Clinical Trials in Russia
Orange Paper
Annual 2014

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

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Executive Summary – English

The Ministry of Health of the Russian Federation (MoH) approved 750 new clinical trials of all types including local and bioequivalence studies during 2014 (5% less than were approved in 2013).

The main contribution to the total number of studies was made by multinational multi-center clinical trials (MMCT). The number of these studies decreased from 359 studies in 2013 to 295 in 2014. The number of bioequivalence studies (BE) remained at the same level: 265 in 2013 and 267 in 2014. The number of local clinical trials (LCT) has increased from 167 to 188 clinical trials. The share of multinational multi-center clinical trials was 39% of the total number of clinical trials in 2014, while the bioequivalence and local studies amounted to 36% and 25% respectively.

Clinical trials in Russia in 2014 were sponsored by companies from 35 countries. The leading number of trials (345) were initiated by Russian sponsors. American sponsors with 103 new studies took the runner-up place; they are followed by Swiss sponsors (46), UK (38) and Indian sponsors (34); finishing the leaders are German (32) and French (22) sponsors.

The number of Phase I clinical trials stood at 37 new studies in 2014, 3 trials more than in 2013. The number of the Phase II, Phase III and Phase IV trials decreased from 91 to 84; from 373 to 338, and from 28 to 24 studies respectively.

The number of subjects planned to be enrolled in Phase I-IV trials launched in 2014 is 58,707, 2% less than 2013 figure, when 57,709 patients were planned to be enrolled.

Novartis, sponsoring 25 new studies is on the top of the heap in 2014 , followed by *GlaxoSmithKline with 18* trials, and *Roche* with 14 trials. The top five are concluded by *Janssen* and *Amgen* with 12 new trials each. Each company differentiated in the number of patients.

The Russian company *Ozon* sponsor ed nine new clinical trials, ranked number one among domestic pharmaceutical manufacturers by the number of new studies in 2014. It is followed by *ZAO R-Pharm* with eight new trials, and *Materia Medica*, *Microgen* and *Lens-Pharm* each having four new trials and differentiating in the number of patients.

49% of new studies in 2014 were initiated in eight leading therapeutic areas: the largest number of studies was initiated in Oncology (84); Pulmonology (61); diseases of Musculoskeletal system and connective tissue (48); Endocrinology (48), Cardiology (45), Infectious and parasitic diseases (35); Gastroenterology (26); and Neurology (23).

The Center for Drug Evaluation and Research (CDER) of the FDA approved 111 new drugs during 2014; 45 of them were (or are being) studied in clinical trials conducted in Russia.

During 2014, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 104 new drug applications[1]. Negative opinions were adopted for six drugs. 64 of the drugs which received positive opinions were (or are being) tested in clinical trials in Russia.

Roszdravnadzor conducted 77 inspections during 2014. Violations of good clinical practices were found in 24 institutions.

At the time of publishing this annual Orange Paper, no data was available from the FDA on inspection results for the year. .

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

Executive Summary – Russian

В 2014 году Министерством здравоохранения Российской Федерации было выдано 750 разрешений на все виды клинических исследований (КИ), что на 5% меньше, чем в 2013 году.

При этом количество новых международных многоцентровых КИ уменьшилось с 359 до 295 исследований по сравнению с 2013 годом. Количество исследований биоэквивалентности, инициированных в 2014 году, осталось почти на прежнем уровне: с 265 в 2013 году до 267 в 2014 году. Количество локальных КИ, проводимых на территории России отечественными и иностранными спонсорами, увеличилось также незначительно с 167 до 188 исследований.

Спонсорами КИ, разрешенных к проведению в России в 2014 году, выступили компании из 35 стран. На первое место вышли российские производители с 345 КИ, за ними идут американские спонсоры (103 новых исследований), Швейцария (46), Соединенное Королевство (38), а также Индия (34). Замыкают группу лидеров Германия и Франция с 32 и 22 новыми исследованиями соответственно.

