Clinical Trials in Russia
Orange Paper
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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 Q1 2017. This represents a 19% decrease from Q1 2017.

The number of new multinational multi-center clinical trials (MMCT) initiated in Q1 2017 is 64, compared to 65 in Q1 2016. The number of bioequivalence studies (BE) decreased from 89 studies in Q1 2016 to 64 in Q1 2017, a 28% decrease from last year's figure. The number of local clinical trials (LCT) has decreased from 68 in Q1 2016 to 52 in Q1 2017, a 24% decrease from last year's figure.

Clinical trials in Russia in Q1 2017 were sponsored by companies from 22 countries. The maximum number of trials (76) were initiated by Russian sponsors. American sponsors with 17 new studies took the runner-up place; they are followed by Swiss sponsors (15 trials), German sponsors (14 trials) and Indian sponsors (13 studies).

The number of Phase I clinical trials has decreased from 21 studies to 14 new studies in Q1 2017 (33% decrease). The number of Phase II trials increased in comparison with Q1 2016 from 18 to 20 new studies. The number of Phase III trials decreased from 90 to 75 studies, 17% less than in Q1 2016. The number of Phase IV trials increased in comparison with Q1 2016 from four to seven studies.

The number of subjects planned to be enrolled in Phase I-IV trials launched in Q1 2017 is 14,195, slightly more than in Q1 2016, when 14,027 subjects were planned to be enrolled.

Novartis is on the top of the heap of foreign pharmaceutical manufacturers in Q1 2017 by sponsoring eight new studies. They are followed by *Hetero Labs Limited* and *Sanofi-Aventis,* having five new trials each, differentiating in number of patients. Top five is concluded by *Janssen* and *Gilead Sciences, Inc.*, each having four new trials.

Top five domestic pharmaceutical manufacturers by the number of new studies in Q1 2017 is headed by *North Star (Severnaya Zvezda),* having seven new trials. They are followed by *Promomed* with six new trials. Top five is concluded by companies *Pharmasyntez*, *Medsyntez* and *CanonPharma Production*, each having four new studies and differentiating in the number of patients.

The top five Russian research sites (BE and Phase I studies) include: *Probiotec Medical Center* (14 new studies), *Eco-Bezopasnost Ltd.* (9 studies), *Bioeq Ltd.* (7 studies), *Kazan (Privolzhsky) State University* and *Road Clinical Hospital at the station Yaroslavl of Russian Railways* (5 studies each).

The top Russian research sites (Phase II-IV studies) include: *Kazan State Medical University* (19 new studies), *First Moscow State Medical University named after I.M. Sechenov* and *Russian Oncological Scientific Center named after N.N. Blokhin* (17 studies each).

The top five CROs in Russia are: *Quintiles* (seven new studies), *Synergy Research Group* (six studies), *Covance Clinical & Periapproval Services Limited* and *Pharmaceutical Research Associates CIS, LLC* (five studies each), and *INC Research* (four studies).

The top therapeutic areas were: Therapy (27 new studies); Oncology and Infectious diseases (20 studies each); Gastroenterology (17 new studies).

The Center for Drug Evaluation and Research (CDER) of the FDA approved 32 new drugs during Q1 2017, and **four** of them were (or are being) studied in clinical trials conducted in Russia.

During Q1 2017, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 18 new drug applications[1]. **Fourteen** 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

В первом квартале 2017 года Министерством здравоохранения Российской Федерации было выдано 180 разрешений на все виды клинических исследований (КИ), что на 19% меньше, чем за аналогичный период 2016 года.

При этом количество новых международных многоцентровых КИ, инициированных в первом квартале 2017 года, составило 64, по сравнению с 65 в аналогичном периоде прошлого года. Количество исследований биоэквивалентности уменьшилось на 28% по сравнению с 2016 годом и составило 64 против 89. Количество локальных КИ, проводимых на территории России, уменьшилось по сравнению с первым кварталом 2016 года на 24% и составило 52 исследования против 68.

Спонсорами исследований, разрешенных к проведению в России в первом квартале 2017 года, выступили компании из 22 стран. На первое место вышли российские производители с 76 КИ, за ними идут американские спонсоры с 17 КИ, Швейцария (15 КИ), Германия (14 КИ) и Индия (13 КИ).

