Clinical Trials in Russia
Orange Paper
1st Quarter 2013

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Contents

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Executive Summary

The Ministry of Health of Russian Federation approved 205 new clinical trials of all types including local and bioequivalence studies during the 1st Quarter of 2013 (7% less than at the same period of the last year).

The main contribution into the total number of studies is made by multinational multi-center clinical trials (MMCT), the number of these studies almost has not changed and stood at 92 new studies in Q1 2013. The number of bioequivalence studies has slightly decreased from 77 studies in Q1 2012 to 69 in Q1 2013. The number of local clinical trials decreased from 54 to 44 clinical trials demonstrating the 19% fall of the rate in comparison with the same period of the last year.

The share of multinational multi-center clinical trials was 45% of the total number of clinical trials in Q1 2013, while the local and bioequivalence studies amounted to 21% and 34%, respectively.

Clinical trials in Russia in Q1 2013 were sponsored by companies from 20 countries. The maximum number of trials (89) was initiated by Russian sponsors. American sponsors with 40 new studies took the runner-up place; they are followed by Swiss sponsors with 17 trials, and Israeli and French sponsors each having nine new studies; the group of leaders is concluded by British sponsors with six new studies.

Seven new clinical trials Phase I were launched in Q1 2013, which is equal to the number of clinical trials Phase I in Q1 2012. The number of the Phase II trials decreased from 23 in Q1 2012 to 19 new studies in Q1 2013. The number of Phase III trials increased from 94 to 99 studies, 5% more than in Q1 2012. Phase IV trials demonstrated the decrease from 18 studies in Q1 2012 to 11 studies in Q1 2013.

The number of subjects which are planned to be enrolled in Phase I-IV trials launched in Q1 2013 is 16,298 - 6% less than in Q1 2012 figure, when 17,270 patients were planned to be enrolled.

Novartis sponsoring eight new studies is on the top of the heap in Q1 2013. It is followed by *Roche* and *Merck&Co.* each having seven new trials and differentiating in the number of subjects. Top five is concluded by *Teva* and *Bristol-Myers Squibb* each having six new trials in Q1 2013.

The Russian company *ZAO RCI Syntez* sponsoring three new clinical trials, ranked number one among domestic pharmaceutical manufacturers by the number of new studies in Q1 2013. Top Five of Q1 2013 includes *Materia Medica, Nativa, Binergia and Lens-Pharm* each with two new trials.

91% of new studies in Q1 2013 were initiated in nine leading therapeutic areas: the largest number of studies was initiated in Oncology (30); 18 new studies were initiated in Pulmonology, 16 studies – in Infectious and Parasitic diseases, 15 new studies – in Musculoskeletal diseases, eight studies - in Cardiology as well as in Hematology, six studies – in Neurology as well as in Psychiatry.

The Center for Drug Evaluation and Research (CDER) of the FDA approved 32 new drugs during Q1 2013, and 12 of them were studied in clinical trials conducted in Russia.

During Q1 2013 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 21 new drug applications[1]. Negative opinion was adopted for three drugs. 14 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 2013 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 2013 года Министерством здравоохранения Российской Федерации было выдано 205 разрешений на все виды клинических исследований (КИ), что на 7% меньше, чем за аналогичный период 2012 года.

При этом количество международных многоцентровых КИ практически не изменилось и составило 92 новых исследования. Количество исследований биоэквивалентности, инициированных в первом квартале 2013 года, несколько снизилось по сравнению с первым кварталом 2012 года и составило 69 против 77. Количество локальных КИ, проводимых на территории России отечественными и иностранными спонсорами, продемонстрировало 19% снижение – с 54 до 44 исследований.

Спонсорами КИ, разрешенных к проведению в России в первом квартале 2013 года, выступили компании из 20 стран. На первое место вышли российские производители с 89 КИ, за ними идут американские спонсоры со 40 новыми исследованиями, Швейцария с 17, а также Франция и Израиль с девятью КИ у каждой. Замыкает группу лидеров Великобритания с шестью новыми исследованиями.

В первом квартале 2013 года было инициировано семь новых КИ I фазы – столько же, сколько и за аналогичный период прошлого года. Количество исследований II фазы за этот период несколько снизилось и составило 19 новых исследований против 23. Количество исследований III фазы возросло с 94 до 99 исследований – на 5% больше по сравнению с прошлым годом. Количество исследований IV фазы уменьшилось с 18 до 11 исследований.

