Clinical Trials in Russia
Orange Paper
4th Quarter 2007

11, 4-Magistralnaya Ul., 123007 Moscow, Russia

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Contents

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Introduction

According to ClinicalTrials.gov[1], there were 4,231 clinical trials started worldwide during the 4th Quarter of the Year 2007. Fifty six per cent, or 2,363 trials were started in the U.S., and 20%, or 855 clinical trials, were initiated in Europe. During the same period the Federal Service on Surveillance in Healthcare and Social Development of Russian Federation (alias RosZdravNadzor, RZN) approved 174 new clinical trials in the territory of Russia, which is only 4.1% of the global number of trials. Despite the steady growth of the number of trials in Russia, its share in the international clinical trials market remains tiny.

One of the landmark events in the Russian clinical trials market in Q4 2007 was the VI International Clinical Trials Conference which took place on 12 October in Moscow. The conference was sponsored by the Russian Academy of Medical Science, Ministry of Health and Social Development, Russian Academy of Science, Social Charity Fund for Healthcare Support 'Zdorovie' (Health), Association of Russian Pharmaceutical Manufacturers (ARPM) and Association of International Pharmaceutical Manufacturers (AIPM).

Another important event for the further development of the clinical trials market in Russia was the foundation in November 2007 of the Association of Clinical Trials Organizations (ACTO) – non-commercial organization of the companies and clinical research community engaged in clinical trials in Russia. The situation involving the export of biological samples, which occurred in May 2007, was the stimulus that led companies to create the Association. At that time there was a lack of uniting power, to appeal on behalf of business. Unfortunately, other pharmaceutical associations are not able to solve effectively the issues related to clinical trials in Russia, as these issues are not the main priorities for them.

The main objectives of the ACTO are:

- Further development of Russia as a leading clinical research country/market by engaging in capacity building and activities to shape the professional environment;
- Generation of awareness of clinical research as a specialty and establishing the high Industry reputation amongst the general public and governmental agencies;
- Creating a favorable business environment for the companies conducting the clinical trials in Russia;
- Maintaining constructive dialogue with regulatory authorities and general public aimed at the development of stable local legislative basis for the clinical trials conduct harmonized with the respective worldwide standards;
- Promoting an ethical business model;
- Representing the interests of the members of the Association;
- Ensure a proper and effective balance between the interests of parties involved in clinical trials including the patients, the medical community, and the general public and governmental agencies.

The Association was founded by seven CROs: Almedis, Evidence, MB Quest, Parexel, PharmaNet, Quintiles and Synergy Research Group.

Executive Summary

During the Q4 2007 the RZN approved 174 new clinical trials in Russia showing a 23% increase over the Q4 2006. The main growth was contributed by international multi-center clinical trials, which increased by 54% and accounted to 131 studies in Q4 2007, - the maximum number during the whole history of clinical trials in Russia.

The number of local clinical trials rose from 28 to 31, and the number of bioequivalence studies decreased from 28 to 12 studies, or 57% down from the Q4 2006 number.

[1] US National Institute of Health (www.clinicaltrials.gov)

The share of international multi-center trials in Q4 2007 stood at 75%, and the shares of local and bioequivalence studies stood at 18% and 7%, respectively. The lions share of clinical trials in Russia is conducted by foreign sponsors, in Q4 2007 82% of the total number of studies were initiated by 71 manufacturers from 20 countries.

Fifty per cent of the total number of clinical trials in Q4 2007 are Phase III studies, the share of Phase II studies grew up to 35%, 10% of studies are Phase IV studies, and the figure for Phase I trials stood at 5%.

The total number of patients to be enrolled in clinical trials started in Q4 2007 is 23,745, which is 2.7 times more than in the corresponding quarter of the past year. The minimal number of subjects is four, and the maximum number of patients is 5,000. The shortest trial lasts two months, while the longest will take five years.

The French sanofi-aventis holds the first place among foreign sponsors in terms of number of trials initiated in Q4 2007. It is followed by American Merck & Co., British GlaxoSmithKline slips to the third place this quarter. Russian sponsors are led by pharmaceutical company LEKKO, it is followed by Microgen and Schelkovsky Vitamin Plant.

21 of 44 new drugs approved by Food and Drug Administration (FDA) and European Medicine Agency (EMEA) in Q4 2007 were, or are being tested in the clinical trials in Russia.

Top six therapeutic areas of the clinical trials started in Russia in Q4 2007 are: oncology, cardiovascular, respiratory; nervous, gastro-intestinal and endocrine disorders.

