Clinical Trials in Russia
Orange Paper
1st Quarter 2014

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Executive Summary – English

The Russian Federation Ministry of Health approved 169 new clinical trials of all types including local and bioequivalence studies during the 1st Quarter of 2014 (18% less than at the same period of the last year).

The main contribution into the total number of studies was made by bioequivalence studies (BE), the number of these studies decreased from 69 studies in Q1 2013 to 62 in Q1 2014. The number of multinational multi-center clinical trials (MMCT) decreased from 92 studies in Q1 2013 to 60 in Q1 2014, 35% decrease from last year's figure. The number of local clinical trials (LCT) has slightly increased from 44 in Q1 2013 to 47 clinical trials in Q1 2014.

Both shares of multinational multi-center clinical trials and bioequivalence studies amounted to 36% of the total number of clinical trials in Q1 2014, while the share of local clinical trials was 28%.

Clinical trials in Russia in Q1 2014 were sponsored by companies from 22 countries. The maximum number of trials (77) was initiated by Russian sponsors. American sponsors with 19 new studies took the runner-up place; they are followed by Swiss sponsors with 15 trials, German sponsors with ten studies and Indian sponsors with eight new studies; the group of leaders is concluded by Israeli and Belgian sponsors having six and five new studies respectively.

The number of Phase I clinical trials changed insignificantly and stood at six new studies in Q1 2014. The number of the Phase II trials decreased from 19 in Q1 2013 to 14 new studies in Q1 2014. The number of Phase III trials decreased from 99 to 81 studies, 18% less than in Q1 2013. Phase IV trials demonstrated the decrease from 11 studies in Q1 2013 to 6 studies in Q1 2014.

The number of subjects which are planned to be enrolled in Phase I-IV trials launched in Q1 2014 is 15,050, 8% less than in Q1 2013 figure, when 16,298 patients were planned to be enrolled.

Novartis sponsoring eleven new studies is on the top of the heap in Q1 2014. It is followed by *Sanofi* with four new trials. Top five is concluded by *GlaxoSmithKline*, *Novo Nordisk* and *Amgen* each having three new trials in Q1 2014 and differentiating in the number of patients.

The Russian company *ZAO R-Pharm* sponsoring three new clinical trials, ranked number one among domestic pharmaceutical manufacturers by the number of new studies in Q1 2014. It is followed by *OOO Endogenics* and *OOO Atoll* each having two new trials. Top five is concluded by *Materia Medica* and *Pharm-Sintez* with one new study each.

81% of new studies in Q1 2014 were initiated in seven leading therapeutic areas: the largest number of studies was initiated in Oncology (19); 16 new studies were instigated in Endocrinology, 13 studies in Pulmonology, 12 new studies in Musculoskeletal diseases, ten studies in Cardiology, six studies in Ophthalmology, and four studies in Neurology.

The Center for Drug Evaluation and Research (CDER) of the FDA approved 22 new drugs during Q1 2014, and five of them were (or are being) studied in clinical trials conducted in Russia.

During the first quarter of 2014 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 29 new drug applications[1]. Negative opinion was adopted for four drugs. 13 of the drugs which received positive opinions were (or are being) tested in clinical trials in Russia.

At the moment of the Orange Paper Q1 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

В первом квартале 2014 года Министерством здравоохранения Российской Федерации было выдано 169 разрешений на все виды клинических исследований (КИ), что на 18% меньше, чем за аналогичный период 2013 года.

При этом количество новых международных многоцентровых КИ уменьшилось с 92 до 60 исследований по сравнению с этим же периодом прошлого года. Количество исследований биоэквивалентности, инициированных в первом квартале 2014 года, несколько снизилось по сравнению с первым кварталом 2013 года и составило 62 против 69. Количество локальных КИ, проводимых на территории России отечественными и иностранными спонсорами, возросло с 44 до 47 исследований.

Спонсорами КИ, разрешенных к проведению в России в первом квартале 2014 года, выступили компании из 22 стран. На первое место вышли российские производители с 77 КИ, за ними идут американские спонсоры с 19 новыми исследованиями, Швейцария с 15 исследованиями, Германия с десятью КИ, а также Индия с восемью новыми исследованиями. Замыкают группу лидеров Израиль и Бельгия с шестью и пятью новыми исследованиями соответственно.

