NEW! TOP 5 CRO IN RUSSIA

Clinical Trials in Russia
Orange Paper
Annual 2015

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

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Contents

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Executive Summary – English

Ministry of Health of the Russian Federation approved 802 new clinical trials of all types, including local and bioequivalence studies during 2015. This represents 7% increase over 2014.

The main contribution into the total number of studies in 2015 was made by multinational multi-center clinical trials (MMCT), the number of these studies is 310 and it is 5% more than in 2014. The number of bioequivalence studies (BE) increased from 267 studies in 2014 to 292 in 2015, a 9% increase from last year's figure. The number of local clinical trials (LCT) slightly increased from 188 in 2014 to 200 in 2015.

Clinical trials in Russia in 2015 were sponsored by companies from 40 countries. The maximum number of trials (337) were initiated by Russian sponsors. American sponsors with 117 new studies took the runner-up place; they are followed by Indian sponsors with 62 new trials, Swiss sponsors with 53 trials, German sponsors with 30 studies, then UK sponsors with 26 studies and French sponsors with 23 studies. The group of leaders is concluded by Belgian sponsors having 16 new studies.

The number of subjects planned to be enrolled in Phase I-IV trials launched in 2015 was 51,338, 12% less than 2014 figure, when 58,707 patients were planned to be enrolled.

Novartis is on the top of the heap in 2015 by sponsoring 22 new studies. It is followed by *Merck&Co.* sponsoring 20 new studies, then *Roche* having 18 new trials and *Janssen* with 17 new studies. *Top* five is concluded by *Bristol-Myers Squibb* having 13 new trials in 2015.

Top five domestic pharmaceutical manufacturers by the number of new studies in 2015 is headed by *Biocad,* having 12 new trials. It is followed by *Valenta* with seven new studies and *Microgen* with six new studies. Top five is concluded by *Akrikhin* and *Pharmasyntez* each having five new studies and differentiating in the number of patients.

The top five Russian study sites were: *Sechenov First Moscow State Medical University* (95 studies), *Pavlov First St.Petersburg State Medical University* (91 studies), *Russian Scientific Oncology Center n/a N.N.Blokhin* (74 studies), *Kazan State Medical University* (61 studies), *Yaroslavl Clinical Hospital No. 3* (51 studies).

The top five CRO's in 2015 were: *Quintiles* with 29 new studies, *PPD Development* (16 new studies), *PRA* with15 new studies, *Parexel* (11 studies) and *PSI* which initiated 7 new studies in 2015.

77% of new studies in 2015 were initiated in eight leading therapeutic areas: the largest number of studies was initiated in Oncology (109); it is followed by Pulmonology (71 studies), Infectious and parasitic diseases (45 studies), Musculoskeletal diseases (43 studies), Neurology and Endocrinology (34 studies each); Gastroenterology (27 studies) and Urology (23 studies).

The Center for Drug Evaluation and Research (CDER) of the FDA approved 123 new drugs during 2015, and 50 of them were (or are being) studied in clinical trials conducted in Russia.

During 2015, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 113 new drug applications[1]. 71 of the drugs which received positive opinions were (or are being) tested in clinical trials in Russia.

Roszdravnadzor conducted 101 inspections during 2015. Violations of good clinical practice were found in 34 institutions.

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

Executive Summary – Russian

В 2015 году Министерством здравоохранения Российской Федерации было выдано 802 разрешения на все виды клинических исследований (КИ), что на 7% больше, чем за 2014 год.

При этом количество новых международных многоцентровых КИ составило 310 исследований, что на 5% больше по сравнению с прошлым годом. Количество исследований биоэквивалентности, инициированных в 2015 году, увеличилось на 9% по сравнению с 2014 годом и составило 292 против 267. Количество локальных КИ, проводимых на территории России отечественными и иностранными спонсорами, незначительно увеличилось по сравнению с 2014 годом и составило 200 исследований против 188.

Спонсорами КИ, разрешенных к проведению в России в 2015 году, выступили компании из 40 стран. На первое место вышли российские производители с 337 КИ, за ними идут американские спонсоры с 117 новыми исследованиями, Индия с 62 исследованиями, затем Швейцария с 53 новыми КИ, Германия с 30 и Великобритания с 26 новыми исследованиями, затем Франция с 23 новыми исследованиями. Замыкает группу лидеров Бельгия с 16 новыми исследованиями.

