Clinical Trials in Russia
Orange Paper
3rd Quarter 2012

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Contents

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Executive Summary - English

The Ministry of Health of the Russian Federation (MoH) approved 210 new clinical trials of all types including local and bioequivalence studies during the third quarter of 2012, demonstrating a 59% increase comparing to the same point of the last year.

The main contribution into the total number of studies is made by the multinational multi-center clinical trials, the number of them increased by 11% from Q3 2011 and stood at 93 new studies in Q3 2012. The number of bioequivalence studies has grown dramatically from 15 studies in Q3 2011 to 64 in Q3 2012 demonstrating over four times increase. The number of local clinical trials has also significantly grown from 33 to 53 clinical trials.

The share of multinational multi-center clinical trials stood at 44% of the total number of clinical trials in Q3 2012, while the local and bioequivalence studies amounted to 25% and 30%, respectively.

Clinical trials in Russia in Q3 2012 were sponsored by companies from 18 countries. The maximum number of trials (106) was initiated by Russian sponsors. American sponsors with 30 new studies took the runner-up place, they are followed by Belgian sponsors with 11 trials and British sponsors with nine new studies, the group of leaders is concluded by French and Swiss sponsors each having started eight new studies in Q3 2012.

Ten new Phase I clinical trials were launched in Q3 2012, seven trials less than in Q3 2011. The number of the Phase II trials has increased and stood at 29 new studies in Q3 2012. The number of Phase III trials has increased from 75 to 94 studies, 25% more than in Q3 2011. Phase IV trials demonstrated the decrease from 21 studies in Q3 2011 to 13 studies in Q3 2012.

The number of subjects planned to be enrolled in Phase I-IV trials launched in Q3 2012 stood at 15,445, a 17% more than in Q3 2011 figure, when 13,211 patients were planned to be enrolled.

Amgen sponsoring seven new studies is on the top of the heap in Q3 2012. It is followed by *Sanofi-aventis* with six studies, and *Janssen, Astra Zeneca and GlaxoSmithKline* each having five new trials and differentiating in the number of patients.

The Russian company *Biocad* sponsoring five new clinical trials, ranked number one among domestic pharmaceutical manufacturers in Q3 2012. It is followed by *OOO NPF Materia Medica Holding, OOO FK Slavyanskaya Apteka and OOO Atoll* each with four new studies and differentiating in the number of patients. Top five is concluded by *Microgen* with three new studies.

More than two thirds of new studies in Q3 2012 were initiated in seven leading therapeutic areas: the largest number of studies was initiated in Oncology (24); 21 new studies were instigated in Endocrinology; 15 – in Infectious diseases; ten studies each in Musculoskeletal diseases and in Pulmonology; eight studies each in Cardiology and in Urology.

The Center for Drug Evaluation and Research (CDER) of the FDA approved 23 new drugs during Q3 2012, and nine of them were studied in clinical trials conducted in Russia.

During the third quarter of 2012 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 20 new drug applications, 14 of which were tested in Russian sites.

Four FDA inspections were conducted in Russia during Q1 and Q2 2012. Three inspections ended with NAI result – no action indicated, and one inspection ended with VAI result – voluntary action indicated.

Executive Summary - Russian

В III квартале 2012 года Министерством здравоохранения Российской Федерации было выдано 210 разрешений на все виды клинических исследований, что на 59% больше, чем в соответствующем квартале прошлого года.

При этом количество международных многоцентровых клинических исследований возросло на 11% и составило 93 новых исследований. Количество исследований биоэквивалентности, инициированных во III квартале 2012 года, значительно возросло с 15 до 64 исследований по сравнению с III кварталом 2011 года. Количество локальных клинических исследований, проводимых на территории России отечественными и иностранными спонсорами, также увеличилось с 33 до 53 исследований.

Спонсорами клинических исследований, разрешенных к проведению в России в III квартале 2012 года, выступили компании из 18 стран. На первое место вышли российские производители со 106 КИ, за ними идут американские спонсоры с 30 новыми исследованиями, Бельгия с 11 и Великобритания с девятью КИ. Замыкают группу лидеров Франция и Швейцария, каждая с восемью новыми исследованиями.