В первом квартале 2013 года первое место среди иностранных производителей по количеству новых исследований заняла фармацевтическая компания *Novartis* с восемью новыми исследованиями. *Roche* и *Merck&Co* инициировали по семь исследований, но с разным количеством субъектов. Замыкают пятерку лидеров *Teva* и *Brisol-Mayers Squibb* с шестью новыми исследованиями у каждого.

Первое место среди отечественных производителей по количеству исследований, начатых в первом квартале 2013 года, занимает *ЗАО АрСиАй «Синтез»* с тремя новыми КИ. В пятёрку лидеров входят также *ООО НПФ «Материа Медика Холдинг», ЗАО «Бинергия», ООО «Натива»* и *ООО «Ленс-Фарм»*, инициировавшие по два новых исследования каждый.

В первом квартале 2013 года 91% всех новых исследований было инициировано в девяти терапевтических областях. Наибольшее количество в области онкологии – 30 КИ; 18 новых исследований в пульмонологии; 16 исследований – в области инфекционных болезней, 15 исследований – в области заболеваний опорно-двигательного аппарата, по восемь исследований в кардиологии и гематологии, и по шесть – в неврологии и психиатрии.

Центр по оценке и исследованию лекарственных средств (Center for Drug Evaluation and Research, CDER) FDA одобрил в первом квартале 2013 года 32 новых лекарственных препарата, по 12 из которых в России проводились КИ.

В течение первого квартала 2013 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 21 новым заявкам и три негативных отзыва. По 14 лекарствам, входившим в число получивших положительный отзыв, проводились КИ в России.

Информация о проверках Росздравнадзора и FDA за первый квартал 2013 года на момент выпуска «Оранжевой Книги» недоступна.

Clinical Trials by Type and Manufacturing Country

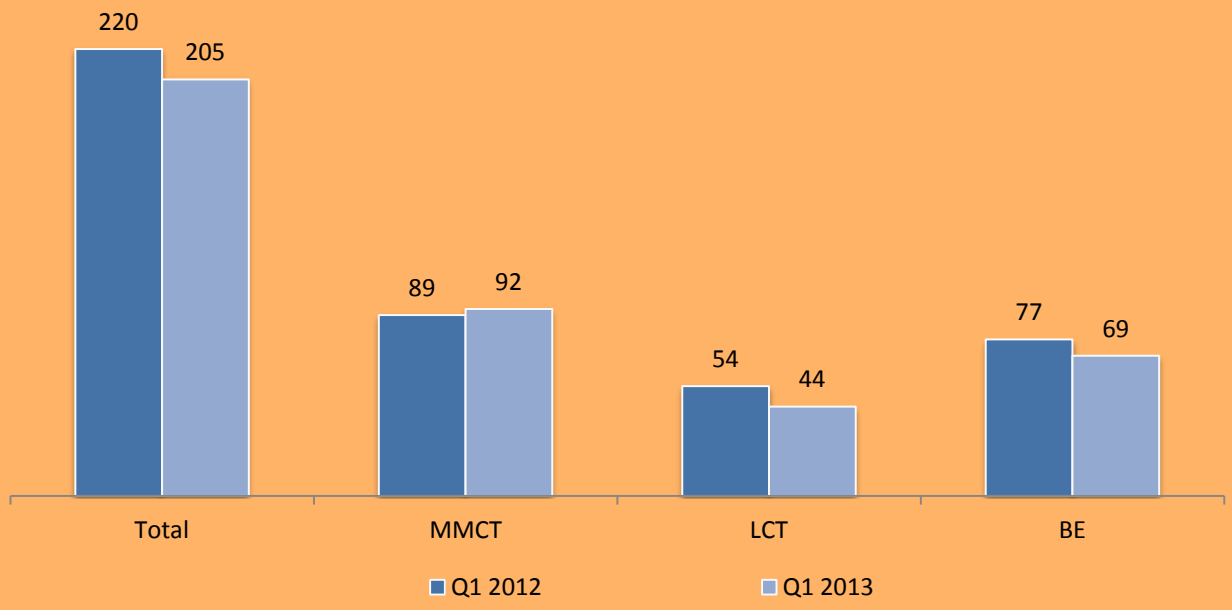
The MoH of Russian Federation approved 205 new clinical trials of all types including local and bioequivalence studies during the 1st Quarter of 2013, demonstrating 7% decrease in comparison with the same point of the last year.