В первом квартале 2017 года было инициировано 14 новых КИ I фазы, что на 33% меньше, чем за тот же период 2016 года (21 КИ). Количество исследований II фазы (20 новых исследований) увеличилось по сравнению с первым кварталом 2016 года (18 КИ). Количество КИ III фазы составило 90, что на 17% меньше по сравнению с аналогичным периодом прошлого года (75 КИ). Количество исследований IV фазы увеличилось по сравнению с первым кварталом 2016 года с четырех до семи исследований.

Количество субъектов для участия в исследованиях I-IV фаз в первом квартале 2017 года составило 14 195, что чуть больше, чем в первом квартале 2016 года, когда планировалось участие 14 027 субъектов.

В первом квартале 2017 года лидирующие позиции среди иностранных производителей по количеству новых исследований заняла компания *Novartis* с восемью новыми исследованиями. Далее следуют компании *Hetero Labs Limited* и *Sanofi-Aventis* с пятью новыми КИ каждая, но с разным количеством пациентов, *Janssen* и *Gilead Sciences, Inc.*, каждая с четырьмя новыми КИ.

Список пяти лидирующих отечественных производителей по количеству новых исследований в первом квартале 2017 года возглавила компания *Северная Звезда* с семью исследованиями. Далее следуют компании *Промомед* (шесть новых КИ), *Фармасинтез, Медсинтез* и *Канонфарма Продакшн* (четыре исследования каждая).

В пятерку передовиков по исследованиям биоэквивалентности и I фазы в первом квартале 2017 года вошли следующие центры: *ООО «Медицинский Центр Пробиотек»* (14 новых КИ), *ООО «Эко-безопасность»* (9 КИ), *ООО «БиоЭк»* (7 КИ), *Казанский (Приволжский) федеральный университет* и *Дорожная клиническая больница на ст. Ярославль ОАО «РЖД»* (5 исследований каждый).

Лидирующие центры по исследованиям II-IV фаз: *Казанский государственный медицинский университет* (19 новых КИ), *Первый медицинский университет им. И.М. Сеченова* и *Российский онкологический научный центр имени Н.Н. Блохина* (17 КИ каждый).

Пятерка лидеров среди КИО в России: *Quintiles* (семь новых КИ), *Synergy Research Group* (шесть КИ), *Covance Clinical & Periapproval Services Limited* и *Pharmaceutical Research Associates CIS, LLC* (по пять КИ каждая) и *INC Research* (четыре КИ).

Наибольшее количество исследований проведено в следующих областях: терапия – 27 новых КИ, онкология и инфекционные болезни – по 20 КИ, гастроэнтерология – 17 КИ.

FDA одобрено в первом квартале 2017 года 32 новых лекарственных препарата, по **четырем** из которых в России проводились (или проводятся) КИ. EMA одобрено в первом квартале 2017 года 18 новых лекарственных препаратов, по **14** из которых в России проводились (или проводятся) КИ.

Clinical Trials by Type and Manufacturing Country

The Russian MoH approved 180 new clinical trials of all types including local and bioequivalence studies during Q1 2017, demonstrating a 19% decrease in comparison with the same point of the last year.

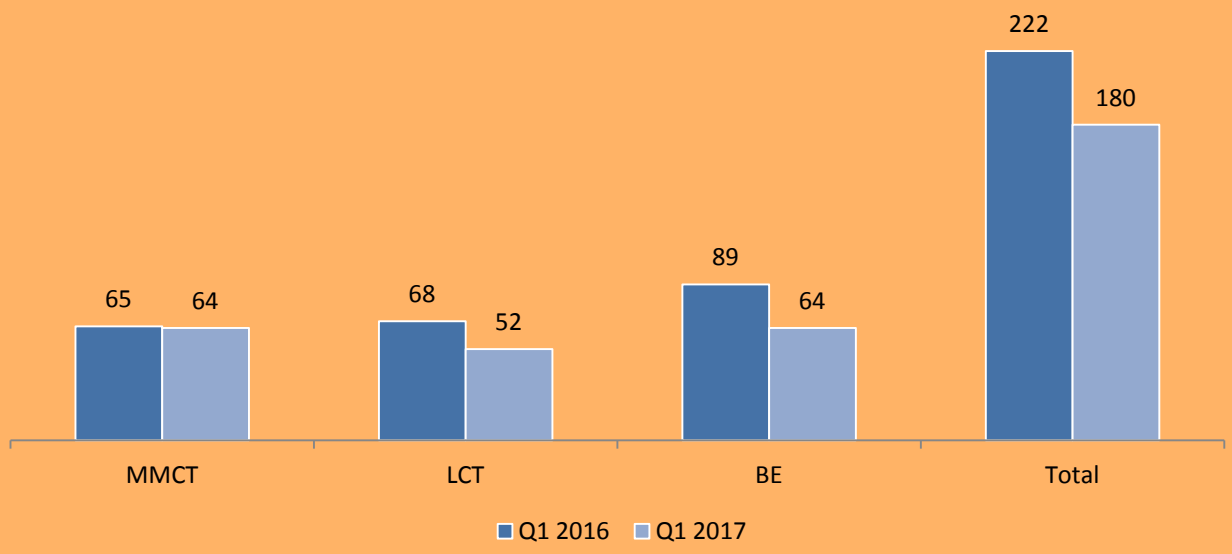
As shown in **Figure 1**, the main contribution into the total number of studies was made by multinational multi-center clinical trials (MMCT) and bioequivalence studies (BE).

