

Clinical Trials in Russia
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Executive Summary

The Federal Service on Surveillance in Healthcare and Social Development of the Russian Federation (alias RosZdravNadzor, RZN) approved 174 new clinical trials during Q2 2008, a 53% increase over the corresponding period of last year. The main contribution is still made by multinational multi-center clinical trials, their number increased by 67% over Q2 2007 and stood at 107 new studies in Q2 2008.

Clinical trials in Russia in Q2 2008 were sponsored by 42 companies from 21 countries. The maximum number of trials (58) was initiated by Russian sponsors, American sponsors (37 trials) took the runner-up place, they are followed by the German (23) and UK (16) companies, and the top six is concluded by French sponsors (10 new trials).

Eight new Phase I clinical trials were launched in the second quarter of 2008; which is one trial up from the corresponding quarter of last year. The number of the Phase II trials increased substantially from 25 trials in the second quarter of 2007 to 40 in the second quarter 2008. The number of Phase III trials demonstrated the biggest increase, the number almost doubled over last year, up from 40 to 83 studies. The number of Phase IV trials slightly decreased from 19 in Q2 2007 to 15 in Q2 2008.

Twelve thousand patients are planned to be enrolled in the Phase II-IV trials launched in the second quarter of 2008, 24% up on last year number of 9,700 patients. It's worth mentioning that the number of Phase III subjects rose by 63% from last year's figure.

The French sanofi-aventis sponsoring 12 new studies returned to the top of the pile in the second quarter of 2008. The German Boehringer Ingelheim, sponsoring eight new trials in Q2 2008, took the runner-up place, it is followed by the American Merck & Co. with eight trials but fewer patient number. The Canadian Patheon and American Johnson & Johnson ranked number four and five, respectively.

The Russian Valenta, sponsoring four new clinical trials enrolling 200 patients in six sites, ranked number one among domestic pharmaceutical manufacturers by the number of new studies in Q2 2008. Central European Pharmaceutical Company with three new trials took the runner-up place. It is followed by Schelkovo Vitamin Plant, Sintez and NIOPIK, all three having the same number of new studies but with different number of patients.

About two-thirds of the new studies in Q2 2008, or 67%, were conducted in the following six therapeutic areas: Neurology; Oncology; Gastrointestinal and Infectious diseases; Endocrine and metabolic diseases and Cardiology.

According to the RZN data, as of the April 3 2008 there were 877 hospitals entitled to conduct clinical trials in Russia. Twenty three new sites were accredited since last period.

According to the FDA data, as of July 1 2008, there were three FDA inspections conducted in the Russian investigative sites during 2008: two inspections were conducted in St.Petersburg, and one inspection was conducted in Yaroslavl.

Clinical Trials by Type and Manufacturing Country

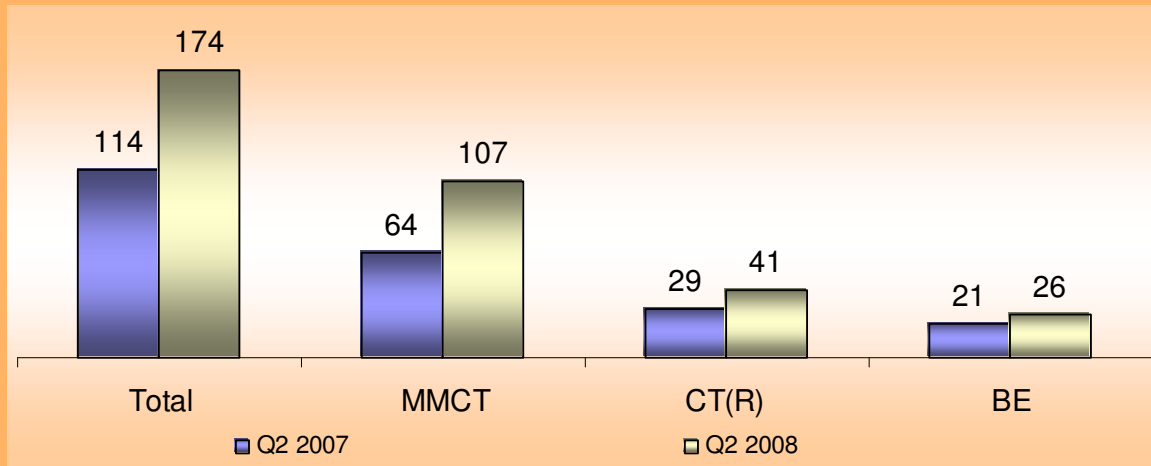
The RZN approved 174 new clinical trials of all types including local and bioequivalence studies during the second quarter 2008; demonstrating a 53% increase over the corresponding period of last year. As shown in the Figure 1, the main contribution into the total number of studies is still made by multinational multi-center clinical trials (presented as MMCT in Figure 1), the number of these studies increased by 67% over Q2 2007 and stood at 107 new studies in Q2 2008.