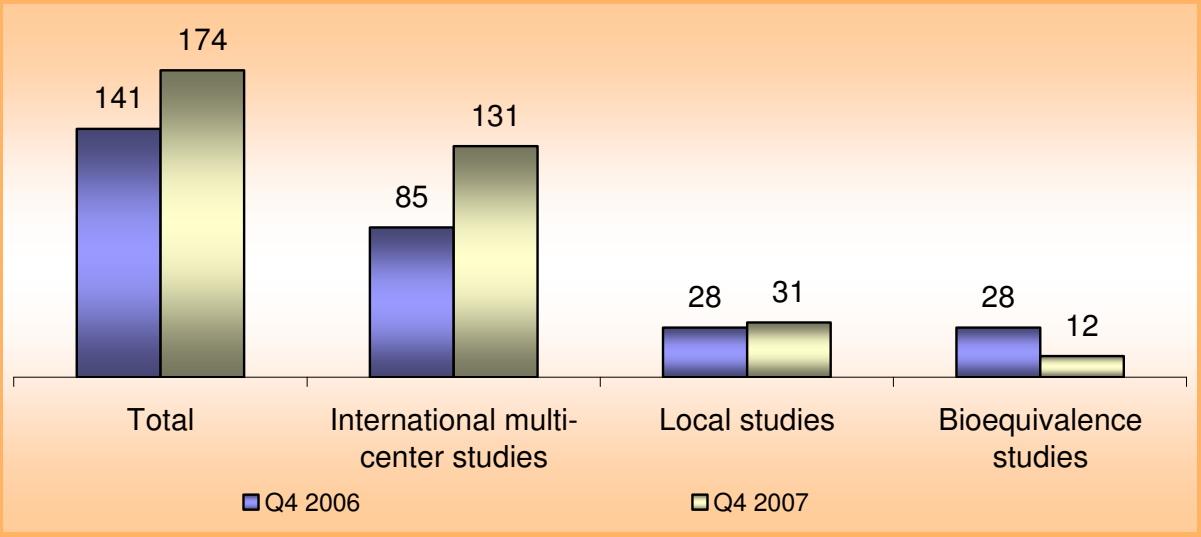
According to the RZN data, as of 9 January 2008 there are 854 investigator sites in Russia, 27 of which were accredited by the RZN in Q4 2007.

Clinical Trials by Type and Manufacturing Country

During Q4 2007 RZN approved 174 new clinical trails in Russia, which is 23% more than in the corresponding quarter of the past year. Figure 1 demonstrates that such growth is mostly attributed by international multi-center clinical trials, which number rose by 54% comparing to Q4 2006 and accounted in Q4 2007 up to 131 studies, - the absolute record of the quarter during the whole history of clinical trials in Russia.

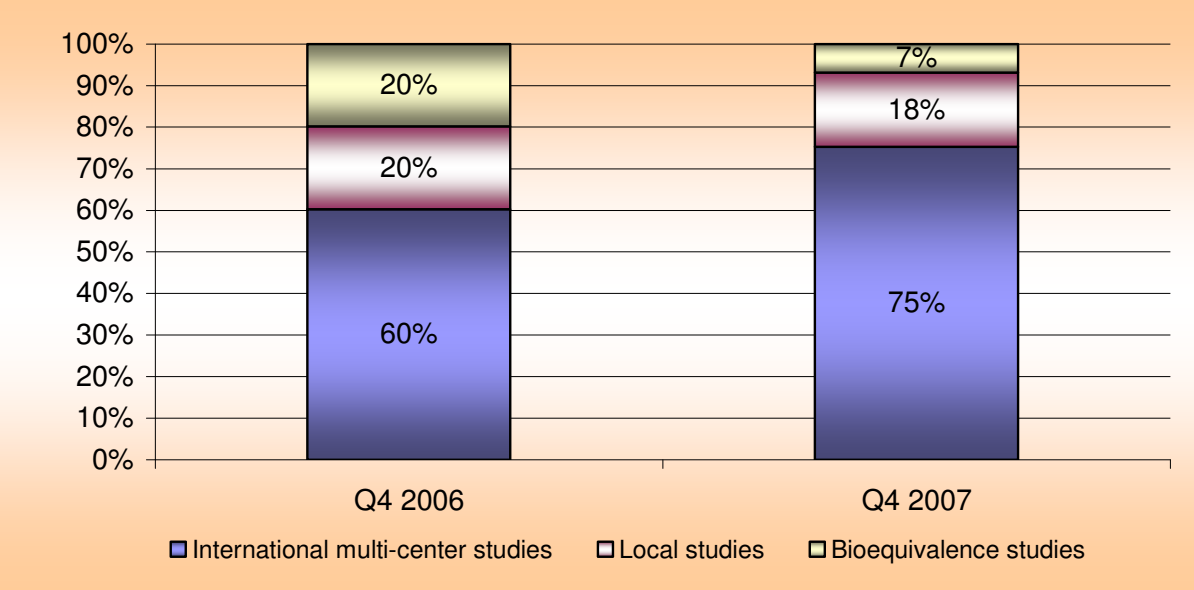
The number of local clinical trials which are conducted only in the territory of Russia increased from 28 to 31 trials, showing an 11% increment over Q4 2006 figure. The number of bioequivalence studies initiated in Q4 2007 decreased by 57% over the past year to 12 studies.

