Clinical Trials in Russia
Orange Paper
1st Quarter 2015

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Contents

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Executive Summary – English

The Ministry of Health of the Russian Federation approved 151 new clinical trials of all types including local and bioequivalence studies during the 1 st Quarter of 2015 (11% less than at the same period of the last year).

The main contribution into the total number of studies was made by multinational multi-center clinical trials (MMCT), the number of these studies is 60 and it is the same as in Q1 2014. The number of bioequivalence studies (BE) decreased from 62 studies in Q1 2014 to 47 in Q1 2015, a 25% decrease from last year's figure. The number of local clinical trials (LCT) has slightly decreased from 47 in Q1 2014 to 44 clinical trials in Q1 2015.

The share of multinational multi-center clinical trials was 40% of the total number of clinical trials in Q1 2015, while the bioequivalence and local studies amounted to 31% and 29% respectively.

Clinical trials in Russia in Q1 2015 were sponsored by companies from 21 countries. The maximum number of trials (65) was initiated by Russian sponsors. American sponsors with 24 new studies took the runner-up place; they are followed by Indian sponsors with 14 trials, UK sponsors with seven studies and Austrian sponsors with six new studies; the group of leaders is concluded by Belgian and German sponsors each having five new studies.

The number of Phase I and Phase II clinical trials increased from six to 11 (83% increase), and from 14 in Q1 2014 to 20 new studies in Q1 2015, respectively. The number of Phase III trials decreased from 81 to 68 studies, 16% less than in Q1 2014. Phase IV trials demonstrated the slight decrease from six studies in Q1 2014 to five studies in Q1 2015.

The number of subjects planned to be enrolled in Phase I-IV trials launched in Q1 2015 is 10,822, 28% less than Q1 2014 figure, when 15,050 patients were planned to be enrolled.

Janssen sponsoring eight new studies are on the top of the heap in Q1 2015. It is followed by *Boehringer Ingelheim* with four new trials, and *Merck&Co* and *Genentech* sponsoring three new studies each. *Top* five is concluded by *GlaxoSmithKline* having two new trials in Q1 2015.

The Russian company *Biocad* sponsoring six new clinical trials, ranked number one among domestic pharmaceutical manufacturers by the number of new studies in Q1 2015. It is followed by *JFC Pharmaceutical Factory of Saint Petersburg* with three new trials. Top five is concluded by *Obnovlenie, Ozon,* and *Sotex* each having two new trials and differentiating in the number of patients.

74% of new studies in Q1 2015 were initiated in eight leading therapeutic areas: the largest number of studies was initiated in Oncology (18); 12 new studies were instigated in Pulmonology; nine studies – in Musculoskeletal diseases; seven new studies – in Circulatory system diseases; seven studies – in Neurology; six studies – in Hematology; six studies – in Endocrinology; five studies - in Infectious and parasitic diseases.

The Center for Drug Evaluation and Research (CDER) of the FDA approved 35 new drugs during Q1 2015, and 16 of them were (or are being) studied in clinical trials conducted in Russia.

During the first quarter of 2015, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 25 new drug applications[1]. 17 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 2015 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 2015 года Министерством здравоохранения Российской Федерации было выдано 151 разрешение на все виды клинических исследований (КИ), что на 11% меньше, чем за аналогичный период 2014 года.

При этом количество новых международных многоцентровых КИ не изменилось по сравнению с этим же периодом прошлого года и составило 60 исследований. Количество исследований биоэквивалентности, инициированных в первом квартале 2015 года, уменьшилось по сравнению с первым кварталом 2014 года и составило 47 против 62. Количество локальных КИ, проводимых на территории России отечественными и иностранными спонсорами, несколько снизилось с 47 до 44 исследований.

Спонсорами КИ, разрешенных к проведению в России в первом квартале 2015 года, выступили компании из 21 страны. На первое место вышли российские производители с 65 КИ, за ними идут американские спонсоры с 24 новыми исследованиями, Индия с 14 исследованиями, затем Соединенное Королевство с семью новыми КИ, а также Австрия с шестью новыми исследованиями. Замыкают группу лидеров Бельгия и Германия с пятью новыми исследованиями каждая.