В первом квартале 2014 года было инициировано 6 новых КИ I фазы – на одно исследование меньше, чем за аналогичный период прошлого года. Количество исследований II фазы несколько снизилось по сравнению с этим же периодом прошлого года и составило 14 новых исследований против 19. Количество исследований III фазы снизилось с 99 до 81 исследования – на 18% меньше по сравнению с прошлым годом. Количество исследований IV фазы уменьшилось с 11 до 6 исследований.

В первом квартале 2014 года первое место среди иностранных производителей по количеству новых исследований заняла фармацевтическая компания *Novartis* с 11 новыми исследованиями. Компания *Sanofi* инициировала четыре исследования. Замыкают пятерку лидеров *GlaxoSmithKline*, *Novo Nordisk* и *Amgen* с тремя новыми исследованиями у каждой, но с разным количеством субъектов.

Первое место среди отечественных производителей по количеству исследований, начатых в первом квартале 2014 года, занимает *ЗАО Р-Фарм* с тремя новыми КИ. За ним идут *ООО Эндодженикс* и *ООО Атолл,* инициировавшие по два новых исследования каждый. Замыкают пятерку лидеров *Материа Медика* и *Фарм-синтез* с одним новым исследованием у каждого, но с разным количеством субъектов.

В первом квартале 2014 года 81% всех новых исследований были инициированы в семи терапевтических областях. Наибольшее количество в области онкологии – 19 КИ; 16 новых исследований – в области эндокринологии; 13 исследований в области пульмонологии; 12 исследований – в области заболеваний опорно-двигательного аппарата; десять исследований в области болезней системы кровообращения; шесть в области офтальмологии и четыре – в области неврологии.

Центр по оценке и исследованию лекарственных средств (Center for Drug Evaluation and Research, CDER) FDA одобрил в первом квартале 2014 года 22 новых лекарственных препарата, по пяти из которых в России проводились (или проводятся) КИ.

В течение первого 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 29 новым заявкам и четыре негативных отзыва. По 13 лекарствам, входившим в число получивших положительный отзыв, проводились (или проводятся) КИ в России.

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

Clinical Trials by Type and Manufacturing Country

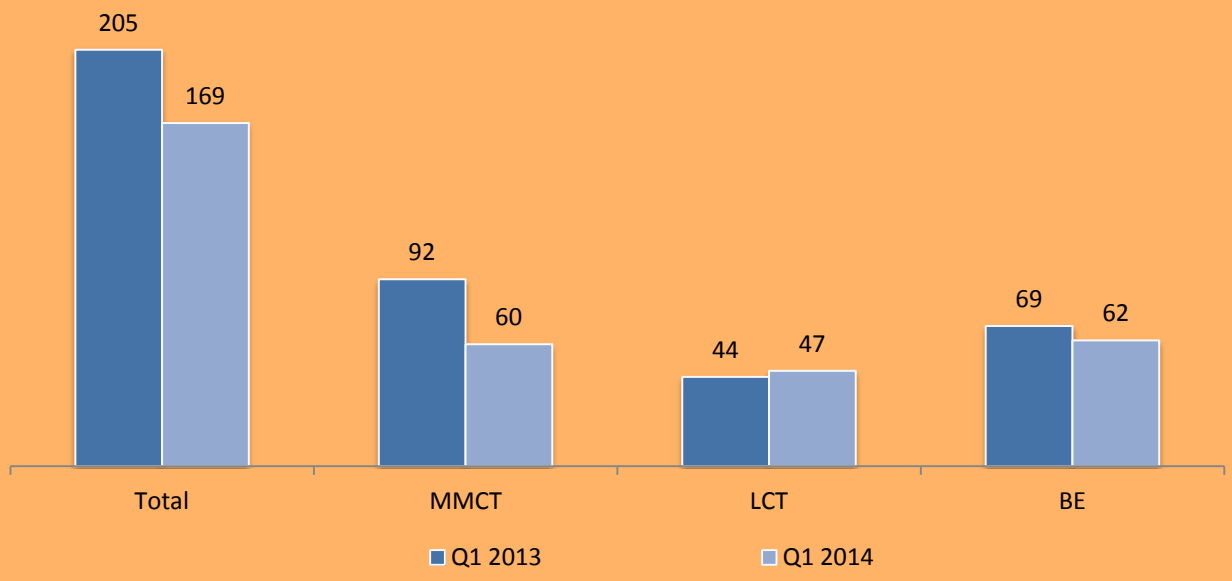
The Russian MoH approved 169 new clinical trials of all types including local and bioequivalence studies during the 1st Quarter of 2014, demonstrating 18% decrease in comparison with the same point of the last year.