Figure 1. Clinical trials approved by RZN in Q4 2007



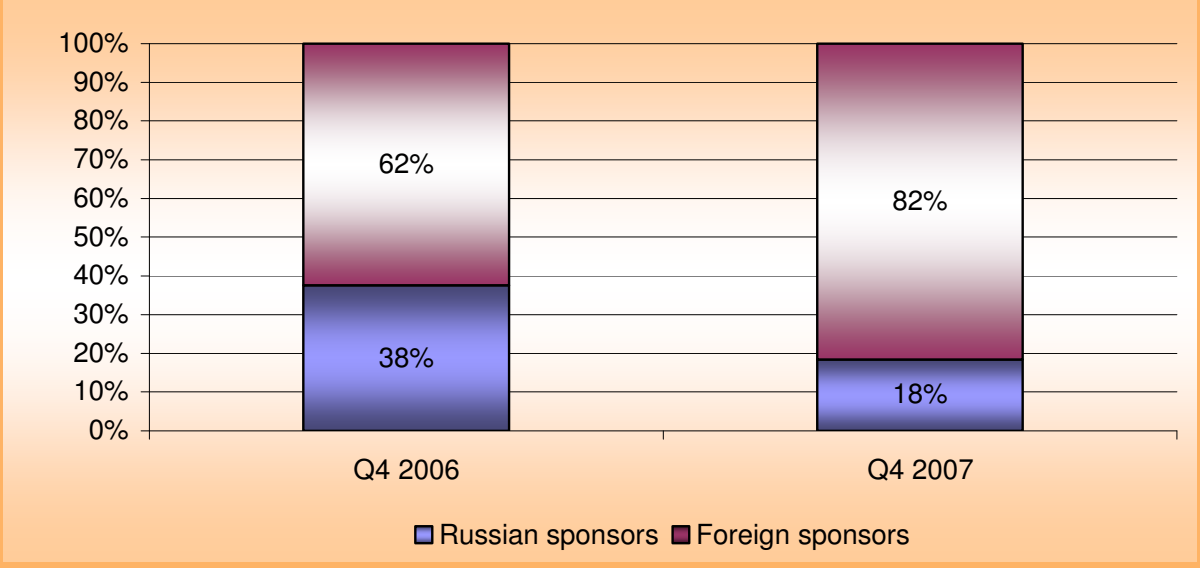
The proportion between different types of clinical trials changed significantly in Q4 2007. The share of international multi-center trials increased from 60% to 75% of the total number of trials. The number of local trials and bioequivalence studies stood at 18% and 7%, respectively, while each of them was equal to 20% in Q4 2006.

Figure 2. Clinical trials by type in Q4 2007



Most of the clinical trials in Russia are conducted by the foreign sponsors, the number of such studies rose from 88 to 142 in Q4 2007, showing the increase from 62% to 82%. The number of trials initiated by Russian manufacturers, including, bioequivalence studies decreased from 53 to 32 studies, and their share decreased more than twice, from 38% to 18%.

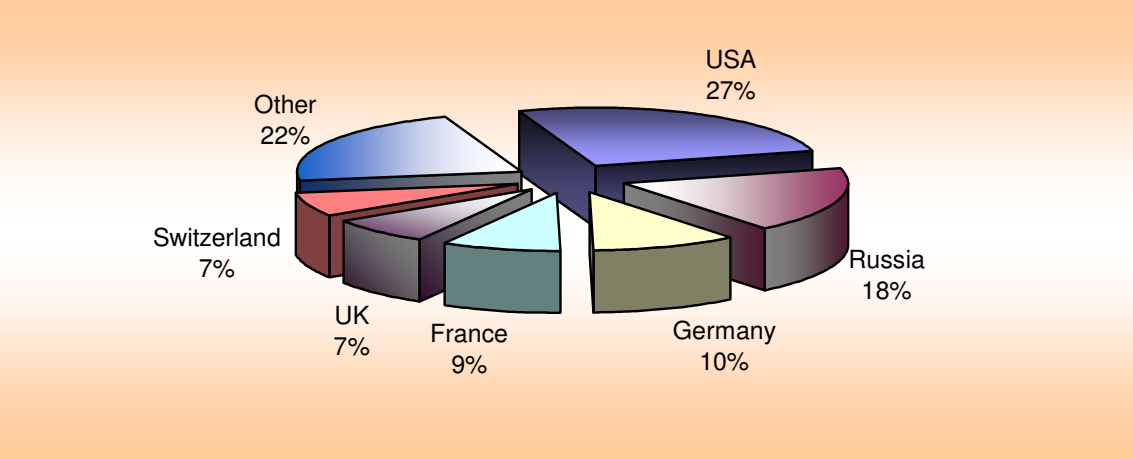
Figure 3. Russian and International sponsors in Q4 2007



