NEW! TOP 5 RESEARCH SITES

Clinical Trials in Russia
Orange Paper
3rd Quarter 2015

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

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Contents

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Executive Summary – English

The Ministry of Health of the Russian Federation approved 203 new clinical trials of all types including local and bioequivalence studies, during the 3rd Quarter of 2015. This represents a 13% increase over the same period of 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 86 and it is 19% more than in Q3 2014. The number of bioequivalence studies (BE) increased from 67 studies in Q3 2014 to 77 in Q3 2015, a 15% increase from last year's figure. The number of local clinical trials (LCT) slightly decreased from 41 in Q3 2014 to 40 in Q3 2015.

The share of multinational multi-center clinical trials was 42% of the total number of clinical trials in Q3 2015, while bioequivalence and local studies amounted to 38% and 20% respectively.

The number of Phase I clinical trials slightly decreased from 13 in Q3 2014 to 12 in Q3 2015. The number of Phase II studies increased from 15 in Q3 2014 to 21 new studies in Q3 2015. The number of Phase III trials increased from 79 to 90 studies, 14% more than in Q3 2014. Phase IV trials showed a decrease from six studies in Q3 2014 to three studies in Q3 2015.

The number of subjects planned to be enrolled in Phase I-IV trials launched in Q3 2015 is 10,689, 16% less than the Q3 2014 figure, when 12,705 subjects were planned to be enrolled.

Roche is on the top of the heap in Q3 2015 by sponsoring nine new studies. It is followed by *Novartis* sponsoring seven new studies, then *Janssen* and *Bristol-Myers Squibb* each having six new trials and differing in the number of patients. The *Top* five are concluded by *Novo Nordisk* having three new trials in Q3 2015.

The Top five domestic pharmaceutical manufacturers by the number of new studies in Q3 2015 is headed by *Valenta* and *Pharmasyntez,* each having three new trials and differing in the number of patients. They are followed by *Akrikhin, Pharmaceutical factory SPb* and *OAO Pharmsyntez*, each having two new trials and differentiating in the number of patients.

The top five Russian study sites by the number of new clinical trials are: *Pavlov First St.Petersburg State Medical University* (24 studies); *Russian Scientific Oncology Center n/a N.N. Blokhin* (22 studies); *St.Petersburg City Oncology Clinic* (15 studies); *Kazan State Medical University* (14 studies) and *Clinical Hospital No.2, Yaroslavl* (13 studies).

83% of new studies in Q3 2015 were initiated in eight leading therapeutic areas: the largest number of studies was initiated in Oncology (28); 25 new studies were instigated in Pulmonology. Ten new studies were initiated in Infectious and parasitic diseases, as well as in Musculoskeletal diseases and Neurology. Nine new studies were started in Gastroenterology, eight new studies – in Endocrinology, and five studies – in Urology.

The Center for Drug Evaluation and Research (CDER) of the FDA approved 30 new drugs during Q3 2015, and 12 of them were (or are being) studied in clinical trials conducted in Russia.

During the third quarter of 2015, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 29 new drug applications[1]. 18 of the drugs which received positive opinions were (or are being) tested in clinical trials in Russia.

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

Executive Summary – Russian

В третьем квартале 2015 года Министерством здравоохранения Российской Федерации было выдано 203 разрешения на все виды клинических исследований (КИ). По сравнению с аналогичным периодом прошлого года рост составил 13%.

При этом количество новых международных многоцентровых КИ выросло на 19% и составило 86 исследований. Количество исследований биоэквивалентности также увеличилось на 15% и составило 77 исследований против 67 в прошлом году. Количество локальных КИ уменьшилось по сравнению с аналогичным периодом 2014 года и составило 40 исследований против 41.

Спонсорами КИ, разрешенных к проведению в России в третьем квартале 2015 года, выступили компании из 28 стран. На первое место вышли российские производители с 81 КИ, за ними идут американские спонсоры с 31 новыми исследованиями, Швейцария с 24 исследованиями, затем Индия с десятью новыми КИ, Бельгия и Словения с шестью новыми исследованиями каждая. Замыкает группу лидеров Великобритания и Франция с пятью новыми исследованиями каждая.

