Clinical Trials in Russia
Orange Paper
Year 2012

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

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Contents

Executive Summary - English 3
Executive Summary - Russian 4
Clinical Trials by Type and Manufacturing Country 5
Figure 1. Clinical trials in Russia in 2012 5
Figure 2. Clinical trials by type in 2012 6
Figure 3. Russian and International sponsors in 2012 6
Figure 4. Countries presented on the Russian clinical trials market in 2012 7
Clinical trials by Phase 7
Figure 5. Clinical trials in Russia in 2012 by phase 7
Figure 6. The proportions between study phases in Russia in 2012 8
Figure 7. The number of patients in 2012 by study phase 8
Rating of international sponsors 9
Table 1. Top-5 international study sponsors in 2012 9
Rating of Russian sponsors 9
Table 2. Top-5 Russian study sponsors in 2012 9
Therapeutic areas of clinical trials in Russia in 2012 10
Figure 8. Clinical trials in Russia in 2012 by therapeutic area 10
Clinical trials results 10
Table 3. New drugs approved by FDA in Q4 2012 and tested in Russian sites 10
Table 4. New Drugs approved by EMEA in Q4 2012 and tested in Russian sites 11
Roszdravnadzor Inspections 11
Figure 9. Findings during Roszdravnadzor inspections in 2012 12
FDA inspections 12

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Executive Summary – English

The Ministry of Health of the Russian Federation (MoH) approved 916 new clinical trials of all types including local and bioequivalence studies during 2012, demonstrating a 60% increase over the last year's figure.

The main contribution into the total number of studies is made by the multinational multi-center clinical trials, the number of them almost has not changed and stood at 377 new studies in 2012. The number of bioequivalence studies has grown dramatically from 85 studies in 2011 to 322 in 2012 demonstrating over three times increase. The number of local clinical trials has also significantly grown from 117 to 217 clinical trials.

The share of multinational multi-center clinical trials stood at 41% of the total number of clinical trials in 2012, while the local and bioequivalence studies amounted to 24% and 35%, respectively.

Clinical trials in Russia in 2012 were sponsored by companies from 38 countries. The maximum number of trials (430) was initiated by Russian sponsors. American sponsors with 143 new studies took the runner-up place, they are followed by Swiss sponsors with 52 trials and Israeli sponsors with 47 new studies, the group of leaders is concluded by British (40) and French (24) sponsors.

39 new Phase I clinical trials were launched in 2012, 25 trials less than in 2011. The number of the Phase II trials has increased and stood at 111 new studies in 2012. The number of Phase III trials has increased from 327 to 396 studies, 21% more than in 2011. Phase IV trials demonstrated the decrease from 75 studies in 2011 to 48 studies in 2012.

The number of subjects planned to be enrolled in Phase I-IV trials launched in 2012 stood at 67,023, a 24% more than in 2011 figure, when 53,958 patients were planned to be enrolled.

GlaxoSmithKline sponsoring 29 new studies is on the top of the heap in 2012. It is followed by *Roche* and *Novartis* each having 23 new trials and differentiating in the number of patients. Top five is concluded by *Teva* and *Bristol-Myers Squibb* with 18 and 17 new trials in 2012.

The Russian company *Biocad* sponsoring 13 new clinical trials, ranked number one among domestic pharmaceutical manufacturers in 2012. *Microgen* with 12 new trials took the runner-up place. It is followed by *OOO FK Slavyanskaya Apteka* and *Materia Medica* with nine and eight new trials, respectively. Top five is concluded by *Veropharm* with six new trials.

More than two thirds of new studies in 2012 were initiated in eight leading therapeutic areas: the largest number of studies was initiated in Oncology (110); 65 new studies were instigated in Pulmonology, 61 studies – in Endocrinology, 55 new studies – in Musculoskeletal diseases, 45 studies – in Infectious diseases, 42 studies – in Cardiology; 35 and 32 new studies – in Gastroenterology and Psychiatry accordingly.

The Center for Drug Evaluation and Research (CDER) of the FDA approved 102 new drugs during 2012, and 21 of them were studied in clinical trials conducted in Russia.

During the fourth quarter of 2012 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) gave positive recommendations on 87 new drug applications, 48 of which were tested in Russian sites.