В III квартале 2012 года было инициировано 10 новых клинических исследований I фазы, что на семь КИ меньше, чем во III квартале прошлого года. Количество исследований II фазы за этот период незначительно увеличилось и составило 29 новых исследований. Количество исследований III фазы заметно возросло с 75 до 94 исследований – на 25% больше по сравнению с прошлым годом. Количество исследований IV фазы уменьшилось и составило 13 новых исследований.

Всего в клинических исследованиях I-IV фаз, начатых в III квартале 2012 года, примет участие 15445 субъектов, что на 17% больше, чем в соответствующем квартале прошлого года, когда в исследования планировалось включить 13211 субъектов.

В III квартале 2012 года первое место среди иностранных производителей по количеству новых исследований заняла фармацевтическая компания Amgen с семью новыми исследованиями. Далее идет Sanofi-aventis с шестью исследованиями. Janssen, AstraZeneca и GlaxoSmithKline инициировали по пять новых исследований с разным количеством субъектов.

Первое место среди отечественных производителей по количеству исследований, начатых в III квартале 2012 года, занимает «Биокад» с пятью новыми клиническими исследованиями. За ним идут ООО НПФ «Материа Медика Холдинг», ООО ФК «Славянская аптека» и ООО «Атолл», каждый с четырьмя новыми исследованиями, но с разным количеством субъектов. Завершает пятёрку лидеров «Микроген», инициировавший три новых исследования.

В III квартале 2012 года более двух третей всех новых исследований было инициировано в семи терапевтических областях: наибольшее количество в области онкологии – 24 КИ; 21 новое исследование в эндокринологии; 15 исследований – в области инфекционных заболеваний; по десять – в пульмонологии и в области заболеваний опорно-двигательного аппарата; по восемь исследований – в кардиологии и урологии.

За первые два квартала 2012 в России были проведены четыре инспекции FDA. Три инспекции завершились с результатом NAI (no action indicated), одна инспекция – с результатом VAI (voluntary action indicated).

Clinical Trials by Type and Manufacturing Country

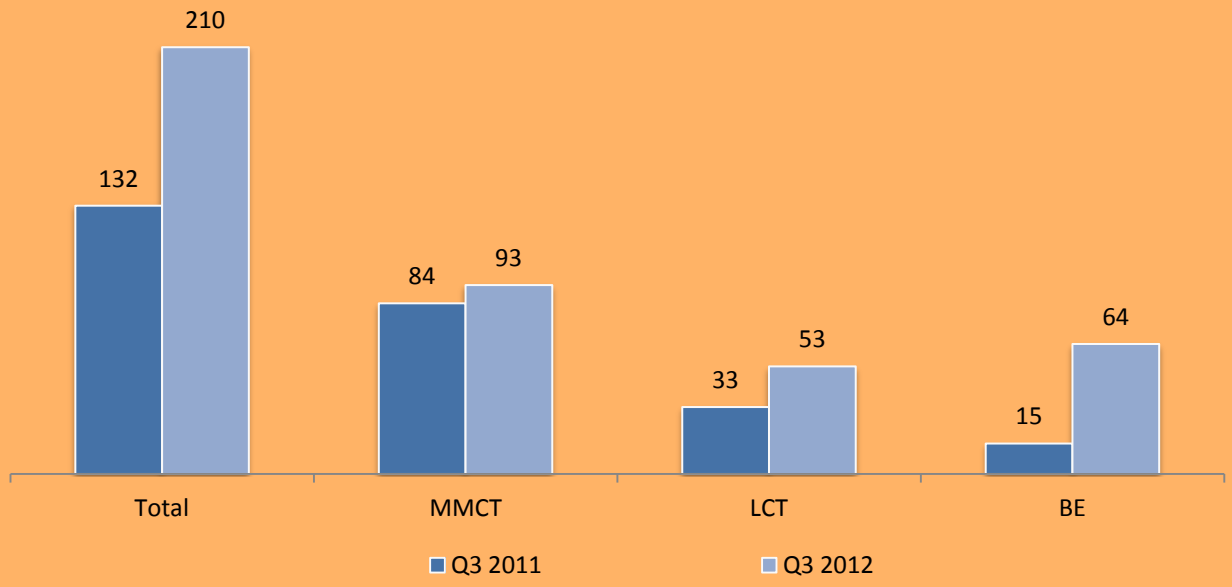
The Russian MoH approved 210 new clinical trials of all types including local and bioequivalence studies during the third quarter of 2012, demonstrating a 59% increase comparing to the same point of the last year.