В третьем квартале 2015 года было инициировано 12 новых КИ I фазы, что на 1 исследование меньше, чем за аналогичный период прошлого года. Количество исследований II фазы увеличилось по сравнению с этим же периодом прошлого года и составило 21 новых исследований против 15. Количество исследований III фазы увеличилось с 79 до 90 исследований – на 14% больше по сравнению с прошлым годом. Количество исследований IV фазы уменьшилось с шести до трех исследований по сравнению с аналогичным периодом прошлого года.

В третьем квартале 2015 года лидирующие позиции среди иностранных производителей по количеству новых исследований заняла компания *Roche* с девятью новыми исследованиями. Далее следует компания *Novartis* с семью новыми исследованиями, затем *Janssen* и *Bristol-Myers Squibb* с шестью новыми исследованиями каждая. Замыкает пятерку лидеров компания *Novo Nordisk* с тремя новыми исследованиями.

Пятерку лидеров по количеству новых исследований, начатых в третьем квартале 2015 года, среди отечественных производителей возглавили компании *Валента* и *Фармасинтез,* с тремя новыми исследованиями у каждой, но разным количеством пациентов. Далее следуют компании *Акрихин, Фармацевтическая фабрика СПб* и *ОАО Фармсинтез*, с двумя новыми исследованиями каждая, но также с разным количеством пациентов.

Начиная с этого выпуска, мы вводим новую рубрику об исследовательских центрах, лидерах рынка по количеству новых исследований за период. С удовольствием представляем пятерку передовиков 3 квартала 2015 года: *Первый Санкт-Петербургский государственный медицинский университет имени академика И.П. Павлова* (24 новых КИ), *Российский онкологический научный центр имени Н.Н. Блохина* (22 исследования), *Городской клинический онкологический диспансер г. Санкт-Петербург* (15 КИ); *Казанский государственный медицинский университет* (14 новых КИ) *и Клиническая больница № 2 г. Ярославля* (13 новых исследований).

В третьем квартале 2015 года 83% новых исследований были инициированы в восьми терапевтических областях. Наибольшее количество в области онкологии – 28 КИ; 25 новых исследований – в области пульмонологии; по десять исследований – в области инфекционных и паразитарных болезней, заболеваний опорно-двигательного аппарата и неврологии; девять новых исследований в области гастроэнтерологии, восемь исследований – в области эндокринологии, и пять исследований – в области урологии.

За отчётный период FDA одобрила 30 новых лекарственных препаратов, по 12 препаратам в России проводились (или проводятся) КИ. Европейское агентство по лекарственным средствам одобрило 29 новых препаратов, 18 из которых были исследованы в Российских центрах.

Clinical Trials by Type and Manufacturing Country

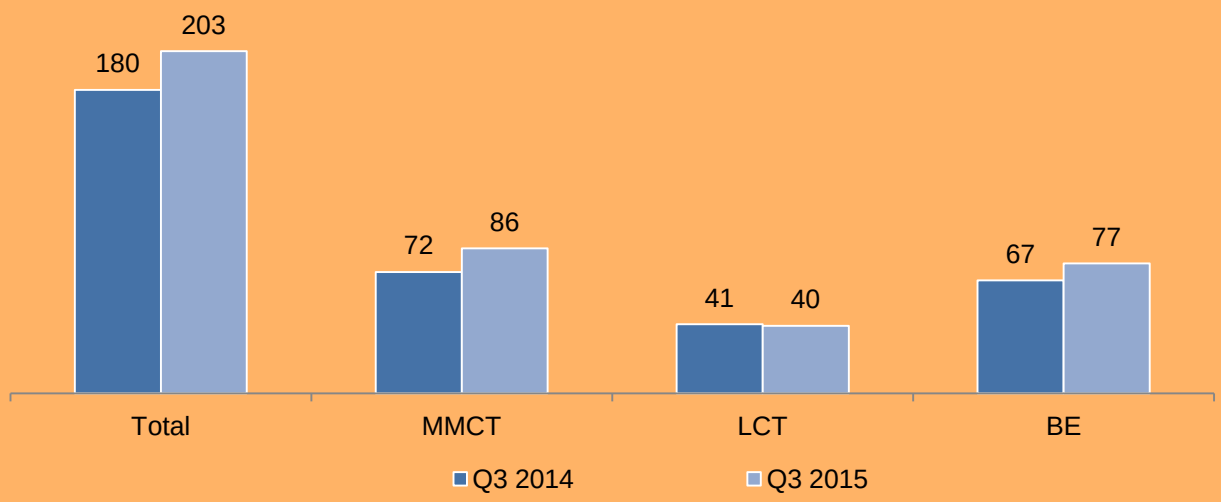
The Russian MoH approved 203 new clinical trials of all types including local and bioequivalence studies during the 3rd Quarter of 2015, demonstrating a 13% increase in comparison with the same time period last year.

