Clinical Trials in Russia
Orange Paper
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11, 4-Magistralnaya Ul., 123007 Moscow, Russia

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Contents

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Executive Summary

The Federal Service on Surveillance in Healthcare and Social Development of the Russian Federation (alias RosZdravNadzor, RZN) approved 170 new clinical trials during Q3 2008, a 20% increase over the corresponding period of last year. The main contribution (58%) is made by multinational multi-center clinical trials, their number increased by 8% over Q3 2007 and stood at 98 new studies in Q3 2008.

Clinical trials in Russia in Q3 2008 were sponsored by manufacturers from 39 countries. The maximum number of trials (58) was initiated by Russian sponsors, American sponsors (38 trials) took the runner-up place, they are followed by the German (14) and Swiss (12) companies, and the top six is concluded by the UK sponsors with 8 new trials.

Eight new Phase I clinical trials were launched in the third quarter of 2008; which is the same as in the corresponding quarter of last year. The number of the Phase II trials slightly decreased from 44 trials in the third quarter of 2007 to 39 in the third quarter of 2008. The number of Phase III trials demonstrated the biggest increase, 62% up over last year, from 58 to 94 studies. The number of Phase IV trials slightly increased from 9 in Q3 2007 to 13 in Q3 2008.

Twenty three thousand patients are planned to be enrolled in the Phase II-IV trials instigated in the third quarter of 2008, 63% up on last year number.

The worldwide pharmaceutical giant *Pfizer* sponsoring seven new studies was on the top of the pile in the third quarter of 2008. The French sanofi-aventis instigating five new trials in Q3 2008 took the runner-up place, it is followed by the Swiss *Roche*, and two Americans – *Eisai* and *Merck & Co.* with the same number of trials but fewer patients/sites.

The Russian *Biocad*, sponsoring seven new clinical trials ranked number one among domestic pharmaceutical manufacturers by the number of new studies in Q3 2008. The top five débutant company *Firn M* with four new trials took the runner-up place. It is followed by *Valenta, NIOPIK* and *Russian Cardio Complex (RKNPK)*.

Almost three-fourth of the new studies in Q3 2008, or 73%, were instigated in the following six therapeutic areas: Oncology (26); Neurology (24); Cardiovascular (20); Blood diseases (19); Endocrine and metabolic diseases (13) and Infectious diseases (12).

According to the RZN data, as of 10 September 2008, there were 931 hospitals entitled to conduct clinical trials in Russia. Fifty six new sites were designated by the RZN since last period.

According to the FDA data, as of 30 September 2008, four new FDA inspections were conducted in the Russian investigative sites since our last review: three inspections were conducted in Moscow, and one inspection was conducted in St. Petersburg.

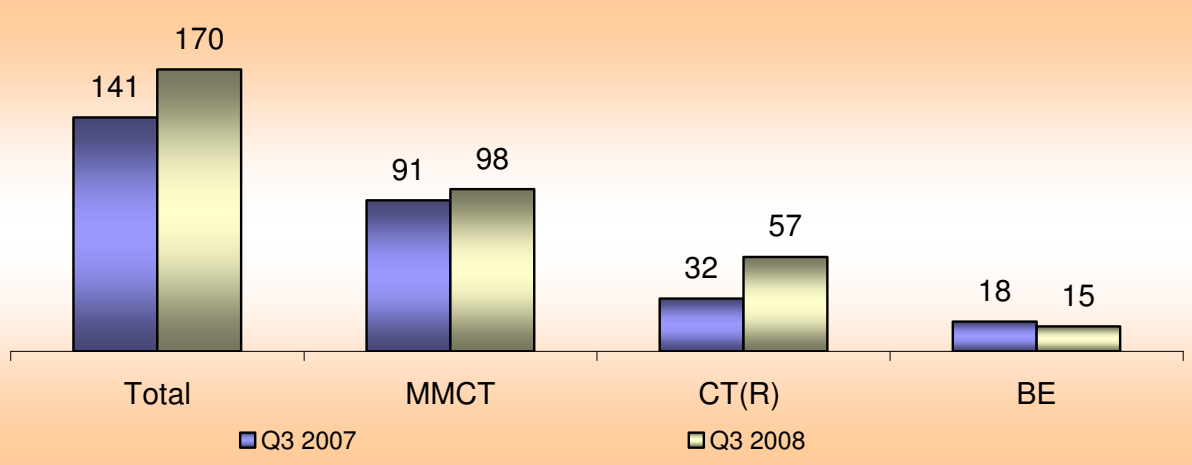
Clinical Trials by Type and Manufacturing Country

The RZN approved 170 new clinical trials of all types including local and bioequivalence studies during the third quarter 2008; demonstrating a 20% 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 8% over Q3 2007 and stood at 98 new studies in Q3 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 32 to 57 clinical trials demonstrating a notable 80% increment over the same point in 2007.

