Clinical Trials in Russia
Orange Paper
1st Quarter 2016

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Executive Summary – English

Ministry of Health of the Russian Federation approved 222 new clinical trials of all types, including local and bioequivalence studies, during Q1 2016. This represents 47% increase over Q1 2015.

The main contribution into the total number of studies in Q1 2016 was made by bioequivalence studies (BE), the number of these studies is 89 and it is 89% more than in Q1 2015. The number of multinational multi-center clinical trials (MMCT) increased from 60 studies in Q1 2015 to 65 in Q1 2016, a 8% increase from last year's figure. The number of local clinical trials (LCT) increased from 44 in Q1 2015 to 68 in Q1 2016.

The share of BE studies was 40% of the total number of clinical trials in Q1 2016, while the multinational multi-center clinical trials and local studies amounted to 29% and 31% respectively.

Clinical trials in Russia in Q1 2016 were sponsored by companies from 28 countries. The maximum number of trials (104) was initiated by Russian sponsors. American sponsors with 23 new studies took the runner-up place; they are followed by Indian sponsors with 16 trials, German sponsors with eight studies, then UK sponsors having seven new studies. The group of leaders is concluded by Belgian, French and Swiss Sponsors, each having six studies.

The number of Phase I clinical trials has increased from 11 studies to 21 new studies in Q1 2016 (91% increase). The number of the Phase II trials decreased by 10% from 20 in Q1 2015 to 18 new studies in Q1 2016. The number of Phase III trials increased from 68 to 90 studies, 32% more than in Q1 2015. The number of Phase IV trials slightly decreased in comparison with Q1 2015 from five to four studies.

The number of subjects planned to be enrolled in Phase I-IV trials launched in Q1 2016 is 14,027, 30% more than Q1 2015 figure, when 10,822 patients were planned to be enrolled.

Janssen and *Merck&Co* are on the top of the heap in Q1 2016 by sponsoring five new studies, differentiating in number of patients. It is followed by *Novartis* and *AbbVie Inc.,* each having four new trials and differentiating in number of patients. *Top* five is concluded by *Teva* with three new studies in Q1 2016.

Top five domestic pharmaceutical manufacturers by the number of new studies in Q1 2016 consists is headed by *Pharmasyntez,* having six new trials. It is followed by *Geropharm* with five new studies, then by *R-Pharm* with three new studies. Top five is concluded by companies *Syntez* and *Soteks*, each having two new studies and differentiating in the number of patients.

The top five Russian study sites are: *Pavlov First St.Petersburg State Medical University* (17 studies), *Clinical Hospital No. 2 Yaroslavl* (16 studies), *Eco-Bezopasnost Ltd.* (11 studies), *Sechenov First Moscow State Medical University* (nine studies), *Ryazan State Medical University* (nine studies).

81% of new studies in Q1 2016 were initiated in nine therapeutic areas: the largest number of studies was initiated in Infectious diseases and Oncology (17 studies each); it is followed by Rheumatology (15 studies), Endocrinology (14 studies), Pulmonology (11 studies), Ophtalmology and Neurology (nine studies each), Dermatology and Gynecology (eight studies each).

The Center for Drug Evaluation and Research (CDER) of the FDA approved 26 new drugs during Q1 2016, and nine of them were (or are being) studied in clinical trials conducted in Russia.

During Q1 2016, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 23 new drug applications[1]. 16 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 2016 production no information about any inspections (FDA or Roszdravnadzor) conducted in the Russian investigative sites was available.

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

Executive Summary – Russian

В первом квартале 2016 года Министерством здравоохранения Российской Федерации было выдано 222 разрешения на все виды клинических исследований (КИ), что на 47% больше, чем за аналогичный период 2015 года.

При этом количество исследований биоэквивалентности, инициированных в первом квартале 2016 года, составило 89 исследования, что на 89% больше по сравнению с аналогичным периодом прошлого года. Количество новых международных многоцентровых КИ увеличилось на 8% по сравнению с 2015 годом и составило 65 против 60. Количество локальных КИ, проводимых на территории России, увеличилось по сравнению с первым кварталом 2015 года и составило 68 исследований против 44.