Roszdravnadzor conducted 110 inspections during 2012. Violations of the clinical practice were found in 16 institutions.

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

Executive Summary – Russian

В 2012 году Министерством здравоохранения Российской Федерации было выдано 916 разрешений на все виды клинических исследований, что на 60% больше, чем в 2011 году.

При этом количество международных многоцентровых клинических исследований практически не изменилось и составило 377 новых исследований. Количество исследований биоэквивалентности, инициированных в 2012 году, значительно возросло с 85 до 322 исследований по сравнению с 2011 годом. Количество локальных клинических исследований, проводимых на территории России отечественными и иностранными спонсорами, также увеличилось с 117 до 217 исследований.

Спонсорами клинических исследований, разрешенных к проведению в России в 2012 году, выступили компании из 38 стран. На первое место вышли российские производители с 430 КИ, за ними идут американские спонсоры со 143 новыми исследованиями, Швейцария с 52 и Израиль с 47 КИ. Замыкают группу лидеров Великобритания и Франция, с 40 и 24 новыми исследованиями соответственно.

В 2012 году было инициировано 39 новых клинических исследований I фазы, что на 25 КИ меньше, чем в прошлом году. Количество исследований II фазы за этот период незначительно увеличилось и составило 111 новых исследований. Количество исследований III фазы заметно возросло с 327 до 396 исследований – на 21% больше по сравнению с прошлым годом. Количество исследований IV фазы уменьшилось и составило 48 новых исследований.

Всего в клинических исследованиях I-IV фаз, начатых в 2012 году, примет участие 67023 субъектов, что на 24% больше, чем в прошлом году, когда в исследования планировалось включить 53958 субъектов.

В 2012 году первое место среди иностранных производителей по количеству новых исследований заняла фармацевтическая компания *GlaxoSmithKline* с 29 новыми исследованиями. *Roche* и *Novartis* инициировали по 23 исследований, но с разным количеством субъектов. Замыкают пятерку лидеров *Teva* и *Brisol-Mayers Squibb* с 18 и 17 новыми исследованиями.

Первое место среди отечественных производителей по количеству исследований, начатых в 2012 году, занимает *«Биокад»* с 13 новыми клиническими исследованиями. За ним идут «*Микроген»* с 12 новыми исследованиями, *ООО ФК «Славянская аптека»* с девятью исследованиями и *ООО НПФ «Материа Медика Холдинг»* с восьмью исследованиями. Завершает пятёрку лидеров *«Верофарм»*, инициировавший шесть новых исследований.

В 2012 году более двух третей всех новых исследований было инициировано в восьми терапевтических областях: наибольшее количество в области онкологии – 110 КИ; 65 новых исследований в пульмонологии; 61 исследование – в эндокринологии; 55 исследований – в области заболеваний опорно-двигательного аппарата, 45 исследований – в области инфекционных болезней, 42 исследования – в кардиологии, 35 исследований в гастроэнтерологии и 32 проекта – в психиатрии.

В 2012 году Росздравнадзор провел 110 проверок деятельности медицинских организаций по проведению клинических исследований. Нарушения были выявлены в 16 организациях.

За 2012 год в России были проведены шесть инспекций FDA. Пять инспекций завершились с результатом NAI (no action indicated), одна инспекция – с результатом VAI (voluntary action indicated).

