

## Pharmacovigilance in Russia: Challenges, Prospects and Current State of Affairs

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### Abstract

This review provides an insight into the main historical milestones of development and narrates on current state of affairs of the system of pharmacological vigilance in Russia. Specific focus has been made on topical issues related to functioning of the system designed to monitor drugs safety nowadays: regular procedures in the field of pharmacovigilance in the Russian Federation, reporting and accountability of pharmaceutical products manufacturers and medical staff, the role played by regional centres for drugs safety monitoring, insufficient understanding of the part taken by patients/consumers in the system of pharmacovigilance, lack of adequate surveillance over safe use of drugs during pregnancy. Further to the foregoing, appropriate consideration has been given to the prospects of Russian pharmacovigilance and its harmonization with global practice.

**Keywords:** Pharmacovigilance; Adverse reactions; Good Pharmacovigilance practice; Roszdravnadzor

### Post-Evaluation of Main Historical Milestones of Pharmacovigilance System Construction in the Russian Federation: The Pros and Cons

Control implemented over safe use of drugs is considered to be a priority direction in the field of healthcare development in the countries worldwide. According to World Health Organization (WHO), adverse reactions (ADRs) are included to the top ten mortalities in many countries, while outlays related to treatment of their consequences often outscore the cost of pharmacotherapies. Magnitude and urgency of the problem of the safety of drug therapies contributed to enactment in many countries of earmarked legislation applicable in the field of pharmacovigilance, obliging manufacturers of drugs to report to public healthcare authorities on the instances of encountered adverse reactions to drugs [1].

As stated by experts in the field of pharmacovigilance, 'in Russia until recently the problem of drugs safety although not entirely ignored, was obviously doomed to take the back seat' [2]. Pharmacovigilance 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 [3].

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. Taking into account historical experience, one might conclude that Russia has any and all premises and prerequisites to warrant effective operation of pharmacovigilance system created; however, certain topical aspects need to be resolved, which issues would be discussed in more detail further in this review.

Pharmacovigilance system in the Russian Federation has almost semicentennial history that started from the disclosure of 'thalidomide tragedy' and conception of the world system for monitoring of drugs safety to the present day. However, a battery of reorganizations, abolitions, obliterations and revivals could not help impacting its functional efficiency [4].

The pharmacovigilance system in Russia was established in 1969 right after the publication of the World Health Assembly resolution 20.51 on initiation of international monitoring of ADRs in a form of ministerial department for registration, classification, and information on ADRs, which was carrying all functions of the Federal Pharmacovigilance Centre [5].

This institution was abolished in 1991 along with the Ministry of Healthcare of the USSR, which effect totally suspended the work focused on monitoring of safety and efficiency of drugs for almost 7 years. Russia was the only European country that for a longer period of time 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 [6].

Later on in Russia the Federal Centre for Drugs Adverse Effects Studying of the Ministry of Healthcare of the Russian Federation was founded (1997) along with a few regional centres for filing of adverse reactions to drugs. Owing to the efforts exerted by these centres, database has been generated with a view to gather information about ADRs in Russia received on account of spontaneous reports.

Initially, the duty of ADRs monitoring was assigned to the medical staff in Russia in 1998; however, the system of ADRs data acquisition failed to operate properly to the full scale in view of poor awareness of healthcare professionals of this issue.

A new impetus in pharmacovigilance system development in Russia dates back to 2007, when the Federal Centre for Drugs Safety

Monitoring was founded on the basis of Roszdravnadzor (the Federal Service on Surveillance and Control in the field of healthcare of the Russian Federation). The Federal Centre has taken care of drugs safety monitoring and conducted experts' examinations of the facts, figures and circumstances of adverse reactions occurrences.

From 2008, regional centres for drugs safety supervision started to grow in numbers in Russia. Then Roszdravnadzor issued a few recommendation circulars related to the subject matter of establishing pharmacovigilance system in the Russian Federation; particularly, the authority suggested to launch a template to report ADRs in routine practice of medical and prophylactic treatment facilities (healthcare centres) [7-9].