Clinical trials in Russia in Q4 2007 were sponsored by 71 companies from 20 countries. Figure 4 demonstrates the input of the six leading countries of sponsor's origin into the total number of

clinical trials. The maximum number of trials (46) were started by American sponsors, they are followed by Russian sponsors which initiated 32 studies, German sponsors with 18 trials are on the third place, 15 trials were initiated by French companies, UK and Swiss manufacturers started 13 and 12 clinical trials, respectively.

Figure 4. Countries presented on the Russian clinical trials market in Q4 2007



Among others are Austria, Belgium, Denmark, Israel, India, Italy, Canada, the Netherlands, Poland, Portugal, Republic of Croatia, Slovenia, Sweden and Japan.

Clinical trials by Phase

Eight Phase I trials were started in Q4 2007 in Russia, 3 studies less than in the corresponding quarter of the past year. Phase II trials demonstrated more than twofold increase, their number rose from 24 studies in Q4 2006 to 54 trials in Q4 2007. The number of Phase III trials also increased from 56 to 79, which is a 41% increment. The number of Phase IV trials decreased from 16 to 15.

Figure 5. Clinical trials in Russia in Q4 2007 by phase

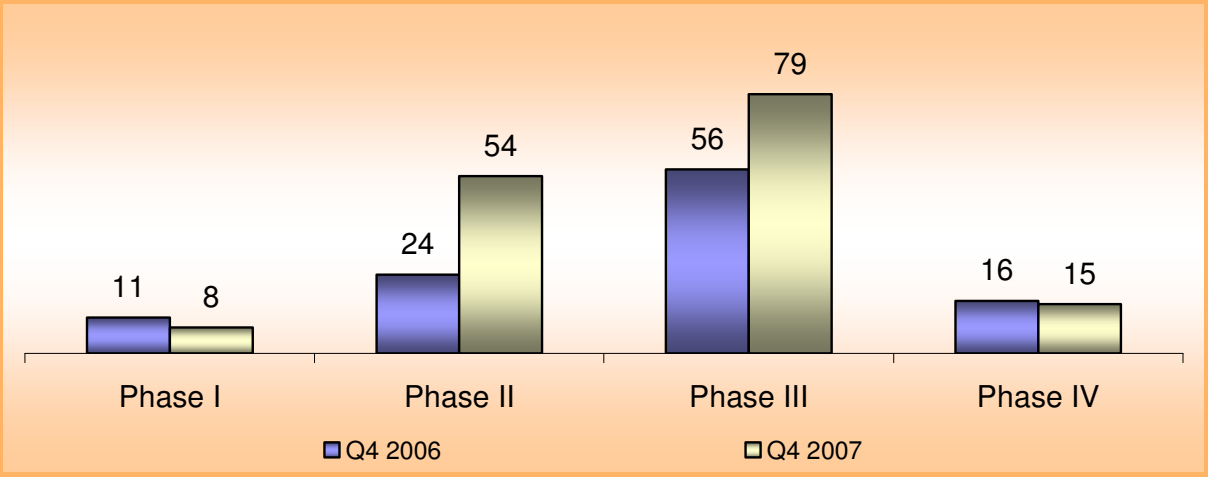
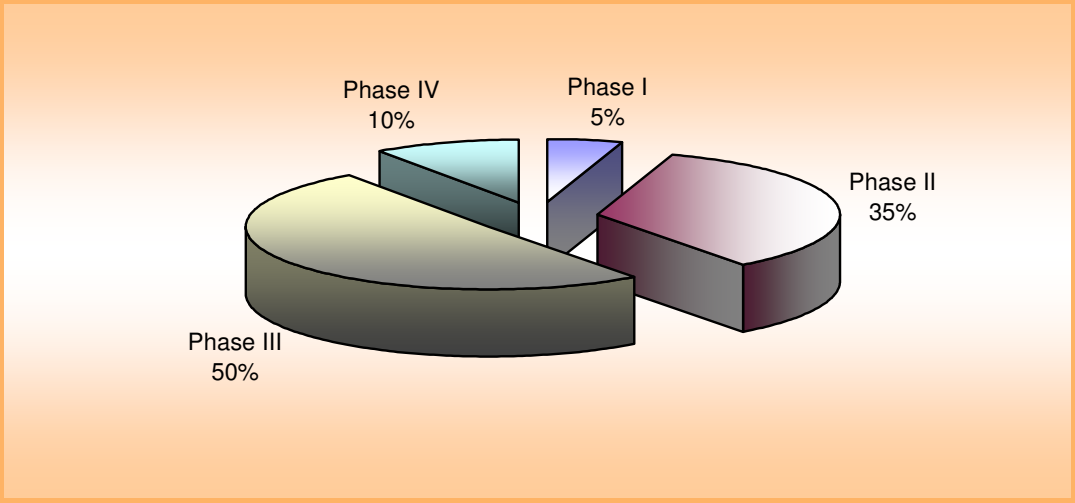