В 2014 году было инициировано 37 новых КИ I фазы, что на 3 исследования больше, чем за прошлый год. Количество исследований II фазы за этот период снизилось и составило 84 исследования против 91. Количество исследований III фазы снизилось с 373 до 338 исследований – на 10% меньше по сравнению с прошлым годом. Количество исследований IV фазы также изменилось незначительно с 28 до 24 исследований.

Всего в клинических исследованиях I-IV фаз, начатых в 2014 году, примет участие 58 707 субъектов, что почти аналогично показателю 2013 года, когда планировалось включить 57 709 субъектов.

В 2014 году первое место среди иностранных производителей по количеству новых исследований заняла компания *Novartis* с 25 новыми исследованиями. *GlaxoSmithKline* и *Roche* инициировали по 18 и 14 исследований соответственно. Замыкает пятерку лидеров компания *Janssen* и *Amgen* с 12 новыми исследованиями, но с разным количеством пациентов.

Первое место среди отечественных производителей по количеству исследований, начатых в 2014 году, занимает компания «*Озон*» с девятью новыми КИ. За ней идут компании «*ЗАО Р-Фарм*» с восемью новыми исследованиями, *«Материа Медика», «Микроген»* и *«Лэнс-Фарм»,* инициировавшие по четыре новых исследований каждая.

В 2014 году почти половина (49%) всех новых исследований были инициированы в восьми терапевтических областях. Наибольшее количество в области онкологии – 84 КИ; 61 новое исследование – в области пульмонологии; 48 исследований – в области заболеваний опорно-двигательного аппарата и неврологии; 48 – в области эндокринологии; 45 – в кардиологии; 35 – в области инфекционных и паразитарных болезней; 26 – в области гастроэнтерологии; и 23 – в неврологии.

Центр по оценке и исследованию лекарственных средств (Center for Drug Evaluation and Research, CDER) FDA одобрил в 2014 году 111 новых лекарственных препаратов, по 45 из которых КИ проводились (или проводятся) в России.

В течение 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 104 новым лекарственным препаратам, и по двум новым биоаналогам. По 64 препаратам, входившим в число получивших положительный отзыв, проводились (или проводятся) КИ в России.

В 2014 году Росздравнадзор провел 77 проверок деятельности медицинских организаций по проведению клинических исследований. Нарушения были выявлены в 24 организациях.

На момент написания Оранжевой книги информации о проводимых инспекциях FDA в российских центрах за период 2014 года недоступна.

Clinical Trials by Type and Manufacturing Country

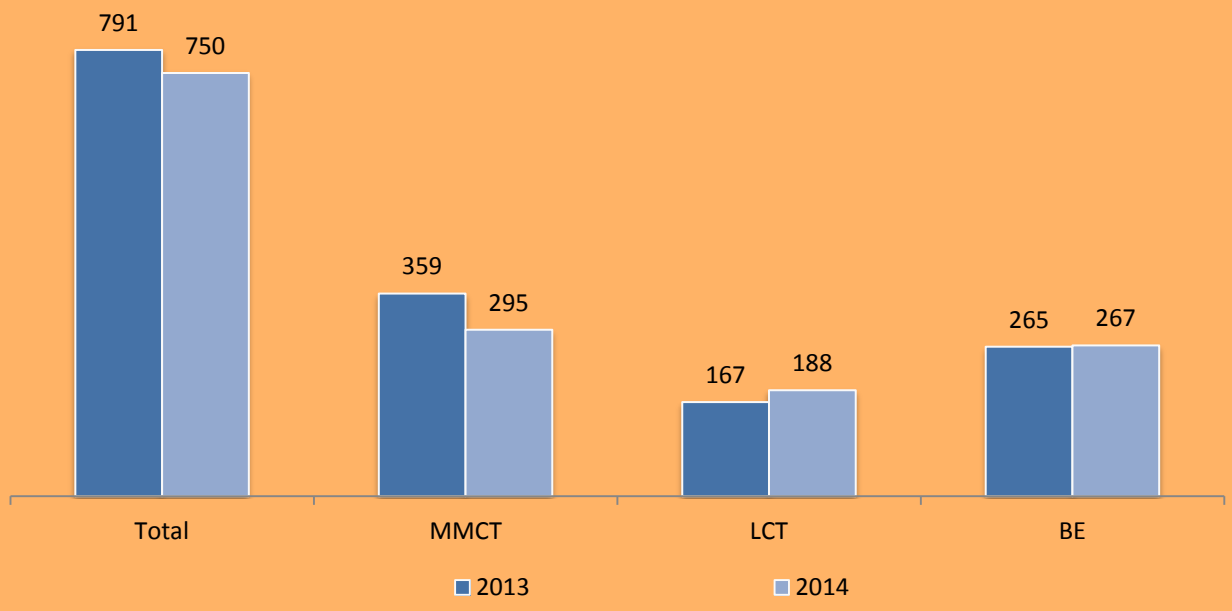
The Russian MoH approved 750 new clinical trials of all types including local and bioequivalence studies during 2014, demonstrating a 5% decrease in comparison with the same period last year.