Спонсорами КИ, разрешенных к проведению в России в первом квартале 2016 года, выступили компании из 28 стран. На первое место вышли российские производители с 104 КИ, за ними идут американские спонсоры с 23 новыми исследованиями, Индия с 16 исследованиями, затем Германия с восемью новыми КИ и Великобритания с семью новыми исследованиями. Замыкают группу лидеров Бельгия, Франция и Швейцария, с шестью новыми исследованиями каждая.

В первом квартале 2016 года было инициировано 21 новых КИ I фазы, что на 91% больше, чем за тот же период 2015 года. Количество исследований II фазы уменьшилось по сравнению с первым кварталом 2015 года и составило 18 новое исследование против 20. Количество КИ III фазы увеличилось с 68 до 90 исследования, что на 32% больше по сравнению с прошлым годом. Количество исследований IV фазы уменьшилось по сравнению с первым кварталом 2015 года и составило пять исследований против четырех.

В первом квартале 2016 года лидирующие позиции среди иностранных производителей по количеству новых исследований заняли компании *Janssen* и *Merck&Co* с пятью новыми исследованиями каждая. Далее следуют компании *Novartis* и *AbbVie* с четырьмя новыми исследованиями каждая. Пятерку лидеров замыкает компания *Teva* с тремя новыми КИ.

Список пяти лидирующих отечественных производителей по количеству новых исследований, в первом квартале 2016 года возглавила компания *Фармасинтез* с шестью исследованиями. Далее следуют компании *Герофарм* (пять новых исследований) и *Р-Фарм* (три новых КИ). Пятерку лидеров замыкают компании *Синтез* и *Сотекс* (два новых исследований каждая).

В пятерку передовиков первого квартала 2016 года вошли следующие исследовательские центры: *Первый Санкт-Петербургский государственный медицинский университет имени И.П.Павлова* (17 новых исследований), *Клиническая больница № 2 города Ярославля* (16 новых КИ), *ООО Эко-безопасность* (11 КИ), *Первый Московский государственный медицинский университет имени И.М. Сеченова* (девять КИ) и *Рязанский государственный медицинский университет* (девять новых КИ).

В первом квартале 2016 года 81% новых исследований был инициирован в девяти терапевтических областях. Наибольшее количество исследований было проведено в областях инфекционных болезней и онкологии – по 17 в каждой. В области ревматологии было проведено 15 новых исследований; в области эндокринологии - 14; в области пульмонологии – 11; в областях офтальмологии и неврологии – по девять новых КИ; в областях дерматологии и гинекологии – по восемь новых исследований.

Центр по оценке и исследованию лекарственных средств (Center for Drug Evaluation and Research, CDER) FDA одобрил в первом квартале 2016 года 26 новых лекарственных препаратов, по девяти из которых в России проводились (или проводятся) КИ. Европейское агентство по лекарственным средствам (European Medicine Agency, EMA) дало в первом квартале 2016 года положительные рекомендации по 23 новым лекарственным препаратам, по 16 из которых в России проводились (или проводятся) КИ.

Информация о проверках Росздравнадзора и FDA за первый квартал 2016 года на момент выпуска «Оранжевой Книги» недоступна.

