Clinical Trials in Russia
Orange Paper
№4/2007. 3rd Quarter 2007

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Contents

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Introduction

Before we start reviewing and analyzing the results of the clinical trials market in Russia in the 3rd Quarter of the Year 2007, we would like to briefly outline the state of the international clinical trials market and evaluate the Russia's role in it, and estimate the degree of capitalization of Russia's resources.

According to the ClinicalTrials.gov as of October 1, 2007, there are 20,110 active international clinical trials[1] worldwide. More than half of these studies are conducted in the USA (11,588 trials) and approximately a quarter of trials – in Europe (5,000). The contribution of Russia is 298 trials, or 1.48%.

If we correlate these trials with the population of regions where they were performed, we see that the USA rate is 38 trials per 1 million of population, in Europe – 10, and in Russia – 2. Assuming that the US potential is utilized at 100%, we can see that Russian resources are utilized only for 5%.

According to the Russian Federal Service of State Statistics the total number of physicians in Russia is 690,000[2]. According to local experts' estimates, approximately 8,000, or only 1.16% of physicians are currently involved into clinical trials.

According to the Federal Service on Surveillance in Healthcare and Social Development of Russian Federation (alias RosZdravNadzor, RZN) there are 800 healthcare facilities by October 17, 2007, which are entitled to conduct clinical trials. In total, there are more than 9,500 healthcare facilities in Russia, which means that at present maximum 8.33% of potential investigator's sites are involved into clinical trials.

The above figures clearly demonstrate that Russia possesses all necessary resources to take a worthy place on the world clinical trials market.

One of the noticeable events on Russian clinical trials market in the 3rd Quarter 2007 was RZN Board meeting dedicated to the problems of clinical trials in Russia. On the Board which took place on September 19 prominent Russian scientists, academics, and heads of leading Russian investigator's sites discussed current issues of conducting clinical trials in Russia including the draft of the new administrative directives on conducting clinical trials in Russia.

We hope that all key players of the Russian clinical trials market including sponsors, regulatory authorities, investigators and contract research organizations (CRO) would be able to establish constructive dialog and harmonize their efforts so that Russia will become one of the leading clinical trials markets in the world.

Executive Summary

In the 3rd Quarter 2007, the overall volume of the clinical trials in Russia and its basic parameters are generally the same as in the corresponding quarter of the last year. In the 3rd Quarter 2007 RZN has issued 141 approvals for conducting new clinical trials, which is 2% more than in Q3 2006. In comparison with the last year the proportion between international clinical trials, local clinical trials and bioequivalence studies remains unchanged.

There is a minor increase in the share of Russian sponsors in the total number of clinical trials which accounts for 31% of the total number of studies initiated during Q3 2007. Among the

[1]ClinicalTrials.gov. A Service of the US National Institutes of Health. http://www.clinicaltrials.gov/ct (as of October 1, 2007) Only those studies, where patient enrollment is still going on or not started yet were taken into account.
[2]Federal Service of State Statistics. Main figures of healthcare http://www.gks.ru/free_doc/2007/b07_12/09-01.htm

foreign sponsor the majority comes from the United States (30% of clinical trials), Germany (10%) and Great Britain (7%).

An increase in the number of Phase II trials (by 57%) and a decrease of the number of phase III trials (by 18%) is observed. The total number of patients who are planned for recruiting has decreased by 12% (from 16,340 to 14,431), compared with the Q3 2006.

Among foreign sponsors the leader is Bristol Meyers Squibb (7 new studies in 95 sites recruiting 2,033 patients in total), among Russian sponsors – OOO ROZFARM. Among the therapeutic areas the maximum number of clinical trials have been initiated in oncology (29 studies in 230 sites with total number of 1,784 patients), on the second place are cardiovascular trials (18 CTs, 220 sites, 4851 patients), then go studies in nervous system diseases (15 trials in 84 sites recruiting 1,112 patients).

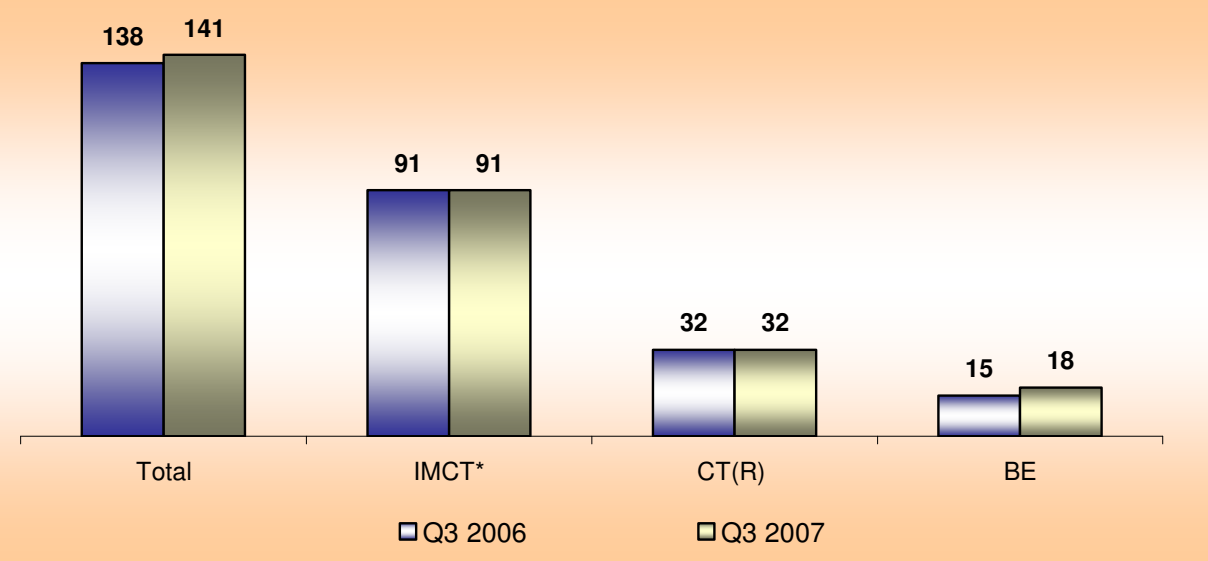
In the 3rd Quarter 2007 the US Food and Drug Administration (FDA) approved 7 new drugs which had been tested in clinical trials conducted on the territory of Russia. European Agency for the Evaluation of Medicinal Products (EMEA) approved 5 marketing applications for drugs which had been tested in clinical trials in Russia.