Clinical Trials by Type and Manufacturing Country

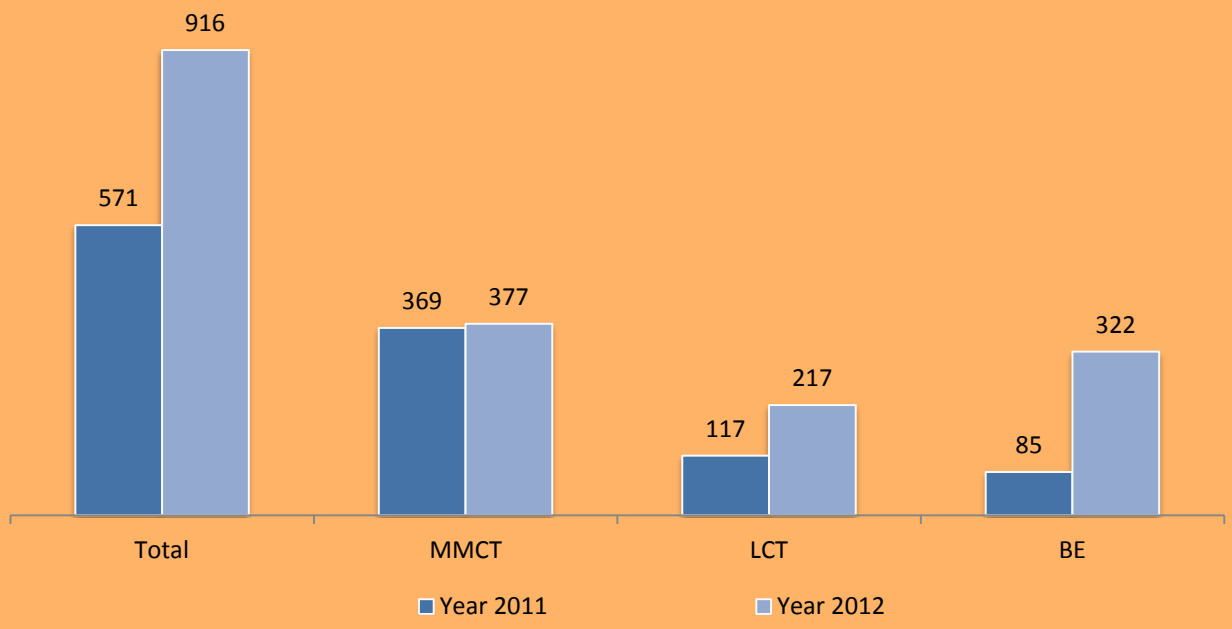
The Russian MoH approved 916 new clinical trials of all types including local and bioequivalence studies during 2012, demonstrating a 60% increase comparing to the same point of the last year.

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 almost has not changed and stood at 377 new studies in 2012.

The number of the local clinical trials (LCT) conducted in Russia by domestic and foreign sponsors increased from 117 to 217 clinical trials, 85% rise from last year's figure.

The number of bioequivalence studies (BE) in 2012 stood at 322 new trials demonstrating an enormous over three times increase comparing with the number of studies in 2011.

