Clinical Trials in Russia
Orange Paper

No. 1/2007. Overview and Year 2006

14, Presnensky Val, 123557 Moscow, Russia

www.synrg-pharm.com

Contents

14, Presnensky Val, 123557 Moscow, Russia

www.synrg-pharm.com

Introduction

According to the report published by IMS Health in late March 2007, the total sales volume of the world pharmaceutical market increased by 7% in 2006 to make up 643 billion US dollars. As many as 31 new drugs were launched on the world market in 2006, and the research portfolio was growing steadily. Thus, 2,075 new molecules were being developed as of the end of 2006, which is 7% as much as a year before. A considerable part of the drugs was at the early stages of clinical trials (Phase I and II); 95 new oncology drugs, 40 antiviral drugs (including anti-HIV drugs) and 27 anti-arthritis drugs underwent Phases III and IV of clinical trials at the same time. About 27% of the drugs being developed are of biologic origin.

Along with the simultaneous growth in the world volume of sales as well as research and development portfolio, drugs with the total sales volume about 18 billion US dollars lost their patent protection in 2006. At the same time, the total volume growth due to the drugs being launched on the market for the previous five years (2000-2005) made up only 13.5 billion USD. In 2007, 23 drugs more will lose their patent protection. As many as 87 drugs with the total sales volume of 51 billion US dollars will lose their patent protection in the following five years. Almost all pharmaceutical manufacturers of the world including Pfizer, J&J, GSK, Merck & Co, Eli Lilly, Abbot Labs, etc. will be affected.

Under such conditions, the reduction in the terms required to launch the drug on the market is not a purely economic issue anymore (it is known that each day of such a delay "costs" about one million US dollars for the developer). It becomes a critical issue and even a matter of life and death for some companies.

From this point of view, Russia as well as India and China have been considered as one of the most attractive regions for conducting clinical trials for more than 15 years. Russia is considered to have the following two key advantages: high patient enrollment rate and moderate cost of the conduction of clinical trials. At the same time, the trial conduction quality remains adequate and high. On the one hand, the related sources keep speaking about lots of so-called "naive" patients regarding the required nosologies, high expert potential at investigative sites and lower cost of clinical trials as compared to the USA and Europe. On the other hand, we have witnessed a number of scandals related to studies conducted in Russia, and customers are dissatisfied with the growing prices for the study-related services, duration of study registration procedures with the regulatory authorities and customs procedures as well as decreased patient enrolment rates and low data quality as a result of the unreasonably large number of studies conducted by investigative sites at the same time.

This Orange Paper is the first document in a series of publications aimed at providing all related parties with objective, unbiased and, the main thing, recent and current information about the Russian market of clinical trials.

This issue is an attempt to present the entire picture of the Russian market of clinical trials as of early 2007 while the following quarterly publications will feature the issues under consideration in a greater detail – general information related to clinical trials in Russia, survey of the current legal basis, analysis of clinical trials being currently conducted in Russia by sponsors, phases and therapeutic fields, rating of the most active foreign and Russian drug developers, review of services and rating of contract research organizations available in Russia, review of investigative sites, laboratories, drug warehouses and other suppliers of services related to clinical trials in Russia.

Clinical Trials Efficacy Criteria

The efficacy of a pharmaceutical company as a drug manufacturer and its ability to help as many people as possible depend on a lot of factors. The company's activity in the field of developing

brand-new drugs, conducting comparative drug efficacy and safety studies and launching drugs on the market are of much importance. As a result of this process flow, doctors gain access to new and powerful drugs to control diseases, extend the active life or soothe suffering for many patients. The successful drug promotion depends on each of the stages, in particular, clinical trials in volunteers. The need to extend the geography of clinical trials results in the increased activity of CSs conducted outside of North America and Western Europe, in particular, in Russia.

Based on the long-term practice of clinical trials, it is well known that the following are the most important factors for conducting clinical trials:

- Patient recruitment rate.
- Quality of the data obtained as a result of the CS.

Recruitment Rate

The patient recruitment rate depends on a number of factors. First, it depends on the total country's population, age and sex composition as well as such medical indices as morbidity, accumulated morbidity and death rate. Such factors as the geographic distribution of the study sample, genetic diversity and environmental impact affect the outcomes and quality of the conducted clinical study. Since both hereditary and environmental factors, which cannot be completely ruled out, affect the development and course of many diseases, the possibility to enroll "a wide range" of patients plays an important part for the further propagation of the data obtained on the general totality.

Second, the current state of the public health system and availability of medical aid for the population as well as structure and form of rendering medical aid play an important role, too.

Quality of Data

The quality of the resulting data follows directly from the competence of study doctors and clinical study monitors as well as their motivation and activities of the staff of pharmaceutical companies and contract research organizations related to the CT management.

At present Russia has a wide but nearly unrealized potential to meet the above-mentioned requirements for high-quality clinical trials and ensure reliable data on the efficacy and safety of new drugs.

General Potential for Clinical Trials in Russia

According to the Federal Agency for State Statistics, the Russian population makes up 142.8 mln. people (as of 2006). The key part of the population is urban population – 104.1 mln. people (73%), and rural population makes up 38.7 mln. people (27%). There are over 9,500 health care institutions in Russia (as of 2005) with the total number of 1.6 hospital beds. The number of outpatient and polyclinic institutions exceeds 21,800 enterprises, and their total capacity makes up 3.6 million visits per shift. A considerable part of the patient flow that could be enrolled to clinical trials as volunteers is not currently covered by the conducted CSs. This is mainly related to the structure of medical aid in Russia.

Investigative Sites

The medical system in Russia is highly centralized. The stage-by-stage nature of rendering medical services is one of its key features. Large-scale medical centers specializing in a different field of medicine are of special interest from the point of view of clinical trials. As a rule, they are research centers and training or advanced training centers for physicians of some particular specialty. Myasnikov Research and Practice Center and N.N. Blokhin Russian Research Center for Oncology can serve as examples of such centers. Their advantages are as follows:

- Federal importance (thousands of patients from all over the country are hospitalized to such centers each year based on references from regional public health administrations).
- High qualification of study doctors in such centers. Many study doctors are members of professional medical associations of Europe and America.
- High level of academic training and fluency in English (fluent reading skills as a minimum and fluent communication skills as a rule).
- Availability of experienced medical staff and possibility of all-round clinical and instrumental patient examinations including complex technical and invasive procedures.