Another important although not fully implemented measure was a proposal to appoint medical officers at all healthcare centres, liable for monitoring of safety and efficiency of drugs, and to introduce a record form 'Report on Adverse Reaction(s) to a Drug' to every medical history and outpatient case record, stipulating for imperative filling regardless of actual reporting on ADRs observed. Regrettably, this mechanism was not put into practice in its entirety, and presently only isolated healthcare centres adhere to these recommendations. Besides, despite rather successful operation of regional centres for drugs safety supervision capable to locally detect drugs safety issues and dealing with independent experts' examination of drugs, in fact activities of such centres were put on hold. From that time, the functions of drugs safety monitoring became rigorously centralized in Russia [10].

Another series of reformations in the system of pharmacovigilance was reasoned by a new Federal Law 'On Circulation of Drugs' enacted in 2010.

In pursuance of the Federal Law passed, the parties to drugs circulation 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 to the drugs leaflets, 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 [11].

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. According to the provisions of newly adopted legislation, all parties to drugs circulation shall perform as the sources of spontaneous reports on adverse effects (viz. physicians, pharmacists, patients and drugs consumers, manufacturers of medicines and holders of registration certificates).

Apart from spontaneous reports coming from various sources, at the preapproval stage (during clinical studies performance), the study sponsor shall be bound to update AIS-Roszdravnadzor system with expedited reports containing relevant data on:

- Any and all locally registered (i.e., reported at Russian centres and facilities) serious unexpected effects related to the study drugs observed in the scope of clinical trials on going in the territory of the Russian Federation.

- Any and all serious unexpected effects related to the study drugs reported in other countries where clinical trials are conducted with participation of Russian centres and facilities.

- Any and all locally registered (i.e., reported at Russian centres and facilities) lethal outcomes, including fatalities not associated by the investigator and the sponsor with the use of study drugs.

Primary expedited reports on unexpected adverse reactions related to the study drugs ending up in patient's death or posing a threat to patient's life, as well as reports on all fatalities registered in Russian centres and facilities shall be provided in 7 days after the study sponsor was made aware of any such episode. Additional information shall be submitted within 8 following days.

Reports on serious unexpected adverse reactions that did not cause patient's death neither endangered patient's life shall be delivered as soon as practicable, but in any case not later than in 15 days after making the study sponsor aware of the issue.

In a set of recent significant documents applicable in the field of pharmacovigilance, one should highlight guidelines issued by Roszdravnadzor to address drugs manufacturers and registration certificate holders with a view to regulate the duties of informing the Federal authorities about the instances of adverse reactions as spontaneous reports and about adverse reactions registered during clinical studies conducting, as well as duties of submitting drugs Periodic Safety Update Reports (PSUR).

Further to the foregoing, the guidelines addressed the work of a subdivision responsible for the activities in regards to pharmacovigilance in the structure of drugs manufacturing companies (providing guidance on appointment of an employee responsible in the company for pharmacovigilance issues, organizational chart of pharmacovigilance unit, ADRs database, programs and schedules for training of the company's personnel in the field of drugs safety, risks management plans, timeframes set for provision of drugs Periodic Safety Update Reports (PSUR), etc.) [12-15].

At the present moment, core functions concerning arrangement of drugs safety and efficiency monitoring system in Russia have been completely assigned to the Federal Service on Surveillance and Control in the field of healthcare.

Today, primary objectives and main lines of business of this regulatory authority (Roszdravnadzor) include search for and analysis of information on drugs safety, scientific and methodic activities related to drugs safety expertise, training and educational activities in the field of drugs safety, international co-operation, preparation of experts opinions and information reference materials on adverse reactions and drugs safety [16].

The Federal Service on Surveillance and Control in the field of healthcare keeps register of ADRs and effects analysis of reports on ADRs, defines causal relationships over all reports received; if so required, Roszdravnadzor requests additional information from regional centres needed to enable comprehensive evaluation of the reports; carries out assessment of compliance of available information on drugs safety and efficiency with data included to guidance on medicinal use of drugs along with assessment of the impact of such additional information on risk-benefit ratio in the scope of drug use; reviews suggestions and opinions of clinical pharmacologists employed by regional centres, carries out consultations and conducts methodic activities. Further to the above, domestic pharmacovigilance system in Russia incorporates 60 regional centres for drugs safety supervision, of which 35 facilities stand for subdivisions of drugs quality control centres; about one third of them have been founded on the basis of

medical and prophylactic treatment facilities. Business activities of regional centres are regulated by local healthcare authorities [17].

