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Overview of Changes to Laws Governing Circulation of Medicinal Products

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*On December 22, 2014 President of the Russian Federation signed Federal Law No. 429-FZ "On Amendments to Federal Law No. 61-FZ "On Circulation of Medicinal Products" (**"Law"**), which introduces significant changes to Federal Law No. 61-FZ "On Circulation of Medicinal Products" (**"Medicines Law"**). While most of the changes are taking effect as of July 1, 2015, some of the new provisions will be effective as of January 1, 2016 or January 1, 2017, as applicable.*

On March 8, 2015 Federal Law No. 34-FZ "On Amendments to Article 61 of the Federal Law "On Circulation of Medicinal Products" was adopted, which introduces changes concerning maximum sale prices for vital and essential drugs. The changes will take effect as of July 1, 2015, except one of them which has already taken effect on March 16, 2015.

Also, on December 23, 2014 the Agreement on Unified Principles and Rules of Circulation of Medicinal Products within the Eurasian Economic Union (EAEU) was signed in Moscow, which should take effect after its ratification by all Member States on January 1, 2016 at the earliest.

Some of the most important changes to the Medicines Law are discussed below.

General – Purpose of Changes to the Medicines Law

The need to update the legal framework for circulation of medicinal products has been pointed out by pharmaceutical and legal experts and professionals for quite a while. The weak points of the old Medicines Law identified by experts are, in particular, inconsistency of terminology, lack of harmonization with global practices, regulatory lacunas in relation to circulation of generic drugs, failure to keep pace with pharmaceutical market developments. Although some changes had been made from time to time to the Medicines Law, they failed to solve the said issues. During 2013 and 2014 legislators were intensely involved in drafting a new tranche of changes to address most critical problems. Several drafts of the amendment law were provided for discussion, including draft No. 555485-6 which was finally approved by the State Duma of the Russian Federation. According to the explanatory note for that draft, the changes purport to optimize the range and ensure adequate quality of medicines circulating in the market; to vest federal authorities with additional powers required for implementation of the Medicines Law; and to increase satisfaction level of applicants seeking authorization of medicinal products.

In pursuance of the changes introduced by the Law, a number of subordinate legislative instruments being currently drafted by the RF Government and the Russian Ministry of Health are to be adopted. Some of the drafts are available for review and discussion at (http://regulation.gov.ru/) (website posting legislative instruments drafted by federal authorities and results of public discussion thereof). Presumably, relevant resolutions of the RF Government will be adopted by July 1, 2015 and departmental regulations of the Ministry of Health during the 3rd quarter 2015.

Updated and New Definitions

The new Medicines Law updates some existing definitions and adds a number of new ones. The Law now provides definitions for drug categories such as *orphan, biological, immunobiological, biotech, gene-therapeutic, homeopathic and biosimilar medicinal drugs.*

Updated are the definitions of *pharmaceutical substance*, *international non-proprietary name, trade name of a medicinal product.*

Some of the existing definitions will be adjusted by the forthcoming amendments made as part of the overall updating of the terminology used in the Medicines Law. Thus, the term "*brand-name medicinal product"* will be replaced by "*reference medicinal drug"* and "*generic medicinal product"* by *"generic medicinal drug".*

Also, the amended Medicines Law provides a new term "*holder of authorization of a medicinal drug"* (holder of product license) which means a drug developer, a drug manufacturer or other legal entity who is entitled to such authorization and bears responsibility for quality, efficacy and safety properties of the drug.

Interchangeable Medicinal Drugs

As defined by the Law, an *interchangeable medicinal drug* means a drug with proven therapeutic equivalence or bioequivalence to a *reference medicinal drug*, which has equivalent qualitative and quantitative composition in active ingredients, equivalent composition in excipients and has equivalent dosage form and route of administration.

Interchangeability of medicinal drugs for human use will be evaluated based on the following six parameters:

1) equivalence (or biosimilar comparability, where applicable) of qualitative and quantitative characteristics of pharmaceutical substances;
2) equivalence of dosage form;
3) equivalence or comparability of excipients;
4) sameness of route of administration;
5) no clinically significant differences revealed by bioequivalence study or therapeutic equivalence study;
6) compliance by the manufacturer of a medicinal product with Good Manufacturing Practice guidelines.

Evaluation of drugs for their interchangeability should be performed by a commission of examiners of an expert institution as part of the national authorization procedure. The guidelines for evaluation of interchangeability of drugs for human use are to be set by a relevant resolution of the RF Government which is expected to be issued on July 1, 2015 at the latest.

