Clinical Trials in Russia
Orange Paper
3rd Quarter 2014

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 180 new clinical trials of all types, including local and bioequivalence studies during the 3rd Quarter of 2014. This represents a 10% decrease over the same period 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 decreased from 102 studies in Q3 2013 to 72 in Q3 2014. The number of bioequivalence studies (BE) increased from 51 studies in Q3 2013 to 67 in Q3 2014, a 31% increase from last year's figure. The number of local clinical trials (LCT) has slightly decreased from 47 in Q3 2013 to 41 clinical trials in Q3 2014.

The share of multinational multi-center clinical trials was 40% of the total number of clinical trials in Q3 2014, while the bioequivalence and local studies amounted to 37% and 23% respectively.

Clinical trials in Russia in Q3 2014 were sponsored by companies from 24 countries. The highest number of trials (83) was initiated by Russian sponsors. American sponsors, with 25 new studies, took the runner-up place; they are followed by UK sponsors with 13 trials, Swiss sponsors with 11 studies and Indian sponsors with ten new studies. The group of leaders is concluded by German and French sponsors having eight and four new studies respectively.

The number of Phase I clinical trials stood at 13 new studies in Q3 2014, the same figure as in Q3 2013. The number of Phase II trials decreased from 32 in Q3 2013 to 15 new studies in Q3 2014. The number of Phase III trials decreased from 94 to 79 studies, 16% less than in Q3 2013. Phase IV trials demonstrateda slight increase from five studies in Q3 2013 to six studies in Q3 2014.

The number of subjects planned to be enrolled in Phase I-IV trials launched in Q3 2014 is 12,705, 7% less than Q3 2013 figure, when 13,709 patients were planned to be enrolled.

GlaxoSmithKline and *Novartis,* each sponsoring six new studies, are on the top of the heap in Q3 2014. They are followed by *Teva* and *AbbVie Inc.* with four new trials each. Top five is concluded by *AstraZeneca,* having three new trials in Q3 2014.

The Russian company *Drugs Formulation* sponsoring three new clinical trials, ranked number one among domestic pharmaceutical manufacturers, as seen by the number of new studies in Q3 2014. It is followed by *ZAO R-Pharm*, *OOO Mir-Pharm*, *ZAO East-Pharm* and *OOO Atoll,* each having two new trials and differentiating in the number of patients.

83% of new studies in Q3 2014 were initiated in eight leading therapeutic areas: the largest number of studies was initiated in Oncology (23); 16 new studies were instigated in Pulmonology; 13 studies in Endocrinology; ten new studies in Circulatory system diseases; nine studies in Infectious and parasitic diseases; seven studies in Musculoskeletal diseases, as well as in Neurology; six studies in Ophthalmology.

The Center for Drug Evaluation and Research (CDER) of the FDA approved 31 new drugs during Q3 2014 and 17 of them were (or are being) studied in clinical trials conducted in Russia.

During the third quarter of 2014, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 24 new drug applications[1] and one positive recommendation on a new biosimilar medicine. 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 Q3 2014 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 третьем квартале 2014 года Министерством здравоохранения Российской Федерации было выдано 180 разрешений на все виды клинических исследований (КИ), что на 10% меньше, чем за аналогичный период 2013 года.

При этом количество новых международных многоцентровых КИ уменьшилось с 102 до 72 исследований по сравнению с этим же периодом прошлого года. Количество исследований биоэквивалентности, инициированных в третьем квартале 2014 года, увеличилось по сравнению с третьим кварталом 2013 года и составило 67 против 51. Количество локальных КИ, проводимых на территории России отечественными и иностранными спонсорами, снизилось с 47 до 41 исследования.

Спонсорами КИ, разрешенных к проведению в России в третьем квартале 2014 года, выступили компании из 24 стран. На первое место вышли российские производители с 83 КИ, за ними идут американские спонсоры с 25 новыми исследованиями, Соединенное Королевство с 13 исследованиями, Швейцария с 11 новыми КИ, а также Индия с десятью новыми исследованиями. Замыкают группу лидеров Германия и Франция с восемью и четырьмя новыми исследованиями соответственно.