В 2015 году было инициировано 55 новых КИ I фазы, что на 48% больше, чем за 2014 год. Количество исследований II фазы уменьшилось по сравнению с прошлым годом и составило 81 новое исследование против 84. Количество исследований III фазы увеличилось с 338 до 352 исследований, что на 4% больше по сравнению с прошлым годом. Количество исследований IV фазы незначительно уменьшилось с 24 до 22 исследований по сравнению с 2014 годом.

В 2015 году лидирующие позиции среди иностранных производителей по количеству новых исследований заняла компания *Novartis* с 22 новыми исследованиями. Далее следует компания *Merck & Co.* с 20 новыми КИ, затем *Roche* с 18 и *Janssen* с 17 новыми исследованиями. Замыкает пятерку лидеров компания *Bristol-Myers Squibb* с 13 новыми КИ.

Пятерку лидеров по количеству новых исследований, начатых в 2015 году, среди отечественных производителей возглавила компания *Биокад* с 12 новыми исследованиями. Далее следуют компании *Валента* (семь новых исследований), *Микроген* (шесть новых исследований). Замыкают пятерку лидеров компании *Акрихин* и *Фармасинтез* с пятью новыми исследованиями каждая, но с разным количеством пациентов.

В пятерку передовиков 2015 года вошли следующие исследовательские центры: *Первый Московский государственный медицинский университет имени И.М. Сеченова* (95 новых исследований), *Первый Санкт-Петербургский государственный медицинский университет имени И.П.Павлова* (91 новое КИ), *Российский онкологический научный центр имени Н.Н. Блохина* (74 КИ), *Казанский государственный медицинский университет* (61 КИ) и *Клиническая больница № 3 города Ярославля* (51 новое КИ).

В 2015 году 77% новых исследований были инициированы в восьми терапевтических областях. Наибольшее количество исследований было проведено в области онкологии – 109. В области пульмонологии было проведено 71 новое исследование; в области инфекционных и паразитарных болезней – 45; в области заболеваний опорно-двигательного аппарата - 43; в областях неврологии и эндокринологии – по 34 новых КИ; в области гастроэнтерологии – 27 и в области урологии – 23 новых исследования.

Центр по оценке и исследованию лекарственных средств (Center for Drug Evaluation and Research, CDER) FDA одобрил в 2015 году 123 новых лекарственных препаратов, по 50 из которых в России проводились (или проводятся) КИ.

В 2015 году Комитет по лекарственным средствам для применения у человека (Committee for Medicinal Products for Human Use, CHMP) Европейского агентства по лекарственным средствам (European Medicine Agency, EMA) дал положительные отзывы по 113 новому лекарственному препарату, по 71 из которых проводились (или проводятся) КИ в России.

Clinical Trials by Type and Manufacturing Country

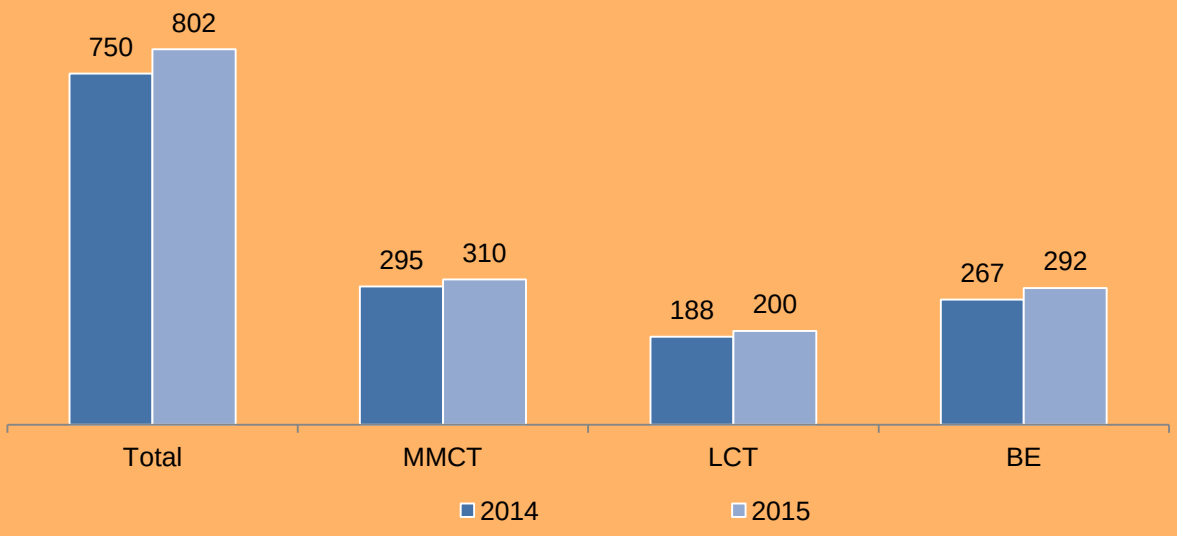
The Russian MoH approved 802 new clinical trials of all types including local and bioequivalence studies during 2015, demonstrating a 7% increase in comparison with the same point of the last year.