Figure 1. Clinical trials in Russia in 2012

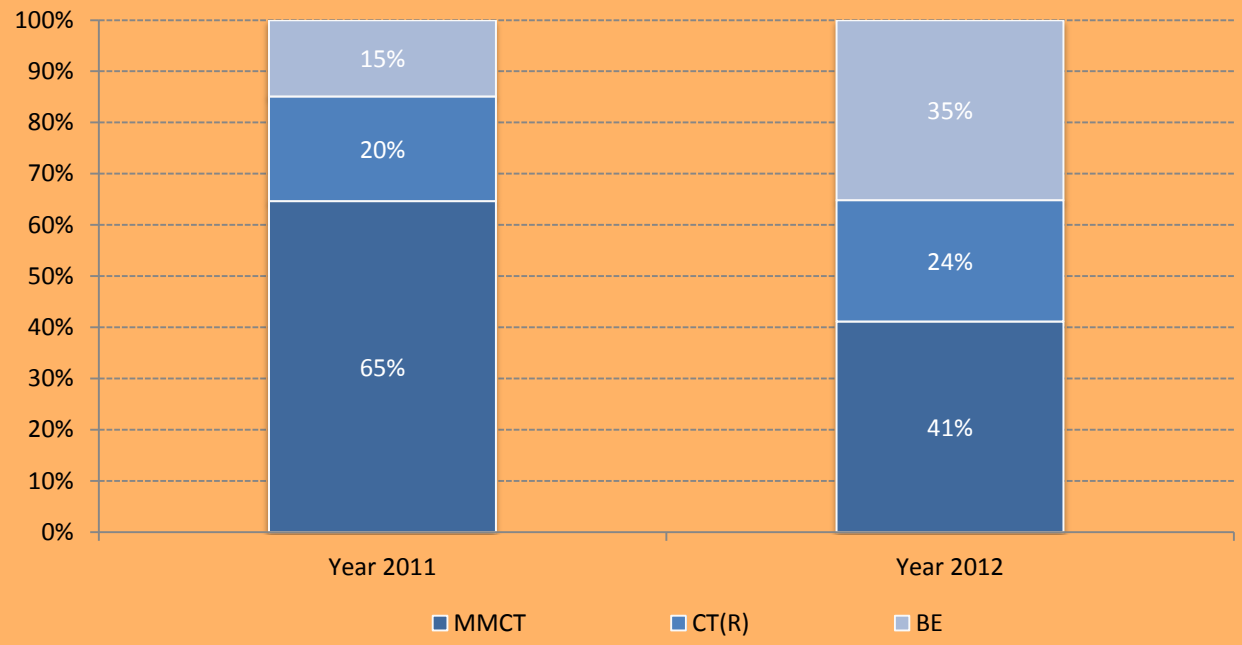


The proportions between different study types (multinational multi-center clinical trials, local studies and bioequivalence trials) notably changed since last year (see **Figure 2**).

The share of bioequivalence studies significantly increased from 15% in 2011 to 35% of the total number of clinical trials approved in 2012.

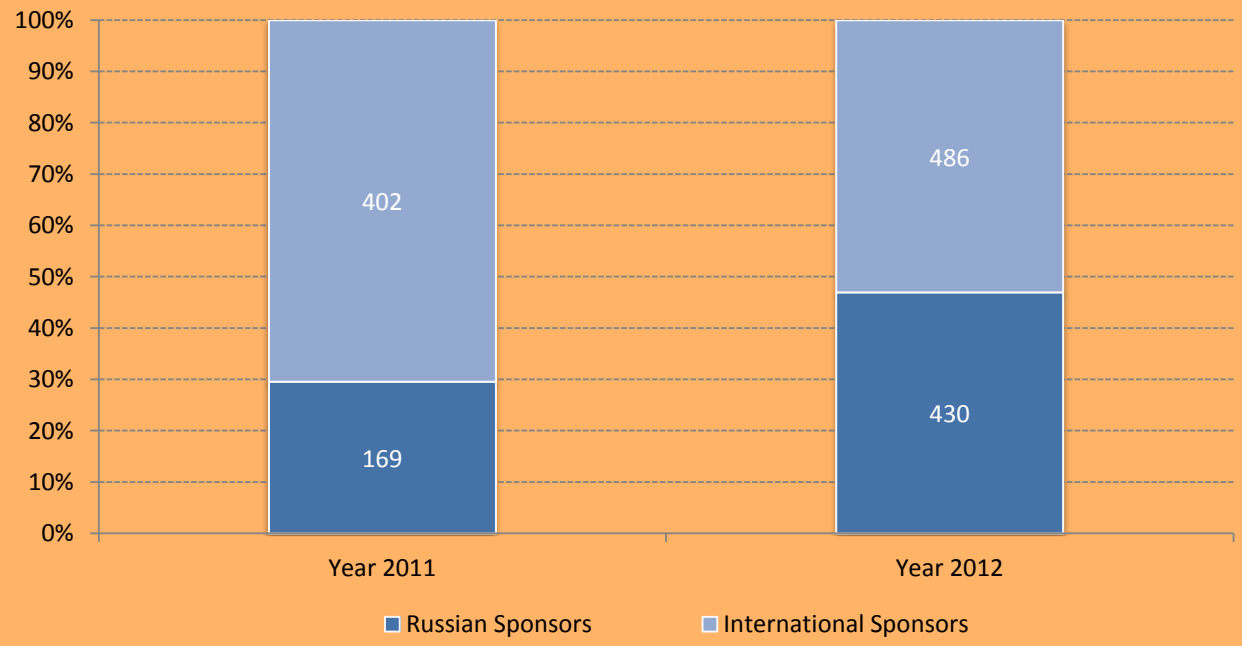
The share of the local trials increased and stood at 24%, and the share of multinational multi-center clinical trials decreased from 65% to 41% of the total number of trials approved during 2012.

Figure 2. Clinical trials by type in 2012



The proportions between sponsors changed significantly since last year. 53% of the total number of new studies in 2012 was sponsored by foreign companies which received 486 study approvals. The share of studies of local manufacturers increased from 30% in 2011 to 47% in 2012, and amounted to 430 studies (**Figure 3**).