32 new investigator's sites in Russia were approved by the RZN for conducting clinical trials, thus the current number of investigative sites in Russia is 800.

Analysis of Clinical Trials by Types and Manufacturing Countries

During the 3rd Quarter of 2007 RZN has approved 141 new clinical trials which is 2% more than in the Q3 2006. From Figure 1 it can be seen that the number of international multicenter clinical trials remains the same as in the 3rd Quarter of the last year. We see the same picture for the local trials. An insignificant increase in the total number of trials initiated in Q3 2007 is associated with the increase of the number of bioequivalence studies. Altogether, regardless the tightening of regulatory requirements and the biological ban early this year no decrease in the number of new clinical trials has been observed.

Figure 1. Clinical trials approved by RZN in Q3 2007



** IMCT – international multicenter clinical trials, CT(R) – clinical trials conducted in Russia only, BE – bioequivalence studies.*

Figure 2. Clinical Trials by Type in Q3 2007.

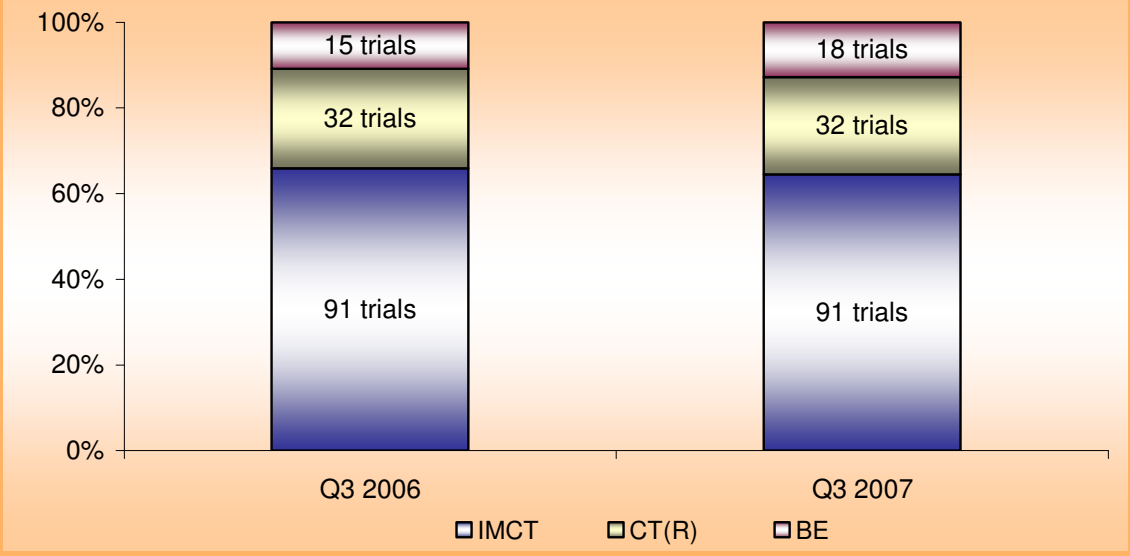
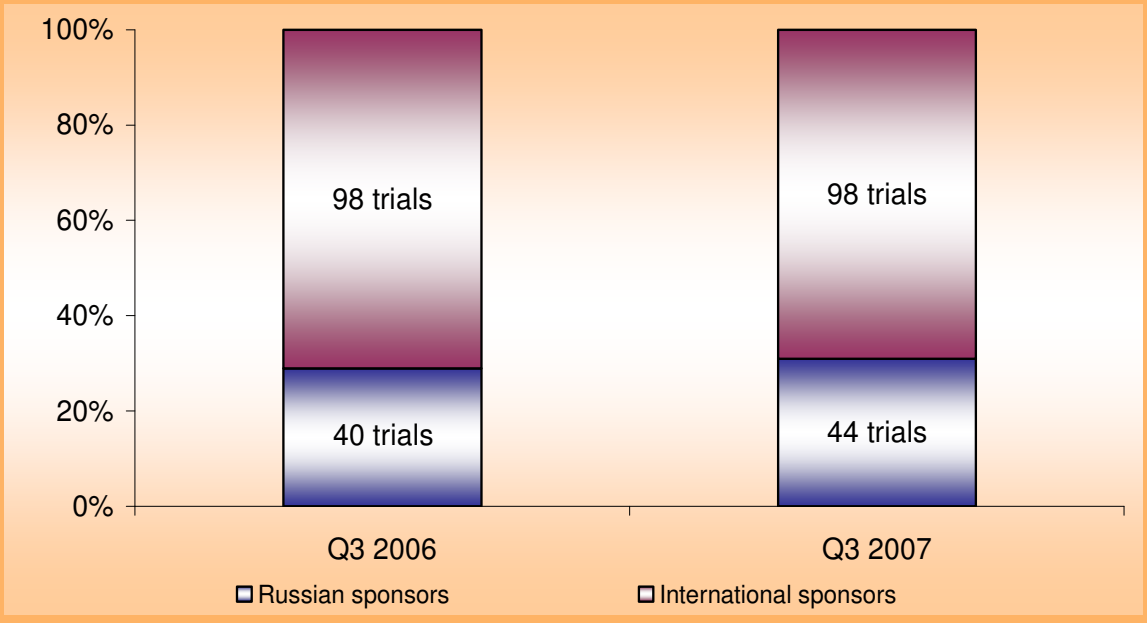