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 decreased from 359 studies in 2013 to 295 in 2014.

The number of local clinical trials (LCT) has increased from 167 in 2013 to 188 clinical trials in 2014, a 13% increase from last year's figure.

The number of bioequivalence studies (BE) slightly increased from 265 studies in 2013 to 267 in 2014.

Figure 1. Clinical Trials in Russia in 2014

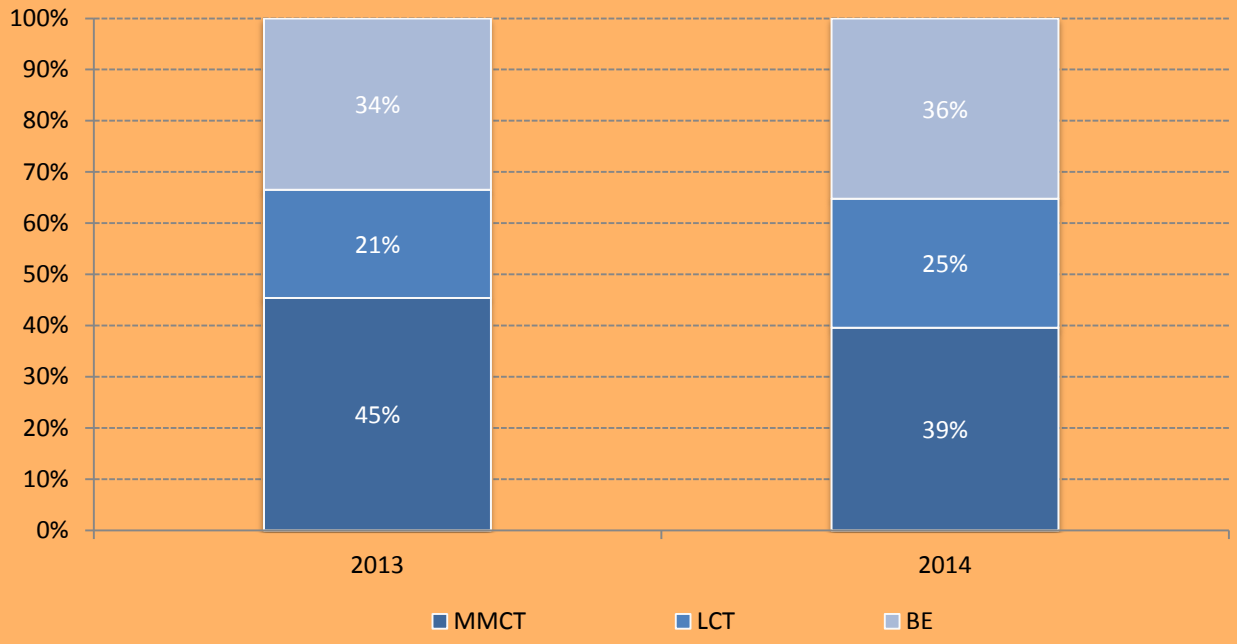


The proportions between different study types (multinational multi-center clinical trials, local studies and bioequivalence trials) changed slightly since l2013 (see **Figure 2**).

