**ORIGNAL ARTICLE**

# Relevant Changes in the Pharmacovigilance System in Russia and the Eurasian Economic Union (EAEU)

Gildeeva G.N., Belostotskiy A.V., Andreeva D.M.

*Department of organization and management of the circulation of medicines Institute of post-graduation education, Federal State Autonomous Educational Institution of Higher Education I.M. Sechenov First Moscow State Medical University of the Ministry of Health of the Russia Federation (Sechenov University, Russia, Moscow)*

***Received: 05th July, 19; Revised: 04th August, 19, Accepted: 07th September, 19; Available Online: 23th September, 2019***

**ABSTRACT**

The Eurasian Economic Union (EAEU) is an international organization for regional economic integration, established by the Treaty on the Eurasian Economic Union, which currently includes five countries–Russia, Kazakhstan, Belarus, Armenia, and Kyrgyzstan. The EAEU ensures the freedom of goods movement, as well as services, capital, and labor, conducting a coordinated, agreed, or unified policy in the sectors of the economy. The EAEU single drug market is a system of 35 regulations, including good practices for the circulation of medicinal products (GMP, GCP, GLP, GDP, GVP). This group of regulations contains basic documents on the inspection of production, confirmation of equivalence of reproduced drugs, the development of biological drugs, and pharmacovigilance (PV).

Drugs in circulation in the EAEU are subject to efficacy and safety monitoring to identify possible negative consequences of their use, individual intolerance, warn medical staff, veterinary specialists, patients or owners of animals and protect them from the use of such drugs.[1,2] In the near future, the Eurasian Union plans to "sanation" of the pharmaceutical market, from which drugs that have not shown their effectiveness, as well as unsafe drugs, will disappear, and therefore issues related to pharmacovigilance become particularly relevant.

**Keywords**: The EAEU, GMP, GCP, Pharmacovigilance and PSUR.

International Journal of Pharmaceutical Quality Assurance (2019); DOI: 10.25258/ijpqa.10.3.17

**How to cite this article:** Gildeeva, G.N., Belostotskiy, A.V. and Andreeva, D.M. (2019). Relevant changes in the pharmacovigilance system in Russia and the EAEU. International Journal of Pharmaceutical Quality Assurance 00(00): 34-37.

**Source of support:** Nil

**Conflict of interest:** None

## INTRODUCTION

The pharmacovigilance system in the Russian Federation, a key member of the EAEU, has almost half a century of history. A new milestone in the development of the pharmacovigilance system in Russia dates back to 2007, when the Federal Center for Drug Safety Monitoring was established, reporting to Roszdravnadzor (Federal Service for Surveillance in Healthcare or Roszdravnadzor)–the Russian executive body responsible for monitoring and supervising in the sphere of health care. In other EAEU countries, a similar function is performed by the National Centers for Pharmacovigilance, for Kazakhstan the function of drug safety monitoring performed by the National Center for Expertise of Medicines, Medical Devices, and Medical Equipment", in Belarus, it is Center for Expertise and Testing in Healthcare," etc.

### Databases of ADRs in the EAEU

According to the World Health Organization (WHO) rules, the monitoring and transfer of information on adverse reactions of drugs (ADRs) to the VigiBase database (Uppsala monitoring center) can only be carried out by organized National pharmacovigilance centers. Each country wishing to become a member of the WHO International Drug Safety Monitoring Program is obliged to organize a database (administrative system for storing and retrieving data about ADRs) and through it submit information about ADRs of drugs to the VigiBase database.[2] Such databases exist in all EAEU countries ("AIS-Roszdravnadzor" in Russia, "examination of medicines, medical devices and medical equipment" in Kazakhstan, etc.).

In 2008 Roszdravnadzor launched an automated information system (AIS-Roszdravnadzor) which is the unified, centralized database of ADRs in Russia. The adoption in 2010 of a new Federal Law of the Russian Federation No. 61-FZ on circulation of medicines pushed forward a new sequence of changes in the pharmacovigilance system.[2,3] According to this law, parties to the circulation of medicinal products, must report to Roszdravnadzor about all cases of side effects not listed in package leaflets, serious adverse reactions, unexpected adverse reactions when using drugs, special interaction with other drugs encountered during clinical trials and the use of drugs. The total number of reports of adverse reactions of drugs received by Roszdravnadzor in

**Author for Correspondence: gilgeln@gmail.com*

2018 amounted to 28,278 reports, which is slightly higher than the Figure for 2017, (27,513). At the same time, the structure and nature of reports have significantly changed, which relates to the improvement of requirements for urgent reporting and their harmonization with international standards, in particular with the recently adopted rules of good pharmacovigilance practice of the Eurasian Economic Union. In other EAEU countries, the level of reporting is at a lower level. For example, in Kazakhstan, the average level of reportage was 53 reports per 1 million people, which is almost two times lower than the minimum level recommended by WHO.