The number of multinational multi-center clinical trials (MMCT) has slightly decreased from 65 studies in Q1 2016 to 64 in Q1 2017, a 1.5% decrease from last year's figure.

The number of bioequivalence studies (BE) decreased from 89 studies in Q1 2016 to 64 in Q1 2017, a 28% decrease from last year's figure.

The number of local clinical trials (LCT) has decreased from 68 in Q1 2016 to 52 in Q1 2017, a 24% decrease from last year's figure.

Figure 1. Clinical Trials in Russia in Q1 2017

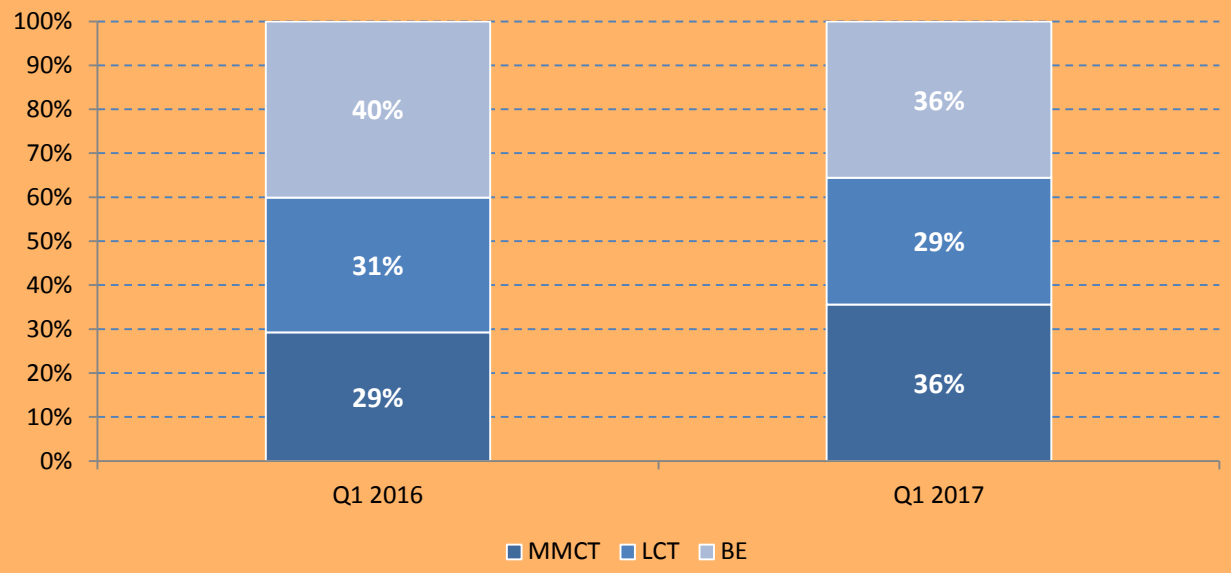


The proportions between different study types (multinational multi-center clinical trials, local clinical trials and bioequivalence studies) changed since last year (see **Figure 2**).

The share of bioequivalence studies decreased from 40% to 36% of the total number of clinical trials approved in Q1 2017.