Figure 6 shows that half of the clinical trials initiated in Russia in Q4 2007 are Phase III trials, the share of Phase II trials grew up to 35%, Phase IV share stands at 10%, and Phase I trials account to 5% of the total number of studies.

Figure 6. The proportion between study phases in Russia in Q4 2007

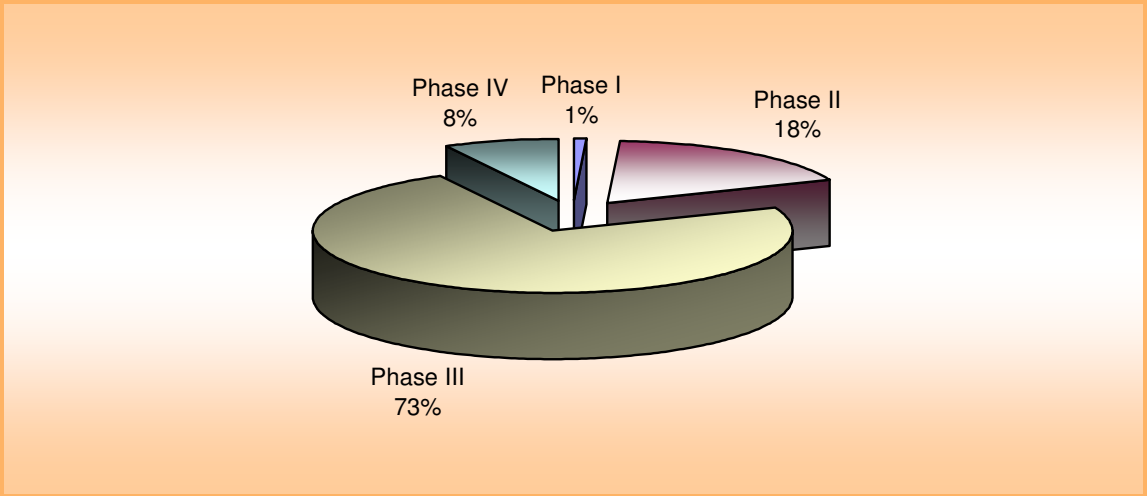


The total number of patients enrolled in clinical trials started in Russia in Q4 2007 is 23,745 which is 2.7 times more than in Q4 2006 when 8,786 patients were planned to be recruited.

One hundred and sixty eight of them will take part in Phase I trials, 4,185 subjects will be enrolled in Phase II studies, 16,923 patients will be recruited into Phase III, and 1,797 patients will take part in Phase IV trials. The remaining 672 subjects will be involved in bioequivalence studies and trials for which the study phase is not specified by sponsor.

The minimal number of patients for the studies in Q4 2007 is four, and the maximum number of patients is 5,000. The share between the number of patients involved in different study phases is shown in Figure 7.

Figure 7. The number of patients in Q4 2007 by study phase



The average duration of the Phase I studies is 13 months, for Phase II this figure stands at 19 months, average Phase III study lasts 23 months, and the average Phase IV study duration is 17

months. The shortest study will last two months, while the longest will take 62 months, or mpore than five years.

Rating of international sponsors

The maximum number of clinical trials in Russia in Q4 2007 was initiated by the French sanofi-aventis which is far ahead others with its 15 trials. It is followed by American Merck & Co. which started 10 new trials in Q4 2007, and UK GlaxoSmithKline with 8 new studies.

German Boehringer Ingelheim and Swiss Novartis both initiated by 7 new studies in Q4 2007, but Boehringer surpasses Novartis in the number of investigator centers and subjects.

