Clinical Trials in Russia
Orange Paper
2nd Quarter 2017

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 178 new clinical trials of all types, including local and bioequivalence studies, during Q2 2017. This represents a 21% decrease from Q2 2017.

The number of new multinational multi-center clinical trials (MMCT) initiated in Q2 2017 is 86, compared to 97 in Q2 2016. The number of bioequivalence studies (BE) decreased from 76 studies in Q2 2016 to 52 in Q2 2017, a 32% decrease from last year's figure. The number of local clinical trials (LCT) has decreased from 53 in Q2 2016 to 40 in Q2 2017, a 25% decrease from last year's figure.

Clinical trials in Russia in Q2 2017 were sponsored by companies from 27 countries. The maximum number of trials (65) were initiated by Russian sponsors. American sponsors with 41 new studies took the runner-up place; they are followed by Indian sponsors (14 trials), Swiss sponsors (12 trials) and British sponsors (seven studies).

The number of Phase I clinical trials has decreased from 23 studies to eight new studies in Q2 2017 (65% decrease). The number of Phase II trials decreased in comparison with Q2 2016 from 19 to 17 new studies. The number of Phase III trials decreased from 103 to 94 studies, 9% less than in Q2 2016. The number of Phase IV trials increased in comparison with Q2 2016 from five to seven studies.

The number of subjects planned to be enrolled in Phase I-IV trials launched in Q2 2017 is 14,555, 9% less than in Q2 2016, when 16,001 subjects were planned to be enrolled.

Dr. Reddy's is on the top of the heap of foreign pharmaceutical manufacturers in Q2 2017 by sponsoring eight new studies. They are followed by *F. Hoffmann-La Roche* with six studies and *Merck & Co.,* having five new trials. Top five is concluded by *Sun Pharmaceutical Industries Ltd.* and *Pfizer*, each having four new trials, differentiating in number of patients.

Top five domestic pharmaceutical manufacturers by the number of new studies in Q2 2017 is headed by *Akrikhin,* having six new trials. They are followed by *Biocad* with five new trials, *Polisan* and *Promomed Rus*, each having four new studies and differentiating in the number of patients. Top five is concluded by *Nanolek* with three new trials.

The top five Russian research sites (BE and Phase I studies) include: *Clinical Hospital #68, Moscow* (nine new studies), *Road Clinical Hospital at the station Yaroslavl of Russian Railways* and *Probiotec Medical Center* (6 new studies each), *Russian Academy of Science Hospital, Troitsk* (five studies) and *Eco-Bezopasnost Ltd.* (4 studies).

The top Russian research sites (Phase II-IV studies) include: *Russian Oncological Scientific Center named after N.N. Blokhin* (23 new studies), *First St.Petersburg State Medical University named after I.P. Pavlov* (20 studies) and *Kazan State Medical University* (18 new studies).

The top five CROs in Russia are: *PPD Development* (11 new studies), *Quintiles* (10 studies), *INC Research* (five studies), and *ICON* and *Smooth Clinical Trials, LLC* (four studies each).

The top therapeutic areas were: Oncology (29 new studies); Hematology (10 new studies), Rheumatology (9 new studies), Cardiology (8 new studies).

The Center for Drug Evaluation and Research (CDER) of the FDA approved 33 new drugs during Q2 2017, and **eight** of them were (or are being) studied in clinical trials conducted in Russia.

During Q2 2017, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 26 new drug applications[1]. **Thirteen** of the drugs which received positive opinions were (or are being) tested in clinical trials in Russia.

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

Executive Summary – Russian

Во втором квартале 2017 года Министерством здравоохранения Российской Федерации было выдано 178 разрешений на все виды клинических исследований (КИ), что на 21% меньше, чем за аналогичный период 2016 года.

При этом количество новых международных многоцентровых КИ, инициированных во втором квартале 2017 года, составило 86, по сравнению с 97 в аналогичном периоде прошлого года. Количество исследований биоэквивалентности уменьшилось на 32% по сравнению с 2016 годом и составило 52 против 76. Количество локальных КИ, проводимых на территории России, уменьшилось по сравнению со вторым кварталом 2016 года на 25% и составило 40 исследований против 53.

Спонсорами исследований, разрешенных к проведению в России во втором квартале 2017 года, выступили компании из 27 стран. На первое место вышли российские производители с 65 КИ, за ними идут американские спонсоры с 41 КИ, Индия (14 КИ), Швейцария (12 КИ) и Великобритания (семь КИ).

Во втором квартале 2017 года было инициировано восемь новых КИ I фазы, что на 65% меньше, чем за тот же период 2016 года (23 КИ). Количество исследований II фазы (17 новых исследований) уменьшилось по сравнению со вторым кварталом 2016 года (19 КИ). Количество КИ III фазы составило 94, что на 9% меньше по сравнению с аналогичным периодом прошлого года (103 КИ). Количество исследований IV фазы увеличилось по сравнению со вторым кварталом 2016 года с пяти до семи исследований.