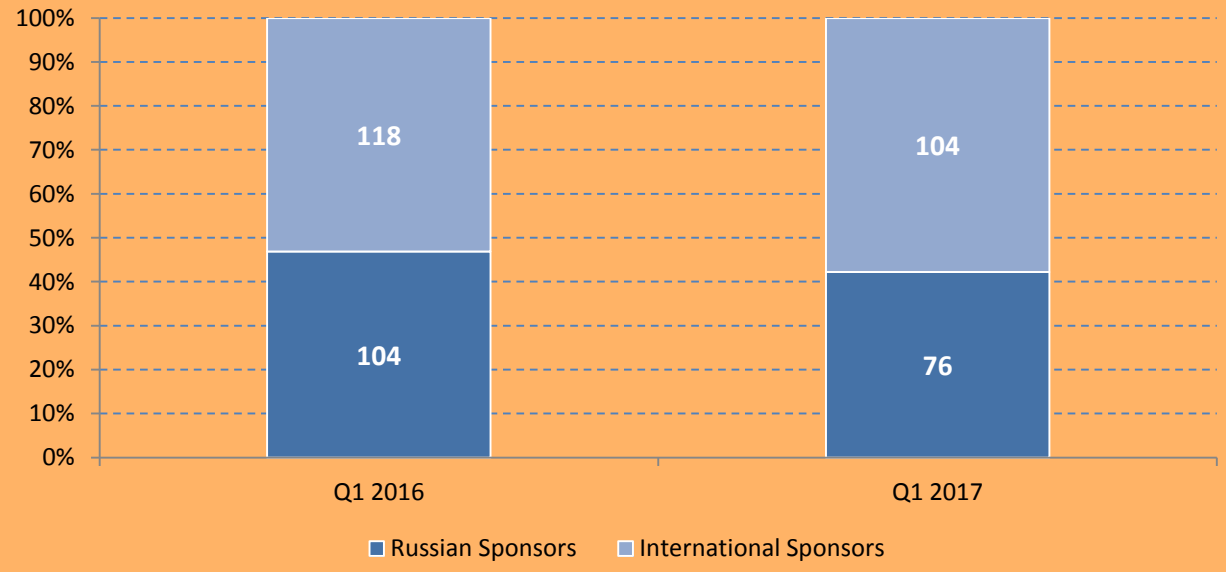
The share of the local clinical trials decreased from 31% in Q1 2016 to 29% in Q1 2017, and the share of multinational multi-center clinical trials was 36% of the total number of trials approved during Q1 2017 (29% in Q1 2016).

Figure 2. Clinical Trials by Type in Q1 2017



The geographic origins of sponsors changed in comparison with last year. 58% of the total number of new studies in Q1 2017 were sponsored by foreign companies which received 104 study approvals (53% in Q1 2016). The share of studies of local manufacturers decreased from 47% in Q1 2016 to 42% in Q1 2017, and amounted to 76 studies (**Figure 3**).

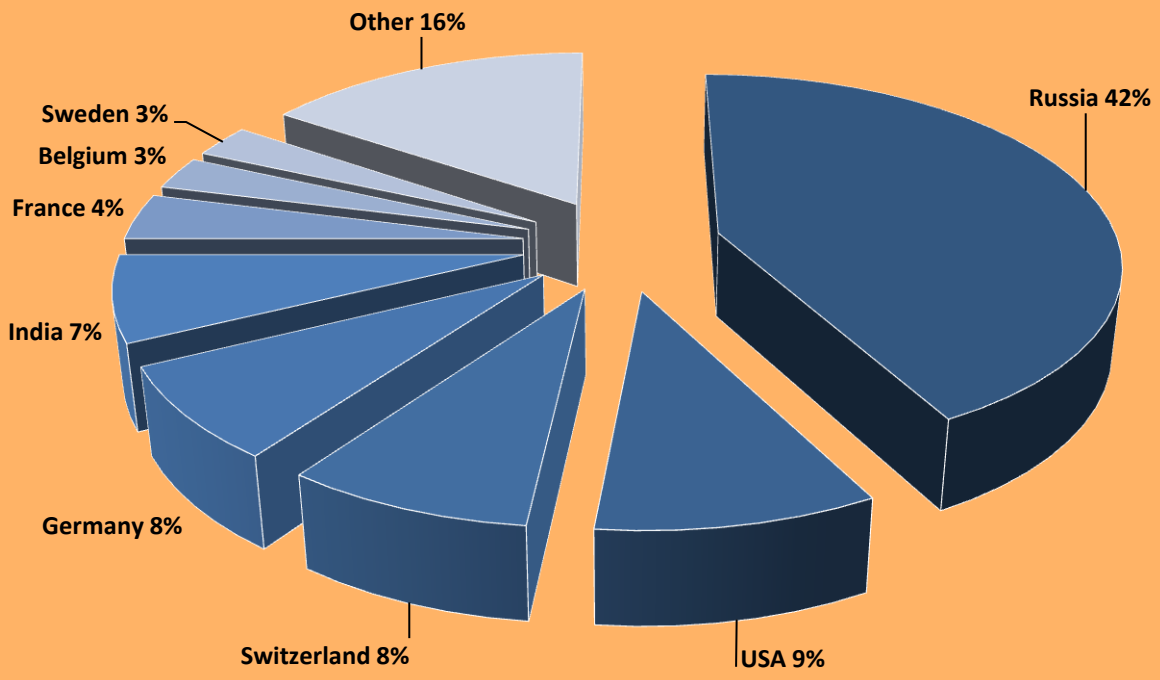
Figure 3. Russian vs International Sponsors in Q1 2017