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 has increased from 295 studies in 2014 to 310 in 2015, 5% increase from last year's figure.

The number of bioequivalence studies (BE) increased from 267 studies in 2014 to 292 in 2015, 9% increase from last year's figure.

The number of local clinical trials (LCT) has slightly increased from 188 in 2014 to 200 in 2015.

Figure 1. Clinical Trials in Russia in 2015

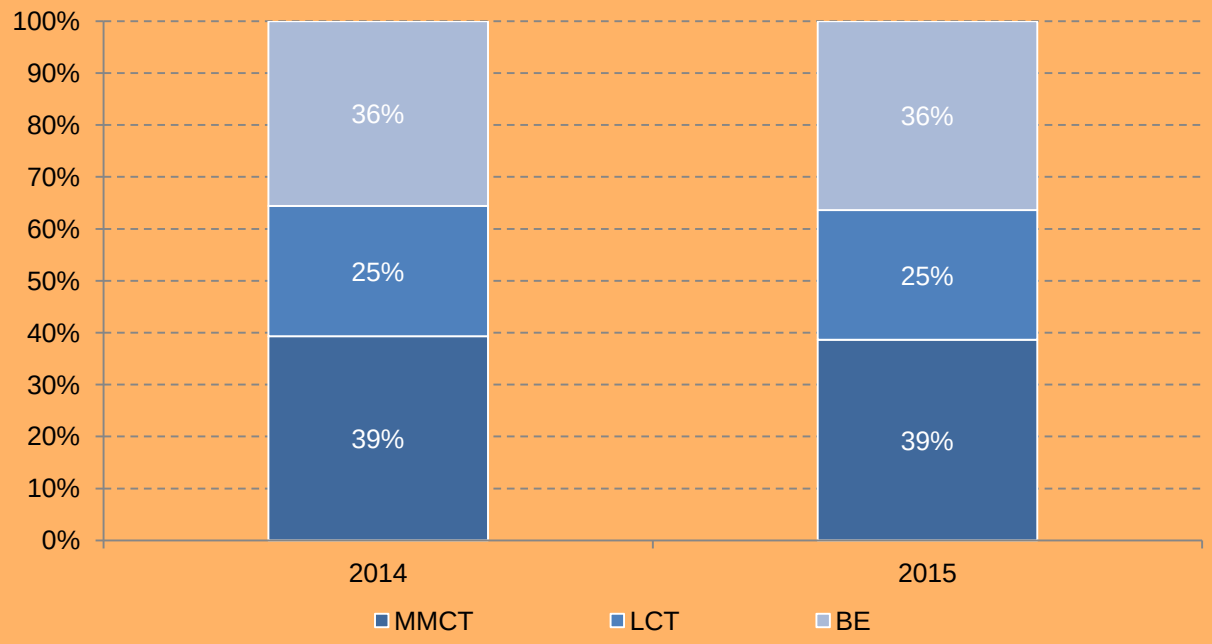


The proportions between different study types (multinational multi-center clinical trials, local studies and bioequivalence trials) has not changed since last year (see **Figure 2**).

