Clinical Trials in Russia
Orange Paper
Summary of Year 2013

11, 4-Magistralnaya Ul., 123007 Moscow, Russia

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Executive Summary – English

The Ministry of Health of the Russian Federation (MoH) approved 790 new clinical trials of all types during 2013, demonstrating a 14% decrease from 2013. The major component of the total number of studies is by the multinational, multi-center clinical trials, which accounted for 358 new studies, approximately the same from the previous year.

The number of bioequivalence studies fell dramatically, from 322 studies in 2012 to 265 in 2013. The number of local clinical trials (Phase I, II and III) has also decreased significantly from 217 to 167 clinical trials.

Multinational, multi-center clinical trials was 45% of the total number of clinical trials in Russia in 2013, while the local and bioequivalence studies amounted to 21% and 34%, respectively.

Clinical trials in Russia in 2013 were sponsored by companies from 31 countries. The maximum number of trials (325) was initiated by Russian sponsors. American sponsors were runner-up with 131 new studies. They were followed by Swiss sponsors with 57 trials and Germany with 34 new studies. UK and Indian sponsors each conducted 32.

34 new Phase I clinical trials were launched in 2013, 5 less than in 2012. The number of Phase II trials decreased to 91 new studies in 2013. The number of Phase III trials decreased from 396 to 372 studies, 6% less than in 2012. Phase IV trials decreased from 48 studies in 2012 to 28 studies in 2013.

In 2012, a total of 67,023 Russian patients were enrolled in clinical trials. This number also decreased to 57,609 in 2013

Novartis led the way in 2013 with the initiation of 34 new studies. . They were followed by *Teva* with 20 studies and *Merck & Co.* with 19 new trials. The Top five list includes GlaxoSmithKline and Roche with 17 and 16 new trials respectively in 2013,.

The Russian company *Atoll* sponsored 30 new clinical trials in 2013, ranked number one among domestic pharmaceutical manufacturers by the number of new studies. . *Vertex*- Russiawas the runner up with 18 new trials. . Vertex was followed by *Biocad with 13 trials* and *Akrikhin* with 11 new trials. The Top Five list of domestic companies is concluded by *Izvarino-Pharma* with 10 new trials

More than two thirds of new studies in 2013 were initiated in eight leading therapeutic areas: the largest number of studies was initiated in Oncology (106); 60 new studies were initiated in Pulmonology, 50 studies in Cardiology and Endocrinology, 48 new studies in Musculoskeletal diseases, 42 studies in Infectious diseases, 30 studies in Neurology; and 27 new studies in Psychiatry.

The Center for Drug Evaluation and Research (CDER) of the FDA approved 114 new drugs during 2013. 53 of them were conducted at least in part in Russia.

During 2013 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 101 new drug applications; 86 of which were tested in Russian sites.

Two FDA inspections were conducted in Russia during 2013. Both inspections ended with only VAI results – voluntary action indicated, a very positive showing for Russian sites and Investigators.

Executive Summary – Russian

В 2013 году Министерством здравоохранения Российской Федерации было выдано 790 разрешений на все виды клинических исследований, что на 14% меньше, чем в 2012 году.

При этом количество международных многоцентровых клинических исследований практически не изменилось и составило 358 новых исследований. Количество исследований биоэквивалентности, инициированных в 2013 году, значительно уменьшилось, с 322 до 265 исследований по сравнению с 2012 годом. Количество локальных клинических исследований, проводимых на территории России отечественными и иностранными спонсорами, также снизилось с 217 до 167 исследований.

Спонсорами клинических исследований, разрешенных к проведению в России в 2013 году, выступили компании из 31 страны. На первое место вышли российские производители с 325 КИ, за ними идут американские спонсоры со 131 новым исследованием, Швейцария с 57 и Германия с 34 КИ. Замыкают группу лидеров Великобритания и Индия, с 32 исследованиями у каждой.