В третьем квартале 2014 года было инициировано 13 новых КИ I фазы – столько же, сколько за аналогичный период прошлого года. Количество исследований II фазы снизилось по сравнению с этим же периодом прошлого года и составило 15 новых исследований против 32. Количество исследований III фазы снизилось с 94 до 79 исследований – на 16% меньше по сравнению с прошлым годом. Количество исследований IV фазы практически не изменилось: шесть исследований – на одно больше, чем в прошлом году.

В третьем квартале 2014 года первое место среди иностранных производителей по количеству новых исследований заняли компании *GlaxoSmithKline* и *Novartis* с шестью новыми исследованиями у каждой. Компании *Teva* и *AbbVie Inc* инициировали по четыре исследования каждая. Замыкает пятерку лидеров компания *AstraZeneca* с тремя новыми исследованиями.

Первое место среди отечественных производителей по количеству исследований, начатых в третьем квартале 2014 года, занимает компания *Технология лекарств* с тремя новыми КИ. За ней идут компании *ЗАО Р-Фарм, ООО Мир-Фарм*, *ЗАО Ист-Фарм* и *ООО Атолл,* инициировавшие по два новых исследования каждая.

В третьем квартале 2014 года 83% всех новых исследований были инициированы в восьми терапевтических областях. Наибольшее количество в области онкологии – 23 КИ; 16 новых исследований – в области пульмонологии; 13 исследований – в области эндокринологии; десять исследований – в области болезней системы кровообращения; девять новых исследований в области инфекционных и паразитарных болезней; по семь новых исследований в области заболеваний опорно-двигательного аппарата и неврологии; а также шесть исследований в области офтальмологии.

Центр по оценке и исследованию лекарственных средств (Center for Drug Evaluation and Research, CDER) FDA одобрил в третьем квартале 2014 года 31 новый лекарственный препарат, по 17 из которых в России проводились (или проводятся) КИ.

В течение третьего квартала 2014 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 24 новым лекарственным препаратам и положительную рекомендацию по одному новому биоаналогу. По 16 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

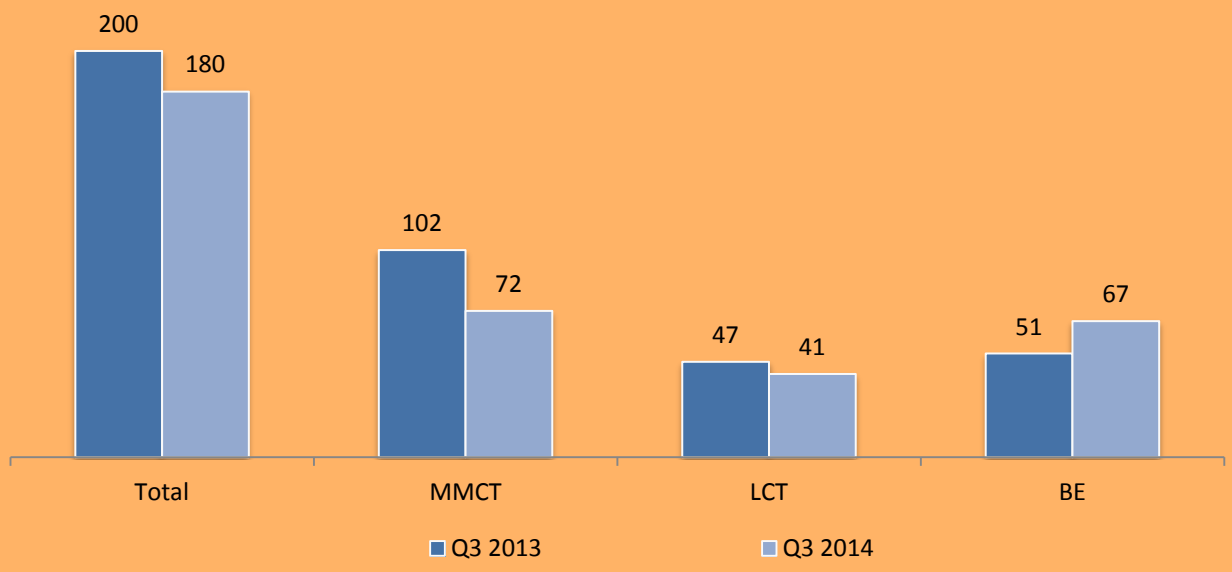
The Russian MoH approved 180 new clinical trials of all types, including local and bioequivalence studies, during the 3rd Quarter of 2014 demonstrating a 10% decrease in comparison with the same quarter last year.

