

**Clinical Trials in Russia**  
**Orange Paper**  
**1<sup>st</sup> Quarter 2008**





## Contents

Introduction .....	3
Executive Summary .....	3
Clinical Trials by Type and Manufacturing Country .....	4
Figure 1. Clinical trials approved by RZN in Q1 2008 .....	5
Figure 2. Clinical trials by type in Q1 2008 .....	5
Figure 3. Russian and International sponsors in Q1 2008.....	6
Figure 4. Countries presented on the Russian clinical trials market in Q1 2008 .....	6
Clinical trials by Phase.....	6
Figure 5. Clinical trials in Russia in Q1 2008 by phase .....	7
Figure 6. The proportion between study phases in Russia in Q1 2008.....	7
Figure 7. The number of patients in Q1 2008 by study phase .....	8
Rating of international sponsors.....	8
Table 1. Top-5 international study sponsors in Q1 2008.....	8
Rating of Russian sponsors.....	8
Table 2. Top-5 Russian study sponsors in Q1 2008.....	9
Therapeutic areas of clinical trials in Russia in Q1 2008.....	9
Figure 8. Clinical trials in Russia in Q1 2008 by therapeutic area .....	9
Clinical trials results .....	9
Table 3. New Drugs approved by FDA in Q1 2008 and studied in Russian sites.....	9
Table 4. New Drugs approved by EMEA in Q1 2008 and studied in Russian sites .....	10
New investigative sites.....	10
RZN inspections.....	10
FDA inspections.....	11
Appendix .....	12
Leader's Profile. Pfizer .....	12
Figure 9. Pfizer's pipeline by Phase .....	12
Figure 10. Pfizer's pipeline by Therapeutic Area.....	13
Table 5. Top-5 Pfizer's blockbusters in 2007.....	13
Figure 11. Clinical trials conducted by Pfizer worldwide .....	14



## Introduction

The beginning of 2008 has seen two remarkable events of the Russian clinical research market, namely acquisitions of two Russian Contract Research Organisations (CROs) by two big multinational companies. In February the global *PPD*, headquartered in North Carolina (USA), acquired the Smolensk company *Innopharm*, and at the beginning of April also the American *i3* declared the acquisition of the Russian *Lege Artis*, headquartered in Moscow. These two events have perfectly demonstrated an increasing interest of global multinational players in Russian clinical trial market.

Commenting on the transaction, chief executive officer of *i3*, Glenn Bilawsky confirmed this fact: "Russia has become a strategic geographic area in the drug development process, with well educated and experienced medical doctors and a vast population of patients who are interested in participating in clinical trials".

One of the quick ways of entering the Russian clinical trial market is when an international CRO buys out an established business from the local or another international CRO. In this case, the company immediately gets a solid local presence, but also an increased risk to have some difficulties down the line with the integration of cross-cultural corporate differences, processes, and technologies.

The volume of investments depends on the business being acquired. Among the companies that have followed this path are Parexel, which bought a local CRO in 1997, Kendle, which acquired Charles River Laboratories in 2006 along with AAIPharma, which, in turn, acquired a local CRO with a head office in Moscow the same year. We believe that the process of buying out local players will also continue in future, since the attractiveness of Russia as a clinical trials market is growing steadily. Unfortunately, at the same time the number of Russian CROs is reducing progressively.

It is with deeper regret, that lately the negative image of clinical trials has continuously been created in the minds of people owing to numerous statements of different so-called experts, saying that foreign companies use Russian people as Guinea Pigs. It is especially surprising to hear such statements from the high-ranking officials of the responsible state department, who consider Russia to be "a remote area of civilization" and claim that today clinical trials are being conducted "whenever but not in the USA and Western Europe".

The good example of this statement is the data provided by the US National Institute of Health - 4,470 new clinical trials were launched worldwide during the 1<sup>st</sup> Quarter of Year 2008 with 2, 422 trials (54 per cent) – in the USA and 996 (22 per cent) in Europe.

## Executive Summary

The Federal Service on Surveillance in Healthcare and Social Development of the Russian Federation (alias RosZdravNadzor, RZN) approved 130 new clinical trials in Russia in Q1 2008; four trials less than in the corresponding period of last year. The main contribution is still made by multinational multi-center clinical trials. Their share in the total volume has not changed in comparison with the last year, amounting to 62 per cent, and their number has slightly declined from 83 to 80 clinical trials.

The share of local clinical trials and bioequivalence studies came to 28 per cent and 10 per cent in the Q1 2008, whereas in Q1 2007 they stood to 25 per cent and 13 per cent of the total number of trials, respectively. The number of local studies conducted only on the territory of Russia by domestic and foreign sponsors, has increased from 34 to 37 trials, and the number of bioequivalence studies initiated in Q1 2008 has slightly decreased from 17 in the last year to 13.

The share of foreign study sponsors In Q1 2008 stood at 68 per cent of the total number of clinical trials, 88 new trials were initiated during this period. Domestic sponsors have launched 42 clinical studies during Q1 2008 and their share accounted to 32 per cent of the total number of trials.



Forty companies from 18 countries have sponsored new trials during Q1 2008. Russia with 42 clinical trials is on the top of the heap, followed by the USA with 33 trials, UK (15 clinical trials), Switzerland (11 clinical trials) and Germany (10 clinical trials).

