CHAPTER 12
RUSSIAN FEDERATION

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Legal System

The Russian Federation is a federal state consisting of a total of 83 republics, regions, federal cities, autonomous regions and autonomous districts.

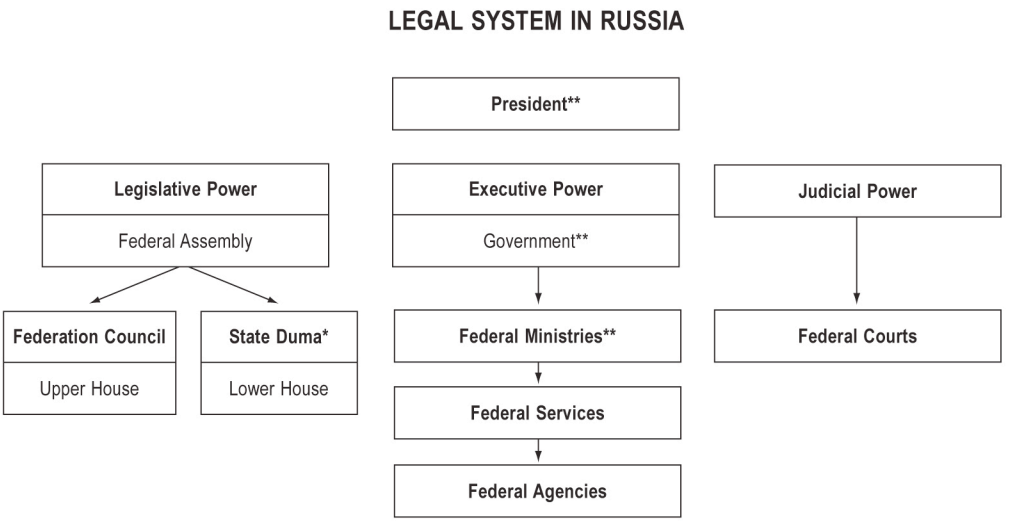
Republics have their own constitutions and legislation, while regions, federal cities, autonomous regions and autonomous districts have their own charter and legislation. The federal system of the Russian Federation is based on its state integrity, unity of state power, and a shared authority and areas of competence between the state authorities of the Russian Federation and its subjects.

The state power in the Russian Federation is exercised by the president, Federal Assembly (consisting of the Federation Council and Duma), government and the courts. The other subjects have varying degrees of autonomy and exercise it through the governing bodies formed by the subjects. In areas of joint competence, state bodies of the Russian Federation and state bodies of the subjects form a united system of state power in the Russian Federation.

The executive power of the federal government is exercised by the government of the Russian Federation, consisting of the Chairman, Deputies Chairman and federal ministers. The federal government ensures a uniform policy in the sphere of healthcare. In accordance with the 1993 Constitution, federal laws and presidential decrees, the government issues decisions and orders that are mandatory for execution in the territory of the Russian Federation.

Healthcare issues are among those which fall within the joint competence of the Russian Federation and its subjects. The role of the federal government in defining state policy is articulated in Chapter 6, Article 114 of the Russian Constitution.[1]

On issues of joint competence, the Russian Federation enacts federal laws, and the subjects enact laws and legislative acts in compliance with the federal laws. The laws and legislative acts enacted by the subjects cannot contradict federal laws. In any cases of contradiction or inconsistency, the federal laws shall supercede any of those enacted by the subjects.



* State Duma enacts federal laws that shall be approved by Federation Council and signed by the President.

** President, Government and Federal Ministries enact legislative acts within their competence.

Legal and Regulatory Processes

Federal Administrative Agencies

Within the Russian federal government, healthcare issues fall within the competence of the Ministry of Healthcare and Social Development (Ministry of Health) and subordinated to it, the Federal Service on Healthcare and Social Development Supervision (Federal Health Service).

In terms of split of authority, the Ministry defines state policy and issues administrative healthcare regulations in its sphere of competence, but cannot perform control and supervisory functions within the set sphere of competencies.

In contrast, the Federal Health Service performs these control and supervisory functions in these areas of healthcare, but cannot issue regulations in this area.

General Framework of Legal Requirements: Federal Legislation

Federal legislation, as enacted by the Duma and approved by the Federal Council, provides the fundamental basis for regulations in the areas of healthcare.