В первом квартале 2015 года было инициировано 11 новых КИ I фазы, что на 83% больше, чем за аналогичный период прошлого года. Количество исследований II фазы также возросло по сравнению с этим же периодом прошлого года и составило 20 новых исследований против 14. Количество исследований III фазы снизилось с 81 до 68 исследований – на 16% меньше по сравнению с прошлым годом. Количество исследований IV фазы практически не изменилось: пять исследований – на одно меньше, чем в прошлом году.

В первом квартале 2015 года первое место среди иностранных производителей по количеству новых исследований заняла компания *Janssen* с восемью новыми исследованиями. Компания *Boehringer Ingelheim* инициировала четыре исследования. Далее следуют *Merck&Co* и *Genentech* с тремя новыми исследованиями каждая. Замыкает пятерку лидеров компания *GlaxoSmithKline* с двумя новыми исследованиями.

Первое место среди отечественных производителей по количеству исследований, начатых в первом квартале 2015 года, занимает компания *Биокад* с шестью новыми КИ. За ней идут компании *ОАО Фармацевтическая фабрика Санкт-Петербурга* с тремя новыми исследованиями, и компании *Обновление, Озон и Сотекс,* инициировавшие по два новых исследования каждая.

В первом квартале 2015 года 74% всех новых исследований были инициированы в восьми терапевтических областях. Наибольшее количество в области онкологии – 18 КИ; 12 новых исследований – в области пульмонологии; девять исследований – в области заболеваний опорно-двигательного аппарата; по семь исследований – в области болезней системы кровообращения и неврологии; по шесть новых исследований в области гематологии и эндокринологии, пять – в области инфекционных и паразитарных болезней.

Центр по оценке и исследованию лекарственных средств (Center for Drug Evaluation and Research, CDER) FDA одобрил в первом квартале 2015 года 35 новых лекарственных препаратов, по 16 из которых в России проводились (или проводятся) КИ.

В течение первого квартала 2015 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 25 новым лекарственным препаратам. По 17 препаратам, входившим в число получивших положительный отзыв, проводились (или проводятся) КИ в России.

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

Clinical Trials by Type and Manufacturing Country

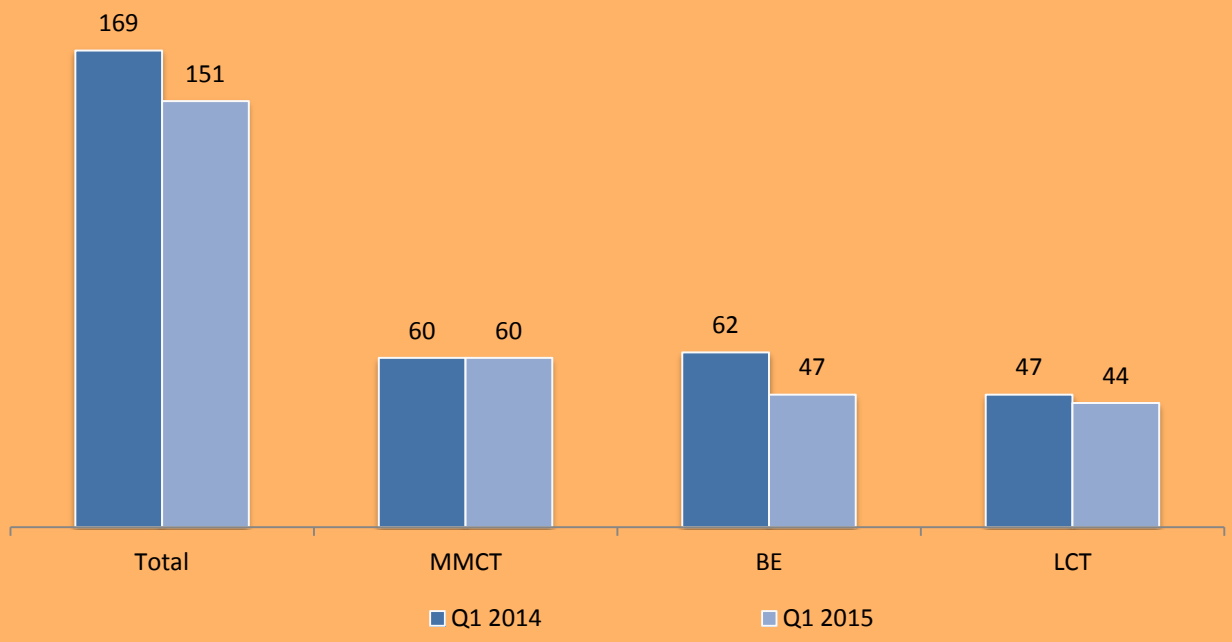
The Russian MoH approved 151 new clinical trials of all types including local and bioequivalence studies during the 1st Quarter of 2015, demonstrating 11% decrease in comparison with the same point of the last year.

