# Clinical Trials in Russia
# Orange Paper
# 2nd Quarter 2015



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## Executive Summary – English

The Ministry of Health of the Russian (MoH) Federation approved 194 new clinical trials of all types, including local and bioequivalence studies, during the 2nd Quarter of 2015, remaining consistent with approval rates from previous years. .

The main contributions to the total number of studies were made by multinational multi-center clinical trials (MMCT). The number of these studies was 78, which was 4% less than in Q2 2014. The number of bioequivalence studies (BE) increased from 59 studies in Q2 2014 to 62 in Q2 2015, a 5% increase from last year's figure. The number of local clinical trials (LCT) was 54 studies, which stayed the same as in Q2 2014.

The share of multinational multi-center clinical trials was 40% of the total number of clinical trials in Q2 2015, while the bioequivalence and local studies amounted to 32% and 28%, respectively.

Clinical trials in Russia in Q2 2015 were sponsored by companies from 20 countries. The greatest number of trials (89) was initiated by Russian sponsors. American sponsors followed with 26 new studies; Swiss sponsors with 14 trials, Indian sponsors with 13 studies, UK sponsors with ten studies, and German sponsors with nine new studies. The group of leaders is concluded by Israeli sponsors having seven new studies.

The number of Phase I clinical trials increased from eight in Q2 2014 to 12 in Q2 2015 (50% increase). The number of Phase II studies decreased from 29 in Q2 2014 to 23 new studies in Q2 2015. The number of Phase III trials decreased from 92 to 88 studies, 4% less than in Q2 2014. Phase IV trials showed an increase from six studies in Q2 2014 to nine studies in Q2 2015.

The number of subjects planned to be enrolled in Phase I-IV trials launched in Q2 2015 is 11,725, which is 24% less than the Q2 2014 figure, when 15,424 subjects were planned to be enrolled.

*Merck&Co* and *Novartis* initiated the most studies in Q2 2015, each sponsoring six studies. They are followed by *Sanofi-Aventis* and *Roche,* each having five new trials. The top five are concluded by *Grifols, who launched* three new trials in Q2 2015.

The top five domestic pharmaceutical manufacturers in Q2 2015 consist of *Materia Medica, Microgen, Biocad, Alvils* and *Feron.*

76% of new studies in Q2 2015 were initiated in eight leading therapeutic areas: the largest number of studies was initiated in Oncology (34); 16 new studies were initiated in Infectious and Parasitic Diseases; and 13 studies were initiated in Pulmonology. Eight new studies were initiated in Musculoskeletal Diseases, as well as in Endocrinology. Seven new studies were started in Cardiology, as well as in Ophthalmology, and six studies were initiated in Gastroenterology.

The Center for Drug Evaluation and Research (CDER) of the FDA approved 19 new drugs during Q2 2015, and three of them were (or are being) studied in clinical trials conducted in Russia.

During the second quarter of 2015, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 31 new drug applications[1]. 21 of the drugs which received positive opinions were (or are being) tested in clinical trials in Russia.

At the moment of the Orange Paper Q2 2015 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

Во втором квартале 2015 года Министерством здравоохранения Российской Федерации было выдано 194 разрешения на все виды клинических исследований (КИ), что равняется количеству разрешений, выданных во втором квартале прошлого года.

При этом количество новых международных многоцентровых КИ составило 78 исследований, что на 4% меньше по сравнению с этим же периодом прошлого года. Количество исследований биоэквивалентности, инициированных во втором квартале 2015 года, увеличилось на 5% по сравнению со вторым кварталом 2014 года и составило 62 против 59. Количество локальных КИ, проводимых на территории России отечественными и иностранными спонсорами, не изменилось по сравнению с аналогичным периодом 2014 года и составило 54 исследования.

