Clinical Trials in Russia
Orange Paper
№3/2007. 2nd Quarter 2007

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Executive Summary

According to the data provided by the US National Institute of Health[1], as many as 2,350 new international multi-center clinical trials were initiated in the world in the second Quarter of 2007, with about one half of them being conducted in the United States (1,175 studies), and over 25% (602 studies) – in Europe. As many as 64 new trials will be conducted in Russia, which is less than 3% of the total number of studies. The closest companions of Russia (in the camp of so called "emerging markets") – India and China – will conduct 28 and 36 new clinical trials in their territories, respectively.

In the 2nd Quarter of 2007, The Federal Agency for Health Care and Social Development (Roszdravnadzor, or RZN) issued 114 permits to conduct clinical trials in Russia. This is 13% as low as in the second Quarter last year; at the same time, the number of international multi-center clinical trials became 25% as low, and the number of local and bioequivalence studies grew inconsiderably.

As a result, the contribution made by Russian sponsors grew by 7% as compared to the second Quarter of 2006 and made up 35% of the total volume of the clinical trials market in Russia. Study sponsors were 72 companies from 23 countries including Russia, which was represented by 22 companies. The leader among foreign countries participating in the clinical trials market is the US (17%) followed by Switzerland (11%) and Germany ranking third with its 7%.

As many as 284 medical institutions will take part in trials initiated in the 2nd Quarter of 2007, which is just over one third of the total number of study sites accredited by RZN for conducting clinical trials. Over 50% of them are located in Moscow and Saint-Petersburg, which is another confirmation of the unequal usage of regional clinical sites. Over 10,000 patients will take part in the trials, and the average trial duration will be 19 months.

The leader among foreign sponsors is Hoffmann-La Roche (10 clinical trials, 89 sites and 1,042 patients), and the leader among Russian sponsors is ZAO Severnaya Zvezda (The Northern Star).

In the 2nd Quarter of 2007 FDA approved 27 new drugs with four of them being tested in clinical trials in Russia. During the same period, the European Medicine Agency (EMEA) approved of 43 marketing applications for drugs with six of them also being or having been tested in clinical trials in Russia.

In the 2nd Quarter of 2007 RZN inspectors conducted 12 regular audits of clinical trial quality and accredited 18 new study sites. FDA carried out five inspections in the territory of Russia for the first six months; in three cases, it reported on NAI (No Action Indicated), and in other cases – on VAI (Voluntary Action Indicated).

We should also mention the 'main event' that occurred on the clinical trials market in Russia during the second Quarter of 2007 – an unexpected and unexplainable export ban for biological samples, which was introduced on May 29, 2007 and was fevering the clinical trials market for almost two weeks. Events of this type do not stimulate the flow of international clinical trials to Russia, and this flow might promote the introduction of advanced methods of treatment to the Russian clinical practice, provision of medical institutions with the most up-to-date equipment, and provision of Russian patients with access to the world innovative drugs.

On June 28, 2007 the Soviet of the Federation had a round table devoted to the role and problems of clinical trials in Russia. Participants were experts and representatives of regulatory authorities, pharmaceutical industries, research and academic institutes, health care centers and contract research organizations as well as members of the Russian State Duma. As a result of the round table, its participants developed a number of recommendations for the Federal Assembly of the Russian Federation, Government of the Russian Federation, Public Chamber of the Russian

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

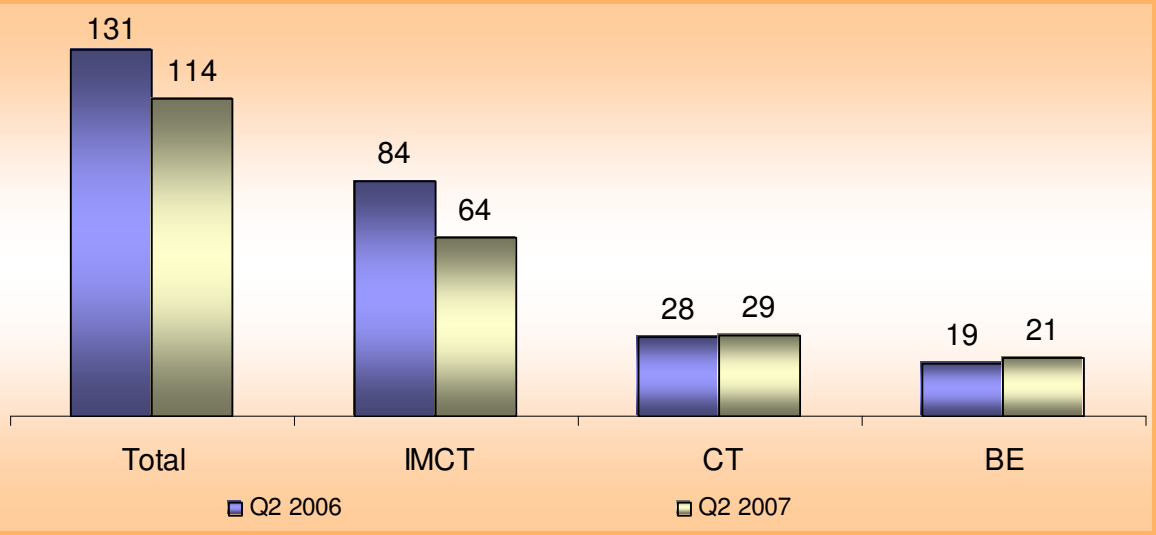
Federation and executive authorities from different subjects of the Russian Federation for forming and developing a civilized clinical trials market in Russia.

We should hope that these measures taken in due time will compensate the damage caused to the Russian clinical trials market by ill-advised actions of the Federal Customs Service – "forgive them, for they have not known what they do" [1] . However, it will be possible to judge upon this by the results for clinical trials in Russia in the third Quarter of 2007, and this will be covered in the next issue of the Orange Paper this October.