В 2013 году было инициировано 34 новых клинических исследования I фазы, что на 5 КИ меньше, чем в прошлом году. Количество исследований II фазы за этот период уменьшилось и составило 91 новых исследований. Количество исследований III фазы несколько уменьшилось, с 369 до 372 исследований – на 6% меньше по сравнению с прошлым годом. Количество исследований IV фазы уменьшилось и составило 28 новых исследований.

Всего в клинических исследованиях I-IV фаз, начатых в 2013 году, примет участие 57609 субъектов, что на 14% меньше, чем в прошлом году, когда в исследования планировалось включить 67023 субъектов.

В 2013 году первое место среди иностранных производителей по количеству новых исследований заняла фармацевтическая компания *Novartis* с 34 новыми исследованиями. *Teva* и *Merck & Co* инициировали по 20 и 19 исследований соответственно, но с разным количеством субъектов. Замыкают пятерку лидеров *GlaxoSmithKline* and *Roche* с 17 и 16 новыми исследованиями.

Первое место среди отечественных производителей по количеству исследований, начатых в 2013 году, занимает *«Атолл»* с 30 новыми клиническими исследованиями. За ним идут «*Вертекс»* с 18 новыми исследованиями, «Биокад» с 13 проектами, и «Акрихин» с 11 новыми исследованиями. Завершает пятёрку лидеров *«Изварино-Фарма»*, инициировавший десять новых исследований.

В 2013 году более двух третей всех новых исследований было инициировано в восьми терапевтических областях: наибольшее количество в области онкологии – 106 КИ; 60 новых исследований в пульмонологии; по 50 исследований – в эндокринологии и кардиологии; 48 исследований – в области заболеваний опорно-двигательного аппарата, 43 исследований – в области инфекционных болезней, 30 исследований в неврологии и 27 проектов – в психиатрии.

В 2013 году Росздравнадзор провел 113 проверок деятельности медицинских организаций по проведению клинических исследований. Нарушения были выявлены в 34 организациях.

За 2013 год в России были проведены две инспекции FDA. Обе инспекции завершились с результатом VAI (voluntary action indicated).

Clinical Trials by Type and Manufacturing Country

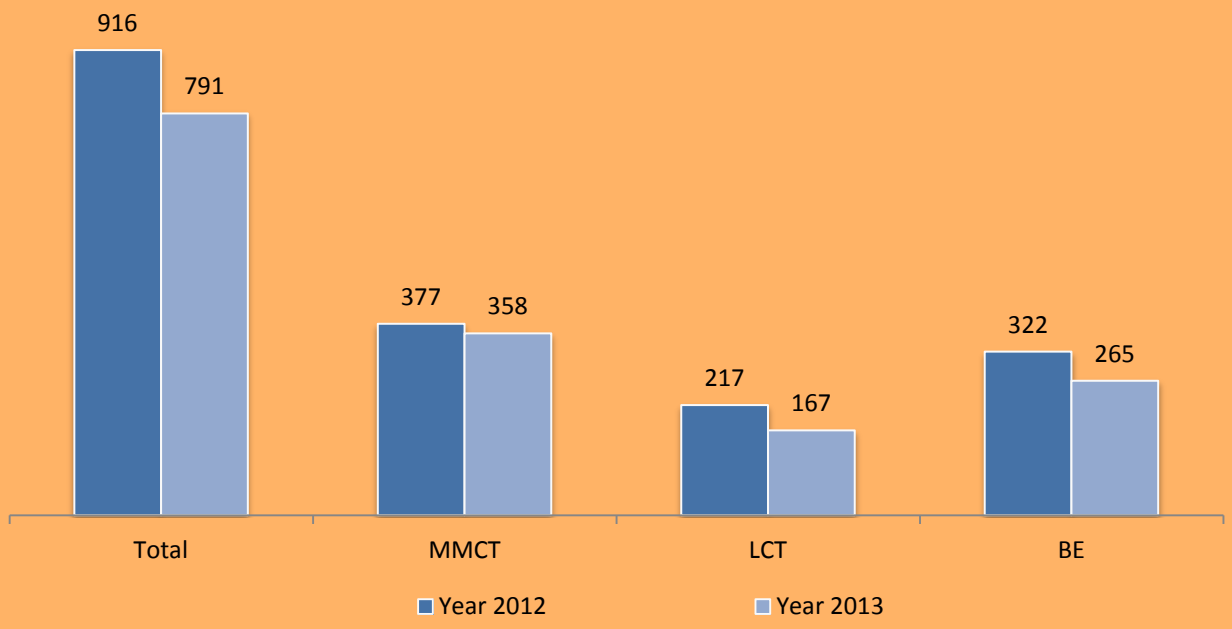
The Russian MoH approved 790 new clinical trials of all types including local and bioequivalence studies during 2013, demonstrating a 14% decrease comparing to last year.