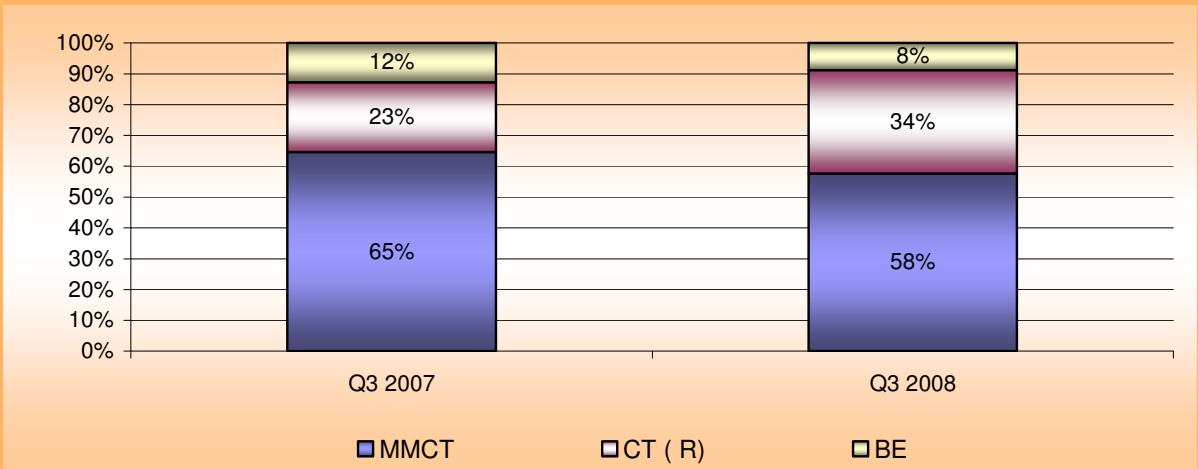
The number of bioequivalence studies (BE in Figure 1) in the third quarter of 2008 stood at 15 new trials, a slight increase from last year's figure.

Figure 1. Clinical trials approved by RZN in Q3 2008



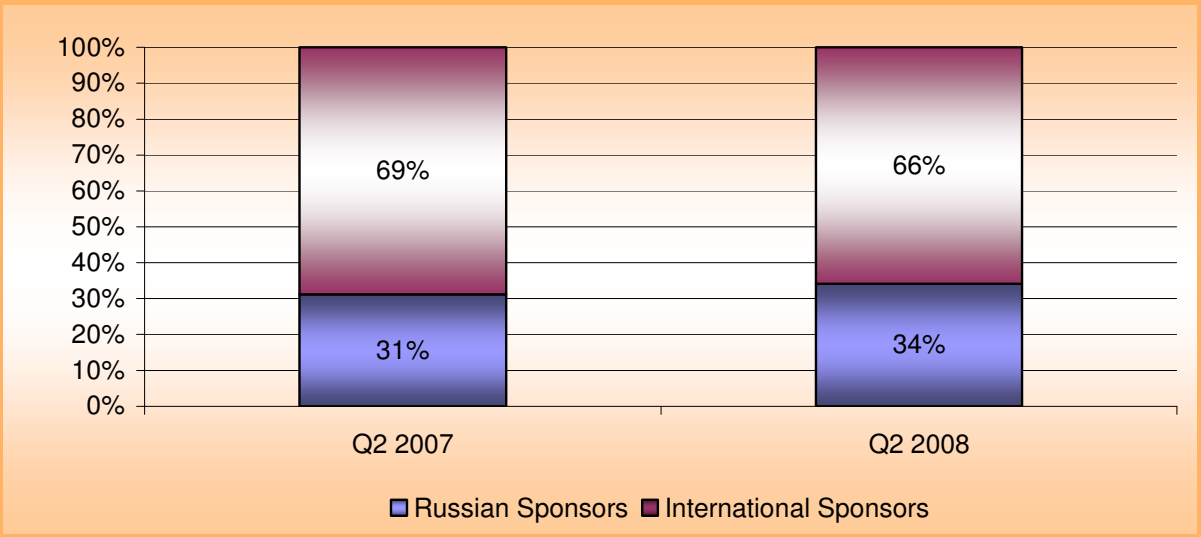
The proportions between different study types (multinational multi-center clinical trials, local studies and bioequivalence trials) did not change significantly over the same point in 2007. The share of multinational multi-center clinical trials slightly decreased from last year's figure and stood at 58% of the total number of clinical trials approved by RZN in the third quarter of 2008. The shares of the local trials and bioequivalence studies in Q3 2008 stood at 34% and 8% of the total number of studies, respectively, while they accounted to 23% and 12% in Q3 2007.