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 has not changed from Q1 2014 to Q1 2015 and amounted to 60 studies.

The number of bioequivalence studies (BE) decreased from 62 studies in Q1 2015 to 47 in Q1 2015, 25% decrease from last year's figure.

The number of local clinical trials (LCT) has slightly decreased from 47 in Q1 2015 to 44 clinical trials in Q1 2015.

Figure 1. Clinical Trials in Russia in Q1 2015

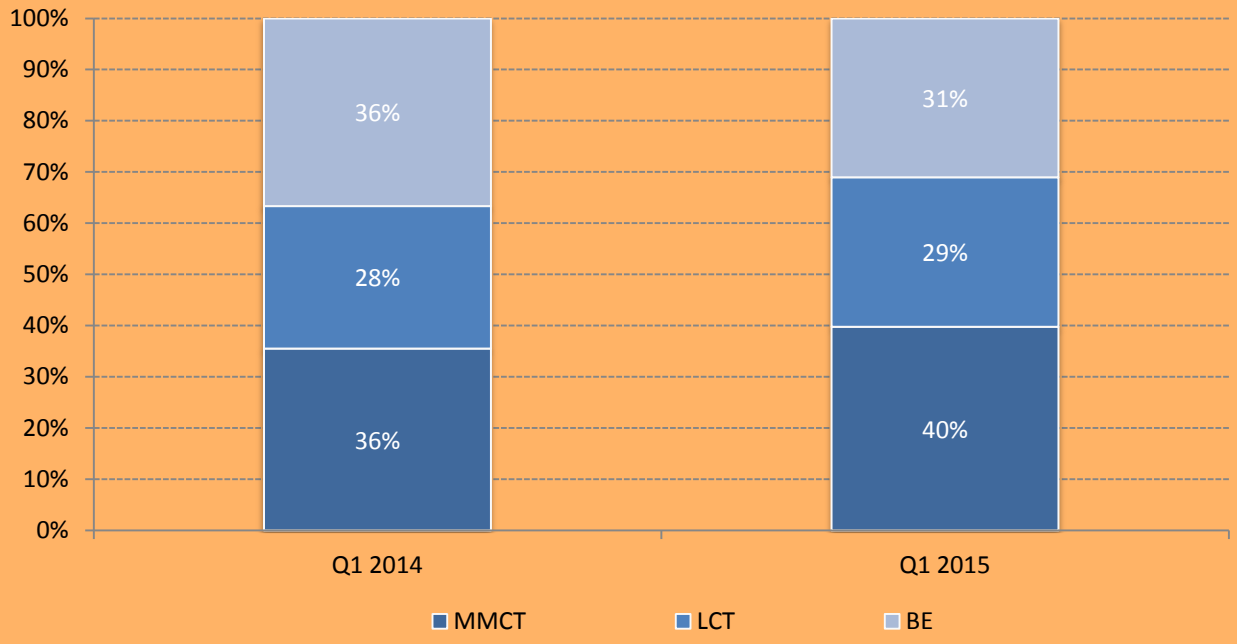


The proportions between different study types (multinational multi-center clinical trials, local studies and bioequivalence trials) changed slightly since last year (see **Figure 2**).

The share of bioequivalence studies decreased from 36% to 31% of the total number of clinical trials approved in Q1 2015.