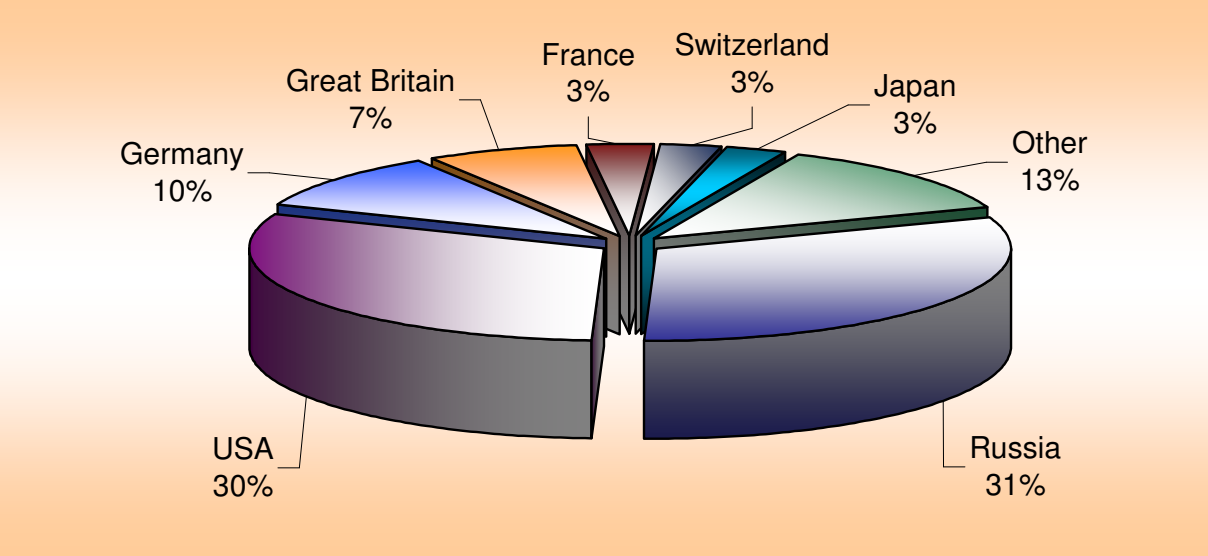
Figure 2 demonstrates that the proportion between international studies, local clinical trials and bioequivalence studies in the 3rd Quarter 2007 remained virtually unchanged compared to the 3rd Quarter 2006. An insignificant increase in the number of bioequivalence studies has been observed.

Figure 3. Proportion between Russian and International Sponsors in Q3 2007.



In the 3rd Quarter 2007 the share of Russian sponsors in the total number of initiated studies has increased. The growth is not significant and can rather be assigned to accidental fluctuations of this value. The number of clinical trials initiated in Q3 2007 by Russian sponsors is approximately 30%, however the share is much less in the number of investigator's sites involved and patients recruited.

Figure 4. Countries presented on the Clinical Trials market in Q3 2007.



Clinical trials in the 3rd Quarter 2007 were initiated by sponsors from 18 countries (Figure 4). Russia with its 44 studies and USA with 43 trials are on top of the list.

Clinical Trials by Phase, and Number of Sites and Patients

Against the background of constant total number of clinical trials conducted in Russia (completely or partly) and along with the constant ratio of different types of CTs, it is impossible not to mention a significant change in the share of different phases of CTs. Compared with the III quarter of the year 2006 the number of phase III trials decreased significantly (by 18%), the number of phase II trials increased (by 57%).

Consequently, the number of centers[1] for the conduction of phase III clinical trials decreased by 15%, the number of centers for conduction of phase II clinical trials increased by 80%. From 22 clinical trials with undetermined phase, the majority are bioequivalence studies.

Among centers in III quarter leaders are: Pavlov State Medical University of Saint Petersburg (31 CT), Russian State Medical University, Moscow (30 CT), N.N. Blokhin Russian Cancer Research Center of the Russian Academy of Medical Sciences, Moscow (28 CT).

This change of the inner structure of the conducted studies resulted in a decrease of the total number of patients involved by almost 2000 people: from 16340 in the III quarter of the year 2006 to 14431 people in the III quarter of the year 2007.

[1] Here and further centers, involved into different CTs are taken into account separately

Figure 5. Change in the Number of Clinical Trials by Phase in Q3 2007.