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 almost has not changed and amounted to 92 new studies in Q1 2013.

The number of bioequivalence studies slightly decreased from 77 studies in Q1 2012 to 69 in Q1 2013.

The number of local clinical trials has decreased from 54 to 44 clinical trials demonstrating the 19% fall of the rate in comparison with the same period of the last year.

Figure 1. Clinical trials in Russia in Q1 2013

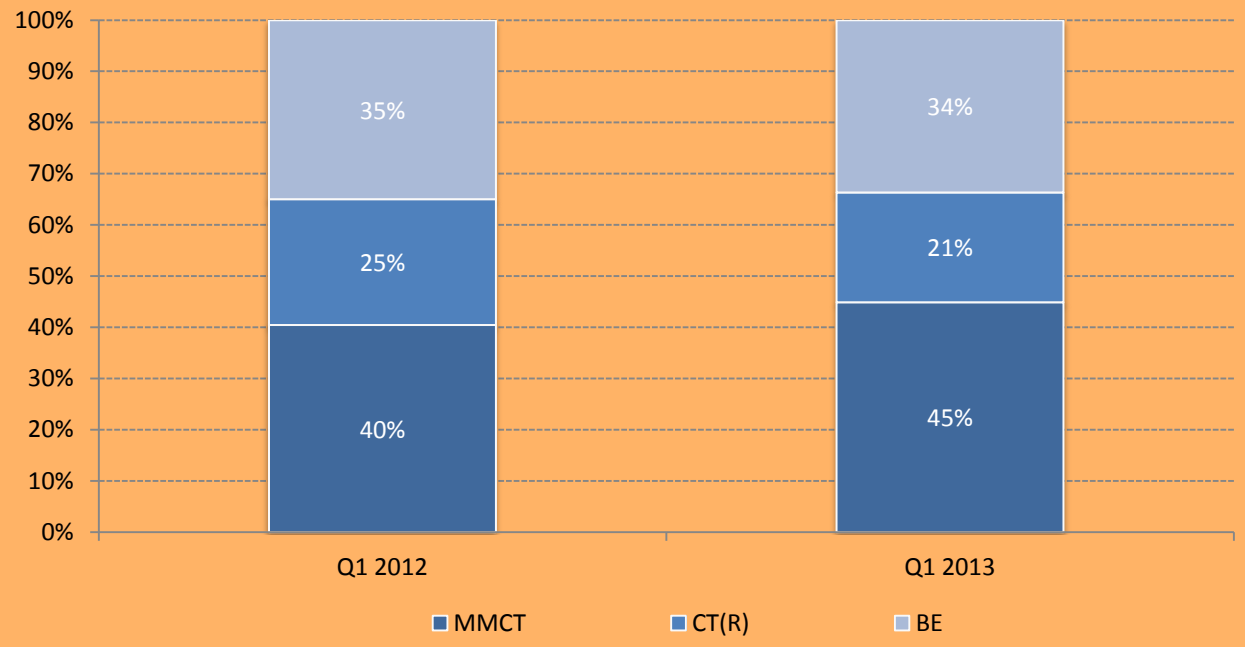


The proportions between different study types (multinational multi-center clinical trials, local studies and bioequivalence trials) slightly changed since last year (see **Figure 2**).

The share of bioequivalence studies stayed almost at the same rate: 34% of the total number of clinical trials approved in Q1 2013.