Analysis of Clinical Trials by Types and Manufacturing Countries

In the 2nd Quarter of 2007, RZN issued 114 permits for all types of studies, which is 13% as low as in the 2nd Quarter of 2006. We can see from Figure 1 that the number of local and bioequivalence studies was almost preserved at the last year's level, while the number of international multi-center clinical trials became almost 25% as low. This is most probably explained by the ban imposed by the Russian Federal Customs Service on the export of biological samples on May 29, 2007, which resulted in a sharp reduction in the number of applications for international multi-center clinical trials. If there had been no ban, the number of international multi-center clinical trials (IMCTs) could have grown by 50% more, and the June would not have been "lost."

Figure 1. Clinical trials approved by RZN in Q2 2007

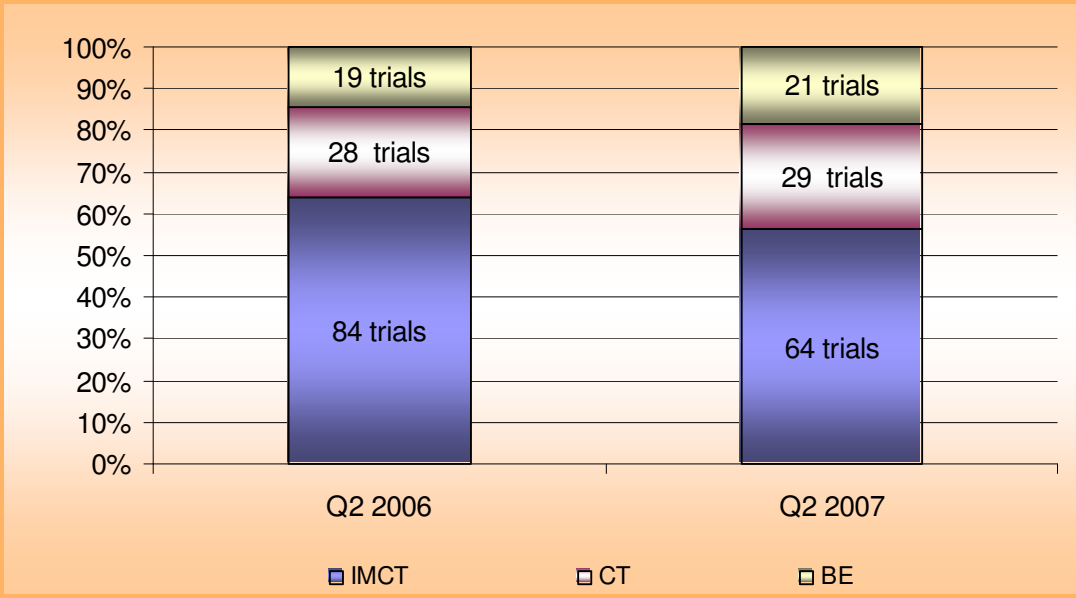


IMCT means international multi-center clinical trials with their centers located in different countries including Russia. The CT(R) abbreviation as used in the diagrams means clinical trials conducted exclusively in the territory of Russia. BE means drug bioequivalence studies.

The balance between IMCTs, CTs and BEs has slightly changed in this Quarter. There is a slight growth in the share of local clinical trials and bioequivalence studies on account of IMCTs. While in the 2nd Quarter of 2006 IMCS, CTs and BEs made up 64%, 21% and 15%, respectively, they amounted to 56%, 25% and 19% in the 2nd Quarter of 2007.

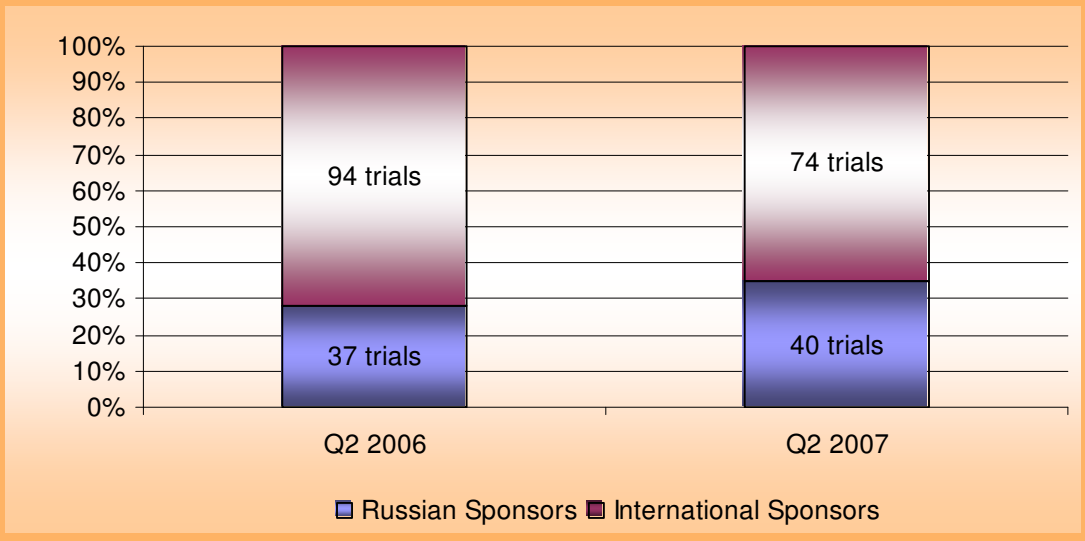
[1] Luke 23: 34

Figure 2. Clinical Trials by Type in Q2 2007.