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 decreased from 102 studies in Q3 2013 to 72 in Q3 2014.

The number of bioequivalence studies (BE) increased from 51 studies in Q3 2013 to 67 in Q3 2014, a 31% increase from last year's figure.

The number of local clinical trials (LCT) has slightly decreased from 47 in Q3 2013 to 41 clinical trials in Q3 2014.

Figure 1. Clinical Trials in Russia in Q3 2014

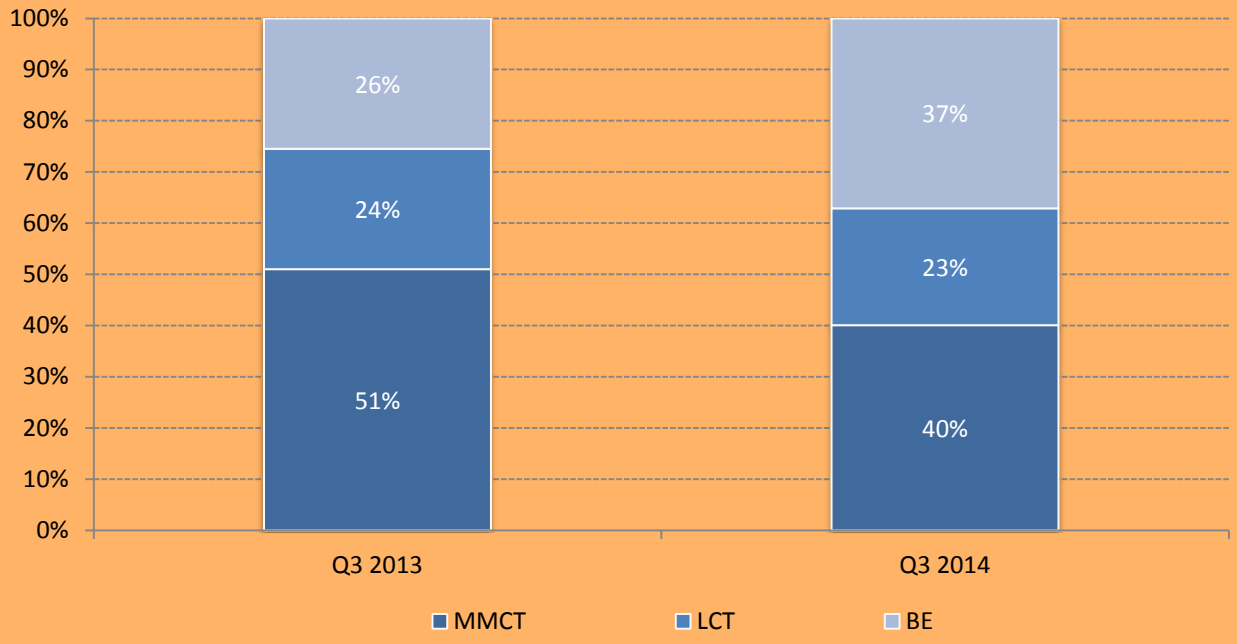


The proportions between different study types (multinational multi-center clinical trials, local studies and bioequivalence trials) changed slightly since last year (see **Figure 2**).

The share of bioequivalence studies increased from 26% to 37% of the total number of clinical trials approved in Q3 2014.