At this time, there is an active work, underway on the integration of pharmacovigilance systems in the EAEU Member States. In 2017, pursuant to the decisions of the Board of the Eurasian Economic Commission, common electronic services were developed for the implementation of interdepartmental and interstate cooperation on seven common processes:

- formation of a unified information database of drugs that do not meet the quality requirements, as well as falsified and (or) counterfeit drugs identified in the territories of the EAEU Member States;
- formation of a unified information database on identified adverse reactions (actions) on drugs, including reports on the ineffectiveness of drugs;
- formation of a unified information database on suspended, withdrawn and prohibited for medical use of drugs;
- formation of a unified register of pharmaceutical inspectors of the EAEU;
- formation of a unified register of medical devices registered within the EAEU;
- formation of a unified register of authorized organizations of the EAEU, conducting investigations testing of medical devices to register them;
- formation of a unified information database monitoring the safety, quality, and efficacy of medical devices.

At the beginning of 2019, the unified information database on identified adverse reactions (actions) on drugs has already started its work, but the number of signals received by it has been insignificant so far.

The unified database contains the following information:

- trade name of the drug;
- pharmaceutical dosage form;
- dosage of the drug;
- pack size of the drug;
- drug batch number indicated on a drug packaging;
- the name of the manufacturer of the medicinal product responsible for its release;
- information about identified adverse reactions to drugs, including reports of the ineffectiveness of drugs;
- information in the form of individual reports of adverse reactions to drugs;
- information in electronic format following the E2B Guideline of the International Conference on Harmonization of technical requirements for registration of drugs for Medical Use "Clinical Safety Data Management - Data Elements for Transmitting Reports on Individual Cases of Adverse Reactions."

**Periodic Safety Update Reposts of medicinal product (PSURs), Risk management Plans (RMPs) in the EAEU**

The most important stage in the life cycle of a drug is a post-registration period. The "risk-benefit" balance is a dynamic indicator that changes with an increase in the experience of drug use. For example, in 2016, the EMA revoked the marketing authorization for drugs containing fusafungine as an active ingredient, due to frequent ADRs with little clinical efficacy, the same applies to direct-acting drugs for the treatment of viral hepatitis C; the future fate of gadolinium-based contrast drugs is questionable due to newly identified ADRs. Therefore, a periodically updated safety report (PSUR) is one of the main reporting documents in relation to drug safety. The PSUR main objective is to present a comprehensive and critical analysis of the "risk-benefit" balance of a drug when taking into account all the new safety data and the cumulative effect of these data on the safety profile and effectiveness of the drug.

The PSUR structure is given in the rules of the EAEU Good Pharmacovigilance Practice. Roszdravnadzor approves the periodicity and submission schedule of the next PSURs for international non-proprietary names (INN) and grouping names of drugs. This list is currently under development. According to the harmonized PV legislation of the RF and the EAEU, the PSUR for drugs which INN or grouping name are not included in the above mentioned list, should be submitted with the following frequency: every 6 months from the international birth date for the first 2 years; yearly for the following 2 years; and every 3 years thereafter. The deadline for PSUR submission is no more than 90 calendar days from the date of the data lock point. The development of a harmonized list of drug "birth dates" and submission schedules for periodic safety reports are upcoming in the EAEU PV legislation.

The PSUR submission documents package should contain: a letter of referral, the PSUR, its summary (including translation into Russian), the current package leaflet. The optimal way to submit the PSUR in Russia is via the Roszdravnadzor AIS, the "Pharmacovigilance" subsystem.

The next PSUR is entered into the database of the AIS Roszdravnadzor as the primary report. As repeated reports are added to the Roszdravnadzor AIS: supplementary data for the reporting period (annexes to the PSUR, translation of resumes, etc.), information on errors and misprints, and a repeated report at the request of Roszdravnadzor. A single PSUR is submitted for one active ingredient. Exceptions apply when an active ingredient in different drug products is presented in different dosage forms and is used for different indications (for example, in the form of tablets to decrease blood pressure or in the form of eye drops for the treatment of glaucoma). Comments of Roszdravnadzor experts regarding the most common errors in PSURs should be taken into account, these are:

- Non-compliance with deadlines;
- Incorrect format of the document;

- Non-compliance with the required sections contents.
- The drug information differs from that obtained by Roszdravnadzor (for example, the number of ADRs).
- Lack of important and relevant scientific and clinical information (literature data, foreign regulatory decisions).
- The information in a package leaflet differs significantly from the information provided in the Reference safety information.
- Non-submission of PSUR.