Federal Law On Pharmaceuticals No. 86-FZ of June 22, 1998 (as amended on December 18, 2006) (the Pharmaceutical Law) establishes the general framework of legal requirements applicable to development, manufacturing and distribution of pharmaceutical products. These also address the related issues of clinical trials, product safety and effectiveness, quality control, and importation and sale. To ensure that the population has access to safe and high-quality pharmaceuticals, the Pharmaceutical Law establishes a primacy of federal control over the production, quality, effectiveness and safety of pharmaceuticals.

This federal regulation over the production and distribution of pharmaceuticals is performed by

- state registration of pharmaceuticals;
- licensing of certain activities related to the distribution of pharmaceuticals;
- review of experts engaged in the sphere of circulation of pharmaceuticals;
- expert review and certification of certain activities related to pharmaceutical product development and distribution[2];
- state control over the production, preparation, quality, safety and effectiveness of pharmaceuticals; and
- state regulation of pharmaceutical pricing.

State Registration of Pharmaceuticals

As a general rule, pharmaceuticals may be produced, imported, sold and used in the Russian Federation only if they are registered with the state authority exercising control over the quality of pharmaceuticals. Presently, these control functions are vested exclusively in the Federal Health Service, which is an agency subordinate to the Ministry of Health.

Specifically, the following types of pharmaceuticals are subject to state registration:

- new pharmaceuticals;
- new combinations of previously registered pharmaceuticals;
- pharmaceuticals previously registered but produced in other medical forms, in new doses or with other compositions of supplementary substances; and
- generic pharmaceutical products.

Pharmaceuticals that meet all necessary requirements for registration are entered into the State Register of Pharmaceuticals. The information on registered pharmaceuticals is placed at the official website of the Federal Health Service and is thus in the public domain.

In keeping with the policies outlined in the Pharmaceutical Law, the Ministry of Health enacted administrative regulations via Order No. 736 of October 30, 2006, which sets out specific registration procedures for pharmaceuticals.[3]

The state registration shall be made in the name of the applicant specified in application for registration of a pharmaceutical. The application shall be submitted either by the sponsor itself or any other legal entity authorized by the sponsor to submit the application.

Domestic and foreign pharmaceuticals enjoy the same treatment for the purposes of registration.

The following documents and information must be filed with the Federal Health Service to register pharmaceuticals:

- a completed application for state registration of a pharmaceutical;
- document(s) evidencing payment of state registration fee;
- the legal address of the pharmaceutical manufacturer;
- the name of the pharmaceutical, including international non-proprietary name, the scientific name in Latin and main chemical synonyms;
- the original or trade name of the pharmaceutical if it is registered as a trademark according to the Russian legislation on trademarks[4];
- a list of ingredients, specifying their quantity[5];

- instructions for use of the pharmaceutical that are in compliance with the requirements of the Pharmaceutical Law requirements[6];
- a quality certificate for the pharmaceutical;
- manufacturing data pertaining to the pharmaceutical and pharmacopoeia[7];
- a description of the methods used for quality control in the production of the pharmaceutical;
- all results of preclinical studies[8];
- results of pharmacological and toxicological tests conducted on the pharmaceutical;
- the results of the relevant clinical trials[9];
- samples of the pharmaceutical for examination of its quality;
- proposals for pricing; and
- documents confirming registration of the pharmaceutical if it was registered outside Russia.

The above documents shall be filed in the Russian language or be supplied with a certified Russian translation.

The documents are reviewed and the decision on registration is made within six months from the date of filing a complete set of documents specified above.

If the differences between a pharmaceutical that is the subject of an application to be registered and one that has been previously registered relate only to excipients and production technology, and if such differences cannot affect the quality, safety and effectiveness of the pharmaceutical, then an expedited registration procedure shall apply and a decision can be received in three months.

Upon successful state registration of a pharmaceutical, the applicant will be issued a registration certificate with an unlimited term of validity.

Amendments to the registration of a pharmaceutical should be made on the basis of a formal application and should include supporting documents filed by the registration certificate holder with the Federal Health Service.

Decisions about amendments to existing registrations that relate to the quality or effectiveness of a pharmaceutical are made within six months from the time the complete set of the

required documents is filed. In all other cases, including those related to information on a new adverse drug reaction or restrictions in product use, a change of product ownership or a change of the trade name or packaging, a decision should be rendered within one month from the date of filing.