Forty seven per cent of the trials in Q1 2008 were Phase III trials; the share of Phase II trials increased to 36 per cent; Phase IV clinical trials reached 11 per cent and the share of Phase I trials stood 6 per cent.

The number of patients to be enrolled in all types of studies stands at 9,358; a 60% decrease over Q1 2007, when 14, 894 patients were planned to be recruited.

The British GlaxoSmithKline remains at the Q1 top for a second consecutive year starting 12 new trials and having considerable advantage. Its major rival, the American Pfizer with six trials has moved up from the fourth position in Q1 2007 to the second position in Q1 2008. The Swiss Novartis also running six trials but with less number of patients is number 3 in the list. The Russian Pharmstandard with four new studies was ranked number one among domestic sponsors.

In Q1 2008 more than half of the new trials (53 per cent) were launched in six leading therapeutic areas. The maximum number of trials (18 clinical trials) traditionally are in oncological diseases; 13 clinical trials were devoted to treating diseases of respiratory system; 11 neurologic and 11 endocrinological trials were started; 10 cardiovascular system trials; seven trials of gastrointestinal disturbance.

23<sup>1</sup> new drugs were approved by the Center for Drug Evaluation and Research (CDER) of the Food and Drug Administration (FDA) for the first quarter 2008. 14 of them were tested in clinical trials in Russia. 28<sup>2</sup> applications for drug marketing on the EU territory were examined by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) in the period from the 1st of January till the 31st of March; seven of them were tested in the Russian investigative sites.

### **Clinical Trials by Type and Manufacturing Country**

The RZN approved 130 new clinical trials of all types, including bioequivalence trials during the first quarter 2008; it is four trials authorizations less, than for the corresponding quarter of last year. As indicated on the picture, the main contribution into the total number is still made by multinational multi-center clinical trials (MMCTs); their quantity has slightly declined from 83 to 80 clinical trials, compared with last year.

The number of local clinical trials, conducted on the territory of Russia by domestic and foreign sponsors, increased from 34 to 37 clinical trials (the abbreviation CT (R) stands for them on the Figure 1).

The number of bioequivalence trials (BE), launched in first quarter 2008, has slightly went down from 17 in last year to 13 this year.

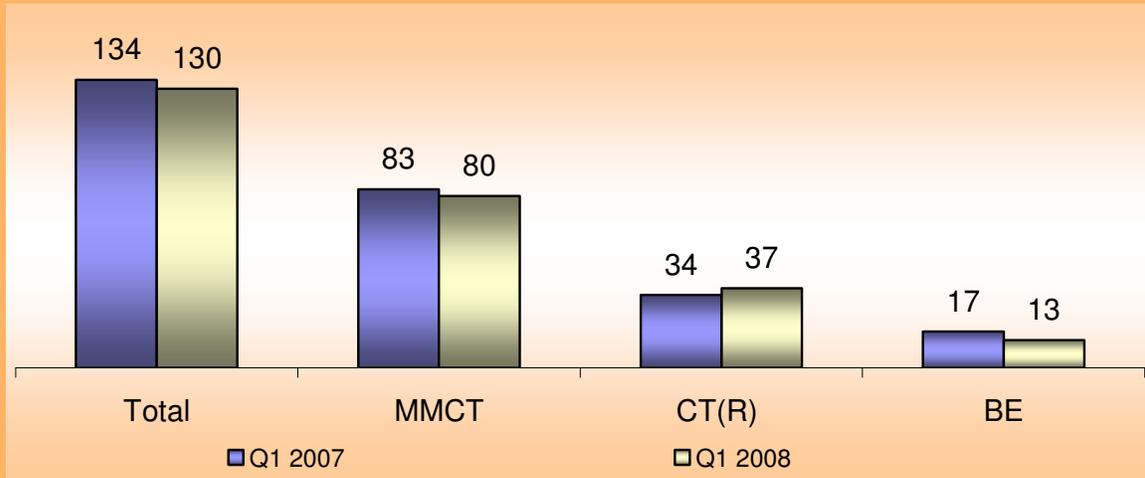
One might say in general, that definite changes didn't take place in the first quarter, compared with the corresponding quarter of last year, quantitative and participatory characteristics remained at the same level.

<sup>1</sup> According to the data from CDER FDA <http://www.fda.gov/cder>

<sup>2</sup> According to the data from CHMP EMA <http://www.emea.europa.eu/index/indexh1.htm>



