



Pharmacovigilance System in Russia and the EAEU

Authors:

Sergey Simeniv

CEO

X7 Research, CRO;

Olga Latysheva

Head of Pharmacovigilance Department

X7 Research, CRO;

Dmitry Kryuchkov

Executive Director

X7 Research, CRO;

Pavel Fedorov

Director of business development

X7 Research, CRO;

Tatiana Syrova

Head of Project Management

X7 Research, CRO.

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According to the current legislation, **pharmacovigilance** is an activity relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problems [1].

Historical background

Pharmaceuticals approved in the Russian Federation are subject to efficacy and safety monitoring in order to detect potential side effects of their use and individual intolerance, and to notify medical professionals, veterinary specialists, patients or pet/animal owners and protection them against the use of these drugs [2]. The pharmacovigilance system in the Russian Federation has almost had a 50-year history from the thalidomide disaster and the origin of a worldwide drug safety monitoring system to date. However, endless reorganizations, abolitions, neglects and reconstructions did affect the effectiveness of its activities. The Department of registration, systematization and expedited reporting of drug side effects (1969) was the pioneer in drug efficacy and safety monitoring in the former USSR. In 1973, it was reorganized into the All-Union organizational and methodological centre for studying drug adverse effects. This centre was abolished in 1991 along with the Ministry of Health of the USSR that completely suspended drug efficacy and safety monitoring activities in the country almost for 7 years. Within a decade since 1997 regulatory bodies designed to provide pharmacovigilance functions could not manage duties imposed in full due to the lack of adequate legislation and resources.

A new stage in the development of the pharmacovigilance system in Russia dates back to 2007 when the Federal Centre of Drug Safety Monitoring was established at the Federal State Budgetary Institution (FSBI) "the Scientific Centre for Expertise of Medical Products" of the Federal Service for Surveillance in Healthcare (Roszdravnadzor). In 2008 Roszdravnadzor launched an automated information system (Roszdravnadzor AIS) which has become the unified centralized database of adverse drug reactions (ADRs) in Russia. The adoption of a new Federal law in 2010 -



the Federal law No. 61-FZ "On Circulation of Medicines" dated on April 12, 2010 pushed forward a new sequence of changes in the pharmacovigilance system [2]. According to this law parties to the circulation of medicines should report to Roszdravnadzor about all cases of adverse effects not listed in the package leaflet, serious adverse reactions, unexpected adverse reactions, special interactions with other drugs encountered in clinical trials and during clinical use of drugs. A procedure for drug safety monitoring was regulated by the Order of the Ministry of Health and Social Development No. 757 dated on 26.08.10. [3].

EAEU Pharmacovigilance system

The Good pharmacovigilance practices (GVP) of the Eurasian Economic Union (EAEU) approved by the resolution No. 87 of the Eurasian Economic Commission dated on 03.11.2016 came into force since 01.01.2017 [1]. Agreements on common principles of the circulation of medicines executed by EAEU member states indicate that national pharmacovigilance systems are being harmonized with the GVP (good pharmacovigilance practices), with no interim period specified. Geographical map of the EAEU member states is presented on the figure 1.



Figure 1 Member states of the EAEU

Therefore, Roszdravnadzor adopted the order No. 1071 dated on 15.02.2017 "On approval of the pharmacovigilance procedure" (registered under No. 46039 by the Ministry of Justice of the RF on 20.03.2017), harmonized with Good pharmacovigilance practices (GVP) and Good clinical practice (GCP) regulations of the Eurasian Economic Union. Pursuant to this order, pharmacovigilance is carried out by the Federal Service for Surveillance in Healthcare (Roszdravnadzor) by means of analysing the information reported by parties to the circulation of medicinal products regarding drug-related side effects, adverse reactions, serious adverse reactions, unexpected adverse reactions, individual intolerance, the lack of drug effectiveness, as well as other facts and circumstances, which are life- or health-threatening when administered to human, revealed at any stage of the circulation of drugs in the Russian Federation and other countries in order to identify possible drug-related adverse effects, individual intolerance, to warn healthcare professionals, patients and to protect them against the use of such drugs [4].



