Changes in the Federal Law ‘On Medicines’ Circulation’

January 2015
The Federal Law dated 22 December 2014 No. 429-FZ (here in after – the 'Law') to become effective from 1 July 2015, introduces important amendments to the Federal Law dated 12 April 2010 No. 61-FZ 'On Medicines’Circulation' (here in after –"the 'FZ-61'”) in order to fill the gaps revealed in the course of the FZ-61 application, to improve the procedures for the state registration of medicines and to enhance state control over medicines’ quality and safety.

1. Terms and Definitions

The terminology of the FZ-61 (Article 4) was supplemented with such terms as: biological medicinal products, immunobiological medicinal products, biotech medicinal products, gene-therapy medicinal products, orphan medicinal products, homeopathic medicinal products, which evidence the actual variety of medicines traded on market.

The ‘original medicine’ concept was replaced with the concept of the ‘reference medicinal product’, which is a product being registered in Russia for the first time and the efficiency and safety of which is proved on the basis of preclinical trials and clinical trials performed in accordance with the FZ-61. A reference medicinal product issued to assess bioequivalence or therapeutic equivalence, quality, efficiency and safety of a generic or biosimilar medicinal product.

The ‘generic medicine’ concept was replaced with the concept of ‘generic medicinal product’; while it is clarified that bioequivalence or therapeutic equivalence of the medicinal product to a reference medicinal product should be supported by the relevant trials.

In this respect, the concepts of “therapeutic equivalence”, “biosimilar medicinal products (biosimilars)” and "interchangeable medicinal product", which is a product with proven therapeutic equivalence or bioequivalence against the reference medicinal product, as well as equivalent qualitative and quantitative composition of the active substance, composition of excipients, dosage form and mode of administration.

Moreover, the Law clarifies other terms such as pharmaceutical substance, unexpected adverse reaction and introduces terms used in the regulatory documents on a medicinal product: marketing authorisation holder, production site, generic name of the medicinal product.

Finally, the Law introduces terms and definitions important in the area of medicine circulation such as dosage, reference substances, pharmacopoeial reference substance.

2. Powers of Federal Executive Authorities

The powers of federal executive authorities in the sphere of medicines’ circulation are clarified and supplemented, they shall include, inter alia:

i. organization and (or) conducting audits of entities engaged in medicines’ circulation (i.e., individuals and legal entities operating in any of the following areas: development, preclinical trials, clinical trials, expertise, state registration,
standardization and quality control, production, manufacture, storage, transportation, import to Russia, export from Russia, advertising, release, sale, transfer, use, destruction of medicines) for compliance with the good manufacturing practices; issue of opinions on the compliance by the pharmaceutical manufacturer with the good manufacturing practices;

ii. issue, establishment of the issue procedures and the form of a document containing information about the stages of the medicine’s manufacturing within the territory of the Eurasian Economic Union;

iii. approval of the rules of good laboratory practice, the rules of good clinical practice, good manufacturing practice, good practice of medicines storage and transportation, good distribution practices, good pharmacy practice, good practice of pharmacovigilance over medicinal products for medical use;

iv. approval of the rules of rational choice of names for medicinal products of medical use, list of dosage forms names, requirements to instructions for medical use of medicinal products, and instructions for the veterinary use of medicinal products;

v. pharmacovigilance - monitoring of efficiency and safety of medicinal products with the aim to identify, assess and prevent adverse effects thereof;

vi. keeping the register of standard instructions for medical use of interchangeable medicinal products;

vii. out of court closing of websites that contain information on remote retail, offer to purchase remotely, remote delivery and (or) transfer of a medicinal products, narcotic and psychotropic medicines to an individual, except for the cases established by the Government of the Russian Federation.