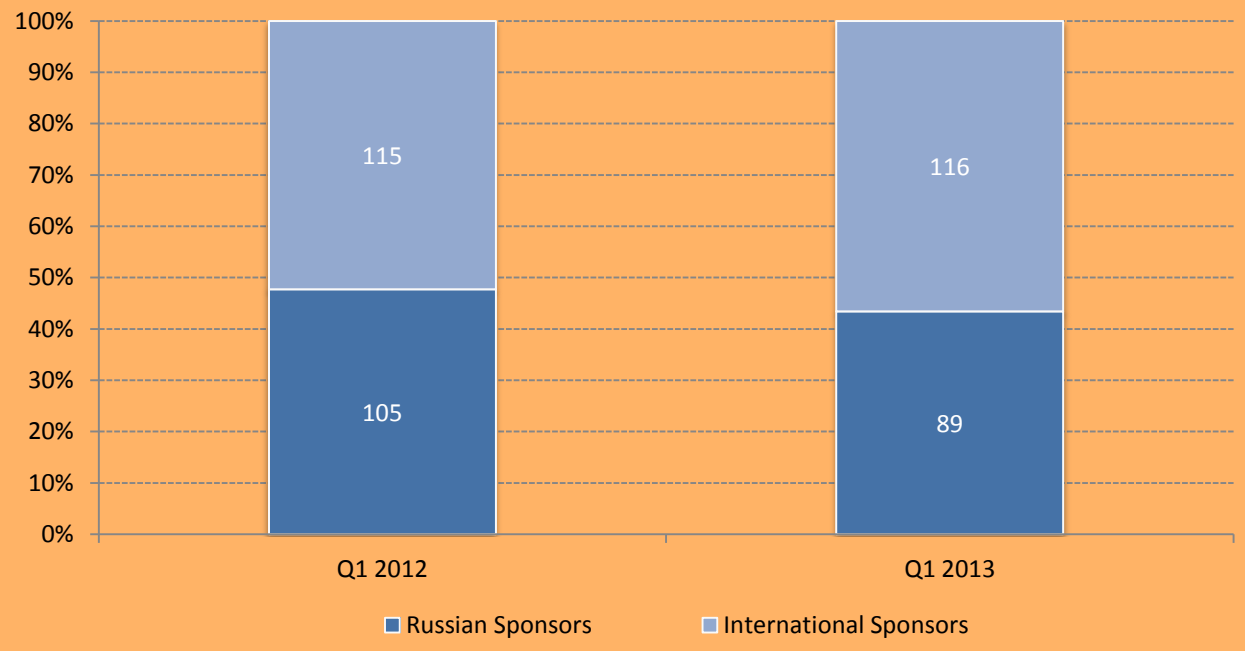
The share of the local trials decreased at 21%, and the share of multinational multi-center clinical trials increased from 40% to 45% of the total number of trials approved during Q1 2013.

Figure 2. Clinical trials by type in Q1 2013



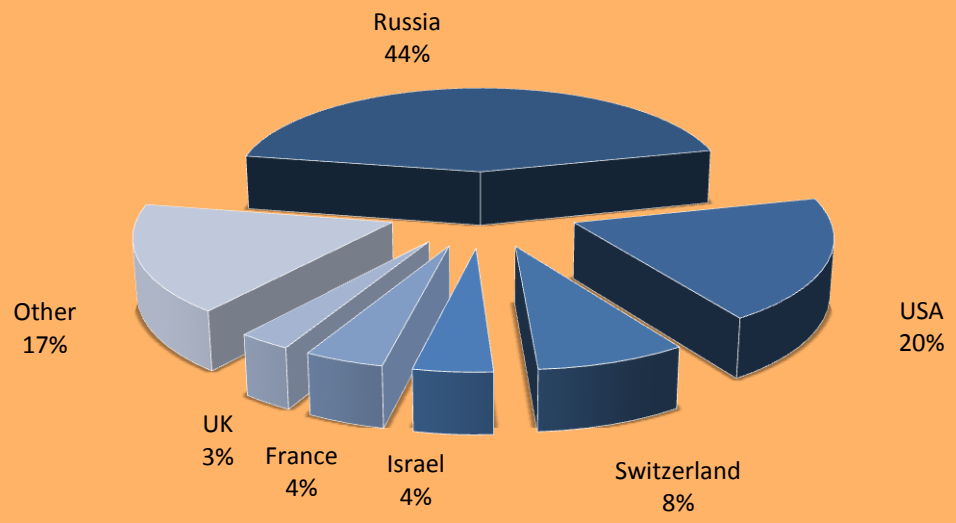
The proportions between sponsors did not significantly change in comparison with the same period last year. 57% of the total number of new studies in Q1 2013 is sponsored by foreign companies which is 116 study approvals (almost the same number as in Q1 2012). But the share of studies of local manufacturers decreased from 48% in Q1 2012 to 43% in Q1 2013, and amounted to 89 studies (**Figure 3**).

Figure 3. Russian and International sponsors in Q1 2013



Clinical trials in Russia in Q1 2013 were sponsored by companies from 20 countries. **Figure 4** demonstrates the input of the leading countries of sponsors' origin into the total number of clinical trials. The maximum number of trials (89) was initiated by Russian sponsors. American sponsors with 40 new studies took the runner-up place; they are followed by Swiss sponsors with 17 trials, and Israeli and France with nine new studies, and the group of leaders is concluded by British (six) sponsors.