Preclinical Studies and Clinical Trials

Preclinical studies are carried out by pharmaceutical sponsors according to the Rules of Good Laboratory Practice. These studies must be approved by the Order of the Russian Federation Ministry of Health prior to their execution, and are subject to its oversight throughout. After the sponsor has concluded and secured the results of these preclinical studies, it must issue an analysis of the available preclinical data as part of the application to conduct clinical trials.

The following documents should be submitted to the Federal Health Service in order to obtain permission to conduct clinical trials for evaluation of a pharmaceutical:

- a completed application from the sponsor;
- documents indicating the consent of the Ethics Committee of the Federal Health Service;
- a summary report of data from any other preclinical trials conducted with the pharmaceutical;
- instruction on the use of the pharmaceutical product in the clinical trial programs.

Clinical trials can be conducted only by medical institutions approved by the Federal Health Service, and only after receipt of a decision by the Federal Health Service that permits the initiation and conduct of the clinical trials.

Ultimately, the legal basis for conducting clinical trials emanates from the decision of the Federal Health Service, as well as a contractual agreement between the product sponsors and medical institutions that conduct the clinical trials. That clinical trial agreement must specify the following information:

- time frame and scope of a clinical trial for a pharmaceutical;
- total cost of the clinical trials program;
- form for presenting the results of the clinical trials to the Federal Health Service;

- terms of insurance for patients enrolled in the clinical trials;
- terms of liability insurance for persons conducting the clinical trials.

Patients enrolled in clinical trials enjoy special protections. The patients must be informed of

- the nature of the pharmaceutical product and the aim of the clinical trials;
- the expected safety and effectiveness of the pharmaceutical and the anticipated nature and degree of risk associated with it;
- any planned actions that will be taken in the event of unanticipated adverse effects;
- the terms of insurance for patients.

The patients must give their written informed consent to participate in the clinical trials and may terminate their participation at any time.

The requirements for conducting clinical trials are further specified in the Rules for Clinical Practice (the Rules) in the Russian Federation issued by the Order of the Ministry of Health No. 266 of June 19, 2003. These Rules apply to all participants of clinical trials conducted on subjects within the Russian Federation.

The rules prohibit direct payments from the sponsors to the specialists of the medical institution conducting the clinical trials, and allow only payments to the medical institution itself against those invoices issued in accordance with the clinical trials agreement. (Note that while the Pharmaceutical Law technically no longer contains these restrictions, the prohibition against direct payment to specialists is maintained in the Rules.)

Violation of the Rules of Good Clinical Practice

Good Clinical Practice Rules (which are similar to International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use GCP) have been adopted into the National Standard.[10] Falsification of the results of clinical trials would result in liability as determined under the appropriate law or regulation.

As a general rule in the case of injury or death caused to persons by unfair actions of medical professionals, damages shall be compensated in full in accordance with statutory requirements. Compensation of damages does not release medical professionals from disciplinary, administrative and criminal liability in accordance with Russian legislation.

Declaration of Compliance

In addition to state registration, domestic and imported pharmaceuticals are subject to declaration of compliance with state quality standards for pharmaceuticals.

Declarations of compliance shall be registered with the bodies accredited for certification of pharmaceuticals listed in the Informational Letter of the Federal Health Service of August 1, 2008.

The certification body shall review the documents and make a decision on registration of the declaration (or a registration denial) within three days from filing the documents.

Licensing of Certain Activities on Distribution of Pharmaceuticals

According to Federal Pharmaceutical Law No. 128-FZ, "On Licensing of Certain Types of Activities" of August 8, 2001 (as amended of December 6, 2007), there are other aspects of pharmaceutical production and distribution that are subject to specific licensing requirements.

Pharmaceutical activity that includes only the wholesale and retail sale of pharmaceuticals and preparation of pharmaceuticals may be carried out by either legal entities or individual entrepreneurs. Licensing to conduct these activities related to the distribution of pharmaceuticals intended for medical use is carried out by the Federal Health Service.