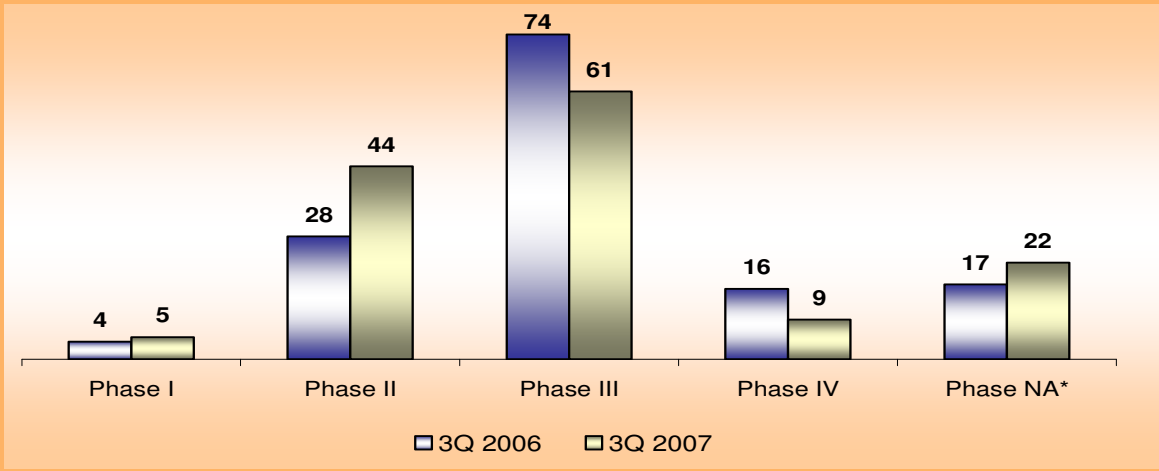


Figure 6. Change in the Number of Investigator's Sites in Q3 2007.

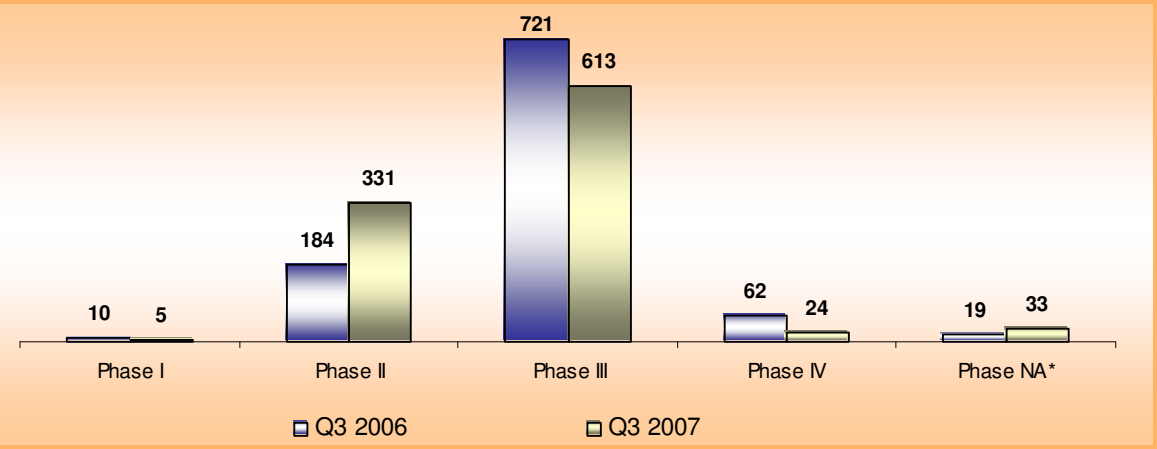
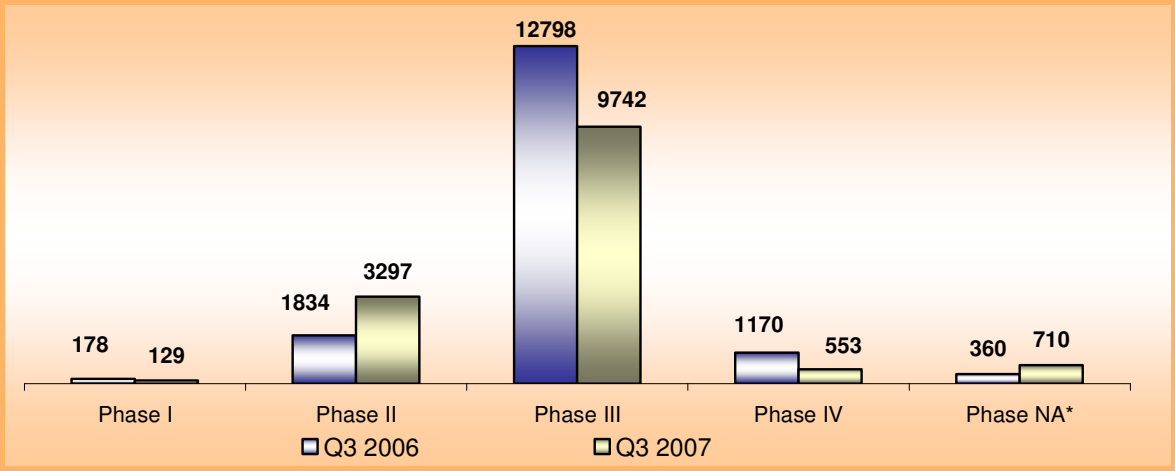


Figure 7. Change in the Number of Patients in Q3 2007.



* Phase is not applicable – mostly for bioequivalence studies

Rating of International Sponsors of Clinical Trials

According to foreign clinical trials sponsors rating (Table 2), in the 3rd Quarter 2007 the leading position according by the number of new trials (7), and by the number of patients (2033) takes Bristol-Myers Squibb. Then goes sanofi-aventis with its seven trials involving 46 centers and 596 patients. GlaxoSmithKline, Roche and Genentech, Inc follow the leaders.

Table 2. Top-5 International Sponsors in Q3 2007.

№	Name	No. of trials in Q3 2007	No. of sites	No. of patients
1	Bristol-Myers Squibb	7	95	2,033
2	sanofi-aventis	7	46	596
3	GlaxoSmithKline	4	24	234
4	Roche	4	53	604
5	Genentech, Inc	3	22	165

Rating of Russian Sponsors of Clinical Trials

The total number of patients planned to be recruited by the leading Russian sponsors in the studies initiated in the 3rd Quarter 2007 is 10 times less than by international sponsors (Table 3). In the 3rd Quarter 2007 the largest number of patients was in Materia Medica Holding studies - 220, the same number of studies with the same number of patients was initiated by BIOTIKI and NIOPIK (both by 3 trials with 210 patients). Among Russian sponsors in the top-5 are also DIOD and ROZPHARM.

