

**Clinical Trials in Russia
Orange Paper
Year 2009**



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Executive Summary

The Federal Service on Surveillance in Healthcare and Social Development of the Russian Federation (alias RosZdravNadzor, RZN) approved 577 new clinical trials during 2009, a 6% lower than last year's figure.

The main contribution (60%) is made by multinational multi-center clinical trials, though their number decreased by 4% over 2008 and stood at 348 new studies in 2009.

Shares of local clinical trials and bioequivalence studies in 2009 amounted to 25% and 15%, whereas in 2008 they were equal to 29% and 12% of the total number of clinical trials.

Clinical trials in Russia in 2009 were sponsored by the pharmaceutical manufacturers from 28 countries. The maximum number of trials (191) was initiated by Russian sponsors as before. American sponsors (128 trials) took the runner-up place, they are followed by the German (51), the Swiss (42), the UK (35) companies, and the top five is concluded by the Japanese sponsors with 34 new trials.

Twenty-five new Phase I clinical trials were launched in 2009; which is thirteen trials less than last year. The number of the Phase II trials decreased from 152 trials in 2008 to 129 in 2009, reduction was 15%.

However, the number of Phase III trials slightly increased from 282 till 289, 2% up over last year. For Phase IV trials drop was 24% (from 62 trials in 2008 to 47 in 2009).

Forty-eight thousand five hundred twenty-one patients are planned to be enrolled in the Phase I-IV trials which started in III quarter 2009. This is twenty thousand one hundred twenty-two patients fewer than in 2008, when sixty thousand six hundred forty-two patients were planned to be enrolled.

The Swiss pharmaceutical giant *Novartis* sponsoring 35 new studies was on the top of the pile by the number of new trials started in 2009. The American *Pfizer* instigating 22 new trials in 2009 took the runner-up place, it is followed by *Merck & Co.* and *GlaxoSmithKline* with 20 new trials each, and *Boehringer Ingelheim* closed the top five with 16 new trials.

The Russian Valenta, sponsoring 13 new clinical trials ranked number one among domestic pharmaceutical manufacturers by the number of new studies in 2009. ZAO Pharmaceutical Company "Obolensky" with 13 new trials took the runner-up place. ZAO "Canonpharma" ranked third with 12 new studies. It is followed by ZAO "Biocad" with 9 new trials and Microgen closed the top five with 8 new trials.

In 2009, 85% of new studies were initiated in six major therapeutic areas: greatest number of studies has been initiated in the field of Oncology – 104 clinical trials; Endocrine and metabolic diseases - 66; Respiratory System – 66; Circulatory System – 64; Musculoskeletal System – 40 and diseases of the Nervous System – 38 new clinical trials.

The Center for Drug Evaluation and Research (CDER) of the FDA approved 97 new drugs during Year 2009; 20 of them are really new molecular entities; others had new dosages, manufacturers or indications of the already marketed drugs. Eight drugs were studied in Russia.

During 2009 the Committee for Medicinal Products for use in humans (CHMP) of the European Medicine Agency (EMA) was considered 153 applications for marketing of medicines in the European Union. Of this, 11 medicines were given a negative decision. Eight medicines have received authorization for marketing in 2009, were or are investigated in clinical trials in Russia.

According to FDA data, seven FDA inspections were conducted in the Russian investigative sites during 2009 with no major findings.



