Man In India, 97 (6) : 27-35

INTERNATIONAL CLINICAL TRIALS: POLICY, LEGAL AND ETHICAL IMPLICATIONS

Viktoriia Sergeevna Savina[*,**], Valentina Nikolaevna Sinelnikova[***], Anna Artemovna Avanesova[**], Anna Mikhailovna Lapa[*], Tatiana Alexandrovna Strutinskaya[**]

Abstract: The article discusses a number of challenges of the Russian legislation relevant to the pharmaceutical industry. It considers the problem of establishing national and international mechanisms for legal protection of clinical trial results. According to the legislation of the Russian Federation, such clinical trials as research and development studies are a kind of studies performed either under a civil contract or a public contract. Research results are presented in respective reports subject to state registration of medicines along with other documents. A research report that refers to intellectual property can be both a way to present research and development studies as well as their integral part and the proof of research. A patent research must ensure timely identification of protectable results of research and development and design and engineering studies so that its legal owner could register his/her intellectual property rights. It is reasonable to develop a mechanism for confirming customer's exclusive rights to use the results of research and development studies if they are made either under a civil contract or a public (municipal) contract.

Keywords: Clinical trials, research and development studies, intellectual property rights, study result.

INTRODUCTION

Modern economy increasingly becomes the scene of intense competition as well as idea, trademark and brand competition. Thus, the development of a successful and sustainable brand requires both creation of solutions providing high quality of goods and services and a marketing strategy making these products and services attractive to consumers. Today, consumers do care whether solutions implemented in products are patented; moreover, they buy products heeding certain trademarks. Another economic development trend involves globalization and expansion of world trade. These trends significantly affect the characteristics of development of the pharmaceutical manufacturing industry and the pharmaceutical market. (Federal Law No. 61-FZ of April 12, 2010)

According to the Ranking of Countries Exporting Pharmaceutical Products based on the World Bank's statistics and published by Russian mass media, (Federal Law No. 323-FZ of November 21, 2011) European countries play a major role in the global pharmaceutical market. Germany is acknowledged as the world's

[*] Russian State Academy of Intellectual Property, 117279, Moscow, Russia, Miklukho-Maklaya, 55A

[**] North-Caucasus Federal University, 355009, Stavropol, Pushkin Street, 1

[***] National Research University "Higher School of Economics", 101000, Moscow, Myasnitskaya Ulitsa, 20

largest exporter, its market share in the pharmaceutical industry is almost 67 billion US dollars. Ireland is the top country by another indicator, namely the share of pharmaceuticals exports of total exports (23%). Russia takes the 36th place of this ranking, its share in the pharmaceutical market amounts to 637 million US dollars, whereas its share of pharmaceuticals exports of total exports is 0.1%. The analysis of these indicators suggests that Russia seems to be a promising pharmaceutical market attractive to the entire international community. (Ranking of Countries Exporting Pharmaceutical Products, 2013).

METHODS

Comprehensive study of the legislative regulation of the use of copyright in the Internet evolution involves the use of various methods of knowledge, the relevant aspects of the diversity of legal reality. The study used the dialectical, formal-logical and comparative legal, specific historical, inductive, deductive methods, systematic approach, analysis and synthesis, as well as the implementation of the principle of unity of historical and logical methods of analysis that can cover the studied phenomenon in all its forms.

FINDINGS OF THE STUDY

One of indicators of international community's interest to Russian developments is the number of clinical trials conducted in Russia.

In 2015, the Ministry of Health of the Russian Federation granted 802 permissions for all types of clinical trials, which is 7% more than in 2014.

Companies from 40 countries became sponsors of clinical trials permitted to be conducted in Russia in 2015. Russian producers with 337 clinical trials took top position followed by American sponsors with 117 new studies, India with 62 studies followed by Switzerland with 53 new clinical trials, Germany and the United Kingdom with 30 and 26 new clinical trials respectively followed by France with 23 new clinical trials. Belgium with 16 new clinical trials rounds out the leadership group. (Russia Pharmaceutical & Healthcare Report Q1 2010)

In addition, in 2015, 77% of new studies in eight therapeutic areas were initiated. Most of those were research studies in the field of oncology, namely 109 studies. 71 new studies in the field of pulmonology were conducted; 45 studies on infectious and parasitic diseases; 43 studies on musculoskeletal system diseases; 34 new clinical trials in neuroscience and endocrinology; 27 and 23 new trials in gastroenterology and urology respectively.