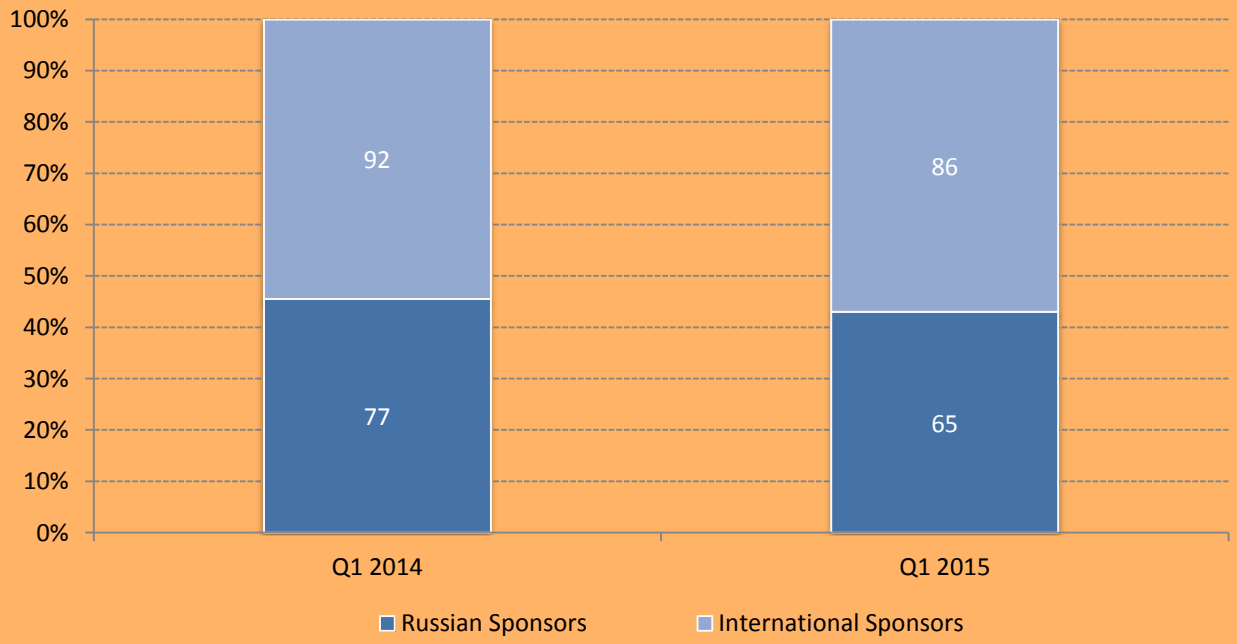
The share of the local trials almost has not changed and amounted to 29% compared to 28% in Q1 2014, and the share of multinational multi-center clinical trials increased from 36% to 40%.

Figure 2. Clinical Trials by Type in Q3 2014



The geographic origins of sponsors did not significantly change in comparison with the same period last year. 57% of the total number of new studies in Q1 2015 were sponsored by foreign companies which received 86 study approvals. The share of studies of local manufacturers decreased from 46% in Q1 2014 to 43% in Q1 2015, and amounted to 65 studies (**Figure 3**).

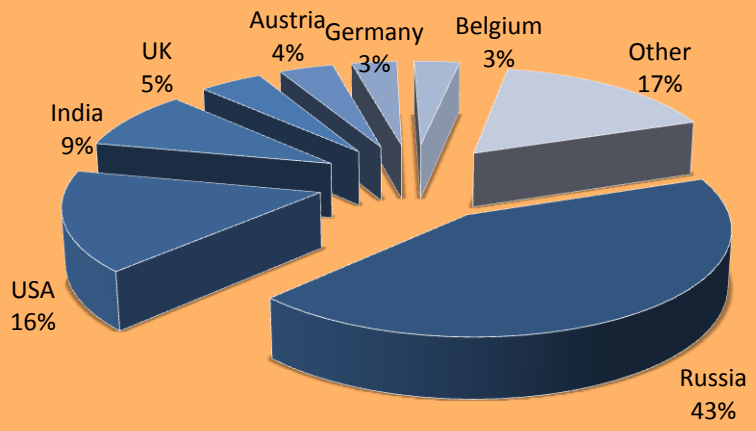
Figure 3. Russian vs International Sponsors in Q1 2015



Clinical trials in Russia in Q1 2015 were sponsored by companies from 21 countries. **Figure 4** indicates the geographic breakdown in sponsors' country of origin.

The maximum number of trials (65) was initiated by Russian sponsors. American sponsors with 24 new studies took the runner-up place; they are followed by Indian sponsors with 14 trials, UK sponsors with seven studies and Austrian sponsors with six new studies; the group of leaders is concluded by Belgian and German sponsors having five new studies each.