The share of bioequivalence studies is 36% of the total number of clinical trials approved in 2015, as in 2014.

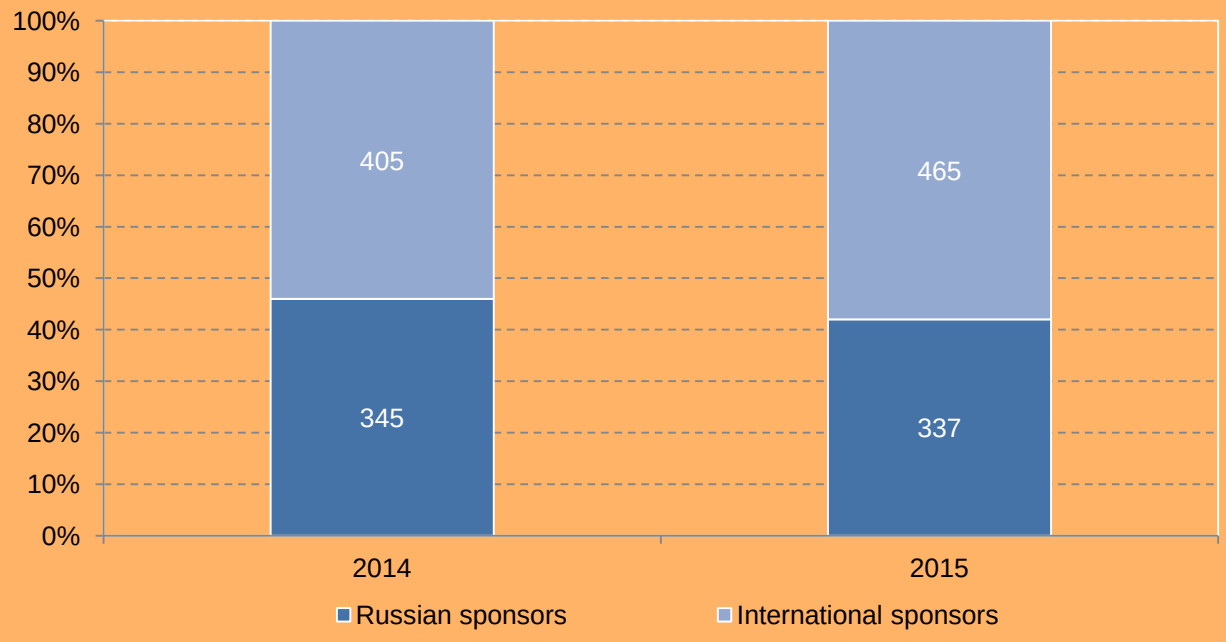
The share of the local trials was the same in 2015 as in 2014 at 25%, and the share of multinational multi-center clinical contained 39% of the total number of trials approved during 2015, as in 2014.

Figure 2. Clinical Trials by Type in 2015



The geographic origins of sponsors did not significantly change in comparison with last year. 58% of the total number of new studies in 2015 were sponsored by foreign companies which received 465 study approvals. The share of studies of local manufacturers decreased from 46% in 2014 to 42% in 2015, and amounted to 337 studies (**Figure 3**).

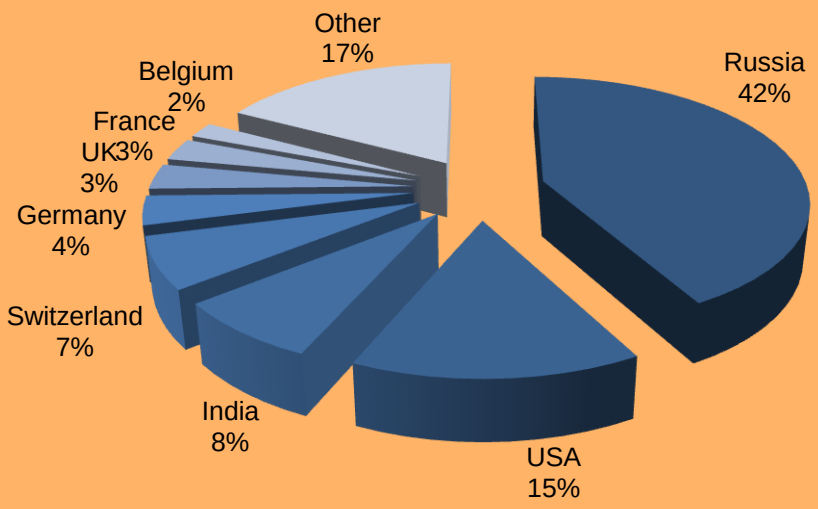
Figure 3. Russian vs International Sponsors in 2015



Clinical trials in Russia in 2015 were sponsored by companies from 40 countries. **Figure 4** indicates the geographic breakdown in sponsors' country of origin.