Figure 2. Clinical trials by type in Q3 2008



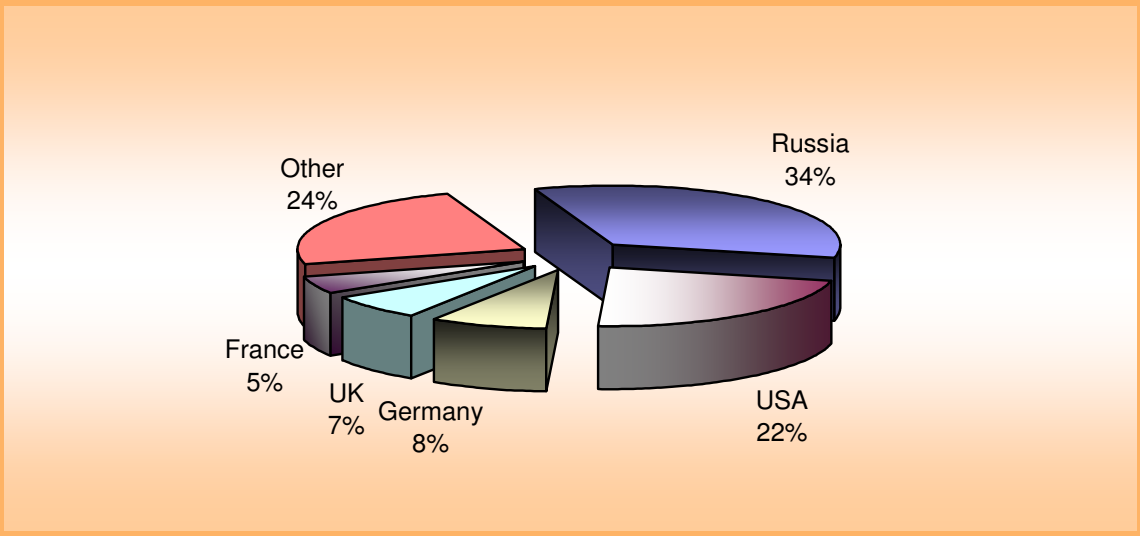
The lion's share of clinical trials in Russia is still being sponsored by foreign companies. Whilst their share slightly decreased from 69% to 66%, their number is up from 94 in Q3 2007 to 112 new studies in Q3 2008, since the number of local studies grew faster during the period. The number of clinical trials initiated by the Russian sponsors, including bioequivalence studies, rose from 44 to 58, their share also increased from 31% to 34%.

Figure 3. Russian and International sponsors in Q3 2008



Clinical trials in Russia in Q3 2008 were sponsored by companies from 39 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 38 studies took the runner-up place, they are followed by the German sponsors with 14 trials, 12 new trials were instigated by the Swiss companies, and the top five is concluded by the UK sponsors with 8 new studies in Q3 2008.

