveillance period, as actually used with all groups of patients. To ensure successful functioning of spontaneous reports

method, the reporting parties should be rather active, not to mention adequate capacity of the database (meaning in other terms the number of reports filed). The minimum level providing for viability of the spontaneous reports method is considered to be 100 reports per 1 million citizens. Mean number of the reports submitted to AIS-Roszdravnadzor system per 1 million Russians reached 162 in 2015. Of note, during 8 years' term (the database was launched by the end of 2008) the number of annual reports uploaded to AIS-Roszdravnadzor system was constantly rising (in 2008 this value was about 0.74—meaning just 107 reports on the average); however, this value is still much lower comparing to the number of reports filed in the European Community or in the USA (the norm of WHO - 600 reports per million). On the other hand, Russia has taken the lead in the post-Soviet space from the viewpoint 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 furnished with somewhat 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 Conclusions

In the Order from 13.02.2013 No66 (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].

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, these new implementations into the legislative framework of the pharmacovigilance system will improve today's state of affairs in the sphere of patients interests safeguarding, facilitate interplay at the international arena in this particular field and ease understanding of foreign manufacturers from the viewpoint of activities to be conducted at entering Russian market.

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