Clinical Trials in Russia
Orange Paper
2nd Quarter 2014

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Executive Summary – English

The Ministry of Health of Russian Federation approved 194 new clinical trials of all types including local and bioequivalence studies during the 2nd Quarter of 2014 (3% less than at the same period of the last year).

The main contribution to the total number of studies was made by multinational multi-center clinical trials (MMCT) and the number of these studies stayed the same as in Q2 2013 – 81 studies. The number of bioequivalence studies (BE) decreased from 76 studies in Q2 2013 to 59 in Q2 2014, a 22% decrease from last year's figure. The number of local clinical trials (LCT) increased from 42 in Q2 2013 to 54 clinical trials in Q2 2014.

The share of multinational, multi-center clinical trials was 42% of the total number of clinical trials in Q2 2014, while bioequivalence and local studies amounted to 30% and 28% respectively.

Clinical trials in Russia in Q2 2014 were sponsored by companies from 24 countries. The highest number of trials (89) was initiated by Russian sponsors. American sponsors with 29 new studies took the runner-up place; they are followed by German and UK sponsors with 11 trials each, Swiss sponsors with ten studies and Israeli sponsors with nine new studies. The group of leaders is concluded by French sponsors having seven studies.

The number of Phase I clinical trials remained about the same and stood at eight new studies in Q2 2014. The number of the Phase II trials increased from 21 in Q2 2013 to 29 new studies in Q2 2014. The number of Phase III trials increased from 88 to 92 studies, 5% more than in Q2 2013. Phase IV trials showed an increase from five studies in Q2 2013 to six studies in Q2 2014.

The number of subjects planned to be enrolled in Phase I-IV trials launched in Q2 2014 is 15,424, 22% more than in Q2 2013 figure, when 12,677 patients were planned to be enrolled.

GlaxoSmithKline sponsoring six new studies is on the top of the heap in Q2 2014. It is followed by *Janssen, Pfizer, Merck & Co.* and *Amgen* each having four new trials in Q2 2014 and differing in the number of patients.

Top five domestic pharmaceutical manufacturers by the number of new studies in Q2 2014 consists of *Microgen, EcoPharmPlus, OOO Atoll, Petrovax* and *Trivium-XXI* each having two new trials and differentiating in the number of patients.

82% of new studies in Q2 2014 were initiated in eight leading therapeutic areas: Oncology, Pulmonology and Musculoskeletal diseases – 16 studies in each area. 14 new studies were instigated in Infectious and Parasitic diseases as well as in Circulatory system diseases. 12 new studies were begun in diseases of the digestive system as well as in Endocrinology and seven studies in Hematology.

The Center for Drug Evaluation and Research (CDER) of the FDA approved 25 new drugs during Q2 2014, and 10 of them were (or are being) studied in clinical trials conducted in Russia.

During the second quarter of 2014 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 28 new drug applications[1]. A negative opinion was adopted for one drug. 18 of the drugs which received positive opinions were (or are being) tested in clinical trials in Russia.

At the moment of the Orange Paper Q2 2014 production no information about any inspections (FDA or Roszdravnadzor) conducted in the Russian investigative sites was available.

[1] Positive opinions on new generic medicines are not included

Executive Summary – Russian

Во втором квартале 2014 года Министерством здравоохранения Российской Федерации было выдано 194 разрешения на все виды клинических исследований (КИ), что на 3% меньше, чем за аналогичный период 2013 года.

При этом количество новых международных многоцентровых КИ осталось на прежнем уровне по сравнению с этим же периодом прошлого года – 81 исследование. Количество исследований биоэквивалентности, инициированных во втором квартале 2014 года, снизилось по сравнению со вторым кварталом 2013 года и составило 59 против 76. Количество локальных КИ, проводимых на территории России отечественными и иностранными спонсорами, возросло с 42 до 54 исследований.

Спонсорами КИ, разрешенных к проведению в России во втором квартале 2014 года, выступили компании из 24 стран. На первое место вышли российские производители с 89 КИ, за ними идут американские спонсоры с 29 новыми исследованиями, Германия и Великобритания с 11 исследованиями у каждой, а также Швейцария и Израиль с десятью и девятью новыми исследованиями соответственно. Замыкает группу лидеров Франция с семью новыми исследованиями.

