On the drug safety monitoring

Safe drug use assurance is one of the global priorities of the modern healthcare. According to the World Health Organization, adverse drug reactions are among the ten most common causes of mortality in many countries.

In compliance with decree No. 650 (20.08.2010) “On the introduction of changes to several Acts of the Russian Federation Government in conjunction with adoption of Federal Law “On drug circulation” of the Russian Federation Government, since 2010, the Federal Service on Surveillance in Healthcare has been exercising the state function of safety monitoring of the drugs circulating in the Russian Federation.

The primary areas of the state pharmacovigilance system development in Russia are improvement in detection of drug safety issues, improvement of data evaluation tools for adverse reactions and development of preventive mechanisms for pharmacotherapeutic complications.

Effective detection of drug safety issues largely depends on doctors’ attention to pharmacovigilance and their willingness to inform the Federal Service on Surveillance in Healthcare of the detected adverse reactions.

Nowadays, healthcare specialists by no means report all the drug-related complications they encounter. This is largely caused by insufficient knowledge of pharmacovigilance, fear of administrative sanctions for development of adverse reactions and underestimation of significance of the reportable information.

Assurance of report completeness and quality sent to the Federal Service on Surveillance in Healthcare remains an important problem. Most adverse reactions may be prevented by capitalizing knowledge of drug peculiarities and risk factors of development of side effects.

Having taken the questions submitted by healthcare specialists and heads of medical organizations into consideration, the Federal Service on Surveillance in Healthcare explains the key aspects of fulfillment of statutory requirements for drug safety monitoring by medical organizations.

According to Federal Law No. 61-FZ (12.04.2010) “On drug circulation” (article 64), the drug circulation subjects are obliged to inform the Federal Service on Surveillance in Healthcare of all cases of the side effects not mentioned in drug package leaflets, severe adverse reactions, unexpected adverse reactions to drug use and the drug interaction peculiarities revealed in the process of clinical studies and drug use.

Definitions “side effect” and “severe adverse reaction” are given in Federal Law No. 61-FZ (12.04.2010) “On drug circulation”.

According to article 64 of the Federal Law No. 61-FZ (12.04.2010) “On drug circulation”, failure to report or disclose the information reportable to the Federal Service on Surveillance in Healthcare in the process of drug safety monitoring obtained by a person on grounds of their professional activities is punishable by law of the Russian Federation.

According to Order No. 757n (26.08.2010) “On the approval of procedures of safety monitoring of the drugs for medical use, of registration of side effects, severe adverse reactions and unexpected adverse reactions to the drugs for medical use” of the Ministry of Health of Russia, the information on severe or unexpected adverse reactions (i.e. the reactions not mentioned in the approved drug package leaflets) is reportable to the Federal Service on Surveillance in Healthcare within the 15 consecutive days from the date of obtainment of these data by the sender.

It is advisable to send a report as soon as minimum information (identifiable patient, medical symptom, reactions or drug [by trade name or manufacturer]) on the adverse reaction has been obtained. Information on the outcome of the adverse reaction, data of instrumental and laboratory studies and other data may be reported as additional notices.

According to letter of information No. 04I-266/12 (11.04.2012) of the Federal Service on Surveillance in Healthcare, it is advisable to report information on fatal adverse reactions within 24 hours from the time of development thereof.

It is also advisable to inform the Federal Service on Surveillance in Healthcare of the following life- and health-threatening facts and circumstances detected in the process of drug use promptly (within 15 consecutive days from the date of detection):

a) obtainment of information on severity, nature or incidence of side effects or severe adverse reactions and on drug interaction peculiarities or on unexpected adverse reactions not consistent with the approved drug package leaflet;

b) detection of life- and health-threatening risk for mothers and/or their fetuses associated with drug use during pregnancy and lactation;

c) detection of resistance of the causative agent of infectious diseases to antibacterial and antiviral drugs;

d) detection of cases of infection transmission via drugs;

e) obtainment of information on the absence of clinical effect of the vital drugs, vaccines and preparations used for birth control, when the absence of clinical effect is not related to the patient's individual peculiarities and/or specificity of his/her disease;

f) detection of incorrect drug use by healthcare specialists and/or patients due to incorrect interpretation of the drug package leaflet's information;

g) detection of cases of drug abuse, deliberate drug overdosage or drug use for intended harm to life and/or health of humans and animals;

h) detection of drug interaction peculiarities characterized by definite or probable cause-effect relationship with the drug use not mentioned in the drug package leaflet or human life- or health-threatening or rendering use of a certain drug with another drug impossible (pharmaceutical incompatibility);

i) obtainment of information on side effects, severe adverse reactions, unexpected adverse reactions and drug interaction peculiarities caused by use of imitation, counterfeit drugs or the drugs, quality whereof does not fulfill the specified requirements.