Спонсорами КИ, разрешенных к проведению в России во втором квартале 2015 года, выступили компании из 20 стран. На первое место вышли российские производители с 89 КИ, за ними идут американские спонсоры с 26 новыми исследованиями, Швейцария с 14 исследованиями, затем Индия с 13 новыми КИ, Великобритания с десятью новыми исследованиями и Германия с девятью новыми исследованиями. Замыкает группу лидеров Израиль с семью новыми исследованиями.

Во втором квартале 2015 года было инициировано 12 новых КИ I фазы, что на 50% больше, чем за аналогичный период прошлого года. Количество исследований II фазы снизилось по сравнению с этим же периодом прошлого года и составило 23 новых исследований против 29. Количество исследований III фазы снизилось с 92 до 88 исследований – на 4% меньше по сравнению с прошлым годом. Количество исследований IV фазы увеличилось с шести до девяти исследований по сравнению с аналогичным периодом прошлого года.

Во втором квартале 2015 года лидирующие позиции среди иностранных производителей по количеству новых исследований заняли компании *Merck&Co* и *Novartis* с шестью новыми исследованиями каждая, но с разным количеством пациентов. Далее следуют *Sanofi-Aventis* и *Roche* с пятью новыми исследованиями каждая, но также с разным количеством пациентов. Замыкает пятерку лидеров компания *Grifols* с тремя новыми исследованиями.

В пятерку лидеров по количеству новых исследований, начатых во втором квартале 2015 года, среди отечественных производителей входят компании *Материа Медика Холдинг, Микроген, Биокад, ООО Алвилс* и *ООО Ферон,* с двумя новыми исследованиями у каждой, но разным количеством пациентов.

Во втором квартале 2015 года 76% всех новых исследований были инициированы в восьми терапевтических областях. Наибольшее количество в области онкологии – 34 КИ; 16 новых исследований – в области инфекционных и паразитарных болезней; 13 исследований – в области пульмонологии; по восемь исследований – в области заболеваний опорно-двигательного аппарата и эндокринологии; по семь новых исследований в области офтальмологии и болезней сердечно-сосудистой системы, шесть – в области гастроэнтерологии.

Центр по оценке и исследованию лекарственных средств (Center for Drug Evaluation and Research, CDER) FDA одобрил во втором квартале 2015 года 19 новых лекарственных препаратов, по трем из которых в России проводились (или проводятся) КИ.

В течение второго 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 31 новому лекарственному препарату. По 21 препарату, входившему в число получивших положительный отзыв, проводились (или проводятся) КИ в России.

Информация о проверках Росздравнадзора и FDA за второй квартал 2015 года на момент выпуска «Оранжевой Книги» недоступна.

## Clinical Trials by Type and Manufacturing Country

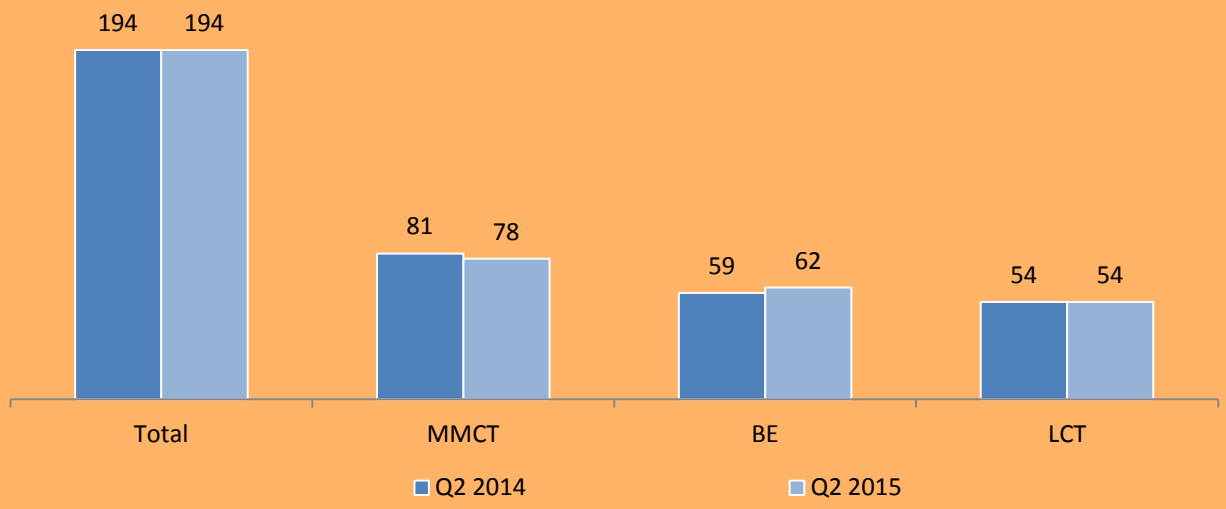
The Russian MoH approved 194 new clinical trials of all types, including local and bioequivalence studies, during the 2nd Quarter of 2015. .

