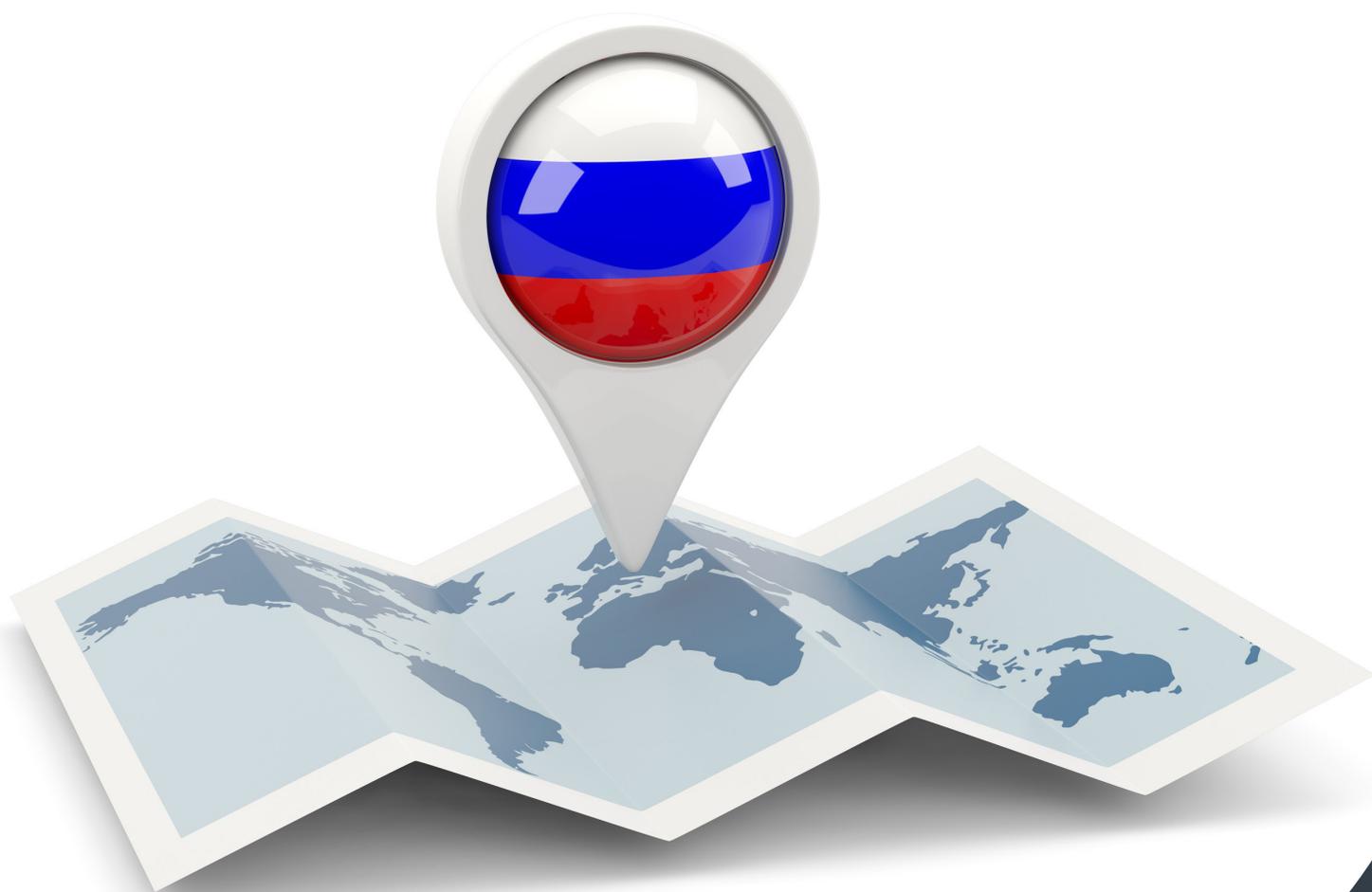


Navigating through the Clinical Trial Authorization Process in Russia

Clinical Endpoint ANDA Program Optimization
White Paper Series



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Introduction

Countries of Eastern Europe, specifically Russia, have become an increasingly attractive venue for conducting clinical trials in the eyes of western pharmaceutical companies. Russian clinics and principal investigators have proven to be highly capable of conducting clinical research at a level of quality equal or greater than that of Western Europe and North America. Sponsors consider Russia as an attractive study venue due to the countries higher enrollment and patient retention rates and lower overall cost. Our overall experience shows that sponsors are satisfied with the results of their clinical trials run in Russia however there remains unfamiliarity with the somewhat unpredictable regulatory environment.