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 has increased from 72 studies in Q3 2014 to 86 in Q3 2015, 19% increase from last year's figure.

The number of bioequivalence studies (BE) increased from 67 studies in Q3 2014 to 77 in Q3 2015, 15% increase from last year's figure.

The number of local clinical trials (LCT) has slightly decreased from 41 in Q3 2014 to 40 in Q3 2015.

Figure 1. Clinical Trials in Russia in Q3 2015

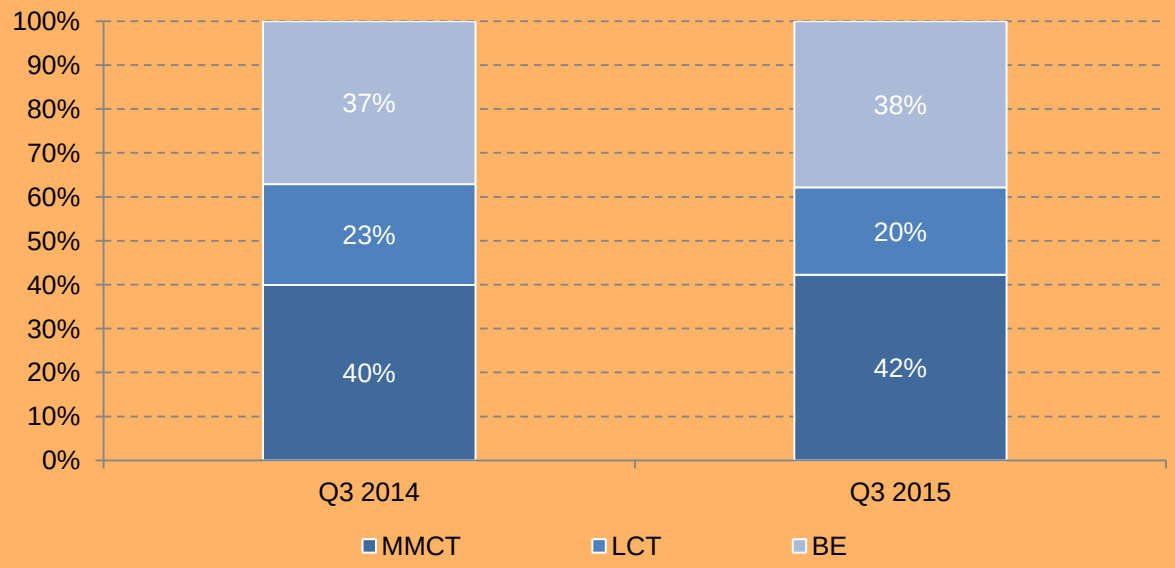


The proportions between different study types (multinational multi-center clinical trials, local studies and bioequivalence trials) changed slightly since last year (see **Figure 2**).

The share of bioequivalence studies has slightly increased from 37% to 38% of the total number of clinical trials approved in Q3 2015.