The Order regulates:

- Arrangement of expertise of drug safety data incoming to Roszdravnadzor in its affiliated expert organization;
- Detailed requirements to urgent reporting of some types of adverse reactions for marketing authorization (MA) holders, organizations conducting clinical trials and medical organizations;
- Requirements to periodic safety update reports (PSUR) and development safety update reports (DSUR);
- Requirements to marketing authorization holders to submit risk management plans (RMP) to Roszdravnadzor in case of new drug safety concerns;
- Templates of the main documents harmonized with ICH and EAEU GVP guidelines (a report on an adverse reaction to registered medicinal product, a report on an adverse reaction to investigational medicinal product).

Pharmacovigilance system master file

The information on the pharmacovigilance system of a marketing authorization holder (MAH) should be contained in a pharmacovigilance system master file (PSMF). A PSMF is a detailed description of the pharmacovigilance system and safety procedures taken by the MAH in the product development. The PSMF ensures that the pharmacovigilance system is implemented as required by the legislation of EAEU member states; validates the system compliance with applicable requirements, provides the information on drawbacks of the system and on risks or failures of certain activities on pharmacovigilance (PV). It is the PSMF that are primarily reviewed by internal and external pharmacovigilance audits. A detailed description of the PSMF contents is given in Chapter 3 of the EAEU Good pharmacovigilance practices.



Summary of the PSMF:

1. Qualified person responsible for pharmacovigilance (QPPV);
2. Organizational structure of the marketing authorization holder (MAH);
3. Safety data sources;
4. Computerized systems and databases;
5. Pharmacovigilance processes;
6. Pharmacovigilance system performance;
7. Quality management system;
8. Appendices.

Qualified person responsible for pharmacovigilance

Subject to Section 2.14 of the EAEU Good pharmacovigilance practices a marketing authorization holder (MAH) must assign a qualified person responsible for pharmacovigilance (QPPV) who must be constantly available in member states. A QPPV may not be a physician or a pharmacist, the education in other natural sciences is permitted. The MAH educates the QPPV in the scope of its PV system before the QPPV takes a position. At present expert organizations (Scientific centre for expert evaluation of medical products) provide trainings and issue certificates of QPPV qualification. According to the legislation of the EAEU it is mandatory for the QPPV to reside on the territory of the EAEU member states. For each PV system, only one QPPV should be appointed, but in addition, the regulatory authorities of the Member States have the right to require the appointment of a contact person for PV at the national level, subordinate to the QPPV.



The MAH QPPV is responsible for:

- Establishing and maintaining/managing of the MAH pharmacovigilance system;
- Having authority and responsibilities in relation to a pharmacovigilance system master file (PSMF);
- Having an overview of drug safety profiles;
- Being completely aware of risk mitigation measures;
- Participating in review and approval of post-authorization safety study protocols;
- Having full information on post-authorization safety studies including their results;
- Supplementing risk management plans;
- Enforcing pharmacovigilance functions performance and submitting all documents in relation to pharmacovigilance in accordance with requirements of the member-states legislation;
- Quality assurance required for the pharmacovigilance data submitted to competent authorities of member states;
- Submitting any information in relation to the risk-benefit assessment to competent authorities;
- Providing assistance in preparing regulatory measures in response to safety emergencies;
- Control of the functioning of every aspect of the pharmacovigilance system;
- Acting as a single contact person for pharmacovigilance on a 24-hour basis.



A QPPV should be directly subordinate to a chief executive officer of the MAH, that is, should be independent on heads of other department including clinical and marketing departments. Moreover, within his/her powers a QPPV should take part in inspecting activities of other department and educate employees with the basics of pharmacovigilance.