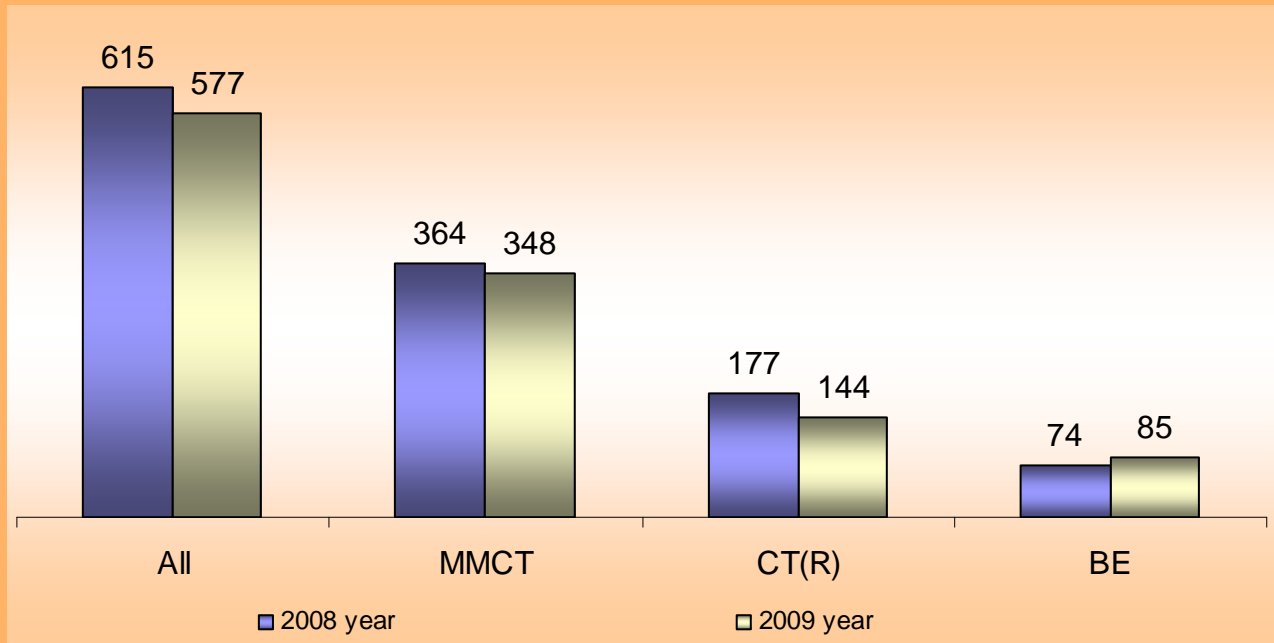
Clinical Trials by Type and Manufacturing Country

The RZN approved 577 new clinical trials of all types including local and bioequivalence studies during 2009; demonstrating a 6% decrease over 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), even though the number of these studies slightly decreased by 4% over 2008 and stood at 348 new studies in 2009.

The number of the local clinical trials conducted in Russia by domestic and foreign sponsors (the CT(R) bar in the Figure 1) is also decreased from 177 to 144 clinical trials demonstrating a decline of 19% compared with last year.

The number of bioequivalence studies (BE in Figure 1) in 2009 stood at 85 new trials, 11 studies on more than last year.

Figure 1. Clinical trials approved by RZN in 2009



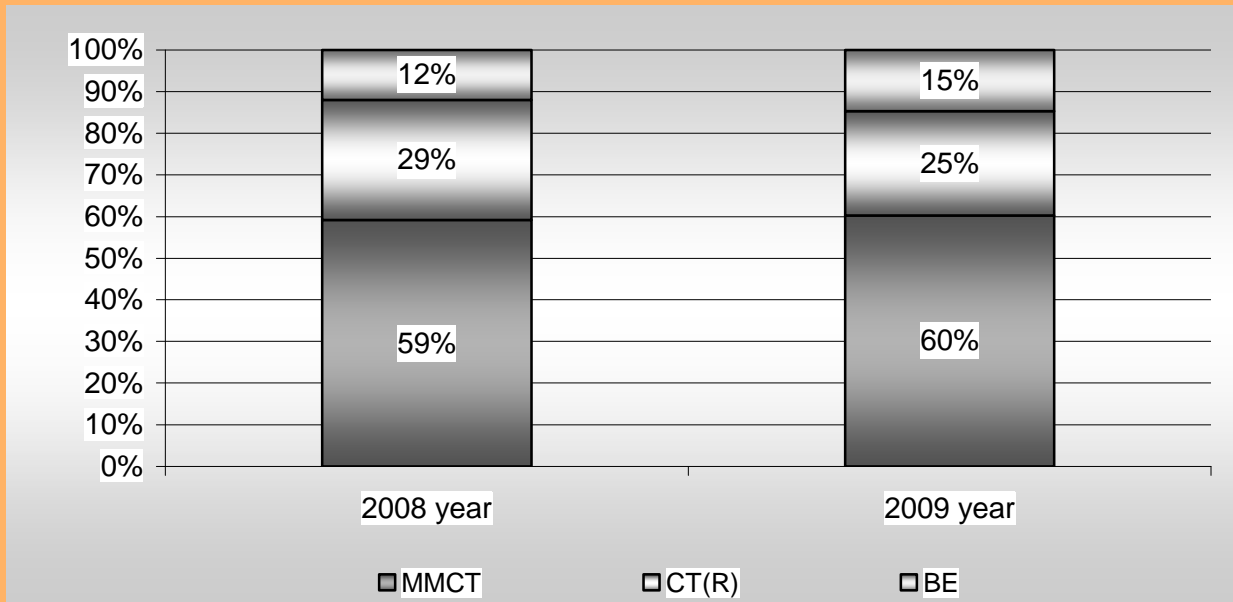
The proportions between different study types (multinational multi-center clinical trials, local studies and bioequivalence trials) did not change significantly over 2009 figures. Likely, this ratio will be the same in the near future.