Figure 4. Sponsors' Country of Origin for Q1 2015 Clinical Trials in Russia



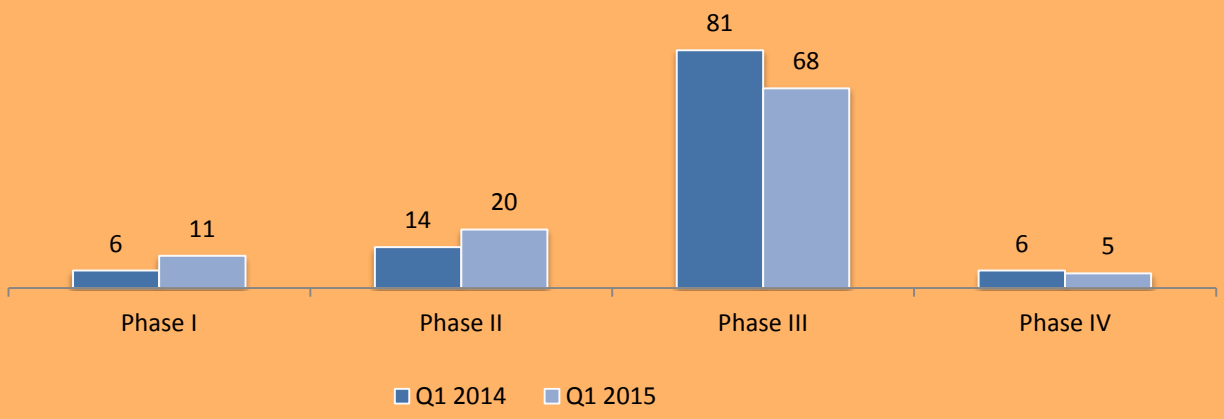
Other sponsors include: Switzerland (five new studies), France (four new studies), Spain, Netherlands, Sweden and Ukraine (two studies each), Greece, Israel, Ireland, Republic of Korea, Romania, Republic of Macedonia, Slovenia and Estonia each started one new study in Q1 2015.

Clinical trials by Phase

The number of Phase I clinical trials demonstrated 83% increase compared to Q1 2014: from 6 studies to 11 new studies in Q1 2015. The number of the Phase II trials increased from 14 in Q1 2014 to 20 new studies in Q1 2015 (**Figure 5**).

The number of Phase III trials decreased from 81 to 68 studies, 16% less than in Q1 2014. Phase IV trials demonstrated the slight decrease from six studies in Q1 2014 to five studies in Q1 2015.

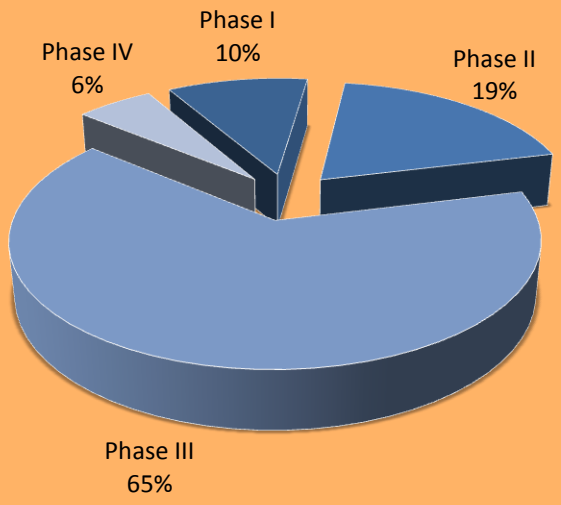
Figure 5. Clinical Trials in Russia in Q1 2015 by Phase[1]



[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 Q1 2015 is 65% of the total number of studies, the share of Phase II trials is 19%, Phase I trials is 10% and the share of Phase IV studies accounted to 6%.

Figure 6. Percentage Breakdown of Russian Clinical Trials by Phase



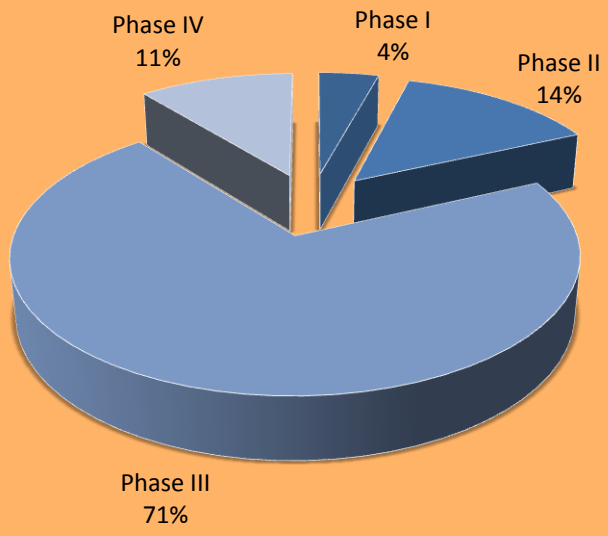
The number of subjects planned to be enrolled in Phase I-IV trials launched in Q1 2015 is 10,822, 28% less than Q1 2014 figure, when 15,050 patients were planned to be enrolled.