The preferred format for reporting such information on adverse drug reactions is the "Notice of a side effect, adverse reaction or absence of the expected drug's therapeutic effect" available for download on the website of the Federal Service on Surveillance in Healthcare (http://www.roszdravnadzor.ru/medicmes/monitor_bezopasnosti_ls/map).

Such a notice may sent to the central office (fax: +7 (495) 698-15-73, e-mail: pharm@roszdravnadzor.ru) or local offices (marked "Urgent" and subsequent sending of a hard copy) of the Federal Service on Surveillance in Healthcare by fax or e-mail.

List of the specialists responsible for drug safety monitoring at local offices of the Federal Service on Surveillance in Healthcare and their contacts are given on the website of the Federal Service on Surveillance in Healthcare (section "Drugs", subsection "Safety monitoring of the drugs circulating in the Russian Federation", heading "Contacts").

It is advisable for those medical organizations who frequently detect adverse reactions to request personalized access to information resource "Pharmacovigilance" of the Automated Information System (hereinafter – AIS) of the Federal Service on Surveillance in Healthcare.

The procedure of obtainment of personalized access to the AIS of the Federal Service on Surveillance in Healthcare is given in letter of information No. 01I-752/08 (02.12.2008) of the Federal Service on Surveillance in Healthcare and Social Development available on the website of the Federal Service on Surveillance in Healthcare (section "Drugs", subsection "Safety monitoring of the drugs circulating in the Russian Federation", heading "Letters of information", tab "2008").

Adverse reaction reporting requires assessment of the cause-effect relationship between the drug use and development of the drug therapy complication. It is advisable to use one of the following algorithms to assess cause-effect relationship between the drug use and development of the adverse reaction: Naranjo, Karch or WHO.

These methods of assessment are given in guidelines (02.10.2008) "Determination of the degree of confidence of cause-effect relationship "Adverse reaction – drug" (classification and methods)" of the Federal Service on Surveillance in Healthcare published on the website of the

Federal Service on Surveillance in Healthcare (section “Drugs”, subsection “Safety monitoring of the drugs circulating in the Russian Federation”, heading “Guidelines”).
Electronic tools (algorithms Naranjo and Karch) for assessment of cause-effect relationship are also available for use on the information website of the Federal Service on Surveillance in Healthcare (section “Drugs”, subsection “Safety monitoring of the drugs circulating in the Russian Federation”, heading “Report form”).
Special consideration ought to be given to the fact that information on adverse reactions is reportable to the Federal Service on Surveillance in Healthcare in compliance with the law of the Russian Federation on personal data protection.
It ought to be emphasized that those patients who have detected adverse reactions themselves are entitled to demand that their attending doctors fill the “notice” and send it to the Federal Service on Surveillance in Healthcare.
In order to assure effective implementation of the statutory requirements to drug safety monitoring, the Federal Service on Surveillance in Healthcare recommends to heads of medical organizations to assign persons responsible for collection, processing and presentation of information on the detected adverse drug reactions (persons responsible for pharmacovigilance) out of the employees with university degree in Medicine, especially those who specialize in clinical pharmacology or have attended advanced vocational training in clinical pharmacology or pharmacovigilance.
It is also advisable for heads of medical organizations to make the responsible employees aware of statutory enactments in the sphere of drug safety monitoring (Federal Law No. 61-FZ [12.04.2010] “On drug circulation” and Order No. 757n [26.08.2010] “On the approval of procedures of safety monitoring of the drugs for medical use, of registration of side effects, severe adverse reactions and unexpected adverse reactions to the drugs for medical use” of the Ministry of Health of Russia) and contacts of a specialist responsible for this sphere at the regional office of the Federal Service on Surveillance in Healthcare of the Russian Federation.
According to Federal Law No. 323-FZ (21.11.2011) “On the principles of health protection of citizens of the Russian Federation” (article 74, clause 2.5), medical and pharmaceutical personnel are obliged to report the information reportable to the Federal Service on Surveillance in Healthcare in the framework of completion of statutory requirements in the sphere of drug safety monitoring to the responsible executive of the medical organization.
It is advisable to regulate the medical organization’s activity for detection and reporting of adverse reactions to the Federal Service on Surveillance in Healthcare with internal documents (orders, instructions, standard operating procedures).
It ought to be mentioned that drug therapy complications, including a significant amount of side effects, severe adverse reactions, unexpected adverse drug reactions and pathological conditions caused by drug interaction, are included into the 10^{th} revision of the International Classification of Diseases of the World Health Organization introduced to healthcare institutions of the Russian Federation by Order No. 170 (27.05.1997) “On the adoption of revision X of the international statistical classification of diseases and health problems by healthcare authorities and institutions” of the Ministry of Health of Russia. Therefore, it is advisable to record the information on the adverse reactions detected by medical organizations and reported to the Federal Service on Surveillance in Healthcare in the patients’ medical documents.
According to Order No. 502n (05.05.2012) “On the approval of procedures of establishment and activity of medical panels of medical organizations” of the Ministry of Health of Russia (as amended by Order No. 886n (02.12.2013) of the Ministry of Health of Russia), episodes of individual drug intolerance constituting grounds for ordering drugs by trade name in the framework of the preferential drug provision program are reportable to the Federal Service on Surveillance in Healthcare by medical panels. The reporting procedure for such information was approved by Order No. 757n (26.08.2010) of the Ministry of Health of Russia.
Along with reporting information on the detected adverse drug reactions to the Federal Service on Surveillance in Healthcare, medical personnel are entitled to inform marketing authorization