Although the absolute number of multinational multi-center clinical trials slightly decreased from last year's figure, their share slightly increased and stood at 60% of the total number of clinical trials approved by RZN in 2009.

The share of the local trials in 2009 stood at 25% of the total number of studies, respectively, while it accounted to 29% in 2008. The share of bioequivalence studies slightly increased from 12% to 15% of the total number of trials approved during Y2009.



Figure 2. Clinical trials by type in 2009



The lion's share of clinical trials in Russia is still being sponsored by foreign companies. The proportions between international and local manufacturers did not change in 2009 year – 33 and 67% as in Y2008.

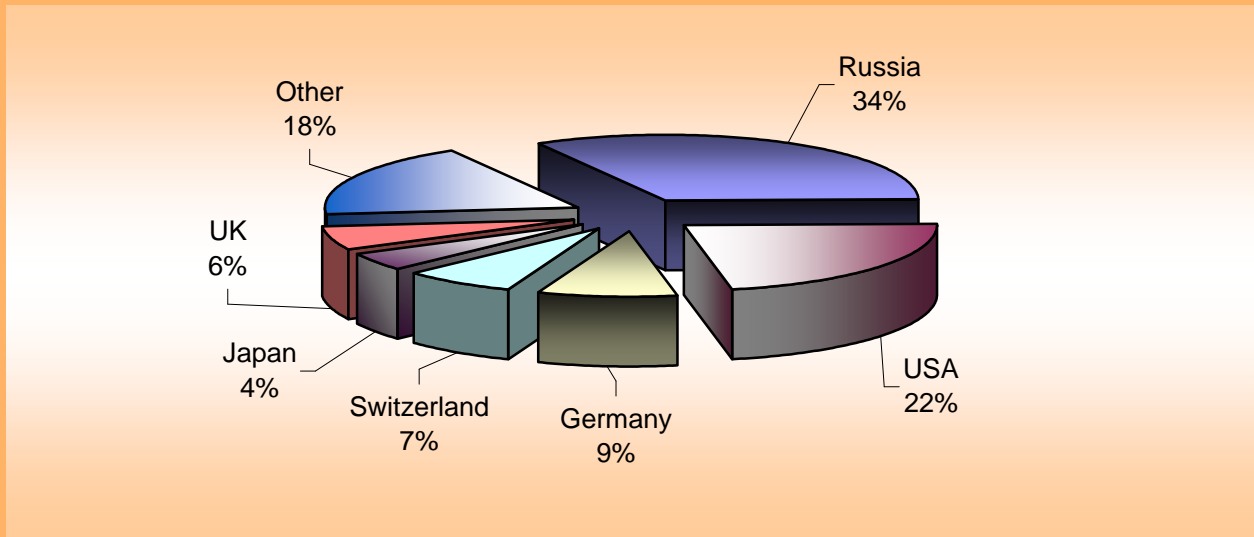
Figure 3. Russian and International sponsors in 2009



Clinical trials in Russia in 2009 were sponsored by the companies from 28 countries. Figure 4 demonstrates the input of the leading countries of sponsor's origin into the total number of clinical trials. The maximum number of trials (191) was initiated by the Russian sponsors. American sponsors with 128 studies took the runner-up place, they are followed by the German sponsors with 51 trials, 42 new trials were instigated by the Swiss companies, 35 trials were instigated by the UK sponsors and the group of leaders is concluded by the Japanese sponsors with 25 new studies in 2009.