There are specialized health care institutions like these in most of the Russian regions. On the one hand, such specialized centers make it possible to conduct clinical trials in patient populations with rare diseases. On the other hand, this public health system (along with the developed system of compulsory medical insurance) ensures the hospitalization of patients from different Russian regions and with different prosperity levels to the centers (both regional and national centers). In its turn, this provides access to the patients who have never been administered any long-term therapy before. This is especially important for Phase II clinical trials. There are many patients in Russia who have never been administered any drug therapy, in particular, oncology patients, HIV-infected people and patients with different hepatitis types.

Large-scale regional medical centers are quite promising from the point of view of clinical trials because an outpatient and polyclinic institution is attached to each of them as a rule. Such regional medical centers located in all large cities in Russia feature nearly all medical specialties.

The Federal Agency for Health Care and Social Development (Roszdravnadzor) accredits health care institutions and provides them with the right to conduct clinical trials of drugs. Only the health care institutions licensed to conduct medical activities and complying with the requirements of the Federal Law about Drugs and GCP regulations applicable in the Russian Federation can be accredited. The term of accreditation for health care institutions is not to exceed five years, and the institution has to undergo repetitive accreditation upon the expiration of the term.

Regional departments of the Federal Agency conduct audits of the accredited institutions on an annual basis to determine whether the activities of these health care institutions comply with the current legislation and Good Clinical Practice regulations. The audits include as follows[1]: control over the documents providing the legal basis for conducting the drug clinical study for their compliance with the current standards, control over the professional level, qualification and experience of the employees engaged in the clinical trials, qualification of the personnel operating hardware and equipment as well as qualification of the laboratory personnel. The health care institution is audited for its organizational and technical provision as well as the study drug handling system: premises, office equipment, communications facilities, medical hardware and laboratory equipment.

The audit commission also examines the study drug handling system: study drug storage premises and equipment as well as restricted access to the study drug. Such documents as study drug flow documents, monitors' visits and audit documents, patient informed consent forms for the participation in the clinical study, compliance with the randomization procedure (with the mandatory accounting of the urgent study drug unblinding procedures) and patients' compliance with the clinical study inclusion criteria are audited. Documentation and activities of local ethics committees are also taken into account.

As of March 5, 2007, as many as 750 Russian health care institutions are entitled to conduct

[1] Order No. 2798-Pr/06 dated December 21, 2006: *About measures aimed at the supervision over clinical trials in health care institutions in the 1st and 2nd quarter of 2007* issued by the head of the Federal Agency for Health Care and Social Development.

clinical trials of drugs. Cities with more than ten investigative sites are given in Table 1.

Though the Public Health Ministry keeps the balance between the regional population and number of health care institutions in the regions, it follows from Fig. 1 that a number of federal districts fall behind the Central Federal District by the average number of accredited institutions per capita. Most of the investigative sites are located in Moscow and Saint Petersburg. Thus, Russian regions are promising from the point of view of developing clinical trials in them.

Table 1. Cities with the number of sites exceeding ten

No.	City	Population,[1] thousand people	Number of sites[2]
1	Moscow[3]	10,101.5	184
2	Saint Petersburg[4]	4,669.4	114
3	Novosibirsk	1,425.6	29
4	Yaroslavl	613.2	19
5	Yekaterinburg	1,293.0	18
6	Nizhni Novgorod	1,311.2	17
7	Rostov-upon-Don	1,070.2	15
8	Kazan	1,105.3	15
9	Smolensk	325.5	14
10	Saratov	873.5	14
11	Krasnodar	644.8	11
12	Volgograd	1,012.8	11
13	Perm	1,000.1	11
14	Samara	1,158.1	10
15	Chelyabinsk	1,07.8	10
16	Tomsk	487.7	10
17	Barnaul	603.5	10
18	Other	N/A	238
	Total	**145,513.0**	**750**

Table 2. Number of Investigative Sites by Federal District

No.	Federal District	Population, mln. people	Number of sites
1	Central	37.1	296
2	North-Western	14.4	146
3	Privolzhsky	31.9	101
4	Ural	12.5	41
5	Siberian	20.7	97
6	Far Eastern	7.2	13
7	Southern	21.7	56
	Total	**145.5**	**750**

[1] According to the 2002 population census.
[2] According to the data for CS centers approved by the Federal Agency for Health Care and Social Development (Roszdravnadzor).
[3] Excluding the Moscow region
[4] Excluding the Leningrad region