Количество субъектов для участия в исследованиях I-IV фаз во втором квартале 2017 года составило 14 555, что на 9% меньше, чем во втором квартале 2016 года, когда планировалось участие 16 001 субъектов.

Во втором квартале 2017 года лидирующие позиции среди иностранных производителей по количеству новых исследований заняла компания *Dr. Reddy's* с восемью новыми исследованиями. Далее следуют компании *F. Hoffmann-La Roche* (шесть КИ), *Merck & Co.* (пять КИ), *Sun Pharmaceutical Industries Ltd.* и *Pfizer* с четырьмя новыми КИ каждая, но с разным количеством пациентов.

Список пяти лидирующих отечественных производителей по количеству новых исследований во втором квартале 2017 года возглавила компания *Акрихин* с шестью исследованиями. Далее следуют компании *Биокад* (пять новых КИ), *Полисан* и *Промомед* (четыре новых КИ каждая) и *Нанолек* (три новых исследования).

В пятерку передовиков по исследованиям биоэквивалентности и I фазы во втором квартале 2017 года вошли следующие центры: *Городская клиническая больница №68 г. Москвы* (девять новых КИ), *Дорожная клиническая больница на ст. Ярославль ОАО «РЖД»* и *ООО «Медицинский Центр Пробиотек»* (шесть новых КИ каждый), *Больница Российской академии наук (г. Троицк)* (пять КИ) и *ООО «Эко-безопасность»* (четыре КИ).

Лидирующие центры по исследованиям II-IV фаз: *Российский онкологический научный центр имени Н.Н. Блохина* (23 новых КИ), *Первый Санкт-Петербургский государственный медицинский университет им. И.П. Павлова* (20 новых КИ) и *Казанский государственный медицинский университет* (18 новых КИ).

Пятерка лидеров среди КИО в России: *PPD Development* (11 новых КИ), *Quintiles* (10 КИ), *INC Research* (пять КИ), и *ICON* и *Smooth Clinical Trials, LLC* (по четыре КИ каждая).

Наибольшее количество исследований проведено в следующих областях: онкология – 29 новых КИ, гематология – 10 новых КИ, ревматология – 9 новых КИ, кардиология – 8 новых КИ.

FDA одобрено во втором квартале 2017 года 33 новых лекарственных препарата, по **восьми** из которых в России проводились (или проводятся) КИ. EMA одобрено во втором квартале 2017 года 26 новых лекарственных препаратов, по **13** из которых в России проводились (или проводятся) КИ.

Clinical Trials by Type and Manufacturing Country

The Russian MoH approved 178 new clinical trials of all types including local and bioequivalence studies during Q2 2017, demonstrating a 21% decrease in comparison with the same point of the last year.

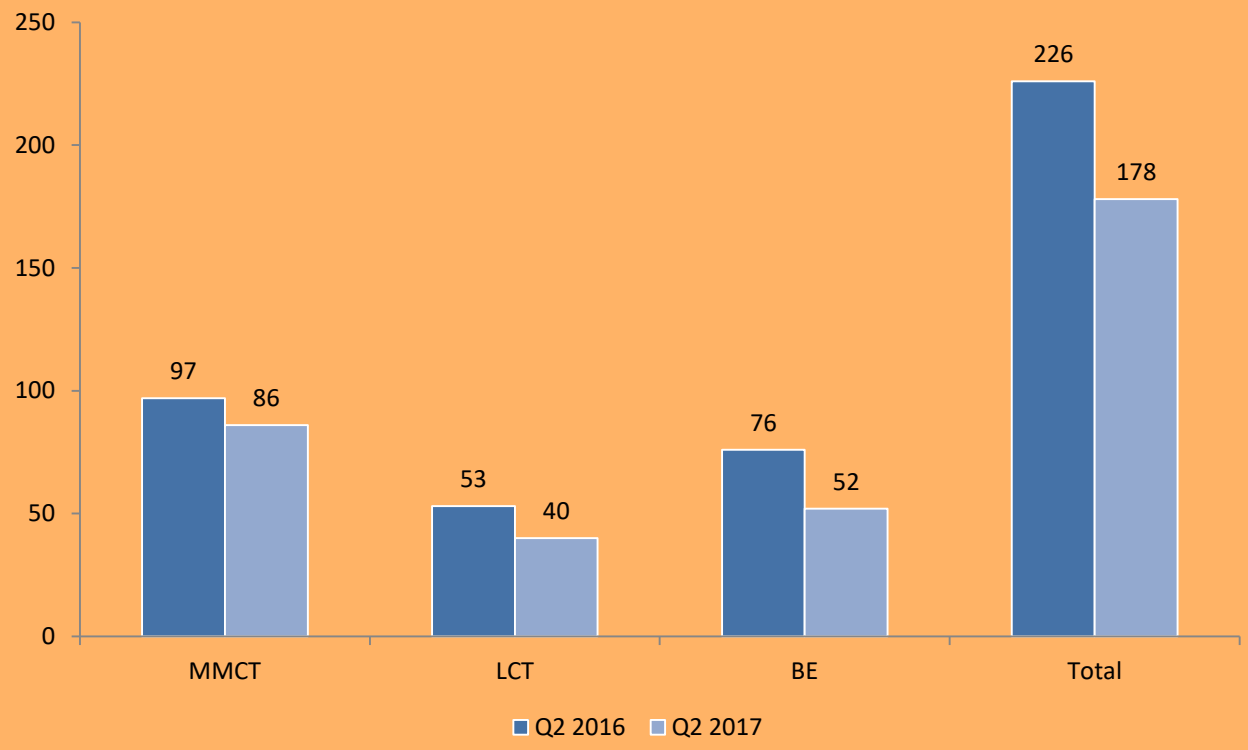
As shown in **Figure 1**, the main contribution into the total number of studies was made by multinational multi-center clinical trials (MMCT) and bioequivalence studies (BE).