The Regulations on Licensing of Pharmaceutical Activity approved by the Decision of the Government No. 416 of July 6, 2006 (as amended of July 19, 2007) set out the following licensing requirements to applicants seeking to engage in these aspects of the distribution of pharmaceuticals:

a) maintenance of suitable premises and equipment in compliance with sanitary and other applicable requirements that are necessary for conducting the activity;
b) compliance of the applicant engaged in the wholesale of pharmaceuticals with relevant requirements set out by the Pharmaceutical Law and wholesale rules governing pharmaceuticals;
c) compliance of the applicant engaged in retail sale of pharmaceuticals with the relevant requirements set out by Pharmaceutical Law and retail sale rules applicable to pharmaceuticals;
d) compliance of the applicant engaged in preparation of pharmaceuticals with the relevant requirements set out by Pharmaceutical Law and the rules for quality control of pharmaceuticals prepared in pharmacies;

e) compliance with requirements prohibiting the sale of pharmaceuticals with expired quality certificates, counterfeit and illegal copies of pharmaceuticals legitimately registered in the Russian Federation, and other pharmaceutical products deemed unfit for human use (this includes compliance with requirements that such products be destroyed); and
f) compliance with the following educational and professional requirements:

- when the applicant is a legal entity, the top executives (e.g., chief executive officers) of any firm involved in the acceptance, storage, release, preparation and destruction of the pharmaceuticals shall have a higher education (university) degree in pharmaceuticals, a qualification certificate (diploma) and at least three years of professional experience;
- individual entrepreneurs shall have a higher or intermediary educational degree in pharmaceuticals and a certificate of expertise;
- employees of any applicant involved in the preparation, storage, release and sale of pharmaceuticals shall have a higher or intermediary educational degree in pharmaceuticals and qualification certificate;
- at least once every five years, appropriate training/upgrading for the professionals involved in the applicant's pharmaceutical activities.

The production of pharmaceuticals may be carried out by legal entities.

Similarly, the Regulations on Licensing of Production of Pharmaceuticals approved by the Decision of the Government No. 415 of July 6, 2006 (as amended of July 19, 2007) outline the following licensing requirements for applicants seeking to engage in the production of pharmaceuticals:

a) suitable premises and equipment (owned or leased) that are in compliance with sanitary and other applicable requirements necessary for the production of pharmaceutical products;
b) compliance of the applicant engaged in production of pharmaceuticals with the relevant requirements set out by Pharmaceutical Law with respect to the production and quality control of pharmaceuticals in those dosage forms approved for production;
c) available legal basis such as license for production of patented and/or innovator pharmaceuticals and their sale in accordance with patent and trademarks legislation requirements;

d) compliance with requirements prohibiting the sale of pharmaceuticals with expired quality certificates, counterfeit and illegal copies of pharmaceuticals legitimately registered in the Russian Federation, and other pharmaceutical products deemed unfit for human use (this includes compliance with requirements that such products be destroyed);
e) available staff specialists responsible for production, quality and labeling of pharmaceuticals who have higher or intermediary educational degrees (chemical and technological, biotechnological, pharmaceutical or medical) and at least three years of professional experience;
f) at least once every five years, appropriate training/upgrading for the professionals involved in the applicant's pharmaceutical activities.

Licenses for pharmaceutical activity and production are issued for five-year terms and may be renewed for terms of the same duration.

State Control Over Quality, Safety and Effectiveness

Federal Health Service Oversight

According to Administrative Regulations on Performing Examination of Quality, Safety and Effectiveness of Pharmaceuticals approved by the Order of the Ministry of Health No. 734 of October 30, 2006, state control over quality, safety and effectiveness of pharmaceuticals is performed by the Federal Health Service. The Federal Health Service's general oversight responsibilities include the following:

- examination of data related to the quality, safety and effectiveness submitted as part of the state registration process;
- collection and analysis of information pertaining to the quality of pharmaceuticals;
- collection and analysis of information pertaining to adverse drug reactions associated with pharmaceutical use;
- examination of quality while performing preliminary state control of pharmaceuticals—this applies to pharmaceuticals produced in or imported to the Russian Federation for the first time, produced under a modified technology, produced after termination of production for three or more years, or for which deterioration of quality has been revealed;
- examination of quality while performing a random state inspection, carried out at the discretion of the Federal Health Service; and
- examination of quality while performing any repeat random state inspections, conducted in cases where there is sustained uncertainty about a pharmaceutical product's quality.

Pharmacovigilance Reporting

The Pharmaceutical Law states that participants in the distribution of registered pharmaceuticals—both individuals and legal entities—shall inform the controlling authority about all adverse drug reactions and drug interactions which do not correspond to the product's use information.