Во втором квартале 2014 года было инициировано восемь новых КИ I фазы – на одно исследование меньше, чем за аналогичный период прошлого года. Количество исследований II фазы увеличилось по сравнению с этим же периодом прошлого года и составило 29 новых исследований против 21. Количество исследований III фазы несколько увеличилось с 88 до 92 исследований – на 5% больше по сравнению с прошлым годом. Количество исследований IV фазы увеличилось с пяти до шести исследований.

Во втором квартале 2014 года первое место среди иностранных производителей по количеству новых исследований заняла фармацевтическая компания *GlaxoSmithKline* с шестью новыми исследованиями. За ней следуют компании *Janssen, Pfizer, Merck & Co.* и *Amgen* с четырьмя новыми исследованиями у каждой, но с разным количеством субъектов.

В пятерку лидеров по количеству новых исследований, начатых во втором квартале 2014 года, среди отечественных производителей входят компании *Микроген, ЭкоФармПлюс, ООО Атолл, Петровакс* и *Тривиум-XXI* с двумя новыми исследованиями у каждой, но с разным количеством субъектов.

Во втором квартале 2014 года 82% всех новых исследований было инициировано в восьми терапевтических областях. Наибольшее количество в области онкологии, пульмонологии и заболеваний опорно-двигательного аппарата – 16 КИ в каждой области; по 14 новых исследований в области инфекционных и паразитарных болезней и болезней системы кровообращения; по 12 исследований в области заболеваний органов пищеварения и эндокринологии, и четыре исследования в области гематологии.

Центр по оценке и исследованию лекарственных средств (Center for Drug Evaluation and Research, CDER) FDA одобрил во втором квартале 2014 года 25 новых лекарственных препарата, по 10 из которых в России проводились (или проводятся) КИ.

В течение второго квартала 2014 года Комитет по лекарственным средствам для применения у человека (Committee for Medicinal Products for Human Use, CHMP) Европейского агентства по лекарственным средствам (European Medicine Agency, EMEA) дал положительные рекомендации по 28 новым заявкам и один негативный отзыв. По 18 лекарствам, входившим в число получивших положительный отзыв, проводились (или проводятся) КИ в России.

Информация о проверках Росздравнадзора и FDA за второй квартал 2014 года на момент выпуска «Оранжевой Книги» недоступна.

Clinical Trials by Type and Manufacturing Country

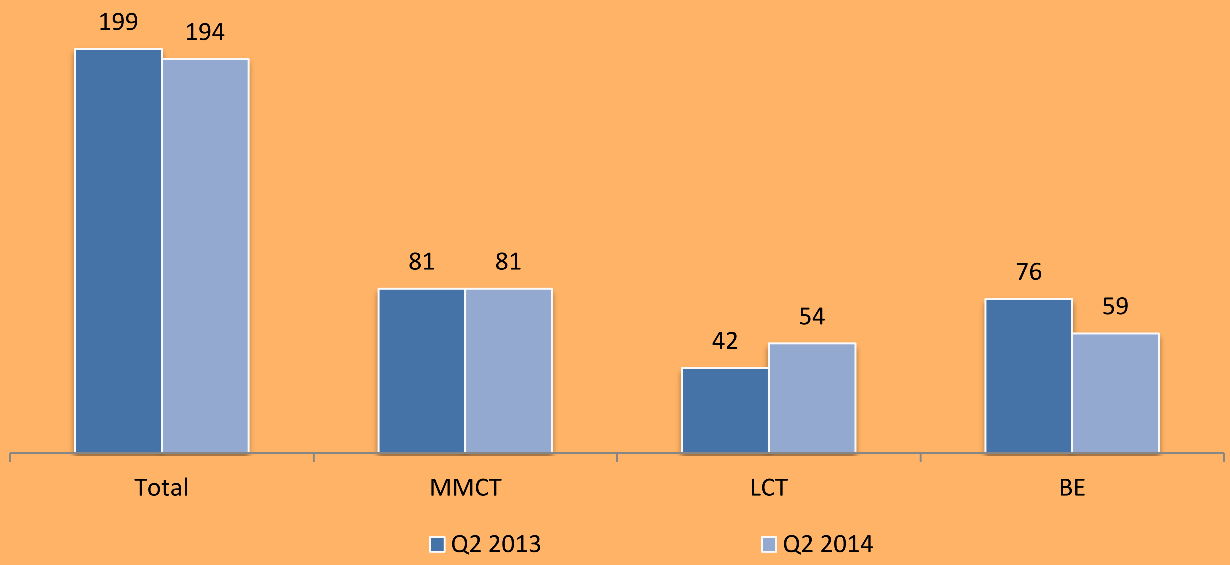
The Russian MoH approved 194 new clinical trials of all types including local and bioequivalence studies during the 2nd Quarter of 2014, demonstrating a 3% decrease in comparison with the same point of the last year.