The number of multinational multi-center clinical trials (MMCT) has decreased from 97 studies in Q2 2016 to 86 in Q2 2017, an 11% decrease from last year's figure.

The number of bioequivalence studies (BE) decreased from 76 studies in Q2 2016 to 52 in Q2 2017, a 32% decrease from last year's figure.

The number of local clinical trials (LCT) has decreased from 53 in Q2 2016 to 40 in Q2 2017, a 25% decrease from last year's figure.

Figure 1. Clinical Trials in Russia in Q2 2017

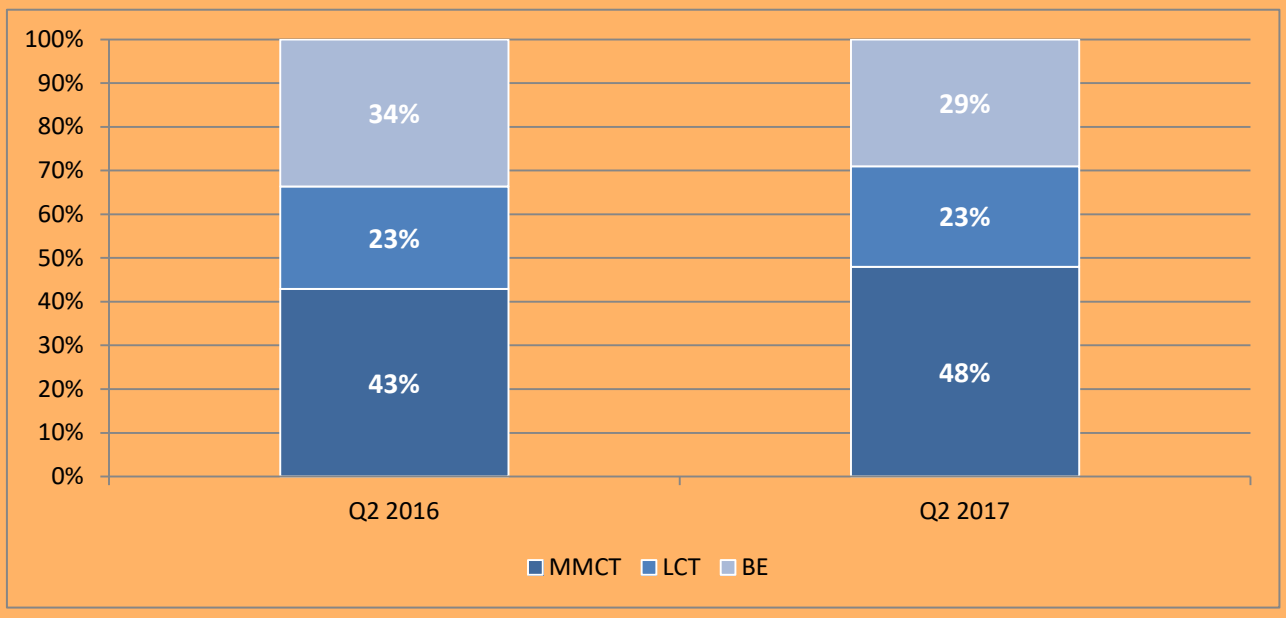


The proportions between different study types (multinational multi-center clinical trials, local clinical trials and bioequivalence studies) changed since last year (see **Figure 2**).

The share of bioequivalence studies decreased from 34% to 29% of the total number of clinical trials approved in Q2 2017.