Table 3. Top-5 Russian Sponsors in Q3 2007.

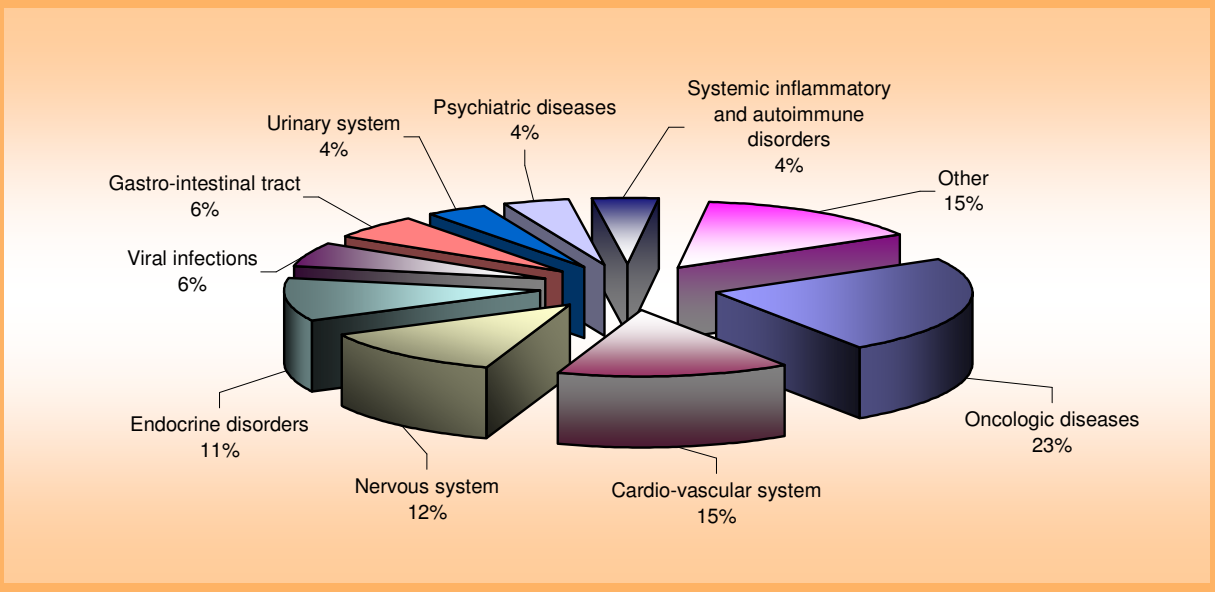
№	Name	No. of trials in Q3 2007	No. of sites	No. of patients
1	OOO ROZPHARM	5	10	90
2	OOO NPF Materia Medica Holding	3	4	220
3	FGUP GNC NIOPIK	3	10	210
4	OOO MNPK BIOTIKI	3	3	210
5	FGP MOSHIMFARM PREPARATY	3	3	72

Therapeutic Areas in the 3rd Quarter 2007

Table 4. Therapeutic areas of clinical trials in Russia in Q3 2007 [1]

Therapeutic Area	Q3 2007		
	No. of trials	No. of sites	No. of patients
Oncologic diseases	29	230	1,784
Cardio-vascular system	18	220	4,851
Nervous system	15	84	1,112
Endocrine disorders	13	125	1753
Viral infections	7	48	859
Gastro-intestinal tract	7	38	416
Urinary system	5	95	825
Psychiatric diseases	5	34	670
Systemic inflammatory and autoimmune disorders	5	27	274
Bacterial infections	4	14	235
Respiratory system	3	13	190
Muscular-skeletal system	2	25	490
Vaccines	нет	нет	Нет
Other	9	25	622
Total	122	978	14081
			Source: RZN

Figure 8. Clinical trials in Russia in Q3 2007 by Therapeutic Area



[1] Bioequivalence studies are not included

Overall picture of the distribution of initiated clinical trials between therapeutic areas in Q3 2007 is presented in Table 4. The maximum number of trials (29) is started in oncology. 18 new trials have been started on cardio-vascular disorders. These two types of trials normally recruit the largest number of subjects. In addition, a significant number of trials are initiated in the therapeutic areas of nervous system diseases, endocrine disorders (particularly diabetes mellitus), and viral infections.

Clinical Trials Results

During the 3rd Quarter 2007 FDA Center for Drug Evaluation and Research (CDER) has approved 7[1] new drugs, which were tested in Russian investigator's sites (see Table 5).

Table 5. New Drugs approved by FDA in Q3 2007 and studied in Russia

Date	Drug	Manufacturer	Indications/Purpose
07/06/2007	Rivastigmine	Novartis	CNS disorders
08/10/2007	Fenofibrate	Lifecycle Pharma	Lipid lowering agents
08/13/2007	Lamivudine; stavudine; nevirapine	Cipla Limited	Antiviral agents
08/17/2007	Zoledronic acid	Novartis	Osteoporosis
09/21/2007	Fludarabine phosphate	EBEWE Pharma	Oncology diseases
09/27/2007	Amlodipine besylate	Synthon Pharma	Cardio-vascular system diseases
09/28/2007	Terbinafine hydrochloride	Novartis	Antifungal agents
Source: FDA http://www.fda.gov/cder			

During Q3 2007 the committee for Medicinal Products for Human Use (CHMP) of European Medicine Agency (EMEA) has approved 10 new medicinal formulations, 2 generics and 14 extensions for the indications of well-known medicinal formulations. Among drugs approved by EMEA during this period 5 had been studied and are still studied in clinical trials in Russia (see Table 6.)