As shown in **Figure 1**, the main contribution into the total number of studies was made by multinational, multi-center clinical trials (MMCT), the number of these studies was exactly the same as last year – 81 studies.

The number of bioequivalence studies (BE) decreased from 76 studies in Q2 2013 to 59 in Q2 2014, a 22% decrease from last year's figure.

The number of local clinical trials (LCT) increased from 42 in Q2 2013 to 54 clinical trials in Q2 2014, a 29% increase from last year's figure.

Figure 1. Clinical Trials in Russia in Q2 2014

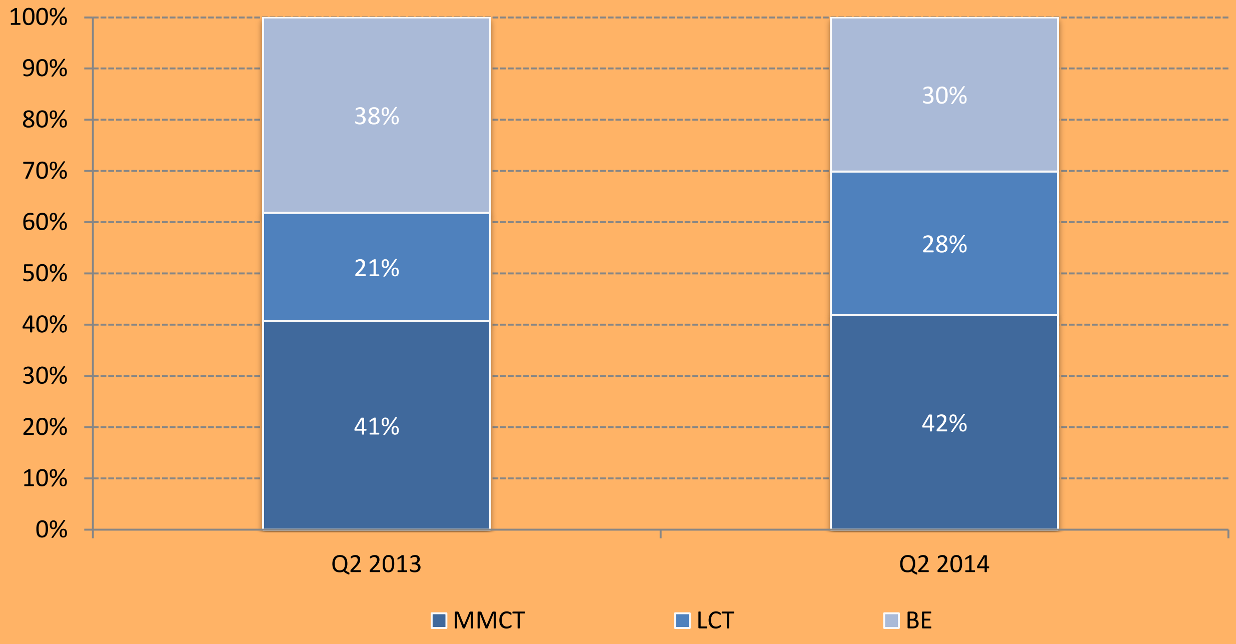


The proportions between different study types (multinational multi-center clinical trials, local studies and bioequivalence trials) changed slightly since last year (see **Figure 2**).

The share of bioequivalence studies decreased from 38% to 30% of the total number of clinical trials approved in Q2 2014.