As shown in **Figure 1**, the main contributor to the total number of studies was made by multinational multi-center clinical trials (MMCT). The number of studies has not changed significantly and stood at 358 new studies in 2013, nearly the same as a year ago.

The number of the local clinical trials (LCT) conducted in Russia by domestic and foreign sponsors decreased from 217 to 167 clinical trials, 13% less than last year's figure.

The number of bioequivalence studies (BE) in 2013 stood at 265 new trials demonstrating significant decrease compared with the number of studies in 2012 (18%).

Figure 1. Clinical Trials in Russia in 2013

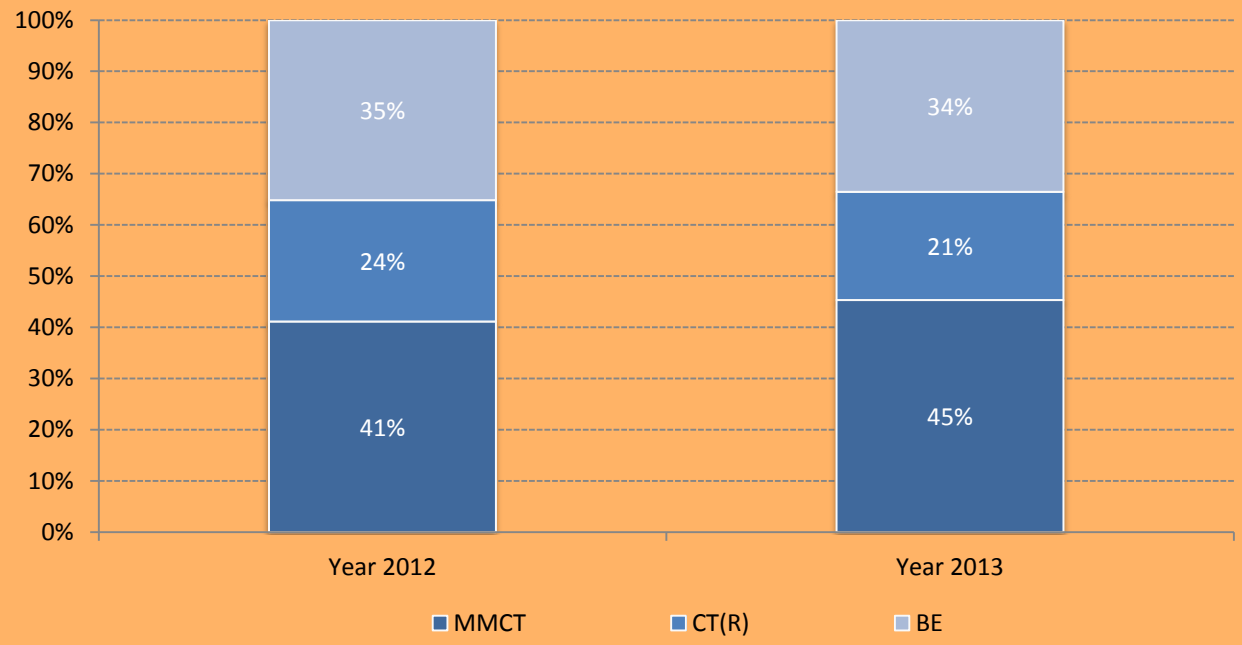


The proportions between different study types (multinational multi-center clinical trials, local studies and bioequivalence trials) changed slightly from last year (see **Figure 2**).

