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# Advantages of Conducting Clinical Trials in the CIS Countries, Georgia and Ukraine

N. V. Pyatigorskaya, S. Y. Simeniv, D. V. Kryuchkov, A. Y. Malikov, E. S. Rogov, N. V. Chertishchev

*Sechenov First Moscow State Medical University, Trubetskaya Street, 8-2, Moscow, Russian Fed., 119991*

**Abstract**

The purpose of this review is to examine the current state of the clinical trial market in the CIS, Ukraine and Georgia from the perspective of new opportunities for conducting clinical research in these countries. Russian clinical trial legislation is harmonized with global industry standards not only on the national level, but also on the level of international unions. An agreement of unified principles and rules for the circulation of drugs and medical devices came into force on February 12, 2016 in the Eurasian Economic Union (EAEU), which includes Belarus, Kazakhstan, Armenia and Kyrgyzstan additionally to Russia as of March 2017. High performance quality and professional competence of the investigators, accessible and diverse population of patients, changes and harmonization of legislation as well as system of clinical trial conduct in general, make the CIS countries, including Georgia and Ukraine, quite attractive for conducting both international and local clinical studies of drugs and medical products.

**Keywords:** current state of a clinical trial market, clinical trials in CIS, Ukraine and Georgia, harmonization of legislation, CRO.

## INTRODUCTION

At present the potential of the Commonwealth of Independent States (CIS) countries in relation to clinical trials (CTs) of drugs and medical products is dramatically undervalued. Participants of the CT market cite a negative previous experience (a complex and long-term process of obtaining CT approvals) and political stability concerns as the main reasons. At the same time, changes in a legal and administrative environment of clinical trials in many countries of the region facilitated optimization of both the time-lines and the approval procedure, and, in general, improved the quality of CTs conducted.

The main criteria taken into consideration by pharmaceutical companies and contract research organizations (CROs) when making a decision whether to include a country in a clinical trial are as follows:

1. the existence of developed regulatory procedures harmonized with recognized international regulatory practices;
2. the time-line of obtaining CT approvals;
3. a "competitively fast" patient recruitment;
4. the quality of CT conduct [1].

We'll consider the current state of a clinical trial market in the region from this perspective.

## Correlation of national and international regulatory standards for clinical trials of medicines and medical products

The Russian Federation (RF) is the country with the largest market of CTs in the region; significant positive changes have recently occurred in the RF legislation in the sphere of drug circulation and clinical trials. GOST R 52379-2005 "Good Clinical Practice" was adopted in the RF in 2006. It is identical to the Guideline for Good Clinical Practice of the ICH (International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use) which in turn was developed taking into consideration the current requirements of good clinical practices in the EU, the USA and Japan as well as Australia, Canada and the World Health Organization (WHO). The existence of this standard makes it possible to state that rules and requirements similar to the ICH GCP are applied in the RF. This document has become one of the main guidelines for writing clinical study documentation and a guidance in the process of their conduct, which contributed to a significant improvement in the CT quality, and the attraction of foreign companies to the Russian market of CTs. The Federal Law No.61-FZ "On Circulation of Medicines" was adopted in 2010 which legislates the basic concepts and procedures in the field of clinical trials. In the same year, the regulatory documentation on clinical studies was approved by orders of the RF Ministry of Health and Social Development (http://www.roszdravnadzor.ru):

- the statement of the Ethics Committee;
- the procedure for organizing and conducting an ethics review of the feasibility to conduct a clinical drug trial;
- model rules of mandatory health and safety insurance for patients participating in a clinical drug study;
- rules of accreditation of medical institutions to conduct clinical drug studies;
- the procedure for publishing a list of medical institutions authorized to conduct clinical drug studies on the official website of the Ministry of Health and Social Development of the Russian Federation, as well as the approved rules for maintaining a register of investigators conducting clinical drug studies;
- the procedure for issuing a clinical drug study approval and the procedure for maintaining and publishing a register of approvals issued for conducting clinical drug studies on the official website;
- rules of the import and export of biological materials obtained in a clinical trial to and from the Russian Federation.

However, the clinical trial legislation does not stay still: more than 20 revisions of the Federal Law No.61-FZ were issued for the period from 2010 to 2016. On April 1, 2016 the Ministry of Health of Russia passed the Order No. 200n "On Approval of the Good Clinical Practice". Along with the Federal Law No. 61-FZ, it became the main document which standards compliance is inspected by Roszdravnadzor (the Federal Service for Surveillance in Healthcare, the body authorized to monitor clinical trials in the RF) when auditing the activity of CT market participants (study sites, pharmaceutical companies and CROs). The base for clinical studies of medical products is actively developing in parallel with the legislation in the field of medicinal products circulation: the Federal Law No.323-FZ "On the Fundamentals of Health Protection in the Russian Federation", the government decree "On approval of the rules for the state registration of medical products", orders of the RF Ministry of Health and relevant GOSTs were adopted.