The number of the local clinical trials conducted in Russia by domestic and foreign sponsors (the CT(R) bar in the Figure 1) is up from 29 to 41 clinical trials demonstrating a 41% increment over the same point in 2007.

The number of bioequivalence studies (BE in Figure 1) in the second quarter of 2008 stood at 26 new trials, a 24% increase from last year's figure.

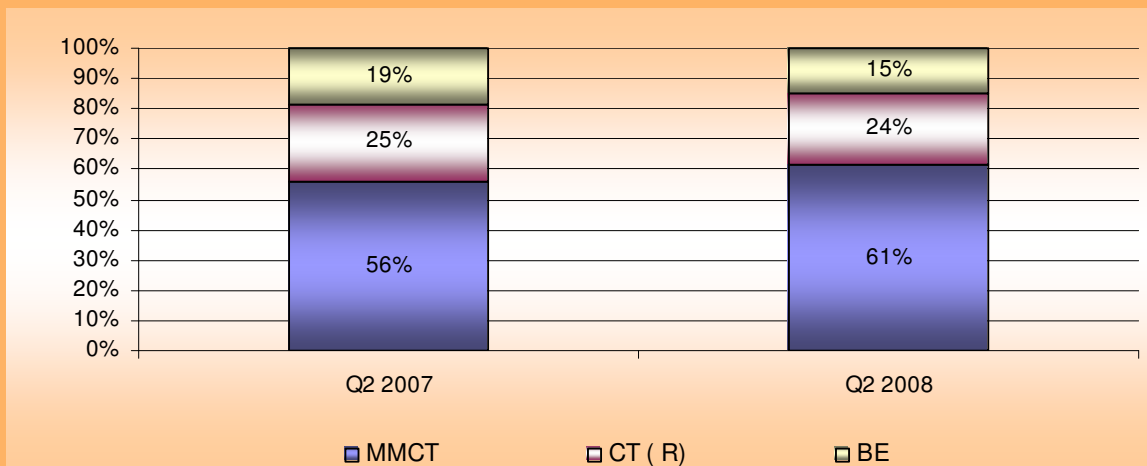


Figure 1. Clinical trials approved by RZN in Q2 2008



The proportions between different study types (multinational multi-center clinical trials, local studies and bioequivalence trials) did not change significantly over the same point in 2007. The share of multinational multi-center clinical trials rose by 5% from last year's figure and stood at 61% of the total number of clinical trials approved by RZN in the second quarter of 2008. The shares of the local trials and bioequivalence studies in Q2 2008 stood at 24% and 15% of the total number of studies, respectively, while they accounted to 25% and 19% in Q2 2007.

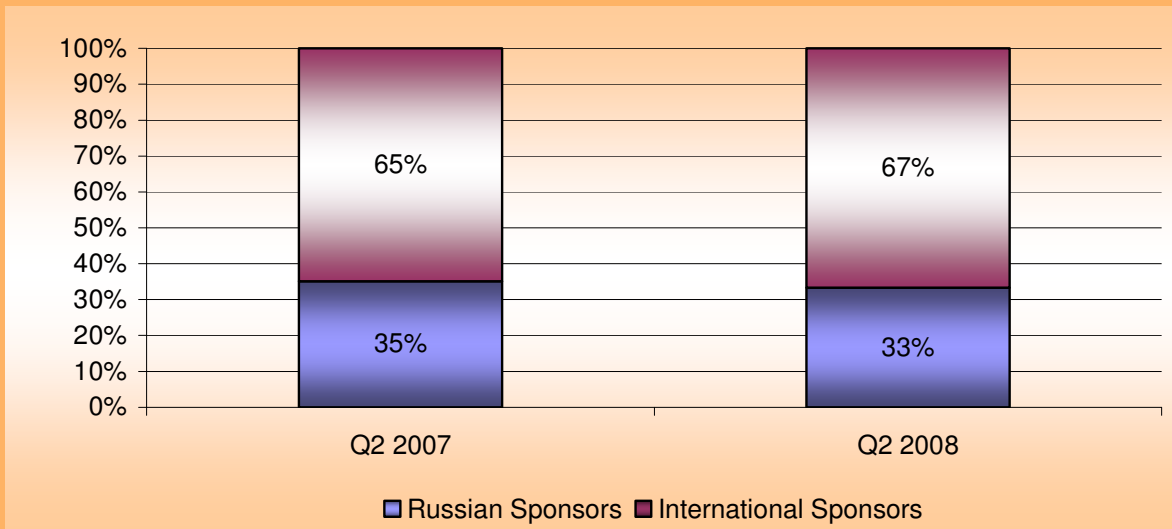
Figure 2. Clinical trials by type in Q2 2008



The lion's share of clinical trials in Russia is still being sponsored by foreign companies. Their share slightly increased from 65% to 67%, and the number is up from 74 in Q2 2007 to 116 new trials in Q2 2008. Whilst the number of clinical trials initiated by the Russian sponsors, including bioequivalence studies, rose from 40 to 58, their share decreased from 35% to 33%, since the number of international studies grew faster.