Clinical trials in Russia in Q1 2017 were sponsored by companies from 22 countries. **Figure 4** indicates the geographic breakdown in sponsors' country of origin.

The maximum number of trials (76) were initiated by Russian sponsors. American sponsors with 17 new studies took the runner-up place; they are followed by Swiss sponsors with 15 trials, then by German sponsors with 14 new studies, and Indian sponsors (13 studies). The group of leaders is concluded by French sponsors (7 studies), and Sweden and Belgium, each having five studies.

Figure 4. Sponsors' Country of Origin for Q1 2017 Clinical Trials in Russia



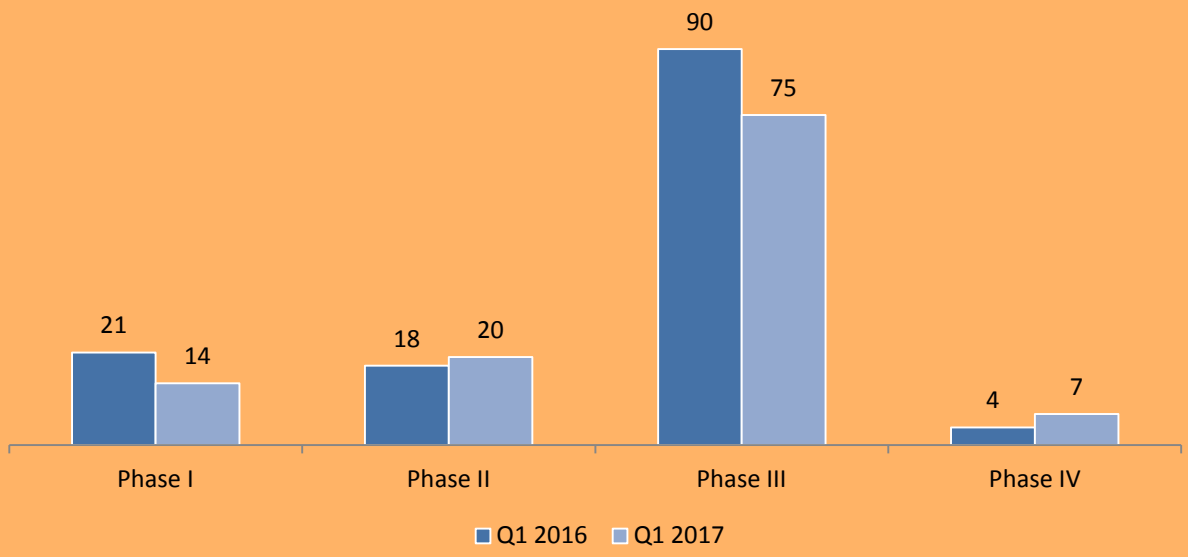
Other sponsors include: United Kingdom and Netherlands (four studies each), Italy and Austria (three studies each), Denmark, Israel, Cyprus and Poland (two studies each), and Spain, Japan, Malta, Bulgaria, Slovenia and Luxembourg, each started one new study in Q1 2017.