The Russian regulator pays much attention to the scientific validity of a design, end points and statistical aspects of clinical studies. The Scientific Center for Expertise of Medical Products of the RF MoH publishes guidelines for clinical trials and drug expert assessment which take into account the international experience and recommendations of the world's leading regulatory agencies (U.S. Food and Drug Administration,

European Medicines Agency) (http://www.regmed.ru/Default.aspx). "Vestnik of Roszdravnadzor" has been published since 2008 which is a peer-reviewed scientific and practical journal for specialists in medicine, the organization of health care and pharmaceutical activities. It also publishes modern recommendations for conducting clinical trials, and reviews of typical errors are.

The Russian clinical trial legislation is harmonized with global industry standards not only at the national level, but also at the level of international unions. An agreement of unified principles and rules for the circulation of drugs and medical devices entered into force on February 12, 2016 in the Eurasian Economic Union (EAEU), which members are Belarus, Kazakhstan, Armenia and Kyrgyzstan in addition to Russia as of March 2017. The rules of GLP, GCP, GMP, GVP, GDP, bioequivalence requirements, rules for a biological medicinal product study, the interchangeability of drugs, the procedure for inspections, drug production requirements (more than 20 documents), requirements to homeopathic medicines (8 documents), guidelines for non-clinical and clinical drug studies (more than 20 documents) and general documents (more than 20 ones) which are harmonized with international rules and requirements have been adopted within the framework of the EAEU (http://www.eurasiancommission.org) [2].

Thus, the procedure for state registration and, in particular, the rules for conducting clinical trials of drugs and medical products in Russia and other countries of the EAEU are strictly regulated and arranged, the norms have approached to international ones, the system has become much more transparent, clear and attractive for both domestic, and foreign pharmaceutical companies and CROs.

In Ukraine clinical trials are regulated by the Health Ministry and the State Expert Center authorized by the Ministry whose powers include, *inter alia*, CT approvals, CT inspections and the provision of GCP educational programs. Owing to the Center's activities, the procedures for drug expert evaluation and registration in Ukraine were harmonized with respective ones in Europe in 2000-2001. The prepared documents contained a number of fundamentally new provisions, which allowed Ukraine to achieve a quantum leap in non-clinical and clinical drug studies, expert assessment, registration and post-authorization surveillance. The requirement of compulsory reporting by healthcare institutions on side effects of drugs was introduced and a chain of response to these reports created. In Ukraine international rules of good practices - GLP and GCP, were implemented with the assistance of the Center: current orders of the Health Ministry of Ukraine, regulating the rules for conducting non-clinical and clinical drug trials in accordance with the best world standards were prepared, a number of textbooks, manuals and guidelines on various aspects of non-clinical and clinical drug trials developed and published. The clinical trial legislation is focused on the compliance with the principles enunciated in the Declaration of Helsinki and harmonized with the ICH and the EU legislation. Ukrainian plans for integration into the EU also imply the conduct of CTs according to the EMA rules and recommendations [2].

Russia, Kazakhstan and the Republic of Belarus are prominent CT participants in the region, packages of key EAEC laws adopted in Armenia and Kyrgyzstan will encourage the dramatic increase of CTs conducted. The legislation and the system of organization of clinical trials in Georgia also make it unusually attractive for conducting international clinical trials.

Georgia leads the region in terms of obtaining CT approvals (1-2 months), and the inclusion of the first patient in international multicenter clinical trials (MMCTs) with the participation of Georgia has traditionally been taking place in this country (http://ascentcrs.com/rus/our-geography/georgia). Documents in the framework of the CT application in Ukraine are submitted to the State Expert Center (reviews the drug dossier) and the Local Ethics Committee associated with a study site (evaluates the clinical study protocol and aspects related to the patient informed consent process) in parallel. A total period for the CT approval, including the obtaining of export/import licenses, is 12-16 weeks, the period which is comparable with EU countries (https://www.dentons.com/en/insights/alerts/2016/january/12/ministry-of-health-of-ukraine-amends-the-procedure-for-conducting-clinical-trials). In Russia, Belarus and Kazakhstan, the approval timing currently ranges from 3 to 4 months; however, the time-line of obtaining approvals and related licenses has been noted to reduce in these countries (especially in the context of developing the EAEU documents package). The Association of International Pharmaceutical Manufacturers (AIPM) regularly monitors the time-line of issuing official documents for clinical trials based on the data provided by companies. In 2014 nineteen international companies took part in the AIPM monitoring, including almost all the top 10 leaders in conduct of MMCTs in the Russian Federation [1]. The key results of the monitoring conducted in 2014 are presented in Table 1.