Starting from January 1, 2018 information on interchangeability of medicinal drugs will be included in the National Register of Medicinal Products. Use of the results of drug interchangeability evaluation for human use will be allowed from January 1, 2018 as well. Until that time the following transitory provisions will apply:

- No later than December 31, 2016 an authorization holder may submit an application for drug interchangeability evaluation, in accordance with the procedure for making amendments to the registration dossier for a drug;
- No later than December 31, 2017 interchangeability of drugs nationally authorized before July 1, 2015 will be evaluated on request of the Ministry of Health by examiners of relevant expert institutions, as part of quality and risk-benefit evaluation of a drug.

As envisioned by the Federal Antimonopoly Service of Russia (who was the initial proponent of including the interchangeability evaluation procedure in the Medicines Law), interchangeability evaluation should increase competition in the medicinal product market and enhance transparency in public procurement of medicinal products.

Good Practice Guidelines (GxP)

One of the key novelty provisions of the Law is required approval of GxPs including:

- *Good Laboratory Practice*, *or GLP* applicable to preclinical studies;
- *Good Clinical Practice, or GCP* applicable to clinical trials;
- *Good Manufacturing Practice, or GMP* applicable to manufacture of medicinal products;
- *Good Storage Practices, or GSP* applicable to storage and transportation of medicinal products;
- *Good Distribution Practice, or GDP* applicable to wholesale trade in medicinal products;
- *Good Pharmacy Practice, or GPP* applicable to retail trade in medicinal products and dispensing of prescription drugs at pharmacies;
- *Good Pharmacovigilance Practice, or GPvP or GVP* applicable to medicines regulatory authorities performing pharmacovigilance and to pharmaceutical entities for the purpose of compliance with pharmacovigilance requirements.

GxP guidelines are a widely used and internationally recognized mechanism to ensure adequate quality of medicinal products, which provides operating standards for each stage of circulation of medicinal products. Currently the Ministry of Health of Russia is developing applicable good practice guidelines which presumably will be issued in the 3rd quarter 2015.

Please note that, in accordance with the Agreement on Unified Principles and Rules of Circulation of Medicinal Products within the Eurasian Economic Union (EAEU), any activities relating to circulation of medicinal products in the EAEU single market must be in conformity - at each circulation stage - with applicable pharmaceutical good practices approved by the EAEU Commission. Now the Commission is developing such practices.

Clinical Trials and Authorization of Medicinal Products

The new Medicines Law significantly changes the clinical trial and authorization (national registration) procedures for medicinal products. The changes relating to national authorization will be introduced in three stages taking effect as of July 1, 2015, January 1, 2016 and January 1, 2017 respectively.

Clinical Trials

The Law takes clinical trials and ethical review out of the national authorization procedure for a medicinal product. Starting from 1, 2015 clinical trials will be a separate procedure requiring an approval of clinical trials of a medicinal drug for human use, which must be conducted in compliance with applicable Good Clinical Practice guidelines. Such approval will be issued based on the findings of expert review of documents submitted for obtainment of an approval to conduct clinical trial and ethical review. Clinical trials may be suspended or terminated if it is discovered that they are conducted by a medical institution otherwise than in compliance with applicable Good Clinical Practice guidelines.

Authorization of Medicinal Products. Timelines

The overall period for authorization of a medicinal drug has been reduced from 210 to 160 business days (provided that this period does not include time required for the Ministry of Health to make inquiries and receive answers).

The maximum period for accelerated expert examination of a drug has been increased from 60 to 80 business days. Once the Law comes into effect, the accelerated examination procedure will be available for *orphan medicinal drugs,* for first three *generic medicinal drugs* applied for authorization in Russia (any subsequent generics will be subject to the general authorization procedure) and for *medicinal drugs intended exclusively for use in the pediatric population*.

It should be noted that, for medicinal drugs declared as *orphan drugs* for authorization*,* a review of documents must first be performed to determine whether or not the medicinal drug can be regarded as orphan before proceeding with the accelerated expert examination of the drug. If the drug is recognized as orphan, the Ministry of Health will order to perform a quality examination and risk/benefit analysis of the drug, in accordance with the accelerated examination procedure.

The maximum period for renewal of national authorization of a medicinal drug has been reduced from 90 to 60 business days after an application for renewal is filed with the Ministry of Health (effective as of January 1, 2017).

