Legal alert

pepeliaev group

January 15, 2015

IMPORTANT AMENDMENTS HAVE BEEN MADE TO THE LAW ON CIRCULATION OF MEDICINES

For the attention of developers and manufacturers of medicines

Pepeliaev Group advises that on 22 December 2014 the Russian President signed Law No. 429-FZ "On amending Federal Law 'On Circulation of Medicines'" (the "Law"). On 23 December 2014 this Law was published on the official online legal information portal (www.pravo.gov.ru).

Importance

The Law has made many amendments to Federal Law No. 61-FZ 'On Circulation of Medicines' dated 12 April 2010 (the "Circulation Law") which are aimed at improving the procedures for the state registration of medicines, filling the gaps in terminology and removing from the market medicines which are ineffective, unsafe or of poor quality.

These amendments have been much anticipated by the business community. They are a result of extensive discussions between state authorities and the pharmaceutical industry. Please note that most amendments will come into effect on 1 July 2015 and for certain provisions other dates have been set when they become effective. These are specified separately in this overview.

Summary of the main changes

1. Improvements and additions to the conceptual framework of the Circulation Law

- Definitions have been set for the first time for certain categories of medicines including orphan, biological, immunobiological, gene therapy and homoeopathic medicines. The concepts of a "registration certificate holder (owner)" and "manufacturing site" have been defined.
- A definition has been introduced of an owner or a holder of the registration certificate for a medicine. These may be the developer of the medicine or the manufacturer of it or another legal entity that has the right to hold the registration certificate.
- The conceptual framework has been developed and set to define the interchangeability of medicines (the following concepts have been defined: an Interchangeable Medicine, a Reference Medicine, Therapeutic Equivalence and Bioequivalence). Further, new definitions have been added for concepts in the area of pharmacovigilance.

2. Orphan Medicines

- In accordance with the amendments, *Orphan Medicines* are medicines intended solely for diagnosing or providing pathogenic treatment (a treatment directed at the mechanisms that lead to the disease developing) of rare (*orphan*) diseases.

- The Russian Ministry of Health decides on the basis of an expert opinion whether a medicine may be treated as an orphan medicine when state registration of it takes place. Once this decision has been made, the registration progresses under an expedited procedure (not more than 80 business days). It is permitted for pre-clinical and clinical trials of a medicine not to be conducted in Russia if such trials of this medicine have already been performed abroad in accordance with the Good Laboratory Practice (GLP) and Good Clinical Practice (GCP) rules.

3. Biologic Medicines

- According to the wording of the Law, *Biologic Medicines* are medicines whose active ingredients are produced or derived from biological sources and which, for their properties and quality to be discerned, require a combination of biological, physical and chemical methods. Such medicines include immunobiological preparations, medications derived from human or animal blood or blood plasma (except for the whole blood), biopharmaceuticals and gene therapy preparations.

- *Immunobiological preparations* are aimed at generating active or passive immunity or diagnosing the availability of immunity or specific acquired changes in the immunological response to allergenic substances (vaccines, anatoxins, toxins, serums, immunoglobulins and allergens). *Biopharmaceuticals* are produced using biotechnological processes and methods (including recombinant DNA technology and methods of controlling expression of genes which encode biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells), hybridoma technology and monoclonal antibody technology. The pharmaceutical substances of *gene therapy preparations* are, or contain, recombinant nucleic acids which can regulate, repair, replace, add or remove a genetic sequence.

- When biopharmaceuticals are registered that are derived from human blood or blood plasma, the source of the biological material from which the preparation is produced is subject to special control. The registration dossier for such medicine must additionally contain a document with the information on: the parties involved in the circulation of the donated blood and/or its components; the place of blood and/or plasma donation; data on parenterally transmissible infectious diseases; and the parties involved in the circulation of the donated blood and/or its components in relation to which the control of the donated blood and/or its components is carried out.