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

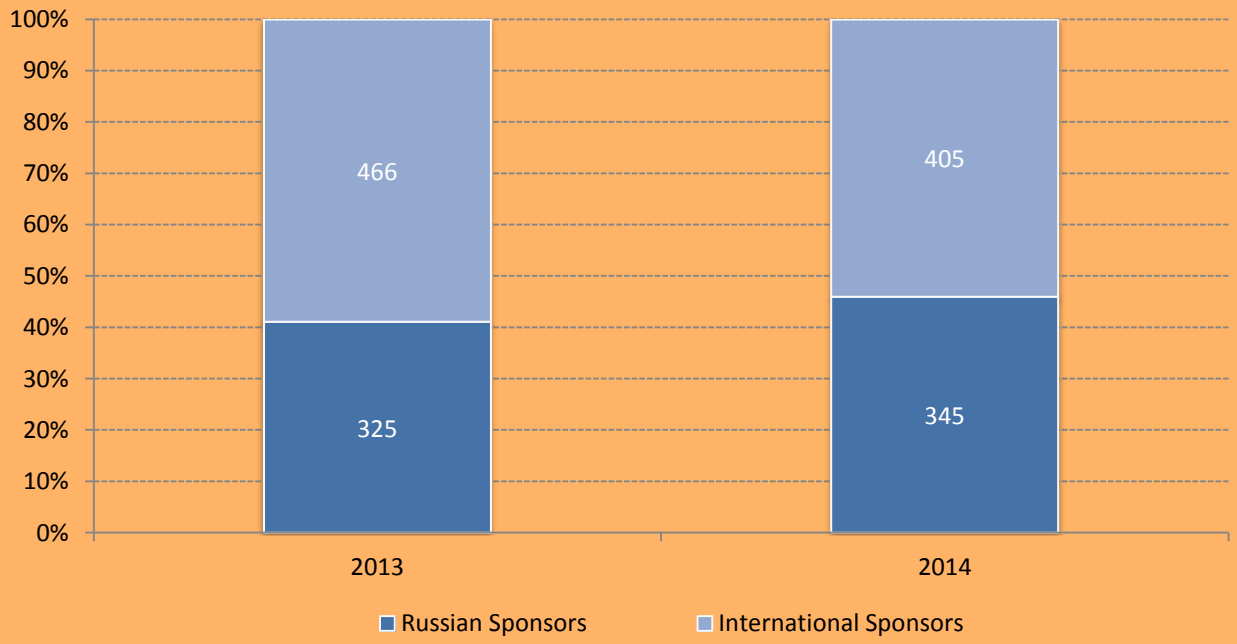
The share of the local trials increased from 21% to 25% and the share of multinational multi-center clinical trials decreased from 45% to 39% of the total number of trials approved during 2014.

Figure 2. Clinical Trials by Type in 2014



The geographic origins of sponsors did not significantly change in comparison with the same period last year. 54% of the total numbers of new studies in 2014 were sponsored by foreign companies, which received 405 study approvals. The share of studies of local manufacturers increased from 41% in 2013 to 46% in 2014, and amounted to 345 studies (**Figure 3**).

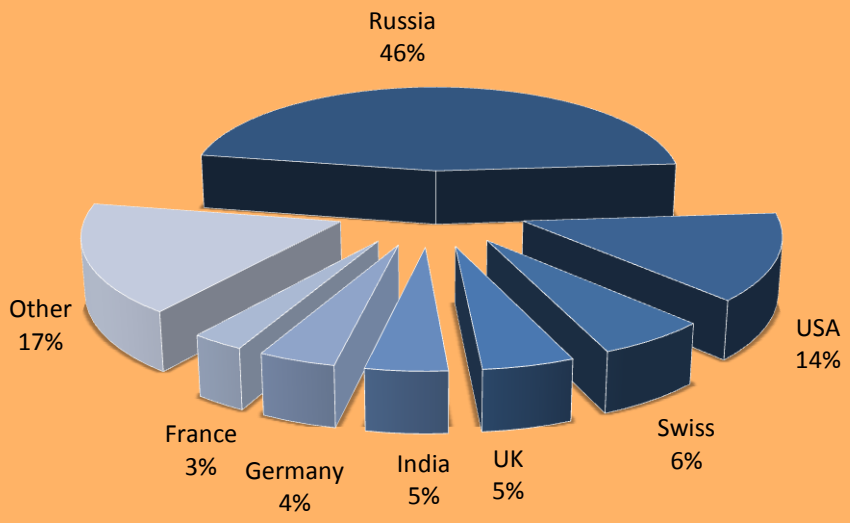
Figure 3. Russian vs International Sponsors in 2014