Scientific Advice

The Law allows entities engaged in circulation of medicinal products ("medicines circulation entities") to obtain scientific advice on issues relating to preclinical studies and clinical trials, evaluation of quality, efficacy and safety or to the national authorization procedure for medicinal drugs. Advice should be provided by federal budget-funded institutions subordinate to the Ministry of Health of Russia, which are not involved in quality evaluation of medicinal drugs for the purposes of national authorization. Advice will be provided on a for-fee basis in the form of a written reply of the Ministry of Health to an advice request. Information on scientific advice provided, including articles, overviews, reference materials and other similar information will be posted on the official website of the Ministry of Health, subject to limitations set by the laws on personal data or commercial and/or state secret.

Registration Dossier

Some changes have been introduced with regard to the content of the registration dossier for medicinal drugs for human use (effective as of January 1, 2016). According to the Law, the

registration dossier for a medicinal drug must be submitted for authorization purposes in the Common Technical Document format that should include the following sections:

- administrative documentation;
- chemical, pharmaceutical and biological documentation;
- pharmacological and toxicological documentation;
- clinical documentation.

The Common Technical Document format is to be determined by the Ministry of Health of Russia.

The Law provides a detailed list of documentation for each of the above-mentioned sections. For certain cases, the Law sets specific requirements regarding the content of some sections of the registration dossier (Common Technical Document) and the procedure for submission of an authorization application. For example, an applicant seeking authorization of a *generic* medicinal drug for human use is allowed to submit an overview of research papers describing the results of preclinical studies of a reference medicinal drug instead of the applicant's report on the results of its own preclinical studies and to submit a report on the results of bioequivalence study instead of a full data package relating to clinical trials. With regard to *orphan* medicinal drugs, an applicant may submit the results of preclinical studies and clinical trials that have been conducted outside Russia in compliance with applicable Good Laboratory Practice and Good Clinical Practice guidelines.

Apart from the registration dossier content, the Law also specifies the procedure for making changes to documents contained in the registration dossier of an already qualified medicinal drug for human use (the new provisions will take effect by stages on July 1, 2015, January 1, 2016 and January 1, 2017 respectively).

Protection of Information on Reference Medicinal Drugs

As in the previous legislation, the Law establishes that the results of preclinical studies of a medicinal product and clinical trials of a medicinal drug for human use submitted by an applicant for national authorization may not be used by others without the applicant's consent *for commercial purposes* during 6 years from the date of national authorization of a reference medicinal drug. However, according to the new rule effective as of January 1, 2016, an application for national authorization of a generic drug may be submitted after 4 years and for a biosimilar drug after 3 years from the date of national authorization of a reference medicinal drug.

According to a novelty requirement effective as January 1, 2016 as well, holders of authorization of a *biotech* or *orphan* medicinal drug must provide for a fee samples of a reference medicinal drug to authorization applicants for conducting clinical trials. A fee payable for such sample may not exceed the maximum sale price for a reference medicinal drug, which is registered in the manufacturer's country.

Withdrawal of National Authorization

The Law adds the following grounds for withdrawal of national authorization of medicinal drugs:

- a medicinal drug has not been circulated in Russia during three or more years (in such event national authorization may not be renewed either);
- an authorization holder or a legal entity authorized by it fails to take measures to ensure safety of medicinal drugs as required by pharmacovigilance authorities;

- an authorization holder or a legal entity authorized by it refuses to make changes to the drug package leaflet required to disclose new proven data, according to which the risk of harm that may be caused by a medicinal drug to human health exceeds the benefit of such drug;
- an authorization holder or a legal entity authorized by it files a request to cancel national authorization of a drug.

Grace Period of Circulation

Changes have been made to the rules concerning circulation of medicinal drugs for human use, whose registration dossier is amended. According to the changes, medicinal drugs manufactured within a 180-days' period after the date of amendments to the dossier may be circulated until their expiration date provided that they have been manufactured in compliance with the specification that was contained in their registration dossier prior to the date of such amendments. Unlike the new Medicines Law, its current version allows only circulation of medicinal drugs manufactured prior to the date of amendments to the dossier and does not grant any grace period of circulation.

National Register of Medicinal Products

The list of information that must be recorded in the National Register of Medicinal Products has been increased significantly. The Register must include *inter alia* information on whether a medicinal drug is a reference drug, a vital and essential drug or an interchangeable one and whether it contains any narcotic or psychotropic substance or its precursor. With regard to *orphan* medicinal drugs, the Register must contain a record on the date when a medicinal drug was recognized as such.