The maximum number of trials (337) was initiated by Russian sponsors. American sponsors with 117 new studies took the runner-up place; they are followed by Indian sponsors with 62 trials, Swiss sponsors with 53 studies, then German sponsors with 30 studies and UK sponsors with 26 studies. The group of leaders is concluded by French sponsors with 23 new studies and Belgian sponsors with 16 new studies.

Figure 4. Sponsors' Country of Origin for 2015 Clinical Trials in Russia



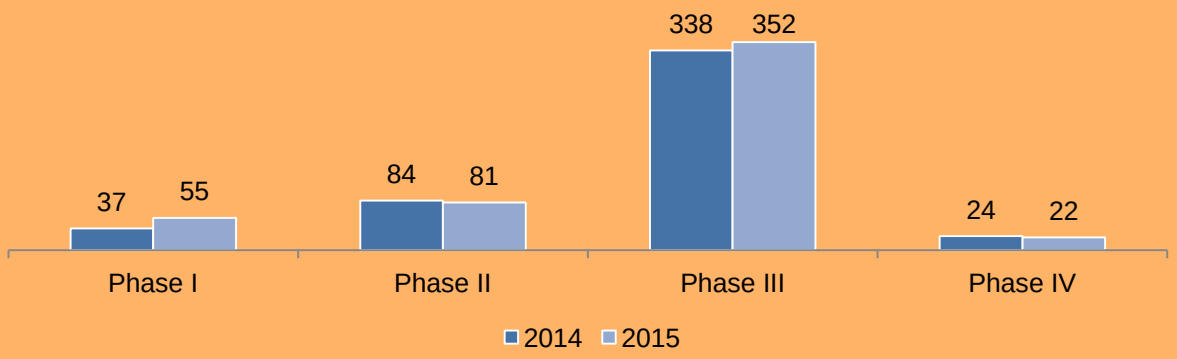
Other sponsors include: Slovenia (13 new studies), Sweden (12 studies), Israel (11 studies), Austria and Denmark (nine studies each), Turkey (eight studies), Poland (seven studies), Spain, Italy and Ukraine (six studies each), Argentina, Hungary and Croatia (five studies each), Romania (four studies), Belarus, Cyprus, China, Netherlands and Macedonia (three studies each), Bulgaria, Ireland, Republic of Korea and Latvia (two studies each), Vietnam, Greece, Pakistan, Panama, Portugal, Singapore, Finland, Estonia and Japan each started one new study in 2015.

Clinical trials by Phase

The number of Phase I clinical trials increased to 48% compared to 2014: from 37 studies to 55 new studies in 2015. The number of the Phase II trials slightly decreased from 84 in 2014 to 81 new studies in 2015, 4% less than in 2014 (**Figure 5**).

The number of Phase III trials increased from 338 to 352 studies, 4% more than in 2014. Phase IV trials demonstrated a decrease to 8% from 24 studies in 2014 to 22 studies in 2015.