The share of bioequivalence studies decreased from 35% in 2012 to 34% of the total number of clinical trials approved in 2013.

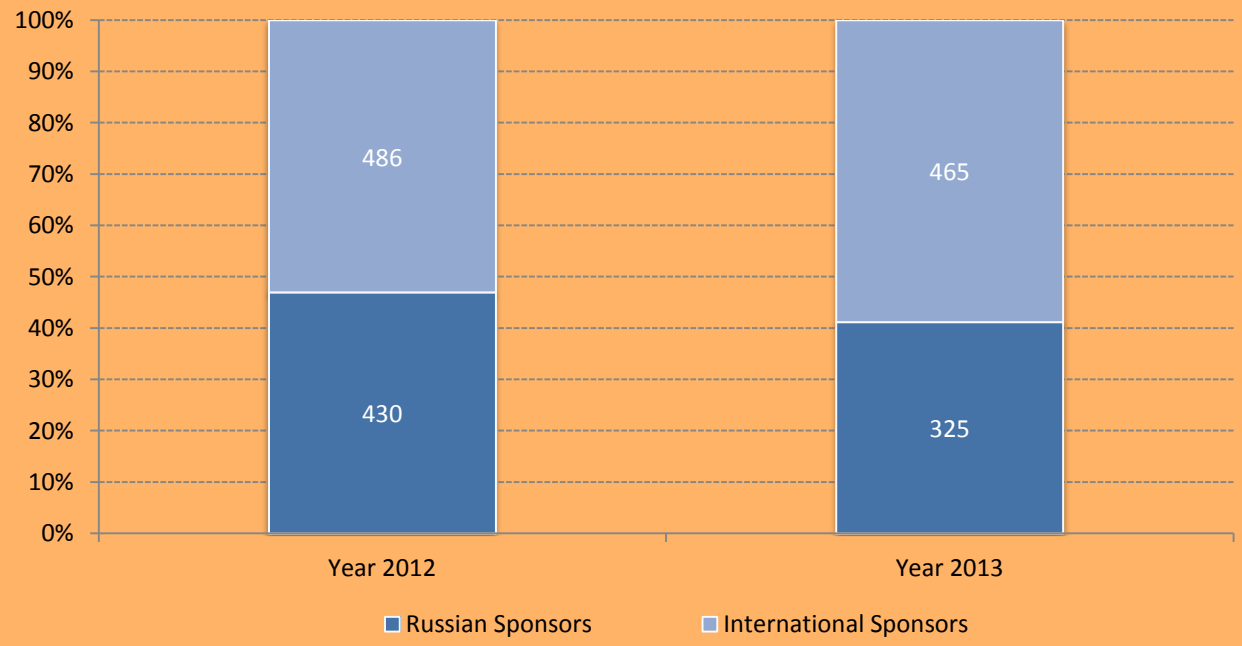
The share of the local trials stood at 21%, slightly less than in 2012 (24%), and the share of multinational multi-center clinical trials increased from 41% to 45% of the total number of trials approved during 2013.

Figure 2. Clinical Trials byType in 2013



The geographic origins of sponsors changed significantly from last year. In 2012, 59% of new studies were sponsored by foreign companies which received 465 study approvals. The share of studies of local manufacturers decreased from 47% in 2012 to 41% in 2013, and amounted to 325 studies (**Figure 3**).