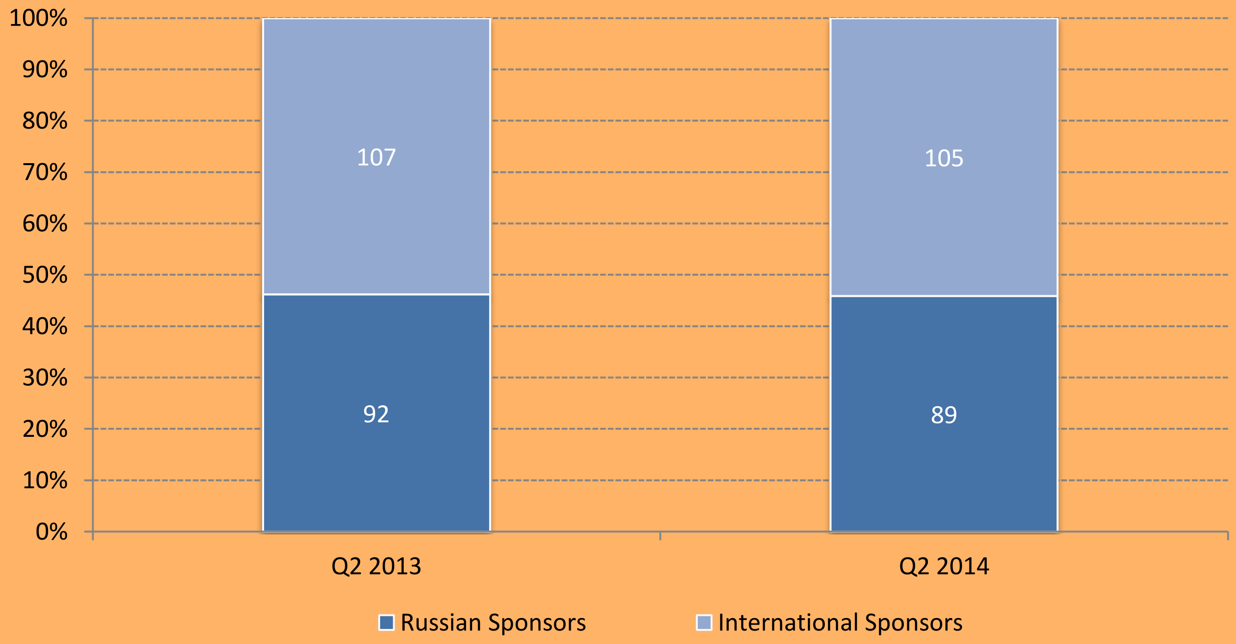
The share of the local trials increased to 28% and the share of multinational multi-center clinical trials slightly increased from 41% to 42% of the total number of trials approved during Q2 2014.

Figure 2. Clinical Trials by Type in Q2 2014



The geographic origins of sponsors did not change in comparison with the same period last year. 54% of the total number of new studies in Q2 2014 are sponsored by foreign companies which received 105 study approvals. The share of studies sponsored by local manufacturers in Q2 2014 was the same as last year – 46%, which amounted to 89 studies (**Figure 3**).

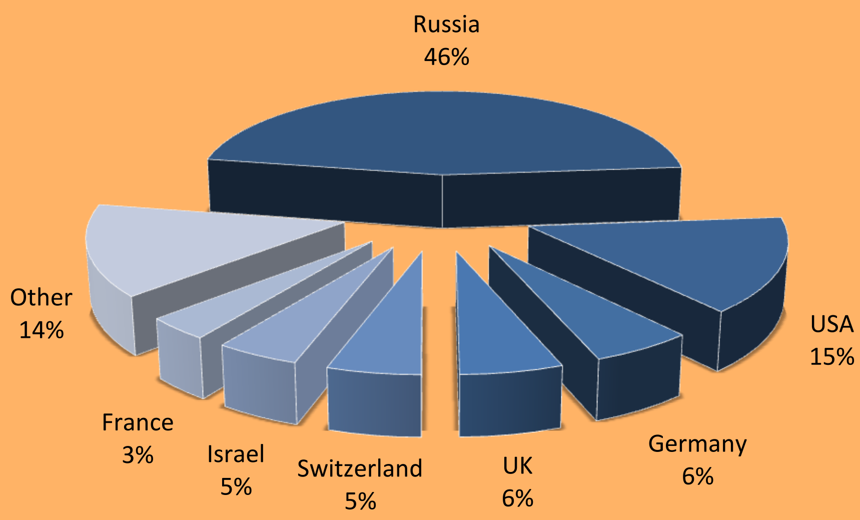
Figure 3. Russian vs International Sponsors in Q2 2014



Clinical trials in Russia in Q2 2014 were sponsored by companies from 24 countries. **Figure 4** indicates the geographic breakdown in sponsors' country of origin.