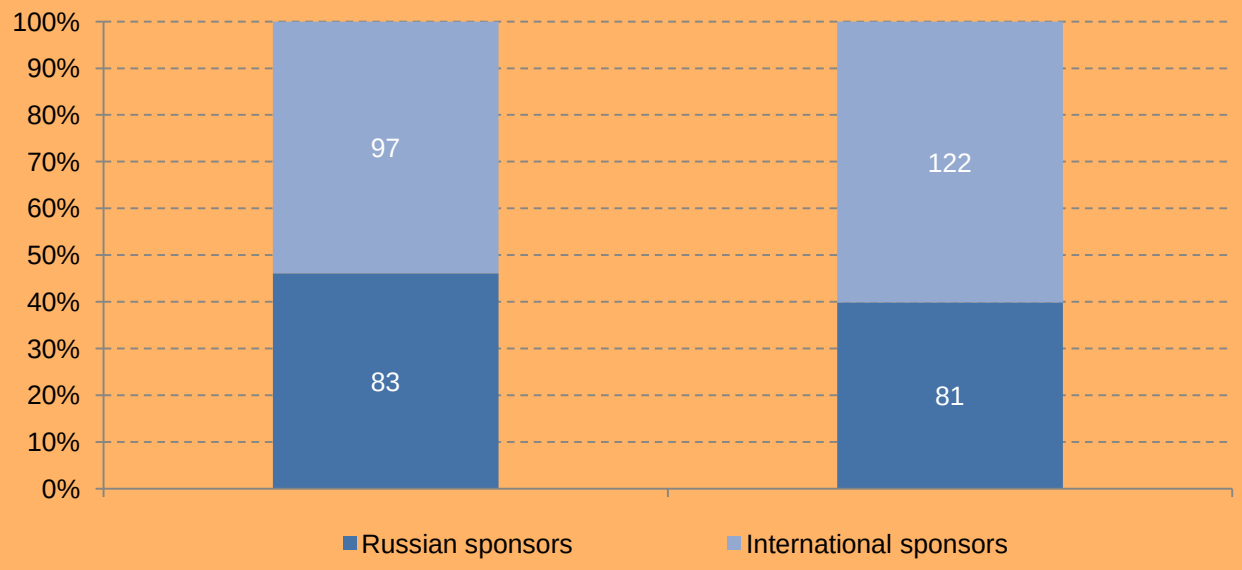
The share of the local trials slightly decreased from 23 % in Q3 2014 to 20% in Q3 2015, and the share of multinational multi-center clinical trials increased from 40% to 42% of the total number of trials approved during Q3 2015.

Figure 2. Clinical Trials by Type in Q3 2015



The geographic origins of sponsors did not significantly change in comparison with the same period last year. 60% of the total number of new studies in Q3 2015 were sponsored by foreign companies which received 122 study approvals. The share of studies of local manufacturers decreased from 46% in Q3 2014 to 40% in Q3 2015, and amounted to 81 studies (**Figure 3**).

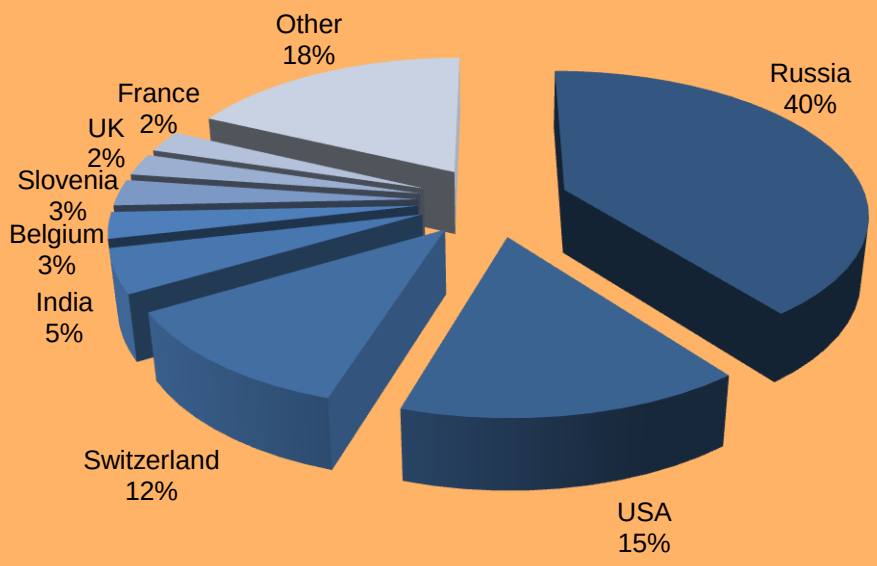
Figure 3. Russian vs International Sponsors in Q3 2015