As shown in **Figure 1**, the main contribution into the total number of studies was made by bioequivalence studies (BE), the number of these studies decreased from 69 studies in Q1 2013 to 62 in Q1 2014.

The number of multinational multi-center clinical trials (MMCT) decreased from 92 studies in Q1 2013 to 60 in Q1 2014, 35% decrease from last year's figure.

The number of local clinical trials (LCT) has slightly increased from 44 in Q1 2013 to 47 clinical trials in Q1 2014.

Figure 1. Clinical Trials in Russia in Q1 2014

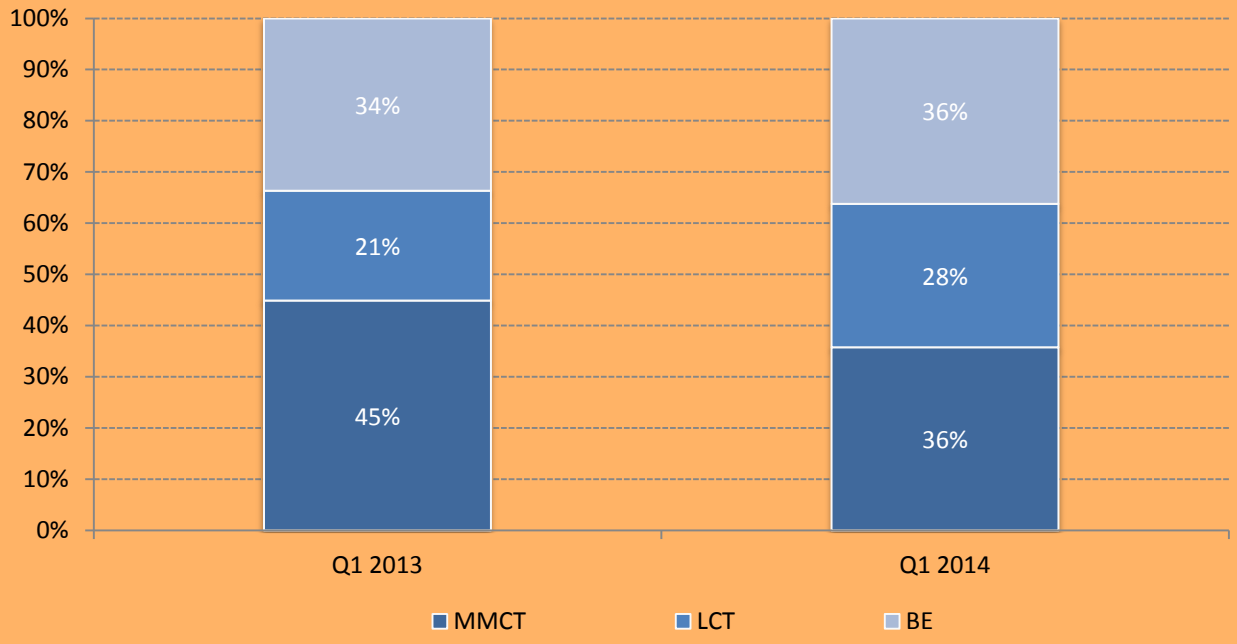


The proportions between different study types (multinational multi-center clinical trials, local studies and bioequivalence trials) changed slightly since last year (see **Figure 2**).

The share of bioequivalence studies increased from 34% to 36% of the total number of clinical trials approved in Q1 2014.