holders of them. Restrictions on attendance of medical and pharmaceutical personnel by representatives of pharmaceutical companies during business hours specified by article 74 of Federal Law No. 323-FZ (21.11.2011) “On the principles of health protection of citizens of the Russian Federation” do not apply to the events dedicated to drug safety monitoring information obtainment.

According to Order No. 757n (26.08.2010) of the Ministry of Health of Russia, the Federal Service on Surveillance in Healthcare is obliged to analyze the information received in the framework of drug safety monitoring. Analysis results are to be sent to the Ministry of Health or Russia in order to make a decision on introduction of changes to drug package leaflets, suspension of circulation, withdrawal from circulation or recommencement of circulation of drugs. The information on regulatory decisions of the Ministry of Health of Russia related to the detected drug safety issues is published on the website of the Federal Service on Surveillance in Healthcare (section “Drugs”, subsection “Safety monitoring of the drugs circulating in the Russian Federation”, heading “Letters of information”).

In this section, the Federal Service on Surveillance in Healthcare also publishes letters of marketing authorization holders on the new data on safety and additional recommendations on assuring safe drug use for healthcare specialists or patients.

Moreover, the Ministry of Health of the Russian Federation publishes requirements to marketing authorization holders for introduction of changes to drug package inserts, which may be related to effectiveness and safety, on its information resource (http://grls.rosminzdrav.ru).

It ought to be mentioned that the Federal Service on Surveillance in Healthcare assesses activity of medical institutions on obtainment and reporting of information on adverse drug reactions to the Federal Service on Surveillance in Healthcare by performing regulatory and supervisory measures at medical organizations.

Interim Acting Head of the Federal Service on Surveillance in Healthcare
M.A. Murashko

Pigeon Corporation took part in organizing a research/practice conference “Issues of organization, protection and support of breastfeeding in Russia” on November 21-22, 2014, at the Scientific Center of Children’s Health

The problem of establishing breastfeeding is rather urgent for Russia – according to the Russian Federation Government, only 41% of the children in Russia were breastfed in 2010, whereas in several European countries up to 98% of the children were breastfed. According to the WHO, it is advisable to breastfeed the child for at least the first six months of life; however, even out of those women who initially went with breastfeeding many wean infants before they are 6 months. One of the primary reasons of weaning is low awareness of the mothers and insufficient attention of doctors to breastfeeding support. The research part of conference “Issues of organization, protection and support of breastfeeding in Russia” was attended by the leading pediatricians, neonatologists, pediatric surgeons, psychologists, dieticians and mammologists. This is outstanding contribution to promotion and development of breastfeeding among Russian mothers.