Figure 4. Countries presented on the Russian clinical trials market in 2009

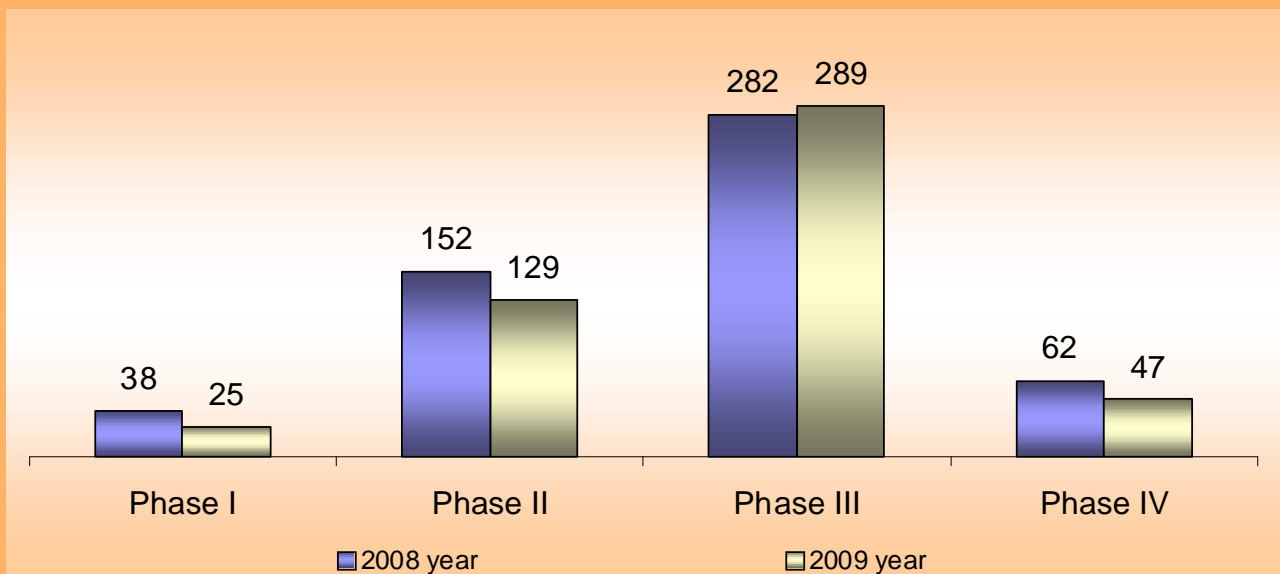


Austria, Belgium, Bulgaria, Canada, China, Croatia, Denmark, Israel, India, Italy, Ireland, Korea, Spain, the Netherlands, Norway, Portugal, Serbia, Sweden, Ukraine, Vietnam are represented among others.