### **Russian Pharmacovigilance System Operation: Principal Issues and Solutions**

Despite of enactment of relevant statutory instruments in the field of pharmacovigilance in the Russian Federation, today's fundamental issue deals with lower activity of Russian manufacturers with respect to exposure, registration and reporting of data on adverse reactions to drugs [18].

According to Roszdravnadzor, about half of all spontaneous reports on ADRs is delivered from healthcare centres, regional centres for drugs safety monitoring and drugs quality control centres located in big cities of Russia.

The second half of reports is submitted to the database of the Federal Service on Surveillance and Control in the field of healthcare from pharmaceutical companies, mainly from major foreign manufacturers holding representative offices in the territory of the Russian Federation, such as Sanofi Aventis Group, F.Hoffmann-La Roche Ltd., GlaxoSmithKline, Servier Laboratories, Schering-Plough, Astra Zeneca.

Activities in the area of drugs safety monitoring are still in the infancy stage with most national manufacturers; however, there are a few domestic companies that succeeded in rapid formation of an appropriate pharmacovigilance system at their facilities. On the whole, efforts of national manufacturers in respect to furnishing of spontaneous reports on adverse reactions remain at a low level.

The second issue of drugs safety monitoring system in Russia is low activity of practical healthcare professionals concerning submittals of spontaneous reports on ADRs. The root causes outlined by the experts include poor motivation of the physicians, shortage of time required to fill and send the template forms, fear of prosecution and insufficient knowledge in the field of pharmacovigilance [19,20].

Roszdravnadzor draws special attention to the necessity of healthcare centres work intensification, importance of changing the understanding of the issue on the part of most physicians, as well as managers of medical and prophylactic treatment facilities and responsible officers of public healthcare authorities, currently prevailing in regards to direct relation of ADRs with medication errors and malpractices, which concept domination paves the way for hushing up of encountered drugs adverse effects.

At the same time, there is a need to set up adequate workforce capacity of pharmacovigilance services at major healthcare centres on account of enhancement of clinical pharmacologists training. The level of ADRs reporting can also be elevated by means of designing simple and user-friendly intuitive interface of web network resources meant for gathering data on drugs safety from healthcare professionals.

Another important element of pharmacovigilance system is pharmacies employees dealing directly with drugs and working in contact with consumers. Regretfully, in Russia pharmacists' involvement to drugs safety monitoring is almost negligible; spontaneous reports to surveillance authorities are sent by very few [21].

The third issue deals with participation of regional centres for drugs safety monitoring in the process of State Pharmacovigilance System development. One of the possible options to involve regional centres

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 centres for safety supervision are capable to render consulting assistance to medical staff with respect to the issues of safe and rational pharmacotherapies.

The forth issue deals with insufficient understanding of the role played by patients and consumers of drugs in the structure of pharmacovigilance in Russia. In the recent years, the role of patients as an element of pharmacovigilance system has been considerably accentuated [22,23].

Experience gained by some countries in regards to participation of consumers in the functioning of pharmacovigilance 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 pharmacovigilance 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 [24].

In Russia, obstacles impeding patients' active participation in pharmacovigilance 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 [25].

The fifth issue of pharmacovigilance system in the Russian Federation is related to the quality of submitted spontaneous reports on ADRs. 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.

The sixth today's issue prevailing in the field of pharmacovigilance deals with quality and quantity of drugs Periodic Safety Update Reports (PSUR). Despite of considerable growth of the numbers of PSUR submitted, their totals still fall beyond the number of drugs registered in the territory of the Russian Federation of both domestic and foreign manufacturing origin.

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 the situation of finding certain changes in the safety profile of a particular pharmaceutical product, many manufacturers do not consider such options of lowering risks of the drug administration as implementation of active monitoring, conducting of observational (surveillance) studies, enhancement of informational support of healthcare professionals and patients with respect to safe use of the drug. Moreover, it should be emphasized that this approach is routinely applied in daily practice of foreign pharmaceutical manufacturers and is capable to ensure appropriate degree of drugs risks control and management in the period of drugs circulation in the pharmaceutical market.