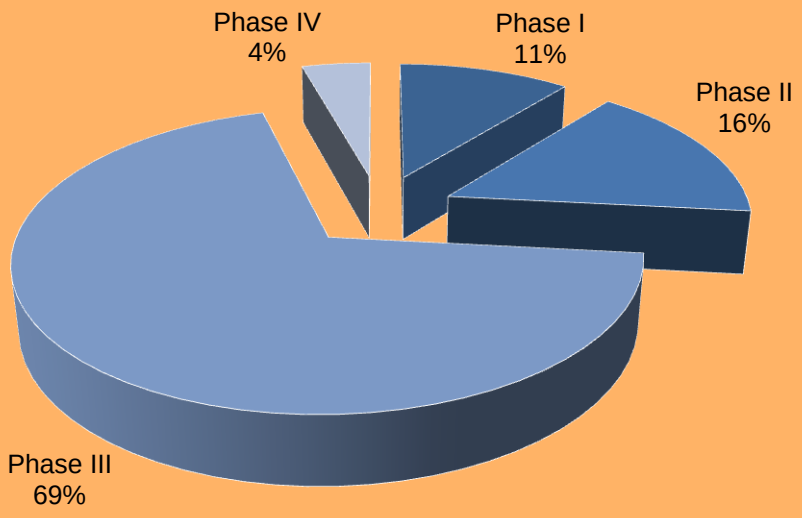
Figure 5. Clinical Trials in Russia in 2015 by Phase[1]



[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 2015 is 69% of the total number of studies, the share of Phase II trials is 16%, Phase I trials is 11% and the share of Phase IV studies accounted to 4%.

Figure 6. Percentage Breakdown of Russian Clinical Trials by Phase



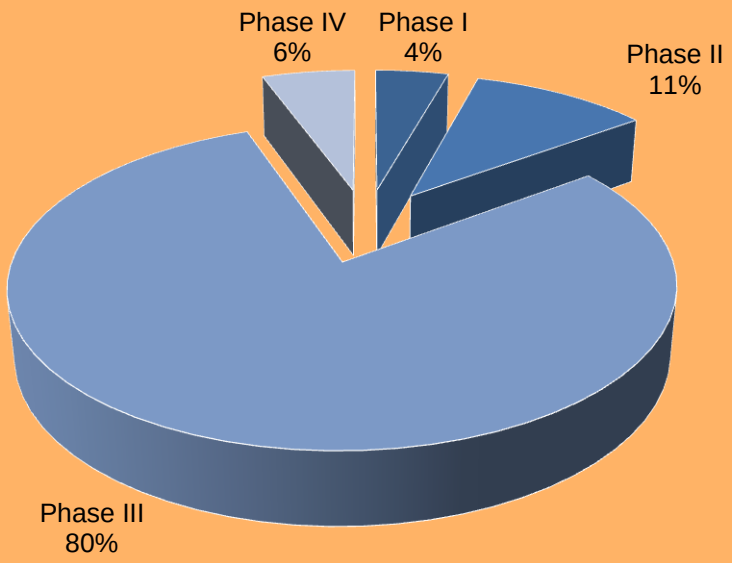
The number of subjects planned to be enrolled in Phase I-IV trials launched in 2015 was 51,338, 12% less than 2014 figure, when 58,707 patients were planned to be enrolled.

2,227 subjects in Phase I trials; 5,422 – in Phase II trials; 40,845 – in Phase III studies and 2,844 subjects will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is one, the maximum number is 1000.

Figure 7 indicates the distribution of subjects 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 Study Subjects in 2015 by Study Phase



The Top Five: Sponsor and Sites

Table 1. Top-5 International Study Sponsors in 2015

№	Company Name	No. studies[1]	No. patients
1	Novartis	22	1 685
2	Merck & Co.	20	1 827
3	Roche	18	796
4	Janssen	17	1 846
5	Bristol-Myers Squibb	13	1 002

Table 2. Top-5 Russian Study Sponsors in 2015

№	Company Name	No. studies	No. patients
1	Biocad	12	1 872
2	Valenta	7	826
3	Microgen	6	705
4	Akrikhin	5	986
5	Pharmasyntez	5	452

Table 3. Top-5 Russian Research Sites in 2015

№	Site Name	City	No. studies
1	Sechenov First Moscow State Medical University	Moscow	95
2	Pavlov First St.Petersburg State Medical University	St. Petersburg	91
3	Russian Scientific Oncology Center n/a N.N.Blokhin	Moscow	74
4	Kazan State Medical University	Kazan	61
5	Clinical Hospital No. 3	Yaroslavl	51