Clinical Trials by Type and Manufacturing Country

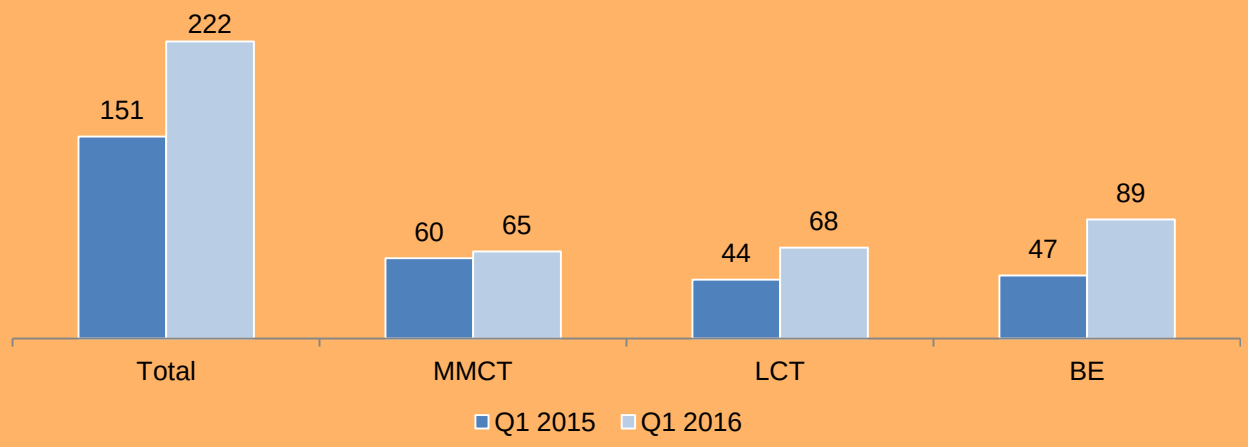
The Russian MoH approved 222 new clinical trials of all types including local and bioequivalence studies during Q1 2016, demonstrating a 47% increase in comparison with the same point of the last year.

As shown in **Figure 1**, the main contribution into the total number of studies was made by bioequivalence studies (BE), the number of these studies has increased from 47 studies in Q1 2015 to 89 in Q1 2016, 89% increase from last year's figure.

The number of multinational multi-center clinical trials (MMCT) increased from 60 studies in Q1 2015 to 65 in Q1 2016, 8% increase from last year's figure.

The number of local clinical trials (LCT) has increased from 44 in Q1 2015 to 68 in Q1 2016.

Figure 1. Clinical Trials in Russia in Q1 2016

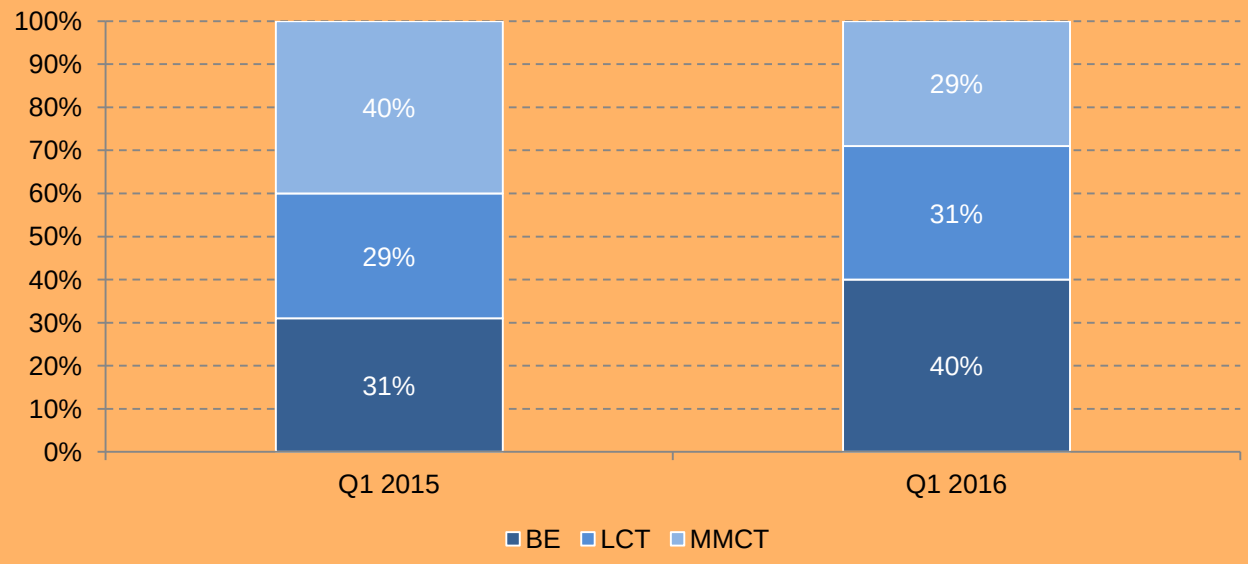


The proportions between different study types (multinational multi-center clinical trials, local studies and bioequivalence trials) have changed since last year (see **Figure 2**).