453 subjects will be recruited in Phase I trials; 1,514 patients in Phase II trials; 7,686 subjects in Phase III studies and 1,169 patients will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is one, the maximum number is 882.

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 Q1 2015 by Study Phase



Number of Studies by Sponsor

Janssen sponsoring eight new studies is on the top of the heap in Q1 2015. It is followed by *Boehringer Ingelheim* with four new trials, and *Merck&Co* and *Genentech* sponsoring three new studies each and differentiating in the number of patients. Top five is concluded by *GlaxoSmithKline* having two new trials in Q1 2015.

Top five international sponsors ranked by the number of new studies in Q1 2015 are presented in **Table 1.**

Table 1. Top-5 International Study Sponsors in Q1 2015

№	*Company Name*	*No. studies*[1]	*No. patients*
1	Janssen	8	900
2	Boehringer Ingelheim	4	1011
3	Merck&Co	3	340
4	Genentech	3	110
5	GlaxoSmithKline	2	600

Rating of Russian sponsors

The Russian company *Biocad* sponsoring six new clinical trials, ranked number one among domestic pharmaceutical manufacturers by the number of new studies in Q1 2015. It is followed by *JSC Pharmaceutical Factory of Saint Petersburg* with three new trials. Top five is concluded by *Obnovlenie, Ozon* and *Sotex* each having two new trials and differentiating in the number of patients.

[1] Excluding BE studies

Table 2. Top-5 Russian Study Sponsors in Q1 2015

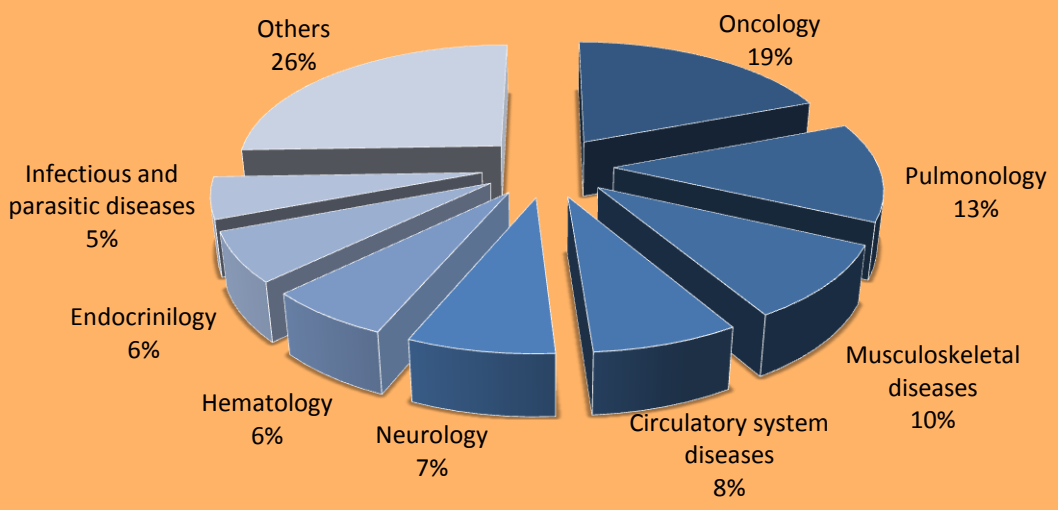
№	*Company Name*	*No. studies*	*No. patients*
1	Biocad	6	828
2	JSC Pharmaceutical Factory of Saint Petersburg	3	291
3	Obnovlenie	2	389
4	Ozon	2	220
5	Sotex	2	188

Therapeutic Areas of Russian Clinical Trials in Q1 2015

74% of new studies in Q1 2015 were initiated in eight leading therapeutic areas: the largest number of studies was initiated in Oncology (18); 12 new studies were instigated in Pulmonology; nine studies – in Musculoskeletal diseases; seven new studies – in Circulatory system diseases; seven studies – in Neurology; six studies – in Hematology; six studies – in Endocrinology; five studies - in Infectious and parasitic diseases.