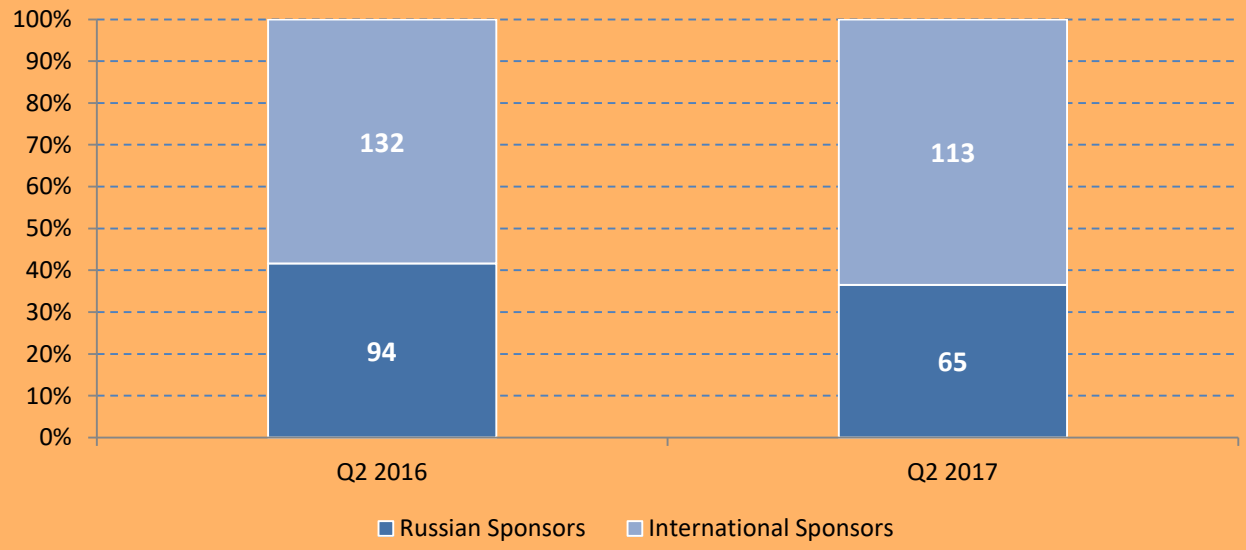
The share of the local clinical trials in Q2 2017 was the same as in Q2 2016 (23%), and the share of multinational multi-center clinical trials was 48% of the total number of trials approved during Q2 2017 (43% in Q2 2016).

Figure 2. Clinical Trials by Type in Q2 2017



The geographic origins of sponsors changed in comparison with last year. 64% of the total number of new studies in Q2 2017 were sponsored by foreign companies which received 113 study approvals (58% in Q2 2016). The share of studies of local manufacturers decreased from 42% in Q2 2016 to 36% in Q2 2017, and amounted to 65 studies (**Figure 3**).

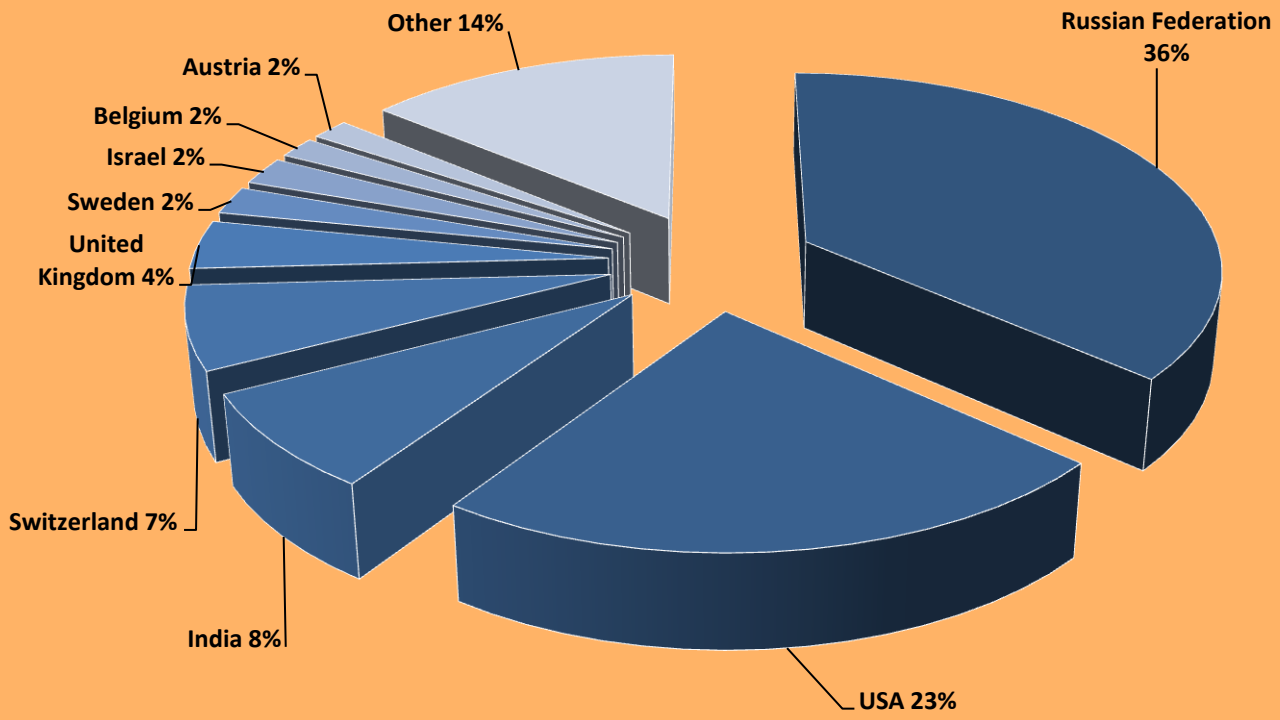
Figure 3. Russian vs International Sponsors in Q2 2017



Clinical trials in Russia in Q2 2017 were sponsored by companies from 27 countries. **Figure 4** indicates the geographic breakdown in sponsors' country of origin.