Top five international sponsors are presented in Table 1.

Table 1. Top-5 international study sponsors in Q4 2007

№	Sponsor	No. of trials	No. of patients	No. of sites
1	sanofi-aventis	15	1,712	110
2	Merck & Co.	10	2,350	71
3	GlaxoSmithKline	8	650	39
4	Boehringer Ingelheim	7	1,475	124
5	Novartis	7	338	52

Rating of Russian sponsors

The Russian clinical trial sponsors are led by the Pharmaceutical Firm LEKKO which started 5 new studies in Q4 2007 recruiting 440 patients in 12 investigator sites. Each of the other four companies of the Top-5 started two new clinical trails, and they were further ranked by number of patients and sites.

Microgen took the second place, Schelkovsky Vitamin Plant is on the third place, and it is followed by Biocad and Doctor N.

It is worth mentioning that in Q4 2007 the Russian Microgen is the absolute leader in the number of patient planned to be recruited in single study – 5,000 patients will be enrolled in its flu vaccine Grifor study.

Table 2. Top-5 Russian study sponsors in Q4 2007

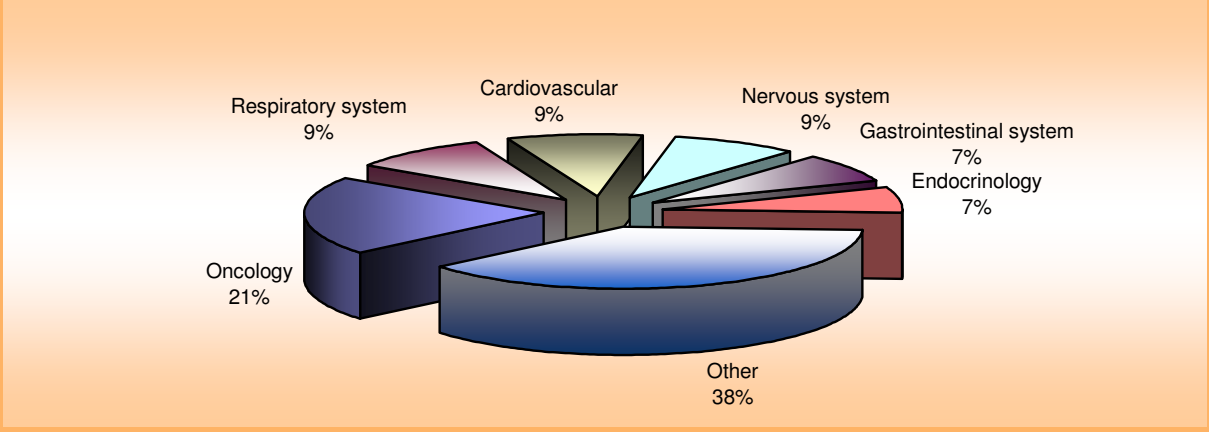
№	Sponsor	No. of trials	No. of patients	No. of sites
1	Pharmaceutical Firm LEKKO	5	440	12
2	Microgen	2	5,040	6
3	Schelkovsky Vitamin Plant	2	1,032	33
4	Biocad	2	128	5
5	Doctor N	2	120	2

Therapeutic areas of clinical trials in Russia in Q4 2007

More than 60% of the total number of trials in Russia in Q4 2007 were initiated in the six most popular therapeutic areas: 36 new studies were started in oncology; 16 studies were started in cardiovascular and respiratory areas each; 15 studies were started in neurology; there were also

initiated13 trials in gastroenterology and 12 studies in endocrinology. The proportion between the therapeutic areas is shown in Figure 8.

Figure 8. Clinical trials in Russia in Q4 2007 by therapeutic area



Clinical trials results

During the 4th Quarter 2007 FDA Center for Drug Evaluation and Research (CDER) approved 21 new drug application (NDA), only eight of them are really new drugs, i.e. are the new molecular entities (NME), other are new dosage, or extensions for the indications of previously registered drugs. Table 3 shows those which were, or are being tested in the Russian investigator sites.