The Law also specifies the list of information that must be recorded in the Register with regard to pharmaceutical substances manufactured for sale.

Pharmacovigilance

The new legislation requires a broader list of information to be submitted by medicines circulation entities to the Federal Service for Healthcare Surveillance (Roszdravnadzor) for the purpose of monitoring safety and efficacy of medicinal drugs. In particular, Roszdravnadzor will request information on the lack of efficacy of a medicinal drug and, generally, all facts showing that a medicinal drug presents danger to human life or health. All the information which is subject to such monitoring will be analyzed both in Russia and on a worldwide basis.

Authorization holders, legal entities who have obtained an approval for clinical trials and other legal entities authorized by them must:

- accept, record, process, analyze and store all notices from medicines circulation entities or government agencies relating to side effects, adverse or significant or unexpected adverse drug reactions, drug-to-drug interactions, idiosyncratic response and other facts or circumstances that present danger to human life or health or affecting the risk/benefit ratio;
- give notice of all of the above-mentioned facts to Roszdravnadzor;

- upon discovery of any of the above-mentioned facts, take measures to eliminate adverse consequences of use of a medicinal drug, to prevent harm that may be caused to human life or health and to collect additional data relating to efficacy and safety of such medicinal drug.

Concealment of such facts or failure to give notice thereof is punishable under Russian laws.

In addition to the foregoing, starting from January 1, 2016 authorization holders will be required to file with Roszdravnadzor a pharmacovigilance report semiannually during 2 years after obtainment of national authorization, then annually during next 3 years and thereafter once every 5 years.

Broadened Powers of Government Authorities

According to the new Medicines Law, Roszdravnadzor may conduct *sample check of medicinal products*, which will include in particular:

- processing information on batches or lots of medicinal products entering into circulation in Russia, which must be provided by medicines circulation entities (such as manufacturers, distributors or retailers);
- taking sample products from medicines circulation entities to test them for compliance with regulatory documentation or specifications;
- making a decision to prohibit or authorize further circulation of a tested medicinal product.

If a medicinal product is repeatedly found to be non-compliant with applicable quality standards, Roszdravnadzor may order to conduct batch analysis of such product and to audit the relevant medicines circulation entity.

If directives issued after sample check of a medicinal product are not complied with, Roszdravnadzor may suspend authorization of such product.

Roszdravnadzor may also suspend authorization of a medicinal product if it discovers that the results of clinical trials are not reliable because the trials have been conducted in violation of the Good Clinical Practice guidelines.

Apart from that, under the new Medicines Law Roszdravnadzor will be able to shut down - without a court's order - a website (with exceptions determined by the RF Government) which contains:

- information on retail distance selling of medicinal drugs; or
- an offer to sell, supply and/or deliver medicinal drugs, narcotic drugs or psychotropic drugs to individuals at a distance from the supplier.

Maximum Sale Prices for Vital and Essential Medicinal Products

The regulation of maximum sale prices for *vital and essential medicinal drugs ("Essential Drugs")* has been amended both by the Law and Federal Law No.34-FZ "On Amendments to Article 61 of the Law "On Circulation of Medicinal Products" dated March 8, 2015.

It is established now that the list of Essential Drugs should be determined by the RF Government based on comprehensive evaluation of medicinal drugs, including comparative effectiveness and safety research as well as assessment of economic effect and additional consequences of use of a medicinal product.

Apart from that, the new Medicines Law allows the RF Government to set specific regulations of maximum sale prices for Essential Drugs as may be required in light of economic and/or social factors. Such factors include, in particular, changes in conditions, manner or cost of manufacture of medicinal drugs or introduction of new forms, methods or ways of government control of prices for medicinal drugs. This provision of the law has taken effect as of March 16, 2015.

According to another novelty provision of the Medicines Law, foreign pharmaceutical manufacturers are allowed now to re-register their registered maximum sale prices for Essential Drugs (previously, such re-registration was allowed to Russian manufacturers only).

Pharmaceutical manufacturers are prohibited from selling or dispensing Essential Drugs at prices exceeding their registered maximum sale prices, and pharmaceutical distributors and retailers are prohibited from selling or dispensing Essential Drugs at markup prices that exceed the manufacturer's actual sale prices determined in accordance with the maximum sale price requirements.

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