Figure 4. Countries presented on the Russian clinical trials market in Q3 2008



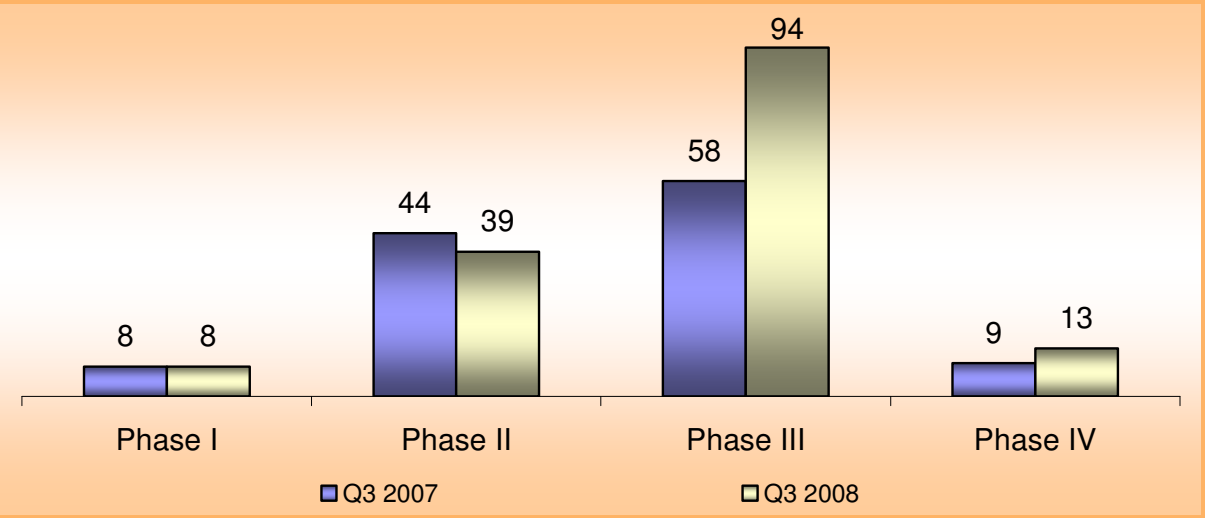
Austria, Belgium, Israel, Spain, Italy, Canada, the Netherlands, Norway, Pakistan, Portugal, Sweden, Japan, as well as Singapore and Puerto-Rico are represented among others.

Clinical trials by Phase

Eight new Phase I clinical trials were launched in the third quarter of 2008; the same as in the corresponding quarter of last year. The number of the Phase II trials slightly decreased from 44 trials in the third quarter of 2007 to 39 in the third quarter 2008. The number of Phase III trials

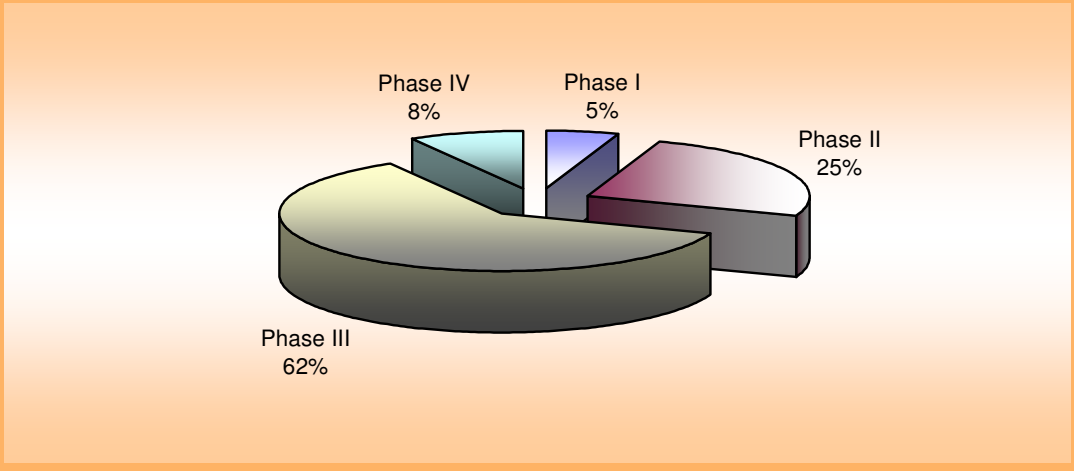
demonstrated the substantial 62% increase over last year number, up from 58 to 94 studies. The number of Phase IV trials slightly increased from 9 in Q3 2007 to 13 in Q3 2008.

Figure 5. Clinical trials in Russia in Q3 2008 by phase



As shown in Figure 6, the share of Phase III trials in Q3 2008 stood at 62% of the total number of studies, the share of Phase II trials accounted at 25%, Phase IV trials stood at 8%, and the share of Phase I studies amounted to five per cent.