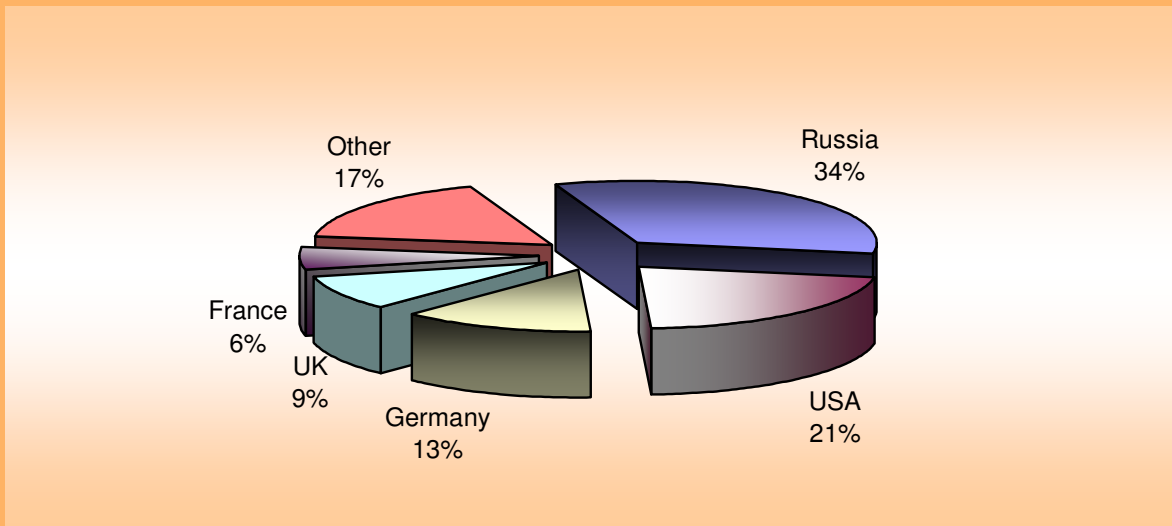


Figure 3. Russian and International sponsors in Q2 2008



Clinical trials in Russia in Q2 2008 were sponsored by 42 companies from 21 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 (58) was initiated by Russian sponsors, American sponsors with 37 studies took the runner-up place, they are followed by the German sponsors with 23 trials, 16 trials were initiated by the UK companies, and the top five is concluded by French sponsors with 10 new studies in Q2 2008.

Figure 4. Countries presented on the Russian clinical trials market in Q2 2008



Australia, Austria, Belgium, Israel, Spain, Italy, Canada, the Netherlands, Norway, Portugal, Switzerland, Sweden, Japan, as well as Singapore and Puerto-Rico are represented among others.

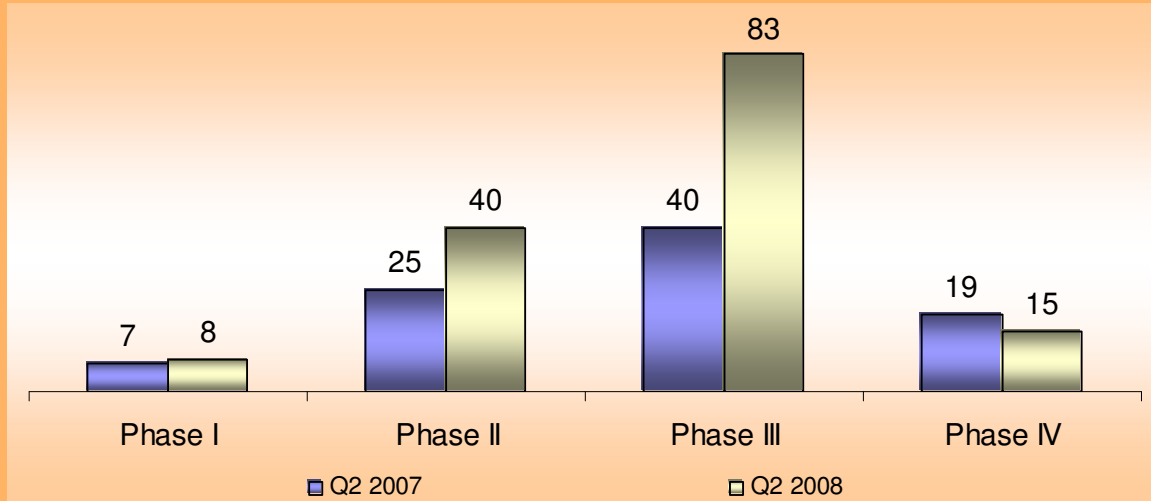
Clinical trials by Phase

Eight new Phase I clinical trials were launched in the second quarter of 2008; which is one trial up from the corresponding quarter of last year. The number of the Phase II trials increased substantially from 25 trials in the second quarter of 2007 to 40 in the second quarter 2008. The