[1] Excluding BE studies

NEW

Table 4. Top-5 CROs in Russia in 2015

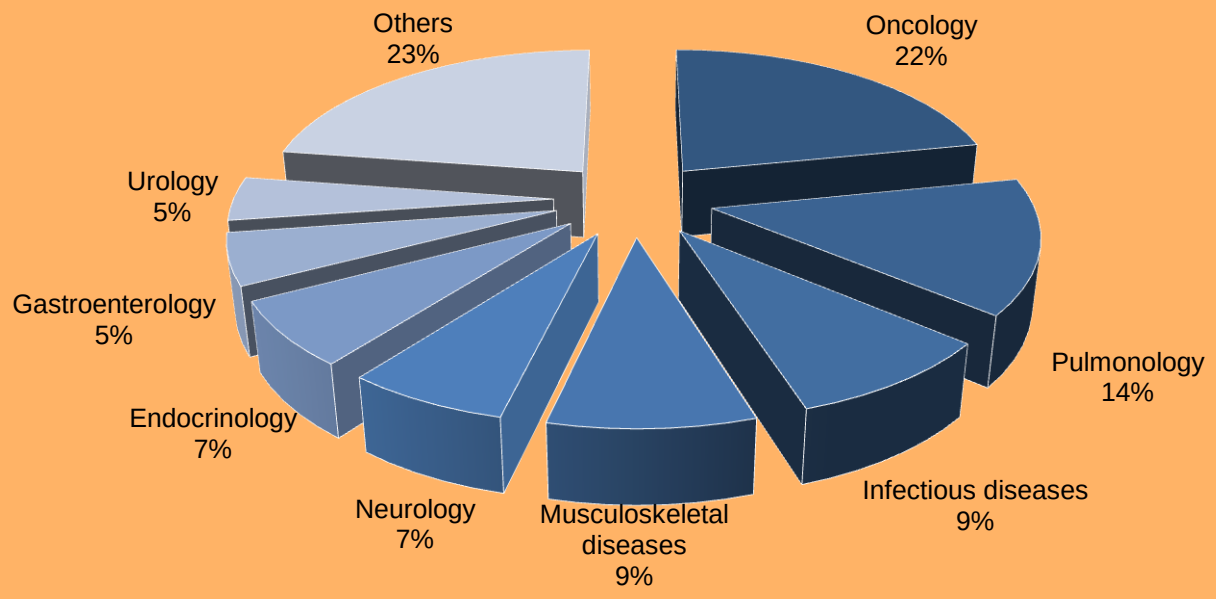
№	*CRO Name*	*No. studies*
1	Quintiles	29
2	PPD Development	16
3	Pharmaceutical Research Associates CIS	15
4	Parexel International	11
5	PSI	7

Therapeutic Areas of Russian Clinical Trials in 2015

77% of new studies in 2015 were initiated in eight leading therapeutic areas: the largest number of studies was initiated in Oncology (109); it is followed by Pulmonology (71 studies), Infectious and parasitic diseases (45 studies), Musculoskeletal diseases (43 studies), Neurology and Endocrinology (34 studies each); Gastroenterology (27 studies) and Urology (23 studies).

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

Figure 8. Clinical Trials in Russia in 2015 by Therapeutic Area



Clinical Trials Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 123 new drugs during 2015; 35 of them are new molecular entities (NME); others are new dosages, combinations, manufacturers or indications of already marketed drugs. 50 of 123 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 2015 that were (or are being) tested in clinical trials in Russia.