The highest number of trials (89) was initiated by Russian sponsors. American sponsors with 29 new studies took the runner-up place; they are followed by German and UK sponsors with 11 trials each, Swiss sponsors with ten studies and Israeli sponsors with nine new studies; the group of leaders is concluded by French sponsors having seven studies.

Figure 4. Sponsors Country of Origin for Q2 2014 Clinical Trials in Russia



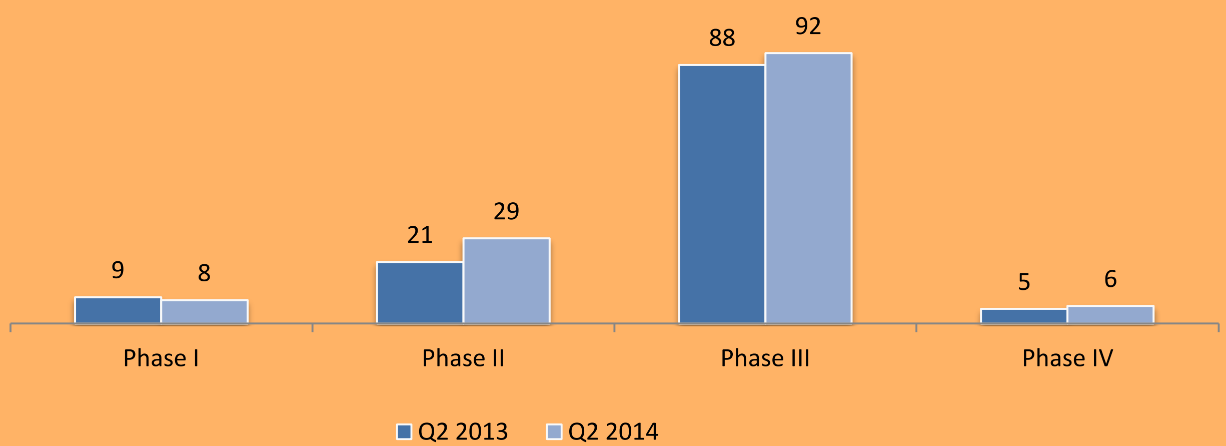
Other sponsors include: Belgium, Netherlands and Japan (three studies each), Austria, Denmark, India, Poland and Ukraine (two studies each). Belarus, Bulgaria, Vietnam, Italy, Canada, Latvia, Turkey, Croatia and Sweden each started one new study in Q2 2014.

Clinical trials by Phase

The number of Phase I clinical trials changed insignificantly and stood at eight new studies in Q2 2014. The number of the Phase II trials increased from 21 in Q2 2013 to 29 new studies in Q2 2014 (**Figure 5**).

The number of Phase III trials increased from 88 to 92 studies, 5% more than in Q2 2013. Phase IV trials demonstrated a slight increase from five studies in Q2 2013 to six studies in Q2 2014.

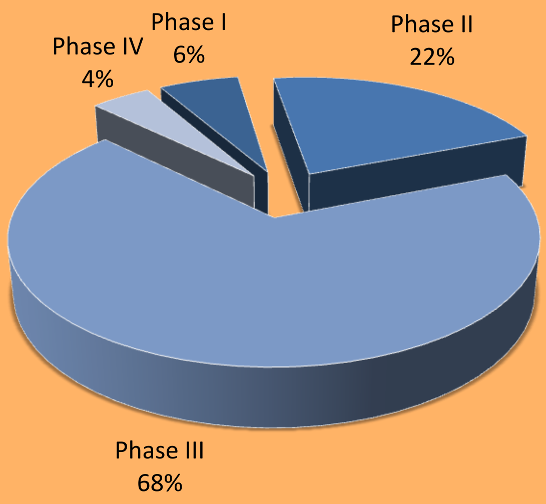
Figure 5. Clinical Trials in Russia in Q2 2014 by Phase[1]



[1] Studies indicated by sponsors as phase I-II in the 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.

As shown in **Figure 6**, the share of Phase III trials in Q2 2014 is 68% of the total number of studies, the share of Phase II trials accounted at 22%, Phase IV trials is 4%, and the share of Phase I studies accounted to 6%.