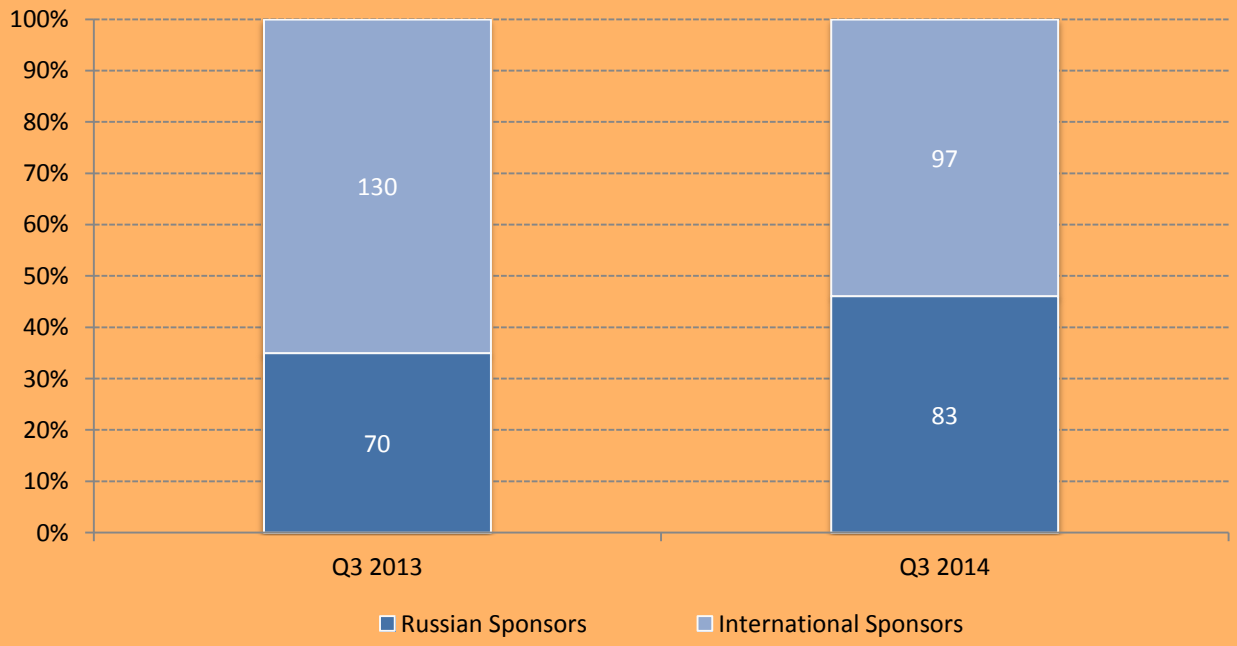
The share of local trials almost did not change and totaled 23%. The share of multinational multi-center clinical trials decreased from 51% to 40% of the total number of trials approved during Q3 2014.

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. 54% of the total number of new studies in Q3 2014 were sponsored by foreign companies, which received 97 study approvals. The share of studies for local manufacturers increased from 35% in Q3 2013 to 46% in Q3 2014, and amounted to 83 studies (**Figure 3**).

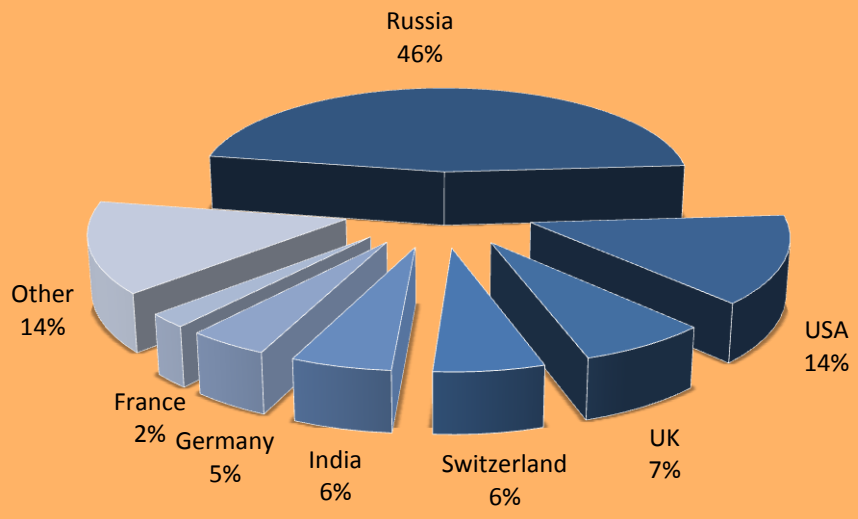
Figure 3. Russian vs International Sponsors in Q3 2014



Clinical trials in Russia in Q3 2014 were sponsored by companies from 24 countries. **Figure 4** indicates the geographic breakdown in sponsors' country of origin.

The highest number of trials (83) was initiated by Russian sponsors. American sponsors, with 25 new studies, took the runner-up place; they are followed by UK sponsors with 13 trials, Swiss sponsors with 11 studies and Indian sponsors with ten new studies. The group of leaders is concluded by German and French sponsors, having eight and four new studies, respectively.