Table 6. New Drugs approved by EMEA in Q3 2007 and studied in Russia

Date	Drug	Manufacturer	Indications/purpose
21.09.2007	Yondelis (ecteinascidin)	PharmaMar S.A.	Oncologic diseases
21.06.2007	Aclasta (zoledronic acid)	Novartis	Osteoporosis
24.05.2007	Avastin (bevacizumab)	Roche	Oncologic diseases
24.05.2007	Glustin (pioglitazone)	Takeda	Diabetes mellitus
24.05.2007	Telzir (fosamprenavir)	GlaxoSmithKline	AIDS
Source: CHMP EMEA http://www.emea.europa.eu/index/indexh1.htm			

[1] According to CDER FDA data http://www.fda.gov/cder

New Investigative Sites

As of October 17 2007 the number of investigator's sites accredited by RZN has accounted up to 800. During Q3 2007 32 new health care facilities were approved (see Table7 for complete list).

Table 7. New Sites accredited by RZN in Q3 2007.

Name	Address
GUZ «Alexandro-Mar'inskaya regional clinical hospital»	414056, Astrakhan, Tatischev street, 2
MUZ «Municipal out-patient hospital № 3»	347381, Volgodonsk, Entuziastov street, 12
GUZ «Voronezh regional children's clinical hospital № 1»	394024, Voronezh, Burdenko street, 1
GUZ «Regional children's clinical hospital № 1»	620149, Ekaterinburg, Serafimy Deriabinoy street, 32
MUZ «Clinical hospital № 1»	664046, Irkutsk, Baikalskaya street, 118
MUZ «Municipal clinical hospital № 8»	664048, Irkutsk, Yaroslavskogo street, 300
MUZ «Central municipal clinical hospital № 18»	420101, Kazan, Mavliutova street, 2
FGU «Interdisciplinary research and technology complex «Microsurgery of the eye» named after academic S.N. Fedorov of Rosmedtechnology», branch in Kaluga	248007, Kaluga, Vishnevskogo street, 1a
FGUZ «Hospital of the Main Department of Internal Affairs on Kemerovskaya district»	650099, Kemerovo, Kuzbasskaya street, 10A
MUZ «Municipal clinical hospital № 11»	650014, Kemerovo, Vahrushev street, 4a
MUZ «Municipal clinical ambulance station»	650036, Kemerovo, Volgogradskaya street, 39
MUZ «Municipal oncology dispensary»	681000, Komsomolsk-na-Amure, Ussurijskaya street, 5
OOO «Territorial Nephrology Center»	350033, Krasnodar, Gheleznodorozhnaya street, 24
MUZ «Central municipal clinical hospital of Lipetsk»	398035, Lipetsk, Kosmonavtov street, 39
FGUN «Moscow scientific and research institution of epidemiology and microbiology named after G.N. Gabrichevsky of Rospotrebnadzor»	125212, Moscow, Admiral Makarov street, 10
GUZ of Moscow «Hospice № 3»	117216, Moscow, Poliany street, 4
MUZ «Central regional hospital of Odintsovo»	143000, Odintsovo, Marshala Biriuzova street, 5
MUZ «Central regional hospital of Ramenskoe»	140100, Moscow region, Ramenskoe, Mahov street, 14
GUZ «Municipal clinical hospital № 3 of Nighegorodskiy district (Geriatric center of Nizhniy Novgotod)»	603155, Nizhniy Novgorod, Verhne-Volzhskaya embankment, 21

MUZ «Municipal perinatal center of Novosibirsk»	630089, Novosibirsk, Lezhena street, 32
GUZ «Regional clinic hospital of Orenburg № 2»	460000, Orenburg, Nevelskaya street, 24
MMUZ «Municipal clinical hospital of ambulance № 1 of Orenburg»	460040, Orenburg, Gagarina street, 23
GUZ «Regional clinical hospital of Penza named after N.N. Burdenko»	440026, Penza, Lermontov street, 28
MUZ «Clinical hospital № 1»	614010, Perm, Kuibishev street, 110
St-Petersburg GUZ «Consultative-diagnostic out-patient clinic № 1»	197183, St-Petersburg, Primorskiy avenue, 3
OOO «Medical-consultative out-patient hospital «Astromed»	167000, Siktivkar, Kommunisticheskaya street, 10
MUZ «Municipal clinical hospital № 5 «MedVAZ»	445846, Togliatti, Zdorovya boulevard, 25
MKLPMU «Municipal hospital № 3»	634034, Tomsk, Nakhimova street, 3
GUZ «Buriatskiy republic oncology dispensary»	670047, Ulan-Ude, Pirogova street, 32
FGU «301th territorial military clinical hospital of Dalnevostochniy military territory of Ministry of Defense of Russia»	680028, Khabarovsk, Serisheva street, 1
GUZ «Center of reconstructive medicine and rehabilitation № 2»	346510, Rostovskaya district, Shakhti, Dubinina street, 4
MUZ «Municipal hospital № 2»	413124, Engels, Poligraficheskaya street, 1
Source: Roszdravnadzor	

Conclusion

We estimate that the number of clinical trials initiated in Russia during 2007 will remain the same as in the last year. Taking into account the ban on exports of biological samples which happened in May 2007 such stability should be interpreted positively. The long-term trend towards growth remains on the level of average 18% per year. We'd like to note that in the past the clinical trials market in Russia passed not only through stagnation periods, but also through periods of significant volume decrease (in 1999 and 2005). To maintain existing status quo and, what is much more important, to develop the Russian clinical trial industry in the highly competitive international environment all Russian clinical trials market players including sponsors, regulatory authorities, investigators and CROs should join and harmonize their efforts.