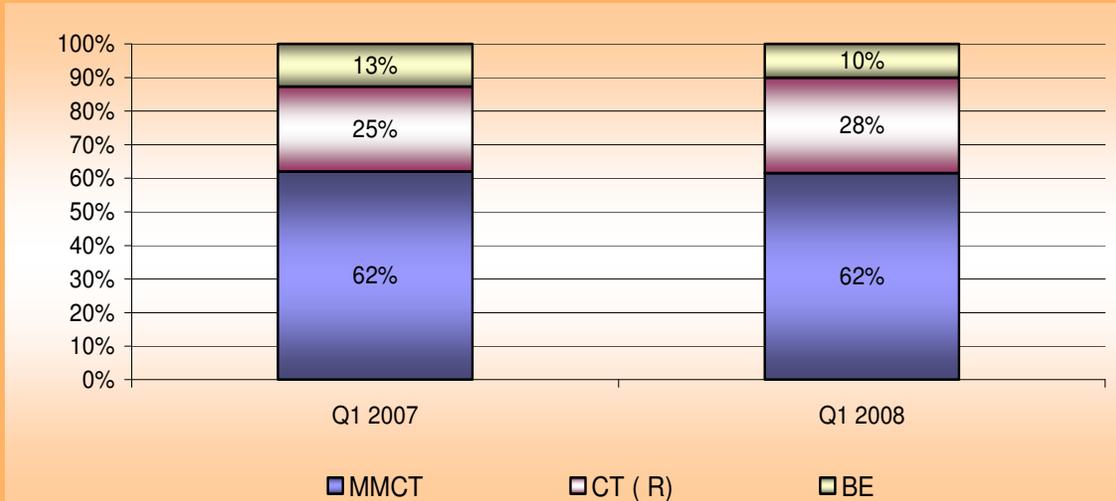
**Figure 1. Clinical trials approved by RZN in Q1 2008**



The ratio of clinical trials types (multinational multi-center clinical trials, clinical trials (Russia), and bioequivalence trials) didn't significantly change compared with the first quarter 2007. Amounting to 62 per cent of the total clinical trials number, the share of multinational multi-center clinical trials remained at the same level, compared with the first quarter 2007.

The shares of local clinical and bioequivalence trials came to 28 and 10 per cent for the first quarter 2008, whereas to 25 and 13 per cent of the total volume for the same quarter 2007.

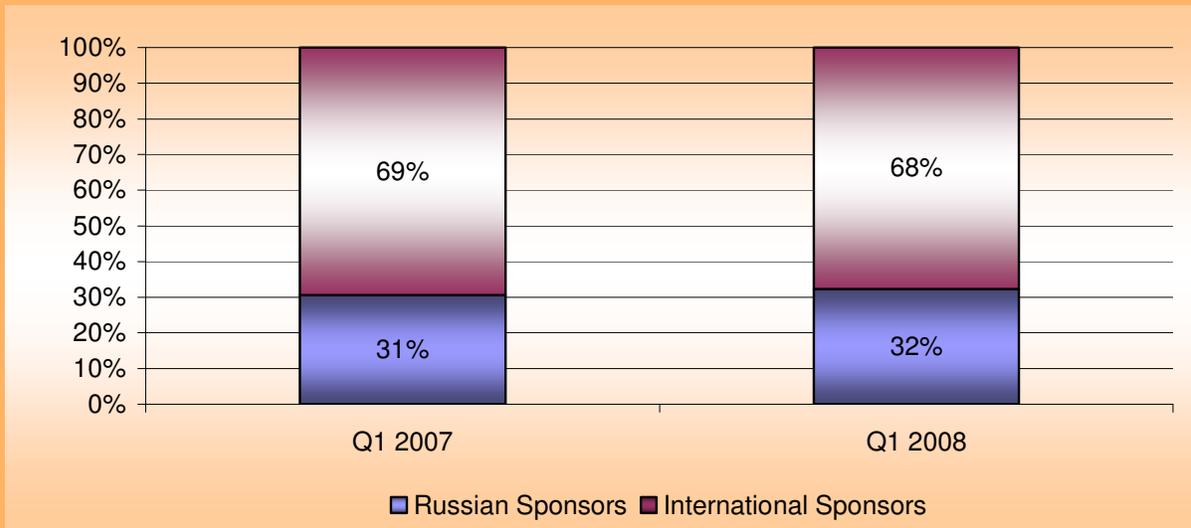
**Figure 2. Clinical trials by type in Q1 2008**



The lion's share of clinical trials on the territory of Russia is still being sponsored by foreign companies. Their share slightly reduced from 69 to 68 per cent and their number went down from 93 to 88 clinical trials, compared to the same period of last year. The number of clinical trials launched by domestic sponsors, including bioequivalence studies, rose from 41 to 42, the share also increased by 1 per cent to 32 per cent of the total number of clinical trials.