Pigeon Corporation (Japan) is the leading manufacturer of products for children and mothers, as well as for patient and elderly care, has been in the market since 1957. All the Pigeon products are based on the fundamental studies conducted in Japan; the company’s business model has been being developed for more than 50 years. Pigeon products are marketed in more than 80 countries, including Russia (www.pigeon.ru).

A Russian-made inactivated subunit influenza vaccine “Sovigripp” (research and production association “Microgen”) is undergoing clinical tests of effiectiveness and safety in children and pregnant women

Microgen (research and production association) specifically emphasizes the fact that broadening of age categories for use of vaccine “Sovigripp” will allow using the preparation to prevent influenza not only in all the age groups of the population, but also in the especially influenza-prone category – pregnant women. Effectiveness and safety of vaccine “Sovigripp” for active annual preventive immunization of over-18 people and the elderly (over-60) against seasonal influenza has been proved. Everyone will be able to immunize against influenza with a Russian-made vaccine “Sovigripp” as early as in epidemic season 2015-2016.

Research and production association “Microgen” (Russia) was founded in 2003 as a result of a merger of unitary state-owned immunobiological drug manufacturers. Microgen is one of the three leading Russian pharmaceutical companies and the largest Russian manufacturer of immunobiological preparations: vaccines, serums, specific immunoglobulins, growth media, allergens and probiotics. Bacteriophage (safe antibacterial preparations alternative to antibiotics) manufacturing is a unique sphere of the Microgen’s research and production. Microgen manufactures more than 60 vital and life-saving drugs and more than 120 immunobiological preparations, including 13 vaccines on the National Immunization Calendar and 10 vaccines against socially significant infectious diseases (www.microgen.ru).

An innovative drug “Brilinta” (ticagrelor, AstraZeneca) for acute coronary syndrome has been awarded the Prix Galien Russia 2014 Prize

On the average, ca. 520,000 cases of acute coronary syndrome are annually registered in Russia. Ca. 110-120 thousand years of potentially active life are lost in Russia due to myocardial infarction mortality in the working age; this equals to full average-expectancy life of 1,500-2,000 people. It ought to be specifically mentioned that the mean incidence of mortality due to acute myocardial infarction is 13.4%, due to acute myocardial reinfarction – 25.03%. Drug “Brilinta” for preventing atherothrombotic complications in adult patients with acute coronary syndrome was registered in Russia in 2011; it has successfully passed pivotal clinical study PLATO (a Study of PLATelet Inhibition and Patient Outcomes). According to the results, Brilinta in combination with acetylsalicylic acid reduces the relative risk of recurrent cardiovascular events by 16% and cardiovascular mortality by 21% within the first year of therapy.

AstraZeneca is an international innovative biopharmaceutical company operating in the sphere of research, development and commercial use of prescription drugs in such therapeutic areas as cardiology, oncology, respiratory diseases and inflammatory processes, infections and psychiatry. The company is represented in more than 100 countries; its innovative drugs are used by millions of patients (www.astrazeneca.com, www.astrazeneca.ru).

Humira (adalimumab, AbbVie) has been approved for use in Russia to treat Crohn’s disease in over-6 children

Crohn’s disease is a severe potentially incapacitating immune gastrointestinal disease, which, if manifested in childhood, negatively affects growth, development and quality of children’s lives. A gradual increase in Crohn’s disease incidence has been observed in recent years around the world. Ca. 30% of all the cases are observed in under-20 patients: 4% - in under-5 children, 20% - in under-10 patients. 20 cases of Crohn’s disease per 100,000 people are annually registered in Russia; ca. 10% thereof are observed in children. The disease is characterized by severer course and a more extensive gastrointestinal affection. Previously, Humira was available in Russia for treating only adult patients with Crohn’s disease. Nowadays, this drug helps more than 840,000 patients with immune-mediated diseases around the world to have a normal life.

This drug has been proving its efficacy and safety for therapy of such severe diseases as rheumatoid, psoriatic and juvenile idiopathic arthritis, ankylosing spondylitis, plaque psoriasis, arthritis, Crohn's disease and ulcerative colitis for many years.

AbbVie is a global research biopharmaceutical company founded in 2013 by separation from Abbott. The company's mission is to use expertise and experience of committed employees and the unique approach to innovations in order to develop and market advanced methods of treating some of the most complex and severest diseases in the world. The number of AbbVie employees around the world is ca. 25,000 people; AbbVie drugs are marketed in more than 170 countries (www.abbvie.com).