Clinical trials in Russia in Q3 2015 were sponsored by companies from 28 countries. **Figure 4** indicates the geographic breakdown in sponsors' country of origin.

The maximum number of trials (81) was initiated by Russian sponsors. American sponsors with 31 new studies took the runner-up place; they are followed by Swiss sponsors with 24 trials, Indian sponsors with ten studies, then Belgian and Slovenian sponsors each with six studies. The group of leaders is concluded by UK and French sponsors each having five new studies.

Figure 4. Sponsors' Country of Origin for Q3 2015 Clinical Trials in Russia



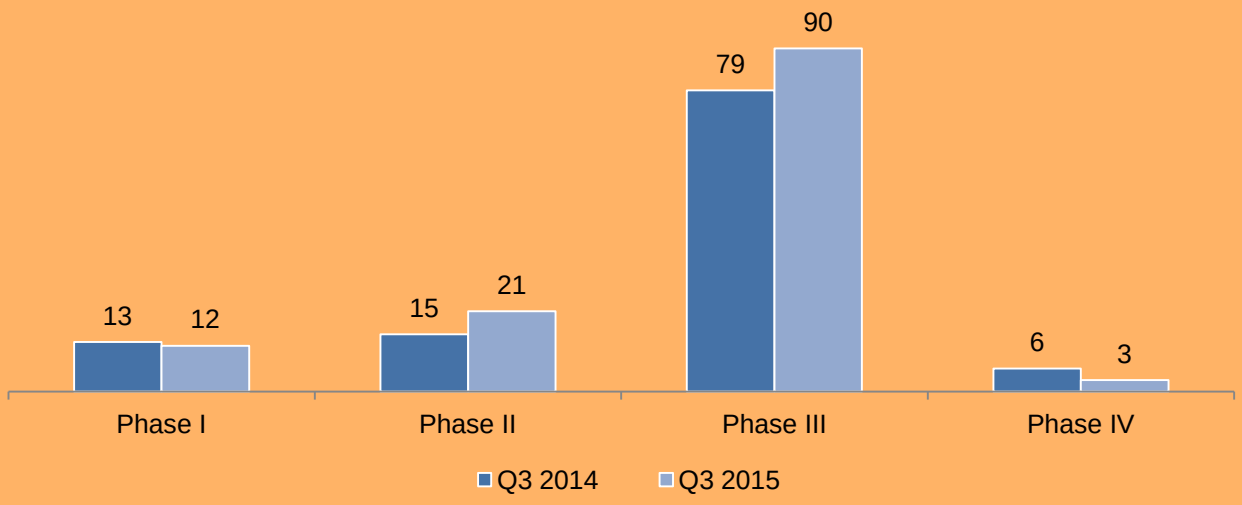
Other sponsors include: Germany and Sweden (four new studies each), Austria, Hungary and Denmark (three studies each), Argentina, Israel and Croatia (two studies each), Vietnam, Ireland, Spain, Italy, Cyprus, Republic of Korea, Netherlands, Panama, Poland, Romania, Turkey and Finland each started one new study in Q3 2015.

Clinical trials by Phase

The number of Phase I clinical trials slightly decreased compared to Q3 2014: from 13 studies to 12 new studies in Q3 2015. The number of the Phase II trials increased in 40% from 15 in Q3 2014 to 21 new studies in Q3 2015 (**Figure 5**).