The share of bioequivalence studies increased from 31% to 40% of the total number of clinical trials approved in Q1 2016.

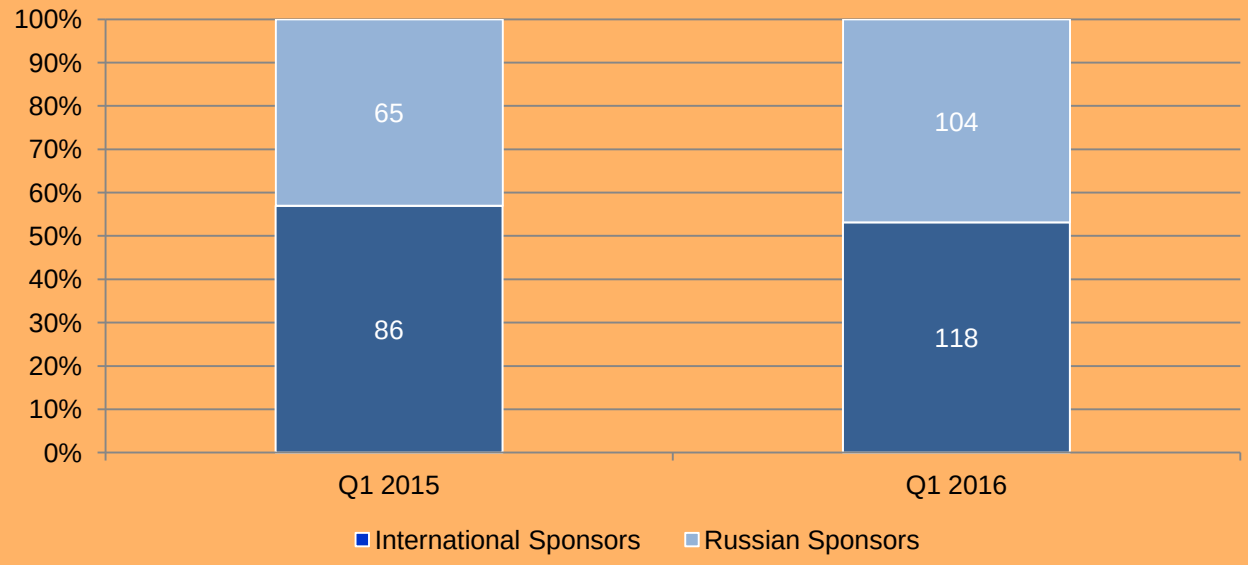
The share of the local trials increased from 29% in Q1 2015 to 31% in Q1 2016, and the share of multinational multi-center clinical contained 29% of the total number of trials approved during Q1 2016 (in Q1 2015 – 40%).

Figure 2. Clinical Trials by Type in Q1 2016



The geographic origins of sponsors changed slightly in comparison with last year. 53% of the total number of new studies in Q1 2016 was sponsored by foreign companies which received 118 study approvals. The share of studies of local manufacturers increased from 43% in Q1 2015 to 47% in Q1 2016, and amounted to 104 studies (**Figure 3**).