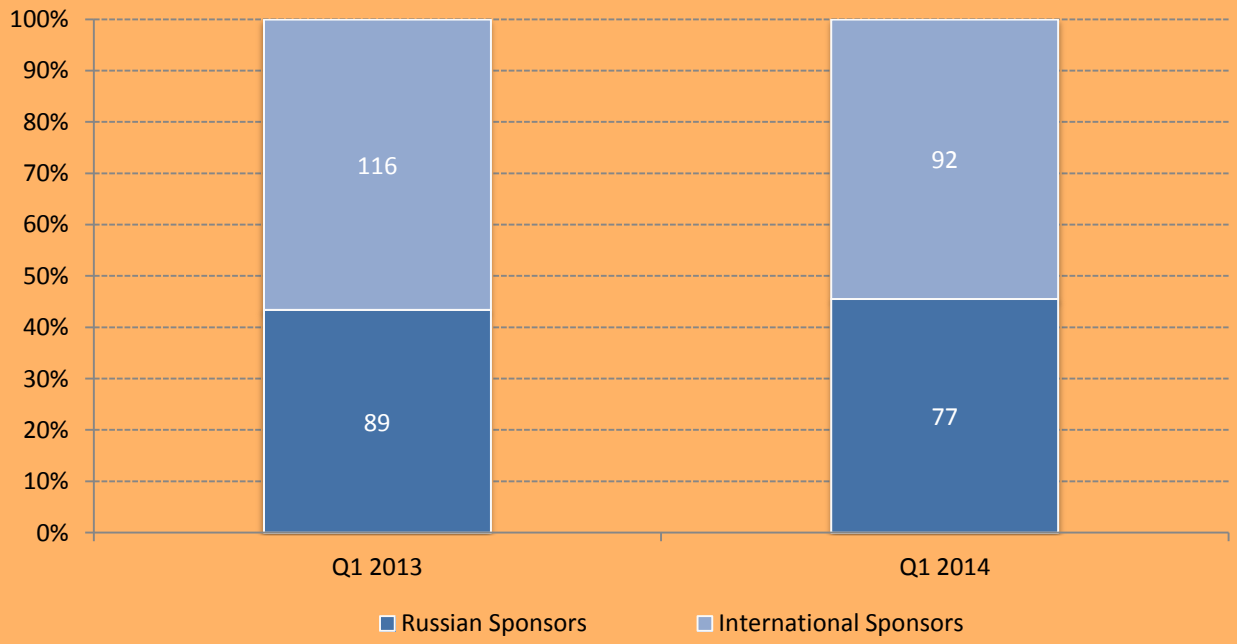
The share of the local trials increased to 28% and the share of multinational multi-center clinical trials decreased from 45% to 36% of the total number of trials approved during Q1 2014.

Figure 2. Clinical Trials by Type in Q1 2014



The geographic origins of sponsors did not significantly change in comparison with the same period last year. 54% of the total number of new studies in Q1 2014 were sponsored by foreign companies which received 92 study approvals. The share of studies of local manufacturers increased from 43% in Q1 2013 to 46% in Q1 2014, and amounted to 77 studies (**Figure 3**).

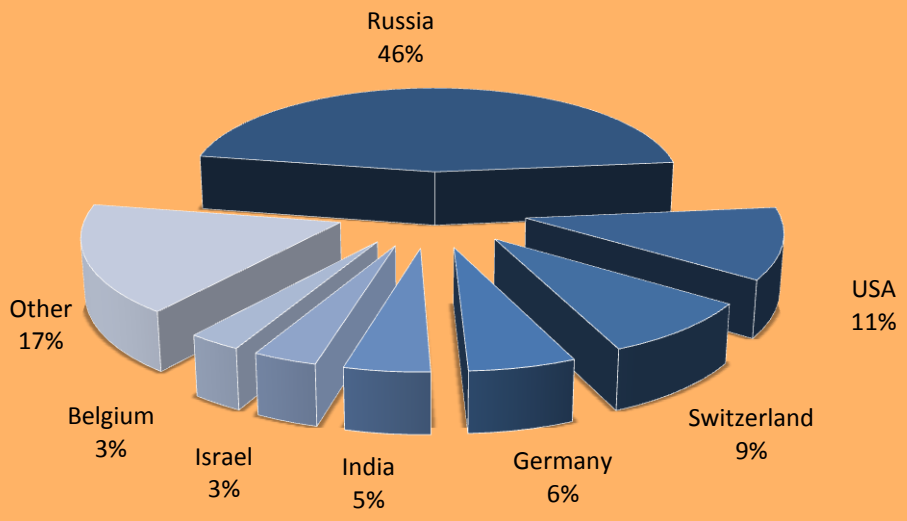
Figure 3. Russian vs International Sponsors in Q1 2014



Clinical trials in Russia in Q1 2014 were sponsored by companies from 22 countries. **Figure 4** indicates the geographic breakdown in sponsors' country of origin.