Another important document within the framework of PV is the risk management plan (RMP) - a detailed description of the risk management system. In accordance with Russian legislation, a RMP is required at the post-registration stage of the drug life cycle, except for biological drug products for which the RMP is submitted as part of the registration dossier. At the same time, the EAEU rules of Good Pharmacovigilance Practice state that the RMP should be submitted as part of the registration dossier for any previously unregistered drug in the EAEU, including previously unregistered combination. A regulatory authority may require the RMP submission in the following cases:

- When making significant changes to the current marketing authorization, application area, aspects of manufacturing process such as: a new drug formulation; a new route of administration; a new production method for biotechnological products; introduction of pediatric indications; other significant changes in indications;
- Upon request of a National regulatory authority in case of any safety issue affecting the balance between benefits and risk;
- When renewing marketing authorization, if there is an existing risk management plan for the drug.

In the course of clinical trials conduct PV is regulated by the Roszdravnadzor Order №1071–the submission of periodic development safety updated reports of the drug being developed (studied) (DSUR). The expedited reports of organizations in whose name the permit for CT conduct has been issued is carried out in accordance with the following requirements:

- 7 calendar days–for lethal or life-threatening serious unexpected ADRs for the drug studied in Russia, unless otherwise specified by the study protocol;
- 15 calendar days: other serious unexpected ADRs on the studied drug identified in clinical trials permitted to be conducted in Russia; threat to life and health due to drug non-efficacy; increased frequency of serious ADRs on the studied drug compared to that described in the CT documentation; threat to life and health revealed in the course of preclinical and other clinical trials of the drug;
- Placebo-related reactions are not subject to reporting.

**Other innovations in the pharmacovigilance system in Russia and the EAEU**

On 01.01.2017, the rules of Good Pharmacovigilance Practice (GVP) of the Eurasian Economic Union, approved by the decision of the Council of the Eurasian Economic Commission №87 came into force.[1] The agreements of the EAEU countries on the general principles of drugs circulation confirm that the national pharmacovigilance systems are being aligned with the GVP, while the interim is not specified. Therefore, Roszdravnadzor prepared the order №1071 "On approval of the Procedure for Pharmacovigilance Implementation," harmonized with the rules of Good Pharmacovigilance Practice (GVP) and Good Clinical Practice (GCP) of the Eurasian Economic Union.4 The order regulates:

- Organization of the expertize of drug safety data incoming to Roszdravnadzor in affiliated the affiliated expert organization of Roszdravnadzor;
- Detailed requirements for urgent reporting of certain types of adverse reactions for marketing authorization (MA) holders, organizations conducting clinical trials (CT), and medical organizations:
- Requirements for the provision of PSURs for registered drugs and safety reports of drugs investigated in clinical trials;
- Requirements for marketing authorization holders to submit RMP to Roszdravnadzor in case of new drug safety concerns identification;
- Templates of the main documents in the field harmonized with the guidelines of the ICH and the EAEU GVP (notification of an adverse reaction to a registered drug, notification of ADR to an investigational drug, PSUR, DSUR, RMP).

According to the new rules, the information on the pharmacovigilance system of marketing authorization (MAH) should be contained in the pharmacovigilance system master file (PSMF). A PSMF is a detailed description of the pharmacovigilance system and safety procedures that an organization performs when developing a product. The PSMF ensures that the pharmacovigilance system is implemented in accordance with the requirements of the legislation of the EAEU Member States; validates the system compliance with applicable requirements; provides the information about the shortcomings of the system; obtain information about the risks or inefficiencies of performing certain directions of activity for PV.

Summary of PSMF in accordance with the EAEU requirements: 1. The qualified person responsible for pharmacovigilance (QPPV); 2. The organizational structure of the marketing authorization holder (MAH); 3. Safety data sources; 4. Computerized systems and databases; 5. Processes; 6. PV system performance; 7. Quality management system; 8. Appendices.

Subject to the EAEU rules of Good pharmacovigilance practice a MAH must assign a qualified person with required qualification responsible for pharmacovigilance (QPPV) who must be constantly available in Member States.[1] At present National pharmacovigilance centers provide training and issue certificates of QPPV qualification. According to the legislation of the Russian Federation, it is mandatory for the qualified person responsible for pharmacovigilance to reside of

the territory of the Russian Federation. One of the unresolved issues in the field of the EAEU pharmacovigilance is the lack of a procedure for approving transnational responsible persons in the EAEU; it is postulated that in each PV system there should be only one QPPV.