As shown in **Figure 1**, the main contribution into the total number of studies is made by multinational multi-center clinical trials (MMCT), the number of these studies increased by 11% over 2011 and stood at 93 new studies in Q3 2012.

The number of the local clinical trials (LCT) conducted in Russia by domestic and foreign sponsors increased from 33 to 53 clinical trials, almost 61% rise from last year's figure.

The number of bioequivalence studies (BE) in Q3 2012 stood at 64 new trials demonstrating an enormous over four times increase comparing with the number of studies in Q3 2011.

Figure 1. Clinical trials in Russia in Q3 2012

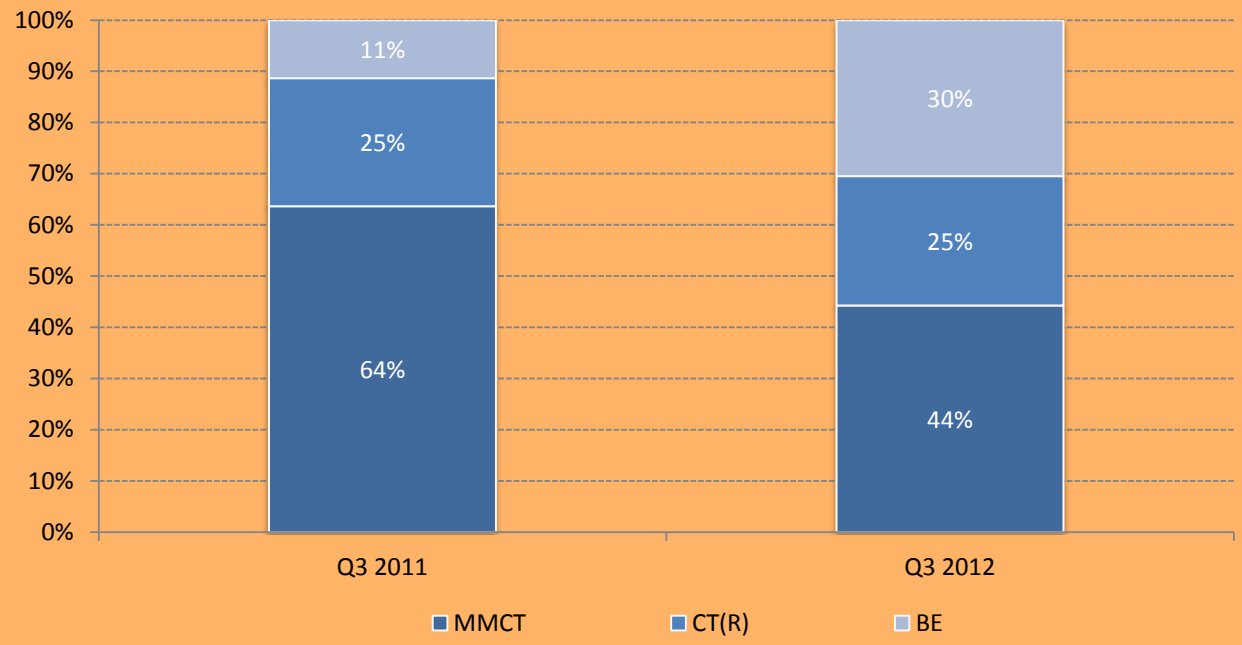


The proportions between different study types (multinational multi-center clinical trials, local studies and bioequivalence trials) notably changed since last year (see **Figure 2**).

The share of bioequivalence studies significantly increased from 11% in Q3 2011 to 30% of the total number of clinical trials approved in Q3 2012.