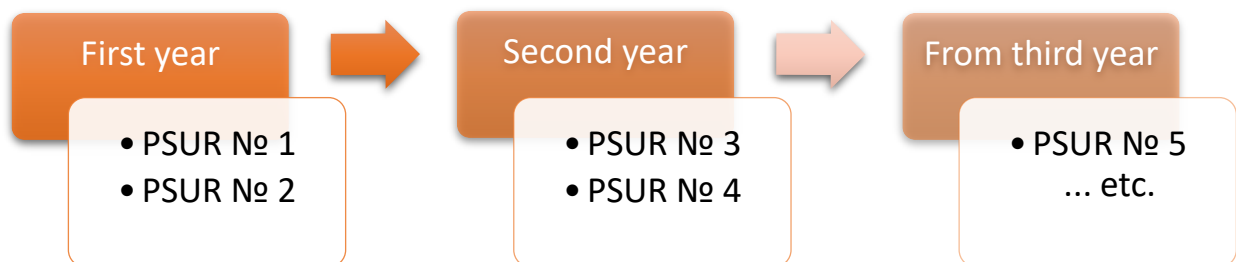
For the first time the EAEU Good pharmacovigilance practices (Section 2.18) provides for the statutory possibility to delegate the MAH pharmacovigilance authority including the functions of a QPPV in full or in part to other entity/organization or a person (if such a person can be subject to the same requirements as the organization). When this is the case, the MAH shall be responsible for pharmacovigilance. It is appropriate to outsource pharmacovigilance when a company portfolio includes few products and the maintenance of its own pharmacovigilance system is unreasonably expensive. This MAH pharmacovigilance system master file should contain a detailed description of outsourcing including MAH audit results for the organization providing the pharmacovigilance system.

Periodic reporting

A post-authorization period is the most important stage of a drug life cycle. A risk-benefit ratio is a dynamics value changing with the increase of a drug use. For example, in 2016 the EMA withdrawn the marketing authorization for drugs containing fusafungine as an active substance due to frequent ADRs with insignificant clinical efficacy. The same applies to direct-acting (antiviral) agents for the treatment of hepatitis C. The future of gadolinium-based contrast agents is questionable due to newly revealed ADRs. Therefore, a periodic safety update 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 benefit to risk ratio of the drug when taking into account all new data on safety and a cumulative effect of these data on the drug safety and efficacy profile. The PSUR structure is given in Section 8 of the EAEU Good pharmacovigilance practices. The periodicity and submission schedule for the next PSURs for international non-



propriety names (INN) and generic names are approved by Roszdravnadzor. This list is under development now. In accordance to the harmonized PV legislation of the RF and EAEU, the PSUR for drugs, which INN or generic names are not included in the list mentioned should be submitted: every 6 months since the international birth date within the first 2 years, yearly for the following 2 years and every 3 years thereafter. The PSUR should be submitted within 90 calendar days after the data lock point. A harmonized list of drug birth dates and the terms for submission of periodic safety reports are upcoming in the EAEU legislation.



The PSUR submission documents package should contain: a cover letter (referral letter), the PSUR, its summary (including its translation into Russian), the current version of the package leaflet. An optimal way to submit the PSUR is via the Roszdravnadzor AIS, a subsystem "Pharmacovigilance" (a number is assigned in the database). A single PSUR is submitted for a single active substance. Exception applies when an active substance is in different formulations in different drugs and is used for different indications (for example, in tablets to decrease blood pressure or in eye drops for the treatment of glaucoma).



Comments of Roszdravnadzor experts on the most frequent errors in PSURs should be taken into account (Polykarpova T.S., 2017), these are:

- Non-compliance with time frames;
- Incorrect format of the document;
- Non-compliance with the required section content;
- The drug information differs from that obtained by Roszdravnadzor (for example, the number of ADRs);
- Omission of important and relevant scientific and clinical information (literature data, foreign regulatory decisions);
- The information in a package leaflet is significantly different from that provided in the Reference safety information;
- Non-submission of PSURs.

A risk management plan (RMP) - a detailed description of the risk management system - is another most important document for PV. Under the Russian legislation a RMP is required at the post-authorization stage of the drug life cycle except for biological products for which the RMP is submitted as part of the application dossier. At the same time, the EAEU Good pharmacovigilance practices state that the RMP should be submitted as part of the application dossier for any drug which has not been authorized in the EAEU including any non-authorized combination.



A regulatory authority may require for the RMP to be submitted:

- When significant changes have been introduced in the current marketing authorization, scope of use, aspects of manufacturing process such as
 - ❖ New drug formulation;
 - ❖ New route of administration;
 - ❖ New production method for biotechnology products;
 - ❖ Introduction of paediatric indications;
 - ❖ Other significant changes in indications.
- Upon request of a national regulatory body in case of any safety concern affecting the benefit-risk ratio;
- In a marketing authorization renewal when there is a current risk management plan for the drug.

The RMP structure is given in detail in Section 6.2.4 of the GVP.