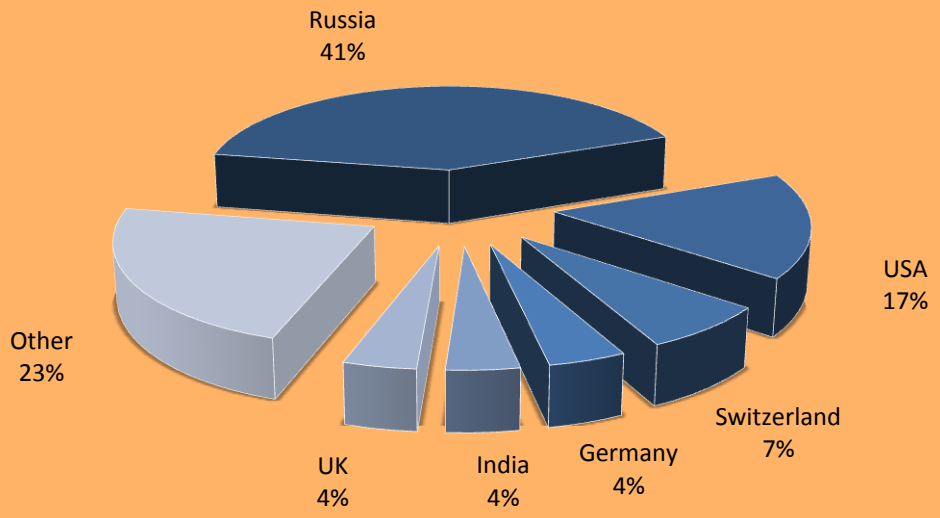
Figure 3. Russian vs International Sponsors in 2013



Sponsors from 31 countries initiated Clinical trials in Russia in 2013. **igure 4** indicates the geographic breakdown in sponsors country of origin.

Russian sponsors initiated the highest number of new studies (325) American sponsors took runner-up with 131 new studies, followed by Swiss sponsors with 57 trials and Germany with 34 new studies Again, the UK and India tied at 32 studies each.

Figure 4. Sponsors Country of Origin for 2013 Clinical Trials in Russia.



Other sponsors include: France (27), Israel (22), Belgium (19), Hungary (12), Denmark (12), Austria (11), Sweden (11), Poland (nine), Czech Rep (seven), Belarus, Italy and Ukraine (six trials each), Croatia (5), Japan, Romania and Slovenia (four studies each), Latvia (three), Netherlands and Korea (two trials each), and Bulgaria, Greece, Canada, Luxemburg, Macedonia, Singapore, and Turkey each started one new study in 2013.

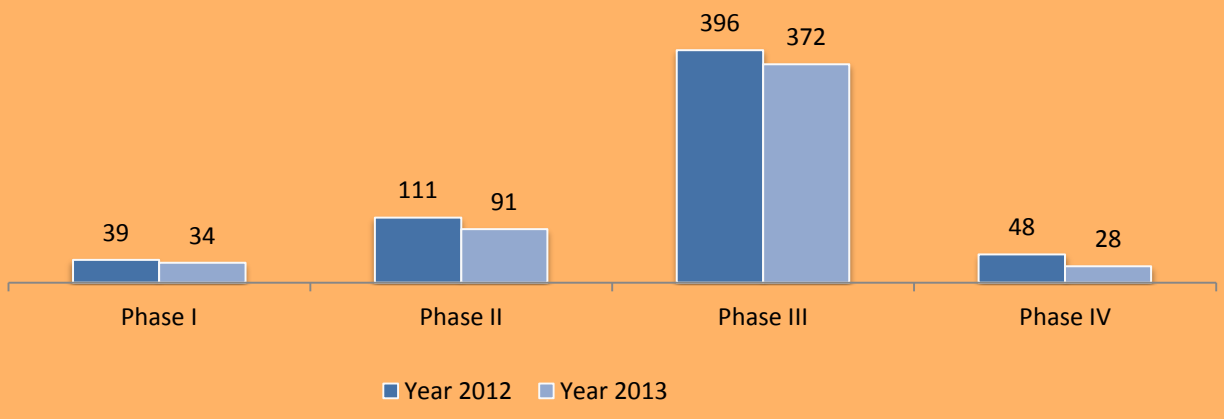
Clinical trials by Phase

34 new Phase I clinical trials were launched in 2013, 5 less than in 2012. The number of Phase II trials decreased from 111 in 2012 to 91 new studies in 2013 (**Figure 5**).

The number of Phase III trials also decreased from 396 to 372 studies, 6% less than in 2012.

Phase IV trials also decreased from 48 studies in 2012 to 28 studies in 2013.