Clinical trials in Russia in 2014 were sponsored by companies from 35 countries. **Figure 4** indicates the geographic breakdown in sponsors' country of origin.

The highest number of trials (345) was initiated by Russian sponsors. American sponsors with 103 new studies, took the runner-up place; they are followed by Swiss sponsors with 46 trials, UK sponsors with 38 studies and Indian sponsors with 34 new studies. The group of leaders is concluded by German and French sponsors having 32 and 22 new studies respectively.

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



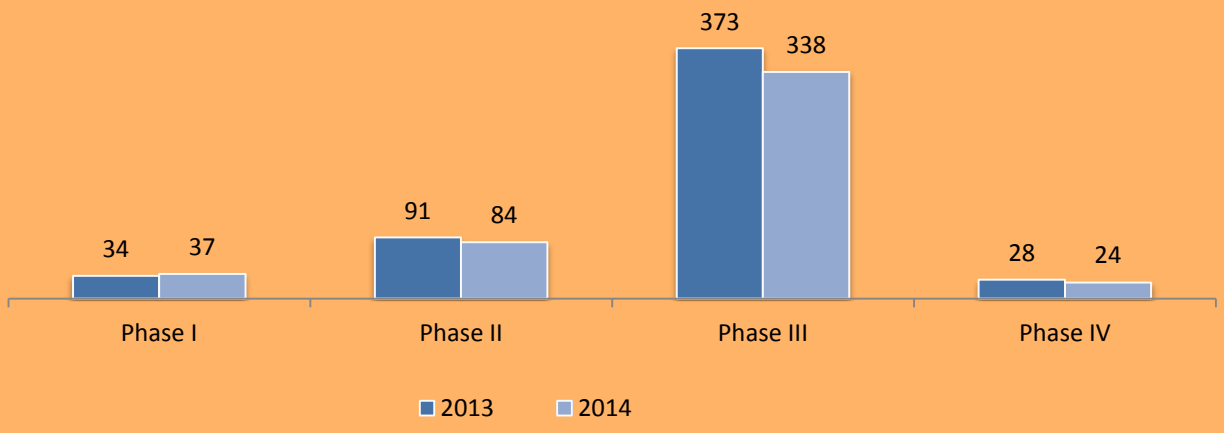
Other sponsors include: Israel (19 new studies), Belgium (16 new studies), Austria, Denmark, Netherlands (nine studies each), Sweden (eight studies), Japan (seven studies), Croatia (six studies), Italy, Republic of Korea, Poland, Slovenia, Ukraine (five studies each), and Canada (three studies). Bulgaria, Hungary, Latvia, Romania, Finland had two studies each whileAustralia, Belarus, Vietnam, Egypt, Spain, Cyprus, China, Panama, Turkey each started one new study in 2014.

Clinical trials by Phase

The number of Phase I clinical trials stood at 37 new studies in 2014, almost the same figure as in 2013. The number of Phase II trials decreased from 91 in 2013 to 84 studies in 2014 (**Figure 5**).

The number of Phase III trials decreased from 373 to 338 studies, 9% less than in 2013. Phase IV trials demonstrated a slight decrease from 28 studies in 2013 to 24 studies in 2014.