Figure 4. Sponsors' Country of Origin for Q3 2014 Clinical Trials in Russia



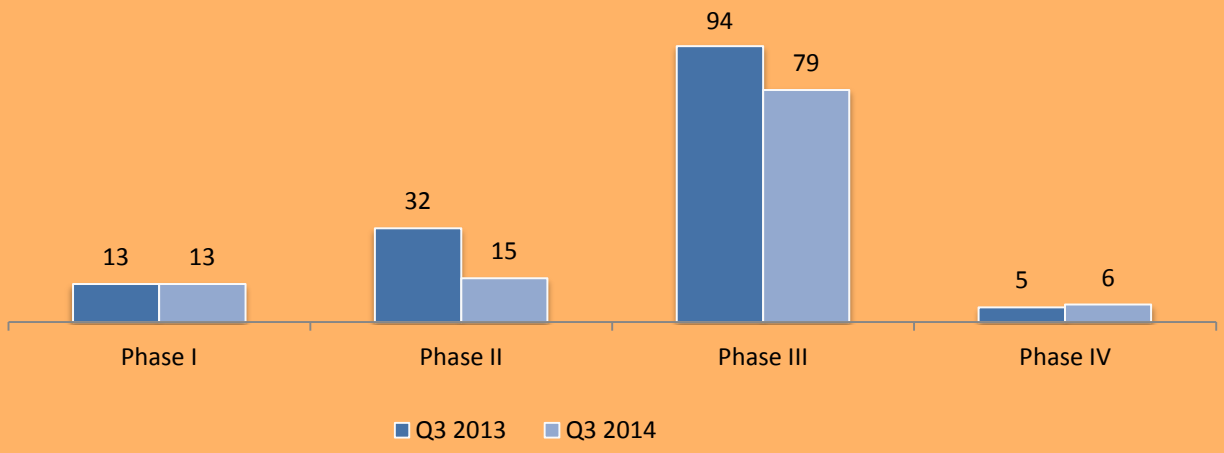
Other sponsors include: Sweden (three new studies), Belgium, Israel, Italy, Canada, Republic of Korea, Netherlands and Ukraine (two studies each). Australia, Austria, Denmark, Spain, Cyprus, Poland, Romania, Slovenia and Croatia each started one new study in Q3 2014.

Clinical trials by Phase

The number of Phase I clinical stood at 13 new studies in Q3 2014, the same figure as in Q3 2013. The number of the Phase II trials decreased from 32 in Q3 2013 to 15 new studies in Q3 2014 (**Figure 5**).

The number of Phase III trials decreased from 94 to 79 studies, 16% less than in Q3 2013. Phase IV trials demonstrated a slight increase from five studies in Q3 2013 to six studies in Q3 2014.

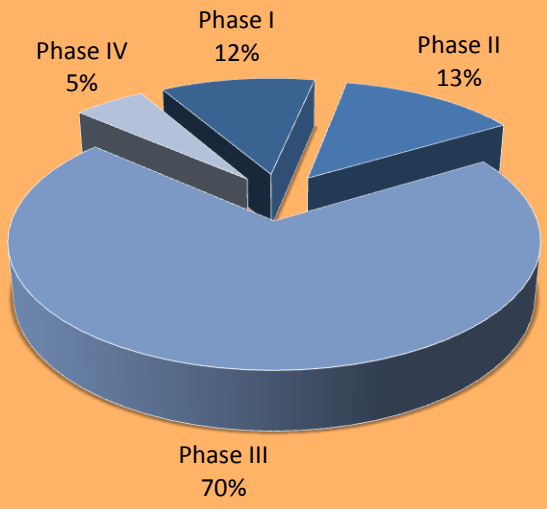
Figure 5. Clinical Trials in Russia in Q3 2014 by Phase[1]



[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 2014 is 70% of the total number of studies, the share of Phase II trials is 13%, Phase I trials is 12% and the share of Phase IV studies totaled 5%.