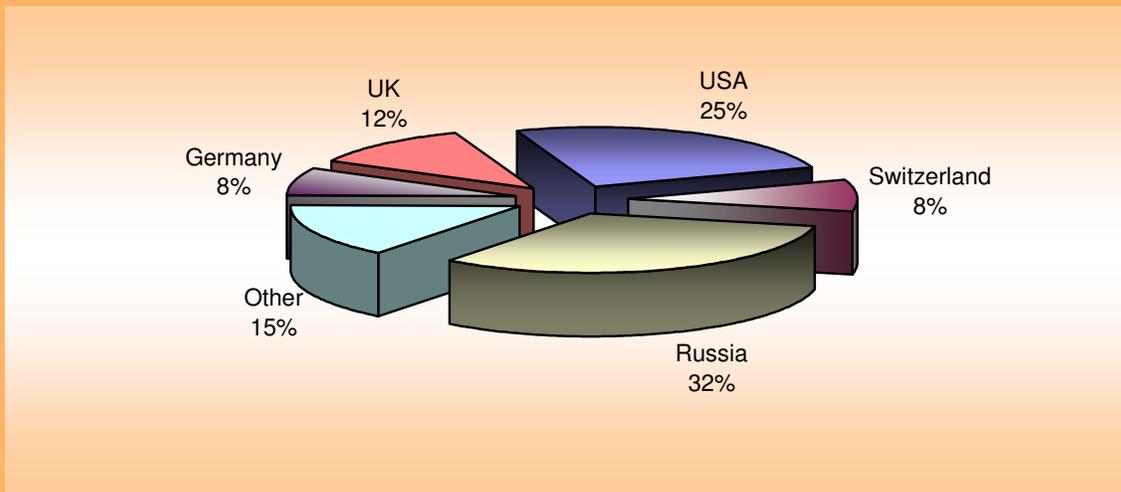


**Figure 3. Russian and International sponsors in Q1 2008**



Clinical trials in Russia in Q1 2008 were sponsored by 40 companies from 18 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 (42) were started by Russian sponsors, they are followed by American sponsors who initiated 33 studies, UK sponsors with 15 trials are listed number three, 11 trials were initiated by Swiss companies, and the top six is concluded by German sponsors with 10 new studies.

**Figure 4. Countries presented on the Russian clinical trials market in Q1 2008**



India, Spain, Italy, the Netherlands, Pakistan, Poland, Slovenia, Ukraine, France, Sweden and Japan are represented among others.

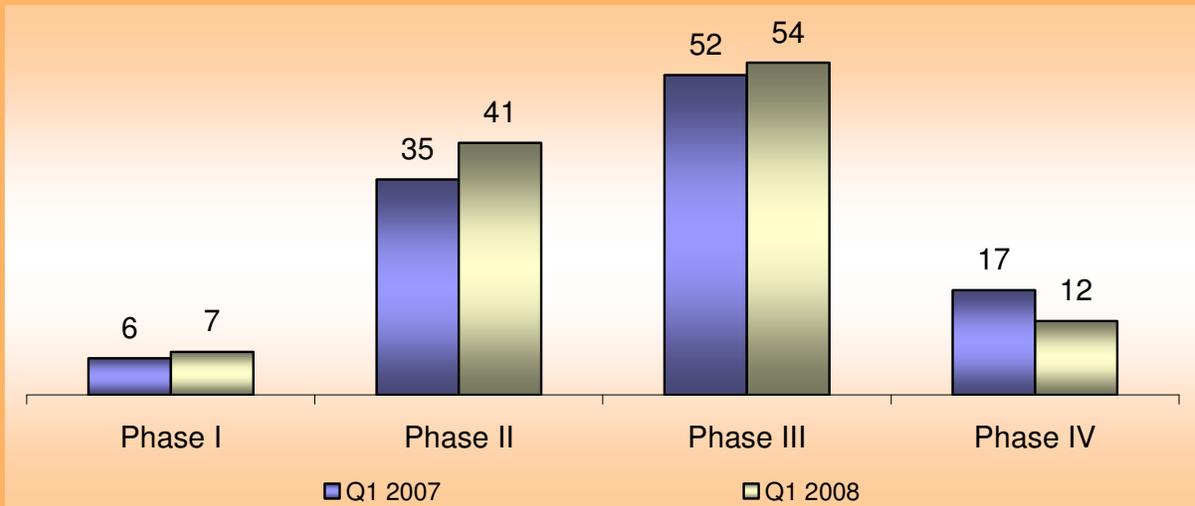
### Clinical trials by Phase

Seven new Phase I clinical trials were launched in the first quarter 2008; it is one trial more, than in the corresponding quarter of last year. The number of the Phase II trials increased from 35 trials in the first quarter 2007 to 41 in the first quarter 2008. The number of Phase III trials also



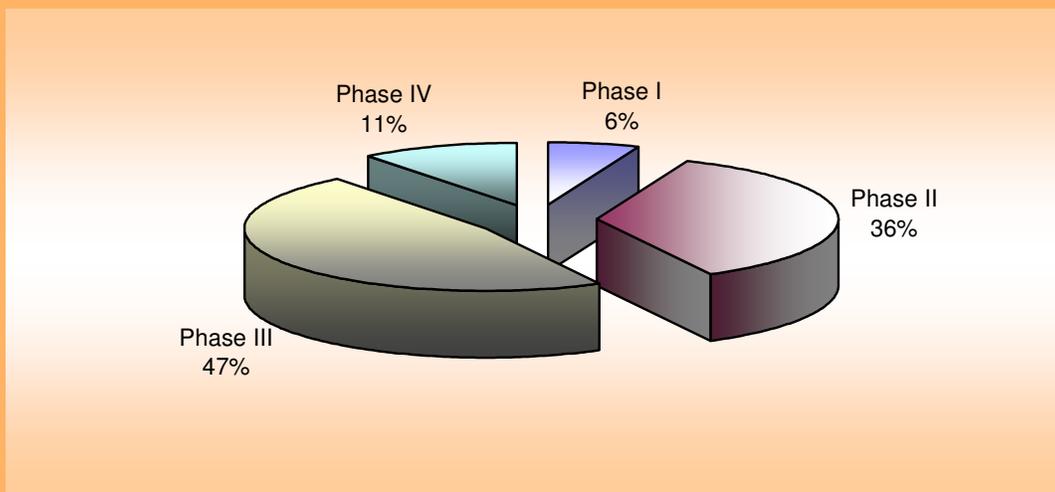
went up from 52 to 54, and the number of Phase IV trials increased from 17 in the first quarter 2007 to 12 in the first quarter 2008.