bioRASI has been conducting ANDA focused trials for over ten years and Russia has been one of the primary venues, especially for clinical endpoint trials.

This paper has been prepared in response to numerous inquiries from our clients wanting to further their understanding of the clinical trial authorization process in Russia. This paper outlines the regulatory requirements for obtaining regulatory approval for clinical studies and addresses certain practical aspects of regulatory submissions in Russia.

Contents

Introduction.....	2
Overview of Russian Market of Clinical Trials.....	3
Regulatory Framework	4
Regulatory Submission Package.....	4
Regulatory Process and Timelines	4
Conclusion	5

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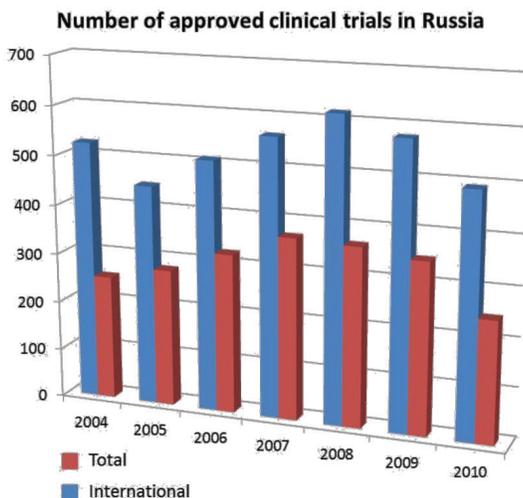
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Overview of Russian Market of Clinical Trials

Russia has a population of 143 million, who are primarily concentrated in the European part of the country and more than 70% of population live in urban areas. The Russian health care system inherited the soviet centralized health infrastructure based on a hierarchy of health care facilities at various levels of territorial administration. These facilities include polyclinics (ambulatory clinics), city and regional hospitals, specialized clinics and ambulatories, as well as scientific research centers primarily located in major cities. Russia has 4.3 doctors per 1,000 population (compared to 2.6 in US) and 9.7 hospital beds per 1,000 population (compared to 3.2 in US).¹

Russia emerged as an attractive venue of clinical trials for foreign sponsors in the early 2000s. The number of multi-country clinical studies has been steadily growing since then. Currently almost all major pharmaceutical companies routinely conduct clinical trials in Russia and approve their products worldwide based on clinical data received from Russian investigational sites. In 2010, 20 out of 101 new drugs approved by FDA were approved with data generated with clinical studies conducted in Russia.² Out of 51 new drugs Approved by EMEA in 2010, 22 new drugs have been studied in Russia.³

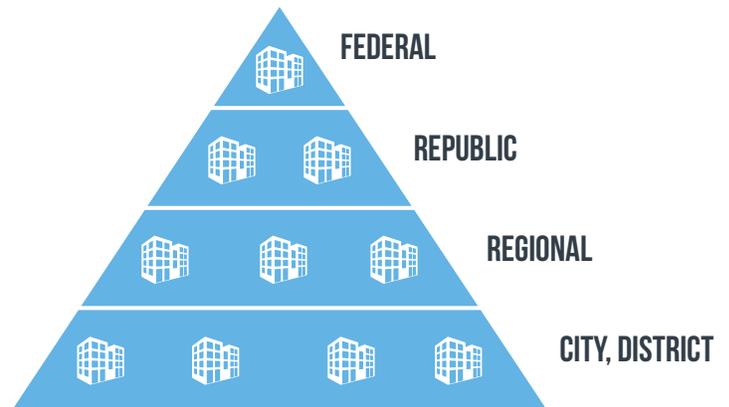
The advantages of running clinical trials in Russia are based on a number of factors presented below:



Source: Ministry of Health and Social Development of Russian Federation, <http://www.minzdravsoc.ru>.