Figure 6. The proportions between study phases in Russia in Q3 2008



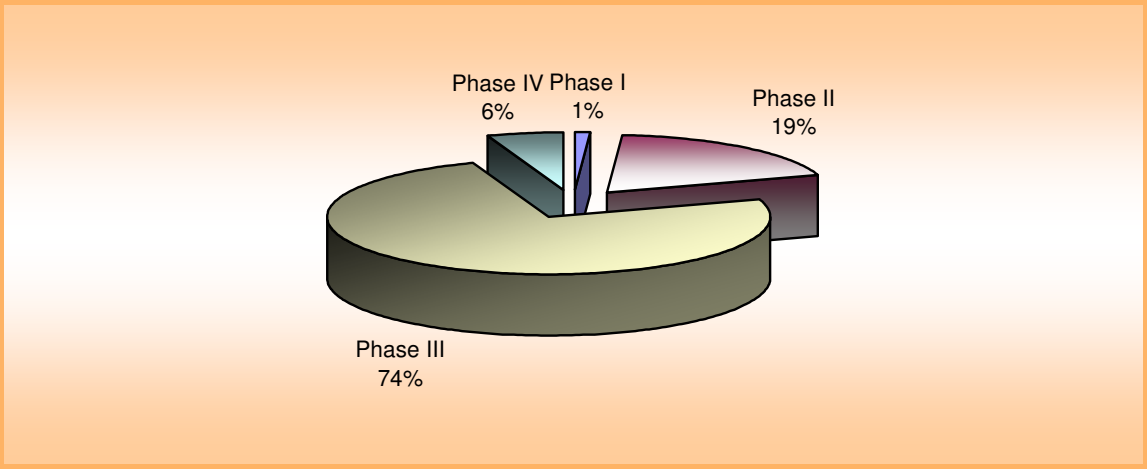
The number of patients which are planned to be enrolled in the Phase II-IV trials launched in the third quarter of 2008 stood at 23,450 patients, a substantial 63% up on last year number. It's worth mentioning that the number of Phase III subjects rose even more, by 77% from last year's figure.

Two hundred and thirty four subjects will be recruited in Phase I trials; 4, 412 patients – in Phase II trials; 17,288 subjects – in Phase III studies and 1,312 patients will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is ten, the maximum number is 800.

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

Figure 7. The number of patients in Q3 2008 by study phase



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

Rating of international sponsors

The American pharmaceutical goliath *Pfizer* sponsoring seven new studies is on the top of the heap in the third quarter of 2008. The French *sanofi-aventis* with five new trials in Q3 2008, took the runner-up place, it is followed by Swiss *Roche* and two American pharmaceutical manufacturers – *Eisai* and *Merck & Co.* with eight trials but fewer patient number.

Top five international sponsors by the number of new studies in Q3 2008 are presented in Table 1.

Table 1. Top-5 international study sponsors in Q3 2008

№	Sponsor	No. of trials	No. of patients	No. of sites
1	Pfizer	7	510	28
2	sanofi-aventis	5	1,244	52
3	Roche	5	684	64
4	Eisai	5	658	61
5	Merck & Co.	5	264	16

Rating of Russian sponsors

The Russian company ZAO *Biocad* sponsoring seven new clinical trials enrolling 420 patients in 57 sites, ranked number one among domestic pharmaceutical manufacturers by the number of new studies in the third quarter 2008.

ZAO *Firn M* with four new trials and 640 subjects in 22 sites, took the runner-up place. It is followed by OAO *Valenta Pharmaceutica*, FGUP *NIOPIK* and FGU *Russian Cardiologic Center*.

Table 2. Top-5 Russian study sponsors in Q3 2008

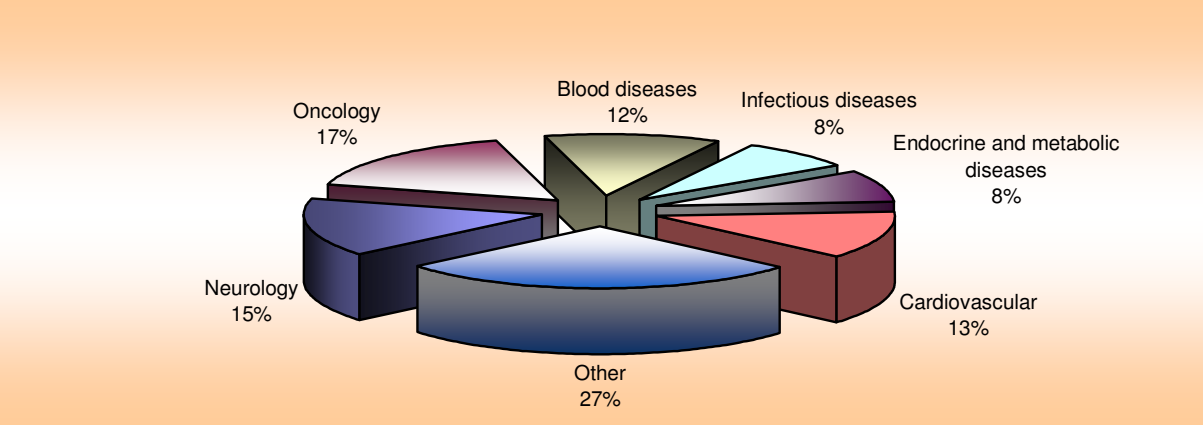
№	Sponsor	No. of trials	No. of patients	No. of sites
1	Biocad	7	420	57
2	Firn M	4	640	22