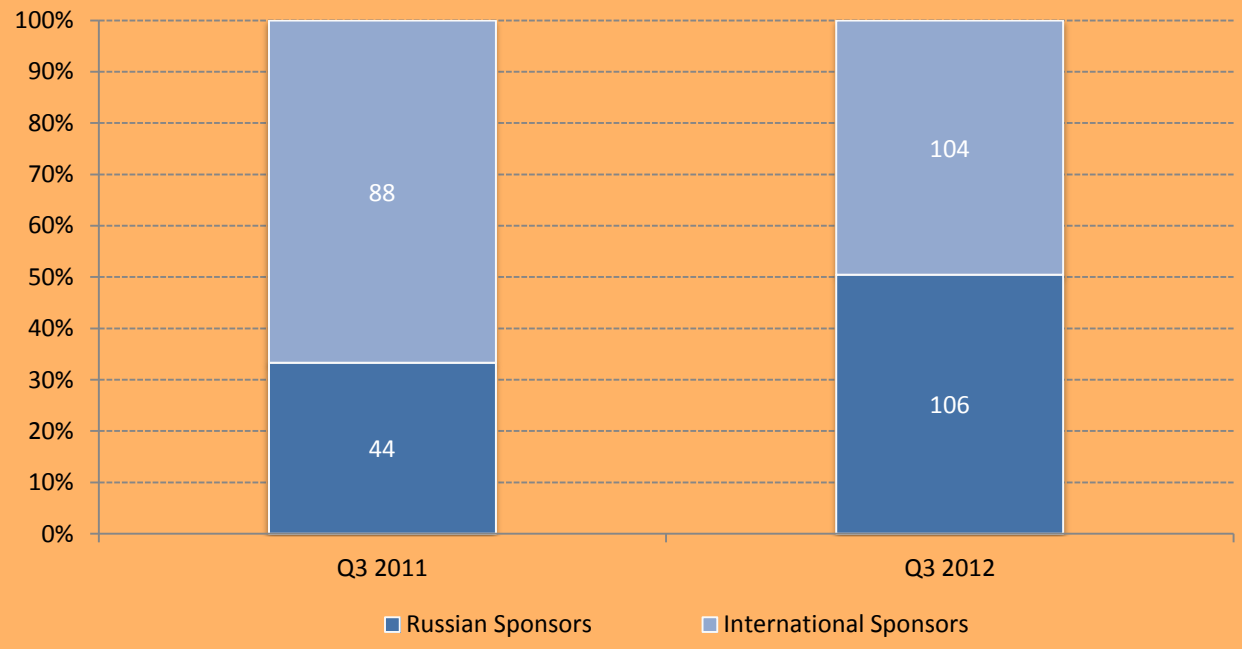
The share of the local trials did not change and stand at 25% - same figure as in Q3 2011, whereas the share of multinational multi-center clinical trials decreased from 64% to 44% of the total number of trials approved during the third quarter of 2012.

Figure 2. Clinical trials by type in Q3 2012



Almost 50% of the total number of new studies in Q3 2012 was sponsored by foreign companies, which received 104 study approvals. The share of studies of local manufacturers increased from 33% in Q3 2011 to 50% in Q3 2012, and amounted to 106 studies (**Figure 3**).

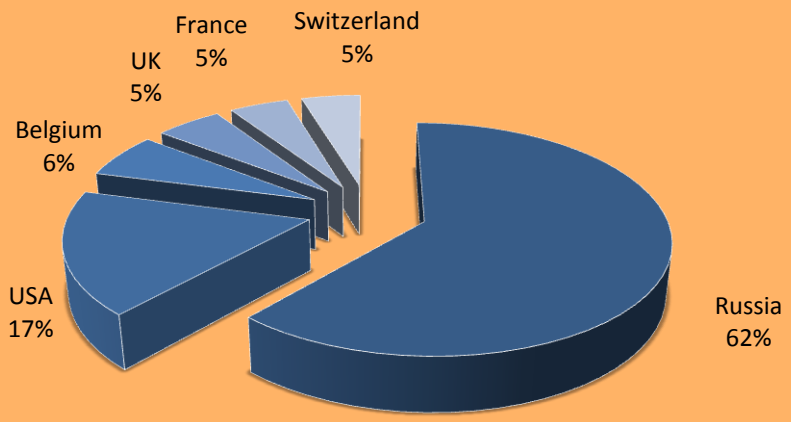
Figure 3. Russian and International sponsors in Q3 2012



Clinical trials in Russia in Q3 2012 were sponsored by companies from 18 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 (106) was initiated by Russian sponsors. American sponsors

with 30 new studies took the runner-up place, they are followed by Belgian sponsors with 11 trials and British sponsors with nine new studies, the group of leaders is concluded by French and Swiss sponsors each having started eight new studies in Q3 2012.