Costs related to new medicines that can be used in medicine should be also specified. These are quite expensive studies - for instance, investments in research and development (R&D) of one pharmaceutical drug is estimated at an average of around 1 billion US dollars; (Clinical Trials in Russia. Orange Paper. Annual 2015)

moreover, it may take years or even decades to introduce a new drug to the market. According to estimates of some Russian scientists, in the context of Russia, an estimated cost of drug development from scratch can reach 1.2 billion rubles (40 million US dollars) and take 7-13 years. (Pugatch 2004)

Considering opportunities for the development of biomedical drugs containing human cell products along with chemicals it is a fair assumption to say that both drug development cost will rise and development time will be extended. Moreover, there will be certain legal problems associated with the use of live human cells. Therefore, entry into force of Federal Law No. 180-FZ of 23.06.2016 "On Biomedical Cell Products" on January 1, 2017 should be recognized as an achievement in both national civilistics and biotechnology, since intellectual outputs of representatives of this specific field of science allowed for the development and use of new methods for preventing, diagnosing and treating a number of human diseases as well as further rehabilitating; and maintenance of pregnancy.

This Law considers the international experience already gained and is aimed at regulating relationships arising in connection with particular development, preclinical and clinical trials, evaluation, state registration, manufacture, sale, storage, transportation, medical use, disposal, imports and exports of biomedical cell products into and from the Russian Federation and export for disease prevention, diagnosis and treatment, as well as in connection with donation of biological materials for the production of biomedical cell products. This Law is definitely just a starting point of the integrated system for the creation and use of natural objects.

Therefore, the relevance of developing a specific legislation is becoming apparent. This legislation would ensure legal protection of preclinical and clinical drug trial results. Considering rapid development of foreign economic relations in the modern world this kind of legislation should be developed at both national and international levels. Many scholars paid attention to the complexity of regulation of these relations.

In Russia, the development of this specific legislation was initiated in 2010 when Federal Law No. 61-FZ of April 12, 2010 "On Circulation of Medicines" came into effect. (Promoting Access to Medical Technologies and Innovation. Intersections between Public Health, Intellectual Property and Trade, 2014) According to Art. 18 Para. 18 of the aforesaid Law, prohibition was imposed against the commercial use of information on preclinical and clinical drug trial results submitted by an applicant for state registration of a medicine without applicant's consent within 6 years from the date of state registration of a medicinal product in the Russian Federation. In addition to these laws, related by-laws and national standards were adopted. Thus, a mechanism was established in the Russian national legislation to provide legal protection of preclinical and clinical drug trial results against unfair commercial use. (Voronkov and Kolobov, 2007)

At the same time, on January 1, 2016, a new provision provided for in Art.18 Para. 20 of Art. No. 61-FZ came into effect. The provision stipulates that an application for state registration of a generic drug can be submitted in 4 years from the date of state registration of a reference medicine.

These changes involved a number of discussions among experts; many of them are worried that this approach doesn't encourage drug manufacturers to conduct new research studies.

There are some proposals to extend the term of protection of information on preclinical and clinical trial results for orphan drugs, pediatric medications as well as drugs used to treat cancer in order to stimulate drug development in these fields of pharmaceutical industry. (Federal Law No. 61-FZ of April 12, 2010)

As for the international legal protection system, Russia acceded to this system in 2012 when the Protocol on the Accession to the Marrakesh Agreement Establishing the World Trade Organization (WTO) came into effect in the Russian Federation. (Federal Law No. 323-FZ of November 21, 2011) It should be noted that according to Art. 15 of the Constitution of the Russian Federation (Article 18 of the Federal Law No. 2010-FZ, 2010) and Art. 7 of the Civil Code of the Russian Federation (Khokhlova 2016.), international treaties ratified by Russia are an integral part of the Russian legal system; they prevail over national laws and can be used only in Russia. In this regard, it seems obvious that the national legislation should become compliant with the provisions provided for in the WTO agreements, in particular, with the provisions of the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS). (Federal Law No. 126-FZ of July 21, 2012)

However, there are some differences in generic drug regulation policies as shown by comparative studies conducted by World Health Organization experts (The Constitution of the Russian Federation) in both Russia and member countries of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals. For instance, state registration of generic drugs (except for certain products, in particular, immunobiological medicinal products) provides for the procedure for the accelerated assessment of medicinal products; however, this doesn't involve relaxation of requirements for quality, safety and efficacy of medicinal products. In this case, results of pharmaceutical substance preclinical trials to be submitted including previously published information on both results of drug substance clinical trials and results of studies of the bioequivalence between original and generic drugs.