The maximum number of trials (77) was initiated by Russian sponsors. American sponsors with 19 new studies took the runner-up place; they are followed by Swiss sponsors with 15 trials, German sponsors with ten studies and Indian sponsors with eight new studies; the group of leaders is concluded by Israeli and Belgian sponsors having six and five new studies respectively.

Figure 4. Sponsors' Country of Origin for Q1 2014 Clinical Trials in Russia



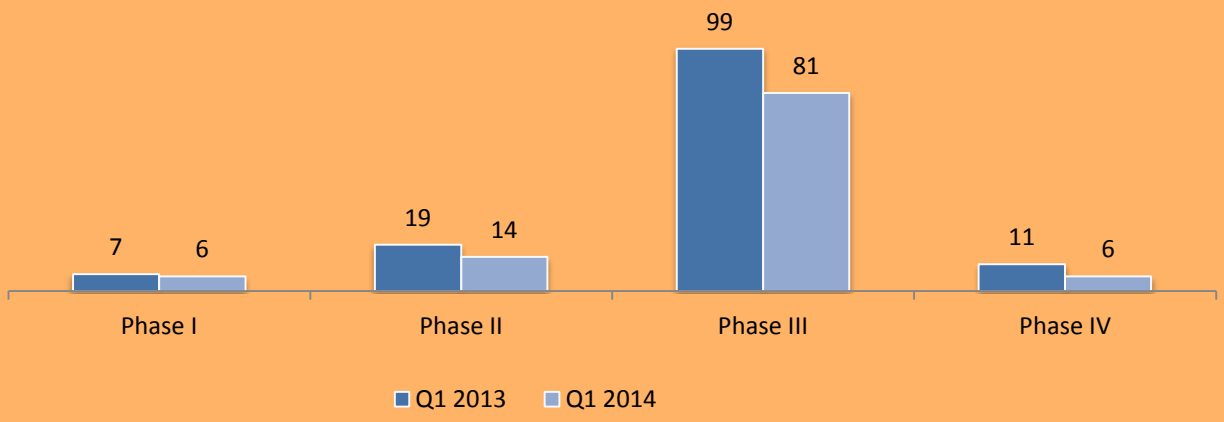
Other sponsors include: UK, France, Croatia (four studies each), Denmark and Japan (three studies each), Poland (two), Austria, Hungary, Egypt, Italy, Panama, Romania, Slovenia, Ukraine and Sweden each started one new study in Q1 2014.

Clinical trials by Phase

The number of Phase I clinical trials changed insignificantly and stood at six new studies in Q1 2014. The number of the Phase II trials decreased from 19 in Q1 2013 to 14 new studies in Q1 2014 (**Figure 5**).

The number of Phase III trials decreased from 99 to 81 studies, 18% less than in Q1 2013. Phase IV trials demonstrated the decrease from 11 studies in Q1 2013 to 6 studies in Q1 2014.

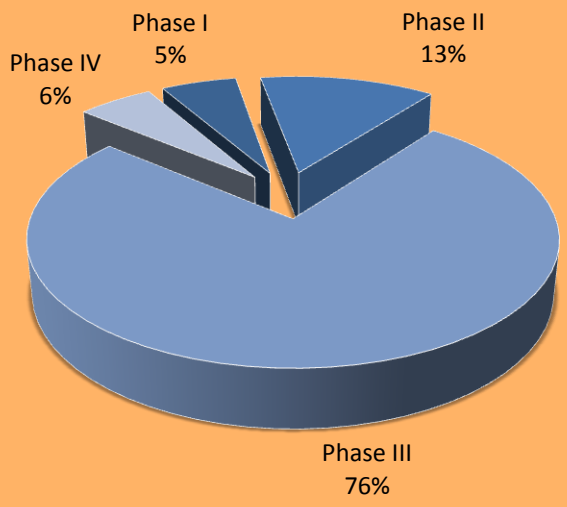
Figure 5. Clinical Trials in Russia in Q1 2014 by Phase[1]



[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 Q1 2014 is 76% of the total number of studies, the share of Phase II trials is 13%, Phase IV trials is 6%, and the share of Phase I studies is 5%.