The state control (supervision) in the area of medicines circulation, in addition to the licensing supervision over manufacturing of medicinal products and pharmaceutical activities, and federal state supervision over medicine circulation, will include sampling control of medicinal products, in particular:

- processing of information provided by entities engaged in medicines’ circulation on the series, lots of medicines coming into circulation in Russia;
- selection of medicines from entities engaged in medicines’ circulation for testing thereof for compliance with regulatory documents or regulations;
- taking a decision based on the results of the tests on further circulation of the given medicine;
- taking a decision to perform batch quality analysis of a medicine in case of repeated non-compliance of the medicine’s quality with the established requirements, and (if necessary) to audit the entity engaged in medicines’ circulation.

3. **State Registration of Medicinal Products**

The Law clarifies that the following is subject to the state registration to be allowed for circulation in Russia:

1. all medicinal products to be put in circulation in Russia for the first time;
2. medicinal products earlier registered but manufactured in different pharmaceutical dosage forms in accordance with the list of pharmaceutical dosage forms, in a new dosage subject to proving its clinical significance and efficiency;

3. new combinations of earlier registered medicinal products.

At the same time, the list of medicinal products that do not require the state registration was expanded: now it includes, inter alia, medicinal products imported to Russia for medical care in critical situation of an individual patient based on a permit issued by the competent federal executive authority (hereinafter - the 'competent authority'); pharmaceutical substances; medicinal products for export.

The term of the state registration of a medicinal product was reduced from 210 to 160 business days from the date of acceptance of the relevant application for state registration by the authorised body. This period still includes the time required for re-examination of the medicinal product.

The authorised body responsible for the state registration of medicinal products (currently - the Ministry of Health of the Russian Federation) will provide a scientific advice as requested by an entity engaged in medicines’ circulation on the issues related to preclinical trials, clinical trials of medicinal products, examination of medicines’ quality, efficiency and safety for the purposes of state registration.

The Law introduced a revised Article 17 of the FZ-61, which establishes the procedure for filing and consideration of application for the state registration of a medicinal product for veterinary use, including detailed requirements to the content of such an application and accompanying documents.

The requirements to the content of an application for the state registration of a medicinal product for medical use (Article 18 of the FZ 61) were also supplemented and amended.

The following deadlines were established for filing an application for the state registration:

- generic medicinal products for medical use - upon the expiry of 4 years from the state registration of the reference medicinal product in Russia;
- biosimilar medicinal products - upon the expiry of 3 years from the state registration of the reference medicinal product in Russia.

The master file for a medicinal product for medical use shall be provided in the form of common technical document and comply with the content requirements to its sections: administrative documents; chemical, pharmaceutical and biological documents; pharmacological, toxicological documents, including preclinical trials report on the medicinal product for medical use.

A preclinical trials report may be replaced with respect to:

- medicinal products approved for medical use in Russia for over 20 years (except for biological medicinal products) – with a review of scientific papers on the results of preclinical trials and clinical trials of medicinal products);
- generic medicinal products for medical use – with a review of scientific papers on the results of preclinical trials of the reference medicinal product, while the results
of clinical trials may be replaced with the results of bioequivalence trials in respect of the generic medicinal product for medical use.

As to orphan medicinal products (products intended solely for the diagnostics or path genetic treatment (treatment aimed at a disease pathogenesis) of rare (orphan) diseases), which were subject to clinical trials outside of Russia in accordance with the rules of good laboratory practice and good clinical practice, the clinical documentation may include a report on the results of such clinical trials instead of the report on the results of the same performed in Russia. Accordingly, there will be no need to conduct clinical trials in Russia in this case.

The authorised body shall verify the completeness, reliability and validity of the master file documents for a medicinal product and decide to issue the assignment for the relevant examination of the medicinal product within 10 business days after the date of application for state registration of the medicinal product.

Depending on the type of a medicinal product, there will conducted:

a. examination of documents submitted to determine whether the medicinal product for medical use can be considered as an orphan medicinal product (within a period not exceeding 30 business days after the receipt of the assignment from the authorised body);

b. examination of the medicine in terms of the quality thereof and the ration of expected benefits to possible risk of the use of the medicinal product for medical use (within a period not exceeding 110 business days after the receipt of the assignment from the authorised body); or

c. examination of the medicine in terms of the quality thereof and the ration of expected benefits to possible risk of the use of the medicinal product for medical use in the fast-track procedure for examination (within a period not exceeding 80 business days);

d. examination of the medicinal product in terms of a product for veterinary use.