**Figure 5. Clinical trials in Russia in Q1 2008 by phase**



As it is shown on the figure 6, Phase III trials amount to 47 per cent of studies, kicked off in the first quarter 2008; the share of phase II trials grew to 36 per cent; phase IV trials came to 11 per cent and the share of phase I trials amounted to six per cent.

**Figure 6. The proportion between study phases in Russia in Q1 2008**



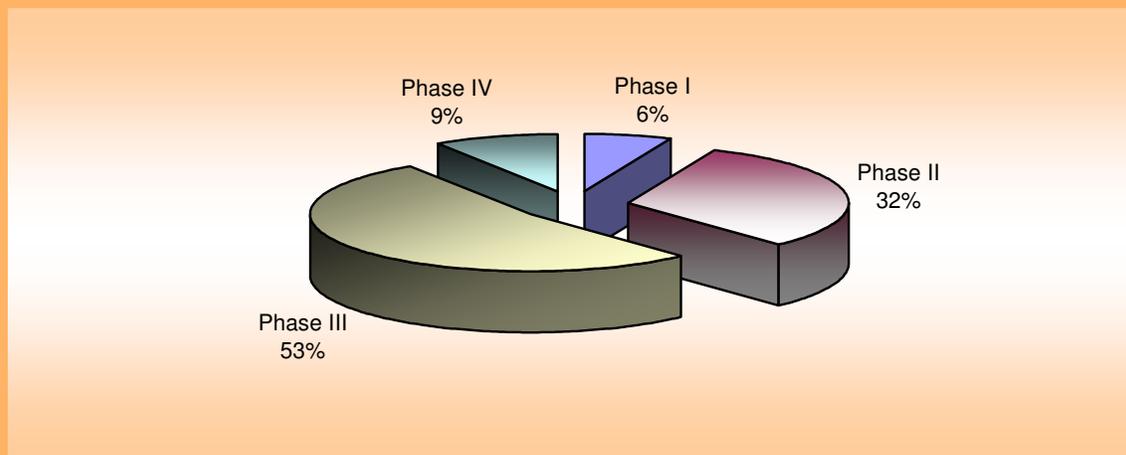
9, 358 patients are planned to be enrolled in the Phase II-IV trials, launched in the first quarter 2008; it is 1.6 times less, than in the same quarter 2007, when patient population was supposed to be 14, 894.

603 patients are to participate in Phase I trials, started in the first quarter 2008; 2, 964 patients – in Phase II trials, 4, 945 – in Phase III trials, 846 patients – in Phase IV studies, 482 patients – in other studies, including bioequivalence trials and clinical studies without Phase indication.

The minimal patient number in a single study is nine, the maximum number is 360.

Percentage of patient population in different Phase trials approved by the RZN in the first quarter 2008 is shown on the Figure 7.

**Figure 7. The number of patients in Q1 2008 by study phase**



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

### Rating of international sponsors

The British company GlaxoSmithKline sponsoring 12 new studies is on the top of the list in the first quarter 2008 in the same way as in last year; the American company Pfizer, sponsoring six trials, rose from the fourth to the runner-up place; the Swiss Novartis lags behind in terms of number of patients.

The American biotechnology company Catalent Pharma Solutions, founded in April 2007 made its debut in this league, ranking number four. It is followed by Bristol-Myers Squibb sponsoring four trials; the same number as Catalent Pharma Solutions, but with fewer number of patients.

Top five international sponsors are presented in Table 1.

**Table 1. Top-5 international study sponsors in Q1 2008**

No	Sponsor	No. of trials	No. of patients	No. of sites
1	GlaxoSmithKline	12	860	66
2	Pfizer	6	470	32
3	Novartis	6	260	28
4	Catalent Pharma Solutions	4	550	61
5	Bristol-Myers Squibb	4	419	48

### Rating of Russian sponsors

The company Pharmstandart, sponsoring four new clinical trials enrolling 160 patients and four study centers, was ranked number one among domestic producers in terms of the number of new trials launched in the first quarter 2008.

Enrolling the same number of patient in the first quarter, ZAO (the closed joint-stock company) Biokard takes the runner-up place, following by OAO (the open joint-stock company) Nizhpharm with fewer study centers. The Schelkovo Vitamin Plant and Canopharma Production both having two new studies conclude the list differing in the number of patients.