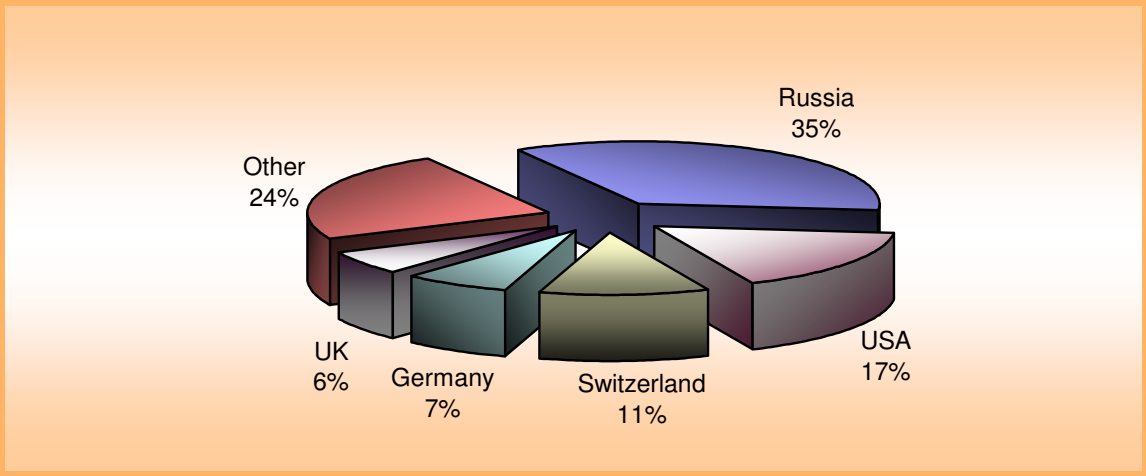
In the 2nd Quarter of 2007, a trend towards the growth in the share of Russian sponsors in the total number of initiated studies remained in effect. In spite of the fact that drug bioequivalence studies cannot be considered as full-fledged clinical studies, the share of Russian sponsors grew by 7% as compared to the second Quarter of 2006 and made up 35% of the total number of clinical trials.

Figure 3. Share between Russian and International Sponsors in Q2 2007.



Study initiators were sponsors from 22 countries, which is 7 countries as much as in the second Quarter of 2006. Figure 4 presents the share of countries being leaders on the clinical trials market in the total number of trials in the 2nd Quarter of 2007.

Figure 4. Countries presented on the Clinical Trials market in Q2 2007.



Other countries are Canada, Japan, Portugal, Puerto-Rico, France, Belgium, Hungary, Denmark, India, Italy, China, Netherlands, Poland, Slovenia, Czech Republic, Sweden and Ireland.

Clinical Trials by Phase, and Number of Sites and Patients

There is a growth in the number of Phase IV trials (by 70% and slight increase in the number of Phase I trials against the background of general reduction in the number of studies as compared to the second Quarter of 2006. The number of Phase II trials became 26% as low, and Phase III trials – 27% as low – and these trials make up a lion's share in the total number of international multi-center clinical trials.

The total amount of involved study centers was 635, which is 21% as low as in the 2nd Quarter of 2006. It should be noted that this figure is combinatory, i.e. when the same center participates in several studies, it is recorded as several centers. For example, the absolute leader in the 2nd Quarter is the Russian State Medical University of Roszdrav, which will be the base for 23 new studies. This means that its share in the total number of centers presented in Figure 6 will be equal to 23. The I.P. Pavlov Saint-Petersburg State Medical University ranks second with 17 concurrent studies, and the N.N. Blokhin Russian Research Center for Oncology ranks third with 14 concurrent studies. Almost all of the leaders are located in Moscow and Saint-Petersburg – only one of the seven centers with over 10 studies is situated in Smolensk.

All in all, 284 medical institutions will take part in trials, which is 37% of the total number of all medical institutions accredited by RZN for conducting clinical trials[1]. The share of Moscow and Saint-Petersburg in the total number of trials initiated in the 2nd Quarter of 2007 is more than one half. This is another confirmation of the fact that the potential of Russian regions is not used quite effectively.

It is planned to enroll 10,268 patients for trials initiated in the 2nd Quarter of 2007, which is 17% as low as in the 2nd Quarter of 2006. At the same time, the minimum duration of trials initiated in this Quarter is 2 months, the maximum duration is 92 months, and the average – 19 months.

[1] RZN http://www.roszdravnadzor.ru/i/upload/files/1181309866.16567-2234.pdf

Figure 5. Change in the Number of Clinical Trials by Phase in Q2 2007.

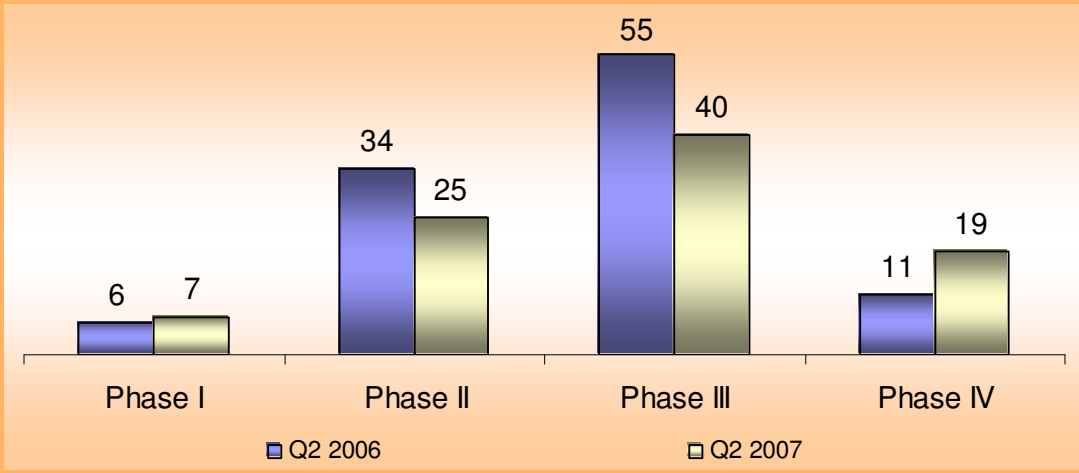


Figure 6. Change in the Number of Investigative Sites in Q2 2007.