3	Valenta	4	312	8
4	NIOPIK	4	140	10
5	Russian Cardiologic Center	3	340	3

Therapeutic areas of clinical trials in Russia in Q3 2008

About three-fourth of the new studies in Q3 2008, or 73%, were conducted in six therapeutic areas. The maximum number of trials (26) were initiated in Oncology; 24 clinical trials in Neurology; 20 studies were targeted at Cardiovascular diseases; 19 – in Blood diseases; 13 studies in Endocrine and metabolic diseases and 12 studies were initiated in Infectious diseases in Q3 2008. The proportions between different therapeutic areas are shown in Figure 8.

Figure 8. Clinical trials in Russia in Q3 2008 by therapeutic area



Clinical trials results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 18[1] new drugs during Q3 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 eight of them which were, or are being tested in clinical trials in Russia.

Table 3. New Drugs approved by FDA in Q3 2008 and tested in Russian sites

Approval date	Drug	Manufacturer
07/01/2008	Requip Xl (Ropinirole Hydrochloride)	GlaxoSmithKline
07/29/2008	Stavzor (Valproic Acid)	Banner Pharmacaps
08/05/2008	Cefepime (Cefepime Hydrochloride)	Baxter
08/11/2008	Docetaxel (Docetaxel)	Hospira
08/26/2008	Novolog Mix (Insulin Aspart Recombinant)	Novo Nordisk
09/12/2008	Lamivudine	Matrix Labs
09/12/2008	Keppra Xr (Levetiracetam)	UCB
09/12/2008	Abacavir	Aurobindo Pharma
Source: CDER FDA http://www.fda.gov/cder		

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

During the period from the July 1 to September 31 2008 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) reviewed 14[1] applications to market drugs in the EU. Negative opinion was adopted for two drugs. Six 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 EMEA in Q3 2008 and tested in Russian sites

Approval date	Drug	Manufacturer
24/07/08	Xarelto (rivaroxaban)	Bayer HealthCare
24/07/08	Ceplene (histamine dihydrochloride)	EpiCept GmbH
24/07/08	Fluticasone Furoate GSK	GlaxoSmithKline
25/09/08	Cancidas (caspofungin)	Merck Sharp & Dohme
25/09/08	Vildagliptin/metformin hydrochloride	Novartis
25/09/08	Irbesartan	KRKA
Source: CHMP EMEA http://www.emea.europa.eu/index/indexh1.htm		

New investigative sites

According to the RZN data, as of the 10 September 2008 there were 931 hospitals entitled to conduct clinical trials in Russia. Fifty six new sites were designated by the RZN since last period.

The Top 10 cities by the number of new sites are shown in Table 5.

Table 5. Top 10 Russian cities by the number of new sites in Q3 2008

№	City	No. of new sites
1	St. Petersburg	7
2	Moscow	6
3	Ekaterinburg, Samara	4 each
4	Perm	3
5	Novosibirsk, Kirov, Ivanovo, Tomsk, Chelyabinsk	2 each
Source: RZN		

RZN inspections

As of 30 October 2008, there's no any information on the official RZN Website on the inspections conducted by the RZN in Q3 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.

FDA inspections

According to the FDA data, as of 30 September 2008, four new FDA inspections were conducted in the Russian investigative sites since our last issue: two inspections were conducted in moscow, and one inspection was conducted in St.Petersburg. No objectionable conditions or practices were found during three of inspections (NAI - No Action Indicated), one inspection in Moscow City Hospital No. 11 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 records and failure to adhere to protocol.

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

Appendix

Leader's Profile. Merck & Co., Inc.