The accelerated registration procedure is also applied in the member countries of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals; however, it is applied exclusively for priority medicinal products. In this case, generic drugs are registered in a short registration dossier, and their registration doesn't require submission of results of preclinical drug substance trials.

An illustrative example of controversial status of generic drug registration that involves the use of published information on clinical trial results is the registration of the Neskler drug developed by the Russian company BioIntegrator. This product is an analogue of Novartis drug named Gilenya.

On March 20, 2015, the Trial Court rejected a claim filed by Novartis for the annulment of registration of the Neskler drug and imposition of the prohibition on sale. BioIntegrator was accused of violating Art. 18 Para. 6 of Law No. 61-FZ "On prohibition of the access to, disclosure and use of information on preclinical and clinical drug trial results submitted by the applicant for state registration of a medicinal product, for commercial purposes and for state registration purposes, without applicant's consent within six years from the date of state registration of the aforesaid medicinal product". Long trials held in 2015 were followed by proceedings in the Intellectual Property Court which nullified the Ruling of the Court of Appeal on December 15. The Ruling of the Trial Court was upheld. The Supreme Court denied transfer of both the cassation appeal and the case filed by Novartis Pharma AG for review at a session of the Judicial Chamber for Commercial Disputes of the Supreme Court of the Russian Federation. (The Civil Code of the Russian Federation)

In regard to ethical aspects of clinical trials, it should be noted that the conduction of such trials and achievement of unbiased results can only be possible subject to compliance with generally accepted international standards that should include Good Laboratory Practice (GLP) and Good Clinical Practice (GCP). This article was not intended to study ethical issues of the pharmaceutical industry; therefore we mainly focus on legal aspects.

From a legal perspective, research and development studies on clinical trials are a kind of studies performed either under a civil contract or a public contract.

Chapter 38 of the Civil Code of the Russian Federation provides for two types of agreements which together constitute one single type of agreement. (greement on Trade-Related Aspects of Intellectual Property Rights, 1994) First, these are research and development agreements, and second, design and engineering agreements. Neither contract was specified in Civil Codes of 1922 and 1964. In the fundamentals of civil legislation of the Russian Federation of 1991, an article on both research and development and design and engineering agreements first appeared in a chapter on contracting.

As researchers aptly noted, the two types of agreement are distinguished by the subject, i.e. the description of actions (works) to be performed by the Contractor. (Meshkovskiy 2013) Paragraph 1 of Article 769 provides that the subject of the first type of agreement is the research studies stipulated by Customer's specifications, and the subject of the second type of agreement is the advanced development of a new product, drawing up product related design documents or development of a new

product technology. Both agreements provide for similar Customer's obligations, namely acceptance of works and payment for works in either case.

Thus, according to Para. 1 of Art. 769 of the Civil Code of the Russian Federation, under the Research and Development Agreement, the Contractor shall conduct research studies specified in Customer's specifications, and the Customer shall accept research studies and pay for the works performed. Public contracts for research and development studies used to satisfy public needs are subject to the provisions provided for in Art. 763-768 Ch. 37 of the Civil Code of the Russian Federation. (A40-188378/2014)

The subject of this Contract is the conduction of research and development studies rather than the development of intellectual property. Under this Contract, the Contractor shall conduct research studies specified in Customer's specifications. These research studies can be both basic and applied. According to the Federal Law of the Russian Federation No. 127-FZ of August 23, 1996 "On Science and State Science and Technology Policy", research and development studies focus on fundamental, experimental or theoretical research activities and are intended to acquire new knowledge about basic patterns of structure, functioning and development of human, society and environment. (Braghinskiy and Vitryanskiy, 2002-2006)

Research results are presented in respective reports subject to state registration of medicines along with other documents. Thus, a research report that refers to scientific works and therefore to intellectual property can be both a way to present research and development studies as well as their component and the proof of research.