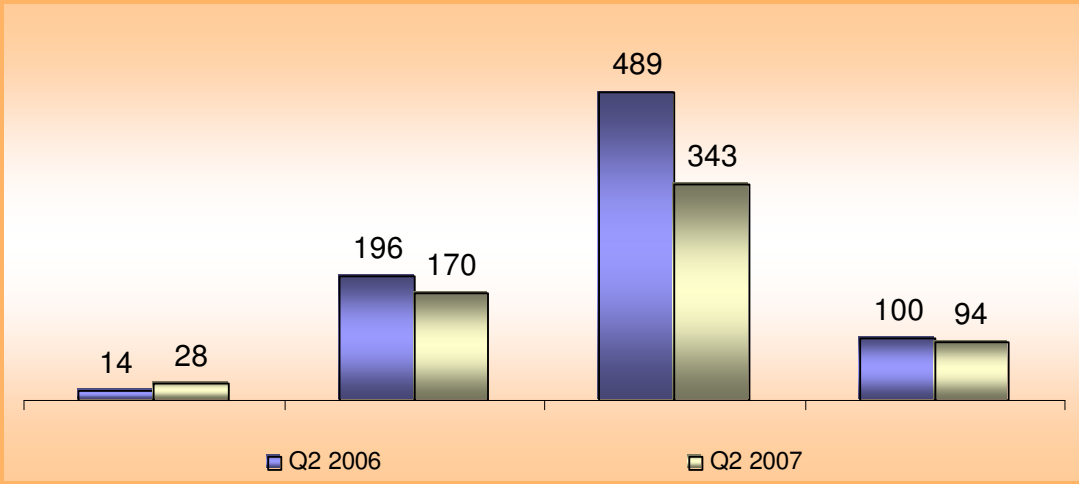
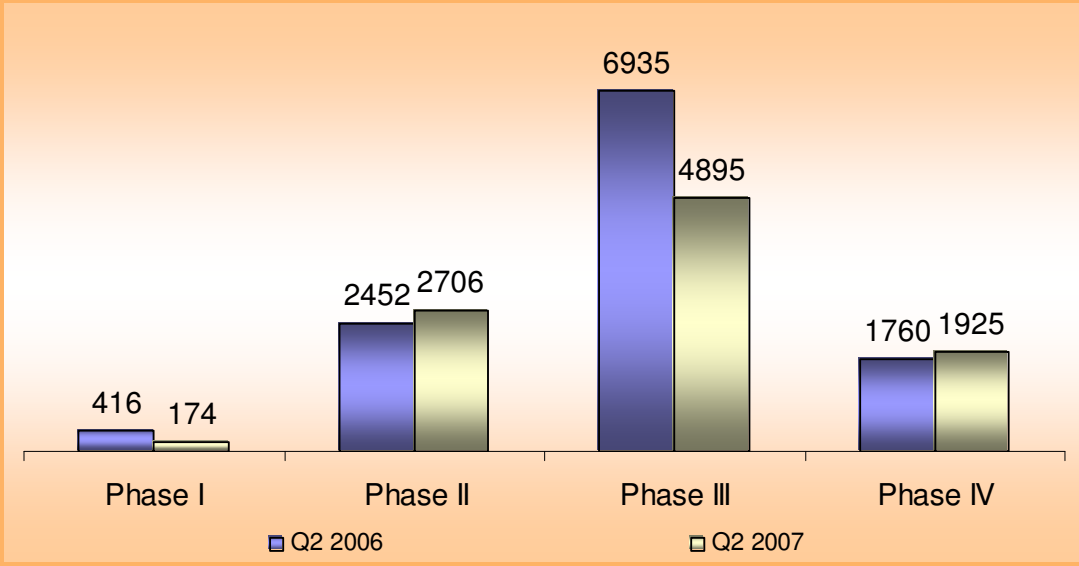


Figure 7. Change in the Number of Patients in Q2 2007.



Rating of International Sponsors of Clinical Trials

In this Quarter, F. Hoffmann-La Roche ranked first by the number of studies – with a great gap separating it from Novartis Pharma AG, which ranked second with its six studies and forced the leader for the previous Quarter – GlaxoSmithKline – to the honorary third place (see Table 1). The leader by the number of patients is Daiichi Sankyo (Japan) with its 1,300 patients followed by F. Hoffmann-La Roche ranking second and GlaxoSmithKline ranking third.

The top three companies by the number of study centers is as follows: F. Hoffmann-La Roche (89); Daiichi Sankyo (53) and GlaxoSmithKline again (37).

Table 1. Top-5 International Sponsors in Q2 2007.

№	Name	Trials started in Q2 2007	No of Patients	No of Sites
1	F. Hoffmann-La Roche	10	1,042	89
2	Novartis	6	660	36
3	GlaxoSmithKline	4	710	37
4	Merck & Co.	4	147	21
5	Patheon	3	380	36

Rating of Russian Sponsors of Clinical Trials

Thirty-nine national studies approved in the second Quarter of 2007 were split up almost in equal shares between local clinical studies (19) and bioequivalence studies (20). Phases in 19 local clinical trials were allocated as follows: Phase I – three trials, Phase II – five trials, Phase III – four trials, and Phase IV – seven trials.

As many as 82 study centers and 1,990 patients will take part in Russian trials, which is almost one fifth of the total number of patients planned to be enrolled in all studies initiated in the second Quarter of 2007.

All in all, 22 Russian companies became sponsors for clinical trials initiated in the 2nd Quarter of 2007.

Table 2. Top-5 Russian Sponsors in Q2 2007.

№	Name	Trials started in Q2 2007	No of Patients	No of Sites
1	Severnaya Zvezda (The Northern Star)	4	72	4
2	Biocad	3	140	6
3	RozPharm	3	54	6
4	Materia Medica Holding	2	498	18
5	Siberian Center for Pharmacology and Biotechnology	2	200	8

Clinical Trials Results

During the second Quarter of 2007 FDA Center for Drug Evaluation and Research (CDER) approved 27[1] new drugs with four of them being new molecular substances, 11 – new doses, and one – for a new indication. Table 3 presents those of them that have already been or are currently tested in clinical trials in Russia.