High Recruitment Rate

In multi-country clinical trials where a portion of the study is conducted in Russia the sites have historically demonstrated higher recruitment rates and retention figures as compared to sites in the US and Western Europe. The Russian hierarchical health care system contains a large number of health care facilities across the country. This infrastructure provides substantial access to various patient populations and enables rapid recruitment of study participants. This is achieved through implementing patient referral mechanisms within the hierarchy of health institutions, as well as through identifying and enrolling the sites with highest patient recruitment potential.



Lower Costs

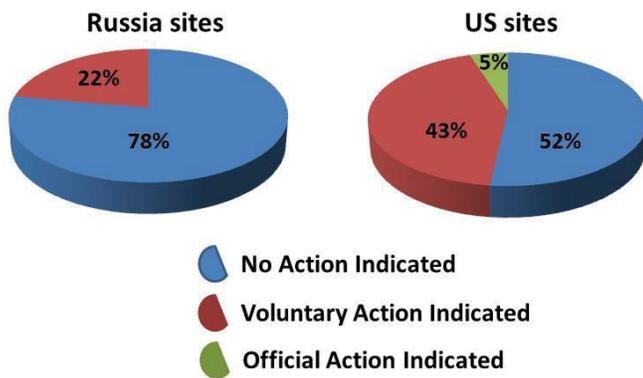
Russia offers lower costs for conducting clinical trials as compared to the US and Western Europe. Our experience shows that compared to the US, Russian sites offer approximately 30-60% savings to sponsors depending on complexity of the study, study specific procedures, patient population, and etc.

Russian clinical sites have been demonstrating continuous improvements in efficiency and quality standards.

Quality

Russian clinical sites have been demonstrating continuous improvements in efficiency and quality standards. Although there are more FDA CDER inspections conducted in the U.S. than in Russia, the figures demonstrate that Russian sites receive more “No Action Indicated,” inspection results than US investigator sites.⁴

FDA CDER Inspections



Patient Population Specifics

Data resulting from studies conducted in Russia are generally transposable to the US given the population similarities between the US and Russia. Other emerging study venues such as Asia, (primarily India) may require bridging studies to address differences in patient population considering physiological, dietary and other differences between European/US and Asian population.

Regulatory Framework

The central legal acts governing the conduct of clinical trials in Russia are the Law on Circulation of Drug (Drug Law) adopted on April 12, 2010 and became enforceable on September 1, 2010. This new law created the National Standard “On Good Clinical Practices”, and several governmental decrees and ministerial orders.

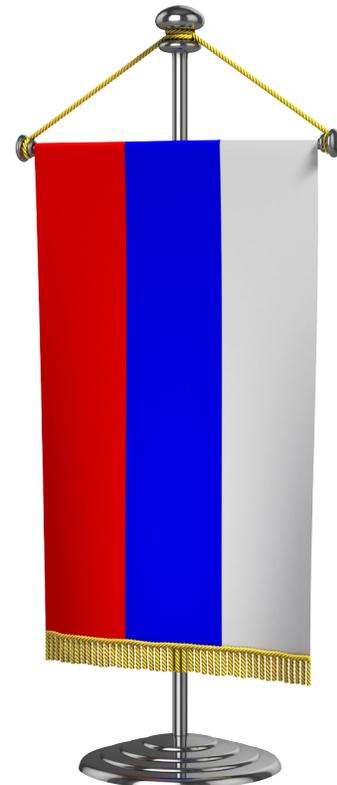
The process of granting clinical trial authorizations is defined by the new Drug Law, which replaces the Law on Medicinal Products, which has been in force since 1998. The new law introduces significant procedural and structural changes associated with review and approval of

clinical trial authorization applications.