Figure 1. Number of sites by Federal Districts of Russia

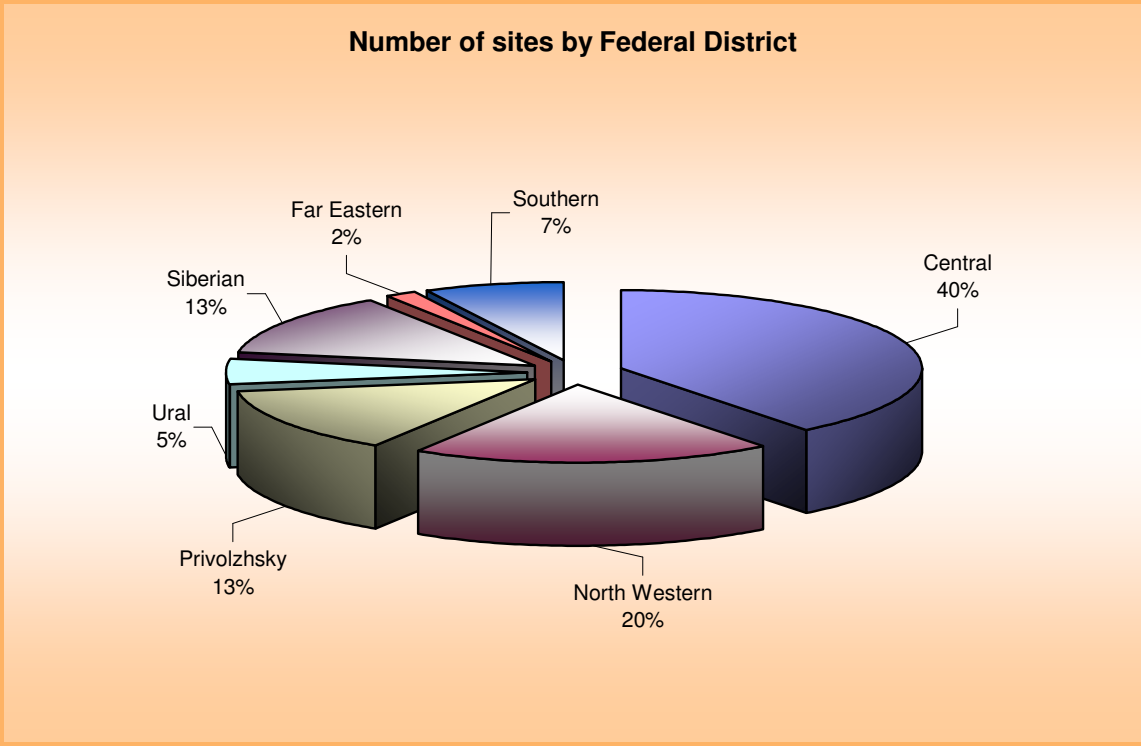
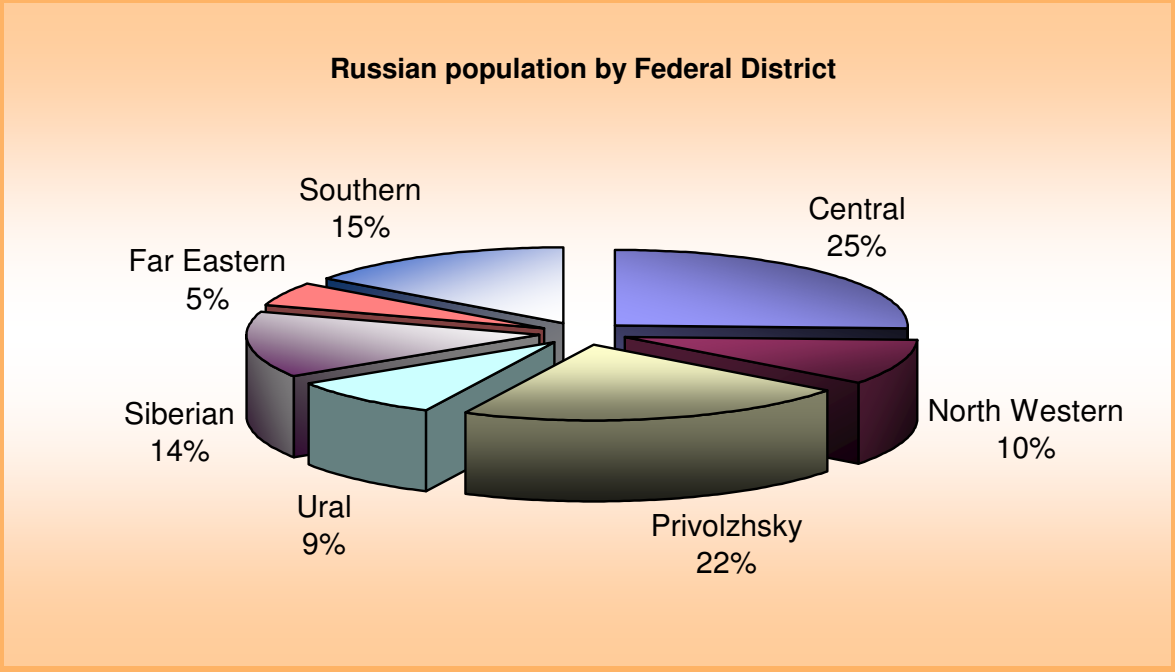


Figure 2. Population in different federal districts of Russia



Characteristics of the Country's Population

Along with the well-developed health care system, Russia is currently characterized by a high level of the population's education. The education level in the overwhelming majority of clinical study subjects is at least special secondary education and higher. This enables physicians to inform their patients in full and in time about the need to get medical aid and drive them to taking part in the study as well as ensures the understanding of doctors' instructions related to the drug application and high-quality feedback with investigators. According to V. Platonov,[1] the average patient enrollment rate for investigative sites from Eastern Europe is higher than in any other region of the world.

In Russia the doctor-patient relations are characterized, first of all, by a high level of the patient's trust for the doctor as well as readiness to cooperate with the doctor to treat the disease. Physicians have authority with their patients. Patients withdraw from studies and study-related procedures or manipulations in very rare cases. They undergo additional examinations to assist the doctor to arrest the disease deliberately and voluntarily.

It is very important for studies of so-called "endpoints" that common Russian people (unlike, for example, U.S. residents) migrate very seldom during their lifetime. In this connection, the rate of patient withdrawal from Russian clinical trials due to changes in their residence is very low.

Quality of Data

Such a characteristic of information as its reliability is of much importance for companies conducting clinical trials in the territory of Eastern European (in particular, in Russia) or Asian countries. In spite of the current prejudice against developing countries regarding the clinical study quality, such doubts are groundless in most cases. Russian investigative sites have to be approved by the Federal Agency for Health Care and Social Development (Roszdravnadzor), investigative sites obtain approvals for each CT for the current calendar year, and centers are supervised for their compliance with ethics requirements and industry standards. The key documents regulating procedures related to the conduction of clinical trials in the territory of Russia are as follows:

1. About Drugs (Federal Law No. 86-FZ dated June 22, 1998).
2. Industry Standard OST 42-511-99: *Regulations on good clinical practice in the Russian Federation* (approved by the Russian Ministry of Health on December 29, 1998).
3. Order No. 103 *About the decision-making process on clinical trials of drugs* issued by the Russian Ministry of Health on March 24, 2000.
4. *About approval of the Clinical Practice Regulations in the Russian Federation* (Order No. 266 issued by the Russian Ministry of Health on June 19, 2003).
5. *Procedure of scheduled audits in the course of clinical trials* (administrative regulations (Vol. 2/15) issued by the Federal Agency for Health Care and Social Development on August 11, 2005).
6. *Procedure of scheduled audits in the course of clinical trials* (administrative regulations (Vol. 3/17) issued by the Federal Agency for Health Care and Social Development on August 11, 2005).
7. *Regulations on the Federal Agency for Health Care and Social Development* approved by Decree No. 323 issued by the Government of the Russian Federation on June 30, 2004.