- A biopharmaceutical whose quality, effectiveness and safety parameters are *similar* to those of the reference biopharmaceutical in the same dosage form and that has an identical form of administration is called *a bio-analogous (biosimilar) preparation*. As distinct from generic medicines, the expedited registration procedure may not be used for biosimilar preparations.

4. Generic Medicines

In accordance with the adjusted definition, a generic medicine is a medicine that has the same qualitative and quantitative composition of active substances in the same dosage form as the reference medicine and whose bioequivalence and therapeutic equivalence to the reference medicine have been confirmed by proper research.

The registration procedure for generic medicines is considered in detail in part 6 of this review.

5. Interchangeability

- Interchangeability has been defined as a set term at the initiative of the Russian Federal Antimonopoly Service (the “FAS”). The antimonopoly regulator's intention for this new development was for competition to increase in the public procurement sector, for state budget funds to be used in a more rational way and for the procurement process for medicines to become more transparent. In accordance with the Law, preparations are treated as interchangeable medicines if their bioequivalence and therapeutic equivalence to the reference medicine have been confirmed and their qualitative and quantitative composition of active substances, composition of auxiliary substances, dosage form and administration form are equivalent to those of the reference medicine.

- Whether preparations are interchangeable for the purposes of medical use is established by an expert commission of an expert organisation. This forms a part of the state registration process and should comply with the procedure set by the Russian Government. Experts check different parameters of the medicines that are being compared including: equivalence (comparability) of qualitative and quantitative characteristics of the pharmaceutical substances; equivalence of the dosage form; equivalence and comparability of the composition of auxiliary substances; equivalence of the forms of administration and application; and the absence of clinically relevant differences when bioequivalence of the medicines is tested or absence of clinically relevant differences between the safety and effectiveness indicators in case of therapeutic equivalence.

- Starting from 1 January 2018, data on the interchangeability of medicines should be entered in the State Register of Medicinal Remedies, and it will be permitted for the results of interchangeability tests of specific medicines to be used. The Law sets several transitional rules for the period up to this date:

  (а) the Russian Ministry of Health should assign to all its subordinate authorities the task for the years 2015-2017 of establishing the interchangeability of medicines which had been registered before the Law came into force;

  (б) on the basis of the task from the Ministry of Health, the authorities must until 31 December 2017 establish the interchangeability of medicines which had been registered before the Law came into force while an expert examination of the medicines is conducted in terms of their quality and/or an analysis of the expected benefit against the possible risk;

  (в) until 31 December 2016 holders and owners of the registration certificates for medicines may file applications to have the interchangeability of medicines established using the procedure for changes to be made to the registration dossier for the medicine.

6. Registration of Medicines

- *Timeframes*

  The timeframe for the state registration of medicines has been reduced from 210 to 160 business days from when the application for the state registration of a medicine is accepted. The timeframe for an expedited registration has been increased from 60 to 80 business days and the expedited registration procedure can now be applied to the first three registered generic medicines, orphan medicines and medicines for children of minority age.

  Registration of the fourth and next generics should be performed according to the regular procedure.

- *Scientific consultations*

  The Ministry of Health has been given a new function - to provide advice to parties to the circulation of medicines further to their requests (electronic or printed) connected with pre-clinical and clinical trials, expert examination of the quality, effectiveness and safety of medicines as well as their state registration. The advice should be provided in the form of the Ministry's written response to the request. To draft the response, authorities should be engaged that are subordinate to the Ministry and are not involved in the expert examination of the medicines' quality for the purposes of their state registration. The fees payable for the advice should be established in accordance with the Russian legislation on state and municipal services. Information on scientific consultations should be published on the official website of the Ministry of Health.