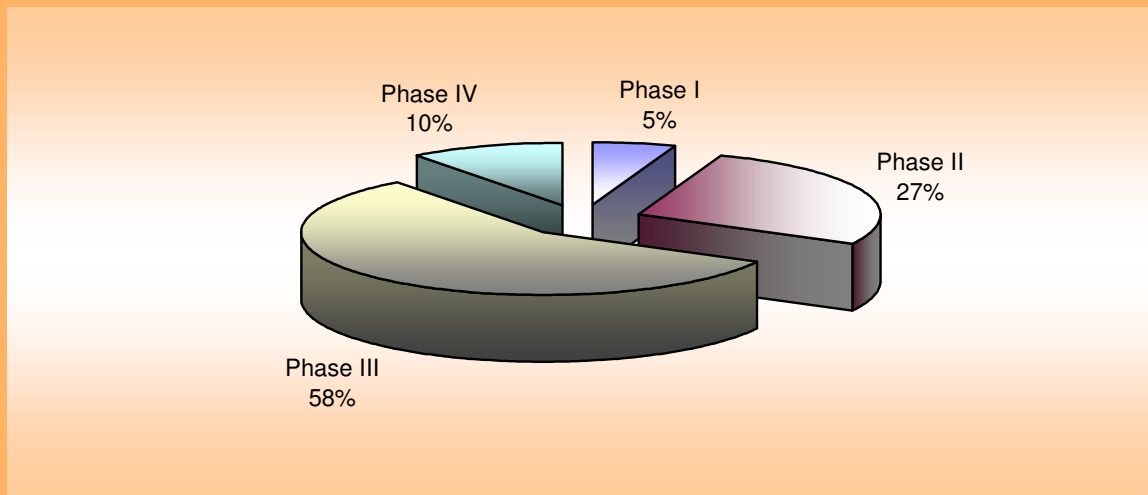
number of Phase III trials demonstrated the biggest increase, the number almost doubled over last year, up from 40 to 83 studies. The number of Phase IV trials slightly decreased from 19 in Q2 2007 to 15 in Q2 2008.

Figure 5. Clinical trials in Russia in Q2 2008 by phase



As shown in Figure 6, the share of Phase III trials in Q2 2008 stood at 58% of the total number of studies, the share of Phase II trials accounted at 27%, Phase IV trials stood at 10%, and the share of Phase I studies amounted to five per cent.

Figure 6. The proportions between study phases in Russia in Q2 2008



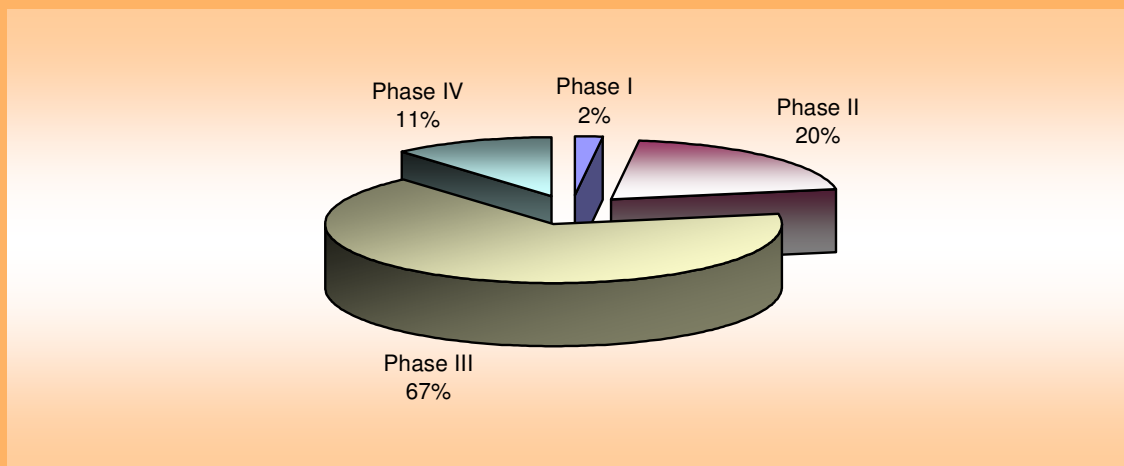
Twelve thousand patients are planned to be enrolled in the Phase II-IV trials launched in the second quarter of 2008, 24% up on last year number of 9,700 patients. It's worth mentioning that the number of Phase III subjects rose by 63% from last year's figure.

Two hundred and twenty four subjects will be recruited in Phase I trials; 2, 441 patients – in Phase II trials; 7, 980 subjects – in Phase III studies and 1,355 patients will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is three, the maximum number is 600.