Pharmacovigilance during the conduct of clinical trials is also regulated by sections 29-33 of the Roszdravnadzor Order No. 1071 dated on 15.02.2017 – the submission of development safety update reports (DSURs).

Expedited reporting

Expedited reporting by organizations provided with the permission to conduct CT should be submitted within:

- 7 calendar days for lethal and 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 observed in the clinical trials permitted to be conducted in Russia;
 - ❖ danger to life and health due to the drug non-efficacy;
 - ❖ increased frequency of serious ADRs as compared to that described in the CT documentation;
 - ❖ danger to life and health revealed in the course of non-clinical and other clinical trials of the drug.
- Placebo-related reactions are not subject to reporting;
- Reactions to an authorized drug are reported as post-marketing expedited reporting.

The Roszdravnadzor Order No. 1071 dated on 15.02.2017 regulates not only pharmacovigilance activities of the MAH but also those of medical organizations. Parties to the circulation of medicines (medical organizations) must no longer than within 3 working days report serious adverse reactions which resulted in death or are life-threatening to Roszdravnadzor. Parties to the circulation of medicines (medical organizations) must within a period no longer than 15 calendar days report to Roszdravnadzor on adverse reactions and other safety and efficacy findings revealed by this medical organization except for adverse reactions observed in the course of clinical trials:

1. Serious adverse drug reactions expect for those specified in section 35 of the Procedure (Order #1071);
2. Cases of an infectious disease transmission with the drug;



3. Cases of the lack of claimed efficacy of drugs used to treat life-threatening diseases, vaccines to prevent infectious diseases, contraceptives, when failed clinical effect is not due to individual characteristics of a patient and (or) the specificity of his/her disease;

4. Adverse drug reactions resulting from drug abuse as intended drug overdose, occupational exposure, or when the drug is used to do wilful harm to human life and health.

The Order requires that a qualified person responsible for pharmacovigilance should be appointed both by the MAH and medical organizations. The management of medical organizations should recognize that, in addition to other criteria, the performance evaluation of medical organizations at present includes the compliance with requirements of the pharmacovigilance legislation. Sample criteria of pharmacovigilance performance evaluation of medical organizations (Glagolev S.V., 2017) are as follows:

- Awareness of medical organization employees on the legislation in the field of drug safety monitoring (Federal Law No.61-FZ "On Circulation of Medicines" dated on 12.04.2010 and the Roszdravnadzor Order No. 1071 dated on 15.02.2017;
- Availability of in-house documents (orders, instructions) regulating the procedure for adverse drug reaction data registration and collection in healthcare institutions and communicating these data to Roszdravnadzor;
- Availability of specialists responsible for collection and communication of the adverse drug reaction data and drug safety concerns to Roszdravnadzor;
- Arrangement of cooperation with a Roszdravnadzor regional body;



- Arrangement for informing the Roszdravnadzor central administrative office or its regional offices in subjects of the Russian Federation on lethal adverse drug reactions within 3 working days after this reaction occurred;
- Availability of a personalised access to the Roszdravnadzor AIS "Pharmacovigilance" portal;
- An average number of adverse reactions observed, the number of reports sent to Roszdravnadzor;
- Skills in filling adverse drug reaction reports (in an electronic format or on a paper copy);
- Recording the findings on adverse drug reactions observed in a healthcare institution in patient medical documentation;
- Notification of individual intolerance cases resulting in the prescription of a medication on a trade-name-basis by health authorities within 5 working days;
- Discussion pharmacovigilance issues in meetings held by a medical institution management (morning conferences, daily briefings);
- Counselling of medical personnel, conducting meetings, trainings aimed to improve the communication of adverse drug reaction reports and their quality.



Conclusion

Thus, a strictly regulated system of pharmacovigilance involving all concerned parties to the circulation of medicines (manufacturers, MAHs, medical organizations and healthcare professionals, patients, and regulatory bodies) is actively in operation in Russia and the EAEU.

The RF pharmacovigilance legislation is harmonized with the EAEU Good pharmacovigilance practices. The immediate tasks of the pharmacovigilance regulatory authorities are as follows (Glagolev S.V., 2017):

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

Continued improvement of pharmacovigilance in Russia and the EAEU would provide the public health care system with safe drugs of high quality.



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