The List of Health Care Institutions Entitled to Conduct Clinical trials of Drugs is also adopted at the federal level. All of the above-mentioned documents strictly comply with the ICH Good Clinical

[1] Platonov, P., Clinical trials in Russia and Eastern Europe: recruitment and quality. Int J Clin Pharmacol Ther, 2003. 41(7): p. 277-80.

Practice principles. Successful audits conducted by the Federal Agency for Health Care and Social Development (Roszdravnadzor), FDA and independent auditors prove the high quality of the data obtained as a result of clinical trials.

According to open FDA sources, the first inspection of Russian clinical centers was carried out in 1996. The FDA audited Russian clinical centers 39 times for the period from 1995 to late 2006. No deviations were discovered as a result of the audits in 15 cases (No Action Indicated, NAI); unwanted facts were revealed in 22 cases but they were considered to be insignificant (Voluntary Action Indicated, VAI); administrative measures (Official Action Indicated, OAI) were taken in two cases (against the same investigator). On average, the level of revealed shortcomings is much lower than in the U.S. or Western Europe for the same period. Both clinical study sponsors and independent organizations have audited Russian centers many times for the aforesaid period. The analysis of the work performed by both investigative sites and physicians has shown strict compliance with the GCP standards and study protocols. Thus, the results of independent inspections and audits confirm the high quality of clinical trials conducted in Russia. They are at least of the same quality as clinical trials carried out in Western Europe and U.S. At present systems for remote data entry to common databases as well as data processing and statistical verification methods ruling out the possibility of any data fabrication as well as untimely or incorrect completion of study forms have been widely implemented.

Ethical Control Over Clinical trials

Clinical trials of drugs to be conducted in Russia are subject to compulsory approval by the Ethics Committee at the Federal Agency of Drug Quality, Efficacy and Safety Control. The Ethics Committee makes an expert assessment of the clinical study protocols, informed consent forms and investigator's brochures. The Ethics Committee also makes an expert assessment of the study drug safety information as well as its dosage regimens, forecasts of probable adverse effects, scientific relevancy of the clinical study of the drug and its expected efficacy and safety. The goal of the Ethics Committee is to protect subjects from any possible negative consequences of the drug administration. The Committee obligatorily informs general public about its activities, goals and objectives as well as its role in protecting subjects' rights through mass media. In addition to the Federal Ethics Committee, local ethics committees (commissions) operate in many medical research centers of Moscow, Saint Petersburg and other cities as well as in centers of the Russian Academy of Medical Sciences and Russian medical higher educational institutions. Both federal and local ethics committees are governed by Industry Standard OST 42-511-99 (*Regulations on good clinical practice in the Russian Federation*), which, in its turn, fully complies with international standards of GCP. Though some investigators in the field of ethics and case history discredit the federal and local ethics committees,[1] most authors tends to give high grades to the authorities and activities of Russian ethics committees.[2]

Pharmacological Supervision

Pharmacological supervision organizations are currently operating in Russia on an efficient basis. They monitor different forms of adverse events including active prospective monitoring (a technique considered to be the fullest method enabling to reveal the maximum number of possible AEs and fully assess any risks related to the drug administration). This reliable system enabling to detect unwanted adverse effects provides certain advantages for Phase IV post-marketing clinical trials.

[1] Lichterman, B.L. Under the shelter of ethics. Journal international de bioethique = International journal of bioethics, 2005. 16(3-4): p. 77-9, 172.
[2] Belousov, U.B. Ethical Expertise of biomedical studies. Clinical lectures. http://www.cardiosite.ru/clinical-lectures/article.asp?id=2774

Russia as an Active Market of Clinical Trials

Large pharmaceutical companies have assessed the prospects of Russia as a territory for conducting clinical trials quite a long time ago. Many of them have had their representative offices in the territory of Russia for more than ten years, and these representative offices conduct clinical trials on their own or engage contract research organizations for such purposes. Sponsors of the greatest number of clinical trials with the participation of Russia (*when the tables and figures were compiled, clinical investigative sites located in the territory of Russia were taken into account for each CT individually*) for the period from 2000 to April 2007 are given in Table 3.

Table 3. Sponsors of international multicenter clinical trials with the total number of involved sites in the territory of Russia

No	Sponsor	Number of studies	Number of sites
1	GlaxoSmithKline	58	315
2	Bristol-Myers Squibb	36	250
3	Pfizer	36	113
4	Sanofi-Aventis	36	73
5	Eli Lilly and Company	34	83
6	AstraZeneca	26	110
7	Hoffmann-La Roche	21	188
8	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	20	213
9	Novartis	16	42
10	Boehringer Ingelheim Pharmaceuticals	15	100
11	UCB	10	32
12	Astellas Pharma Inc	9	43
13	Bayer Corporation	7	7
14	Novo Nordisk	9	10
15	Organon	9	55
16	Solvay Pharmaceuticals	9	79
17	European Organization for Research and Treatment of Cancer	7	8
18	Merck	7	26
19	ALTANA Pharma	6	6
20	Biogen Idec	6	40
	Other	142	914
	Total	**519**	**2,707**

Source: www.clinicaltrials.gov

An intensive growth both in the total number of international multicenter clinical trials with the participation of Russia (Fig. 2) and in the number of centers involved in international multicenter clinical trials (IMCS) in the Russian territory (Fig. 3) has been observed for the recent years.