Figure 5. Clinical Trials in Russia in 2013 by Phase[1]

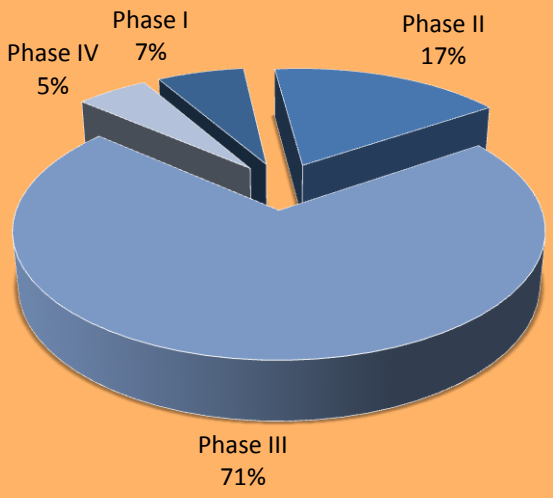


[1] Studies indicated by sponsors as Phase I-II for applications submitted to MoH are shown in Phase II studies group; Phase II-III – in Phase III group; Phase III-IV – in phase IV group. BE studies were not included in any Phase group, even in case a specific Phase was indicated in the application.

As shown in **Figure 6**, the share of Phase III trials in 2013 stood at 71% of the total number of studies while the share of Phase II trials accounted for 17%.

Phase IV trials stood at 5%, and the share of Phase I studies amounted to 7%.

Figure 6. Percentage Breakdown of Russian Clinical Trials, by Phase.



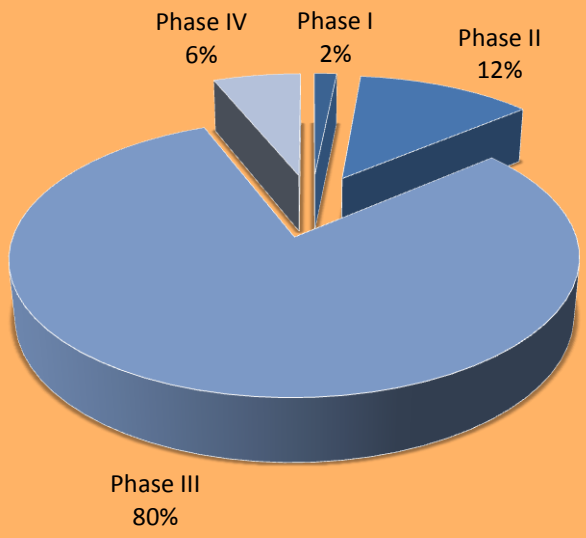
The number of subjects planned to be enrolled in Phase I-IV trials in 2013 was 57,609, 14% less than in 2012 when 67,023 patients were planned to be enrolled.

A total of 902 subjects will be recruited in Phase I trials; 7,076 patients in Phase II trials; 46,101 subjects in Phase III studies and 3,530 patients will be enrolled in Phase IV studies.

The smallest number of subjects enrolled in a single study is two, the maximum number is 2,510.

Figure 7 indicates the distribution of patients by study phase, with Phase 3 clearly enrolling the majority of patients, as is to be expected

Figure 7. Number of Patients in 2013 by Study Phase



Number of Studies by Sponsor

Novartis leads the way with 34 studies submitted in 2013.They are followed by *Teva* with 20 studies and *Merck & Co.* with 19 new trials. The Top five is concluded by GlaxoSmithKline and Roche with 17 and 16 new trials respectively, submitted in 2013.

Top five international sponsors ranked by the number of new studies in 2013 are presented in **Table 1**.

Table 1. Top-5 International Study Sponsors in 2013

№	*Company Name*	*No. studies*[1]	*No. patients*
1	Novartis	34	2,244
2	Teva	20	1,451
3	Merck & Co.	19	1,357
4	GlaxoSmithKline	17	1,539
5	Roche	16	2,061

Rating of Russian sponsors

The Russian company *Atoll* sponsored 30 new clinical trials, ranked number one among domestic pharmaceutical manufacturers by the number of new studies in 2013. *Vertex* was second with 18 new trials. They are followed by *Biocad with 13 trials* and *Akrikhin* with 11 new trials. The Top five is concluded by *Izvarino-Pharma* with ten new trials (see Table 2 for details).