The development of serious adverse drug reactions (ADRs) such as death, hospitalization or long-term disability that are not reflected in the instruction for use shall be reported to territorial departments of the Federal Health Service within five business days from the moment of revealing such ADR, and in case of obtaining additional information, a subsequent notification shall be served within the next five business days.

In all other cases, notifications on ADR not qualifying as serious or unexpected shall be served to the Federal Center for Monitoring of Drugs Safety within ten days from the revealing such ADR.

The form of ADR notification was introduced by Letter of the Federal Health Service of August 15, 2008.

According to the most recent Letter of the Federal Health Service of February 5, 2009, the information on all suspected ADRs revealed in Russia shall be entered into the database of the Federal Health Service by the person responsible for pharmacovigilance in a pharmaceutical company. The terms for serving a notification on suspected ADR are the following: i) on ADR resulting in death or creating a danger to life within five business days, ii) for unexpected and/or serious ADR not creating a danger to life within 10 business days, iii) in case of therapeutic non-effectiveness within 10 business days and iv) for other (not serious) cases within 30 business days.

The information on serious ADRs revealed abroad should be submitted with Periodic Safety Update Reports (PSURs) within the terms set out by the Federal Health Service in electronic version, including the original of PSUR, Russian translation of resume section, data of sales in Russia and summary of ADR revealed in Russia.

Notifications on changes in registration status of pharmaceutical and instruction for medical use should be submitted to the department on monitoring of effectiveness and safety of the Federal Health Service.

Submission of drug safety data for products which have not been registered but are undergoing clinical trials is regulated by the Good Clinical Practice Rules approved by

the Industry Standard OST 42-511-99 of December 29, 1998, and the National Standard GOST R 52379-2205 of September 27, 2005.

According to the Good Clinical Practice Rules, all serious and unexpected ADRs should be reported by the sponsor to all persons involved in clinical trials, including the investigator, medical institution, Ethics Committee and regulatory authorities, as soon as possible.

Enforcement and Penalties

Liability

Injury as a result of use of pharmaceuticals and/or by the illegal actions of persons or entities involved in the circulation of pharmaceuticals shall be compensated according to the requirements set out by the Fundamentals of the Legislation of the Russian Federation on Protection of the Health of Citizens No. 5487-1 as of 22 July 1993 (as amended of October 18, 2007).

Pursuant to the Pharmaceutical Law, if injury is caused to human health as a result of use of a pharmaceutical, the manufacturer shall compensate the damage caused to the injured person if it is proved that either a) the pharmaceutical was used according to prescription, in compliance with the instruction for use, and its harmful effect was caused by errors in production of the pharmaceutical, or b) injury to human health was caused due to erroneous instruction for use of a pharmaceutical issued by the manufacturer.

If an injury to human health is caused as a result of use of a pharmaceutical that became unfit for use due to violation of pharmaceuticals wholesale rules or the rules for pharmaceutical activity by pharmaceutical institutions, the injury shall be compensated by the wholesale organization or by the pharmaceutical institution.

In addition to compensation of damage caused to the injured person, the guilty individual(s) may bear criminal liability (e.g., infliction of gross or average injury to health by negligence). It is noteworthy that under Russian criminal law, only an individual—not a legal entity—may be held criminally liable.

Developing Issues and Future Plans

The Russian Federation is an increasingly important market for pharmaceuticals. Accordingly, major changes are occurring in the regulatory environment to account for and accommodate the growing presence of local and international pharmaceutical companies in the country.