The list of medicinal products, which may apply for the fast-track examination procedure was expanded so to include:

– orphan medicinal products;
– first 3 medicinal products registered in Russia as generics medicinal products (now the number of such products is not limited);
– medicinal products intended solely for under-age citizens.

In addition, there is a list of medicinal products, which cannot apply for the fast-track examination procedure, which includes, in particular, biosimilars, reference products (except for orphan products) and new combinations of earlier registered medicinal products.

The decision on the state registration of a medicinal product will be taken by the authorised body within a period not exceeding 10 business days after the receipt of the expert committee opinion on the results of examination of the medicine in terms of
the quality thereof and the expected benefits vs. possible risk of the use of the medicinal product.

A holder of the registration certificate for a biotech or orphan medicinal product shall be obliged to provide for a fee samples of reference medicinal products to applicants for clinical trials.

4. **Confirmation of the State Registration of Medicinal Products. Amending a Master File.**

The term of validity of the registration certificate of a medicinal product registered in Russia for the first time will remain 5 years, upon expiry of which a registration certificate without limitation of term will be issued provided that the state registration of the medicinal product has been confirmed.

The period for the issue of the term less registration certificate was reduced from 90 to 60 business days from the date of receipt of the relevant application by the authorised body.

The application for confirmation of the state registration of a medicinal product shall be filed with the authorised body no earlier than 180 days prior to the expiry of the initial registration certificate.

The state registration of a medical product that has not been in circulation in Russia for 3 or more years, as well as of medicines in packages labelled before the entry of FZ-61 into force may not be confirmed.

The list of instances for amending the master file documents of a registered medicinal product in which examination of the medicinal product in terms of quality and (or) the expected benefit vs. the possible risk of the use of the medicinal product for medical use is up-dated, such instances include changes:

1) data provided in the patient information leaflet;
2) preparation formula;
3) manufacturing site producing the medicinal product;
4) factor of the quality of a medicinal product and (or) quality control methods;
5) medicinal product expiration date.

The relevant medicinal product may be in circulation until its expiry date, provided that it has been produced within 180 days after the confirmation of its state registration or amendment of the master file documents.

5. **Cancellation of the State Registration of Medicinal Products**

Additional grounds for cancellation of the state registration of medicinal products are provided for:

a. no circulation of the medicinal product in Russia for 3 or more years;
b. a failure of the holder of the registration certificate or an entity authorised by the latter to take measures to ensure the safety of the medicinal product as established by the authorised body in the course of pharmacovigilance;
c. a refusal by the holder of the registration certificate or an entity authorised by the latter to amend the patient information leaflet with new confirmed information on the risk of harm to human or animal health that may be caused by the medicinal product exceeds its efficiency.

6. State Register of Medicinal Products

The list of information on medicinal products contained in the state register of medicinal products (here in after - the 'Register') was expanded to include, in particular:

- qualitative and quantitative composition of the active substance, composition of excipients;
- inclusion of the product in the list of vital and life-saving medicinal products;
- information on whether the product is a reference medicinal product;
- information on the product’s interchange ability;
- a term of product’s circulation.

In addition, the Law established the list of information to be included in the Register in respect of pharmaceutical substances produced for sale.

The procedure for inclusion in and exclusion from the Register of a pharmaceutical substance produced for sale was updated.

By analogy with the medicinal products, it is prohibited to include into the Register one pharmaceutical substance produced for sale by the same manufacturer as two or more register entries.

7. Interchange ability of Medicinal Products for Medical Use

The FZ-61 was supplemented with Article 27.1, which provides for the procedure for determining the interchange ability of medicinal products for medical use, in particular, parameters for comparison. However, this procedure does not apply to the reference medicinal products, herbal medicinal products, homoeopathic medicinal products and medicinal products approved for medical use in Russia for over 20 years and which are impossible to be examined in terms of bioequivalence.