Figure 6. Percentage Breakdown of Russian Clinical Trials by Phase



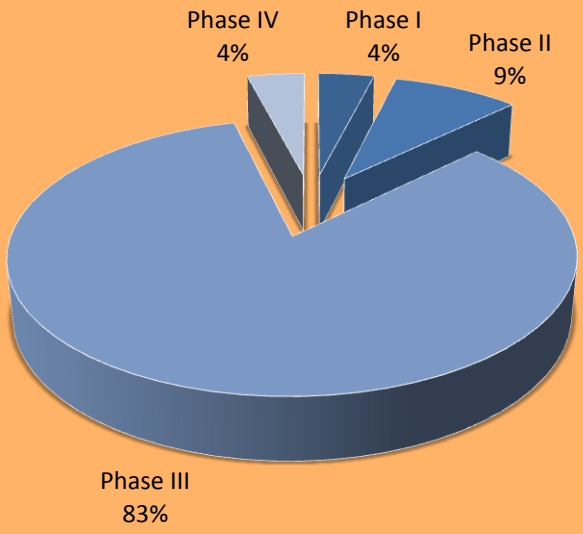
The number of subjects planned to be enrolled in Phase I-IV trials launched in Q3 2014 is 12,705, 7% less than Q3 2013 figure, when 13,709 patients were planned to be enrolled.

495 subjects will be recruited in Phase I trials; 1122 patients in Phase II trials; 10,580 subjects in Phase III studies and 508 patients will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is four, the maximum number is 800.

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 Q3 2014 by Study Phase



Number of Studies by Sponsor

GlaxoSmithKline and Novartis, each sponsoring six new studies, are on the top of the heap in Q3 2014. They are followed by *Teva* and *AbbVie Inc.* with four new trials each. The top five is concluded by *AstraZeneca* having three new trials in Q3 2014.

Top five international sponsors ranked by the number of new studies in Q3 2014 are presented in **Table 1.**

Table 1. Top-5 International Study Sponsors in Q3 2014

№	*Company Name*	*No. studies*[1]	*No. patients*
1	GlaxoSmithKline	6	1,563
2	Novartis	6	233
3	Teva	4	560
4	AbbVie Inc	4	132
5	AstraZeneca	3	1,080

Rating of Russian sponsors

The Russian company *Drugs Formulation (Tekhnologiya lekarstv),* sponsoring three new clinical trials, ranked number one among domestic pharmaceutical manufacturers by the number of new studies in Q3 2014. It is followed by *ZAO R-Pharm*, *OOO Mir-Pharm*, *ZAO East-Pharm* and *OOO Atoll* each having two new trials and differentiating in the number of patients.

Table 2. Top-5 Russian Study Sponsors in Q3 2014

№	*Company Name*	*No. studies*	*No. patients*
1	Drugs Formulation	3	70
2	ZAO R-Pharm	2	396
3	OOO Mir-Pharm	2	240
4	ZAO East-Pharm	2	220
5	OOO Atoll	2	190

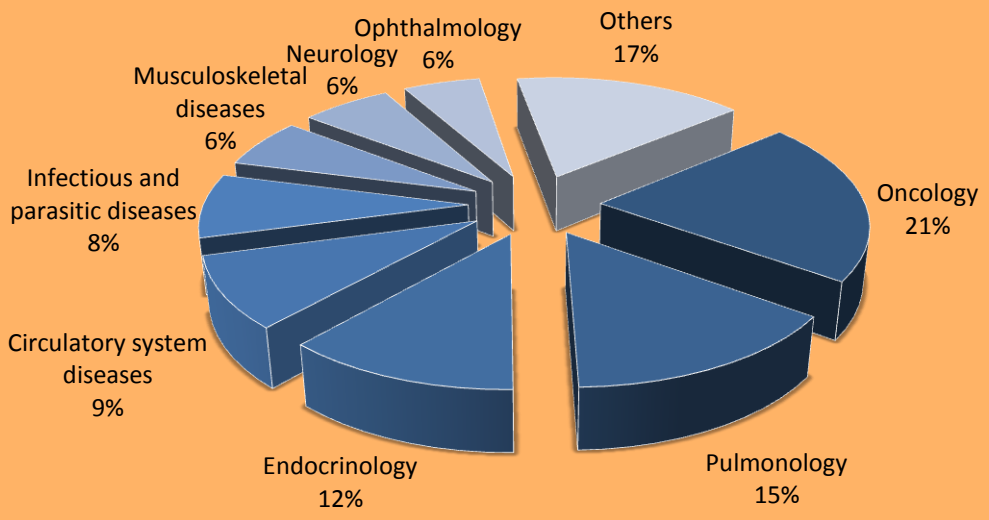
[1] Excluding BE studies

Therapeutic Areas of Russian Clinical Trials in Q3 2014

83% of new studies in Q3 2014 were initiated in eight leading therapeutic areas: the largest number of studies was initiated in Oncology (23); 16 new studies were instigated in Pulmonology; 13 studies in Endocrinology; ten new studies in Circulatory system diseases; nine studies in Infectious and parasitic diseases; seven studies in Musculoskeletal diseases as well as in Neurology and six studies in Ophthalmology.