Table 1. Comparison of regulatory procedure time-lines in 2014 [1].

| Type of application | Number of submissions | Number of approvals | Number of refusal | Approval timeline under FZ No.361 and Government Order No.673 (working days) | Timeline of obtaining approvals, official (working days) | | Timeline of obtaining approvals, actual (working days) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | Min-Max | Ave. | Min-Max | Ave. |
| CT approval | 91 | 67 | 15 | 45 | 32-177 | 61 | 40-180 | 66 |
| Biosample import/export license (permit) | 195 | 191 | 4 | 10 | 3-29 | 10 | 7-33 | 15 |
| Drug import license (permit) | 100 | 94 | 4 | 5 | 2-13 | 5 | 5-21 | 11 |
| Protocol amendments | 177 | 167 | 1 | 30 | 3-58 | 35 | 6-71 | 41 |
| Other | 240 | 228 | 5 | N/A | 2-70 | 16 | 5-75 | 21 |
| Resubmission due to refusal | 10 | 8 | 2 | 45 | 36-85 | 54 | 43-105 | 64 |
| Registration CT | 18 | 11 | 1 | 45 | 2-160 | 66 | 16-168 | 82 |

**The potential of clinical trial markets in the countries of EAEU, Ukraine and Georgia**

The territory of the EAEU is more than 20 million square km or 14% of the world's land; the total population is 182.7 million people, of which 147 million live in Russia. This is obvious, even taking into account the region scale to be a huge, but still untapped market. The capacity of the Russian pharmaceutical market is estimated by experts to be 13.5-16 billion dollars. Russia is in the top 10 countries in terms of the capacity of a retail market of finished pharmaceutical products [3]. The clinical trial market in Russia was estimated to cost 880 million US dollars in 2015, with an obvious growth expected. Even based upon a very restrained growth forecast of 4.65% per year, approximately 1,086 MMCTs will be conducted in Russia, and the market volume will be 1.6 billion US dollars by 2020.

A high recruitment rate counts in favor of conducting CTs in the region, which has a rational explanation. According to the official data, in the Russian Federation 1,052 well-equipped healthcare institutions were authorized to conduct clinical trials as of the end of 2014, with 1,099 ones accredited by the end of 2015. Most of these medical institutions are located in large Russian cities such as Moscow, St. Petersburg, Novosibirsk, etc., which is primarily due to peculiarities of the domestic healthcare system [4]. The urban residence prevails in Russia, this facilitates recruitment for studies. The recruitment rate is facilitated by the high prevalence of different diseases, including rare and even orphan ones for other countries (for example, tuberculosis, pancreatic necrosis), a large number of treatment-"naive" (i.e., previously untreated) patients, a low availability of free specialized and high-technology medical care, and a highly qualified medical personnel of study sites, that induces patients to participate in clinical trials, while the willingness to cooperate with a physician contributes to a small percentage of withdrawal [5]. The system of compulsory medical insurance in Ukraine provides for only the most basic types of medical care, modern drugs, advanced methods of diagnosis and treatment are available only for patient's personal costs or under expensive insurance. Therefore, patients are highly motivated to participate in clinical trials. Moreover, environmental catastrophes (the Chernobyl tragedy of 1986, the Kyshtym accident of 1957 resulted in the formation of the East Urals radioactive trail), as well as the results of political crises in the region over the past 30 years, caused an increased prevalence of chronic and oncological diseases. It should be kept in mind that the vast majority of the population of the EAEU countries, Georgia and Ukraine are caucasians (which makes the results easily generalizable) with a unique diversity of genotypes (which significantly increases the appeal of the region for studies in oncology and immunology).

Ukraine is the eighth largest European country by population (45 million people), with 70% of the population living in urban centers. The country has more than 570 clinical study sites, which can recruit subjects for MMCTs, and in total in Ukraine there are more than 1,500 investigational sites experienced in conducting CTs. In 2013-2014 clinical study sites were closed off in Donetsk and Lugansk regions, which area is not more than 3-4% of the total territory of the country (the majority of clinical study subjects preferred to continue their participation in nearby sites). Since 2014 clinical studies in Crimea have been conducted according to the Russian legislation. Thus, political unrest in the region almost has not affected the potential to conduct MMCTs in Ukraine and Crimea. At the same time, only 15% of the Ukraine's potential is currently used for conducting clinical trials (https://www.dentons.com/en/insights/alerts/2016/january/12/ministry-of-health-of-ukraine-amends-the-procedure-for-conducting-clinical-trials, http://www.dec.gov.ua/index.php/ua/). According to the Pharmaxi estimations, the volume of the Ukrainian clinical trial market reaches 300 million US dollars, and the number of CT subjects being roughly 50-60 thousand people per year. 79 CTs were conducted in the country in 1996, with 233 and 269 CTs conducted in 2013 and 2014, respectively, despite a political crisis. At the same time, the efforts the regulator has made to harmonize the legislation with international standards, as well as to quality control of clinical trials are confirmed by the results of FDA audits: of 17 inspections conducted from 2009 through 2017, 10 resulted in “NAI” (no action indicated), while 7 resulted in “VAI” (voluntary action indicated).