Clinical trials by Phase

The number of Phase I clinical trials decreased to 33% compared to Q1 2016: from 21 studies to 14 new studies in Q1 2017. The number of Phase II trials increased to 11% compared to Q1 2016 from 18 studies to 20 new studies (**Figure 5**).

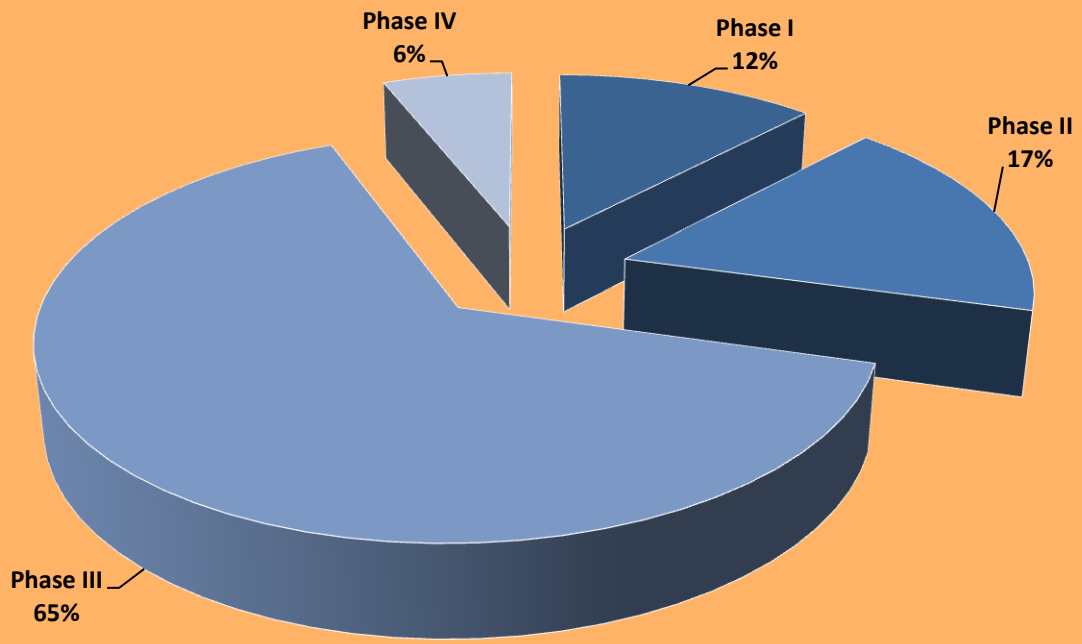
The number of Phase III trials decreased from 90 to 75 studies, 17% less than in Q1 2016. The number of Phase IV trials increased in comparison with Q1 2016 from four to seven studies in Q1 2017.

Figure 5. Clinical Trials in Russia in Q1 2017 by Phase[1]



As shown in **Figure 6**, the share of Phase III trials in Q1 2017 is 65% of the total number of studies, the share of Phase I trials is 12%, Phase II trials is 17% 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.

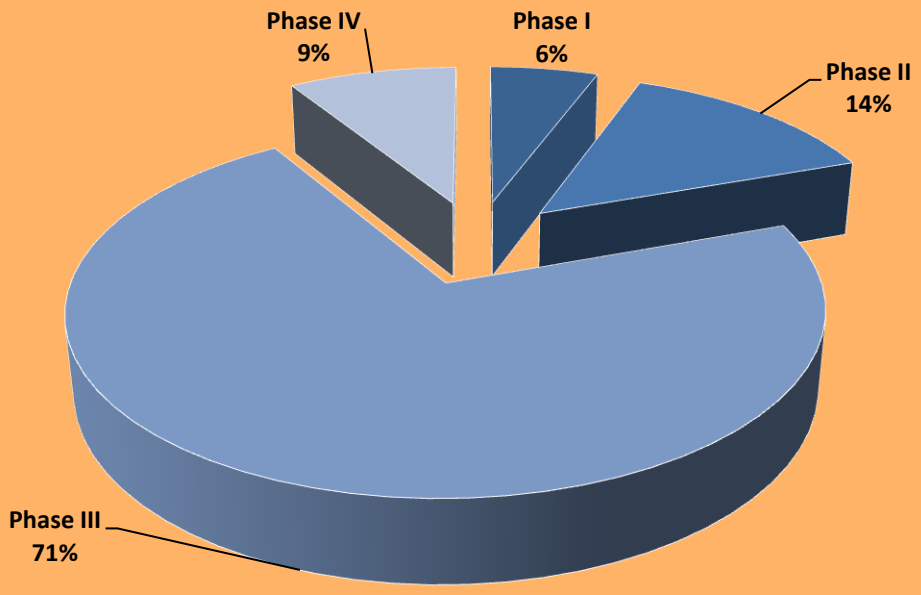
The number of subjects planned to be enrolled in Phase I-IV trials launched in Q1 2017 is 14,195, slightly more than in Q1 2016, when 14,027 subjects were planned to be enrolled.