Table 3. New Drugs approved by FDA in Q4 2007 and studied in Russian sites

Approval date	Drug	Manufacturer	Indication
09.10.2007	Simvastatin	Synthon	Hypercholesterolemia
11.10.2007	Hycamtin (topotecan)	GlaxoSmithKline	Lung cancer
12.10.2007	Doribax (doripenem)	Johnson & Johnson	Bacterial pneumonia
16.10.2007	Ixempra (ixabepilone)	Bristol-Myers Squibb	Breast cancer
17.10.2007	Voltaren (diclofenac sodium)	Novartis	Rheumatoid arthritis
29.10.2007	Tasigna (nilotinib)	Novartis	Myeloid leukemia
02.11.2007	Lamivudine	Matrix	HIV
04.12.2007	Omeprazole	Dexcel Pharma	Heartburn
21.12.2007	Valproic Acid	Banner Pharmacaps	Bipolar disorder
Source: CDER FDA http://www.fda.gov/cder			

The Committee for Medicinal Products for Human Use (CHIMP) of the European Medicine Agency (EMEA) examined 26[1] applications for drug marketing in the territory of the European Union during the period from 1 October to 31 December 2007. Among these applications, there are 7 new drugs and 14 new indications for earlier registered drugs were approved, negative opinions were adopted for three drugs. Twelve of the approved drugs have already been or are currently being tested in clinical trials in Russian investigator sites. (see Table 4).

[1] CHMP EMEA http://www.emea.europa.eu/index/indexh1.htm

Table 4. New Drugs approved by EMEA in Q4 2007 and studied in Russian sites

Approval date	Drug	Manufacturer	Indication
18.10.2007	Abraxane	Abraxis BioScience	Breast cancer
18.10.2007	Ariclaim (duloxetine)	Eli Lilly	Diabetic peripheral neuropathic pain
18.10.2007	MabCampath (alemtuzumab)	Genzyme	Chronic lymphocytic leukemia
18.10.2007	Taxotere (docetaxel)	sanofi-aventis	Head and neck cancer
15.11.2007	Avastin (bevacizumab)	Roche	Metastatic renal cell cancer
15.11.2007	Caelyx (doxorubicin)	SP Europe	Relapse multiple myeloma
15.11.2007	Januvia	Merck & Co	Type-II diabetes
15.11.2007	Xelevia	Merck & Co	Type-II diabetes
14.12.2007	Tyverb (lapatinib)	GlaxoSmithKline	Breast cancer
14.12.2007	Avastin (bevacizumab)	Roche	Colorectal cancer
14.12.2007	Mabthera (rituximab)	Roche	Non-Hodgkin's lymphoma
14.12.2007	Xeloda (capecitabine)	Roche	Colorectal cancer
Source: CHMP EMEA http://www.emea.europa.eu/index/indexh1.htm			

New investigator sites

According to the data provide by the RZN, as of 9 January 2008 there are 854[1] investigator sites in Russia which are accredited by the RZN to conduct clinical trials. Twenty seven of them were accredited during 4th Quarter of the Year 2007.

The leader among the cities by the number of new sites is Kazan, seven new sites were accredited there, it is followed by Vladivostok with three new sites, and Saint-Petersburg where two new sites were accredited. The complete geography of the new investigator sites in Q 4 2007 is presented in Table 5.

Table 5. New Russian investigator sites in Q4 2007 by city

City	No. of new sites
Barnaul	1
Blagoveschensk	1
Vladivostok	3
Kazan	7
Kaluga	1
Kemerovo	1
Kursk	1
Lipetsk + region	1
Moscow region	2
Novosibirsk + region	1
Penza	1
Perm	1
Rostov-on-Don	1
Saint Petersburg	2
Saransk	1
Tver + region	1
Tumen	1
Source: RZN	

[1] http://www.roszdravnadzor.ru/i/upload/files/1200902430.21666-6421.doc

RZN inspections

Six inspections of the investigator sites were planned by the RZN in Q4 in the following cities: Moscow (2 sites), Jaroslavl (2 sites), and Belgorod (2 sites).

FDA inspections

No FDA inspections of the Russian investigator sites were conducted in Q4 2007.

Appendix

Leader's Profile. Novartis

Novartis was created in 1996 through the merger of two Swiss pharmaceutical and chemical giants - Ciba-Geigy and Sandoz. At that time it was the largest merger ever. The name, derived from the Latin *novae artes*, means "new skills".

Today Novartis is NO. 5 pharmaceutic company in the world, and ranks No. 83 in the list of World's 2,000 Largest Public Companies by Forbes magazine. Novartis annual sales in 2007 rose by 10% over the past year and accounted to 38.072[1] billion US Dollars, and the market value stands at 125.73 billion US Dollars[2].

Novartis keeps the leading position on the Russian DLO market (the State Reimbursement Program) among manufacturers, its share stands at 13% of the program total value[3].

Novartis concentrates its Research and Development resources and scientific expertise on ten strategic therapeutic areas: Autoimmunity & Transplantation; Cardiovascular; Diabetes & Metabolism; Gastrointestinal; Infectious Diseases; Musculoskeletal Diseases; Neuroscience; Oncology; Ophthalmology and Respiratory Diseases.