Comparison of parameters of registered medicinal products for medical use to determine their interchange ability shall be performed by the expert committee of an expert institution when examining such products for the purpose of the state registration.

There are the following transitional provisions to determine the interchange ability of medicinal products for medical use registered before 1 July 2015: interchange ability of such medicinal products shall be determined by the expert committee of the authorised federal state-financed institution in the course of the examination of medicinal products for medical use in terms of quality thereof and (or) the expected benefit vs. the possible risk of
the use of such products, based on the assignment issued by the authorised body before 31 December 2017.

Holders of registration certificates may apply for determining the interchangeability of medicinal products for medical use according to the procedure specified by the FZ-61 (as amended by the Law) until 31 December 2016.

The results of such determination may be used (in particular, in the course of state or municipal procurement tenders) starting from 1 January 2018.

From the same date information on the interchangeability of medicinal products for medical use shall be included in the Register.

8. Clinical Trials

The procedure for submission of documents to obtain a permit for clinical trials of a medicinal product for medical use and for taking decision by the authorised body to conduct clinical trials was updated.

Examination of the documents filed to obtain a clinical trial permit and ethical review, as well as provision by the experts committee and the ethics council of opinions on the possibility or impossibility of such clinical trials and submission of the opinions to the authorised body shall be performed within 30 business days after the receipt by an expert institution of the assignment for the respective examination.

An opinion of the expert committee or an opinion of the ethics council on the impossibility of clinical trials of a medicinal product based on the results of examinations is provided as the only reason for the refusal in issuing a permit for the respective clinical trials.

A decision of the authorised on the refusal in granting a clinical trial permit, as well as the refusal in the state registration of a medicinal product, opinions of the expert committee or the ethics council may be appealed according the procedure specified by the laws.

Clinical trials of a medicinal product for medical use may be suspended or terminated, if the authorised body comes to a conclusion upon the results of audit of one or several medical institutions engaged in the clinical trials that such trials have been performed with violations of the good clinical practice.

If upon the results of such audit violations of the good clinical practice are revealed affecting the completeness and (or) accuracy of the clinical trials, the decision to conduct the clinical trial shall be withdrawn by the authorised body.

9. Manufacturing of Medicines

Instead of the rules of the manufacturing management and quality control of medicines (currently the Rules approved by the Order of Ministry of Industry and Trade of Russia dated 14 June 2013 No. 916 are in effect) manufacturing of medicines must comply with the rules of good manufacturing practice approved by the competent authority.
Opinions on compliance by medicines’ manufacturers with the requirements of good manufacturing practice will be issued upon the results of inspections of the manufacturers in accordance with the procedure established by the Government of the Russian Federation, for a fee.

The Government will also adopt requirements for the containers’ size, packaging, completeness of certain medicinal products.

Pharmaceutical substances not included in the Register and produced for clinical trials and export may be used for manufacturing of medicines.

10. Pharmaceutical Practice

Wholesale of medicines shall be performed by medicines’ manufacturers and medicines’ wholesale organisations according to the rules of good distribution practice and the good practices of storage and transportation of medicinal products approved by the authorised bodies.

The authorised body will also approve the rules of good pharmacy practice under which the medicines’ retail sale will be carried out.

11. State Regulation of Prices for Medicinal Products

The list of vital and essential medicinal products (VEMP) will be adopted by the Government of the Russian Federation based on a comprehensive assessment of medicinal products, including review of data on comparative clinical efficacy and safety of a medicinal product, assessment of the economic effects of the medicinal product use and study of additional effects of the medicinal product use.

State regulation of prices for medicinal products for medical use will be also performed by the introduction of reference pricing mechanisms.

Calculation of the maximum sale prices for medicinal products included in the list of VEMP, in case of their state registration or re-registration, will be made in accordance with the methods approved by the Government of the Russian Federation, taking into account, inter alia:

- actual sale price of medicinal products in Russia, price of import of medicinal products to Russia, as well as prices for similar medicinal products being in circulation in Russia;
- costs of medicinal products’ manufacturer to produce and sell the product;
- price of a foreign medicinal product, its price in the country of origin and in the countries where the medicinal product was registered and (or) imported in by a foreign manufacturer.