807 subjects will be recruited in Phase I trials; 1,969 – in Phase II trials; 10,159 – in Phase III studies and 1,216 subjects will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is five, the maximum number is 900.

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 Q1 2017 by Study Phase



The Top Five: Sponsors, Sites and CROs

Table 1. Top-5 International Study Sponsors in Q1 2017

№	*Company Name*	*No. studies*[1]	*No. patients*
1	Novartis	8	499
2	Hetero Labs Limited	5	205
3	Sanofi-Aventis	5	227
4	Janssen	4	305
5	Gilead Sciences, Inc	4	209

Table 2. Top-5 Russian Study Sponsors in Q1 2017

№	*Company Name*	*No. studies*	*No. patients*
1	North Star (Severnaya Zvezda)	7	236
2	Promomed Rus	6	385
3	Pharmasyntez	4	464
4	Medsyntez	4	166
5	CanonPharma Production	4	154

Table 3. Top-5 Russian Research Sites (BE and Phase I studies) in Q1 2017

№	*Site Name*	*City*	*No. studies*
1	Probiotec Medical Center	Moscow Region	14
2	Eco-Bezopasnost Ltd.	Saint-Petersburg	9
3	Bioeq Ltd.	Saint-Petersburg	7
4	Kazan (Privolzhsky) State University	Kazan	5
5	Road Clinical Hospital at the station Yaroslavl of Russian Railways	Yaroslavl	5

[1] Excluding BE studies.

Table 4. Top-5 Russian Research Sites (Phase II-IV studies) in Q1 2017

№	*Site Name*	*City*	*No. studies*
1	Kazan State Medical University	Kazan	19
2	First Moscow State Medical University named after I.M. Sechenov	Moscow	17
3	Russian Oncological Scientific Center named after N.N. Blokhin	Moscow	17
4	First St.Petersburg State Medical University named after I.P. Pavlov	Saint-Petersburg	15
5	North-West State Medical University named after I.I. Mechnikov	Saint-Petersburg	13

Table 5. Top-5 Russian Research Sites (all studies) in Q1 2017

№	*Site Name*	*City*	*No. studies*
1	Kazan State Medical University	Kazan	19
2	Russian Oncological Scientific Center named after N.N. Blokhin	Moscow	18
3	First Moscow State Medical University named after I.M. Sechenov	Moscow	17
4	First St.Petersburg State Medical University named after I.P. Pavlov	Saint-Petersburg	15
5	Probiotec Medical Center	Moscow Region	14