The proportions of the number of patients between different Phases is shown on the Figure 7.

Figure 7. The number of patients in Q2 2008 by study phase



The duration of the shortest trial is three month; of the longest one – seven years.

Rating of international sponsors

The French sanofi-aventis sponsoring 12 new studies returned to the top of the pile in the second quarter of 2008. The German Boehringer Ingelheim, sponsoring eight new trials in Q2 2008, took the runner-up place, it is followed by the American Merck & Co. with eight trials but fewer patient number.

The Canadian Patheon and American Johnson & Johnson ranked number four and five, respectively.

Top five international sponsors by the number of new studies in Q2 2008 are presented in Table 1.

Table 1. Top-5 international study sponsors in Q2 2008

No	Sponsor	No. of trials	No. of patients	No. of sites
1	sanofi-aventis	12	1252	127
2	Boehringer Ingelheim	8	766	66
3	Merck & Co.	8	464	33
4	Patheon	6	805	71
5	Johnson & Johnson	6	614	77

Rating of Russian sponsors

The company OAO Valenta Pharmaceutica, sponsoring four new clinical trials enrolling 200 patients in six sites, ranked number one among domestic pharmaceutical manufacturers by the number of new studies in the second quarter 2008.

ZAO Central European Pharmaceutical Company with three new trials and 300 subjects in five sites, took the runner-up place. It is followed by OAO Schelkovo Vitamin Plant, OAO Sintez and FGUP NIOPIK, all having the same number of new studies but with different number of patients.

Table 2. Top-5 Russian study sponsors in Q2 2008

No	Sponsor	No. of trials	No. of patients	No. of sites
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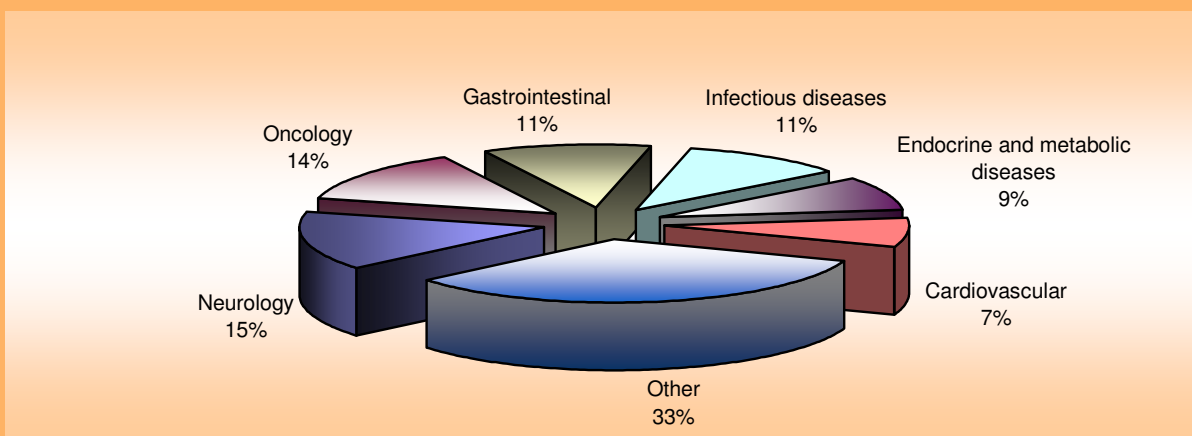


1	Valenta Pharmaceutica	4	220	6
2	Central European Pharmaceutical Company	3	300	5
3	Schelkovo Vitamin Plant	2	150	2
4	Sintez	2	110	2
5	NIOPIK	2	75	6

Therapeutic areas of clinical trials in Russia in Q2 2008

About two-thirds of the new studies in Q2 2008, or 67%, were conducted in six therapeutic areas. The maximum number of trials (26) were initiated in Neurology; 24 clinical trials in Oncology; 19 studies were targeted at Gastrointestinal and Infectious diseases; 15 studies in Endocrine and metabolic diseases and 13 Cardiovascular studies were initiated in Q2 2008. The proportions between different therapeutic areas are shown in Figure 8.

Figure 8. Clinical trials in Russia in Q2 2008 by therapeutic area



Clinical trials results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 27¹ new drugs during Q2 2008; 3 of them are new molecular entities; others had new dosages, manufacturers or indications of the already marketed drugs. The Table 3 represents those which were, or are being tested in clinical trials in Russia.