Figure 6. Percentage Breakdown of Russian Clinical Trials by Phase



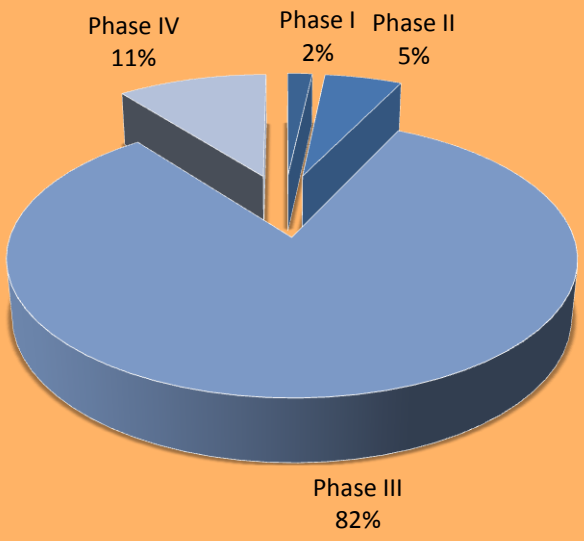
The number of subjects planned to be enrolled in Phase I-IV trials launched in Q1 2014 is 15,050, 8% less than in Q1 2013 figure, when 16,298 patients were planned to be enrolled.

260 subjects will be recruited in Phase I trials; 816 patients in Phase II trials; 12,400 subjects in Phase III studies; and 1,574 patients will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is ten, the maximum number is 999.

Figure 7 indicates the distribution of patients by study phase (only studies in which phase is specified were included), with Phase 3 clearly enrolling the majority of patients, as is to be expected.

Figure 7. Number of Patients in Q1 2014 by Study Phase



Number of Studies by Sponsor

Novartis sponsoring eleven new studies is on the top of the heap in Q1 2014. It is followed by *Sanofi* with four new trials. Top five is concluded by *GlaxoSmithKline*, *Novo Nordisk* and *Amgen* each having three new trials in Q1 2014 and differentiating in the number of patients.

Top five international sponsors ranked by the number of new studies in Q1 2014 are presented in **Table 1.**

Table 1. Top-5 International Study Sponsors in Q1 2014

№	*Company Name*	*No. studies*[1]	*No. patients*
1	Novartis	11	1530
2	Sanofi	4	715
3	GlaxoSmithKline	3	1234
4	Novo Nordisk	3	385
5	Amgen	3	236

Rating of Russian sponsors

The Russian company *ZAO R-Pharm* sponsoring three new clinical trials, ranked number one among domestic pharmaceutical manufacturers by the number of new studies in Q1 2014. It is followed by *OOO Endogenics* and *OOO Atoll* each having two new trials. Top five is concluded by *Materia Medica* and *Pharm-Sintez* with one new study each.

Table 2. Top-5 Russian Study Sponsors in Q1 2014

№	*Company Name*	*No. studies*	*No. patients*
1	ZAO R-Pharm	3	935
2	OOO Endogenics	2	236
3	OOO Atoll	2	170
4	Materia Medica	1	572
5	Pharm-Sintez	1	480