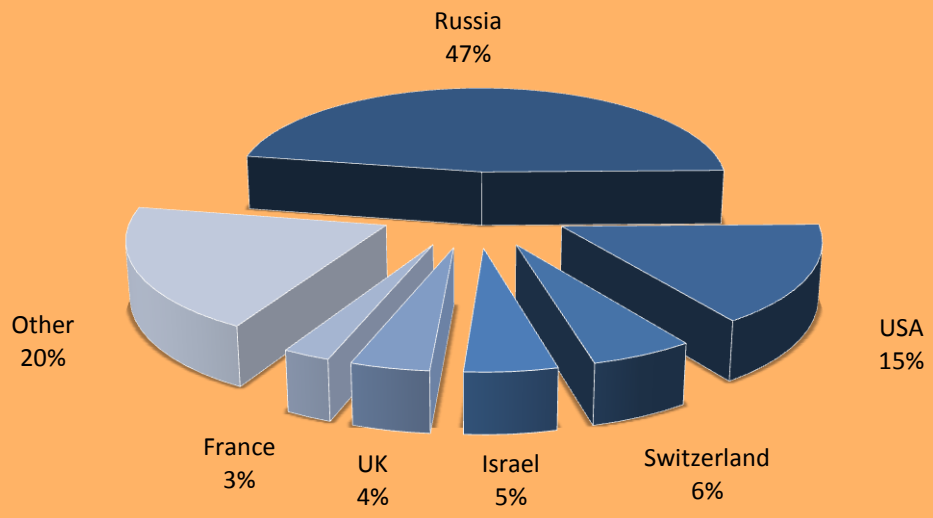
Figure 3. Russian and International sponsors in 2012



Clinical trials in Russia in 2012 were sponsored by companies from 38 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 (430) was initiated by Russian sponsors. American sponsors with 143 new studies took the runner-up place, they are followed by Swiss sponsors with 52 trials and Israeli with 47 new studies, the group of leaders is concluded by British (40) and French (24) sponsors.

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



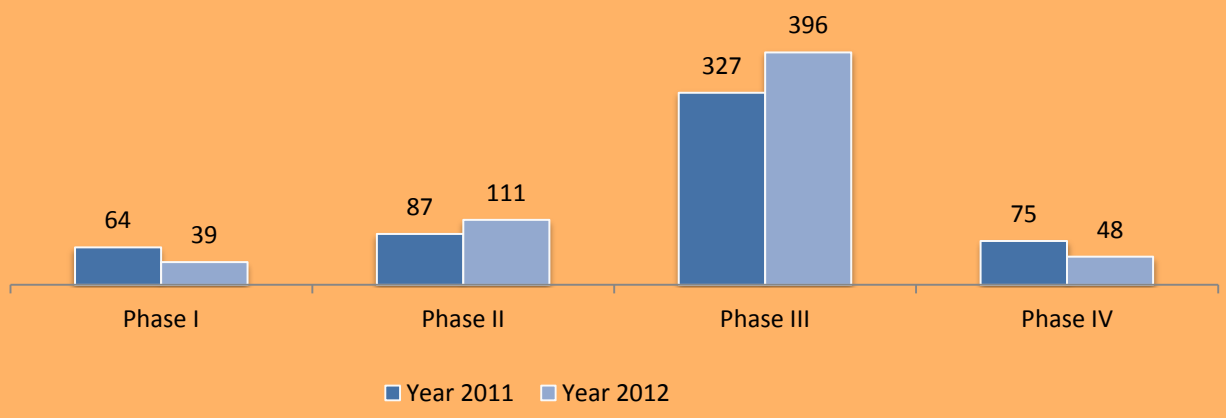
Among others are: Belgium (22), Germany (20), Denmark (19), Sweden and Austria (14 trials each), India (11), Netherlands (ten), Belarus, Hungary, Italy, Slovenia (six trials each), Poland, Ukraine (five trials each), Romania, Czech Republic (four), Republic of Korea, Macedonia, Tunisia started three new studies each; Argentina, Brazil, Ireland, Canada, China each started two new studies each; Greece, Iceland, Spain, Kirghizia Cuba, Latvia, Portugal, Croatia, Japan each started one new study in 2012.

Clinical trials by Phase

39 new Phase I clinical trials were launched in 2012, which is 25 trials less than in 2011. The number of the Phase II trials increased from 87 in 2011 to 111 new studies in 2012 (**Figure 5**).