Georgia is also a country of great opportunities for conducting CTs. With full harmonization of the country's legislation with international requirements, the time period for obtaining a CT approval is least here (less than 2 months), with the highest CT quality, that is confirmed by the results of 12 recent FDA inspections: 100% of the inspections resulted in NAI. The peculiarities of CT organization in Georgia include the need for LEC approval (1-2 weeks) before submitting documents to regulatory authorities (the State regulatory agency for medical activities, the approval period is 3-5 weeks); no need to obtain import/export licenses for study drugs, laboratory kits and biosamples (a letter of authorization and a certificate from the regulator are sufficient). All documents are submitted in paper and electronic form; paper documents are provided in English with a notarized translation into Georgian. To conduct a study, it is necessary to conclude an agreement with a local company or an individual entrepreneur, as foreign organizations or their subdivisions cannot initiate a submission for a CT. A contract (agreement) with an investigator and a medical institution is executed in parallel with documents submission to the LEC and regulatory authorities, a total period from the beginning of submission for a CT to the initiation of the first study site takes 56 days on average (http://cromospharma.com/images/files/2016-11_clincical_trials_in_georgia.pdf).

The staff is also important. In Russia 89 higher educational institutions have medical faculties, which annually about 20,000 physicians graduate from. Based on the official data, in 2014 there were 703,000 or 491 physicians per 100,000 people - that is more than in any other country [6]. The number of physicians in Ukraine is 352 per 100,000 people, which is, for example, more than in the US (approximately 250 per 100,000 people). The population of Georgia is 3,720,000 people, with there being 24,300 physicians and 259 hospitals in the country; patient treatment follows world standards.[18] GCP courses and advanced training in clinical trials are both available in state and private institutions, in topical seminars and conferences. Well-trained specialists work as both principle investigators and co-investigators in accredited clinical study sites and are employed in contract research organizations that provide the high-quality conduction of clinical trials.

## CONCLUSIONS

Russia maintains the state policy of support of a pharmaceutical market and medical industry (for example, the state program "Pharma 2020", planned for implementation in the period from 2013 to 2020). In accordance with the RF legislation the state registration of many generic drugs requires to conduct bioequivalence or therapeutic equivalence studies, while it is required to conduct the entire cycle of non-clinical and all (in most cases) phases clinical trials for biosimilars and reference drugs to be registered. Therefore, even in the setting of an economic crisis and an unstable political situation, the clinical trial market in the RF is constantly growing due to the participation of Russian clinical study sites in both MMCTs and local studies. In 2016, the Ministry of Health of the Russian Federation issued 895 approvals of all types of clinical trials (CTs), which is more by 12% than in 2015. At the same time,

there were 319 new international multicenter CTs initiated in 2016, which is more by 3% than in the previous year. The number of bioequivalence studies has increased by 3% as compared to 2015 and amounted to 302 versus 292. The number of local CTs conducted in Russia significantly increased as compared to 2015 and amounted to 276 versus 200 studies. Companies from 39 countries sponsored CTs which conduction was approved in Russia in 2016. Russian manufacturers (373 CTs) were the top first, followed by American sponsors (138 CTs), sponsors from India (80 CTs) and Switzerland (38 CTs). 83 new Phase I clinical trials were initiated in 2016, that is more by 51% than in 2015 (55 CTs). The number of Phase II clinical trials (92 new studies) increased by 14% as compared to 2015 (81 CTs). The number of Phase III clinical trials increased from 352 to 387, that is more by 10% than in the previous year. The number of Phase IV clinical trials increased from 22 to 32 as compared to 2015. In 2016 the FDA approved 103 new drugs, 27 of them were (are) under clinical studies in Russia. The EMA approved 105 new drugs in 2016, most of them (71) were (are) under clinical studies in Russia (http://synergycro.ru/orange_paper/SynRG_Orange_Paper_Y2016.pdf). A relatively low cost of conducting clinical trials, a more rapid drug launch, associated competitive advantages and return on investment undoubtedly cover the expenses for registration MMCTIs with the participation of study sites in Russia, in other countries of the EEAU, as well as in Ukraine and Georgia.

The availability of an accessible and diverse population of patients, high performance quality and professional competence of investigators as well as positive changes and harmonization of legislation and the system of clinical trial conduct in general, make the CIS countries, Georgia and Ukraine very attractive for conducting both international and local clinical studies of drugs and medical products.

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