- *Data Exclusivity*

  In accordance with the Law, there has been no change to the exclusivity period for data concerning the results of pre-clinical and clinical trials. This has remained 6 years from the date of the state registration of the original medicine in Russia. At the same time, the current version of the Law provides that the data exclusivity rules apply to data being received, disclosed or used for commercial purposes and for the purposes of state registration. However, in accordance with the new version of the Law the 6-year exclusivity will apply only to the use for commercial purposes of data concerning the results of pre-clinical and clinical trials. To register a generic medicine its manufacturer may submit an application 4 years after the state registration date of the original medicine in Russia. Manufacturers of biosimilar preparations may submit such applications 3 years after the state registration date of the original medicine in Russia.

The Law stipulates that a holder (owner) of the registration certificate to a biopharmaceutical or orphan medicine must, for a fee, provide applicants with samples of the reference medicine for the purposes of clinical trials. At the same time, if the medicine is on the list of vital and essential medicines, the fee for a sample of it may not exceed the registered selling price limit for such medicine or the price of such medicine in the country of the manufacturer.

- *Registration Dossier*

  There has been a change to the requirements for the form of the registration dossier for a medicine. Now the dossier will need to be drafted in the form of a common technical document containing administrative, chemical, pharmaceutical, biological, pharmacological, toxicological and clinical documentation. The new format is similar to dossiers in CTD (Common Technical Document) format, as used in other countries. The Law sets detailed requirements for the content and configuration of the documentation in each section of a common technical document. The common technical document format is yet to be approved by the Ministry of Health. These amendments will come into force on 1 January 2016.

- *Additional cases when registration of a medicine may be revoked*

  Now a medicine may also have its registration revoked in the following cases:

  - where a holder (owner) of the registration certificate or any other legal entity it has authorised[1] files an application for the state registration of the medicine to be revoked;
  - where state registration is being obtained for a medicine under a trademark of a medicine that has previously been registered and has had a different qualitative composition of active substances;
  - where the medicine has not been in circulation in Russia for three or more years;
  - where a holder (owner) of the registration certificate or any other legal entity it has authorised fails to take steps to ensure the safety of medicines required by the Federal Service for Surveillance in Healthcare and Social Development (known in Russia by the abbreviation 'Roszdravnadzor') in the context of pharmacovigilance;
  - where a registration certificate holder (owner) or any other legal entity it has authorised refuses to make amendments to the patient information leaflet with regard to new confirmed data that the risk of harm being caused to the health of people or animals as a result of the medicine being taken is higher than the effectiveness of the medicine.

7. Control and supervision of the circulation

- It is expressly stated that a competent authority (Roszdravnadzor) is in charge of the federal state supervision of the circulation of medicines. The supervision procedure is established by Federal Law No. 294-FZ 'On protecting the rights of legal entities and individual entrepreneurs in the course of state (supervisory) and municipal control' dated 26 December 2008 (the “Law on Audits”). This takes account of specific matters set out in the Circulation Law. At the same time no changes have been made to the article of the Law on Audits that allows specific aspects of audits to be determined for entities in various industries. Neither does it contain clauses providing that exemptions may be established in other federal laws with regard to audits of parties involved in the circulation of medicines. In other words, at present there is a contradiction.

- The Law provides for an exception from the general rule of the Law on Audits. This general rule holds that any unscheduled audits should be agreed in advance with prosecuting authorities and that entities being audited should be notified in advance when the audit should start. According to the Law no such preliminary arrangements or notifications are now required. Prosecuting authorities will be informed of unscheduled audits by relevant documents being sent within 3 business days after an audit has been completed.

These provisions are in conflict with the Law on Audits, thus placing controlled entities in a worse position. The provisions of these two laws need to be harmonised.

[1] Previously, only the developer of the medicine or a party it had authorised had this opportunity.