Merck & Co., Inc. was established in 1891 in the US. Today Merck is a global research-driven pharmaceutical company whose products are sold in more than 140 countries

According to the Merck's annual report[1] sales in 2007 rose by 7% over 2006 figure and accounted to $24,19 billion.

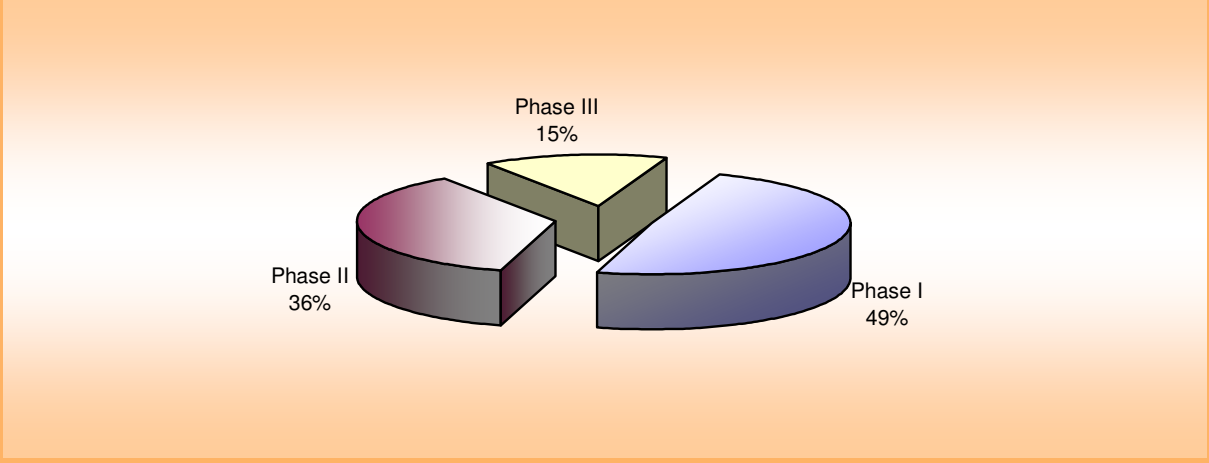
Current Merck's research and development (R&D) activities of 9,500 employees in the US, Canada, Europe and Asia focus on the following therapeutic areas: Alzheimers; Atherosclerosis; Cardiovascular Disease; Diabetes; Novel Vaccines; Obesity; Oncology; Pain and Sleep Disorders.

The Company's investment in research and development was $4,9 billion in 2007, or 20% total annual sales – very high percentage.

As of the 4th of March 2008 the Merck's pipeline comprised of 47 new drugs at different stages of development, three new drugs recently approved by FDA, and one product under FDA approval.

According to the 2007 corporate annual report the pipeline is distributed between different development stages as follows: 23 compounds are undergoing Phase I clinical trials; 17 drugs are in Phase II clinical development; and seven compounds are in Phase III clinical development.

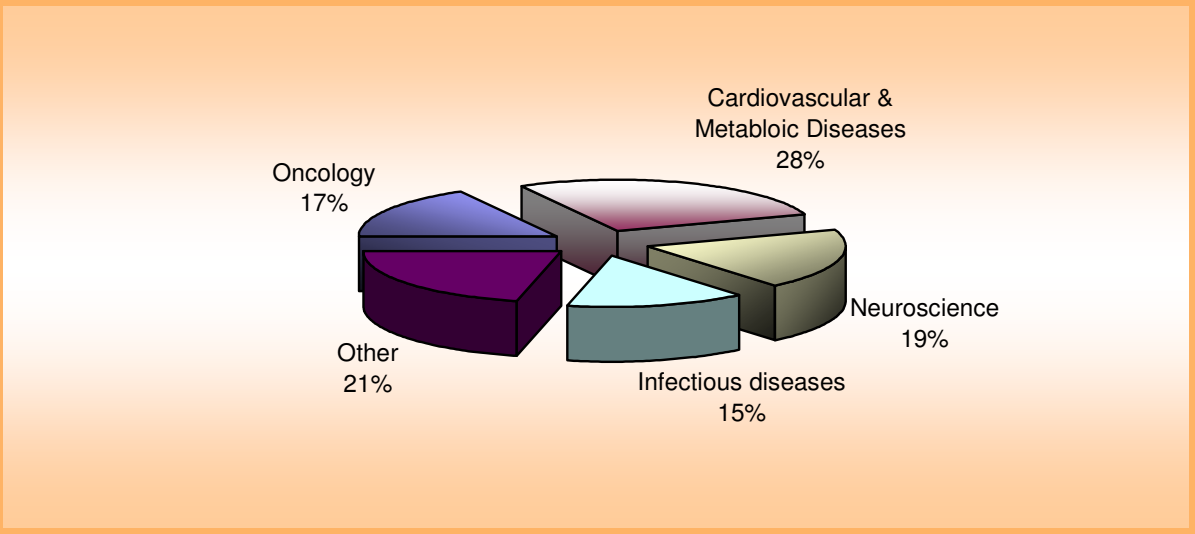
Figure 10. Merck's pipeline by study phase