Table 3. New Drugs approved by FDA in Q2 2008 and tested in Russian sites

Approval date	Drug	Manufacturer
04/22/2008	Cimzia (Certolizumab Pegol)	UCB Inc.
04/25/2008	Zidovudine (Zidovudine)	Hetero Drugs Ltd
05/20/2008	Entereg (Alvimopan)	Adolor
05/20/2008	Venlafaxine (Venlafaxine)	Osmotica Pharm
05/29/2008	Mesalamine (Mesalamine)	Procter and Gamble
06/13/2008	Requip (Ropinirole)	GlaxoSmithKline
06/13/2008	Cymbalta (Duloxetine Hydrochloride)	Eli Lilly

¹ CDER FDA <http://www.fda.gov/cder>



06/13/2008	Pegintron/Rebetol	Schering
06/19/2008	Lamivudine	Cipla Limited
06/23/2008	Aptivus	Boehringer Ingelheim
Source: CDER FDA http://www.fda.gov/cder		

During the period from the April 1 to June 30 2008 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) reviewed 27¹ applications to market drugs in the EU. Negative opinion was adopted for three drugs. Twelve of the drugs which received positive opinions were (or are being) tested in clinical trials in Russia (see Table 4).

Table 4. New Drugs approved by EMA in Q2 2008 and tested in Russian sites

Approval date	Drug	Manufacturer
24/04/2008	Janumet/Velmetia/Efficib	Merck Sharp & Dohme Ltd
24/04/2008	Abilify (aripiprazole)	Otsuka Pharmaceutical
24/04/2008	Apidra (insulin glulisine)	Sanofi-Aventis
24/04/2008	Mimpara (cinacalcet)	Amgen
24/04/2008	Parareg (cinacalcet)	Amgen
24/04/2008	Reyataz (atazanavir sulphate)	Bristol Myers Squibb
30/05/2008	Doribax (doripenem)	Janssen-Cilag
30/05/2008	Erbitux (cetuximab)	Merck KGaA
30/05/2008	Gardasil	Sanofi-Aventis
26/06/2008	Intelence (etravirine)	Janssen-Cilag
26/06/2008	Vimpat (lacosamide)	UCB Pharma
26/06/2008	Cymbalta (Duloxetine Hydrochloride)	Eli Lilly
Source: CHMP EMA http://www.emea.europa.eu/index/indexh1.htm		

New investigative sites

According to the RZN data, as of the April 3 2008 there were 877 hospitals entitled to conduct clinical trials in Russia. Twenty three new sites were accredited since last period.

The new city appeared on the Russian clinical trial map, the first investigative site was accredited by RZN in Birobidjan, the capital of the Jewish Autonomous Republic, located in Russia's Far East. Four new sites were accredited in Moscow, two in both St.Petersburg and Nizhny Novgorod. The Top 10 cities by the number of sites are shown in Table 5.

Table 5. Top 10 Russian cities by the number of sites

No	City	No. of sites
1	Moscow	196
2	Saint-Petersburg	127
3	Novosibirsk & region	35
4	Kazan	25
5	Nizhny Novgorod	24
6	Yaroslavl	21
7	Ekaterinburg	20

¹ CHMP EMA <http://www.emea.europa.eu/index/indexh1.htm>



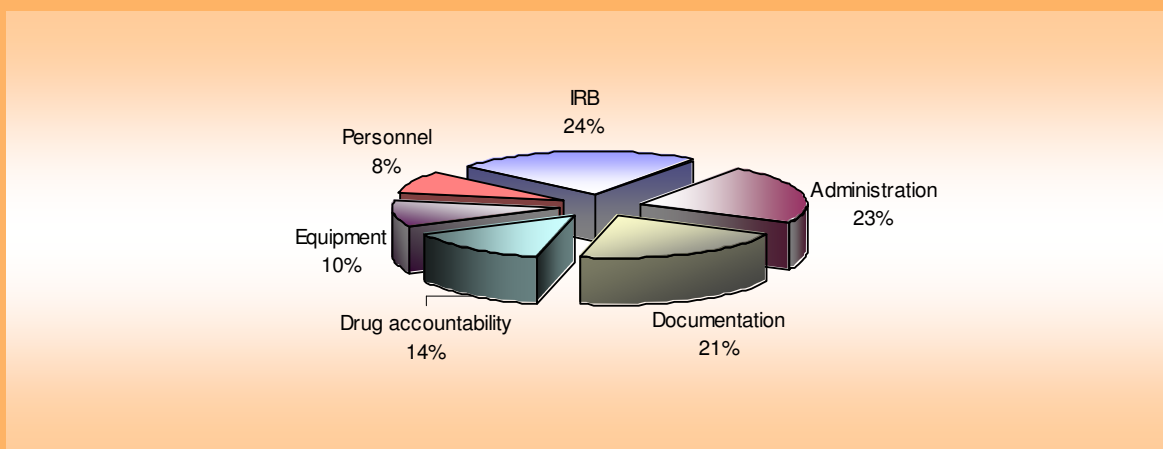
8	Rostov-on-Don	16
9	Perm	15
10	Saratov and Smolensk	no 14
Source: RZN		

RZN inspections

As of July 15 2008, there's no any information on the official RZN Website on the inspections made by RZN in Q2 2008.

Forty eight investigative sites in 30 Russian cities were inspected by RZN during 2007. The nature of observations found during the inspections is shown in Figure 9.