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

Figure 8. Clinical Trials in Russia in Q1 2015 by Therapeutic Area



Clinical Trials Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 35 new drugs during Q1 2015; eight of them are new molecular entities (NME); others are new dosages, combinations, manufacturers or indications of the already marketed drugs. 16 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 2015 that were being tested in clinical trials in Russia.

Table 3. New Drugs Approved by FDA in Q1 2015 and Tested in Russian sites

Appr.date	*Drug (active ingredient)*	*Company*
01/08/2015	Savaysa (Edoxaban Tosylate)	Daiichi Sankyo
01/09/2015	Duopa (Carbidopa, Levodopa)	Abbvie Inc
01/15/2015	Phenylrphrine Hydrochloride (Phenylrphrine Hydrochloride)	Akorn Inc
01/21/2015	Cosentyx (Secukinumab)	Novartis Pharm Corp
01/23/2015	Natpara (Parathyroid Hormone)	NPS Pharm Inc
01/29/2015	Prezcobix (Cobicistat; Darunavir Ethanolate)	Janssen Prods
01/30/2015	Glyxambi (Empagliflozin; Linagliptin)	Boehringer Ingelheim
02/03/2015	Ibrance (Palbociclib)	Pfizer Inc
02/13/2015	Lenvima (Lenvatinib Mesylate)	Merck Sharp Dohme
02/23/2015	Farydak (Panobinostat)	Eisai Inc
02/25/2015	Avycaz (Avibactam Sodium; Ceftazidime)	Cerexa Inc
02/25/2015	Toujeo Solostar (Insulin Glargine Recombinant)	Sanofi Us Services
03/02/2015	Elepsia XR (Levetiracetam)	Sun Pharma Advanced Reserch co LTD
03/04/2015	Opdivo (Nivolumab)	Bristol Myers Squibb
03/06/2015	Zarxio (Filgrastim-SNDZ)	Sandoz Inc
03/30/2015	Jadenu (Deferasirox)	Novartis Pharm Corp
		Source: FDA

During the first quarter of 2015, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 25 new drug applications[1]. 17 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 2015 and Tested in Russian sites

Appr. date	*Drug (active ingredient)*	*Manufacturer*
01/23/2015	Saxenda (Liraglutide)	Novo Nordisk A/S.
01/23/2015	Sivextro (Tedizolid Phosphate)	Cubist
01/23/2015	Abraxane (Paclitaxel)	Geldene Europe Limited
01/23/2015	Aloxi (Palonosetron)	Helsinn Birex Pharmaceuticals Ltd

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

01/23/2015	Eylea (Aflibercept)	Bayer Pharma AG
01/23/2015	Jakavi (Ruxolitinib)	Novartis Europharm Ltd
01/23/2015	Prevenar 13 (Pneumococcal Polysaccharide conjugate vaccine (13-valent, adsorbed)	Pfizer Limited
02/27/2015	Jinarc (Tolvaptan)	Otsuka Pharmaceutical Europe Ltd
02/27/2015	Zykadia (Ceritinib)	Novartis Europharm Ltd
02/27/2015	Avastin (Bevacizumab)	Roche Registration Ltd
02/27/2015	Humira (Adalimumab)	AbbVie Ltd
02/27/2015	Soliris (Eculizumab)	Alexion Europe SAS
02/27/2015	Sustiva (Efavirenz)	Briston-Myers Squibb Pharma EEIG
02/27/2015	Vectibix (Panitumumab)	Amgen Europe B.V.
03/27/2015	Akynzeo (Netupitant/Palonosetron)	Helsinn Birex Pharmaceuticals Ltd
03/27/2015	Lenvima (Lentatinib)	Eisai Europe Ltd
03/27/2015	Synjardy (Empagliflorin/metfomin)	Boehringer Ingelheim GmbH
		Source: EMEA

Regulatory Inspections

At the moment of the Orange Paper Q1 2015 production no information about any inspections (FDA or Roszdravnadzor) conducted in the Russian investigative sites was available.

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.