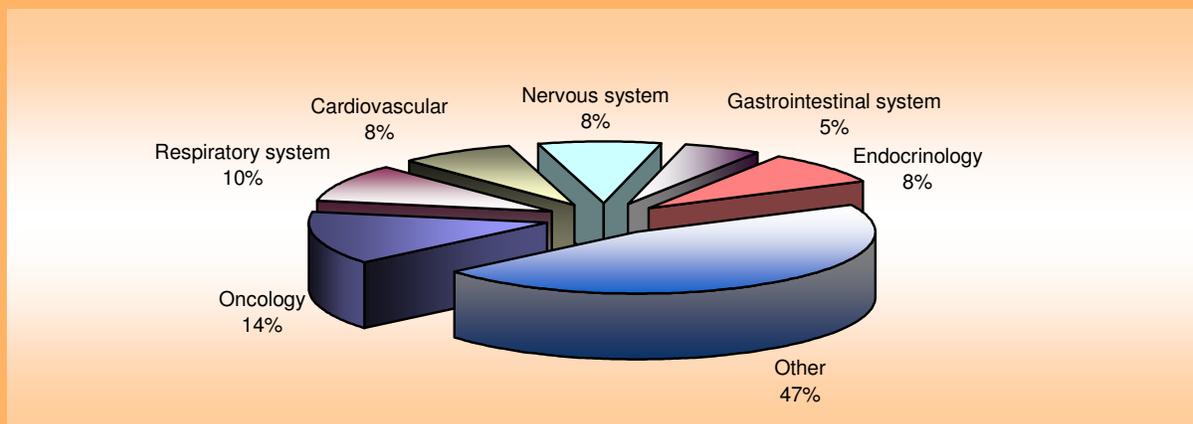
**Table 2. Top-5 Russian study sponsors in Q1 2008**

No	Sponsor	No. of trials	No. of patients	No. of sites
1	Pharmstandart	4	160	4
2	ZAO Biocad	3	200	5
3	OAO Nizhpharm	3	200	4
4	OAO Schelkovo Vitamin Plant	2	220	4
5	ZAO Canonpharma Production	2	126	4

### Therapeutic areas of clinical trials in Russia in Q1 2008

In the first quarter 2008 more than half of all new studies, namely 58 per cent, were focused on 6 therapeutic areas. So the majority of trials (18 clinical trials) traditionally fell to the share of oncological diseases; 13 clinical trials were devoted to treating diseases of respiratory system; 11 neurologic and 11 endocrinological trials; 10 cardiovascular system trials; seven trials of gastrointestinal disturbance. The distribution of studies by therapeutic area is shown in the Figure 8.

**Figure 8. Clinical trials in Russia in Q1 2008 by therapeutic area**



### Clinical trials results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 23<sup>1</sup> new drugs during the first quarter 2008; among them only 3 drugs were really new, i.e. represented new molecular substances; others had new dosage forms, manufacturers or new indications for use. The Table 3 represents those drugs, which are undergoing or have already tested in clinical trials in Russia.

**Table 3. New Drugs approved by FDA in Q1 2008 and studied in Russian sites**

Approval date	Drug	Manufacturer
01/10/2008	Alvesco (Ciclesonide)	Nycomed
01/17/2008	Flo-Pred (Prednisolone Acetate)	Taro
01/18/2008	Tekturna (Aliskiren)	Novartis
01/18/2008	Intelence (Etravirine)	Tibotec

<sup>1</sup> По данным CDER FDA <http://www.fda.gov/cder>



01/23/2008	Moxatag (Amoxicillin)	Middlebrook Pharma
01/25/2008	Emend (Fosaprepitant)	Merck & Co
02/15/2008	Simcor (Niacin)	Abbott
02/27/2008	Nexium (Esomeprazole)	AstraZeneca
03/07/2008	Levoleucovorin	Spectrum Pharms
03/17/2008	Morphine Sulfate	Roxane
03/20/2008	Stavudine	Strides Arcolab
03/20/2008	Prilosec (Omeprazole)	AstraZeneca
03/20/2008	Stavudine	Strides Acrolab
03/24/2008	Depakote Er (Divalproex Sodium)	Abbott

Source: CDER FDA <http://www.fda.gov/cder>

For the period from the 1st of January to the 31st of March 2008 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) reviewed 28<sup>1</sup> applications to market drugs on the EU territory. Among them eight drugs were approved for the first time, five drugs were rejected, the rest was made up of the generics of drugs, approved before. Seven drugs, approved for marketing, are undergoing or underwent clinical trials in Russia (see Table 4).

**Table 4. New Drugs approved by EMA in Q1 2008 and studied in Russian sites**

Approval date	Drug	Manufacturer
21/02/08	Abilify (aripiprazole)	Otsuka Pharmaceutical
21/02/08	Alimta (pemetrexed)	Eli Lilly
21/02/08	Forsteo (teriparatide)	Eli Lilly
21/02/08	Azomyr (desloratadine)	Schering-Plough
21/02/08	Aerius(desloratadine)	Schering-Plough
21/02/08	Neoclarityn (desloratadine)	Schering-Plough
19/03/08	Viread (tenofovir disoproxil fumarate)	Gilead Science International Limited

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

### New investigative sites

According to the Federal Service on Surveillance in Healthcare and Social Development of the Russian Federation, as of the 9th of January 2008 there were 854 health care facilities, entitled to conduct clinical trials of drugs in Russia. As of the 30th of April 2008 there is no any renewed report, published on the official Internet-page of the Federal Service on Surveillance in Healthcare and Social Development of the Russian Federation.