Figure 9. Deficiencies found during RZN inspections in Russia in 2007



FDA inspections

According to the FDA data, as of July 1 2008, there were three FDA inspections conducted in the Russian investigative sites during 2008: two inspections were conducted in St.Petersburg, and one inspection was conducted in Yaroslavl. No objectionable conditions or practices were found during two inspections (NAI - No Action Indicated), one inspection resulted in VAI (Voluntary Action Indicated), i.e. objectionable conditions were found but the problems did not justify further regulatory action, and any corrective action was left to the investigator to take voluntarily. The objections related to inadequate drug accountability and failure to adhere to protocol.



Appendix

Leader's Profile. Bristol-Myers Squibb

Bristol-Myers Squibb (BMS) was founded by William McLaren Bristol and John Ripley Myers in 1887 in Clinton, New York.

Today BMS is one of the largest pharmaceutical companies in the world, ranking number 257 in the list of World's 2000 largest companies published by the Forbes magazine in February 2008. According to the magazine the BMS current market value is \$44.75 billion¹. According to the recent corporate annual report² sales in 2007 rose by 12% over 2006 figure and accounted to \$19.35 billion.

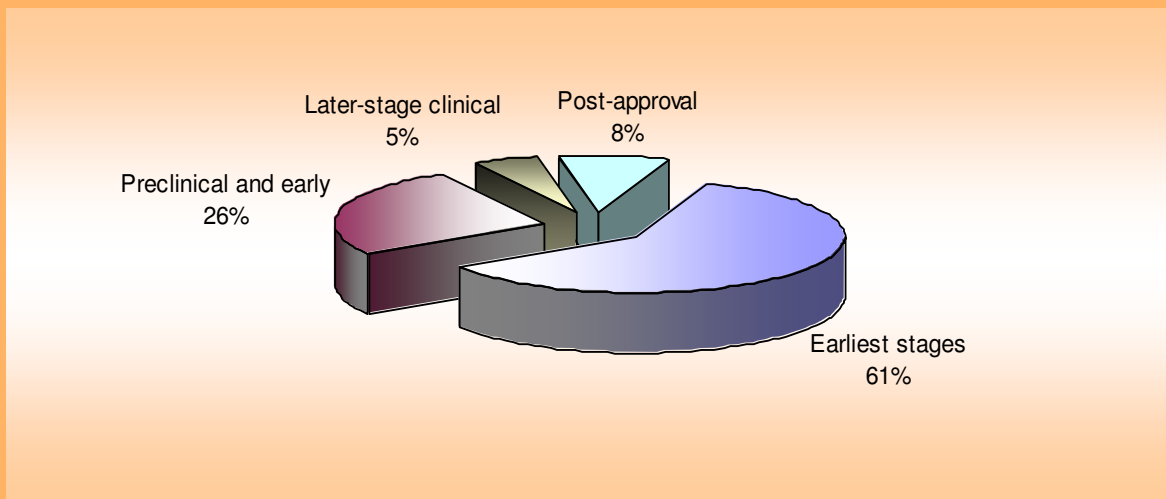
The BMS Research and Development (R&D) organization is one of the world's most innovative, productive, and respected scientific research organizations working to discover and develop treatments specifically for: cancer, atherosclerosis/thrombosis, diabetes, obesity, psychiatric disorders, Alzheimer's disease, hepatitis, HIV/AIDS, rheumatoid arthritis and solid organ transplant rejection.

The Company's investment in research and development was \$3,282 million in 2007, an increase of 10% over 2006.

As of the 28th of February 2008 the BMS pipeline comprised of 118 new drugs.

According to the 2007 corporate annual report the pipeline is distributed between different development stages as follows: 71 compounds are at the earliest stages of research; 31 drugs are in preclinical or early clinical development; six compounds are in later-stage clinical development or have been submitted to regulatory agencies for approval and 10 approved medicines are undergoing continued clinical development for additional indications and formulations.