Figure 3. Growth in the number of IMCS with the participation of Russia in 2003-2006 (according to www.clinicaltrials.org)[1]

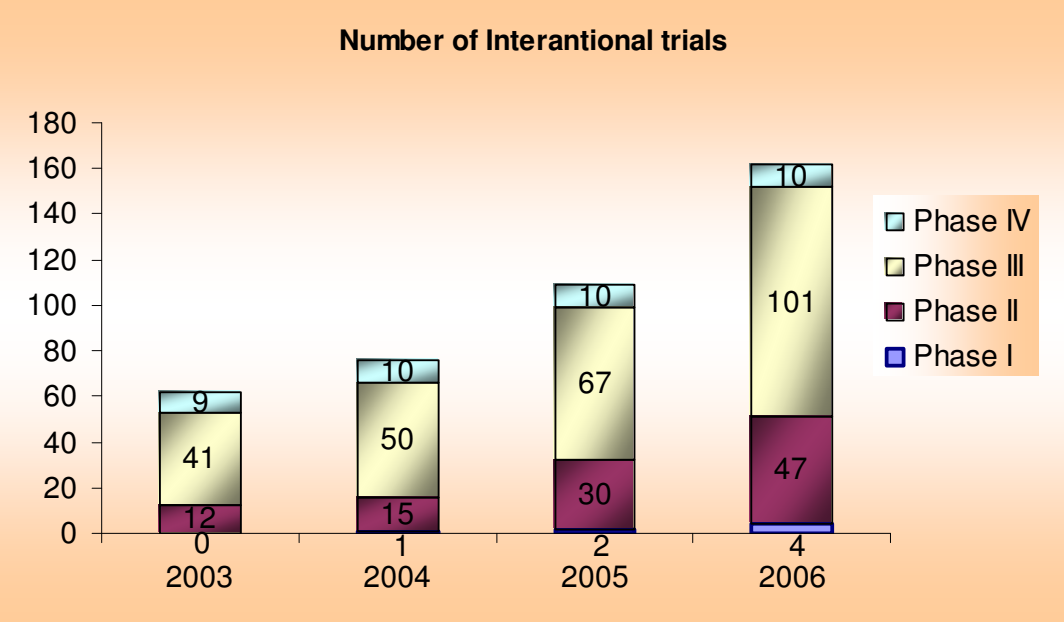
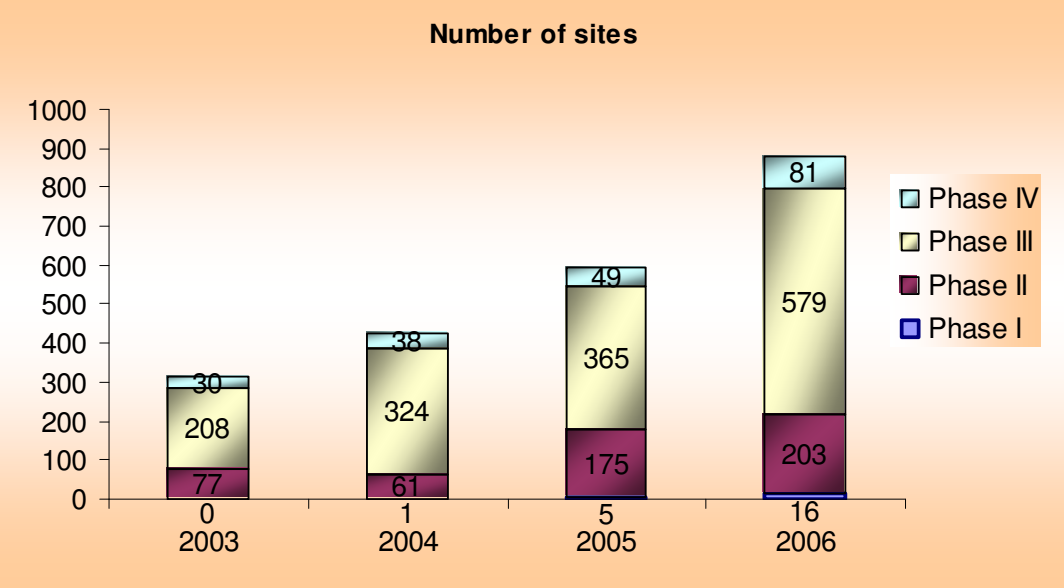


Figure 4. Growth in the number of centers in the Russian territory involved in international multicenter clinical trials (according to www.clinicaltrials.org)[2]



[1] Hereinafter efficacy studies of different drugs held on the basis of the same clinical center are taken into account independently.
[2] Efficacy studies of different drugs conducted on the basis of the same clinical center are taken into account independently hereinafter.

Year 2006

The total number of international multicenter clinical trials **initiated** in the Russian territory in 2006 amounted to 151. The total expected patient enrolment rate exceeds 154,000 people; the expected number of Russian clinical investigative sites taking part in IMCS in 2006 makes up 846. According to clinicaltrials.org, the leading sponsors in 2006 are as follows:

Table 4. Clinical trials with the participation of Russian sites in 2006.

No.	**Sponsor**	**Number of trials**	**Number of sites**	**Number of patients**
1	GlaxoSmithKline	**25**	118	18,230
2	Sanofi-Aventis	22	22	31,611
3	Bristol-Myers Squibb	10	131	32,661
4	Eli Lilly and Company	9	31	5,621
5	Pfizer	7	18	6,369
6	Hoffmann-La Roche	6	87	N/A
7	AstraZeneca	5	50	19,559
8	Novartis	5	13	6,866
9	Boehringer Ingelheim Pharmaceuticals	5	62	6,793
10	Johnson & Johnson Pharmaceutical Research & Development, LLC.	4	36	1,836
11	Novo Nordisk	3	3	1,941
12	Wyeth	3	7	222
13	Takeda Global Research & Development Center, Inc.	3	5	2,420
14	Mannkind Corporation	3	45	1,451
15	UCB	2	2	–
16	Astellas Pharma Inc	2	11	1560
17	Merck	2	12	2522
18	ALTANA Pharma	2	2	2550
19	Bayer Corporation	1	1	N/A
20	Solvay Pharmaceuticals	1	10	N/A
	Other	31	180	10,699
	Total	**151**	**846**	**154,041**

The data presented in Table 3-4 and Fig, 2-3 are somewhat underestimated (with a high degree of certainty) as compared to the actual figures. As a rule, pharmaceutical companies and research organizations directly involved in clinical trials provide information with a delay because they are interested in setting a priority for the conducted study. To make a comparison, we used the data about the studies approved by the Federal Agency for Health Care and Social Development in 2006.