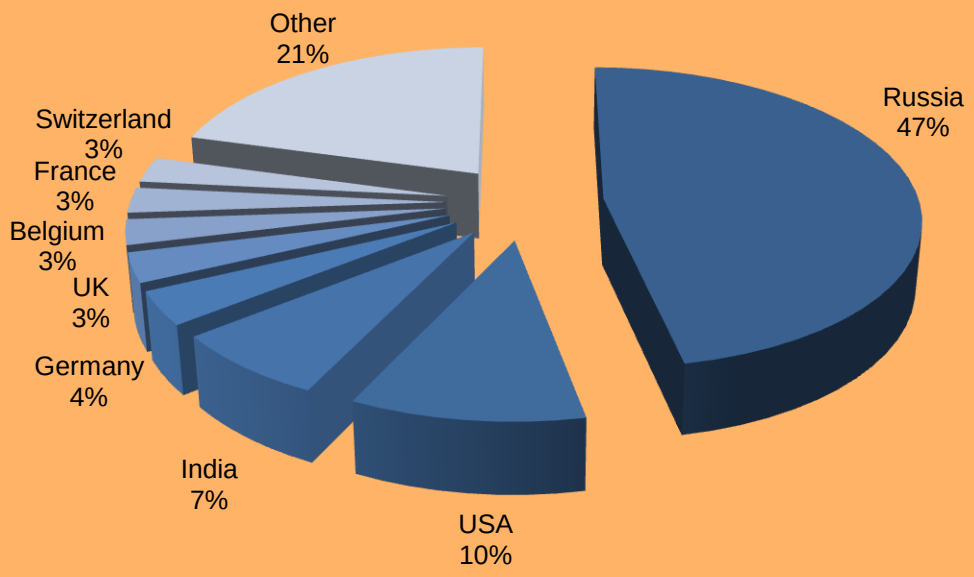
Figure 3. Russian vs International Sponsors in Q1 2016



Clinical trials in Russia in Q1 2016 were sponsored by companies from 28 countries. **Figure 4** indicates the geographic breakdown in sponsors' country of origin.

The maximum number of trials (104) was initiated by Russian sponsors. American sponsors with 23 new studies took the runner-up place; they are followed by Indian sponsors with 16 trials, German sponsors with eight studies, then UK sponsors having seven new studies. The group of leaders is concluded by Belgian, French and Swiss Sponsors, each having six studies.

Figure 4. Sponsors' Country of Origin for Q1 2016 Clinical Trials in Russia



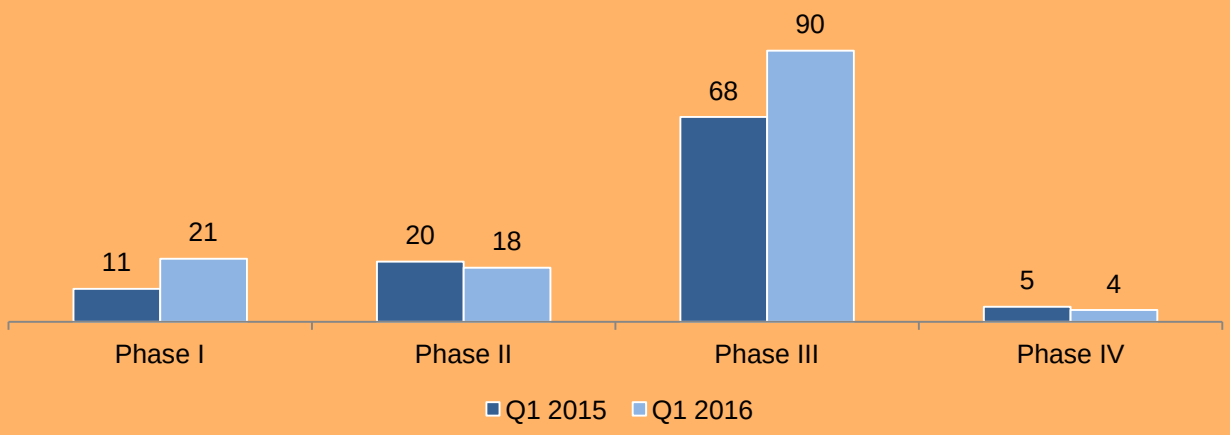
Other sponsors include: Cyprus and Poland (five studies each), Israel and Turkey (four studies each), Denmark, Spain and Slovenia (three studies each), Hungary, Austria, Republic of Macedonia, Romania, Ukraine and Sweden (two studies each) and Belarus, Latvia, UAE, Bulgaria, Czech Republic, Netherlands and Ecuador, each started one new study in Q1 2016.