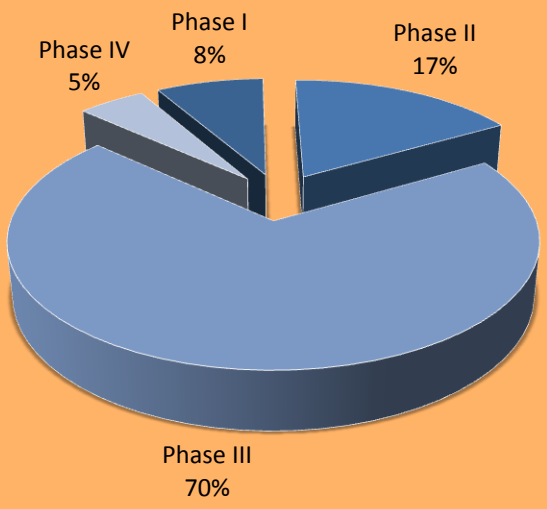
Figure 5. Clinical Trials in Russia in 2014 by Phase[1]



[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 Russia in 2014 is 70% of the total number of studies, the share of Phase II trials is 17%, Phase I trials is 8% and the share of Phase IV studies accounted to 5%.

Figure 6. Percentage Breakdown of Russian Clinical Trials by Phase



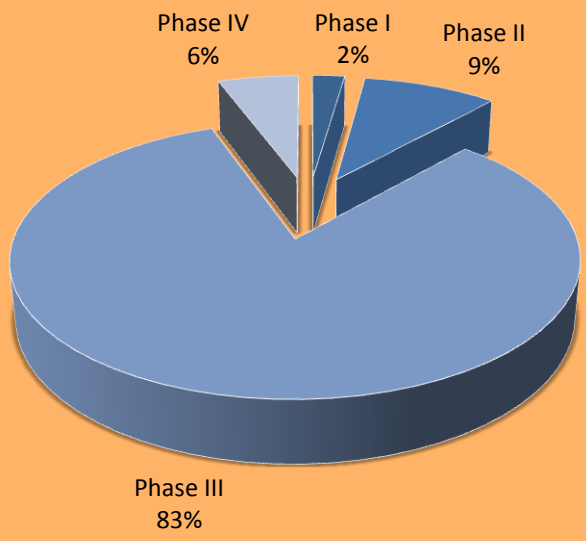
The number of subjects planned to be enrolled in Phase I-IV trials launched in 2014 was 58,707 , 2% less than 2013 figure, when 57,709 patients were planned to be enrolled.

1,332 subjects were recruited in Phase I trials; 5,509 patients in Phase II trials; 48,566 subjects in Phase III studies and 3,310 patients were enrolled in Phase IV studies.

The lowest number of subjects in a single study is three, the highest number is 1,300 .

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.

Figure 7. Number of Patients in 2014 by Study Phase



Number of Studies by Sponsor

Looking at the number of studies by sponsor, Novartis, with 25 new studies, is on the top of the heap in 2014. It is followed by *GlaxoSmithKline* with 18 studies and *Roche* with 14 trials. The top five are concluded by *Janssen* and *Amgen* with 12 new trials each and differentiating in the number of patients.

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

Table 1. Top-5 International Study Sponsors in 2014

№	Company Name	No. studies[1]	No. patients
1	*Novartis*	25	3 268
2	*GlaxoSmithKline*	18	3 761
3	*Roche*	14	1 147
4	*Janssen*	12	2 605
5	*Amgen*	12	976

Rating of Russian Sponsors

The Russian company *Ozon* sponsored nine new clinical trials, and ranked number one among domestic pharmaceutical manufacturers by the number of new studies in 2014. It is followed by *ZAO R-Pharm* having eight new trials, and by *Materia Medica*, *Microgen* and *Lens-Pharm* each having four new trials and differentiating in the number of patients.