The number of Phase III trials increased from 327 to 396 studies, 21% more than in 2011. Phase IV trials demonstrated the decrease from 75 studies in 2011 to 48 studies in 2012.

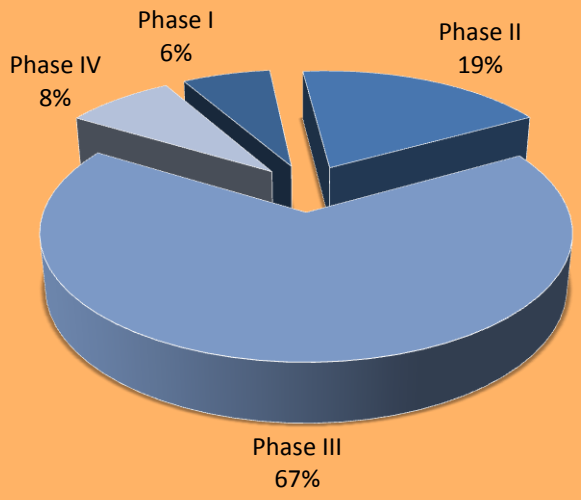
Figure 5. Clinical trials in Russia in 2012 by phase[1]



[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 2012 stood at 67% of the total number of studies, the share of Phase II trials accounted at 19%, Phase IV trials stood at 8%, and the share of Phase I studies amounted to 6%.

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



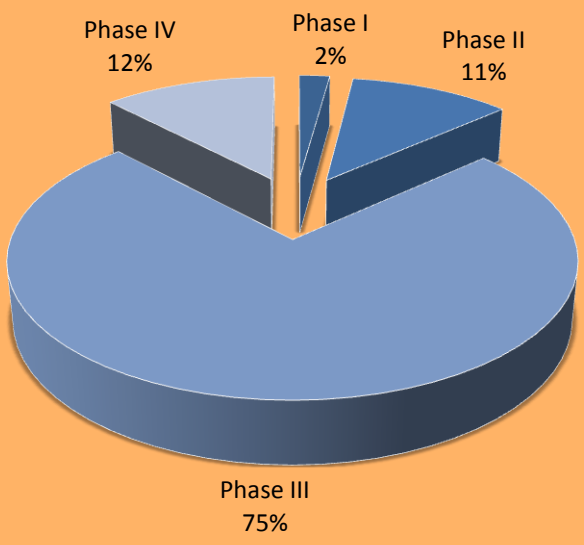
The number of subjects which are planned to be enrolled in Phase I-IV trials launched in 2012 stood at 67,023, a 24% more than in 2011 figure, when 53,958 patients were planned to be enrolled.

1,430 subjects will be recruited in Phase I trials; 7,562 patients – in Phase II trials; 49,932 subjects – in Phase III studies and 8,099 patients will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is two, the maximum number is 2,373.

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 2012 by study phase



Rating of international sponsors

GlaxoSmithKline sponsoring 29 new studies is on the top of the heap in 2012. It is followed by *Roche* and *Novartis* each having 23 new trials and differentiating in the number of subjects. Top five is concluded by *Teva* and *Bristol-Myers Squibb* with 18 and 17 new trials in 2012.

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

Table 1. Top-5 international study sponsors in 2012

№	*Company Name*	*No. studies*[1]	*No. patients*
1	GlaxoSmithKline	29	3307
2	Roche	23	3844
3	Novartis	23	1803
4	Teva	18	2391
5	Bristol-Myers Squibb	17	1179

Rating of Russian sponsors

The Russian company *Biocad* sponsoring 13 new clinical trials, ranked number one among domestic pharmaceutical manufacturers by the number of new studies in 2012. *Microgen* with 12 new trials took the runner-up place. It is followed by *OOO FK Slavyanskaya Apteka* and *Materia Medica* with nine and eight new trials, respectively. Top five is concluded by *Veropharm* with six new trials (see Table 2 for details).