### RZN inspections

As of the 30th of April 2008 the official Internet-page of the Federal Service on Surveillance in Healthcare and Social Development of the Russian Federation does not contain any information on checks-up, made in the first quarter 2008.

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



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### **FDA inspections**

According to the FDA in the first quarter 2008 there were no inspections of the FDA at Russian study centers as of the 31th of March 2008.

## Appendix

### Leader's Profile. Pfizer

Pfizer was founded by cousins Charles Pfizer and Charles Erhart in 1849 in New York.

For the moment Pfizer is the largest pharmaceutical company in the world, ranking number 33 in the list of top 2000 world companies published by the Forbes magazine in February 2008. According to the magazine the sales volume of Pfizer amounted to \$51, 3 billion in 2007, and the market value of \$192.05 billion<sup>1</sup>.

According to the DSM Group<sup>2</sup>, Pfizer ranks number 7 in terms of sales volume in the Russian commercial market according to the financial results for the first six months of Year 2007.

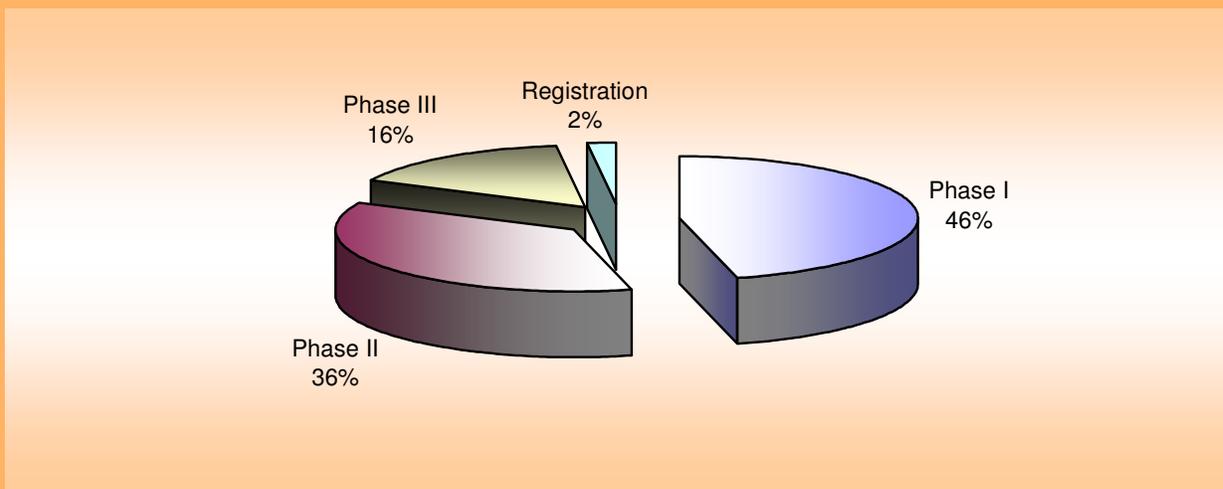
Pfizer is focused on discovering and developing new medicines across 10 Therapeutic Areas: Allergy & Respiratory; Cardiovascular, Metabolic and Endocrine Diseases; Gastrointestinal & Hepatology; Genitourinary/Sexual Health; Infectious Diseases; Inflammation; Neuroscience; Oncology; Ophthalmology and Pain.

In the year 2007 the budget for scientific research increased by six per cent and amounted to \$8.089 billion, compared to the budget of 2006. (According to the Pfizer<sup>3</sup> annual report, it is 16.7 per cent of the total sales volume).

As of the 28th of February 2008 the R&D portfolio of the company comprised of 102 new drugs; among them there were 85 new molecular substances and 17 new indications for use of drugs registered before.

The structure of Pfizer's pipeline by development stage is represented on the Figure 9. Forty seven projects are in the early phase, 37 drugs are undergoing Phase II trial, 16 drugs – Phase III trial, two drugs are being submitted to Regulatory agencies for registration.

**Figure 9. Pfizer's pipeline by Phase**



According to Dr. Martin Mackay, president of Pfizer Global Research & Development, the Year 2008 marks the start of a multi-year period of increased productivity for Pfizer. Throughout this year and the next, the Company anticipates a strong flow of medicines progressing from Phase II to Phase III. Pfizer expects:

<sup>1</sup> Forbes. The World's 2,000 Largest Public Companies

<sup>2</sup> <http://www.dsm.ru/analytics/2007>

<sup>3</sup> <http://media.pfizer.com/files/annualreport/2007/annual/review2007.pdf>