Table 3. New Drugs approved by FDA in Q2 2007 and studied in Russia

Date	Drug	Manufacturer	Indication
15.06.2007	Nuvigil (armodafinil)	Cephalon, Inc	Sleep disorders
14.06.2007	Lexiva (fosamprenavir)	GlaxoSmithKline	HIV infection
17.05.2007	Seroquel XR (quetiapine fumarate)	AstraZeneca	Schizophrenia
16.04.2007	Reclast (zoledronic acid)	Novartis	Osteoporosis
Source: CDER FDA http://www.fda.gov/cder			

The Committee for Medicinal Products for Human Use (CHIMP) of the European Medicine Agency (EMEA) examined 46[2] applications for drug marketing in the territory of the European Union during the period from April 1 to June 30, 2007. Among these applications, 19 new drugs and 12 new indications for earlier registered drugs were approved, negative decisions were taken for three drugs, and six of the approved drugs have already been or are currently tested in clinical trials in Russia (see Table 4).

Table 4. New Drugs approved by EMEA in Q2 2007 and studied in Russia

Date	Drug	Manufacturer	Indication
21.06.2007	Arixtra, Quixidar (fondaparinux)	GlaxoSmithKline	Anticoagulant
21.06.2007	Rasilez, Enviage, Sprimeo, Tekturna, Riprazo (aliskiren)	Novartis	Hypertension
24.05.2007	Aerinaze (desloratadine)	Schering-Plough	Allergy
24.05.2007	Forsteo (teriparatide)	Eli Lilly	Osteoporosis
24.05.2007	Plavix, Iscover (clopidogrel)	sanofi-aventis, Bristol-Myers Squibb	Anticoagulant
27.04.2007	Invega (paliperidone)	Janssen-Cilag	Schizophrenia
Источник: CHMP EMEA http://www.emea.europa.eu/index/indexh1.htm			

New Investigative Sites

According to RZN, the Russian Federation had 768 medical institutions accredited for conducting clinical trials of drugs as of May 31, 2007[3] . Eighteen institutions were accredited in the 2nd Quarter of 2007 (see Table 5).

[1] According to CDER FDA http://www.fda.gov/cder
[2] According to CHMP EMEA http://www.emea.europa.eu/index/indexh1.htm
[3] RZN http://www.roszdravnadzor.ru/i/upload/files/1181309866.16567-2234.pdf

The map of clinical trials conducted in Russia now has two new cities where clinical trials will be conducted from now on – Bryansk and Nalchik. Leaders by the number of new centers accredited in the 2nd Quarter of 2007 are Novosibirsk and Saint-Petersburg (three new centers in each of these cities), and two study centers were accredited in Nizhni Novgorod.

Table 5. New Sites accredited by RZN in Q2 2007.

Healthcare Institution Name	Address
Bryansk Regional Oncology Dispensary (a public health care institution)	241033, Bryansk, pr. St. Dimitrova 96
City Clinical Hospital No. 14 (a municipal institution)	620039, Yekaterinburg, ul. XXII Partsyezda 15a
Kirov Regional Center for Prevention and Treatment of AIDS and Infectious Diseases (a public regional health care institution)	610000, Kirov, ul. Maklina 3
Municipal City Hospital No. 2 (a health care institution)	141070, Moscow region, Korolyov, ul. Dzerzhinskogo 11
Central Hospital No 4 of OAO RZhD (a non-state health care institution)	143121, Moscow region, Ruza district, Pokrovskoye
Center of Medical and Ecological Studies – a branch of the State Research Center of the Russian Federation (Institute of Medical and Biological Problems, Russian Academy of Sciences)	360051, Nalchik, pr. Shogentsukova 40
Nizhni Novgorod Research Institute of Hygiene and Professional Pathologies of the Rospotrebnadzor (a federal state research institute)	603950, Nizhni Novgorod, ul. Semashko 20
Nizhni Novgorod Regional Clinical and Diagnostics Center (a public health care institution)	603006, Nizhni Novgorod, ul. Reshetnikovskaya 2
Research Institute of Physiology, Siberian branch of the Russian Academy of Medical Sciences (a public institution)	630117, Novosibirsk, ul. Akademika Timakova 4.
Central Clinical Hospital of the Siberian branch of the Russian Academy of Medical Sciences	630090, Novosibirsk, ul. Pirogova 25
OOO Bioterapiya Research and Clinical Center for Oncology and Neurology	630090, Novosibirsk, ul. Institutskaya 4/1
City Hospital No. 9 (a public health care institution in Saint-Petersburg)	197110, Saint-Petersburg, Krestovsky pr. 18
OOO Vena	199178, Saint-Petersburg, Bolshoi pr. V.O. 89, A, 13-H
OOO NMC	191104, Saint-Petersburg, Liteinyi pr. 55a
N.P. Ogaryov Mordova State University of the Federal Agency for Education (a state higher education institution)	430000, Saransk, ul. Bolshevistskaya 68
Stavropol Territorial Clinical Consultative and Diagnostic Center (an autonomous non-for-profit medical organization)	355017, Stavropol, ul. Lenina 304
M.P. Litvinov Regional Clinical Psychiatric Hospital No. 1 (a public health care institution)	170546, Tver region, Kalininsky district, Burashevo
Regional Clinical Specialized Psychoneurological Hospital No. 1 (a public health care institution)	454087, Chelyabinsk, ul. Kuznetsova 2
	Source: RZN

RZN Inspections in Q2 2007

For three years of RZN existence, its inspectors conducted 88[1] scheduled audits in Russian medical institutions accredited for conducting clinical trials of drugs. Table 6 presents study centers where RZN exercised control over the conduction of clinical trials and compliance with Good Clinical Practice (GCP) in the second Quarter of 2007.

Table 6. Sites inspected by RZN in Q2 2007.