Table 2. Top-5 Russian Study Sponsors in 2014

№	Company Name	No. studies[1]	No. patients
1	*Ozon*	9	830
2	*ZAO R-Pharm*	8	1 591
3	*Materia Medica*	4	1 102
4	*Microgen*	4	1 053
5	*Lens-Pharm*	4	262

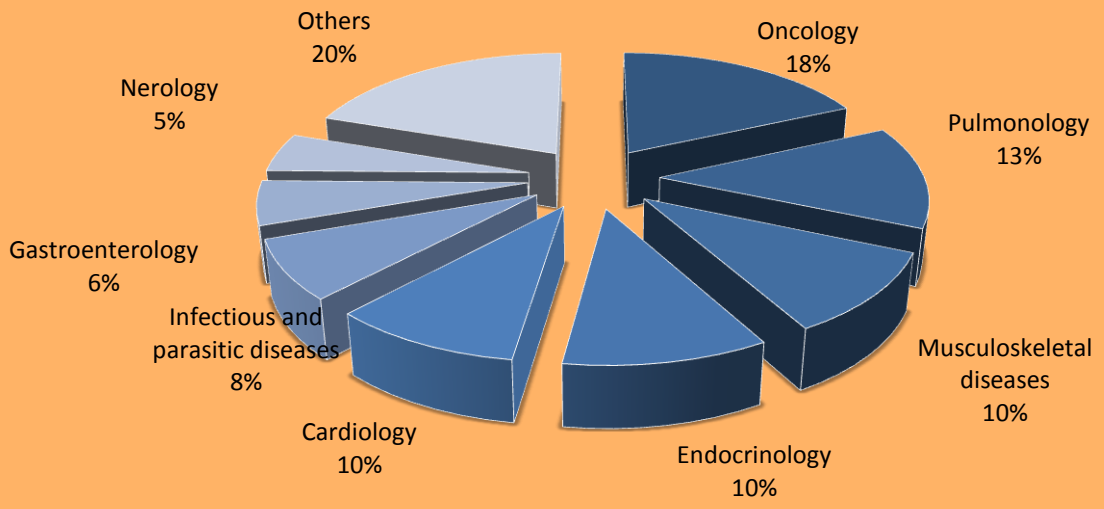
[1] Excluding BE studies

Therapeutic Areas of Russian Clinical Trials in 2014

49% of new studies in 2014 were initiated in eight leading therapeutic areas: the largest number of studies was initiated in Oncology (84); Pulmonology (61); studies in diseases of Musculoskeletal system and connective tissue; 48 studies in Endocrinology (48), Cardiology (45), Infectious and parasitic diseases (35); Gastroenterology (26); and Neurology (23).

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

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



Clinical Trials Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 111 new drugs during 2014; 34 of them are new molecular entities (NME); others are new dosages, combinations, manufacturers or indications of the already marketed drugs. 45 of 111 drugs were (or are being) studied in clinical trials involving Russian sites.

The **Table 3** shows the drugs which were approved by FDA in Q4 2014 that were being tested in clinical trials in Russia.

Table 3. New Drugs Approved by FDA in Q4 2014 and Tested in Russian sites

Appr.date	*Drug (active ingredient)*	*Company*
10/10/2014	Akynzeo (Netupitant; Palonosetron hydrochloride)	Helsinn Hlthcare
10/15/2014	Ofev (Nintedanib)	Boenhringer Ingelheim
10/29/2014	Xigduo XR (Dapagliflozin; Metformin Hidrochloride)	Asrtazeneca AB
12/03/2014	Blincyto (Blinatumomab)	Amgen
12/15/2014	Signifor Lar (Pasireotide Pamoate)	Novartis Pharms Corp
12/19/2014	Olaparid (Olaparid)	Astrazeneca Pharms
12/19/2014	Rapivab (Peramivir)	Biocryst

12/22/2014	Opdivo (Nivolumab)	Cubist Pharms
		Source: FDA

During 2014 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 104 new drug applications[1], and two positive recommendations on new biosimilar medicines. A negative opinion was adopted for six drugs. 64 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 2014 (Q1-Q3 data is presented in the previous issues of SynRG Orange Paper).