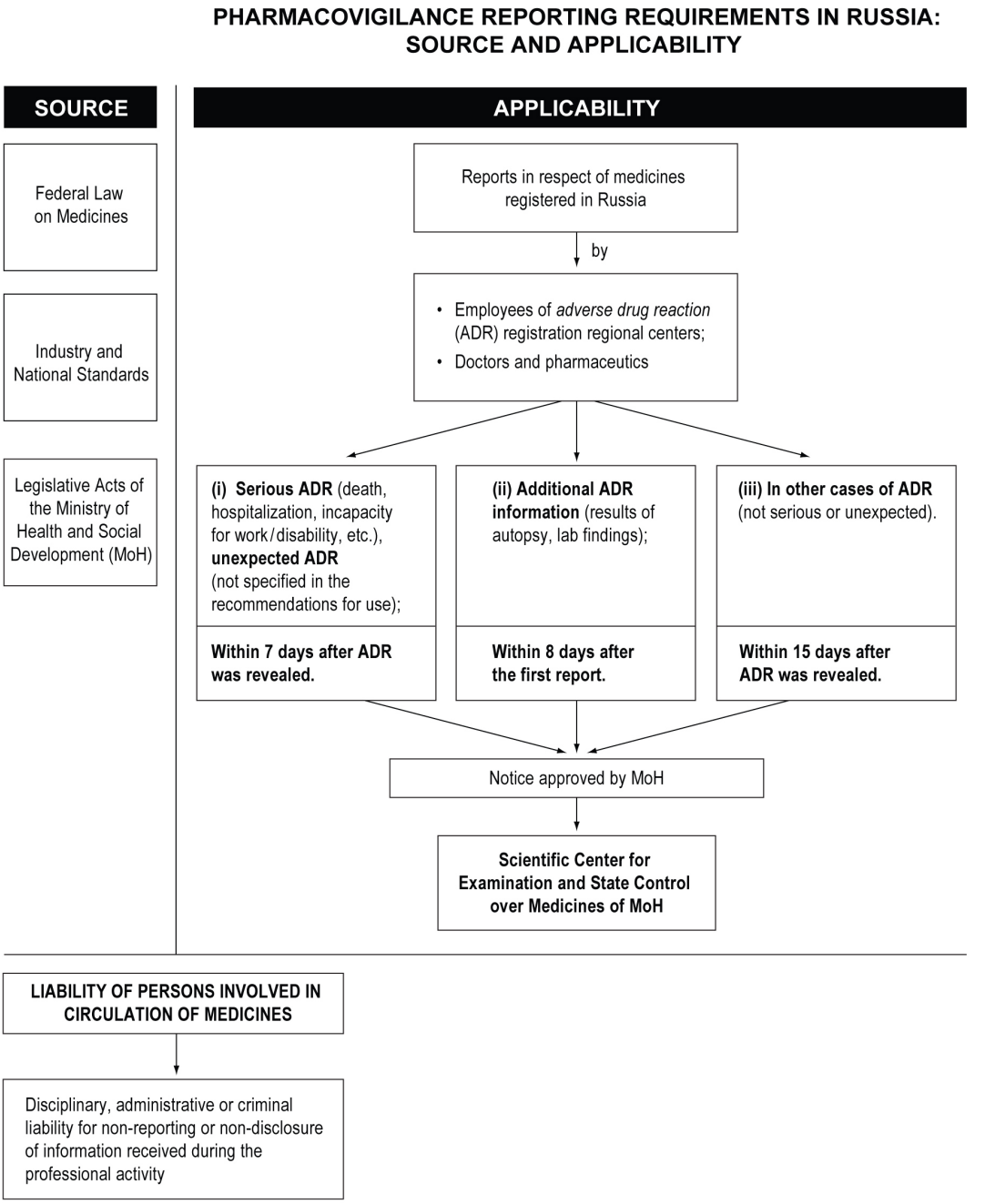
Right now, there is a clear trend toward a more market-oriented system of regulation—including regulation of pharmaceutical issues at a lower level—facilitated by the development and use of administrative regulations on the part of the Ministry of Health rather than by federal laws, providing greater flexibility in the adoption of regulations on an as-needed basis.