Clinical trials by Phase

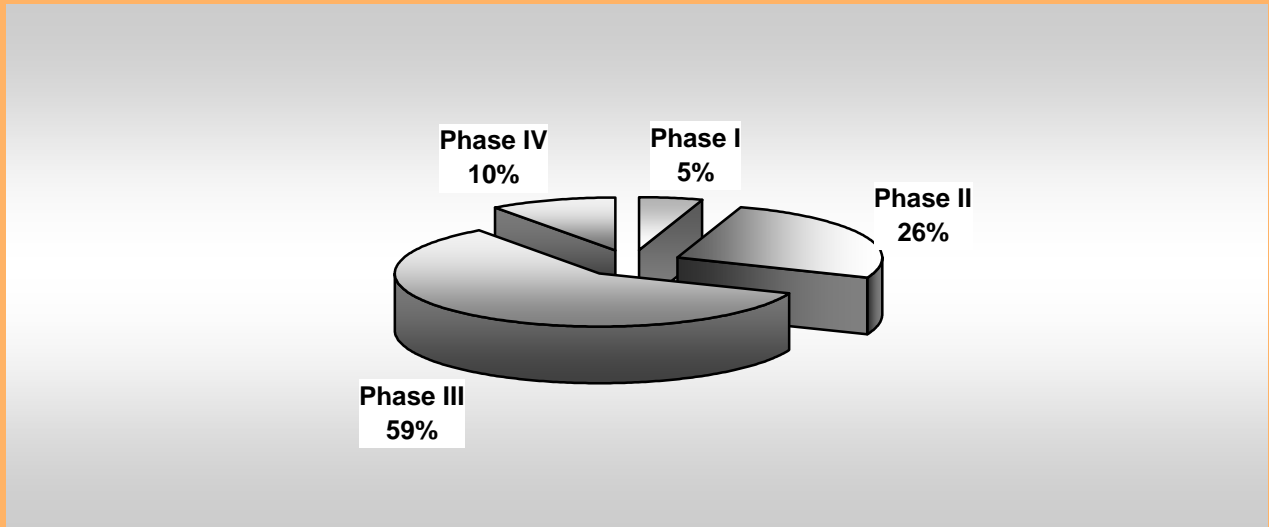
Twenty five new Phase I clinical trials were launched in 2009, which is 13 trials less than during the year 2008. The number of the Phase II trials decreased from 152 trials in 2008 to 129 in 2009, drop was 15%. However, the number of Phase III trials increased from 282 to 289 studies, growth is 2% compared to 2009. For Phase IV trials the drop was 24% (from 62 in 2008 to 47 studies in 2009)

Figure 5. Clinical trials in Russia in 2009 by phase



As shown in Figure 6, the share of Phase III trials in 2009 stood at 59% of the total number of studies, the share of Phase II trials accounted at 26%, 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 2009



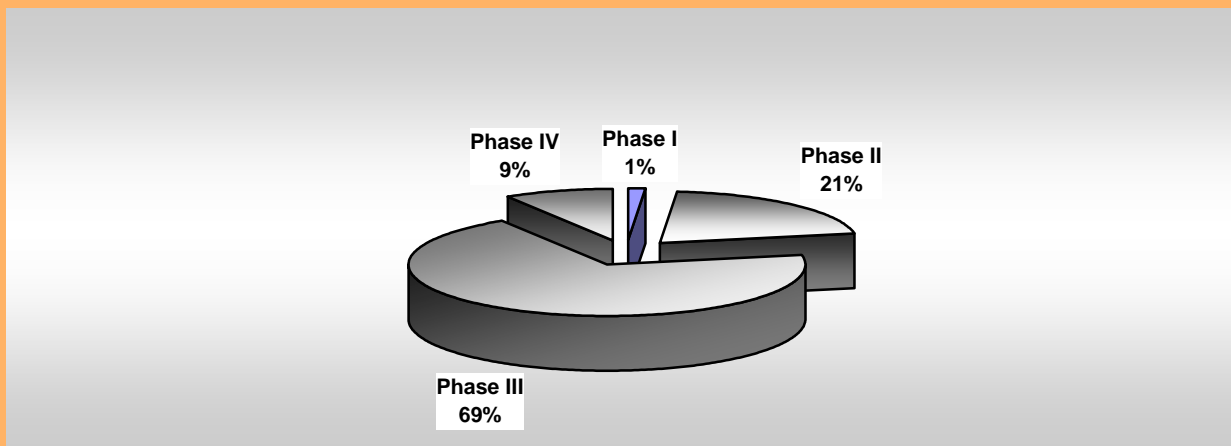
The number of patients which are planned to be enrolled in the Phase II-IV trials launched in 2009 stood at 48,521 patients that at 12122 patients fewer than in 2008, when the number of patients which were planned to be enrolled stood at 60643 patients.

664 subjects will be recruited in Phase I trials; 9 988 patients – in Phase II trials; 33 584 subjects – in Phase III studies and 4 285 patients will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is ten, the maximum number is 1 800.