- An opportunity has been introduced for Roszdravnadzor to perform a sample quality check of medicines. The state authority carries out such checks based on the information which parties involved in the circulation of medicines submit on a compulsory basis with regard to series and lots of medicines that are put into commercial circulation in Russia. Previously such an opportunity was established by Roszdravnadzor's administrative regulations[2]. Now the same opportunity has been enshrined on the level of a federal law. During a sample check, specimens of medicines are selected and tested to find out whether the medicines meet the requirements set out in regulatory documents. Based on the test results, Roszdravnadzor may take a decision to continue the civil circulation of the relevant medicine. If it has been discovered for a second time that the quality of the medicine fails to meet the set requirements, Roszdravnadzor may take a decision to change the basis for the batch sample checking of such medicine, and to audit (if necessary) the party involved in the circulation of medicines. The law determines that expenses concerning such batch sample checking are covered by manufacturers of the medicine or the holder (owner) of the registration certificate for the medicine.

8. Pharmacovigilance

- An important new development of the Law is that responsibility for the quality, effectiveness and safety of a medicine is expressly imposed on the holder of the registration certificate. The holder of the certificate is now obliged:
  - to implement a pharmacovigilance system and ensure that it functions properly. This means the holder must accept, keep a record of, process, analyse and store notices from parties involved in the circulation and from state authorities. Such notices may concern side effects, adverse effects, serious or unexpected adverse reactions occurring when a medicine is taken, specific aspects of its interaction with other medicines, or individual intolerance. They may also concern other facts and circumstances that pose a threat to the life or health of people or animals or affect the risk/benefit ratio of the medicine.
  - to inform Roszdravnadzor of all the above events, including of the medicine's lack of effectiveness if this has been identified while the medicine was being circulated in Russia and abroad.
  - to report pharmacovigilance results to Roszdravnadzor every six months during the two years after the medicine was registered in Russia, every year during the following three years and every five years subsequently.
- If the certificate holder or any other legal entity it has authorised fails to take actions to ensure that medicines are safe, this may result in the state registration of the medicine being revoked in Russia or its use being suspended within Russia.

9. Good practices (GxP)

- It has been determined that the fact of a manufacturer of medicines meeting the requirements of the good manufacturing practice (GMP) should be confirmed by the Ministry of Health's statement that the manufacturer complies with the GMP rules (the “GMP certificate”). The Ministry should issue a GMP certificate based on the results of the manufacturing facilities inspection.
- The Ministry of Health has powers to organise and/or hold such inspections, to issue GMP certificates, to establish the procedure for keeping the state register of GMP certificates issued, and to keep the register.
- It has been laid down that the Ministry of Health must develop and approve good practice rules to replace the existing Rules of retail trading in pharmaceuticals, Rules of wholesale trading in pharmaceuticals and the Procedure for monitoring the safety of preparations intended for medical use[3]. Such documents include Good Distribution Practices, Good Pharmaceutical Storage and Transportation Practices (for wholesale purposes), Good Pharmacy Practices (for retail trade purposes), and Good Pharmacovigilance Practices.

[2] Administrative regulations of the Federal Service for Surveillance in Healthcare and Social Development concerning the state function of organising expert checks for quality, effectiveness and safety of medicines (approved by Order No. 734 of the Russian Ministry of Health and Social Development dated 30 October 2006)

[3] Approved by Order No. 757n of the Russian Ministry of Health and Social Development dated 26 August 2010.

The trend of bringing activities of parties involved in circulation in line with good practice corresponds to the general approach in the healthcare policy. Such approach is aimed at turning the system of regulating the circulation of medicines into the one conforming to the world's best practices. This should make Russian medicines more competitive on the world market and lead to Russia being a country in which the production of pharmaceuticals may be localised.

10. The Rules have been clarified in relation to the procedure for including pharmaceutical substances in the list of registered pharmaceutical substances and keeping such list of registered pharmaceutical substances.

At present, pharmaceutical substances do not need to be registered as such. The current version of the Circulation Law contains a term for such substances -"pharmaceutical substances not used for manufacturing medicines" - and this term has turned out not to be entirely satisfactory. In the new version the term has been changed for "pharmaceutical substances produced to be sold". A procedure has also been established to include the substances in (or exclude them from) the register, with requirements set for the register entries concerning the substances, and a procedure for an expert examination of such substances' quality.