Figure 4. Countries presented on the Russian clinical trials market in Q3 2012



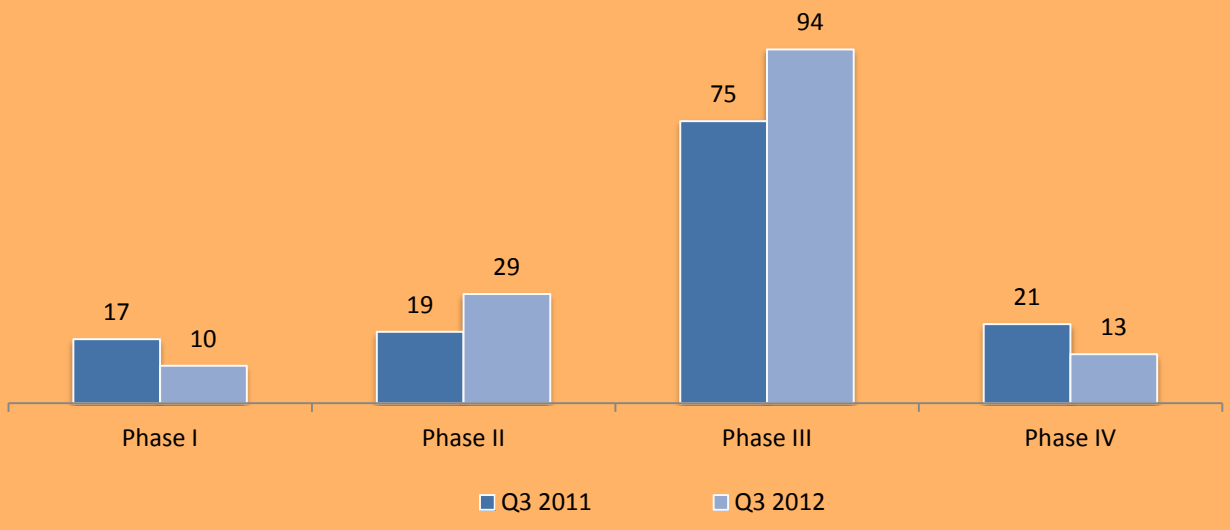
Among others are: Denmark and Israel (six studies each); Germany and Sweden (five); Austria (four); Czech Republic (three); Hungary, Italy and Republic of Korea started two new studies each; India, Netherlands and Romania each started one new study in Q3 2012.

Clinical trials by Phase

Ten new Phase I clinical trials were launched in Q3 2012, which is seven trials less than in Q3 2011. The number of the Phase II trials increased from 19 in Q3 2011 to 29 new studies in Q3 2012 (**Figure 5**).

The number of Phase III trials increased from 75 to 94 studies, 25% more than in Q3 2011. Phase IV trials demonstrated the decrease from 21 studies in Q3 2011 to 13 studies in Q3 2012.

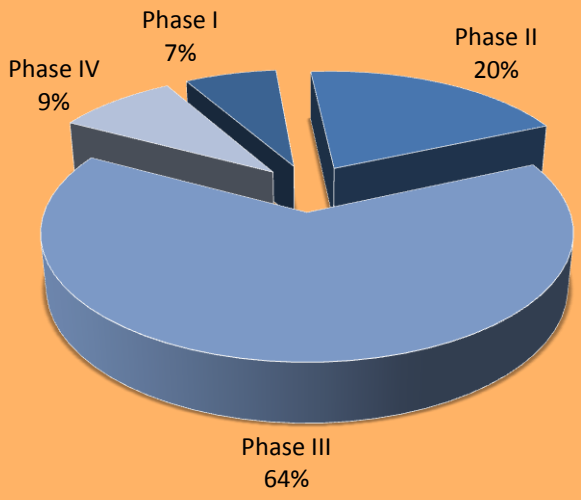
Figure 5. Clinical trials in Russia in Q3 2012 by phase[1]



[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 Q3 2012 stood at 64% of the total number of studies, the share of Phase II trials accounted at 20%, Phase IV trials stood at 9%, and the share of Phase I studies amounted to 7%.