The proportion of the number of patients between different Phases is shown on the Figure 7. Studies were included in which phase were specified.

Figure 7. The number of patients in 2009 by study phase



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



Rating of international sponsors

The Swiss pharmaceutical giant *Novartis* sponsoring 35 new studies is on the top of the heap in 2009. The American *Pfizer* with 22 new trials in 2009 took the runner-up place; it is followed by *Merck and GlaxoSmithKline* with 20 trials each and *Boehringer Ingelheim* closed the top five with 16 new trials.

Top five international sponsors by the number of new studies in 2009 are presented in Table 1.

Table 1. Top-5 international study sponsors in 2009

| No | Sponsor | No. of trials | No. of patients | No. of sites |
|----|----------------------|---------------|-----------------|--------------|
| 1 | Novartis | 35 | 2219 | 266 |
| 2 | Pfizer | 22 | 1155 | 101 |
| 3 | GlaxoSmithKline | 20 | 2054 | 133 |
| 4 | Merck & Co. | 20 | 1722 | 107 |
| 5 | Boehringer Ingelheim | 16 | 1540 | 147 |

Rating of Russian sponsors

The Russian company *ZAO Valenta Pharmaceutica* sponsoring 13 new clinical trials, ranked number one among domestic pharmaceutical manufacturers by the number of new studies in 2009. *ZAO Pharmaceutical Company "Obolensky"* with 13 new trials took the runner-up place.

ZAO "Canonpharma" ranked third with 12 new studies. It is followed by *ZAO "Biocad"* with 9 new trials and *Microgen* closed the top five with 8 new trials.

Table 2. Top-5 Russian study sponsors in 2009

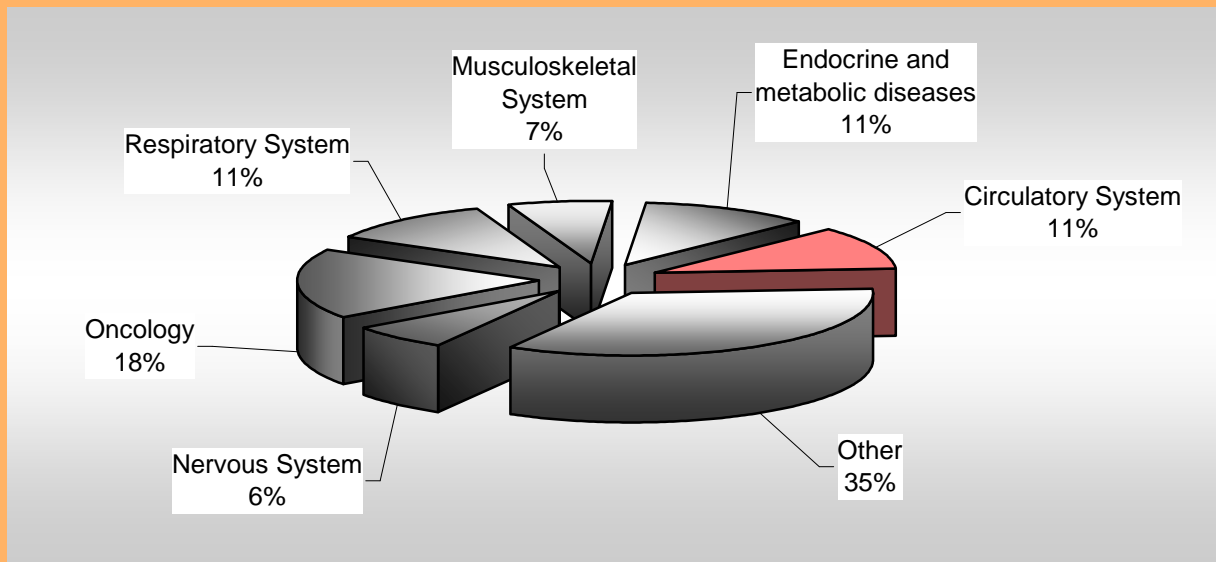
| No | Sponsor | No. of trials | No. of patients | No. of sites |
|----|-------------|---------------|-----------------|--------------|
| 1 | Valenta | 13 | 983 | 22 |
| 2 | Obolensky | 13 | 298 | 13 |
| 3 | Canonpharma | 12 | 522 | 15 |
| 4 | Biocad | 9 | 890 | 32 |
| 5 | Microgen | 8 | 1050 | 18 |