Under this law, the Ministry of Health and Social Development of Russian Federation (MoH) is the central entity responsible for approval and oversight of clinical trials conducted in Russia. Other entities which are involved in the process of review of clinical trial authorization application are Ethics Council (also known as National Ethics Committee or NEC) and the Federal State Enterprise “Scientific Center of Expertise of Medicinal Products” (SCEMP). The NEC is responsible for review of clinical trial applications and providing opinions on ethical aspects of clinical trials. The SCEMP’s role is to review quality, efficacy and safety data of new drugs and scientific expertise of the proposed clinical studies.

According to the new Law on Drugs, foreign sponsors may apply for clinical trial authorization under two circumstances:

1. As part of the registration process for a new drug in Russia (marketing authorization) or,
2. As part of an international multi-country study (if is the study is not conducted for purposes of registration in Russia).



Regulatory Submission Package

The Drug Law specifies a list of documents to be included in the regulatory submission package for authorization of multi-country clinical trials. The Drug law unfortunately does not provide sufficient details or specificity about the content, format and other requirements for each document to be submitted and, through experience we have found that the number of documents for regulatory submission typically includes several other documents that are not explicitly listed in regulations.

The table below lists the documents that must be presented for obtaining clinical trial authorization and provides further descriptions and requirements for particular documents to be submitted.

	Document	Comments
1.	Application letter	Application letter should contain the following information: <ul style="list-style-type: none"> - name and address of the sponsor's and applicant's (if application is made not by sponsor), - protocol title and number, - name, dose and drug form of the investigational product, - number of patients to be enrolled in Russia, - countries where the study is to be conducted (for multi-country studies)
2.	Proof of payment of state duty	A state duty should be paid prior to submission of the application.
3.	Report on preclinical trials of the medicinal product and report on earlier clinical trials of the investigational drug (if any).	There is not a specific format prescribed by the law for reports of preclinical and clinical studies. Typically the regulatory authorities expect applicants to provide toxicity data (acute, sub acute, sub chronic, chronic toxicity), specific influences (cancerogenity, mutagenic and teratogenic effects, embryo-toxicity, allergic and local-irritative effects, if applicable), available efficacy data (preclinical and clinical), and summary information of the side effects, if applicable.
4.	Clinical trial protocol	The content and format of the clinical trial protocol should mesh with ICH-GCP requirements.
5.	Investigator's Brochure	The content and format of Investigator Brochure must comply with ICH-GCP requirements.
6.	Informed consent form and information sheets of the patients	Inform Consent Form must comply with requirements of ICH-GCP. In addition, the ICF

	Document	Comments
	enrolled in the clinical trial	should provide the information about life and medical insurance, contact information of the insurance company and a procedure for submitting claims.
7.	Data about the investigators' work experience in the relevant specializations and their clinical trial experience	The application should contain signed and dated CV of investigators, copies of diplomas, certificates and similar documents demonstrating investigators qualification, as well as their previous experience in clinical trials. The law requires investigators to have at least 5 years of clinical research experience.
8.	Information about health care institution, where the clinical trial is to be conducted	The name, form of legal entity, and address of the clinical site should be provided. According to the law, health care institutions have to be accredited by the MoH to conduct clinical studies. As of the date of this white paper only 655 institutions have been accredited, however this number is rapidly growing.
9.	Information about proposed timelines for the clinical trial.	Application should specify projected duration of the trial, its start and end dates.
10.	Copies of policies for compulsory life and medical insurance of patients to be enrolled in the clinical trials	The law requires sponsors to arrange life and medical insurance for study participants. The law also defines the minimum coverage for clinical study participants.
11.	Information about composition of the investigational product	It is recommended that applicants provide a comprehensive set of documentation about composition, master manufacturing formula, details of the formulation including inactive ingredients, in-process quality control check, finished product specification, recipient compatibility, validation of the analytical method, packing specifications, process validation, etc.
12.	Document by the manufacturer providing data about the characteristics (parameters) of the investigational product manufactured for the clinical trial.	Certificate of Analysis and GMP certificates are to be submitted.