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 decreased from 81 studies in Q2 2014 to 78 in Q2 2015, which represents a 4% decrease from last year's figure.

The number of bioequivalence studies (BE) increased from 59 studies in Q2 2014 to 62 in Q2 2015, which is a 5% increase from last year's figure.

The number of local clinical trials (LCT) has not changed from Q2 2014 to Q2 2015 and amounted to 54 studies.

**Figure 1. Clinical Trials in Russia in Q2 2015**

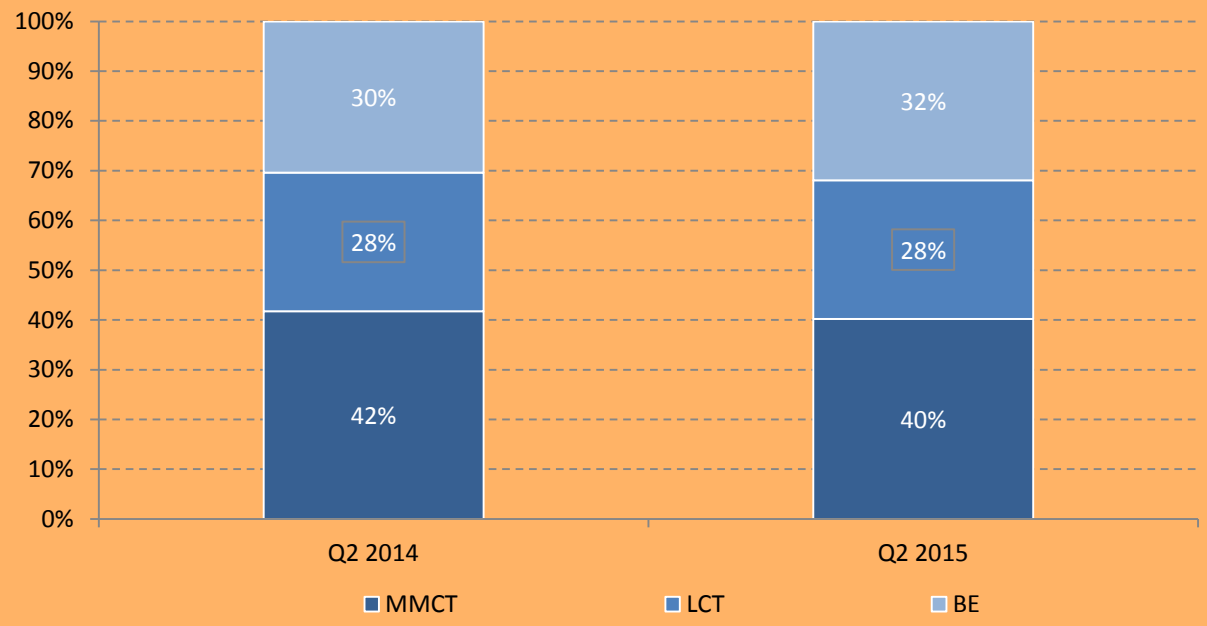



The proportions between different study types (multinational multi-center clinical trials, local studies and bioequivalence trials) changed slightly since last year (see **Figure 2**).