The number of Phase III trials increased from 79 to 90 studies, 14% more than in Q3 2014. Phase IV trials demonstrated the decrease from six studies in Q3 2014 to three studies in Q3 2015.

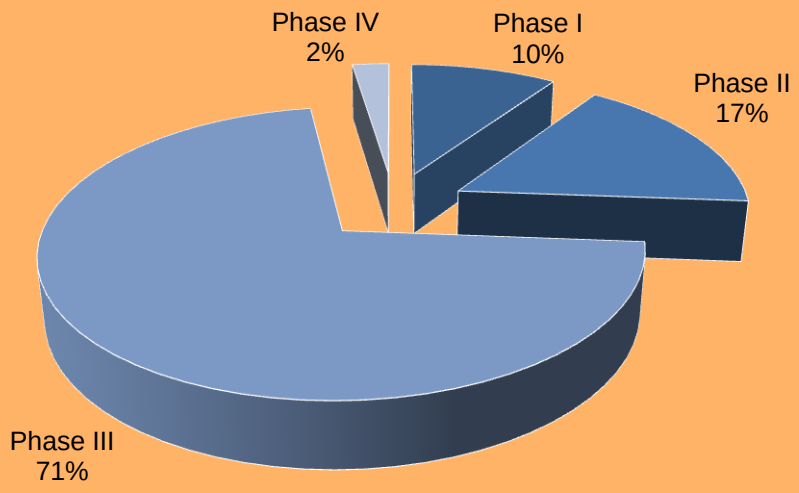
Figure 5. Clinical Trials in Russia in Q3 2015 by Phase[1]



[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 Q3 2015 is 71% of the total number of studies, the share of Phase II trials is 17%, Phase I trials is 10% and the share of Phase IV studies accounted to 2%.

Figure 6. Percentage Breakdown of Russian Clinical Trials by Phase



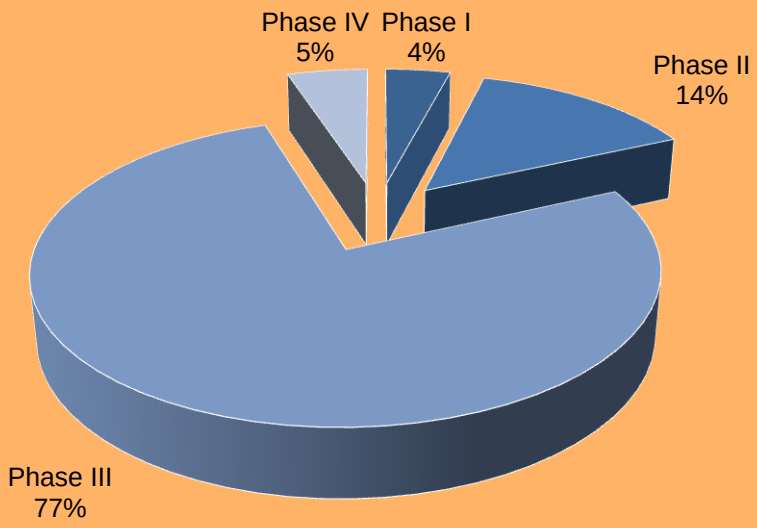
The number of subjects planned to be enrolled in Phase I-IV trials launched in Q3 2015 is 10,689, 16% less than Q3 2014 figure, when 12,705 patients were planned to be enrolled.

436 subjects will be recruited in Phase I trials; 1,515 – in Phase II trials; 8,198 – in Phase III studies and 540 subjects will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is one, the maximum number is 400.