Eight compounds are being developed for cancer; five – for treating atherosclerosis/thrombosis; three – for diabetes; seven are targeted for psychiatric disorders treatment; two – for Alzheimer's disease; 7 - for infectious diseases and five compounds – for cardiovascular diseases.

[1] http://www.merck.com/finance/annualreport/ar2007/

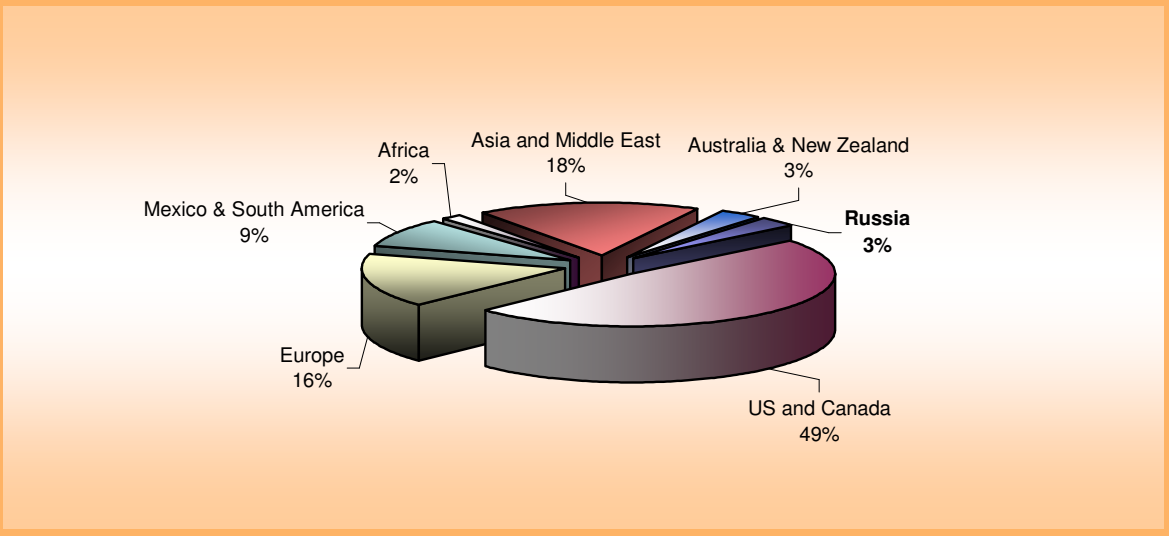
Figure 11. Merck's pipeline by Therapeutic Area



Today Merck's key products are the following: COZAAR®/HYZAAR®2 - medicines for the treatment of hypertension; GARDASIL® - vaccine for the prevention of cervical cancer and genital warts caused by certain types of HPV; JANUVIA® - medicine for the treatment of type 2 diabetes; SINGULAIR® - once-a-day oral medicine for the treatment of asthma, allergic rhinitis and exercise-induced bronchoconstriction; VYTORIN®3 - medicine to treat the two sources of cholesterol marketed through the Merck/Schering-Plough joint venture and ZETIA®4 - cholesterol-absorption inhibitor marketed through the Merck/Schering-Plough joint venture.

According to Clinical Trials.gov as of October 30, 2008 Merck conducted 252 clinical trials[1] worldwide; the lion's share of trials was performed in North America and Europe.

Figure 12. Clinical trials conducted by Merck worldwide[2]



According to the RZN, during the period from January 2004 to October 2008, 39 clinical trials were initiated by Merck & Co., Inc. in Russia.

[1] Only those clinical trials were taken into account where enrollment process was still going or hadn't started yet.
[2] ClinicalTrials.gov as of 3 April 2008. Open studies only