The share of bioequivalence studies increased from 30% to 32% of the total number of clinical trials approved in Q2 2015.

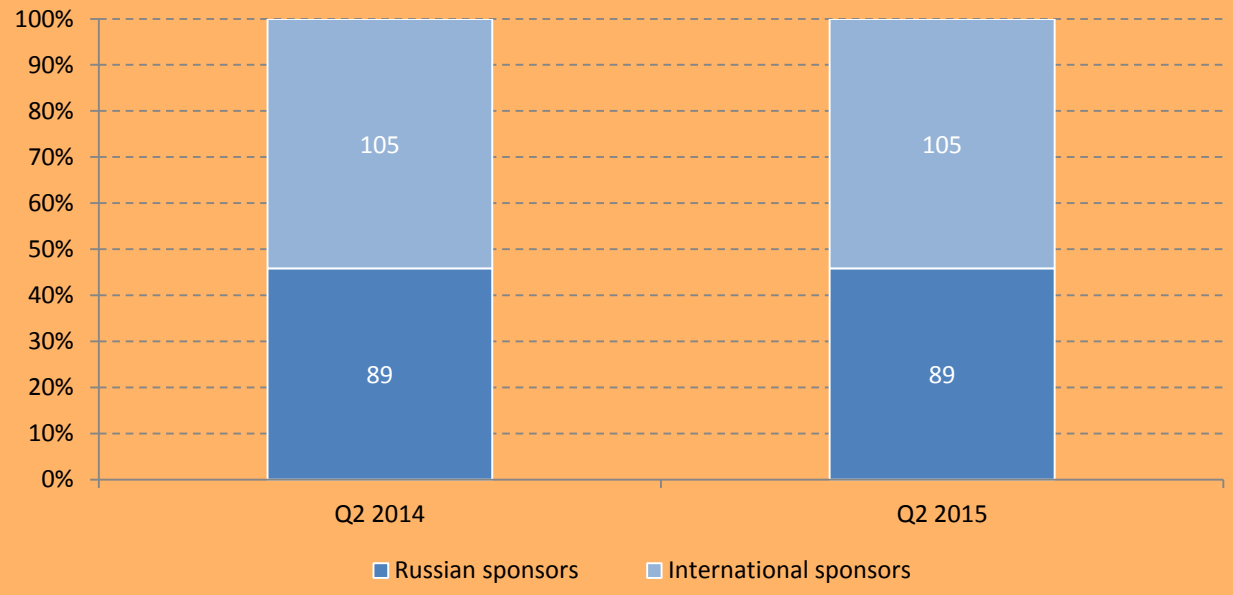
The share of the local trials has not changed and amounted to 28% in Q2 2015, while the share of multinational multi-center clinical trials decreased from 42% to 40%.

**Figure 2. Clinical Trials by Type in Q2 2015**




The geographic origins of sponsors did not change in comparison with the same period last year. 54% of the total number of new studies in Q2 2015 were sponsored by foreign companies, which received 105 study approvals. The share of studies of local manufacturers was 46% in Q2 2015, and amounted to 89 studies (**Figure 3**).