Table 2. Top-5 Russian study sponsors in 2012

№	*Company Name*	*No. studies*[1]	*No. patients*
1	Biocad	13	1854
2	Microgen	12	2275
3	OOO FK Slavyanskaya Apteka	9	640
4	Materia Medica	8	1800
5	Veropharm	6	536

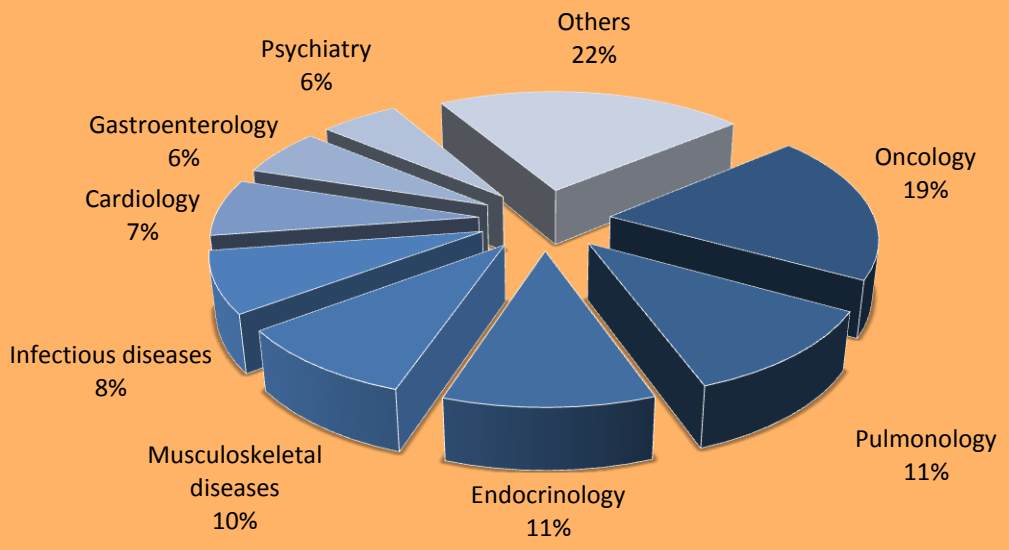
[1] Excluding BE studies

Therapeutic areas of clinical trials in Russia in 2012

More than two thirds of new studies in 2012 were initiated in eight leading therapeutic areas: the largest number of studies was initiated in Oncology (110); 65 new studies were instigated in Pulmonology, 61 studies – in Endocrinology, 55 new studies – in Musculoskeletal diseases, 45 studies – in Infectious diseases, 42 studies – in Cardiology; 35 and 32 new studies – in Gastroenterology and Psychiatry, accordingly.

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

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



Clinical trials results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 102 new drugs during Year 2012; 34 of them are new molecular entities (NME); others are new dosages, manufacturers or indications of the already marketed drugs. 21 of 102 drugs were studied in clinical trials conducted in Russia.

The **Table 3** represents drugs which were approved by FDA and were being tested in clinical trials in Russia in Q4 2012 (Q1-Q3 data is presented in the previous issues of SynRG Orange Paper).

Table 3. New drugs approved by FDA in Q4 2012 and tested in Russian sites

Appr.date	*Drug (active ingredient)*	*Company*
10/15/2012	Nucynta (Tapentadol Hydrochloride)	Janssen Pharms
10/19/2012	Oxtellar XR (Oxcarbazepine)	Supernus Pharms
10/22/2012	Fycompa (Perampanel)	Eisai Inc
11/29/2012	Cometriq (Cabozantinib S-malate)	Exelixis
12/14/2012	Signifor (Pasireotide diaspartate)	Novartis Pharms
12/28/2012	Eliquis (Apixaban)	Bristol Myers Squibb
		Source: FDA

During the year 2012 the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMEA) approved 87 new drug applications. Negative opinion was adopted for eight drugs. 48 of the drugs which received positive opinions were (or are being) tested in clinical trials in Russia.

The **Table 4** represents those of them which were, or are being tested in clinical trials in Russia in Q4 2012 (Q1-Q3 data is presented in the previous issues of SynRG Orange Paper).