Table 2. Top-5 Russian study sponsors in 2013

№	*Company Name*	*No. studies*[1]	*No. patients*
1	Atoll LLC	30	1 188
2	Vertex - Russia	18	544
3	Biocad	13	1 089
4	Akrikhin	11	538
5	Izvarino-Pharma	10	320

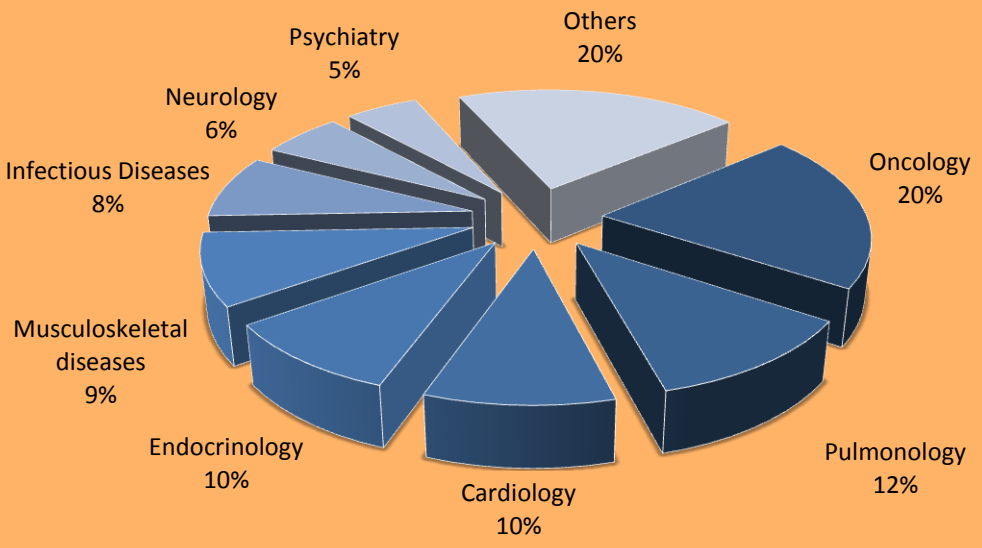
[1] Excluding BE studies

Therapeutic Areas of Russian Clinical Trials in 2013

More than two thirds of new studies in 2013 were initiated in eight leading therapeutic areas. The largest number of studies was initiated in Oncology (106); 60 new studies were initiated in Pulmonology, 50 studies in Cardiology and Endocrinology, 48 new studies in Musculoskeletal diseases, 42 studies in Infectious diseases, 30 studies in Neurology; and 27 new studies in Psychiatry.

The breakdown of therapeutic areas is shown in **Figure 8**.

Figure 8. Clinical Trials in Russia in 2013 by Therapeutic Area



Clinical Trials Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 114 new drugs during 2013; 24 of them are new molecular entities (NME); others are new dosages, manufacturers or indications of already marketed drugs. 53 of the 114 drugs were studied in clinical trials conducted in Russia.

The **Table 3** represents drugs which were approved by FDA and were being tested in clinical trials in Russia in Q4 2013 (Q1-Q3 data is presented in the previous issues of SynRG Orange Paper).

Table 3. New Drugs Approved by FDA in Q4 2013 and Tested in Russian sites

Appr.date	*Drug (active ingredient)*	*Company*
10/03/2013	Duavee (bazedoxifene acetate, estrogens, conjugated)	Wyeth Pharms Pfizer
10/08/2013	Adempas (riociguat)	Bayer Healthcare
10/18/2013	Opsumit (macitentan)	Actelion Pharms LTD
10/21/2013	Actemra (tocilizumab)	Genentech
11/01/2013	Gazyva (obinutuzumab)	Genentech