R&D budget in 2007 rose by 20% over the past year and accounted to 6.43 billion US Dollars, or 16.9% of the net sales.

R&D global headquarters is located in Cambridge Massachusetts (US) and accommodates more than 1300 scientists and technology experts. The other large R%D site in Basel, Switzerland is located at the Novartis global corporate headquarters is home to more than 1500 scientists and technology experts. Other large sites in East Hanover and Emeryville in the US, Horsham, UK, Vienna, Austria, and Tsukuba, Japan together house over 800 scientists and technology experts.

Table 6. Novartis R&D Centers

Country	City
Austria	Vienna
UK	Horsham
China	Shanghai
US	Cambridge
Switzerland	Basel
Japan	Tsukuba

Novartis is widely recognized as having one of the industry's most attractive development pipelines. The R&D portfolio includes 138 projects in clinical development, more than ever before. Several latestage projects are progressing on track toward regulatory submissions. These include **FTY720** (multiple sclerosis), **QAB149** (respiratory diseases), **RAD001** (cancer), **ACZ885** (Muckle-Wells syndrome) and **SOM230** (Cushing's disease).

In the next three years the Novartis is planning to submit 29 new drug applications, 15 of them are new molecular entities (NME).

Thirteen more new drugs will be submitted for registration after 2011.

Fifty one per cent of the total Novartis sales are attributed to twenty company blockbusters. Top five of them are shown in Table 7.

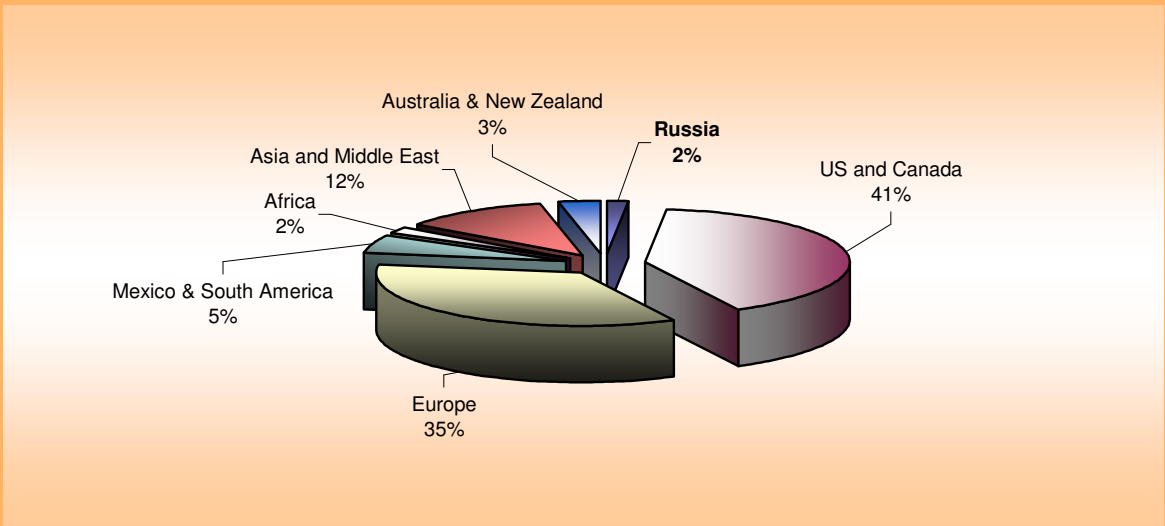
[1] Novartis Group Financial Report 2007
[2] Forbes. The World's 2,000 Largest Public Companies
[3] Pharmexpert. INPHARMACIA – Analytic pharmamarket review №12 2007

Table 7. Top-5 Novartis blockbusters in 2007

Drug	Y2007 Sales in billion US Dollars	No. of open trials in Russia	Indication
Diovan®	5,012	7	Hypertension
GleevecTM/Glivec®	3,050	7	Chronic myeloid leukemia
Zometa®	1,297	8	Cancer complications
Sandostatin®	1,027	-	Acromegaly
Sandimmun Neoral®	944	-	Transplantation
Source: Novartis, US National Institute of Health			

According to ClinicalTrials.gov, as of 3 February 2008 Novartis was conducting 431 clinical trials on five continents, almost three fourth of them were conducted in the US, Canada and Europe. According to the data from the site there are 11 open studies conducted by Novartis in Russia.

Figure 9. Clinical trials conducted by Novartis worldwide[1]



According to the data provided by RZN, Novartis initiated 71 clinical trials in Russia since 2004.

[1] ClinicalTrials.gov as of 3 February 2008. Open studies only