**Figure 3. Russian vs International Sponsors in Q2 2015**

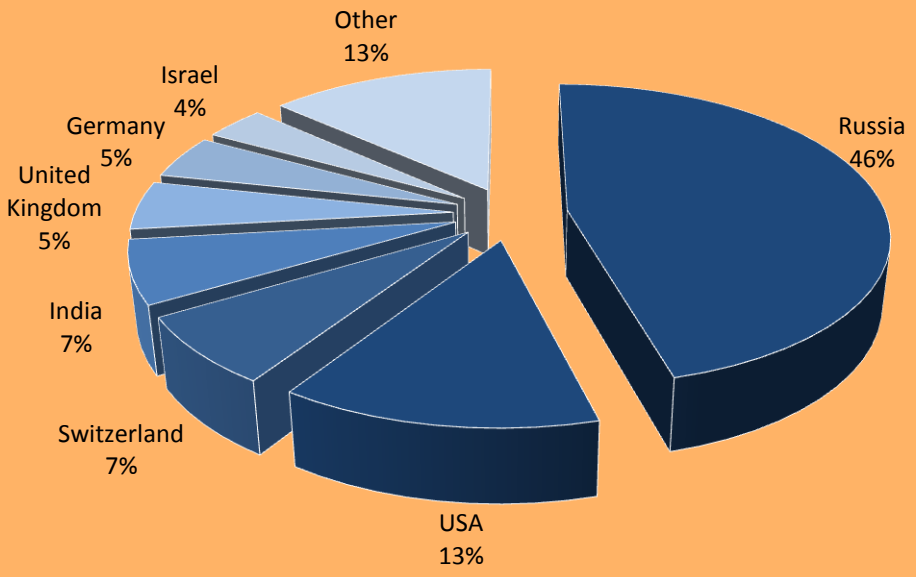



Clinical trials in Russia in Q2 2015 were sponsored by companies from 20 countries. **Figure 4** indicates the geographic breakdown in sponsors' countries of origin.

The greatest number of trials (89) was initiated by Russian sponsors, followed by American sponsors with 26 new studies; they are followed by Swiss sponsors with 14 trials, Indian sponsors

with 13 studies, UK sponsors with ten studies, and German sponsors with nine new studies; the group of leaders is concluded by Israeli sponsors having seven new studies.

**Figure 4. Sponsors' Country of Origin for Q2 2015 Clinical Trials in Russia**



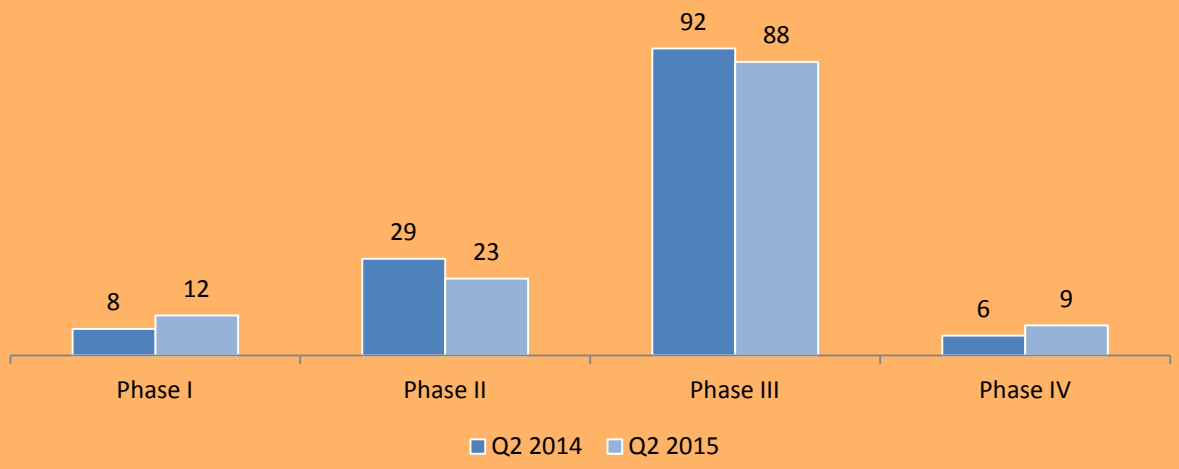

Other sponsors include: France (six new studies), Slovenia (four new studies), Argentina, Belarus, Belgium, Spain, and Ukraine (two studies each). Denmark, Italy, Cyprus, Singapore, Sweden, and Japan each started one new study in Q2 2015.

## Clinical Trials by Phase

The number of Phase I clinical trials demonstrated 50% increase compared to Q2 2014: from eight studies to 12 new studies in Q2 2015. The number of the Phase II trials decreased from 29 in Q2 2014 to 23 new studies in Q2 2015 (**Figure 5**).