Figure 4. Countries presented on the Russian clinical trials market in Q1 2013



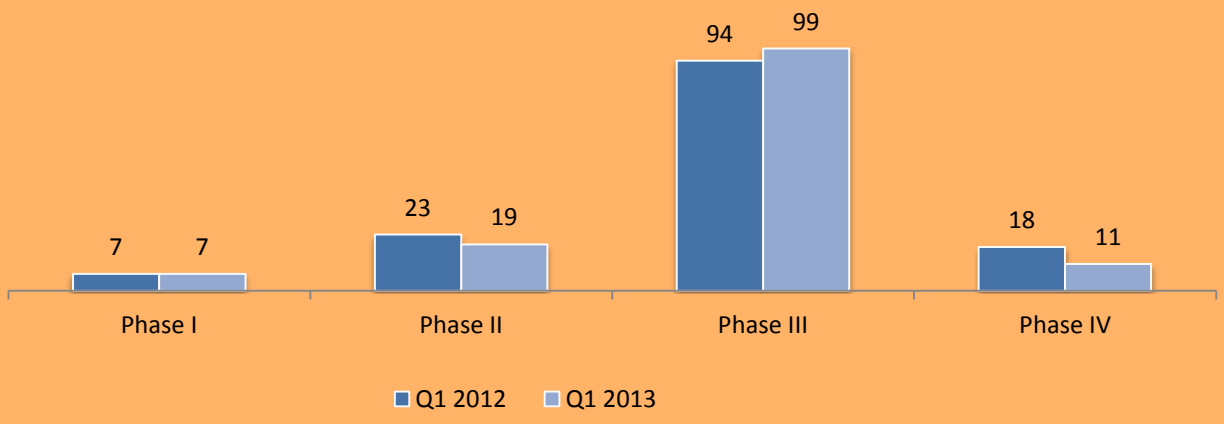
Among others are: Belgium (five), Austria, Hungary, Germany, Sweden (four studies each), Poland (three), Slovenia and Ukraine, Czech Republic (two trials each), Belarus, Denmark, India, Latvia, Croatia each started one new study in 2012.

Clinical trials by Phase

Seven new Phase I clinical trials were launched in Q1 2013, which is equal to the number of clinical trials Phase I in Q1 2012. The number of the Phase II trials decreased from 23 in Q1 2012 to 19 new studies in Q1 2013 (**Figure 5**).

The number of Phase III trials increased from 94 to 99 studies, 5% more than in Q1 2012. Phase IV trials demonstrated the decrease from 18 studies in Q1 2012 to 11 studies in Q1 2013.

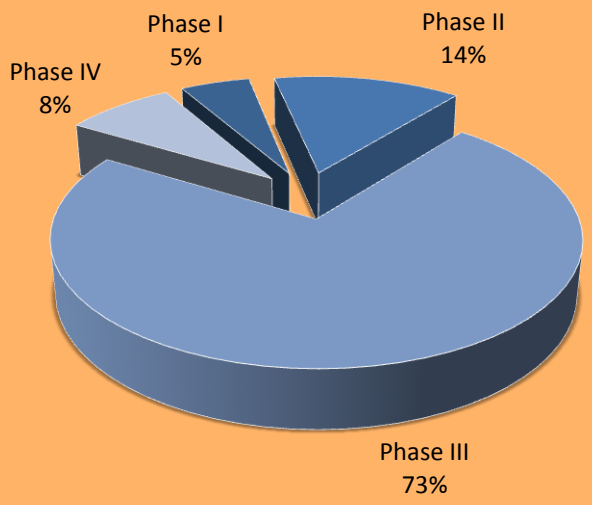
Figure 5. Clinical trials in Russia in Q1 2013 by phase[1]



[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, even in case a specific phase was indicated in the application.

As shown in **Figure 6**, the share of Phase III trials in Q1 2013 is 73% of the total number of studies, the share of Phase II trials accounted at 14%, Phase IV trials is 8%, and the share of Phase I studies amounted to 5%.