### **Current Indices Reflecting Activities of Pharmacovigilance in Russia**

So far, the method of spontaneous reports stands for the principal layout of pharmacovigilance 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-Roszdraznador 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-Roszdraznador 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. 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 of 2014–2015 AIS-Roszdraznador system was annually furnished with somewhat 700 drugs Periodic Safety Update Reports (PSUR), which figure also significantly outscores values of the past.

In 2015 alone almost 805 randomized clinical studies were conducted in Russia (with participation of 100,000 subjects). According to information released by AIS-Roszdraznador system, indices of preapproval pharmacological surveillance covered 15,000 reports on ADRs episodes, meaning about 1 report per 6–7 study subjects per year.

Implementation of pharmacovigilance system in Russia resulted in consistent growth of the number of reports on adverse reactions and the number of drugs Periodic Safety Update Reports, along with improvement of quality of such reports and enhancement of effectiveness of detecting concerns related to the issues of drugs safety. According to available statistics, in the period from 2014 to 2015 basing on the results of drugs safety monitoring, 45 recommendations have been delivered to the Ministry of Healthcare of the Russian Federation on the subject matter of consideration of the options of changing existing drugs use instructions, suspension of the drugs' use,

recall from market circulation or resumption of the drugs' use. Besides, on account of adverse reactions identification potentially related to the drugs quality, it has been arranged for targeted quality expertise of 79 batches of drugs; 14 batches of drugs have been recalled from the market in consideration of the quality experts' examinations findings. 138 information circulars have been published to cover the issues related to drugs safety monitoring [26].

### **Outlook for Pharmacovigilance in Russia**

Notwithstanding some serious problems prevailing in the field of pharmacovigilance, active steps have been taken in Russia in the search for their solution. Namely, in 2015–2016 fundamental changes were introduced to applicable legislation with a focus on improvement and harmonization of the rules that govern basic aspects of the pharmacovigilance system. Besides, in 2016 Russia will face coming into effect of Good Pharmacovigilance Practice (GVP) rules that regulate all activities dedicated to exposure, evaluation, interpretation and prevention of undesired consequences of drugs administration and medicinal products use. In fact, Russian version of GVP rules stands for a translation of a similar valid document in effect in the territory of the European Union, considering some specific local aspects [27].

According to Russian variant of GVP rules, holders of registration certificates issued for the drugs are obliged to arrange for acceptance, accounting, processing, analysis and storing of all incoming reports and communications with information on side effects, undesired adverse reactions, serious and unexpected unwanted reactions developing at the background of drugs administration.

In the situation of exposing information about serious and unforeseen adverse reactions, as well as finding other facts capable to induce change of the ratio between expected benefits and possible risks of drugs administration, holders of registration certificates are bound to take reasonable measures to eliminate negative consequences of use of such drugs and to ensure additional gathering of data on safety and efficiency of the drugs concerned.

Pursuant to Russian version of GVP rules, Roszdraznador has the right to suspend circulation of a drug in the market, if pharmacovigilance requirements have not been met. This is considered to be an effective means of protection of patients from administration of potentially hazardous drugs.

### **Conclusion**

Accounting for new Russian legislation coming into effect applicable in the field of pharmacovigilance along with Good Pharmacovigilance Practice (GVP) rules, sporadic efforts exerted for registering of the episodes of undesired medicinal events and their reporting to the competent authorities, which approach is quite typical for major part of pharmaceutical companies shall be transformed to strictly governed scientific practice implemented under control and in tight co-operation with regulatory agencies. From now onwards, pharmacovigilance duties of registration certificates holders include not only gathering, identification and scientific analysis of information about drugs safety, but also arrangement and uphold of operability of systemic activities related to management of the risks of pharmacological safety, devoted to patients' healthcare.

Undoubtedly, harmonization of the requirements to the system of pharmacovigilance currently underway in Russia 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.