Figure 6. The proportions between study phases in Russia in Q3 2012



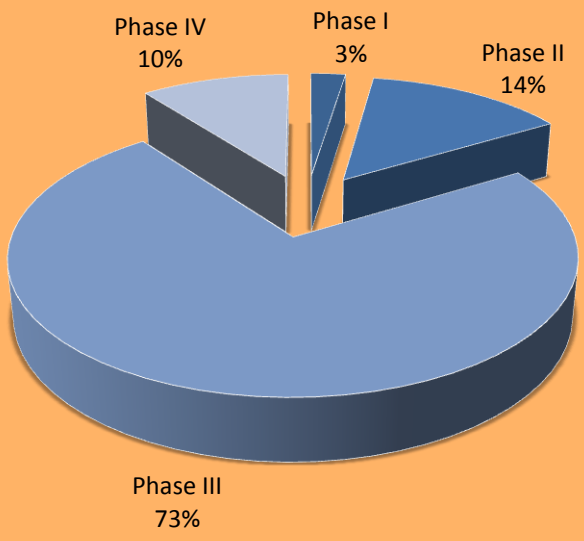
The number of subjects which are planned to be enrolled in Phase I-IV trials launched in Q3 2012 stood at 15,445, a 17% more than in Q3 2011 figure, when 13,211 patients were planned to be enrolled.

375 subjects will be recruited in Phase I trials; 2,160 patients – in Phase II trials; 11,311 subjects – in Phase III studies and 1,599 patients will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is four, the maximum number is 1,350.

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 Q3 2012 by study phase



Rating of international sponsors

Amgen sponsoring seven new studies is on the top of the heap in Q3 2012. It is followed by *Sanofi-aventis* with six studies, and *Janssen, Astra Zeneca* and *GlaxoSmithKline* each having five new trials and differentiating in the number of patients.

Top five international sponsors by the number of new studies in Q3 2012 are presented in **Table 1**.

Table 1. Top-5 international study sponsors in Q3 2012

№	*Company Name*	*No. studies*[1]	*No. patients*
1	Amgen	7	1250
2	Sanofi-aventis	6	956
3	Janssen	5	362
4	Astra Zaneca	5	322
5	GlaxoSmithKline	5	221

Rating of Russian sponsors

The Russian company *Biocad* sponsoring five new clinical trials, ranked number one among domestic pharmaceutical manufacturers in Q3 2012.

It is followed by *OOO NPF Materia Medica Holding, OOO FK Slavyanskaya Apteka and OOO Atoll* each with four new studies and differentiating in the number of patients. Top five is concluded by *Microgen* with three new studies (**Table 2**).

Table 2. Top-5 Russian study sponsors in Q3 2012

№	*Company Name*	*No. studies*[1]	*No. patients*
1	Biocad	5	352
2	OOO NPF Materia Medica Holding	4	776
3	OOO FK Slavyanskaya Apteka	4	340
4	OOO Atoll	4	300
5	Microgen	3	360