Table 4. New Drugs Approved by EMEA in Q4 2014 and Tested in Russian sites

Appr. date	*Drug (active ingredient)*	*Manufacturer*
10/23/2014	Lynparza (Oleparib)	AstraZeneca AB
10/23/2014	Rixubis (Nonacog Gamma)	Baxter Innovations GmbH
10/23/2014	Xtandi (Enzalutamide)	Astellas Pharma Europe B.V.
11/20/2014	Cerdelga (Eliglustat)	Genzyme Europe BV
11/20/2014	Cosentyx (Secukinumab)	Novartis Europharm Ltd
11/20/2014	Exviera (Dasabuvir)	AbbVie Ltd
11/20/2014	Ofev (Nintedanib)	Boehringer Indelheim International GmbH
11/20/2014	Otezla (Apremilast)	Celgene Europe Limited
11/20/2014	Travatan (Travoprost)	Alcon Laboratories (UK) Ltd
12/18/2014	Xydalba (Dalbavancin)	Durata Therapeutics International B.V.
12/18/2014	Revlimid (lenalidomide)	Celdene Europe Limited
12/18/2014	Tresiba (Insulin degiudec)	Novo Nordisk A/S
12/18/2014	Velcade (Bortzomib)	Janssen-Cilag International N.V.
		Source: EMEA

Inspections

FDA inspections

At the time of publishing this 2014 Orange Paper, no data was available on FDA investigator site inspection results. .

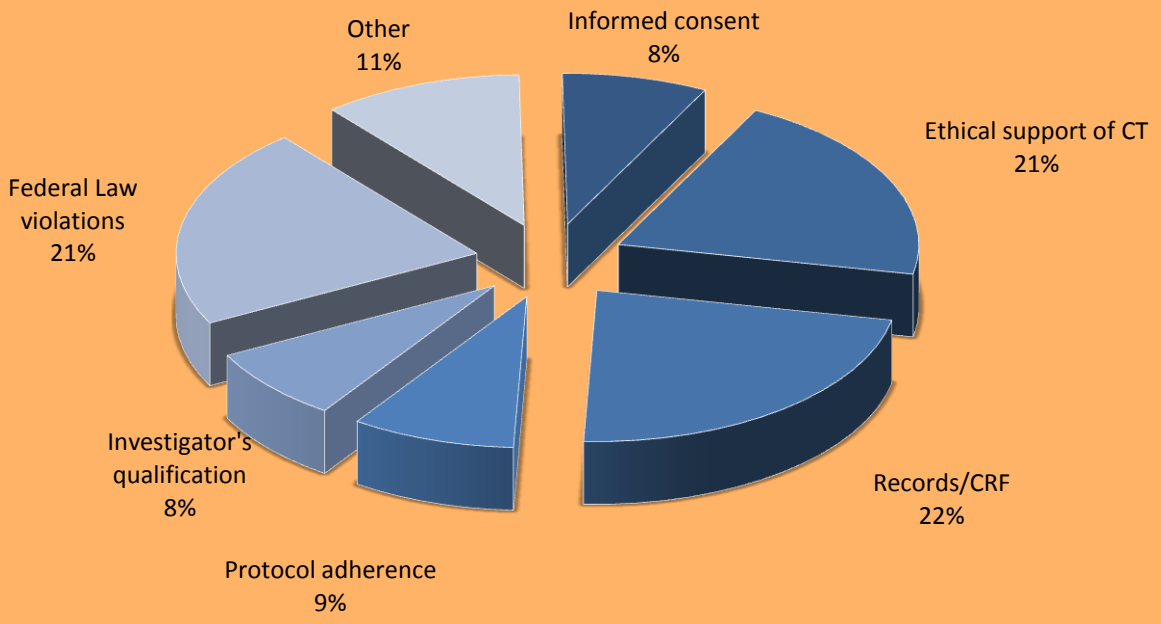
[1] Positive opinions on new generic and hybrid medicines are not included

Roszdravnadzor Inspections

According to the annual Roszdravnadzor report[1], 77 inspections were conducted in institutions performing preclinical and clinical trials and located in 67 Russian cities during 2014. Violations of good clinical practice were found in 24 institutions.

The analysis of findings is shown in the **Figure 9.**

Figure 9. Findings during Roszdravnadzor inspections in 2014



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. Patients in the region are compliant and stay in the study.

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.

[1] http://www.roszdravnadzor.ru/drugs/controllslp/documents/1483