Table 4. New Drugs approved by EMEA in Q4 2012 and tested in Russian sites

Appr. date	*Drug (active ingredient)*	*Manufacturer*
10/18/2012	Betmiga (mirabegron)	Astellas Pharma Europe BV
10/18/2012	Tresiba (insulin degludec)	Novo Nordisk A/S
10/18/2012	Humira (adalimumab)	Abbott Laboratories Ltd
10/18/2012	Isentress (raltegravir)	Merck Sharp & Dohme Ltd
10/18/2012	Xarelto (rivaroxaban)	Bayer Pharma AG
11/15/2012	Lyxumia (lixisenatide)	Sanofi-Aventis
11/15/2012	Zaltrap (aflibercept)	Sanofi-Aventis
11/15/2012	Intelence (etravirine)	Janssen-Cilag International N.V.
11/15/2012	Exjade (deferasirox)	Novartis Europharm Ltd
11/15/2012	Zytiga (abiraterone)	Janssen-Cilag International N.V
12/13/2012	Perjeta (pertuzumab)	Roche Registration Ltd
12/13/2012	Selincro (nalmefene)	H.Lundbeck A/S
12/13/2012	Abilify (aripiprazole)	Otsuka Pharmaceutical Europe Ltd
12/13/2012	Ilaris (canakinumab)	Novartis Europharm Ltd
		Source: EMEA

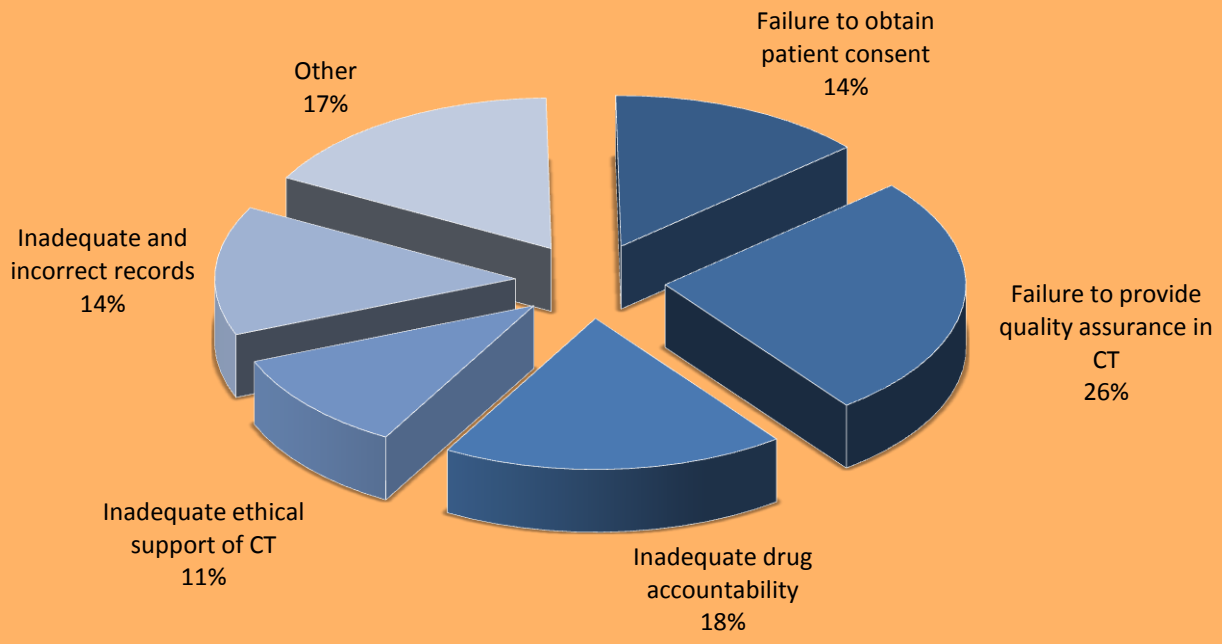
Roszdravnadzor Inspections

According to the quarterly Roszdravnadzor reports[1], 110 inspections were conducted in institutions performing preclinical and clinical trials and located in 47 Russian cities during 2012. Violations of the clinical practice were found in 16 institutions.

The analysis of findings is shown in the **Figure 9.**

[1] http://www.roszdravnadzor.ru/medicines/control_for_doklin_i_klin_issl/info_letters

Figure 9. Findings during Roszdravnadzor inspections in 2012



FDA inspections

According to the FDA data, six 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), two in Moscow (on 02-May-2012 and 05-May-2012), and two in Saint Petersburg (on 02-Apr-2012 and 14-May-2012). Five inspections ended with NAI result – no action indicated, and one inspection ended with VAI result – voluntary action indicated.