The law does not prohibit applicants to supplement their submission package with any additional relevant documents. Experience shows that the following documents, although not required by law, often are expected by the regulatory authorities and facilitate regulatory review:

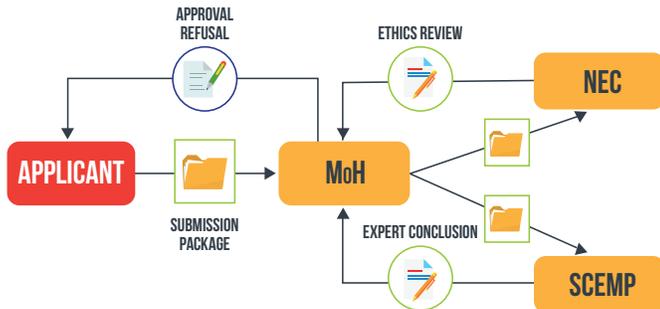
- Case Report Form;
- Stability data (Final release specification, reference standard characterization, material safety data sheet)
- Information about packaging
- Information about regulatory status in other countries.

All the above documents shall be submitted in English (or other language, as applicable) and in Russian.

If clinical trial authorization application is made by a CRO or other party representing the sponsor, the application should include a Power of Attorney authorizing the CRO or a third party to represent sponsor before the MoH. Power of Attorney should be notarized and apostilled, with certified translation into Russian.

Regulatory Process and Timelines

The regulatory process for obtaining clinical trial authorization can be illustrated as follows:



The regulatory process starts with submission of the application to the MoH. Once the application is received, within 5 working days the MoH shall review the completeness of submission and, if the application is not found to be deficient, shall forward it to the NEC and SCEMP for review or, return it if the application is incomplete or otherwise deficient.

Upon receipt at the SCEMP the application undergoes review by different expert group, including experts in CMC, toxicology, pharmacology, clinicians, etc.

At the NEC the copies of application package are distributed to the members of the committee. The NEC reviews the application during their routine committee sessions which is typically held once a month. Decisions at

the NEC session are made by simple majority of members present at the session.

Conclusion

The Russian regulatory environment for obtaining clinical trial authorizations is relatively complex and somewhat unpredictable. The regulations often lack descriptions of specific requirements for certain documents or processes, which leaves room for various interpretations of the regulatory requirements by the industry and regulatory authorities. Despite the fact that regulations define specific timelines for review of regulatory applications and issuance of approvals, the regulatory timelines are not followed on routine basis.

Preparation of the comprehensive submission package for clinical trial authorization takes in-depth knowledge of the regulations as well as experience in submitting and working with the Russian regulatory agencies. A crucial component of this process is also anticipating and addressing potential inquiries by regulatory authorities in initial submission, as well as responding to inquiries in an expedited and comprehensive manner. Therefore, foreign sponsors planning to conduct clinical studies in Russia need to rely on the expertise of local regulatory experts to ensure proper navigation through the regulatory process.

bioRASI has been providing regulatory and clinical operations expertise for the conduct of clinical trials in Russian Federation since the emergence of Russia as a potent and capable venue for clinical trials. bioRASI has developed numerous guidelines, forms, templates and checklists for regulatory submissions, and routinely update internal procedures to comply with frequently changing regulatory requirements. bioRASI regulatory experts also maintain current communications with the Russian MoH to ensure emerging regulatory changes are well understood prior to implementation.

1 "Core Health Indicators." World Health Organization. N.p., n.d. Web. 30 Sept. 2011. <apps.who.int/whosis/database/core/core_select_process.cfm>.

2 "New and Generic Drug Approvals." U S Food and Drug Administration Website. N.p., n.d. Web. 1 Oct. 2011. <<http://www.fda.gov/Drugs/NewsEvents/ucm130961.htm>>

3 "European Medicinal Agency." European Medicinal Agency Website. N.p., n.d. Web. 26 Sept. 2011. <www.ema.europa.eu>.

4 "Inspections Database." U S Food and Drug Administration Home Page. N.p., n.d. Web. 30 Sept. 2011. <<http://www.fda.gov/ICECI/EnforcementActions/ucm222557.htm>>.



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