Clinical trials by Phase

The number of Phase I clinical trials increased in 91% compared to Q1 2015: from 11 studies to 21 new studies in Q1 2016. The number of the Phase II trials slightly decreased from 20 in Q1 2015 to 18 new studies in Q1 2016, 10% less than in Q1 2015 (**Figure 5**).

The number of Phase III trials increased from 68 to 90 studies, 32% more than in Q1 2015. The number of Phase IV trials slightly decreased in comparison with Q1 2015 from five to four studies.

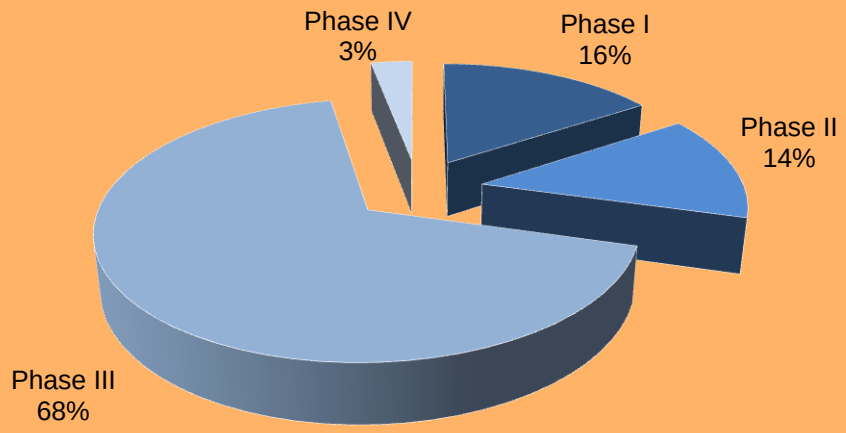
Figure 5. Clinical Trials in Russia in Q1 2016 by Phase[1]



As shown in **Figure 6**, the share of Phase III trials in Q1 2016 is 68% of the total number of studies, the share of Phase I trials is 16%, Phase II trials is 14% and the share of Phase IV studies accounted to 3%.

[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.

Figure 6. Percentage Breakdown of Russian Clinical Trials by Phase



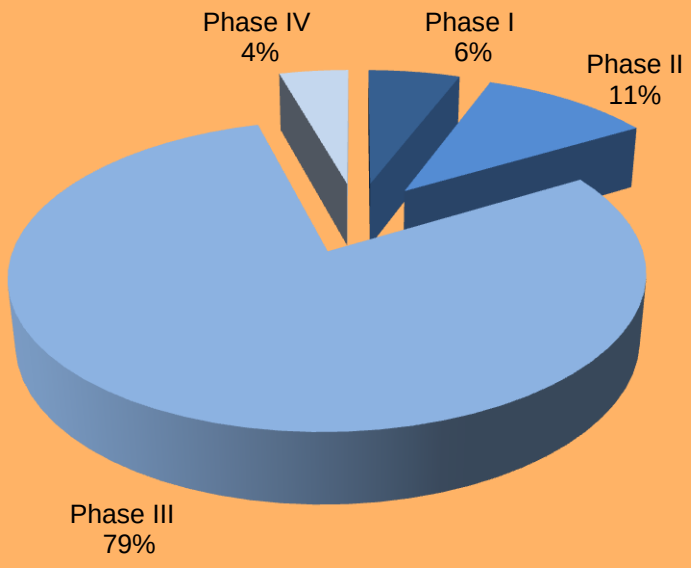
The number of subjects planned to be enrolled in Phase I-IV trials launched in Q1 2016 is 14,027, 30% more than Q1 2015 figure, when 10,822 patients were planned to be enrolled.