Figure 10. Bristol-Myers Squibb pipeline by development phase



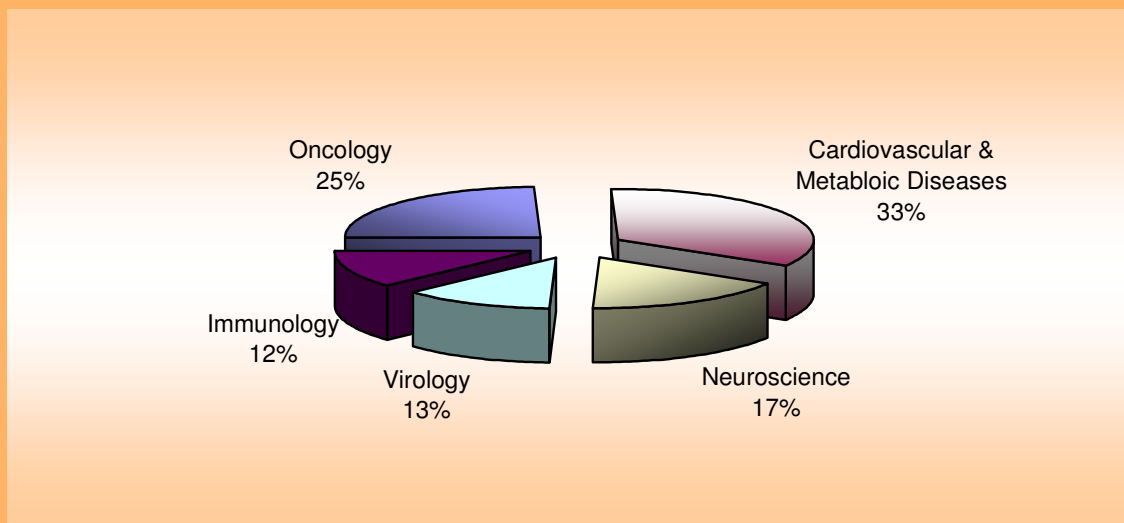
Twenty nine compounds are being developed for cancer; 15 – for treating atherosclerosis/thrombosis; 11 – for diabetes; 14 - for obesity; 16 are targeted for psychiatric disorders treatment; 4 – for Alzheimer's disease; 9 - for hepatitis; 6 - HIV/AIDS; 3 - for rheumatoid arthritis and one compound – for resolving the problem of solid organ transplant rejection. Eleven more drugs are developed in Immunology.

¹ Forbes. The World's 2,000 Largest Public Companies

² <http://thomson.mobular.net/thomson/7/2578/3053/>



Figure 11. BMS pipeline by Therapeutic Area



Today BMS 15 leading drugs provide two-thirds of the total sales volume. The Table 6 shows the top five BMS blockbusters according to the annual 2007 results.

Table 6. Top 5 BMS blockbusters in 2007

Drug	Y2007 Sales in billion US Dollars	No. of open trials in Russia	Area
Plavix	4,755	12	Cardiovascular
Abilify	1,660	6	Neuroscience
Avapro/Avalide	1,204	8	Cardiovascular
Sustiva (Franchise)	956	6	Virology
Erbix	692	4	Oncology

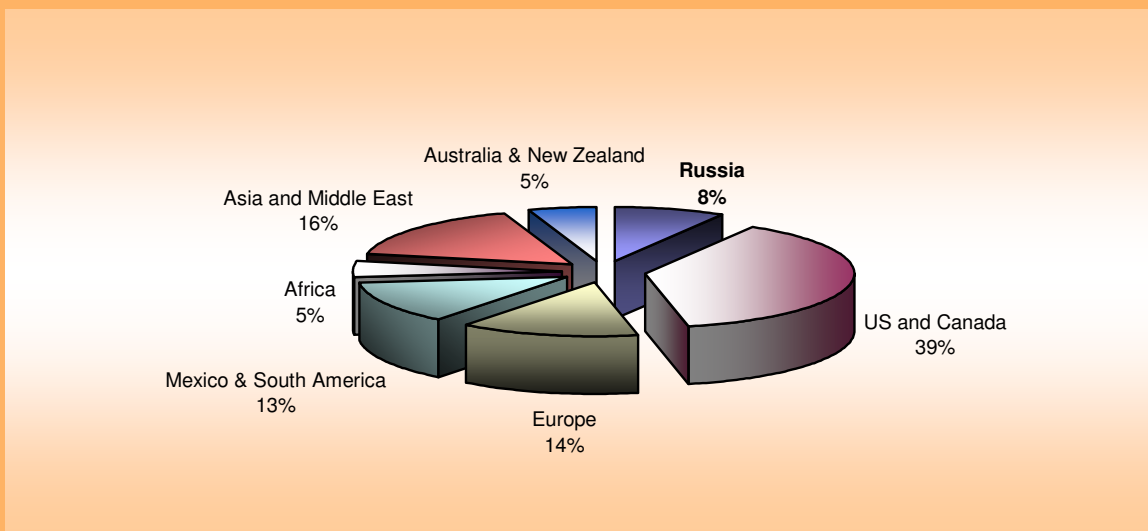
Source: BMS, US National Institute of Health

According to Clinical Trials.gov as of July 15 2008 the BMS conducted 212 clinical trials¹ worldwide; the lion's share of trials was performed in North America and Europe. According to the data provided by BMS Russia, 44 active studies are conducted by BMS in Russia today.

¹ Only those clinical trials were taken into account where enrollment process was still going or hadn't started yet.



Figure 12. Clinical trials conducted by BMS worldwide¹



According to the RZN, during the period from January 2004 to July 2008, 49 clinical trials were initiated by Bristol-Myers Squibb in Russia.

¹ ClinicalTrials.gov as of 3 April 2008. Open studies only