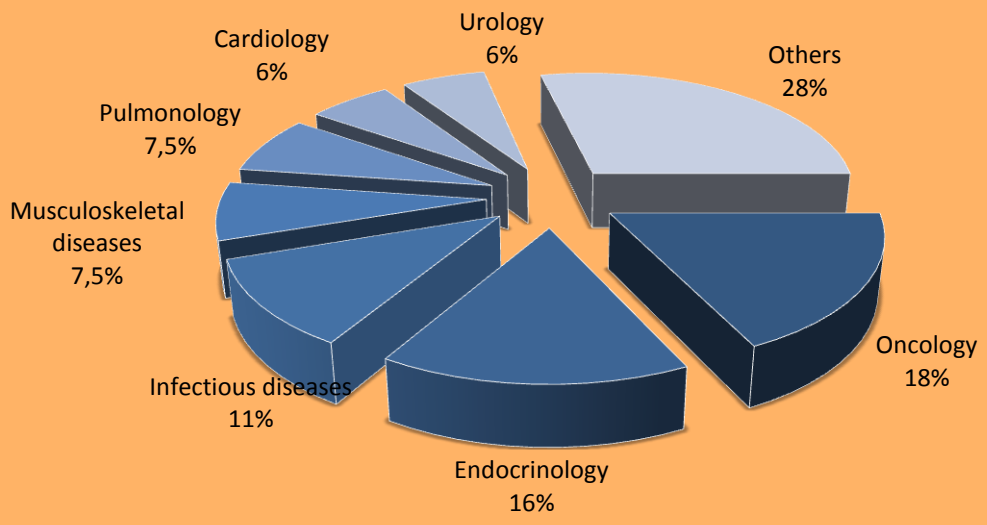
[1] Excluding BE studies

Therapeutic areas of clinical trials in Russia in 2012

More than two thirds of new studies in Q3 2012 were initiated in seven leading therapeutic areas: the largest number of studies was initiated in Oncology (24); 21 new studies were instigated in Endocrinology; 15 new studies in Infectious diseases; ten studies each in Musculoskeletal diseases and in Pulmonology; eight studies each in Cardiology and Urology.

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

Figure 8. Clinical trials in Russia in Q3 2012 by therapeutic area



Clinical trials results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 23 new drugs during Q3 2012; ten of them are new molecular entities (NME); others are new dosages, manufacturers or indications of the already marketed drugs. Nine drugs were studied in clinical trials involving Russian sites.

The **Table 3** shows the drugs which were approved by FDA and were being tested in clinical trials in Russia in Q3 2012.

Table 3. New drugs approved by FDA in Q3 2012 and tested in Russian sites

Appr.date	*Drug (active ingredient)*	*Company*
08/03/2012	Zaltrap (Ziv-Aflibercept)	Sanofi Aventis US
08/29/2012	Afinitor Disperz (Everolimus)	Novartis Pharm
08/30/2012	Revatio (Sildenafil Citrate)	Pfizer
08/31/2012	Xtandi (Enzalutamide)	Medivation
09/04/2012	Bosulif (Bosutinib)	Wyeth Pharms Inc
09/12/2012	Aubagio (Teriflunomide)	Sanofi Aventis US
09/27/2012	Stivarga (Regorafenib)	Bayer Healthcare Pharms
07/20/2012	Kyprolis (Carfilzomib)	Onyx Pharms

07/23/2012	Tudorza Pressair (Aclidinium Bromide)	Forest Labs Inc
		Source: FDA

During the third quarter of 2012 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 20 new drug applications[1]. Negative opinion was adopted for one drug. 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 Q3 2012 and tested in Russian sites

Appr. date	*Drug (active ingredient)*	*Manufacturer*
26/09/2012	BindRen (colestilan)	Mitsubishi Pharma Europe Ltd.
20/09/2012	Eliquis (apixaban)	Bristol-Myers Squibb / Pfizer EEIG
20/09/2012	Avastin (bevacizumab)	Roche Registration Ltd
20/09/2012	Cialis (tadalafil)	Eli Lilly Nederland B.V.
20/09/2012	Komboglyze (saxagliptin / metformin hydrochloride)	Bristol-Myers Squibb / AstraZeneca EEIG
20/09/2012	Trajenta (linagliptin)	Boehringer Ingelheim International GmbH
20/09/2012	Viread (tenofovir disoproxil (as fumarate))	Gilead Sciences International Ltd
20/09/2012	Votubia (everolimus)	Novartis Europharm Ltd
20/09/2012	Eucreas / Icandra / Zomarist (vildagliptin / metformin hydrochloride)	Novartis Europharm Ltd
20/09/2012	Galvus / Jalra / Xiliarx (vildagliptin)	Novartis Europharm Ltd
19/07/2012	Adcetris (brentuximab vedotin)	Takeda Global Research and Development Centre (Europe) Ltd
19/07/2012	Xalkori (crizotinib)	Pfizer Ltd
19/07/2012	Humira (adalimumab)	Abbott Laboratories Ltd
19/07/2012	Prezista (darunavir)	Janssen-Cilag International NV
		Source: EMEA

FDA inspections

According to the FDA data, four FDA inspections were conducted in the Russian investigative sites during the first half of 2012 year, one in Omsk (on 26-Mar-2012), one in Syktyvkar (on 17-Apr-2012), and two in Moscow (on 02-May-2012 and 05-May-2012). Three inspections ended with NAI result – no action indicated, and one inspection ended with VAI result – voluntary action indicated.

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