The total number of clinical trials **approved** in Russia in 2006 amounted to 507. Including: 76 bioequivalence studies of Russian and foreign drugs, 107 clinical trials of drugs (manufactured both in Russia and abroad) and 324 international multicenter clinical trials. The total number of patients to be enrolled in the studies exceeds 49,200 patients and the total number of involved centers makes up over 3,200. It can be seen from Fig. 4 that international multicenter clinical trials make up only 64% of the total number of conducted studies; there is a substantial share of studies with all centers located in the Russian territory as well as drug bioequivalence studies.

Figure 5. Types of clinical trials conducted in Russia in 2006 (according to the Roszdravnadzor). IMCT - international multi-center clinical trials; CT - clinical trials conducted in the Russian territory; BE - bioequivalence and pharmacokinetics studies.

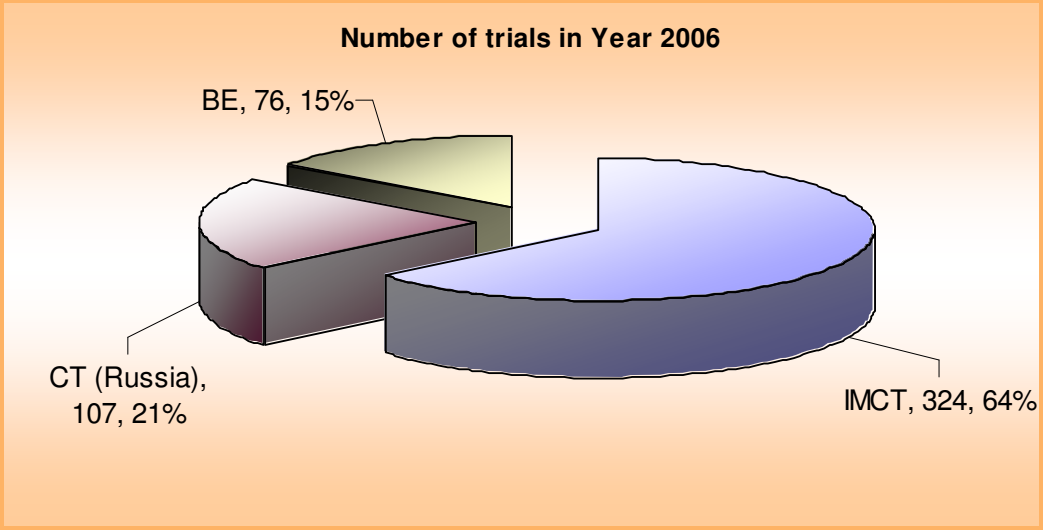


Table 5. Clinical trials conducted in the Russian territory in 2006 (according to the Roszdravnadzor).

CS Phase	Number of studies	Number of patients	Number of centers
I	14	618	39
II	122	7,372	727
III	240	33,917	2,129
IV	45	4,194	276
Other	86	3,140	112
Total	**507**	**49,241**	**3,283**

Figure 6. Share of different phases in the total number of CT conducted in 2006.

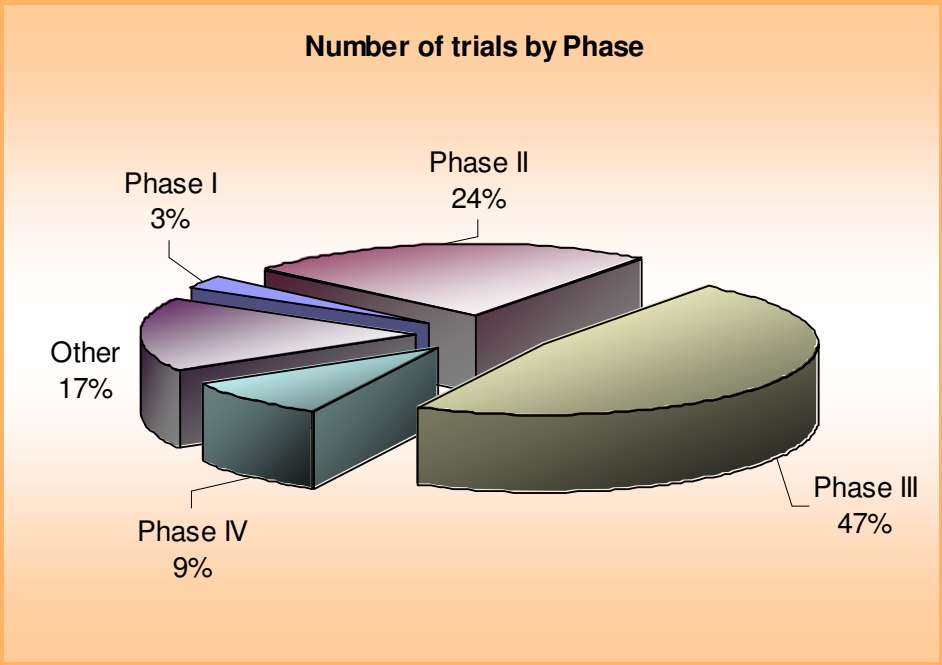


Figure 7. Number of patients enrolled in clinical trials (phases I-IV and other) in 2006.