In respect of patentable subject matters (employee's inventions, utility models and industrial designs), Para. 4 of Art. 1370 of the Civil Code of the Russian Federation provides that unless otherwise agreed in the Employment Agreement, the Employee shall notify the Employer in writing of the invention that can be subject to legal protection which resulted from the carrying out of employee's duties, either specifically assigned to him/her. Para. 4 of Art. 1430 of the Civil Code of the Russian Federation contains a regulation providing that the Employee shall notify of a selection invention made by him/her. (Braghinskiy 1996)

DISCUSSION OF RESEARCH FINDINGS

There is no regulation in respect of research and development outcomes, i.e. intellectual property; however, *most researchers believe* that at this phase of legal regulation, partial similarity of legal framework for selection and inventions and achievements, utility models and industrial designs is quite justified, since it complies with the unbiased methods and techniques for the creation of intellectual property used in activities related to both inventions and selection inventions.

A similar situation prevails in judicial arbitration practices: if the Contractor fails to notify the Customer of completion of works, the Acceptance Certificate unilaterally drawn up by the Contractor shall not be deemed to be the proof of completion of works. This conclusion is provided in both the Newsletter of the Presidium of the Supreme Arbitration Court of the Russian Federation No. 51 of January 24, 2000, and (The Civil Code of the Russian Federation) the Ruling of the Supreme Arbitration Court of the Russian Federation No. VAS-13442/09 dated October 30, 2009, Case No. A65-25558/2008-SG5-51 (Federal Law No. 127-FZ of August 23, 1996) as well as other judicial decisions.

In respect of the exclusive right to use the results of a scientific work developed under a civil contract or a public contract, Para. 1 of Art. 1298 of the Civil Code of the Russian Federation states that the exclusive rights shall be reserved to the Executive (Contractor), i.e. the Author or any Third Party responsible for the execution of the Public Contract, unless the Public Contract provides that these rights shall be reserved to the Russian Federation or the Subject of the Russian Federation on whose behalf the Public Customer (Public Contracting Authority) acts; the rights shall be jointly reserved to either the Russian Federation and the Executor or the Subject of the Russian Federation and the Executor.

Special regulations are laid down in respect of unlawful use of the exclusive rights reserved to a Third Party and arising in connection with the works to be performed by the Executive (Contractor). According to Article 773 of the Civil Code of the Russian Federation, the Executive (Contractor) shall ensure that the results obtained under the Contract are transferred to the Customer and that they do not infringe the exclusive rights reserved to a Third Party. Therefore, shall the Customer be responsible for the infringement of these rights, the Customer shall be entitled to recover the amount paid from the Executive (Contractor) by way of recourse (unless it is proved that the Customer is responsible for this infringement). A patent research must ensure timely identification of protectable results of research and development and design and engineering studies, so that its legal owner could register his/her intellectual property rights. (The Civil Code of the Russian Federation; Newsletter of the Presidium of the Supreme Arbitration, 2004; Decision of the Supreme Arbitration Court of the RF No. VAS-13442/09, 2009; Pylneye 2007).

CONCLUSION

With reference to the subject mentioned above, we consider that it is reasonable to develop a mechanism for confirming customer's exclusive rights to use the results of research and development studies if they are made either under a civil contract or a public (municipal) contract.

1. This contract (agreement) should include the following:
    - Provision providing that the exclusive rights shall be either reserved to the Customer or a Third Party on whose behalf the Customer acts or jointly reserved to both of them;
    - Procedure for the Customer notification of completion of works;
    - Procedure for the acceptance and assessment of the results of works performed;
    - Procedure for the conclusion of Agreements on Alienation of Exclusive Rights or License Agreements.
2. The Acceptance Certificate for research and development studies involving clinical trials to be signed by the Parties may include the following:
    - Novelty and perspectives of proposed research and engineering solutions;
    - Amount of national and international achievements in science and technology used in the implemented development;
    - Estimated (projected) performance of new products or engineering procedures in terms of the level of patent protection of developments delivered, the level of competitiveness in the respective sector as well as the level of compliance with customer needs.

Since the national legal system doesn't classify live cells as a specific category "subject matter of civil rights", it can be assumed that this "legal loophole" will cripple clinical trials. Therefore, we propose to make appropriate changes to the Civil Code of the Russian Federation.

References

A40-188378/2014. Date Views 18.06.2016 kad.arbitr.ru.

Agreement on Trade-Related Aspects of Intellectual Property Rights. Marrakesh, (1994). Date Views 10.06.2016 www.wto.org/english/docs_e/legal_e/27-trips.doc.

Article 18 of the Federal Law No. 2010-FZ of April 18, 12 "On Circulation of Medicines". Rossiyskaya Gazeta, 5157 of April 14, 2010.