11/08/2013	Aptiom (eslicarbazerine acetate)	Sunovion Pharms INC
11/13/2013	Imbruvica (ibrutinib)	Pharmacyclics INC
11/25/2013	Noxafil (posaconazole)	Merck Sharp Dohme
12/06/2013	Solvadi (solosbuvir)	Gilead Sciences INC
12/18/2013	Anoro ellipta (umeclidinium bromide, vilanteroltrrifenatate)	Glaxo GRP LTD
12/20/2013	Isentress (raltegravir potassium)	Merck Sharp Dohme
		Source: FDA

During 2013 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) approved 101 new drug applications. Negative opinion was adopted for eight drugs. 86 of the drugs which received positive opinions were (or are) being tested in clinical trials in Russia.

Table 4 represents drugs which were or are being tested in clinical trials in Russia in Q4 2013 (Q1-Q3 data is presented in the previous issues of SynRG Orange Paper).

Table 4. New Drugs Approved by EMEA in Q4 2013 and Tested in Russian sites

Appr. date	*Drug (active ingredient)*	*Manufacturer*
10/21/2013	Brintellix (vortioxetine)	H.Lundbeck A/S
10/21/2013	Opsumit (macitentan)	Actelion Registration Ltd
10/21/2013	Cimzia (certolizumab pegol)	UCB Pharma SA
10/21/2013	Eviplera (emtricitabine, rilpivrine, tenofovir disoproxil)	Gilead Sciences International Ltd
10/21/2013	Pandemic Influenza Vaccine Baxter H5N1 (H5N1, whole virion, Vero cell derived, inactivated)	Baxter AG
11/18/2013	Para-aminosalicilic acid Lucane (para-aminosalicilic acid)	Lucane Pharma SA
11/18/2013	Sovaldi (sofosbuvir)	Gilead Sciences International Ltd
11/18/2013	Tivicay (dolutegravir)	ViiV Healthcare
11/18/2013	Xigduo (dapagliflozin, metformin)	Bristol-Myers Squibb / AstraZeneca EEIG
11/18/2013	Abraxane (paclitaxel)	Celgene Europe Limited
11/18/2013	Pradaxa (dabigatran etexilate)	Boehringer Ingelheim International GmbH
11/18/2013	Velcade (bortezomib)	Janssen-Cilag International N.V.
12/16/2012	Comertiq (cabozantinib)	TMC Pharma Services Ltd
12/16/2013	Izba (travoprost)	Alcon Laboratories (UK) Ltd

12/16/2013	Sirturo (bedaquiline)	Janssen-Cilag International N.V
12/16/2013	Tritanrix HB (diphtheria, tetanus, pertussis and hepatitis B vaccine)	GlaxoSmithKline Biological S.A.
12/16/2013	Jentaduento (linagliptin, metformin)	Boehringer Ingelheim International GmbH
		Source: EMEA

FDA inspections

Two FDA inspections were conducted in Russian investigative sites during the 2013 year: one in Moscow (on 18-Feb-2013), and the second in St Petersburg (on 03-Jun-2013). Both inspections ended with VAI result – voluntary action indicated.

Summary

In summary, Russian remains a very popular geography for local, regional, and global pharmaceutical companies to conduct clinical trials. Sponsors mention the following reasons for conducting studies in Russia:

1. **Fast patient enrollment** due to the centralized medical infrastructure.
2. **Nearly 100% patient retention**
3. **GCP trained and certified Investigative Sites** generating high-quality data
4. **Low cost:** Average per patient cost is 60% to 70% below US and European prices due to the low cost of Investigators and the high concentration of patients in therapeutically aligned medical centers.

About Synergy Research Group

Synergy Research Group is a Russian contract research organization successfully operating in Russia since 2002. Synergy provides a full range of CRO services to help Russian and foreign pharmaceutical and biotechnological companies conduct cost-effective clinical trials. Today, Synergy is represented in Moscow, Saint-Petersburg, Novosibirsk, Yekaterinburg, Perm, Krasnodar, and also in Almaty and Astana (Kazakhstan) and Kyiv (Ukraine). The company's headquarters are in Moscow.