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



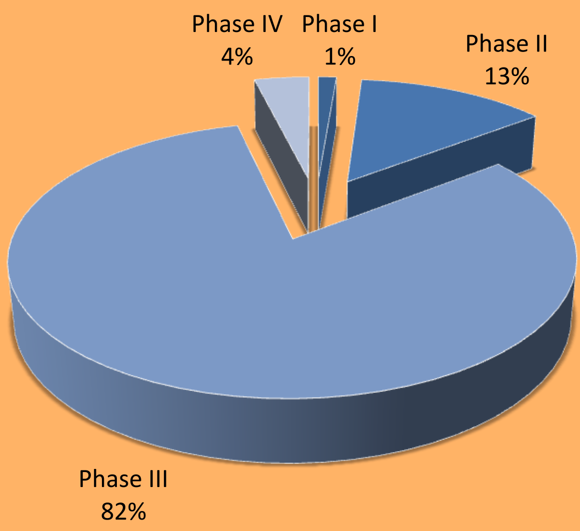
The number of subjects planned to be enrolled in Phase I-IV trials launched in Q2 2014 is 15,424, 22% more than in Q2 2013, when 12,677 patients were planned to be enrolled.

197 subjects will be recruited in Phase I trials; 2,050 patients in Phase II trials; 12,585 subjects in Phase III studies and 592 patients will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is three, the maximum number is 1300.

Figure 7 indicates the distribution of patients by study phase (only studies in which phase is specified were included), with Phase III clearly enrolling the majority of patients, as is to be expected.

Figure 7. Number of Patients in Q2 2014 by Study Phase



Number of Studies by Sponsor

GlaxoSmithKline sponsoring six new studies is on the top of the heap in Q2 2014. It is followed by *Janssen, Pfizer, Merck & Co.* and *Amgen,* each having four new trials in Q2 2014 and differing in the number of patients.

Top five international sponsors ranked by the number of new studies in Q2 2014 are compared in **Table 1.**

Table 1. Top-5 International Study Sponsors in Q2 2014

№	*Company Name*	*No. studies*[1]	*No. patients*
1	GlaxoSmithKline	6	580
2	Janssen	4	875
3	Pfizer	4	561
4	Merck & Co.	4	389
5	Amgen	4	260

Rating of Russian Sponsors

The top five domestic pharmaceutical manufacturers by the number of new studies in Q2 2014 consists of *Microgen, EcoPharmPlus, OOO Atoll, Petrovax* and *Trivium-XXI,* each having two new trials and differing in the number of patients.

Table 2. Top-5 Russian Study Sponsors in Q2 2014

№	*Company Name*	*No. Studies*[1]	*No. patients*
1	Microgen	2	353
2	EcoPharmPlus	2	232
3	OOO Atoll	2	200
4	Petrovax	2	170
5	Trivium-XXI	2	170