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 Q3 2015 by Study Phase



The Top Five: Sponsor and Sites

Table 1. Top-5 International Study Sponsors in Q3 2015

№	Company Name	No. studies[1]	No. patients
1	Roche	9	486
2	Novartis	7	1,112
3	Janssen	6	616
4	Bristol-Myers Squibb	6	330
5	Novo Nordisk	3	372

Table 2. Top-5 Russian Study Sponsors in Q3 2015

№	Company Name	No. studies	No. patients
1	Valenta	3	520
2	Pharmasyntez	3	382
3	Akrikhin	2	310
4	Pharmaceutical factory SPb	2	230
5	OAO Pharmsynthez	2	112

Table 3. Top-5 Russian Research Sites in Q3 2015

№	Site Name	City	No. studies
1	Pavlov First St.Petersburg State Medical University	St.Petersburg	24
2	Russian Scientific Oncology Center n/a N.N. Blokhin	Moscow	22
3	City Oncology Clinic	St.Petersburg	15
4	Kazan State Medical University	Kazan	14
5	Clinical Hospital No.2	Yaroslavl	13

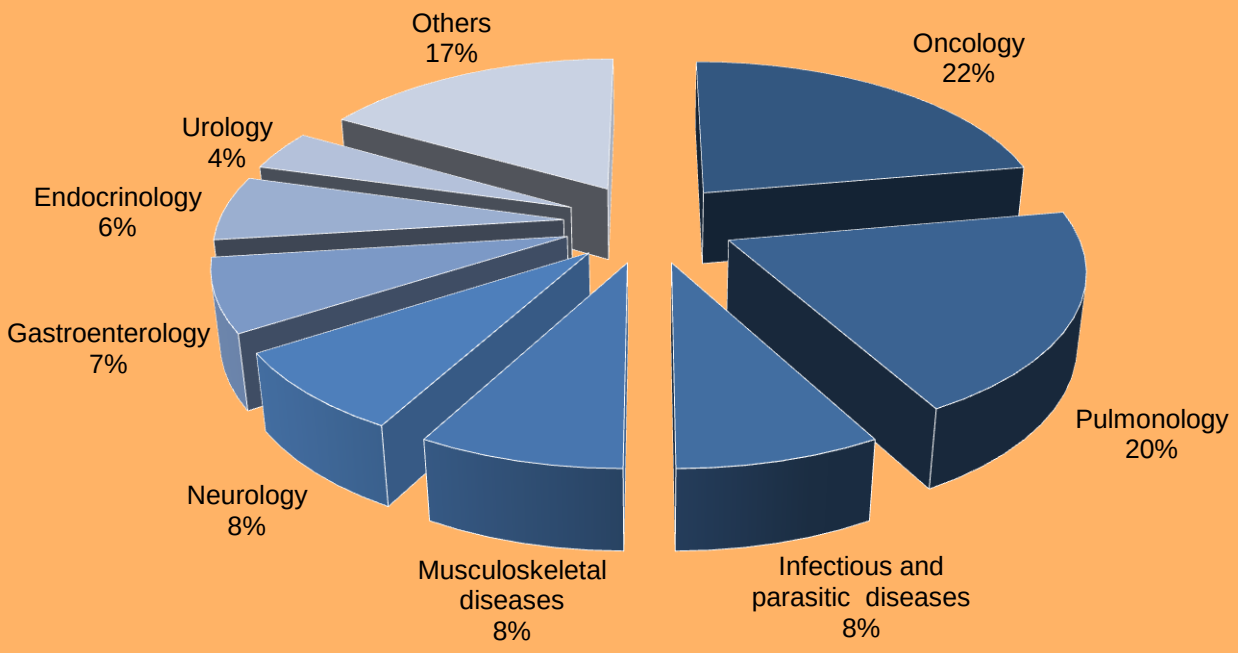
[1] Excluding BE studies

Therapeutic Areas of Russian Clinical Trials in Q3 2015

83% of new studies in Q3 2015 were initiated in eight leading therapeutic areas: the largest number of studies was initiated in Oncology (28); 25 new studies were instigated in Pulmonology; ten new studies – in Infectious and parasitic diseases, as well as in Musculoskeletal diseases and Neurology; nine new studies – in Gastroenterology; eight new studies – in Endocrinology; five new studies were started in Urology.