The number of Phase III trials decreased from 92 to 88 studies, 4% less than in Q2 2014. Phase IV trials demonstrated an increase from six studies in Q2 2014 to nine studies in Q2 2015.

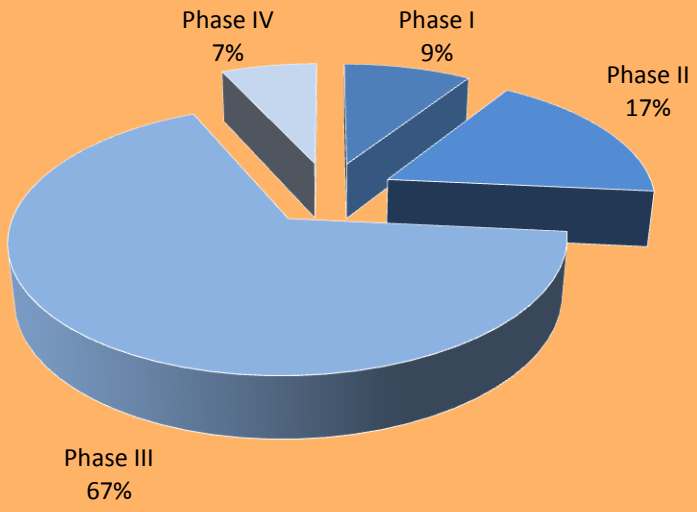
**Figure 5. Clinical Trials in Russia in Q2 2015 by Phase[1]**




[1] Studies indicated by sponsors as phase I-II in the applications submitted to MoH are shown in the phase II studies group; phase II-III are shown in the phase III group; and phase III-IV are shown in the phase IV group. BE studies were not included in any phase group.

As shown in **Figure 6**, the share of Phase III trials in Q2 2015 is 67% of the total number of studies, the share of Phase II trials is 17%, Phase I trials is 9%, and the share of Phase IV studies accounted for 7%.

**Figure 6. Percentage Breakdown of Russian Clinical Trials by Phase**



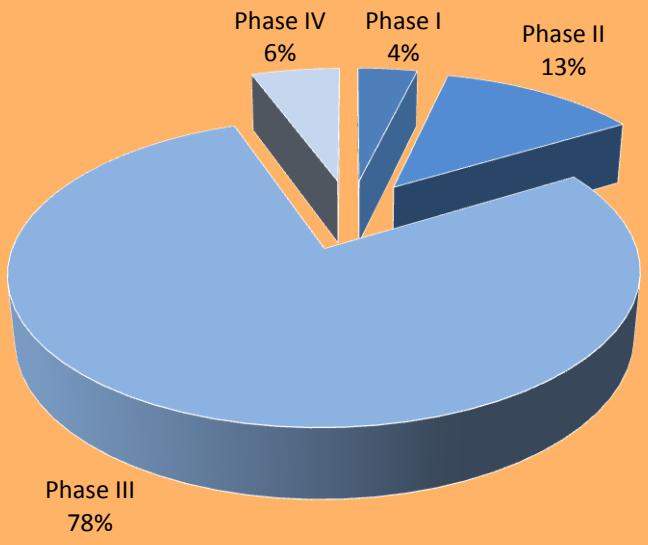

The number of subjects planned to be enrolled in Phase I-IV trials launched in Q2 2015 is 11,725, which is 24% less than the Q2 2014 figure, when 15,424 patients were planned to be enrolled.

441 subjects will be recruited in Phase I trials; 1,479 in Phase II trials; 9,149 in Phase III studies; and 656 subjects will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is two and the maximum number is 750.

**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 Q2 2015 by Study Phase**



## Number of Studies by Sponsor

*Merck&Co.* and *Novartis initiated the most new studies in Q2 215,* each sponsoring six studies Q2 2015. They are followed by *Sanofi-Aventis* and *Roche,* each with five new trials. The top five are concluded by *Grifols* having three new studies in Q2 2015.