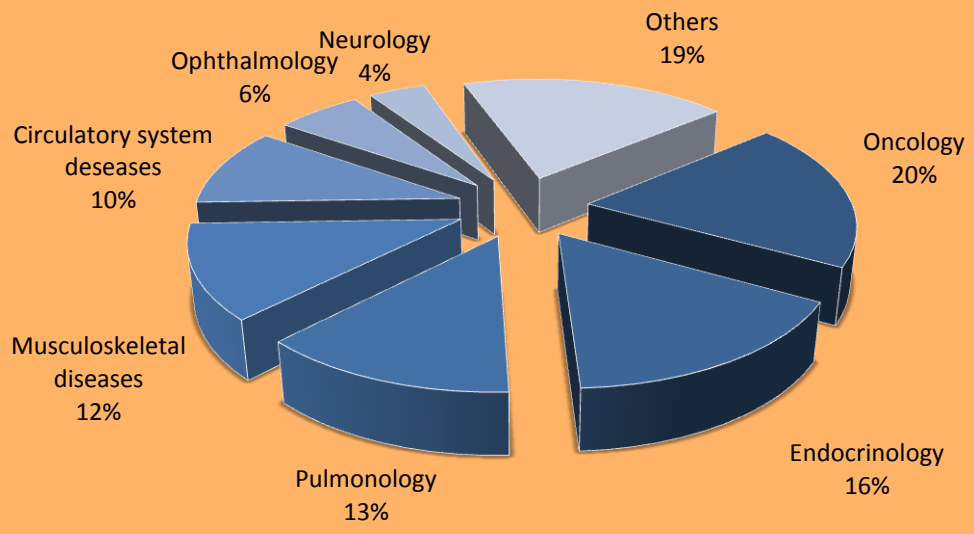
[1] Excluding BE studies

Therapeutic Areas of Russian Clinical Trials in Q1 2014

81% of new studies in Q1 2014 were initiated in seven leading therapeutic areas: the largest number of studies was initiated in Oncology (20); 16 new studies were instigated in Endocrinology, 13 studies in Pulmonology, 12 new studies in Musculoskeletal diseases, ten studies in Circulatory system diseases, six studies in Ophthalmology, and four studies in Neurology.

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

Figure 8. Clinical Trials in Russia in Q1 2014 by Therapeutic Area



Clinical Trials Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 22 new drugs during Q1 2014; seven of them are new molecular entities (NME); others are new dosages, combinations, manufacturers or indications of the already marketed drugs. Five drugs were (or are being) studied in clinical trials involving Russian sites.

The **Table 3** shows the drugs which were approved by FDA in Q1 2014 that were being tested in clinical trials in Russia.

Table 3. New Drugs Approved by FDA in Q1 2014 and Tested in Russian sites

Appr.date	*Drug (active ingredient)*	*Company*
01/08/2014	Farxiga (Dapagliflozin)	AstraZeneca AB
03/13/2014	Docetaxel (Docetaxel)	Pfizer
03/13/2014	Noxafil (Posaconazole)	Merck Sharp & Dohme
03/14/2014	Hemangeol (Propranolol hydrochloride)	Pierre Fabre
03/21/2014	Otezla (Apremilast)	Celgene
		Source: FDA

During the first quarter of 2014, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 29 new drug applications[1]. Negative opinion was adopted for four drugs. 13 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 Q1 2014 and Tested in Russian sites

Appr. date	*Drug (active ingredient)*	*Manufacturer*
01/23/2014	Adempas (Riociguat)	Bayer Pharma AG
01/23/2014	Eperzan (Albiglutide)	GlaxoSmithKline Trading Services
01/23/2014	Stelara (Ustekinumab)	Janssen-Cilag International N.V.
01/23/2014	Xolair (Omalizumab)	Bristol-Myers Squibb
02/20/2014	Anoro (Umeclidinium bromide / Vilanterol	Glaxo Group Ltd
02/20/2014	Hemangiol (Propranolol)	Pierre Fabre Dermatologie
02/20/2014	Incruse (Umeclidinium bromide)	Glaxo Group Ltd
02/20/2014	Vokanamet (Canagliflozin / Metformin)	Janssen-Cilag International N.V.
03/20/2014	Jardiance (Empagliflozin)	Boehringer Ingelheim International GmbH
03/20/2014	Sylvant (Siltuximab)	Janssen-Cilag International N.V.
03/20/2014	Pegasys (Peginterferon alfa-2a)	Roche Registration Limited
03/20/2014	Tresiba (Insulin degludec)	Novo Nordisk A/S
03/20/2014	Victoza (Liraglutide)	Novo Nordisk A/S
		Source: EMEA

Inspections

At the moment of the Orange Paper Q1 2014 production no information about any inspections (FDA or Roszdravnadzor) conducted in the Russian investigative sites was available.

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

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

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.