Figure 6. The proportions between study phases in Russia in Q1 2013



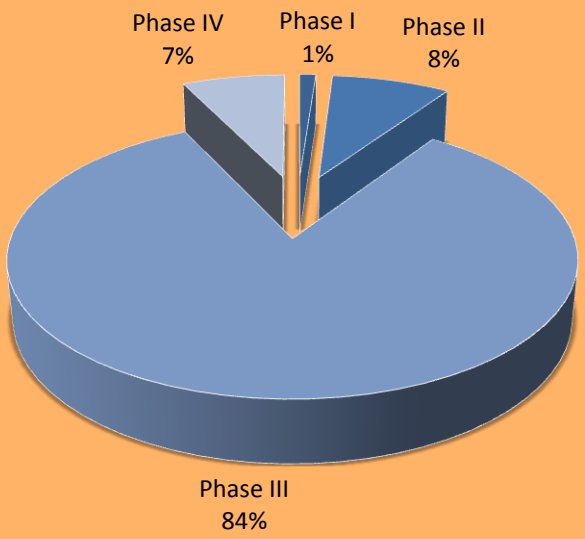
The number of subjects which are planned to be enrolled in Phase I-IV trials launched in Q1 2013 is 16,298, 6% less than in Q1 2012 figure, when 17,270 patients were planned to be enrolled.

186 subjects will be recruited in Phase I trials; 1,353 patients – in Phase II trials; 13,587 subjects – in Phase III studies and 1,172 patients will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is three, the maximum number is 2,510.

The proportion of the number of patients between different Phases is shown on **Figure 7**. Only studies in which phase is specified, were included.

Figure 7. The number of patients in Q1 2013 by study phase



Rating of international sponsors

Novartis sponsoring eight new studies is on the top of the heap in Q1 2013. It is followed by *Roche* and *Merck&Co.* each having seven new trials and differentiating in the number of subjects. Top five is concluded by *Teva* and *Bristol-Myers Squibb* each having six new trials in Q1 2013.

Top five international sponsors by the number of new studies in Q1 2013 are presented in **Table 1**.

Table 1. Top-5 international study sponsors in Q1 2013

№	*Company Name*	*No. studies*[1]	*No. patients*
1	Novartis	8	592
2	Roche	7	1603
3	Merck&Co	7	654
4	Teva	6	786
5	Bristol-Myers Squibb	6	253

Rating of Russian sponsors

The Russian company *ZAO RCI Syntez* sponsoring three new clinical trials, ranked number one among domestic pharmaceutical manufacturers by the number of new studies in Q1 2013. Top Five of Q1 2013 includes *Materia Medica, Nativa, Binergia and Lens-Pharm* each with two new trials.

Table 2. Top-5 Russian study sponsors in Q1 2013

№	*Company Name*	*No. studies*[1]	*No. patients*
1	ZAO RCI Syntez	3	160
2	Materia Medica	2	426
3	Nativa	2	196
4	Binergia	2	160
5	Lens-Pharm	2	120