Top five international sponsors ranked by the number of new studies in Q2 2015 are presented in **Table 1.**

**Table 1. Top-5 International Study Sponsors in Q2 2015**

| *№* | *Company Name* | *No. studies*[1] | *No. patients* |
|---|---|---|---|
| 1 | Merck & Co. | 6 | 490 |
| 2 | Novartis | 6 | 295 |
| 3 | Sanofi-Aventis | 5 | 812 |
| 4 | Roche | 5 | 184 |
| 5 | Grifols | 3 | 177 |

## Rating of Russian sponsors

The top five domestic pharmaceutical manufacturers, ranked by the number of new studies in Q2 2015 consist of *Materia Medica*, *Microgen, Biocad, Alvils* and *Feron,* each having two new trials and differing in the number of patients.

**Table 2. Top-5 Russian Study Sponsors in Q2 2015**

| *№* | *Company Name* | *No. studies* | *No. patients* |
|---|---|---|---|
| 1 | Materia Medica | 2 | 448 |
| 2 | Microgen | 2 | 320 |
| 3 | Biocad | 2 | 270 |
| 4 | Alvils | 2 | 216 |
| 5 | Feron | 2 | 194 |

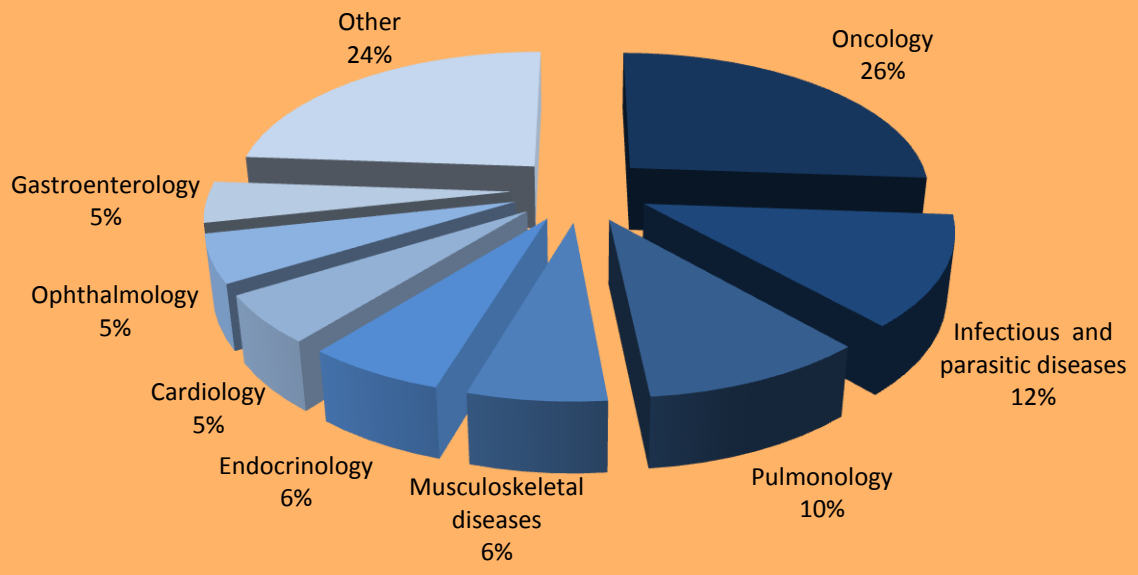
[1] Excluding BE studies

## Therapeutic Areas of Russian Clinical Trials in Q2 2015

76% of new studies in Q2 2015 were initiated in eight leading therapeutic areas: the largest number of studies was initiated in Oncology (34); 16 new studies were initiated in Infectious and Parasitic Diseases; 13 studies in Pulmonology; eight new studies in Musculoskeletal Diseases, as well as in Endocrinology; seven studies in Cardiology, as well as in Ophthalmology; and six new studies were started in Gastroenterology.