The maximum number of trials (65) was initiated by Russian sponsors. American sponsors with 41 new studies took the runner-up place; they are followed by Indian sponsors with 14 trials, then by Swiss sponsors with 12 new studies, and British sponsors (seven studies). The group of leaders is concluded by Swedish and Israeli sponsors (four studies each), and Belgium and Austria, each having three studies.

Figure 4. Sponsors' Country of Origin for Q2 2017 Clinical Trials in Russia



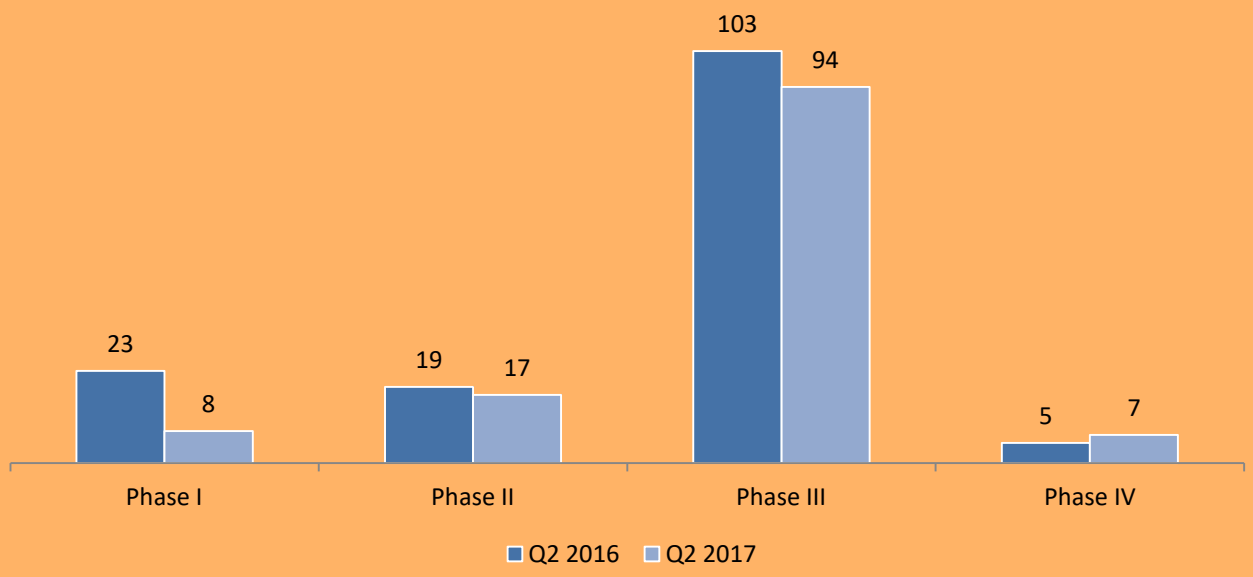
Other sponsors include: Republic of Belarus, Hungary, France, Germany, Denmark, Japan and Canada (two studies each), and Finland, Croatia, Czech Republic, Italy, Macedonia, Malta, Netherlands, Poland, Republic of Kazakhstan, Turkey and United Arab Emirates, each started one new study in Q2 2017.

Clinical trials by Phase

The number of Phase I clinical trials decreased to 65% compared to Q2 2016: from 23 studies to eight new studies in Q2 2017. The number of Phase II trials decreased to 11% compared to Q2 2016 from 19 studies to 17 new studies (**Figure 5**).