Institution	**Address**
City Oncology Dispensary (a public health care institution)	Kazan, ul. Baturina 7
Kemerovo Regional Clinical Hospital (a public health care institution)	Kemerovo, pr. Oktyabrsky 22
City Clinical Hospital No. 2 (a municipal health care institution)	Novosibirsk, ul. Polzunova 21
Orenburg Regional Clinical Oncology Dispensary (a public health care institution)	Orenburg, pr. Gagarina 11
Pyatigorsk Oncology Dispensary (a municipal health care institution)	Pyatigorsk, ul. Kalinina 31
Regional Hospital No. 2 (a public health care institution)	Rostov-upon-Don, ul. Pervoy Konnoy Armii 33
Samara Oncology Dispensary (a public health care institution)	Samara, ul. Solnechnaya 50
Saratov State Medical University of the Rosdzrav (a public higher education institution)	Samara, ul. Bolshaya Kazachya 112
Stavropol Territorial Clinical Oncology Dispensary (a public health care institution)	Stavropol, ul. Oktyabrskaya 182a
Tambov Regional Oncology Dispensary (a public health care institution)	Tambov, ul. Moskovskaya 29b
Republican Oncology Dispensary (a public health care institution)	Ufa, pr. Oktyabrya 73/1
City Clinical Hospital No. 3 (a municipal health care institution)	Chelyabinsk, pr. Pobedy 287
Source: Roszdravnadzor. http://www.roszdravnadzor.ru/medcontrol/clinic	

The goal of such audits is to determine whether the health care institutions' activities related to the conduction of clinical trials comply with the current legislation of the Russian Federation and Good Clinical Practice (GCP). As a rule, a six-month audit plan is made in the form of an order, and the list of the institutions to be audited is officially published on RZN's web site.

In the course of the audits, the commission members usually comprising two employees from Roszdravnadzor's territorial authorities check the institution's licenses to conduct medical activities, assess the bedspace (hospital stock) and structure of the structural units taking part in the clinical trials, and define which of the medical higher education institutions operate on the basis of the clinical study center.

Having collected the general information about the institution, the commission audits the following aspects of clinical trials:

1. General information – name of the study drug, number and name of the clinical study protocol.

2. The legal basis for carrying out the clinical trial – Roszdravnadzor's permit to carry out the clinical trial, contract with the sponsor or contract research organization (CRO), clinical trial

[1] N.V. Yurgel. Regulation of the system of clinical trials organization and conduction in the Russian Federation (in pediatric practice as well). Report presented at the round table of the Soviet of the Federation devoted to clinical trials on June 28, 2007.

insurance contract and documents issued by the Independent Ethics Committee and Local Ethics Committee as well as in-house clinical trial-related documents (orders issued by the institution, etc.); copies of the documents are to be enclosed.

3. Professional level, qualification and experience of the employees involved in the clinical trial. The legality of the approval of the principal investigator's candidature by the Independent Ethics Committee and Local Ethics Committee as well as compliance of the principal investigator's and co-investigators' professional level, qualification and experience with the complexity and specifics of the clinical trials being carried out as well as delegation of authorities between them are checked. CVs, diplomas and advanced training certificates including GCP certificates are to be enclosed to the report.

4. Organizational and technical level of the clinical study center. The fitness of the premises for the principal investigator and co-investigators as well as premises for storing and archiving the clinical trial-related documents, availability of office equipment, communications facilities and required medical and laboratory equipment as well as qualification of the technical personnel including the metrological and maintenance services (diplomas, certificates, contracts, etc.) are audited.

5. Organization of the study drug storage and handling procedures. Drug storage premises and equipment as well as provision of special storage conditions if available (such as refrigerator, air conditioner, etc.) and storage condition control devices (thermometers, hygrometers, backup power, etc.) are audited. Study drug movement documents as well as randomization and urgent unblinding procedures, list of personnel having access to the study drugs, procedure of their issue and shelf life are audited.

6. The keeping of clinical trial-related documents. The clinical trial protocol, its versions and amendments, trial brochure, CRF and IC forms as well as their updated versions, randomization-related documents as well as AE and SAE documents, documents related to the monitor's visits and audits as well as procedures and accurateness of filling in the CRFs, obtaining IC and keeping source documents are checked.

7. Activity of the Local Ethics Committee. The membership of the committee (chairman, secretary, number of members, sexual composition, presence of people that do not belong to the research team and employees of the health care institution and rotation of the committee's membership) as well as its standard procedures – frequency of meetings, procedure of examining the clinical trials materials (primary and secondary), procedure of examining the study drug-related safety data and procedure of examining deviations from clinical trial protocols – are checked. Copies of the Local Ethics Committee's proceedings are to be enclosed.

The commission makes the Report as a result of the audit and assesses the institution's clinical trial-related activities. If any shortcomings are revealed during the audit, the commission will set them out in the Audit Report and make proposals related to their elimination. The Report is to be signed by the commission members, on the one part, and representatives of the health care institution including the Chief Investigator, on the other part, and delivered to Roszdravnadzor within a 10-day term.

FDA Inspections in 2007

Russian study centers are also inspected by FDA. The key goal of such inspections is to make sure that the data obtained in the center during the clinical trial are reliable based on available source documents. There are two types of inspections: specific trial-oriented inspections and audits aimed at specific investigators. All of the inspections carried out by FDA in Russia belong to the first type.

The date of FDA inspector's visit is agreed upon with the principal investigator in advance (as a rule, 2-3 months before the visit) and then the center obtains an official notification about the

data of the inspector's visit. During the audit FDA inspector is entitled to get access to any medical documents related to the clinical trial .

Table 7. Russian Sites inspected by FDA in 2007[1]

Institution	Address	Result
N.V. Solovyov Emergency Care Clinical Hospital (a municipal health care institution)	150003, Yaroslavl, ul. Zagorodnyi sad 11	NAI
Emergency Care City Clinical Hospital No. 1 (a municipal health care institution of the Voronezh city district)	394065, Voronezh, pr-t Patriotov, 23	NAI
City Hospital No. 15 (a public health care institution in Saint-Petersburg)	198205, Saint-Petersburg, ul. Avangardnaya 4	NAI
Mental Clinical Hospital No. 15 (a public health care institution in Moscow)	115522, Moscow, ul. Moskvorechiye 7	VAI
Moscow Research Institute of Psychiatry, Roszdrav (a federal public institution)	107076, Moscow, ul. Poteshnaya 3	VAI
Sources: FDA and Roszdravnadzor		

Conclusion

To be sure, the ban imposed by the Federal Customs Service on the export of biological samples from Russia makes all attempts to track any trends on the Russian clinical trials market in the 2nd Quarter of 2007 senseless. However, according to the available data we can assume that the demarche will not produce any effect on the favorable development of the clinical trials market in Russia in the long run, and May 29, 2007 will not become the "Black Tuesday" for the Russian clinical trials market.