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

**Figure 8. Clinical Trials in Russia in Q2 2015 by Therapeutic Area**




## Clinical Trials Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 19 new drugs during Q2 2015; four of them are new molecular entities (NME); others are new dosages, combinations, manufacturers, or indications of already marketed drugs. Three drugs were (or are being) studied in clinical trials involving Russian sites.

**Table 3** shows the drugs which were approved by FDA in Q2 2015 that were (or are being) tested in clinical trials in Russia.

**Table 3. New Drugs Approved by FDA in Q2 2015 and Tested in Russian sites**

| *Appr.date* | *Drug (active ingredient)* | *Company* |
|---|---|---|
| 05/18/2015 | Invega Trinza (Paliperidone Palmitate) | Janssen Pharms |
| 05/26/2015 | Humalog Kwikpen (Insulin Lispro Recombinant) | Eli Lilly and Co |
| 05/21/2015 | Stiolto Respimat (Olodaterol Hydrochloride; Tiotropium Bromide) | Boehringer Ingelheim |
| | | *Source: FDA* |

During the second quarter of 2015, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 31 new drug

applications[1]. Negative opinion was adopted for two drugs. Twenty-one 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 Q2 2015 and Tested in Russian Sites**

| *Appr. date* | *Drug (active ingredient)* | *Manufacturer* |
|---|---|---|
| 04/23/2015 | Lixiana (Edoxaban) | Daiichi Sankyo Europe GmbH |
| 04/23/2015 | Opdivo (Nivolumab) | Bristol-Myers Squibb Pharma EEIG |
| 04/23/2015 | Invega (Paliperidone) | Janssen-Cilag International N.V. |
| 04/23/2015 | Levemir (Insulin Detemir) | Novo Nordisk A/S |
| 04/23/2015 | Tygacil (Tigecycline) | Pfizer Limited |
| 05/21/2015 | Keytruda (Pembrolizumab) | Merck Sharp & Dohme Limited |
| 05/21/2015 | Nivolumab BMS (Nivolumab) | Bristol-Myers Squibb Pharma EEIG |
| 05/21/2015 | Repatha (Evolocumab) | Amgen Europe B.V. |
| 05/21/2015 | Fycompa (Perampanel) | Eisai Europe Ltd |
| 05/21/2015 | Imbruvica (Ibrutinib) | Janssen-Cilag International NV |
| 05/21/2015 | Kuvan (Sapropterin) | Merck Serono Europe Limited |
| 05/21/2015 | Simponi (Golimumab) | Janssen Biologics B.V. |
| 05/21/2015 | Stelara (Ustekinumab) | Janssen-Cilag International N.V. |
| 05/21/2015 | Xultophy (Insulin Degludec / Liraglutide) | Novo Nordisk A/S |
| 06/25/2015 | Farydak (Panobinostat) | Novartis Europharm Ltd |
| 06/25/2015 | Kanuma (Sebelipase Alfa) | Synageva BioPharma Ltd |
| 06/25/2015 | Respreeza (Human Alpha1-Proteinase Inhibitor) | CSL Behring GmbH |
| 06/25/2015 | Humira (Adalimumab) | AbbVie Ltd |
| 06/25/2015 | Levemir (Insulin Detemir) | Novo Nordisk A/S |
| 06/25/2015 | Perjeta (Pertuzumab) | Roche Registration Ltd |
| 06/25/2015 | Voncento (Human Coagulation Factor VIII / Human von Willebrand Factor) | CSL Behring GmbH |
| | | *Source: EMEA* |

## Inspections

At the time of publishing this Orange Paper Q2 2015, no information about any inspections (FDA or Roszdravnadzor) conducted in Russian investigative sites during this period was available.

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

## Summary

In summary, Russia remains a strong contributor to the global new drug development and approval process. . Sponsors site 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.

**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 is in Moscow.