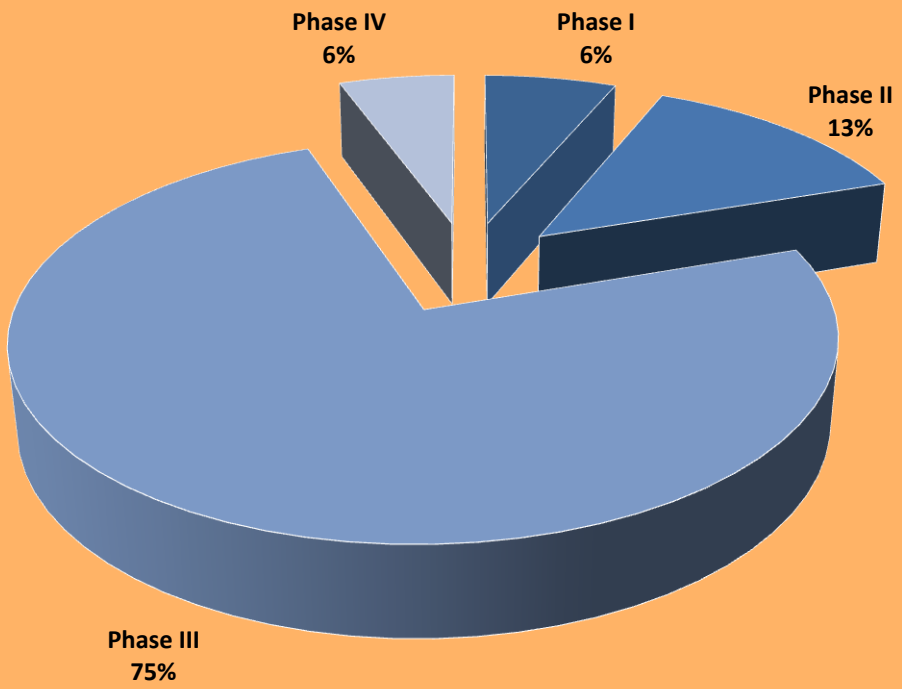
The number of Phase III trials decreased from 103 to 94 studies, 9% less than in Q2 2016. The number of Phase IV trials increased in comparison with Q2 2016 from five to seven studies in Q2 2017.

Figure 5. Clinical Trials in Russia in Q2 2017 by Phase[1]



As shown in **Figure 6**, the share of Phase III trials in Q2 2017 is 75% of the total number of studies, the share of Phase I trials is 6%, Phase II trials is 13% and the share of Phase IV studies accounted to 6%.

Figure 6. Percentage Breakdown of Russian Clinical Trials by Phase



[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.

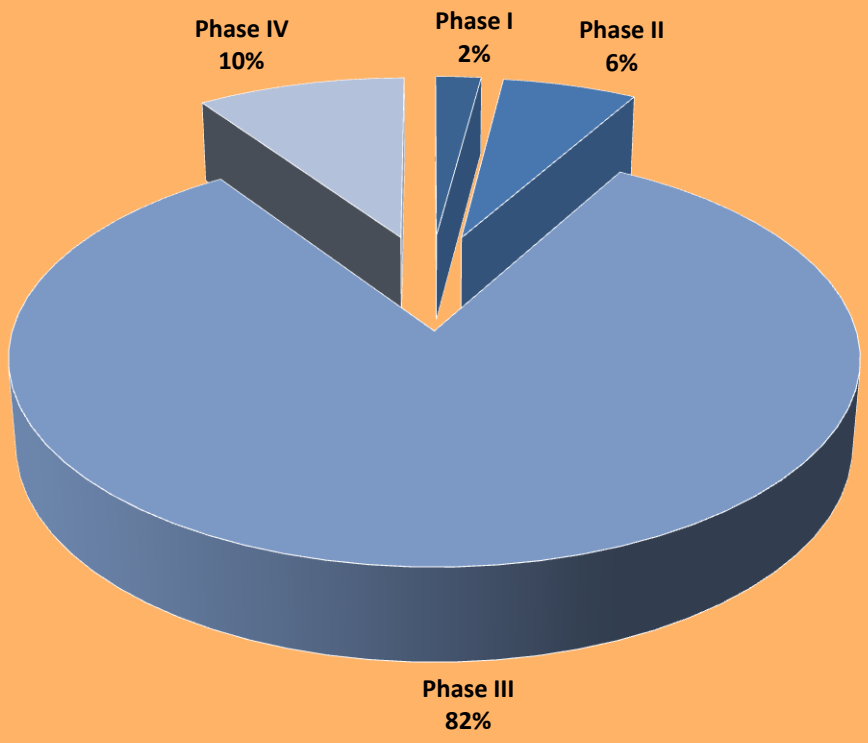
The number of subjects planned to be enrolled in Phase I-IV trials launched in Q2 2017 is 14,555, 9% less than in Q2 2016, when 16,001 subjects were planned to be enrolled.

301 subjects will be recruited in Phase I trials; 893 – in Phase II trials; 11,979 – in Phase III studies and 1,382 subjects will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is one, the maximum number is 831.