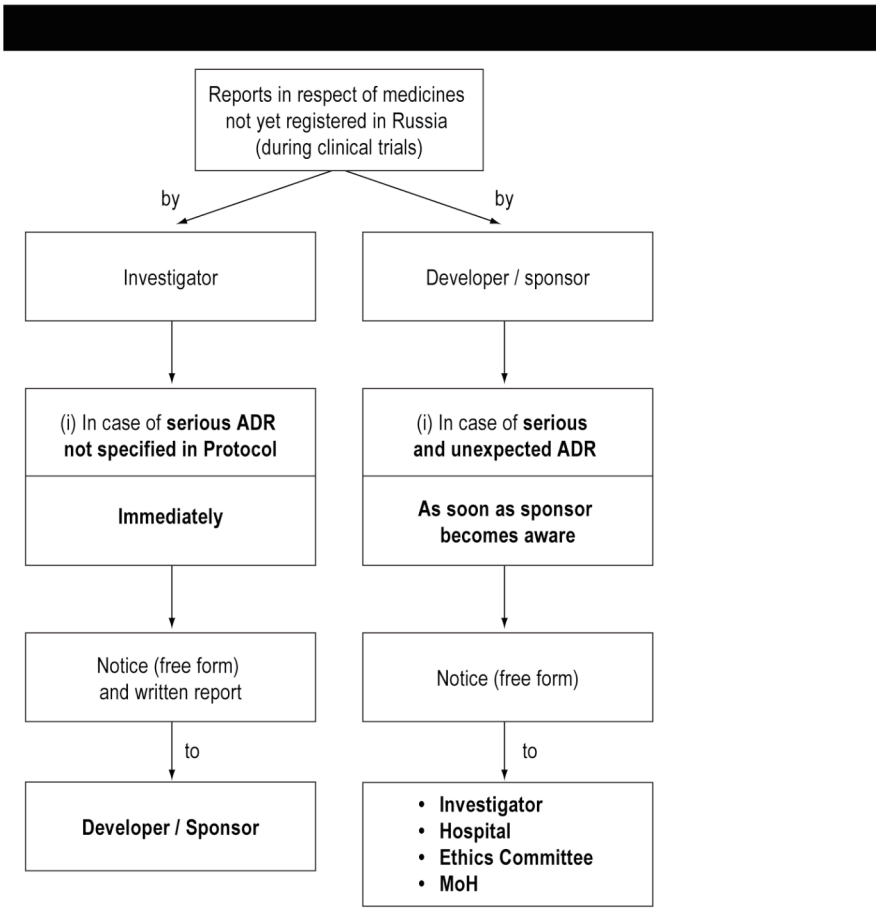
Other trends that may emerge in the Russian Federation's regulation of pharmaceuticals include tighter control over the market concentration of players, introduction of pharmaceutical insurance, formal adoption of international quality standards and promotion of investment potential in conditions of financial crisis.

Endnotes

1. *Available at* http://www.constitution.ru/en/10003000-07.htm.
2. The federal health authority arranges for examination of experts to ensure their professional upgrade.
3. These types of administrative regulations are enacted by the legislative acts (orders) issued by the Ministry within its competence. Numbers and dates are necessary for identification and search purposes.
4. It shall be registered in Russia unless it is protected in Russia on the basis of an international application.
5. All components (main and auxiliary) shall be specified.
6. Note that the instruction for use is mainly the information for patients.
7. Pharmacopoeia is a Russian state/federal standard of a pharmaceutical specifying the list of indices and methods of pharmaceutical quality control.
8. According to Russian law, preclinical trials shall be carried out by the innovator (sponsor) of a pharmaceutical according to the laboratory practice rules. On the basis of these trials, the innovator shall make a statement on a possibility of clinical trials.
9. Note that normally, registration of pharmaceuticals in Russia would be made on the basis of the clinical trials carried out in Russia in accordance with the Clinical Practice Rules and National Standard Good Clinical Practice.
10. Approved by the legislative act of the Federal Agency for Technical Regulation and Metrology; binding for clinical trials.

Appendix A


PHARMACOVIGILANCE REPORTING REQUIREMENTS IN RUSSIA: SOURCE AND APPLICABILITY
SOURCE
APPLICABILITY
Federal Law on Medicines
Industry and National Standards
Legislative Acts of the Ministry of Health and Social Development (MoH)
Reports in respect of medicines registered in Russia
by
• Employees of adverse drug reaction (ADR) registration regional centers;
• Doctors and pharmaceutics
(i) Serious ADR (death, hospitalization, incapacity for work/disability, etc.), unexpected ADR (not specified in the recommendations for use);
Within 7 days after ADR was revealed.
(ii) Additional ADR information (results of autopsy, lab findings);
Within 8 days after the first report.
(iii) In other cases of ADR (not serious or unexpected).
Within 15 days after ADR was revealed.
Notice approved by MoH
Scientific Center for Examination and State Control over Medicines of MoH
LIABILITY OF PERSONS INVOLVED IN CIRCULATION OF MEDICINES
Disciplinary, administrative or criminal liability for non-reporting or non-disclosure of information received during the professional activity


Reports in respect of medicines not yet registered in Russia (during clinical trials)
by
by
Investigator
Developer / sponsor
(i) In case of **serious ADR not specified in Protocol**
Immediately
(i) In case of **serious and unexpected ADR**
As soon as sponsor becomes aware
Notice (free form) and written report
Notice (free form)
to
to
Developer / Sponsor
• **Investigator**
• **Hospital**
• **Ethics Committee**
• **MoH**