Appendix

Leader's Profile. Roche

Swiss company Roche is founded in 1896 in Basel, Switzerland. The main fields of concern of the company are pharmaceutical industry and diagnostic equipment production. In this area (Drugs & Biotechnology) at present, Roche Holding is the sixth company by size in the world. In the list of the 2000 biggest world companies, published by Forbes magazine in 2007, Roche Holding is on the 85th place. The volume of international sales of Roche Holding in the year 2006 was 34,47 billion of US dollars (27,7% increase since the year 2005)[1]. The marketing value of the company is 135,55 billion of US dollars[2]. At present, the company incorporates 74,000 of employees.

The main fields of concern of the pharmaceutical department of Roche company are the development, production and sales of medicinal preparations, utilized in oncology (Herceptin, Avastin and MabThera/Rituxan), for the treatment of viral diseases (Tamiflu), for the treatment of osteoporosis (Bonviva/Boniva). Other therapeutic areas of company's concern are diseases of central nervous system, infectious diseases, cardio-vascular agents, medications for the treatment of autoimmune diseases and anti-inflammatory drugs and also dermatology, transplantology and metabolic disorders. The result of the work of the pharmaceutical department of Roche in the year 2006 was the increase of sales by 21%, which composed 26,6 billion US dollars[3], the company strengthened its leading positions in the world in the field of oncology.

In Russia, according to results of the year 2006, the sales volume of Roche increased by 24% compared to the previous year which made 68 million US dollars. In the Additional pharmacological support sector the increase of sales of Roche composed 257%, the cost volume increased from 47,2 million US dollars to 168,2 million US dollars. In the II quarter of the year 2007, the company took the first place by the number of initiated clinical trials in Russia.

Table 8. Roche[4] Pipeline

Therapeutic area	Phase I	Phase II	Phase III	Registration	Total
Hematology and nephrology	0	1	0	1	**2**
Inflammatory, autoimmune and bone tissue disorders	3	2	6	0	**11**
Cardio-vascular and metabolic disorders	3	3	0	0	**6**
Neurological and psychiatric disorders	6	1	0	0	**7**
Oncology	5	5	20	6	**36**
Respiratory system	0	1	0	0	**1**
Viral and other infectious	3	2	1	0	**6**

[1] Rosche Annual Report 2006
[2] Forbes. The World's 2,000 Largest Public Companies
[3] Here and below for the converse into US dollars the mean rate of exchange of the year 2006 is taken: 1,2538 CHF=1 USD (according to PACIFIC Exchange Rate Service data)
[4] Source: Hoffman-La-Roche, as for July 27, 2007

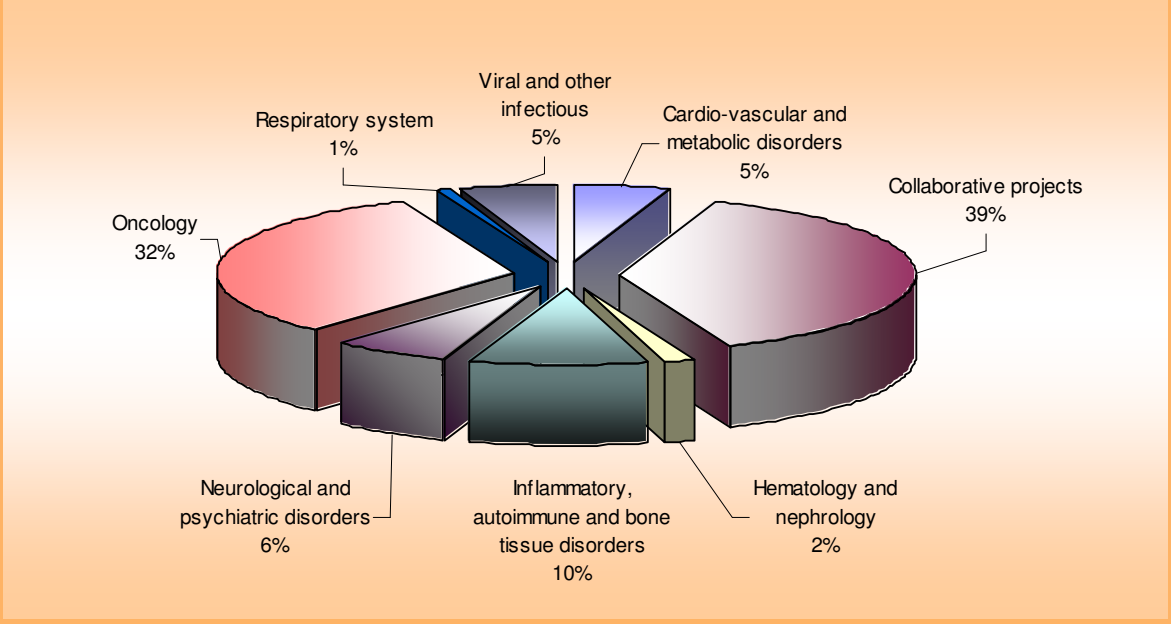
(Table 8. Continued)

Collaborative projects	11	19	10	3	43
Total	**31**	**34**	**37**	**10**	**112**

Source: Roche

The company carries out scientific research and develops medications for the therapy of: anemia, cardiovascular diseases, central nervous system diseases, skin diseases, infectious, inflammatory and autoimmune diseases, metabolic disorders, oncology diseases, respiratory system diseases, transplantology.

Figure 9. Roche Portfolio by Therapeutic Area



The growth and profitability of the pharmaceutical department of the company is the consequence of the sales of ten bestsellers: (Herceptin, Avastin, Tamiflu, MabThera/Rituxan, Lucentis, Tarceva, Bonviva/Boniva, Xeloda, CellCept, Xolair). These 10 medications (bestsellers) represent 59% of the company's portfolio (in 2005 – 47% of portfolio, in 2004 – 37% portfolio). In total the sales of these bestsellers in the year 2006 increased by 50%, which made more than 5,2 billion of US dollars of additional sales.