Nevertheless, we can assess the situation in a greater detail only based on the results for the 3rd Quarter on the clinical trials market. The forthcoming issue of the Orange Book to be presented in the form of a report to be delivered at the Clinical Studies of Drugs, the 6th International Conference, in Moscow, on October 12, 2007.

[1] According to the FDA Office for Regulatory Affairs as of July 3, 2007 http://www.fda.gov/cder/regulatory

Appendix

Starting from this issue of the Orange Book, we are going to inform our readers about research portfolios of the leading innovative pharmaceutical companies in a great detail. sanofi-aventis (France) is the main topic of our today's issue.

Leader's Profile. sanofi-aventis

sanofi-aventis (France) was established in 2004 as a result of a merger of Sanofi Synthelabo and Aventis. At present it is the third largest pharmaceutical company in the world and ranks 74th on the list of World's 2,000 Largest Public Companies published by Forbes in 2007. The volume of the world sales of sanofi-aventis in 2006 increased by almost 4% and made up 37.92 billion USD; the market price made up 115.24 billion USD .

In 2006, sanofi-aventis raked first on the Russian pharmaceutical market and was offering over 70 drugs. The company's share in the total volume of drugs market increased by 20% as compared to 2005 and amounted to 6.58%; as for the hospital sector, such indices made up to 30% and 8% of the total volume of sales on the hospital market of Russia, respectively. According to the Pharmexpert Marketing Surveys Center, in 2006 the share of sanofi-aventis in the Additional Drug Supply Program increased by 26% as compared to 2005 and made up 5.66%. The company ranks 4th in the Additional Drug Supply Program rating in 2006.

The company conducts research activities and develops brand-new drugs in the key seven therapeutic fields: oncology, cardiovascular diseases, metabolic disorders, diseases of the central nervous system (CNS), thromboses, medical diseases and vaccine development (Sanofi-Pasteur). In 2006, the research and development budget increased by 9.5% as compared to 2005 and amounted to 5.92 billion USD (15.6% of the total volume of sales).

About 17,000 employees are employed with 28 research and development units of the company (see Table 8) situated in 9countries of the world. Senior Vice-President for Science and Medicine Marc Cluzel, who succeeded Gerard le Fur on January 1, 2007, supervises over their activities.

Table 8. sanofi-aventis R&D Centers Worldwide

Country	City
UK	Alnwick
Hungary	Budapest
Germany	Frankfurt, Kastengrund
Spain	Alcobendas, Riells
Italy	Milan
Canada	Toronto
USA	Bridgewater, Cambridge, Great Valley, Tuccon and Swiftwater
France	Bagneux, Chilly-Mazarin, Croix-de-Berny/Antony, Evry, Labege, Marcy-l'Etoile, Montpellier, Porcheville, Rueil-Malmaison, Strasbourg, Toulouse, Vitry-Alfortville
Japan	Kawagoe, Tokyo

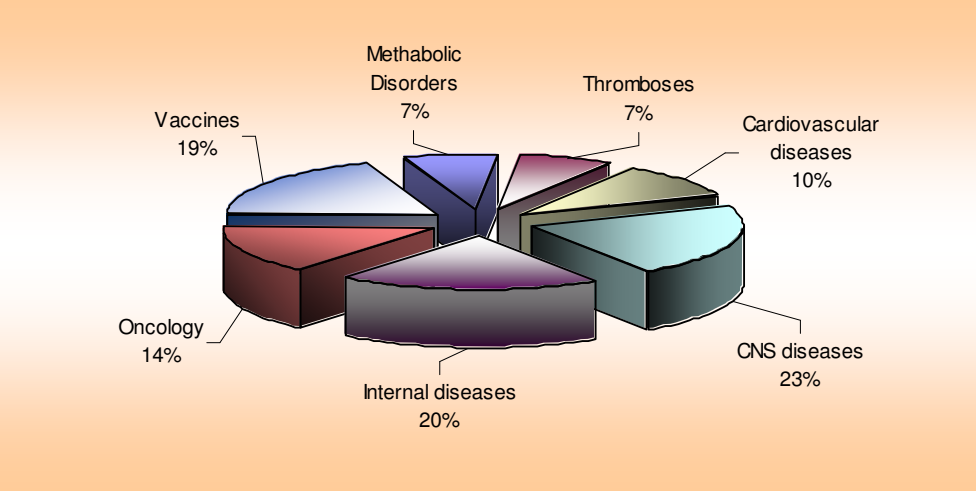
The sanofi-aventis R&D portfolio includes 125 drugs (see Table 9), 46 of them are at the final stages of clinical trials, which is one third as much as during the same period of 2005. As many as 67 new substances undergo pre-clinical and Phase I clinical trials at present. At present this is one of the largest R&D portfolios among pharmaceutical companies. Many analysts agree that it is one of the most balanced portfolios as well (see Table 9 and Figure 8).

Table 9. sanofi-aventis Pipeline (as of February 13, 2007).

Therapeutic area	Pre-clinical studies	Phase I	Phase IIa	Phase IIb	Phase III	Total
Metabolic disorders	2	1	2	4	0	**9**
Thromboses	3	1	0	3	2	**9**
Cardiovascular diseases	2	5	1	4	1	**13**
CNS diseases	8	8	1	4	6	**27**
Internal diseases	9	5	5	4	2	**25**
Oncology	7	4	1	0	6	**18**
Vaccines	7	5	2	2	8	**24**
Total	**38**	**29**	**12**	**21**	**25**	**125**

Source: sanofi-aventis

Figure 8. sanofi-aventis R&D portfolio by Therapeutic Areas



At present 15 leading drugs manufactured by sanofi-aventis provide for 67.5% of the total volume of sales. Table 10 presents the first five so called "blockbusters" made by sanofi-aventis, which are sales leaders according to the results for 2006.