809 subjects will be recruited in Phase I trials; 1,500 – in Phase II trials; 11,108 – in Phase III studies and 610 subjects will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is five, the maximum number is 600.

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 Q1 2016 by Study Phase



The Top Five: Sponsor and Sites

Table 1. Top-5 International Study Sponsors in Q1 2016

№	Company Name	No. studies[1]	No. patients
1	Janssen	5	475
2	Merck & Co.	5	430
3	Novartis	4	760
4	AbbVie Inc	4	500
5	Teva	3	430

Table 2. Top-5 Russian Study Sponsors in Q1 2016

№	Company Name	No. studies	No. patients
1	Pharmasyntez	6	404
2	Geropharm	5	426
3	R-Pharm	3	850
4	Syntez	2	294
5	Soteks	2	270

Table 3. Top-5 Russian Research Sites in Q1 2016

№	Site Name	City	No. studies
1	Pavlov First St.Petersburg State Medical University	St. Petersburg	17
2	Clinical Hospital No. 2	Yaroslavl	16
3	Eco-Bezopasnost Ltd.	St. Petersburg	11
4	Sechenov First Moscow State Medical University	Moscow	9
5	Ryazan State Medical University	Ryazan	9

[1] Excluding BE studies

Table 4. Top-5 Russian CROs in Q1 2016

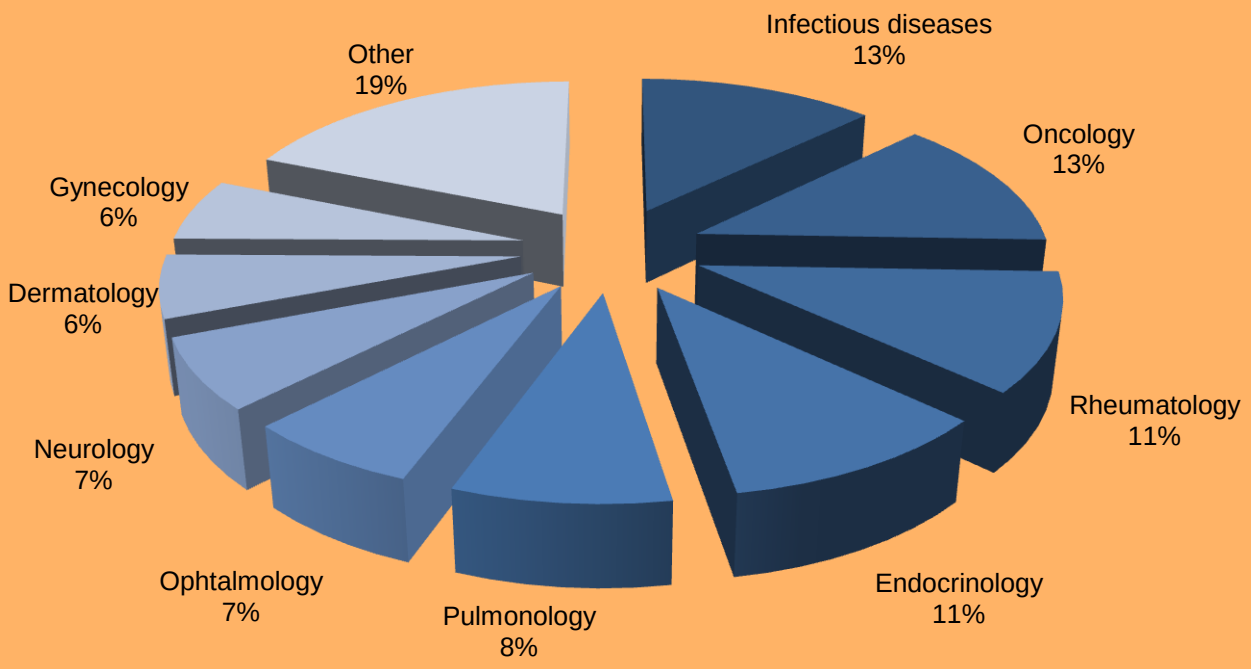
№	CRO Name	No. studies	No. patients
1	Synergy Research Group	5	640
2	OCT RUS	4	496
3	Quintiles	4	209
4	PPD Development	3	256
5	PSI	3	94