The first 20 drugs according to the sales results (TOP-20) increased the sales by 30% and only Rocephin decreased markedly the profitability, as a consequence of the patent expiration in the USA in 2005.

Table 9. Roche bestsellers tested in Russia

Medication	2006 sales, mln. USD[1]	Sales ratio, %	Patent expiration date	No. of current trials in Russia	Therapeutic area
MabThera/ Rituxan	3859	15	-	9	Oncology/ anti-inflammatory drugs
Herceptin	3132	12	-	4	Oncology
Avastin	2362	9	-	4	Oncology
Pegasys	1170	4	-	4	Antiviral medications
Xeloda	774	3	13-Jan-11	5	Oncology
Tarceva	648	2	-	1	Oncology

In the area of new medications development, more than 12,000 of researchers are involved in Roche company. The research center in Basel (Switzerland) specializes on metabolic disorders and central nervous system diseases. The center of oncology trend is placed in Nutley (USA), virusology and anti-inflammatory drugs – in Palo Alto (USA), complex protein structures – in Penzberg (Germany), medical chemistry, including synthesis and screening NME – in Shanghai (China).

In 2006 Roche company filed 13 new applications for medication use and received 14 permissions. The same year there was an increase of the budget for clinical trials by 718 million US dollars (19% in local currency) which made in total 4,7 billion US dollars. The research budget accounted for 17,7% of sales level. In addition, Roche Company spent about 480 million. US dollars on licensing of medications, which are under development and research. The company spent a total of 5,2 billion US dollars on in-house and ordered in other companies scientific researches. Nine phase III clinical trials of Roche company were successfully brought to the primary endpoints in 2006.

At the beginning of 2007 year there were 101 clinical studies under development in the department of research of Roche, among them 48 were dedicated to new molecular elements (NME) and 53 to the widening of the indications for use. Twenty-five from these NMEs are in I phase of clinical study, 18 in the II phase, 5 – in the III phase or under registration.

According to the US National Institute of Health ClinicalTrials.gov Service data by the beginning of September 2007, 212 trials involving Roche medications were in the phase of initiation or patient enrollment into the trial. In total, there are 492 trials, conducted by Roche, registered in the ClinicalTrials.gov database (taking into account only trials with finished patient recruiting).

Table 10. Clinical trials conducted by Roche in 2007[2] worldwide

Region	Not yet recruiting	Recruiting	No longer recruiting	Completed
USA and Canada	12	99	0	157
Europe	14	94	1	54
Russia	9	16	0	4
Asia and Middle East	6	30	0	13

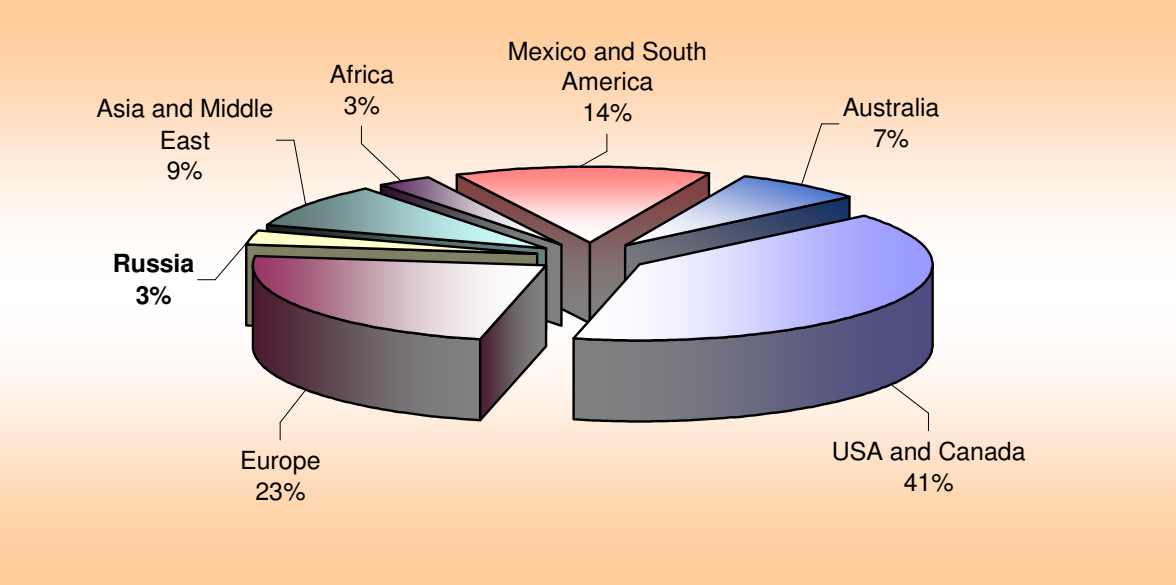
[2] Showed only trials, in which enrollment is performed or not started yet

(Table 10. Continued)

Africa	0	9	0	5
Mexico and South America	3	33	0	44
Australia	3	18	0	17
Unique studies*	25	187	1	169
Source: US National Institute of Health (www.clinicaltrials.gov)				

* *The majority of studies are conducted simultaneously in several countries*

Figure 10. Clinical trials conducted by Roche in 2007 by Region



According to ClinicalTrials.gov there are 17 ongoing Roche studies in Russia: 7 of Phase II, 3 – in Phase III, and 7 – in phase IV. According to RZN more than 181 centers in Russia are involved in these studies. The worldwide annual growth of investigator's sites involved in Roche clinical trials is about 500.