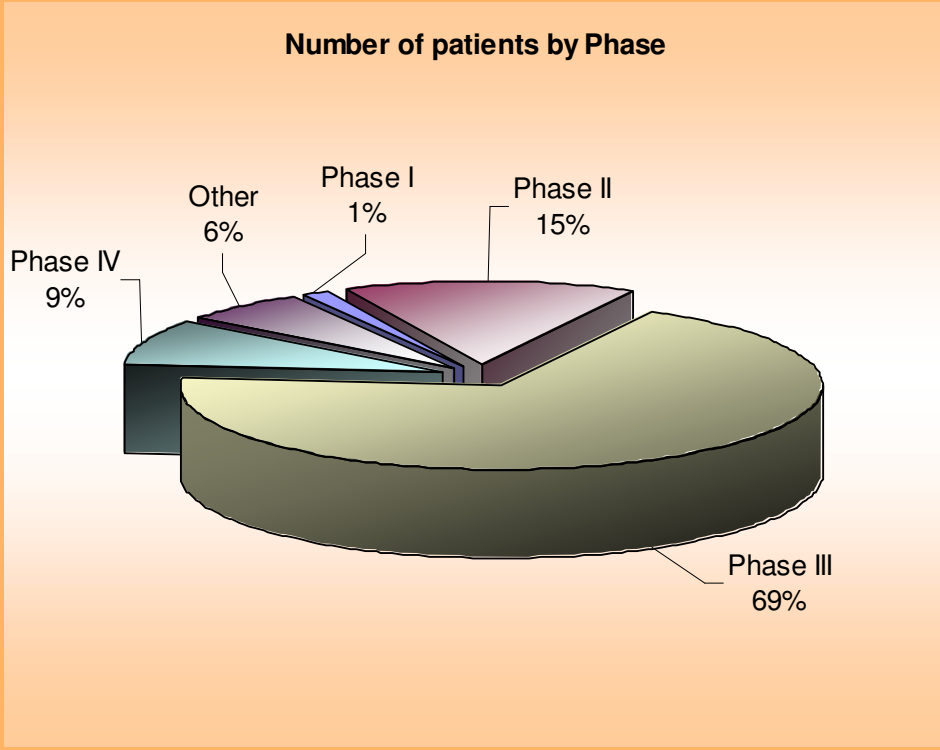
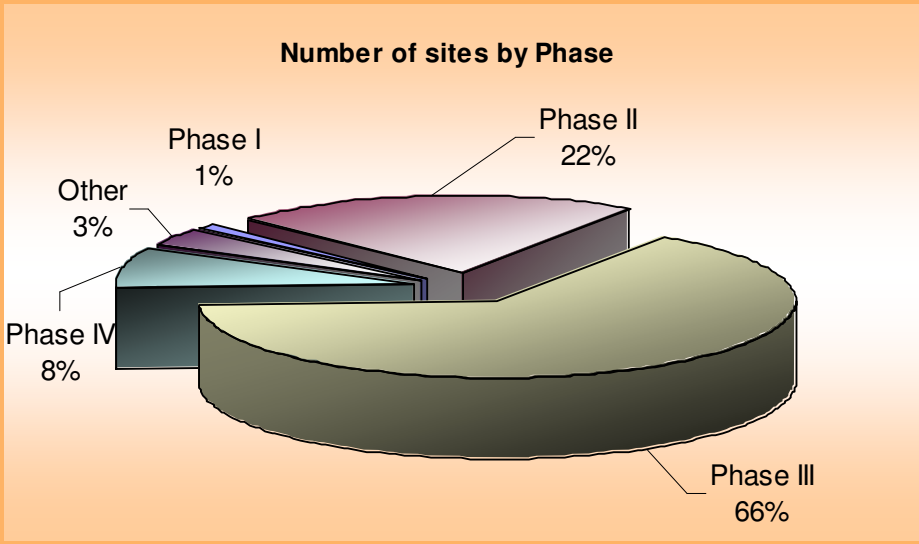


Figure 8. Number of investigative sites (phases I-IV and other) in 2006.



Prevalence of Phase III studies over other studies is characteristic of both international multicenter clinical trials and total pool of CT in Russia.

Contract Research Organizations in the Territory of the Russian Federation

Contract research organizations (CRO) came into being in Russia in the early 1990s as soon as Russia joined international clinical trials. On the one hand, foreign-based CROs opened their representative offices in Russia. On the other hand, forward-looking and enterprising Russian investigators established their own companies rendering services related to the organization of clinical trials. This was the beginning of the first Russian CROs and era of clinical trials in Russia.

At present there are about 40 companies rendering different services in the field of clinical trials in Russia. While at first pharmaceutical companies engaged them to perform the simplest functions, local CROs began rendering outsourcing services as the number of conducted studies grew and they gained experience. Thus, according to the Roszdravnadzor, it was contract research organizations that initiated 41.8% of studies in Russia in 2004. At present developing companies can spend up to 75% of their budgets for outsourcing services in Russia – from pre-clinical to pharmacoeconomic studies.

In general, the state of the CRO market in Russia is fully compatible with the CRO market trends in the world: global CROs have the lion's share of the market, and top five of them control over 50% of the market in terms of money. Global CROs have always been considered as high-quality contractors and render their local services at the world prices. Such an approach affected the price level of the local CROs being on the market for more than five years: they leveled up their prices as well thus causing displeasure on the part of sponsors.

An in-depth market analysis of Russian contract research organizations will be covered in one of the forthcoming issues.

Some of the contract research organizations operating in the territory of Russia are given in Table 8 below.

Table 6. Contract research organizations operating in the territory of Russia (in alphabetical order)**.**

Name	Brief Description
AAIPharma	Global CRO. Established in 1979. Headquarters in Wilmington (US). In 2006 it acquired Cvitkovic & Associes Consultants that had a branch in Russia. Full range of services. Office in Moscow.
ALMEDIS	Russian CRO. The year of foundation is unknown, allegedly – 2006. Wide range of services related to Phase II-IV clinical trials. Office in Moscow.
bioRASI	Initiative of the Russian Academy of Sciences. International CRO with the headquarters in Miami (US). Wide range of services. Offices in Moscow, Belgrade, Riga, San-Diego and Los-Angeles.
ClinStar	CRO from the US specializing in conducting II-IV Phase clinical trials in Russia. Founder – an individual being a US citizen. Headquarters in San-Francisco. Offices in Moscow and Saint-Petersburg. Staff – 180 employees.
CONGENIX	Russian CRO. Services: monitoring, project management, regulatory services, quality assurance. Corporate website in English, German, French and Japanese. Office in Moscow.
Eastern European department of the Kriger Research Center	Virtual CRO. It deals with planning, conducting and interpreting clinical trials in the territory of Eastern Europe. Training. No physical address.
Evidence Clinical and Pharmaceutical Research Institute	Established in 1989. It conducts clinical trials in Russia and Eastern European countries. Staff – over 100 employees. Its headquarters are located in Los-Altos (US), and its offices are in Saint-Petersburg, Moscow and Tbilisi.
Hesperion	International CRO. Established in 1996. Full range of services. Headquarters in the United States. Offices in the UK, Netherlands, France, Switzerland and Israel. Its Russian representative office is located in Moscow.
ICON Clinical	Global CRO. Established in 1990. Full range of services related to Phase I-IV clinical trials. Its office in Moscow was opened in 2003.
IN VIVO	Russian CRO. Established in 2004 by a group of experts from the I.M. Sechenov Moscow Medical Academy. Full range of services related to Phase III and Phase IV clinical trials. Moscow.
INC Research	Global specialized CRO, which was established in 1985. Therapeutic areas: CNS, infectious diseases, oncology and pediatry. Headquarters in Raleigh (US). Offices in Moscow and Saint Petersburg.
InnoPharm	Independent Russian CRO, which was established in 1991 on the basis of the Smolensk Medical Institute. Data processing, biostatistics, IT, quality assurance. Headquarters in Smolensk. In addition, it has representative offices in Moscow, Saint Petersburg and Kyiv.