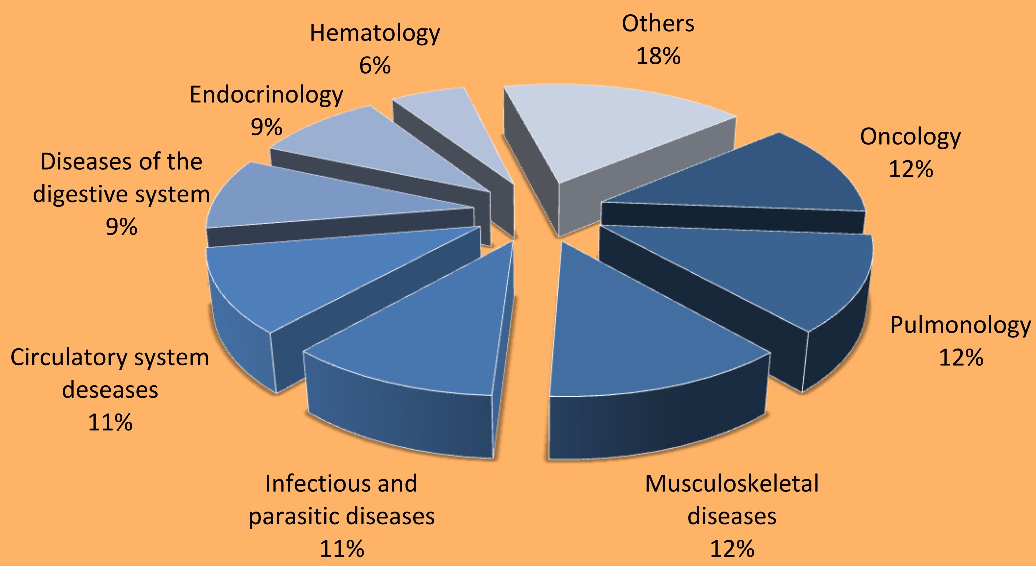
[1] Excluding BE studies

Therapeutic Areas of Russian Clinical Trials in Q2 2014

82% of new studies in Q2 2014 were initiated in eight leading therapeutic areas: the largest number of studies was initiated in Oncology, Pulmonology and Musculoskeletal diseases – 16 studies in each area; 14 new studies were instigated in Infectious and parasitic diseases, as well as in Circulatory system diseases. 12 new studies were started in diseases of the digestive system, as well as in Endocrinology and seven studies in Hematology.

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

Figure 8. Clinical Trials in Russia in Q2 2014 by Therapeutic Area



Clinical Trials Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 25 new drugs during Q2 2014; six of them are new molecular entities (NME); others are new dosages, combinations, manufacturers or indications of already marketed drugs. Ten drugs were (or are being) studied in clinical trials involving Russian sites.

The **Table 3** shows the drugs which were approved by FDA in Q2 2014 that were being tested in clinical trials in Russia.

Table 3. New Drugs Approved by FDA in Q2 2014 and Tested in Russian sites

Appr.date	*Drug (active ingredient)*	*Company*
04/15/2014	Tanzeum (Abiglutide)	GlaxoSmithKline LLC
04/21/2014	Cyramza (Ramucirumab)	Eli Lilly and Co
04/22/2014	Sylvant (Siltuximab)	Janssen Biotech
04/25/2014	Asmanex HFA (Mometasone furoate)	Merck Sharp & Dohme
04/30/2014	Incruse Ellipta (Umeclidinium bromide)	Glaxo GRP England
05/05/2014	Epanova (Omega-3 carboxylic acids)	AstraZeneca Pharms

05/23/2014	Dalvance (Dalbavancin hydrochloride)	Durata Theraps Intl
06/02/2014	Reyataz (Atazanavir)	Bristol Myers Squibb
06/20/2014	Sivextro (Tedizolid phosphate)	Cubist Pharms
06/27/2014	Afrezza (Insulin Human)	Mannkind Corp
		Source: FDA

During the second quarter of 2014 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 28 new drug applications[1]. A negative opinion was adopted for one drug. 18 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 Q2 2014 and Tested in Russian sites

Appr. date	*Drug (active ingredient)*	*Manufacturer*
04/25/2014	Mekinist (Trametinib)	Glaxo Group Ltd
04/25/2014	Gilenya (Fingolimod)	Novartis Europharm Ltd
04/25/2014	Invega (Paliperidone)	Janssen-Cilag International N.V.
04/25/2014	Nexavar (Sorafenib)	Bayer Pharma AG
04/25/2014	Pradaxa (Dabigatran etexilate)	Boehringer Ingelheim International GmbH
04/25/2014	Prolia (Denosumab)	Amgen Europe B.V.
05/22/2014	Gazyvaro (Obinutuzumab)	Roche Registration Ltd
05/22/2014	Arzerra (Ofatumumab)	Glaxo Group Ltd
05/22/2014	Halaven (Eribulin)	Eisai Europe Ltd
05/22/2014	Vfend (Voriconazole)	Pfizer Ltd
05/22/2014	Daklinza (Daclatasvir)	Bristol-Myers Squibb Pharma EEIG
05/22/2014	Triumeq (Abacavir sulfate / Dolutegravir sodium / Lamivudine)	ViiV Healthcare Uk Limited
05/22/2014	Avastin (Bevacizumab)	Roche Registration Ltd
06/26/2014	Eliquis (Apixaban)	Bristol-Myers Squibb / Pfizer EEIG
06/26/2014	Enbrel (Etanercept)	Pfizer Ltd
06/26/2014	Eylea (Aflibercept)	Bayer Pharma AG
06/26/2014	Isentress (Raltegravir)	Merck Sharp & Dohme Ltd
06/26/2014	Stivarga (Regorafenib)	Bayer Pharma AG
		Source: EMEA

[1] Positive opinions on new generic medicines are not included

Inspections

At the time of the Orange Paper Q2 2014 production no information about any inspections (FDA or Roszdravnadzor) conducted in the Russian investigative sites was available.

Summary

In summary, Russia 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.