Table 10. sanofi-aventis Blockbusters in Y2006

Drug	Sales worldwide in 2006, mln. USD	Patent expiration date	Ongoing clinical trials in Russia
Lovenox ®	3,255	24.12.2004[1]	5
Plavix ®	2,979	07.11.2011	4
Stilnox ®/Ambien ®	2,707	21.10.2006	0
Taxotere ®	2,341	14.05.2010	3
Eloxatin ®	2,262	09.09.2016	2

Sources: sanofi-aventis, US Patent and Trademark Office, US National Institute of Health

As you can see from the table, one of the "bestsellers" – Ambien ®, a drug for treating drug disorders – had its patent expired in late 2006. Drugs losing their patent protection are followed by a range of new developments of the company being tested in clinical trials of the last phases and being prepared for registration with the appropriate regulatory authorities of the US, Europe, Canada, Japan and Russia. Now we will describe some of the drugs that are currently tested in clinical trials conducted in Russian study sites.

Acomplia ® (rimonabant). Japan has successfully completed Phase IIb of studies and has ongoing Phase III studies where the drug is used for treating type 2 diabetes and weight loss. An application for the drug registration is expected to be filed in Japan in 2009. Two Phase III studies of the drug are also ongoing in Russia at present.

AVE2268, a sodium-dependent glucose (co-) transporter (type 2), has already been tested successfully in Phase I studies and confirmed the expediency of further studies. Phase IIb studies were initiated in July 2006, and their results are expected to be produced in late 2007.

SSR126517, a selective inhibitor of factor Xa. The Phase III CASSIOPEA study was initiated in Russia in July 2006. The drug was tested in the form of a subcutaneous solution to treat patients with symptomatic pulmonary embolism with or without symptomatic deep vein thrombosis.

SR123781, a thrombin and factor Xa inhibitor to prevent severe complications on the part of the cardiovascular system at the acute coronary syndrome. Two Phase II trials of the drug are ongoing in Russia now: DRIVE and SHINE. The patient enrolment stage is over and trial results are expected in the second part of 2007.

AVE5026, a low-molecular heparin, thrombin and factor Xa inhibitor. The enrollment of patients to the Phase III trial in Russia is completed. The results are expected in the second half of 2007.

Otamixaban (XRP0673), a synthetic selective inhibitor of factor Xa. Phase II trial of the drug was initiated in Russia last October and the patient enrolment process is going on.

Saredutant (SR48968), a NK2 receptor antagonist. At present four Phase III clinical trials are ongoing in the world. The substance is aimed at treating major depressive disorder and general anxiety disorder. One of them (for patients aged over 60) was initiated in Russia in December of 2006. The patient enrolment process is currently going on.

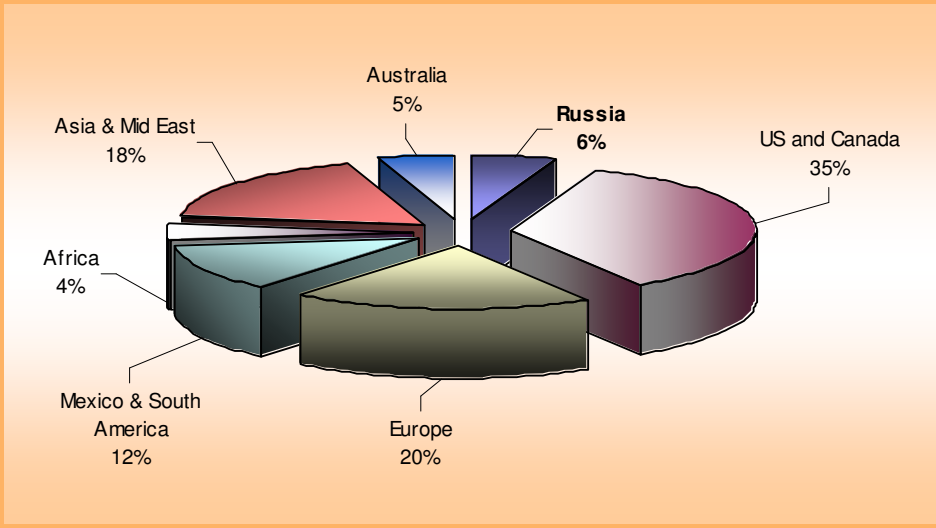
sanofi-aventis currently carries out over 200 clinical trials at the five continents. More than a half of them (55%) are carried out in the USA, Canada and Europe. The US National Institute of Health registered 23 clinical trials carried out on the basis of Russian sites.

Table 11. Clinical Trials conducted by sanofi-aventis Worldwide (as of June 13, 2007)

Region	Not yet recruiting	Recruiting	No longer recruiting	Completed	**Total**
US & Canada	6	165	123	125	**419**
Europe	7	100	61	64	**232**
Russia	0	23	14	7	**44**
Asia and Middle East	0	76	54	37	**167**
Africa	0	18	14	11	**43**
Mexico and South America	0	50	32	21	**103**
Australia	0	21	9	13	**43**
Total	**13**	**243**	**198**	**225**	**679**

Source: US National Institute of Health (www.clinicaltrials.gov)

Figure 9. Clinical Trials conducted by sanofi-aventis in 2007 by Region.



In addition to international multi-center clinical studies conducted on the initiative of the Marketing Department of sanofi-aventis, post-marketing studies – Phase IV clinical studies and multi-center registers – are also conducted in Russia. Marina Atarshchikova, the Medical Director of the company's branch in Russia, was awarded with the Platinum Ounce in the Manager of the Year nomination this year. Tatiana Zhiganova heads the Department of Clinical Trials.