Table 3. New Drugs Approved by FDA in 2015 and Tested in Russian sites

Appr.date	*Drug (active ingredient)*	*Company*
10/05/2015	Aristada (aripiprazole lauroxil)	Alkermes Inc.
10/16/2015	Praxbind (idarucizumab)	Boehringer Ingelheim
10/21/2015	Veltassa (patiromer sorbitex calcium)	Relypsa Inc.
10/23/2015	Strensiq (asfotase alfa)	Alexion Pharm
10/23/2015	Yondelis (trabectedin)	Janssen Prods
10/29/2015	Seebri (glycopyrrolate)	Novartis Pharms corp.
10/29/2015	Utibron (glycopyrrolate; indacaterol maleate)	Novartis Pharms corp.
11/04/2015	Nucala (mepolizumab)	Glaxosmithkline LLC.
11/05/2015	Genvoya (cobicictat; elvitegravir; emtricitabine; tenofovir alafenamide fumarate)	Gilead Sciences Inc.
11/10/2015	Cotellic (cobimetinib fumarate)	Genentech Inc.
11/16/2015	Darzalex (daratumumab)	Janssen Biotech
11/20/2015	Ninlaro (ixazomib citrate)	Millenium Pharms
11/23/2015	Nexium 24HR (esomeprazole magnesium)	AstraZeneca LP
11/24/2015	Portrazza (necitumumab)	Eli Lilly Co.
11/30/2015	Empliciti (elotuzumab)	Bristol Myers Squibb
12/08/2015	Kanuma (sebelipase alfa)	Alexion Pharm
12/11/2015	Alecenza (alectinib)	Hoffmann-la-Roche
12/16/2015	Basaglar (insulin glargine)	Eli Lilly and Co.
12/21/2015	Uptravi (selexipag)	Actelion Pharms Ltd.
		Source: FDA

During 2015, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 113 new drug applications[1], 17 positive recommendations on new generic medicines and four for new hybrid medicines. A negative opinion was adopted for four drugs. 71 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).

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

Table 4. New Drugs Approved by EMA in 2015 and Tested in Russian sites

Appr. date	*Drug (active ingredient)*	*Manufacturer*
10/22/2015	Cosentyx (secukinumab)	Novartis Europharm Ltd
10/22/2015	Cubicin (daptomycin)	Novartis Europharm Ltd
10/22/2015	Edurant (rilpivirine)	Janssen-Cilag International N.V.
10/22/2015	Volibris (ambrisentan)	Glaxo Group Ltd
10/22/2015	Xalkori (crizotinib)	Pfizer Limited
11/19/2015	Briviact (brivaracetam)	UCB Pharma SA
11/19/2015	Cimzia (certolizumab pegol)	UCB Pharma SA
12/17/2015	Iblias (octocog alfa)	Bayer Pharma AG
12/17/2015	Kovaltry (octocog alfa)	Bayer Pharma AG
12/17/2015	Portrazza (necitumumab)	Eli Lilly Nederland B.V.
12/17/2015	Brilique (ticagrelor)	AstraZeneca AB
12/17/2015	Cyramza (ramucirumab)	Eli Lilly Nederland B.V.
12/17/2015	Nplate (romiplostim)	Amgen Europe B.V.
12/17/2015	Revolade (eltrombopag / eltrombopag olamine)	Novartis Europharm Ltd
12/17/2015	Tarceva (erlotinib)	Roche Registration Ltd
		Source: EMA

Inspections

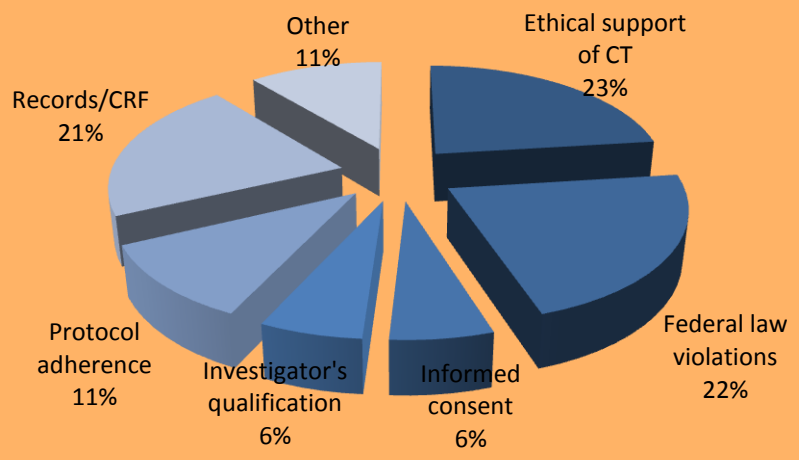
FDA Inspections

No published reports on FDA inspections were available as of the date of this 2015 Orange Paper.

Roszdravnadzor inspections

According to the annual Roszdravnadzor report, 101 inspections were conducted in 96 institutions performing preclinical and clinical trials during 2015, including 87 sites, 8 sponsors and 1 CRO. Violations of good clinical practice were found in 34 institutions.

Figure 9. Findings during Roszdravnadzor inspections during 2015



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.