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

Figure 8. Clinical Trials in Russia in Q3 2015 by Therapeutic Area



Clinical Trial Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 30 new drugs during Q3 2015; 11 of them are new molecular entities (NME); others are new dosages, combinations, manufacturers or indications of already marketed drugs. 12 drugs were (or are being) studied in clinical trials involving Russian sites.

Table 4 shows the drugs which were approved by the FDA in Q3 2015 that were (or are being) tested in clinical trials in Russia.

Table 4. New Drugs Approved by FDA in Q3 2015 and Tested in Russian sites

Appr.date	*Drug (active ingredient)*	*Company*
07/10/2015	Rexulti (Brexpiprazole)	Otsuka Pharm Co Ltd
07/13/2015	Iressa (Gefitinib)	AstraZeneca Pharms
07/24/2015	Praluent (Alirocumab)	Sanofi Aventis
07/24/2015	Daklinza (Daclatasvir Dihydrochloride)	Bristol-Myers Squibb
07/24/2015	Technivie (Ombitasvir / Paritaprevir / Ritonavir)	Abbvie Inc.
08/24/2015	Promacta (Eltrombopag Olamine)	Novartis Pharms Corp

08/26/2015	Synjardy (Empaglifozin / Metformin Hydrochloride)	Boehringer Ingelheim
08/27/2015	Repatha (Evolocumab)	Amgen Inc.
09/15/2015	Spiriva Respimat (Tiotropium Bromide)	Boehringer Ingelheim
09/17/2015	Vraylar (Cariprazine)	Forest Labs LLC
09/25/2015	Ryzodeg 70/30 (Insulin degludec / Insulin Aspart)	Novo Nordisk Inc.
09/25/2015	Tresiba (Insulin degludec)	Novo Nordisk Inc.
		Source: FDA

During the third quarter of 2015, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 29 new drug applications[1], seven positive recommendations on new generic medicines and one for new hybrid medicine. 18 of the drugs which received positive opinions were (or are being) tested in clinical trials in Russia (See **Table 5**).

Table 5. New Drugs Approved by EMA in Q3 2015 and Tested in Russian sites

Appr. Date	*Drug (active ingredient)*	*Manufacturer*
07/23/2015	Cresemba (Isavuconazole)	Basilea Medical Ltd.
07/23/2015	Obizur (Susoctocog Alfa)	Baxalta Innovations GmbH
07/23/2015	Praluent (Alirocumab)	Sanofi-Aventis Groupe
07/23/2015	Mekinist (Trametinib)	Novartis Europharm Ltd.
07/23/2015	Qutenza (Capsaicin)	Astellas Pharma Europe BV
07/23/2015	Revolade (Eltrombopag / Eltrombopag Olamine)	Novartis Europharm Ltd.
07/23/2015	Tafinlar (Dabrafenib)	Novartis Europharm Ltd.
09/24/2015	Blincyto (Blinatumomab)	Amgen Europe B.V.
09/24/2015	Cotellic (Cobimetinib)	Roche Registration Ltd.
09/24/2015	Genvoya (Elvitegravir / Cobicitat / Emtricitabine / Tenofovir Alafenamide)	Gilead Sciences International Ltd.
09/24/2015	Kyprolis (Carfilzomib)	Amgen Europe B.V.
09/24/2015	Nucala (Mepolizumab)	GlaxoSmithKline Trading Services
09/24/2015	Praxbind (Idarucizumab)	Boehringer Ingelheim International GmbH
09/24/2015	Eylea (Aflibercept)	Bayer Pharma AG
09/24/2015	Gilenya (Fingolimod)	Novartis Europharm Ltd.

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

09/24/2015	Opdivo (Nivolumab)	Bristol-Myers Squibb Pharma EEIG
09/24/2015	Rebetol (Ribavirin)	Merck Sharp & Dohme Limited
09/24/2015	Vidaza (Azacitidine)	Celgene Europe Limited
		Source: EMEA

Regulatory Inspections

No published reports on FDA, EMA or Roszdravnadzor inspections were available as of the date of this Orange Paper.

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