Therapeutic areas of clinical trials in Russia in 2009

In 2009, 85% of new studies were initiated in six major therapeutic areas: greatest number of studies has been initiated in the field of Oncology – 104 clinical trials; Endocrine and metabolic diseases - 66; Respiratory System – 66; Circulatory System – 64; Musculoskeletal System – 40 and diseases of the Nervous System – 38 new clinical trials.

The proportions between different therapeutic areas are shown in Figure 8.

Figure 8. Clinical trials in Russia in 2009 by therapeutic area



Clinical trials results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 97 new drugs during Year 2009; 18 of them are really new molecular entities; others had new dosages, manufacturers or indications of the already marketed drugs. Eight drugs were studied in Russia.

The Table 3 represents drugs which were approved by FDA and were being tested in clinical trials in Russia in Q4 2009 (Q1 – Q3 data is presented in the previous issues of SynRG Orange Paper).

Table 3. New Drugs approved by FDA in Q4 2009 and tested in Russian sites

| Approval date | Drug (active substance) | Manufacturer |
|---------------|------------------------------------|-------------------|
| 10/16/2009 | COLCRYL (COLCHICINE) | MUTUAL PHARMA |
| 10/19/2009 | VOTRIENT (PAZOPANIB HYDROCHLORIDE) | GLAXOSMITHKLINE |
| 10/26/2009 | ARZERRA (OFATUMUMAB) | GLAXO GRP LTD |
| 10/30/2009 | BYETTA (EXENATIDE SYNTHETIC) | AMYLIN |
| 11/05/2009 | ISTODAX (ROMIDEPSIN) | GLOUCESTER PHARMS |
| 11/16/2009 | QUTENZA (CAPSAICIN) | NEUROGESX |
| 11/18/2009 | REVATIO (SILDENAFIL CITRATE) | PFIZER |
| 11/24/2009 | Efavirenz (Efavirenz) | MATRIX LABS LTD |

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



During the year 2009 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) reviewed 153¹ applications to market drugs in the EU. Negative opinion was adopted for eleven drugs. Twenty seven of the drugs which received positive opinions were (or are being) tested in clinical trials in Russia.

The Table 4 represents those of them which were, or are being tested in clinical trials in Russia in Q4 2009 (Q1 – Q3 data is presented in the previous issues of SynRG Orange Paper).

Table 4. New Drugs approved by EMA in Q4 2009 and tested in Russian sites

| Approval date | Drug | Manufacturer |
|--|-------------------------------------|---|
| 17/12/2009 | Revolade (<u>eltrombopag</u>) | GSK |
| 17/12/2009 | Ristaben(<u>sitagliptin</u>) | Merck Sharp & Donme |
| 17/12/2009 | Prolia (<u>denosumab</u>) | Amgen |
| 17/12/2009 | Herceptin (<u>trastuzumab</u>) | Hoffmann-La Roche |
| 17/12/2009 | Orencia (<u>abatacept</u>) | Bristol-Myers Squibb |
| 19/11/2009 | Docetaxel Teva (<u>docetaxel</u>) | Teva Pharmaceutical Industries |
| 22/10/2009 | Adcirca (<u>tadalafil</u>) | Eli Lilly and Company |
| 22/10/2009 | Micardis (<u>telmisartan</u>) | Boehringer Ingelheim Pharmaceuticals |
| | | |
| Source: CHMP EMA http://www.emea.europa.eu/index/indexh1.htm | | |

FDA inspections

According to the FDA data, seven FDA inspections were conducted in the Russian investigative sites during 2009, all of them with NAI result – no actions indicated.

If you find an error or typo in the text of the Orange Book, or you have any questions or suggestions on its content, please, send your comments to orangepaper@synrg-pharm.com

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