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 Q2 2017 by Study Phase



The Top Five: Sponsors, Sites and CROs

Table 1. Top-5 International Study Sponsors in Q2 2017

№	Company Name	No. studies[1]	No. patients
1	Dr. Reddy's	8	1082
2	F. Hoffmann-La Roche	6	198
3	Merck & Co.	5	470
4	Sun Pharmaceutical Industries Ltd.	4	216
5	Pfizer	4	201

Table 2. Top-5 Russian Study Sponsors in Q2 2017

№	Company Name	No. studies	No. patients
1	Akrikhin	6	494
2	Biocad	5	746
3	Polisan	4	1367
4	Promomed Rus	4	235
5	Nanolek	3	415

Table 3. Top-5 Russian Research Sites (BE and Phase I studies) in Q2 2017

№	Site Name	City	No. studies
1	Clinical Hospital #68	Moscow	9
2	Road Clinical Hospital at the station Yaroslavl of Russian Railways	Yaroslavl	6
3	Probiotec Medical Center	Serpukhov, Moscow Region	6
4	Russian Academy of Science Hospital, Troitsk	Troitsk, Moscow Region	5
5	Eco-Bezopasnost Ltd.	Saint-Petersburg	4

[1] Excluding BE studies.

Table 4. Top-5 Russian Research Sites (Phase II-IV studies) in Q2 2017

№	*Site Name*	*City*	*No. studies*
1	Russian Oncological Scientific Center named after N.N. Blokhin	Moscow	23
2	First St.Petersburg State Medical University named after I.P. Pavlov	Saint-Petersburg	20
3	Kazan State Medical University	Kazan	18
4	Federal North-West Medical Research Centre named after V.A. Almazov	Saint-Petersburg	13
5	Ural State Medical University	Ekaterinburg	13

Table 5. Top-5 Russian Research Sites (all studies) in Q2 2017

№	*Site Name*	*City*	*No. studies*
1	Russian Oncological Scientific Center named after N.N. Blokhin	Moscow	23
2	First St.Petersburg State Medical University named after I.P. Pavlov	Saint-Petersburg	20
3	Kazan State Medical University	Kazan	18
4	Federal North-West Medical Research Centre named after V.A. Almazov	Saint-Petersburg	13
5	Ural State Medical University	Ekaterinburg	13

Table 6. Top-CROs in Russia in Q2 2017

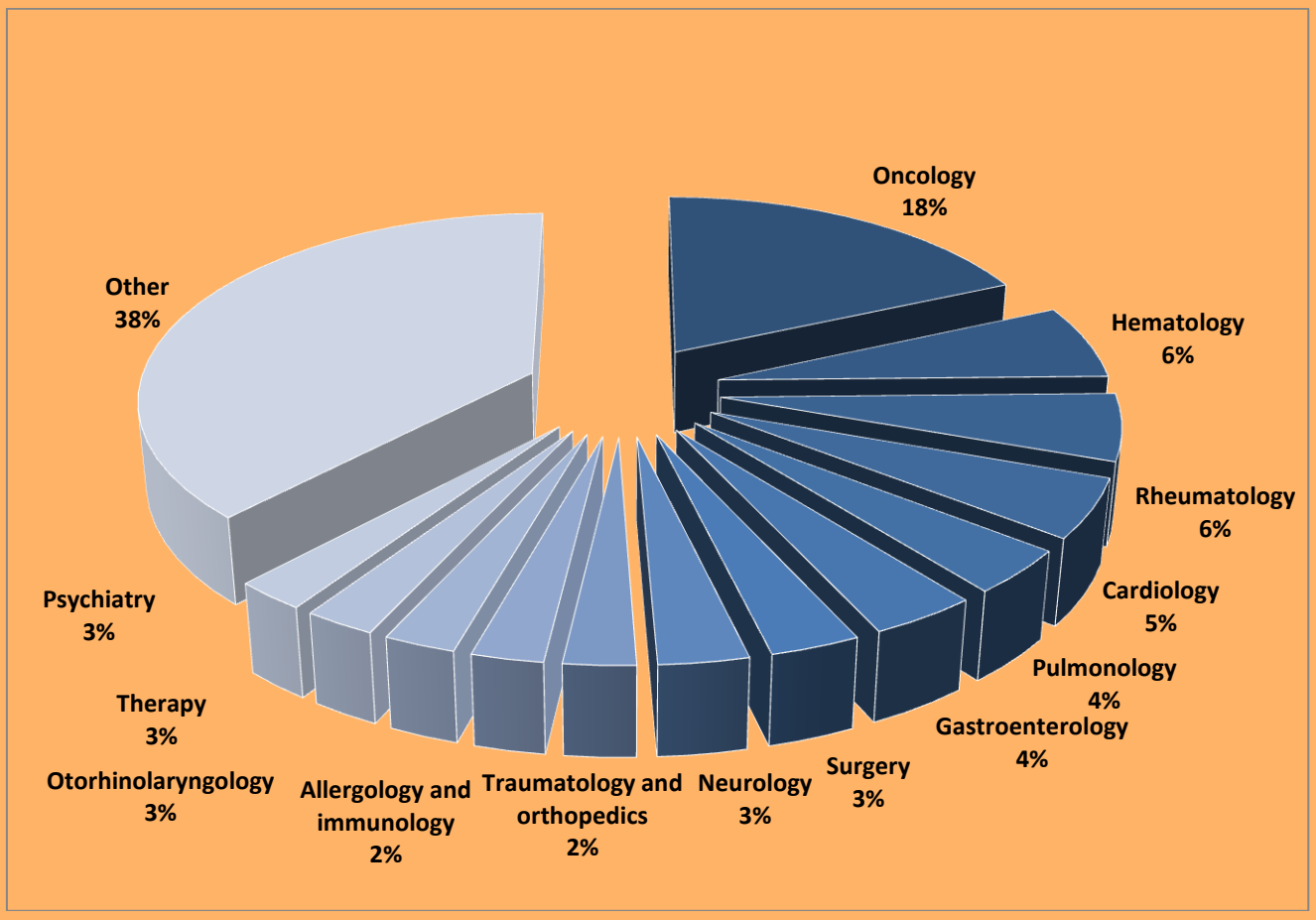
№	*CRO Name*	*No. studies*	*No. patients*
1	PPD Development	11	753
2	Quintiles	10	2004
3	INC Research	5	438
4	ICON	4	373
5	Smooth Clinical Trials, LLC	4	1367