The Law prohibits sale, including retail sale, of:

i. medicinal products being VEMP, for which the manufacturers have not registered the maximum sale price;
ii. medicinal products by manufacturers at prices higher than the registered maximum sale prices for the respective medicinal products;
iii. medicinal products by wholesalers and retailers at prices exceeding the actual sale price given the ultimate limit wholesale and retail mark-ups.

12. Pharmacovigilance. Suspension of a Medicinal Product’s Use

Pharmacovigilance will be performed by the authorised body by means of review of the information provided by entities engaged in circulation of medicines and related to facts and circumstances evidencing a threat to life or health of a person or animal by the use of medicinal products identified at all stages of circulation of medicinal products both in Russia and in other countries.

Holders of registration certificates and entities in whose name the permits for clinical trials in Russia have been issued, or entities authorised thereby (hereinafter - the ‘holders of registration certificates or their authorised representatives’) shall be liable for the acceptance, recording, processing, analysis and storage of the following information received from any entities engaged in circulation of medicines and state authorities:

- on side and adverse effects;
- on serious unexpected adverse effect of using medicinal products;
- on the features of the medicinal product’s interaction with other medicinal products, on idiosyncrasy;
- on other facts and circumstances that pose a threat to the life or health of a person or animal or involving a change in the expected benefit vs. the possible risk of medicine’s use ratio.

A holder of a registration certificate is required to report to the authorised body on the results of pharmacovigilance once every 6 months during 2 years after the state registration of a medicinal product in Russia, each year during the next 3 years and thereafter once every 5 years.

The relevant persons shall be liable for failure to report or concealment of the abovementioned information (currently such a liability is established by Article 19.7.8 of the Code on Administrative Offences of the Russian Federation for a failure to report or a delay in provision of information to the federal executive authority for control and supervision in the area of healthcare, its territorial division, or for knowingly provision of false information, in the form of an administrative fine on officials in the amount of 10,000 to 15,000 roubles, on legal entities - in the amount of 30,000 to 70,000 roubles).

Holders of registration certificates or their authorised representatives will be also required to take measures to eliminate the negative effects of the use of medicinal products, to prevent harm to life or health of users of medicinal products, to collect additional data on the efficacy and safety of medicinal products in identifying information on serious unexpected adverse effects of using medicinal products, on the features of their interactions with other medicinal products, on idiosyncrasy and other facts and circumstances involving a change in the expected benefit vs. the possible risk of the use of medicinal products ratio.
The grounds for suspension of the use of medicinal products by the authorised body were also clarified:

- receipt of information on adverse effects of using medicinal products not specified in the direction for use, serious unexpected adverse effects, features of their interactions with other medicinal products that may pose a threat to the life or health, non-compliance efficiency and safety data to the data contained in the patient’s information leaflet, including information provided by competent authorities of foreign countries;
- a failure to perform or improper performance by the holders of registration certificates or their authorised representatives of obligations to provide information;
- submission by the relevant authorised body of the opinion on the unreliability of the results of clinical trials of a medicinal products for medical use;
- a failure to observe an instruction issued by the authorised body on the basis of medicinal products’ sampling control results.

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Many of the amendments introduced to the FZ-61, in particular those concerning the state registration of medicinal products, performance of pharmacovigilance by the authorised body, procedure for determining the interchange ability of medicinal products, methods of calculation of maximum wholesale price for VEMP, must be specified by bylaws – decrees of the Government of the Russian Federation, orders of the Ministry of Healthcare and other authorities. In addition, the rules of good manufacturing practice, good distribution practices, good practices of storage and transportation of medicinal products, as well as good pharmacy practice must be approved.

We will keep you informed on further developments in the regulation of the medicines’ market as the relevant regulations are adopted and entered into force.

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Best Regards,

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