## References

1. Yurgel NV, Cookes VG (2009) *Prophylaxis of Adverse Reactions: Medical Tactics for Rational Choice of Drugs* Moscow. GEOTAR-Media Publishing Group 448.
2. Astakhova AV, Lepakhin VK (2008) *Adverse Reactions and Safety Monitoring*, 2nd (edn.), Moscow, EKSMO Publishing 256.
3. Vlasova I, Lepakhin V *Drugs Safety System in the Russian Federation is Still Unrestored*.
4. Kolbin AS, Zagorodnikova KA, Burbello AT (2012) *Pharmacovigilance in the Russian Federation and in the European Community in the Light of New EC Directive: Should We Expect Changes*. Remedium Publishing 8: 8–14.
5. World Health Assembly 20 (1967) WHO Pilot Research Project for International Monitoring of Adverse Reaction to Drugs.
6. Ovchinnikova EA (2003) Role of drugs safety monitoring in resolving the issue of drugs rational use. *Good Clinical Practice* 4: 88–95.
7. Information Circular No. 01I-29A/08 by Roszdravnadzor issued on 29/01/2008 'On setting up of regional centers for drugs safety monitoring.
8. Information Circular No. 0I-455/08 by Roszdravnadzor issued on 22/07/2008 'On implementation of drugs safety monitoring.
9. Information Circular No. 0I-518/08 by Roszdravnadzor issued on 15/08/2008 'On adverse reactions to drugs.
10. Information Circular No. 04-1192/11 by Roszdravnadzor issued on 28/11/2011 'On Information Circulars of Roszdravnadzor with respect to drugs safety monitoring.
11. The Federal Law of the Russian Federation No. 61-FZ enacted on 12th of April 2010 'On circulation of drugs', *Rossiyskaya Gazeta* newspaper, 14th of April 2010, No. 5157.
12. Guidance for arrangement of the system for drugs safety monitoring (pharmacovigilance) at the drugs manufacturing companies or at the facilities of registration certificates holders, published on 05th of October 2009.
13. Roszdravnadzor (2008) Evaluation of confidence level for cause and effect relationship between adverse reactions and drugs.
14. PSUR (2013) Guidance for developers and manufacturers of drugs registered for circulation in the territory of the Russian Federation on the issues of preparation of drugs Periodic Safety Update Reports.
15. Roszdravnadzor (2010) Information circular issued on provision of information about adverse reactions to drugs in the scope of clinical studies via Automated Information System (AIS) of Roszdravnadzor.
16. <http://www.rozdravnadzor.ru>
17. Kosenko VV, Glagolev SV (2011) Arrangement of Registered Drugs Safety Monitoring in the Russian Federation. *Roszdravnadzor Bulletin* 6: 31–39.
18. Yurgel NV, Khubieva MY, Ushkalova EA (2010) Pharmacovigilance System in the Russian Federation: summary for 2009. *Roszdravnadzor Bulletin* 2: 20–28.
19. Lepakhin VK, Romanov BK, Toropova IA (2012) Analysis of Reports on Adverse Reactions to Drugs. *Bulletin of the Scientific Center for Experts Examination of Medicinal Products* 1: 22–25.
20. Khoseva EN, Morozova TE, Ermakov DA, Oshorova SD (2013) Issues of Safety Monitoring for Pharmacotherapies in Common Clinical Practice: Viewpoints of Patients and Healthcare Professionals. *Postgraduate Medic* 2: 203–212.
21. Zvetov VM, Ketova GG (2004) Pharmacists Awareness of the Issues Related to Side Effects of Drugs. *Rational Use of Drugs: Materials of Russian Academic and Research Conference Perm* 352–355.
22. Van Grootheest K, de Jong van den Berg L (2004) Patients' Role in Reporting Adverse Drug Reactions. *Expert Opinions for Drug Safety* 3: 363–368.
23. 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. *European Journal of Clinical Pharmacology* 63: 979–980.
24. Drugs Safety and Pharmacovigilance (2009) Meeting of representatives of national centres for pharmacovigilance of the countries participating in WHO program for drugs safety international monitoring: review data 1: 3–8.
25. Khoseva EN, Morozova TE, Andrushishina TB (2012) Safety and Efficacy of Today's Remedies from Patients' Viewpoint. *Clinical Pharmacology and Therapy* 21: 30–34.
26. <https://www.rosminzdrav.ru>
27. <https://docs.eaeunion.org/ru-ru/Pages/DisplayRIA.aspx?s=e1f13d1d-5914-465c-835f-2aa3762eddda&w=9260b414-defe-45cc-88a3-eb5c73238076&l=d70984cf-725d-4790-9b12-19604c34148c&EntityID=128>