Therapeutic Areas of Russian Clinical Trials in Q2 2017

The largest number of studies were initiated in Oncology (29 studies), and is followed by Hematology (10 studies), Rheumatology (9 studies), Cardiology (8 studies), Pulmonology and Gastroenterology (6 studies each), Surgery and Neurology (5 studies each), Traumatology and orthopedics, Allergology and immunology, Otorhinolaryngology, Therapy, Psychiatry (4 studies each).

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

Figure 8. Clinical Trials in Russia in Q2 2017 by Therapeutic Area



Clinical Trials Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 33 new drugs during Q2 2017; nine of them are new molecular entities (NME); other approvals concern new dosages, combinations or manufacturers. Eight of 33 drugs were (or are being) studied in clinical trials involving Russian sites.

The **Table 7** shows the drugs which were approved by FDA in Q2 2017 that were (or are being) tested in clinical trials in Russia.

Table 7. New Drugs Approved by FDA in Q2 2017 and Tested in Russian Sites

Appr.date	*Drug (active ingredient)*	*Company*
05/01/2017	Imfinzi (durvalumab)	Astrazeneca UK Ltd
05/09/2017	Bavencio (avelumab)	EMD Serono Inc
05/18/2017	Jadenu sprinkle (deferasirox)	Novartis Pharms Corp
05/22/2017	Kevzara (sarilumab)	Sanofi Synthelabo
06/07/2017	Norvir (ritonavir)	Abbvie Inc
06/19/2017	Baxdela (delafloxacin)	Melinta Therapeutics Inc
06/19/2017	Baxdela (delafloxacin)	Melinta Therapeutics Inc
06/23/2017	Bevyxxa (betrixaban)	Portola Pharma Inc
		Source: FDA

During Q2 2017, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 26 new drug applications[1], four positive recommendations on new generic medicines and seven for new biosimilar medicines. Negative opinion was adopted for three drugs. Thirteen of the drugs which received positive opinions were (or are being) tested in clinical trials in Russia.

The **Table 8** represents those of them which were, or are being tested in clinical trials in Russia in Q2 2017.

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

Table 8. New Drugs Approved by EMA in Q2 2017 and Tested in Russian Sites

Appr. date	*Drug (active ingredient)*	*Manufacturer*
04/21/2017	Besponsa (inotuzumab ozogamicin)	Pfizer Limited
04/21/2017	Kevzara (sarilumab)	Sanofi-Aventis groupe
04/21/2017	Avastin (bevacizumab)	Roche Registration Limited
04/21/2017	Opdivo (nivolumab)	Bristol-Myers Squibb Pharma EEIG
05/18/2017	Reagila (cariprazine)	Gedeon Richter
05/18/2017	Komboglyze (saxagliptin / metformin hydrochloride)	AstraZeneca AB
05/18/2017	Onglyza (saxagliptin)	AstraZeneca AB
05/18/2017	Renvela (sevelamer carbonate)	Genzyme Europe BV
05/18/2017	Sevelamer carbonate Zentiva (sevelamer carbonate)	Genzyme Europe BV
05/18/2017	Zykadia (ceritinib)	Novartis Europharm Ltd
06/22/2017	Kisqali (ribociclib)	Novartis Europharm Ltd
06/22/2017	Mavenclad (cladribine)	Merck Serono Europe Limited
06/22/2017	Maviret (glecaprevir / pibrentasvir)	AbbVie Ltd
		Source: EMA

Inspections

FDA inspections

At the moment of the Orange Paper Q2 2017 production no information about FDA inspections conducted in the Russian investigative sites was available.

Roszdravnadzor inspections

According to the Roszdravnadzor quarterly report[1], 14 inspections were conducted in institutions performing preclinical and clinical trials and located in 13 Russian cities during Q2 2017. Violations were found in 11 institutions.

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.

[1] http://www.roszdravnadzor.ru/i/upload/images/2017/7/10/1499691665.06717-1-22602.pdf