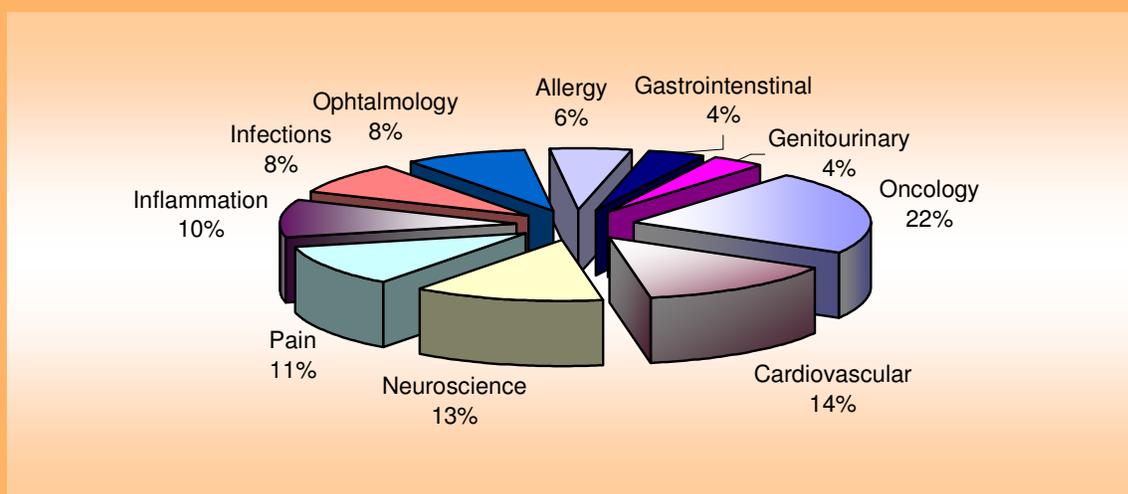


- a total of 15 to 20 Phase III starts by the end of 2009 in disease areas ranging from cancer, to diabetes, to pain;
- to grow the number of Phase III programs by 50 to 75 percent, to at least 24 – and as many as 28 — by December 2009, up from 16 today; and
- 15-20 regulatory submissions between 2010 and 2012.

Figure 10 shows that the structure of scientific research portfolio of Pfizer by therapeutic areas conveys the world tendency – oncology and cardiovascular disease are “the most popular” for conducting clinical trials.

Allergy & Respiratory; Cardiovascular, Metabolic and Endocrine Diseases; Gastrointestinal & Hepatology; Genitourinary/Sexual Health; Infectious Diseases; Inflammation; Neuroscience; Oncology; Ophthalmology and Pain.

**Figure 10. Pfizer’s pipeline by Therapeutic Area**



Today 10 leading drugs by Pfizer are covering 56 per cent of the total sales volume. The Table 5 shows the top five Pfizer’s blockbusters according to the annual 2007 results.

**Table 5. Top-5 Pfizer’s blockbusters in 2007**

Drug	Y2007 Sales in billion US Dollars	No. of open trials in Russia	Indication
Lipitor	12.7	7	Hypolipidemic agent
Norvasc	3	4	Slow calcium channel blocker
Celebrex	2.3	3	Non-steroidal anti-inflammatory drug
Lyrica	1.8	3	Fibromyalgia
Viagra	1.8	5	Erectile dysfunction

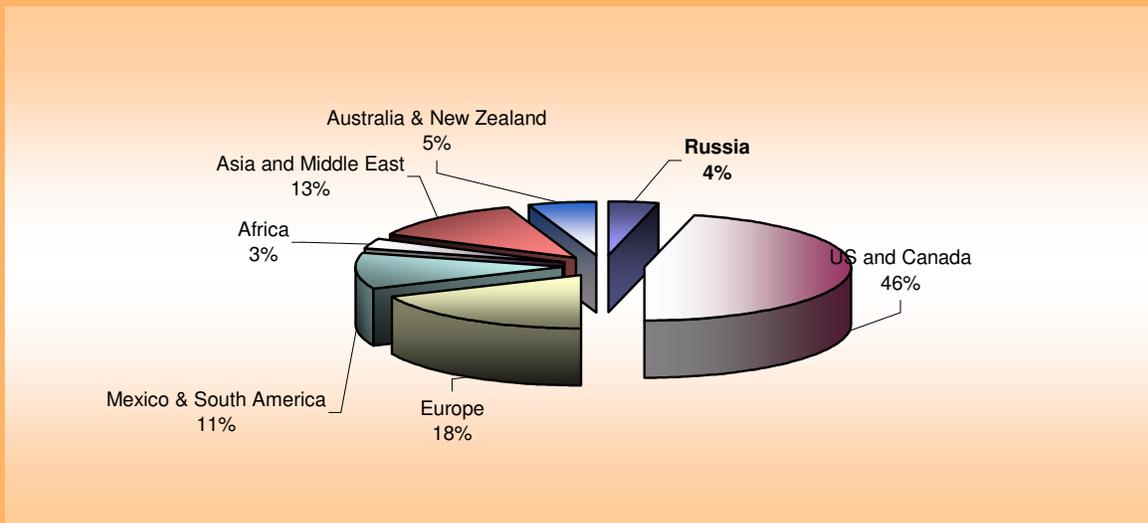
Источники: Pfizer, US National Institute of Health

According to Clinical Trials.gov as of the 3rd of May 2008 the company Pfizer was conducting 441 clinical trials<sup>1</sup> worldwide; two thirds of trials were performed in the Latin America and Europe. According to the data published on the web site 23 active trials are being conducted in Russia.

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



**Figure 11. Clinical trials conducted by Pfizer worldwide<sup>1</sup>**



According to the Federal Service on Surveillance in Healthcare and Social Development of the Russian Federation, for the period from January 2004 to April 2008 55 clinical trials were initiated by Pfizer in Russia.

<sup>1</sup> ClinicalTrials.gov as of 3 April 2008. Open studies only