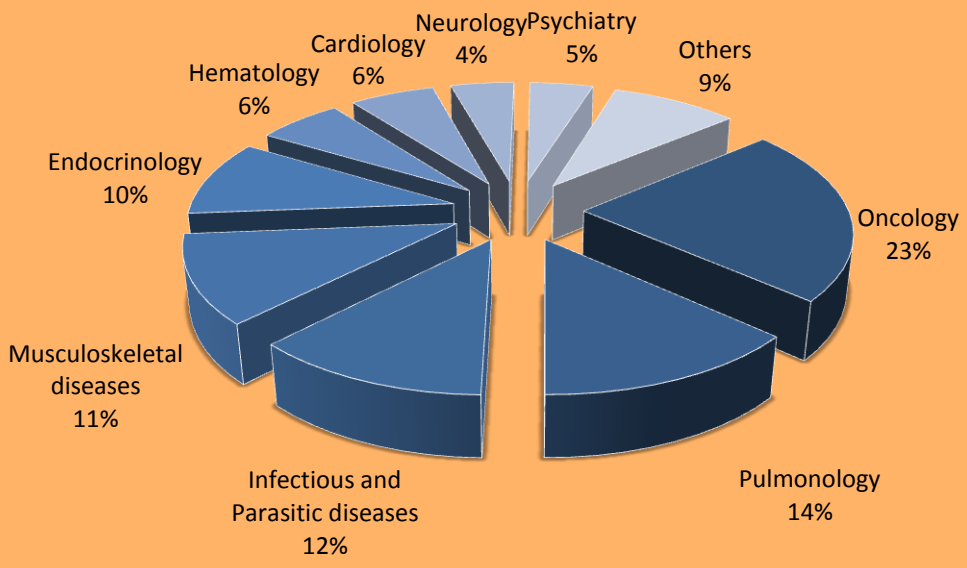
[1] Excluding BE studies

Therapeutic areas of clinical trials in Russia in Q1 2013

91% of new studies in Q1 2013 were initiated in nine leading therapeutic areas: the largest number of studies was initiated in Oncology (30); 18 new studies were instigated in Pulmonology, 16 studies – in Infectious and Parasitic diseases, 15 new studies – in Musculoskeletal diseases, eight studies – in Cardiology as well as in Hematology, six studies – in Neurology as well as in Psychiatry.

The proportions between different therapeutic areas are shown in **Figure 8**.

Figure 8. Clinical trials in Russia in Q1 2013 by therapeutic area



Clinical trials results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 32 new drugs during Q1 2013; ten of them are new molecular entities (NME); others are new dosages, manufacturers or indications of the already marketed drugs. 12 drugs were studied in clinical trials involving Russian sites.

The **Table 3** shows the drugs which were approved by FDA in Q1 2013 that were being tested in clinical trials in Russia.

Table 3. New drugs approved by FDA in Q1 2013 and tested in Russian sites

Appr.date	*Drug (active ingredient)*	*Company*
01/18/2013	Uceris (Budesonide)	Santarus
01/25/2013	Nesina (Alogliptin bezoate)	Takeda Pharms USA
01/25/2013	Oseni (Alogliptin benzoate/ Pioglitazone hydrochloride)	Takeda Pharms USA
01/25/2013	Kazano (Alogliptin benzoate/ Metformin hydrochloride)	Takeda Pharms USA
01/29/2013	Kynamro (Mipomersen sodium)	Genzyme Corp
02/01/2013	Delzicol (Mesalamine)	Warner Chilcott LLC

02/08/2013	Pomalyst (Pomalidomide)	Celgene
02/25/2013	Stivarga (Regorafenib)	Bayer Healthcare Pharms
02/28/2013	Abilfy Maintena Kit (Aripiprazole)	Otsuka Pharm Co Ltd.
03/22/2013	Tobi Podhaler (Tobramycin)	Novartis Pharms
03/27/2013	Tecfidera (Dimethyl fumarate)	Biogen Idec
03/29/2013	Invocana (Canagliflozin)	Janssen Res. and Dev.
		Source: FDA

During the first quarter of 2013 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 21 new drug applications[1]. Negative opinion was adopted for three drugs. 14 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 2013 and tested in Russian sites

Appr. date	*Drug (active ingredient)*	*Manufacturer*
01/17/2013	Bosulif (Bosutinib)	Pfizer Ltd.
01/17/2013	Humira (Adalimumab)	Abbott Laboratories Ltd.
01/17/2013	Ilaris (Canakinumab)	Novartis Europharm Ltd.
01/17/2013	Komboglyze (Saxagliptin / Metformin hydrychloride)	Bristol-Myers Squibb
01/17/2013	Onglyza (Saxagliptin)	Astra Zeneca EEIG
01/17/2013	Pegasys (Peginterferon alfa-2a)	Roche Registration Ltd.
02/21/2013	Cervarix (Human papillomavirus vaccine [types 16, 18] (recombinant, adjuvanted, absorbed))	GlaxoSmithKline Biologicals
02/21/2013	Privigen (Human normal immunoglobulin (Ivig))	CSL Behring GmbH
03/21/2013	Aubagio (Teriflunomide)	Sanofi-Aventis
03/21/2013	Stribild (Elvitegravir / Cobicistat / Emtricitabine / Tenofovir disoproxil)	Gilead Sciences International Ltd.
03/21/2013	Tecfidera (Dimethyl fumarate)	Biogen Idec Ltd.
03/21/2013	MabThera (Rituximab)	Roche Registration Ltd.
03/21/2013	Viread (Tenofovir disoproxil fumarate)	Gilead Sciences International Ltd.
03/21/2013	Xarelto (Rivaroxaban)	Bayer Pharma AG
		Source: EMEA

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

Inspections

At the moment of the Orange Paper Q1 2013 production no information about any inspections (FDA or Roszdravnadzor) conducted in the Russian investigative sites was available.