Table 6 *(Continued from Page16)*

Kendle	Global CRO. Headquarters in Cincinnati (US). About 3,000 employees in the whole world. Office in Moscow.
LEGE ARTIS	Russian contract research organization. Headquarters in Moscow. It provides regulatory services, training, logistics and monitoring services for Phase I-IV clinical trials.
Matrix Pharmaceutical Researcli	Independent Russian CRO. Full range of services related to Phase II-IV clinical trials. Headquarters in Moscow.
Omnicare	Global CRO providing a full range of services related to Phase I-IV clinical trials. Its headquarters are located in Pennsylvania (US). Member of the Association of Contract Research Organizations (ACRO). Office in Moscow.
Osmos	The company was established in 2004 by Boris Iossel (native of Russia) for conducting clinical trials in Russia and Eastern European countries. Site selection, partner selection, consultations in logistics and training. Its headquarters are located in San-Francisco (US).
Outsourcing Clinical Trials (OCT)	Russian CRO with the headquarters in Saint Petersburg. It offers services for conducting clinical trials in the territory of Russia, Ukraine, Baltic states, Bulgaria and other Eastern European countries. Established in 2006.
Parexel	Global CRO. Established in 1983. Over 5,000 employees in 35 countries. Full range of services. Headquarters in Waltham (US). Office in Moscow.
Pharmanet	Global CRO providing a full range of services related to clinical and pre-clinical trials. Established in 1996. Staff – about 1,200 employees in the whole world. Office in Saint Petersburg.
Pharm-Olam International	Global CRO. Established in 1994. It has representative offices in 40 countries. Full range of services. Headquarters in Houston (US). No details about its Russian office are available.
PRA International	Global CRO. Established in 1981. Staff – 2,700 employees. Full range of services. Its headquarters are located in Reston (US). Office in Moscow.
Premier Research	Established in 1998. Representative offices in more than 30 countries. Specialization: CNS disorders, infectious diseases, oncology. Headquarters in Philadelphia (US). Office in Moscow.
PSI	CRO specializing in conducting clinical trials in Eastern European countries. Established by individuals. Staff – over 600 employees. Headquarters in Saint Petersburg and office in Moscow.
RCT-Global	Regional CRO conducting clinical trials in the territory of the former USSR and in Eastern Europe. Established in 2001. Full range of services. Headquarters in Princeton (US). Office in Moscow.
Synergy Research Group	Independent Russian CRO. Established in 2002. Wide range of services. Staff – over 50 employees. Headquarters in Moscow. In addition, it has representative offices in Saint Petersburg, Novosibirsk, Yekaterinburg and Almaty.

Russian sponsors of clinical trials

At present there is a belief that clinical trials conducted by Russian drug manufacturers are of poorer quality than international multi-center studies conducted by foreign drug manufacturers. The lack of funding and mainly domestic orientation of Russian manufacturers results in the lowering of reporting requirements set for CROs.

Nevertheless, when analyzing the current situation one should take into account that about 44% of studies sponsored by Russian manufacturers are bioequivalence studies with quite different requirements set for them. At the same time, most of the studies sponsored by foreign manufacturers are Phase III studies, and bioequivalence studies make up only about 2% on the whole.

The fast growth of both the quantity and quality of studies sponsored by Russian manufacturers along with the growth of the number of enrolled patients has been observed for the past years. The market of Russian clinical trials will be examined in a greater detail in one of our subsequent reports.

Table 7. List of Russian clinical trials in 2006 (according to the Roszdravnadzor).

No.:	Sponsor	Number of trials	Total number of sites	Total number of patients
1	Doctor N	11	11	630
2	GNTs NIOPIK*	8	25	290
3	Materia Medica Holding	6	13	692
4	Nizhpharm	5	8	304
5	Firn M	4	8	540
6	V.V. Zakusov Research Institute of Pharmacology	4	4	165
7	Petrovax Pharm	3	6	460
8	Naturpharmpreparaty Pharmaceutical Plant	3	6	360
9	PHARMACLON	2	2	300
	Others	42	71	2,694
	Total	**88**	**154**	**6,435**

* Research Institute of Organic Half-Finished Products and Dying Agents

Summary

The current situation in Russia is favorable for the conduction of clinical trials of drugs. The huge population of the country, well-developed and structured medical aid system, high personnel qualification and growth in the number of accredited investigative sites – all this can still ensure the prompt enrollment of the required number of patients.

The implementation of GCP regulations in the industry standards, availability of ethics committees as well as pharmaceutical supervision and control committees as well as emerging independent audit system in Russia ensure the high quality of the resulting data.

The presence of major international pharmaceutical companies on the Russian market of clinical trials is steadily growing, thus resulting in both general increase in the number of clinical trials conducted with the participation of Russia and expansion of the geography of research centers

involved in clinical trials. Moreover, the number of clinical trials conducted by Russian pharmaceutical and biotechnological companies as a part of national high-end industries development programs grows.

Thus, the first quarter of 2007 shows the positive dynamics of the growth on the market of clinical trials in Russia, and enables us to conclude that Russia remains one of the most attractive regions for conducting clinical trials of brand-new drugs.

The next issue of the Orange Paper (Clinical Trials in Russia) will cover clinical trials conducted in the 1st Quarter 2007.