Therapeutic Areas of Russian Clinical Trials in Q1 2016

81% of new studies in Q1 2016 were initiated in nine leading therapeutic areas: the largest number of studies was initiated in Infectious diseases and Oncology (17 studies each); it is followed by Rheumatology (15 new studies), Endocrinology (14 studies), Pulmonology (11 studies), Ophtalmology and Neurology (nine studies each), Dermatology and Gynecology (eight studies each).

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

Figure 8. Clinical Trials in Russia in Q1 2016 by Therapeutic Area



Clinical Trials Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 26 new drugs during Q1 2016; five of them are new molecular entities (NME); others are new active ingredients, dosages, combinations, manufacturers or indications of already marketed drugs. Nine of 26 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 2016 that were (or are being) tested in clinical trials in Russia.

Table 3. New Drugs Approved by FDA in Q1 2016 and Tested in Russian sites

Appr.date	*Drug (active ingredient)*	*Company*
01/26/2016	Dexilant solutab (dexlansoprazole)	Takeda Pharms USA
02/12/2016	Rosuvastatin zinc (rosuvastatin zinc)	Watson Labs Inc
02/18/2016	Briviact (brivaracetam)	UCB Inc
02/18/2016	Briviact (brivaracetam)	UCB Inc
02/18/2016	Briviact (brivaracetam)	UCB Inc
02/23/2016	Xelianz XR (tofacitinib citrate)	Pfizer Inc
03/01/2016	Palonosetron hydrochloride (palonosetron hydrochloride)	Dr Reddys Labs Ltd.
03/22/2016	Taltz (ixekizumab)	Eli Lilly and Co
03/23/2016	Cinqair (reslizumab)	Teva Respiratory LLC
		Source: FDA

During Q1 2016, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 23 new drug applications[1], five positive recommendations on new generic medicines and one for new biosimilar medicine. 16 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 Q1 2016.

Table 4. New Drugs Approved by EMA in Q1 2016 and Tested in Russian sites

Appr. date	*Drug (active ingredient)*	*Manufacturer*
01/28/2016	Coagadex (factor x)	Bio Products Laboratory
01/28/2016	Empliciti (elotuzumab)	Bristol-Myers Squibb
04/01/2016	Uptravi (selexipag)	Actelion Registration Ltd
01/28/2016	Revlimid (lenalidomide)	Celgene Europe Limited
01/28/2016	Revolade (eltrombopag / eltrombopag olamine)	Novartis Europharm Ltd
02/25/2016	Descovy (emtricitabine / tenofovir alafenamide)	Gilead Sciences International Ltd
02/25/2016	Taltz (ixekizumab)	Eli Lilly Nederland B.V.
02/25/2016	Giotrif (afatinib)	Boehringer Ingelheim International GmbH

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

02/25/2016	Humira (adalimumab)	AbbVie Ltd
02/25/2016	Opdivo (nivolumab)	Bristol-Myers Squibb Pharma EEIG
02/25/2016	TachoSil (human thrombin / human fibrinogen)	Takeda Austria GmbH
02/25/2016	Zydelig (idelalisib)	Gilead Sciences International Ltd
04/01/2016	Darzalex (daratumumab)	Janssen-Cilag International N.V.
04/01/2016	Halaven (eribulin)	Eisai Europe Ltd
04/01/2016	Humira (adalimumab)	AbbVie Ltd
04/01/2016	Opdivo (nivolumab)	Bristol-Myers Squibb Pharma EEIG
		Source: EMA

Inspections

At the moment of the Orange Paper Q1 2016 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.