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

Figure 8. Clinical Trials in Russia in Q3 2014 by Therapeutic Area



Clinical Trials Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 31 new drugs during Q3 2014. 14 of them are new molecular entities (NME); others are new dosages, combinations, manufacturers or indications ofalready marketed drugs. 17 drugs were (or are being) studied in clinical trials involving Russian sites.

The **Table 3** shows the drugs which were approved by FDA in Q3 2014 that were being tested in clinical trials in Russia.

Table 3. New Drugs Approved by FDA in Q3 2014 and Tested in Russian sites

Appr.date	*Drug (active ingredient)*	*Company*
07/03/2014	Beleodaq (Belinostat)	Spectrum Pharms
07/23/2014	Flonase Allergy Relief (Fluticasone Propionate)	GlaxoSmithKline Cons
07/23/2014	Zydelig (Idelalisib)	Gilead Sciences
08/01/2014	Jardiance (Empagliflozin)	Boehringer Ingelheim
08/08/2014	Invokamet (Canagliflozin / Metformin Hydrocloride)	Janssen Pharms
08/15/2014	Plegridy (Peginterferon Beta-1A)	Biogen Idec Inc
08/18/2014	Basaglar (Insulin Glargine)	Eli Lilly and Co

08/19/2014	Cerdelga (Eliglustat Tartrate)	Genzyme Corp
08/20/2014	Arnuity Ellipta (Fluticasone Furoate)	GlaxoSmithKline
08/22/2014	Triumeq (Abacavir Sulfate / Dolutegravir Sodium / Lamivudine)	ViiV Healthcare
09/04/2014	Keytruda (Pembrolizumab)	Merck Sharp Dohme
09/18/2014	Trulicity (Dulaglutide)	Eli Lilly and Co
09/23/2014	Otezla (Apremilast)	Celgene Corp
09/24/2014	Spiriva Respimat (Tiotropium Bromide)	Boehringer Ingelheim
09/24/2014	Vitekta (Elvitegravir)	Gilead Sciences Inc
09/24/2014	Tybost (Cobicistat)	Gilead Sciences Inc
09/24/2014	Fosrenol (Lanthanum carbonate)	Shire Development
		Source: FDA

During the third quarter of 2014, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 24 new drug applications[1] and one positive recommendation on a new biosimilar medicine. 16 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 Q3 2014 and Tested in Russian sites

Appr. date	*Drug (active ingredient)*	*Manufacturer*
07/24/2014	Imbruvica (Ibrutinib)	Janssen-Cilag International N.V.
07/24/2014	Xultophy (Insulin degludec / Liraglutide)	Novo Nordisk A/S
07/24/2014	Zydelig (Idelalisib)	Gilead Sciences International Ltd
07/24/2014	Baraclude (Entecavir)	Bristol-Myers Squibb Pharma EEIG
07/24/2014	Busilvex (Busulfan)	Pierre Fabre Medicament
07/24/2014	Ecalta (Anidulafungin)	Pfizer Limited
07/24/2014	Humira (Adalimumab)	AbbVie Ltd
07/24/2014	RoActemra (Tocilizumab)	Roche Registration Ltd
07/24/2014	Xgeva (Denosumab)	Amgen Europe B.V.
09/25/2014	Brimica Genuair (Aclidinium / Formoterol fumarate dihydrate)	Almirall S.A.
09/25/2014	Cyramza (Ramucirumab)	Eli Lilly Nederland B.V.
09/25/2014	Duaklir Genuair (Aclidinium /	Almirall S.A.

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

	Formoterol fumarate dihydrate)	
09/25/2014	Trulicity (Dulaglutide)	Eli Lilly Nederland B.V.
09/25/2014	Vargatef (Nintedanib)	Boehringer Ingelheim International GmbH
09/25/2014	Prezista (Darunavir)	Janssen-Cilag International N.V.
09/25/2014	Signifor (Pasireotide)	Novartis Europharm Ltd
		Source: EMEA

Inspections

At the moment of the Orange Paper Q3 2014 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.