The rules of the EAEU good pharmacovigilance practice provide for the first time a statutory provision for delegating all or part of PV responsibilities of the MAH, including the functions of the QPPV to another organization or person (if such a person can be subject to the same requirements as the organization). At the same time, the responsibility for the fulfillment of tasks and responsibilities under PV carries by the MAH. It is advisable to outsource PV system with a small number of drug products in the company's portfolio, when maintaining your own PV system becomes unreasonably expensive. In this case, the master file of the MAH PV system should contain a detailed description of the outsourcing, including the results of audits of the organization providing the PV system by the MAH.[5]

The Roszdravnadzor Order №1071 regulates not only pharmacovigilance activities of the MAH but also those of medical organizations. Parties to drugs circulation (medical organizations) must report to the Roszdravnadzor about serious adverse reactions with a lethal outcome or a threat to life within a period of no more than three working days. Parties to drugs circulation (medical organizations) must report to the Roszdravnadzor about the following adverse reactions and other safety and efficacy information revealed by this medical organization within no more than 15 calendar days except for adverse reactions observed in the course of clinical trials:

- Serious adverse drug reactions except for those specified in section 35 of the Procedure;
- Cases of infectious disease transmission through a drug;
- Cases of the lack of claimed efficacy of drugs used to treat life-threatening diseases, vaccines to prevent infectious diseases, contraceptives, when a failed clinical effect is not caused by the patient's individual characteristics and (or) the specificity of his/her disease;
- Adverse reactions resulting from drug abuse, in cases of deliberate overdose of a drug, when drug exposure is associated with a professional activity or in cases when a drug is used to cause harm to human life and health intentionally.

The order assumes the appointment of a qualified person responsible for pharmacovigilance not only by the MAH but also in medical organizations. The management of medical organizations should recognize that, in addition to other criteria, the performance assessment of medical organization now includes compliance with the requirements of legislation in the field of pharmacovigilance.

Thus, a strictly regulated pharmacovigilance system involving all concerned parties in drugs circulation (manufactures and MAHs, medical organizations and healthcare professionals, patients, regulatory bodies) is actively functioning in Russia and the EAEU.

The RF pharmacovigilance legislation is harmonized with the rules of the EAEU Good Pharmacovigilance Practice. Among the tasks of the pharmacovigilance regulatory authority for the near future are the following[6,7]:

- Development of a harmonized list of drug "birth dates" and submission schedule for periodic safety reports;
- Participation in the development of the EAEU documents for inspection of pharmacovigilance systems;
- Translation of the MedDRA into Russian;
- Training of pharmacovigilance specialists.

## CONCLUSION

The EAEU is a large market for pharmaceutical manufacturers; the number of 5 countries included in this Association is more than 175 million people. At present, the entire population of the participating countries consumes medicinal products for 17 billion dollars, and this amount is constantly increasing.

At the same time, the Russian Federation accounts for 85% of the total, followed in descending order by Kazakhstan (7%), Belarus (5%), Kyrgyzstan (2%) and Armenia (1%).

The intensive development of the pharmaceutical market requires a unidirectional and symmetrical improvement of tools for drug safety supervision at the international level since this system affects the social and economic aspects of the development of all States without exception. The understanding of the social significance of the drug safety problem has contributed to the consolidation of most countries efforts and the formation of a unified pharmacovigilance system under the auspices of the EAEU. Further improvement of pharmacovigilance in Russia and the EAEU will provide the health care system with high-quality and safe medicinal products.

## REFERENCES:


1. Good Pharmacovigilance Practice (GVP) [Electronic resource]. —Available from: http://www.eurasiancommission.org/ru/act/texnreg/deptexreg/konsultComitet/Pages/drug_products.aspx
2. Federal law «On circulation of medicines» 61-FZ, 2014 (in Russian).
3. Khoseva EN, Morozova TE problems of development of a pharmacovigilance in Russia at the present stage (review). Good clinical practice, 2013; 3: 40-45 (in Russian).
4. The Order of Roszdravnadzor «On approval of the Procedure for implementation of pharmacovigilance» of 15.02.2017 №1071 (Registered by the Ministry of Justice of Russia 20.03.2017 № 46039). Roszdravnadzor, 2017.
5. Gildeeva G, Belostotsky A. Pharmacovigilance in Russia: current state of affairs, challenges, and prospects. Current Medical Research and Opinion. 2017; 33(12):2161-2166.
6. Glagolev SV, Olefir YuV, Romanov BK, Alyautdin RN. Guidelines for the planning and implementing of pharmacovigilance systems audit. Safety and Risk of Pharmacotherapy 2016; 3: 5–13 (in Russian).
7. Gildeeva GN, Glagolev SV, Yurkov VI Problems of drug safety monitoring in Russia: role of pharmacovigilance experts. Vestnik Roszdravnadzora = Bulletin of Roszdravnadzor. 2016; (5): 114–8 (in Russian).