Please note that regulations concerning the procedure for performing an expert examination of the quality of pharmaceutical substances will come into force on 1 January 2016.

11. Amendments to the rules for clinical trials of medicines

- The requirements for professional experience have been reduced for a principal investigator in clinical trial programmes. Now a head of a medical institution conducting clinical trials may appoint a person as principal investigator if he/she has a minimum of 3 years' professional experience, as opposed to the 5 years previously required.
- The law provides that the Ministry of Health may engage experts from the ethics board to consider requests for amendments that need to be made to the clinical trial report. This will be done to evaluate whether the proposed amendments are justified and to assess the degree of risk for patients participating in the trial.
- A clinical trial may be suspended or terminated if Roszdravnadzor provides a statement that the trial has been conducted with violations of good clinical practices. Such statements should be drafted based on the audit results of the medical institutions which are performing the trial. The Ministry of Health should cancel a decision to carry out a clinical trial if, following the audit of medical institutions which are performing the trial, a report is provided to Roszdravnadzor stating that in the course of the trial violations of good clinical practices have been identified and such violations affect the completeness and/or reliability of the clinical trial.

12. Registering prices for pharmaceuticals included in the list of vital and essential medicines

- The law has allowed all manufacturers to annually re-register the maximum selling price for pharmaceuticals included in the list of vital and essential medicines. (Now only Russian manufacturers have this opportunity.)
- To date, when the maximum selling price was registered or re-registered to a pharmaceutical included in the list of vital and essential medicines, the Russian Ministry of Health has been taking into account the actual selling price for the medicine in Russia, its price in other countries, prices for similar medicines circulated in Russia, expenses connected with developing, manufacturing and selling it, and the inflation. According to the new rules, in addition to the above quantifiable parameters, the Ministry of Health should consider whether the balance is observed between the interests of consumers and the interests of manufacturers of pharmaceuticals included in the list of vital and essential medicines.

It appears that such an approach presupposes that extensive powers will be granted to the Ministry of Health to act at its discretion when registering (or re-registering) maximum prices. And its practical application should be clarified/made more specific by way of amendments being made to the Guidelines for manufacturers of medicines for setting maximum selling prices to pharmaceuticals included in the list of vital and essential medicines[4].

What to think about and what to do

In view of the global nature of the amendments, we recommend that you analyse relevant plans and strategies of the company for the coming period subject to the new regulatory developments which have opened up opportunities but at the same time have imposed new obligations on parties involved in circulating medicines.

Help from your adviser

Pepeliaev Group's lawyers are ready to advise you on how the new legal provisions are applied, to work out the necessary documents and internal regulations, to represent your company before state authorities in relation to state registration, clinical trials, manufacturing and ensuring pharmacological vigilance with regard to your company's medicines. We will be happy to answer all the questions that arise in relation to of the above developments.

Contact details

Vladimir Sokov
Senior Partner,
Head of Corporate Division
Pepeliaev Group
T.: +7 (495) 967-00-07
v.sokov@pgplaw.ru

Oxana Migitko
Head of Commercial Practice
Pepeliaev Group
T.: +7 (495) 967-00-07
o.migitko@pgplaw.ru

Sergey Klimenko
Senior Associate,
Project coordinator for the pharmaceutical and medical industry
Pepeliaev Group
T.: +7 (495) 967-00-07
s.klimenko@pgplaw.ru

Sergey Spasennov
Partner (St Petersburg)
Pepeliaev Group
T.: +7 (812) 640-60-10
s.spasennov@pgplaw.ru

Egor Lysenko
Head of Siberian office
in Krasnoyarsk
Pepeliaev Group
T.: +7 (391) 277-73-00
e.lysenko@pgplaw.ru

[4] Guidelines for manufacturers of medicines for setting maximum selling prices for pharmaceuticals included in the list of vital and essential medicines (approved by Order No. 961n of the Russian Ministry of Health and Social Development and No. 527-a of the Russian Federal Tariff Service dated 3 November 2010).