Clinical Trials in Russia. Orange Paper. Annual 2015. CRO Synergy Research Group. Moscow, 2016. Date Views 07.06.2016 synergycro.ru/analytics/orange-paper.html.

Federal Law No. 61-FZ of April 12, 2010 "On Circulation of Medicines". Rossiyskaya Gazeta. Federal Issue No. 5157 of April 14, 2010.

Federal Law No. 323-FZ of November 21, 2011 "On Citizens' Health Protection in the Russian Federation". Rossiyskaya Gazeta. November 23, 2011. Federal Issue No. 5639.

Federal Law No. 61-FZ of April 12, 2010 "On Circulation of Medicines". Rossiyskaya Gazeta, 5157 of April 14, 2010.

Federal Law No. 323-FZ of November 21, 2011 "On Citizens' Health Protection in the Russian Federation". Rossiyskaya Gazeta, November 23, 2011, Federal Issue No. 5639.

Federal Law No. 126-FZ of July 21, 2012 "On Ratification of the Protocol on the Accession of the Russian Federation to the Marrakesh Agreement Establishing the World Trade Organization of April 15, 1994". Rossiyskaya Gazeta, 5839 of July 23, 2012.

Federal Law No. 127-FZ of August 23, 1996. (Rev. of November 2, 2013) "On Science and State Science and Technology Policy". Compilation of Legislation of the RF, 1996, No. 35. Art. 4137.

Decision of the Supreme Arbitration Court of the RF No. VAS-13442/09 of October 30, 2009, Case No. A65-25558/2008-SG5-51, 2013. Consultant Plus Legal Reference System.

Khokhlova, V.V., (2016). Some Issues on Legal Protection of Reference Medicines. Journal of the Court for Intellectual Property Rights, pp. 19.

Meshkovskiy, A.P., (2013). A Comparison of Mechanisms for Regulating Pharmaceutical Market of Russia and Countries with Strict Regulatory Requirements. Relevant Issues on Pharmaceutical Market Regulation (according to WHO's reference materials). Compilation of Documents and Articles. Moscow, pp. 102.

Newsletter of the Presidium of the Supreme Arbitration Court of the RF No. 51 of January 24, 2000 "Review of Dispute Settlement Practices under a Construction Contract", 2000. Vestnik of the Supreme Arbitration Court of the RF, 3.

Promoting Access to Medical Technologies and Innovation. Intersections between Public Health, Intellectual Property and Trade, (2014). World Health Organization, World Intellectual Property Organization, World Trade Organization.

Pugatch, M.P., (2004). Intellectual Property and Pharmaceutical Data Exclusivity in the Context of Innovation and Market Access. ICTSD-UNCTAD Dialogue on Ensuring Policy Options for Affordable Access to Essential Medicines. University of Haifa.

Pylneye, Yu., (2007). Conducting Patent Researches. Intellectual Property. Industrial Property, 5: p. 52.

Ranking of Countries Exporting Pharmaceutical Products: Europe Ahead of the Curve. Russian News Agency RIA Novosti. July 18, 2013.

Russia Pharmaceutical & Healthcare Report Q1 2010 (including 5-year industry forecast), 2010. Business Monitor International.

The Civil Code of the Russian Federation (Part one) No. 51-FZ of 30.11.1994 (Rev. of 31.12.2014). Compilation of Legislation of the RF. 05.12.1994. No. 32. Art. 3301.

The Civil Code of the Russian Federation (Part two) No. 14-FZ of January 26, 1996 (Rev. of 31.12.2014). Compilation of Legislation of the RF, 1996. No. 5. Art. 410.

The Civil Code of the Russian Federation (Part four) No. 230-FZ of December 18, 2006 (Rev. of July 23, 2013). Compilation of Legislation of the RF. 2006, No. 52, Part 1. Art. 5496.

The Constitution of the Russian Federation (adopted by national popular vote on 12.12.1993) (as amended by the Laws of the RF on Amendments to the Constitution of the Russian Federation of No. 6-FKZ of 30.12.2008, No. 7-FKZ of 30.12.2008, No. 2-FKZ of 05.02.2014, No. 11-FKZ of 21.07.2014). Compilation of Legislation of the RF. 04.08.2014. No. 31. Art. 4398.

Voronkov, M. and D. Kolobov, 2007. Mythology of Innovative Medicines. Moscow Pharmacies, 5, 12-13.