Table 6. Top-CROs in Russia in Q1 2017

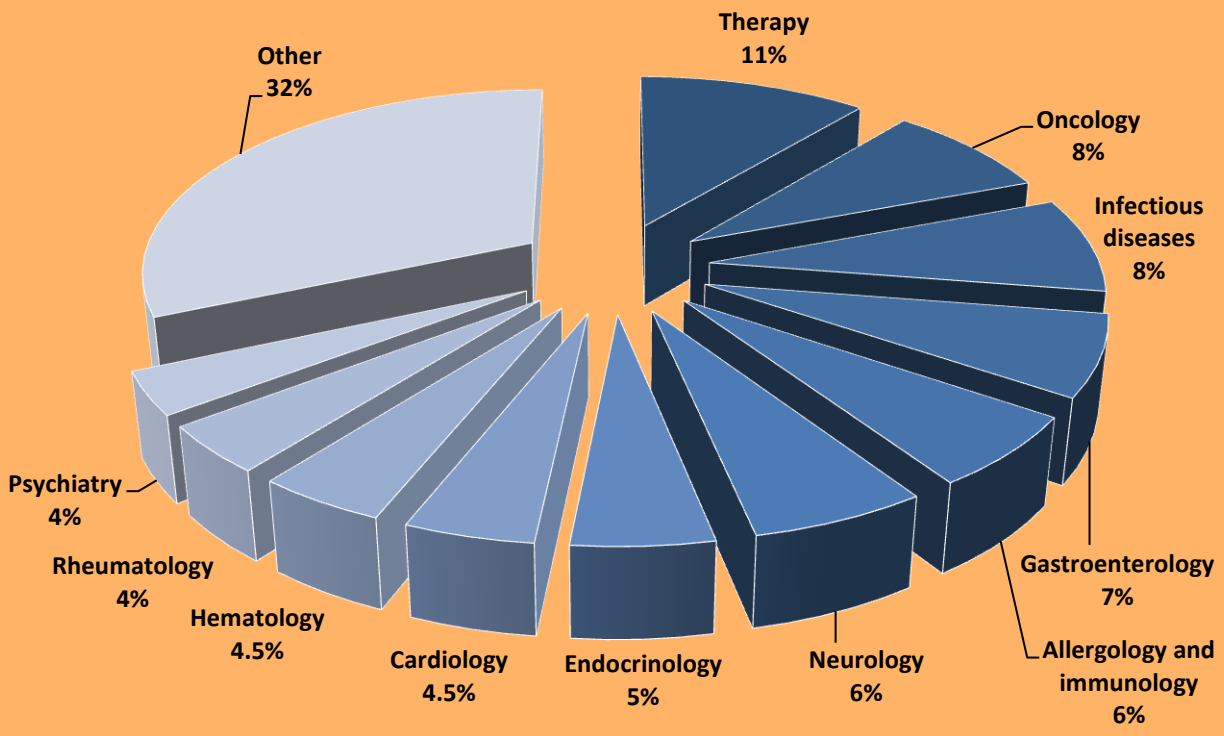
№	*CRO Name*	*No. studies*	*No. patients*
1	Quintiles	7	311
2	Synergy Research Group	6	524
3	Covance Clinical & Periapproval Services Limited	5	349
4	Pharmaceutical Research Associates CIS, LLC	5	239
5	INC Research	4	253

Therapeutic Areas of Russian Clinical Trials in Q1 2017

The largest number of studies were initiated in Therapy (27 studies), and is followed by Oncology and Infectious diseases (20 studies each), Gastroenterology (17 new studies), Allergology and immunology and Neurology (15 studies each), Endocrinology (12 studies), Cardiology, Hematology (11 studies each), Rheumatology (10 studies), and Psychiatry (9 studies).

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

Figure 8. Clinical Trials in Russia in Q1 2017 by Therapeutic Area



Clinical Trials Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 32 new drugs during Q1 2017; nine of them are new molecular entities (NME); other approvals concern new dosages, combinations or manufacturers. Four of 32 drugs were (or are being) studied in clinical trials involving Russian sites.

The **Table 7** shows the drugs which were approved by FDA in Q1 2017 that were (or are being) tested in clinical trials in Russia.

Table 7. New Drugs Approved by FDA in Q1 2017 and Tested in Russian Sites

Appr.date	*Drug (active ingredient)*	*Company*
01/27/2017	Airduo Respiclick (fluticasone propionate / salmeterol xinafoate)	Teva Pharm
01/27/2017	Armonair Respiclick (fluticasone propionate)	Teva Pharm
03/23/2017	Bavencio (avelumab)	EMD Serono Inc
03/28/2017	Dupixent (dupilumab)	Regeneron Pharmaceuticals
		Source: FDA

During Q1 2017, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 18 new drug applications[1], five positive recommendations on new generic medicines, one for new hybrid medicines and two for new biosimilar medicines. Fourteen 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 Q1 2017.

Table 8. New Drugs Approved by EMA in Q1 2017 and Tested in Russian Sites

Appr. date	*Drug (active ingredient)*	*Manufacturer*
01/26/2017	Xeljanz (tofacitinib)	Pfizer Limited
01/26/2017	Tadalafil Lilly (tadalafil)	Eli Lilly Nederland B.V.
01/26/2017	Amgevita (adalimumab)	Amgen Europe B.V.
01/26/2017	Solymbic (adalimumab)	Amgen Europe B.V.
01/26/2017	Revlimid (lenalidomide)	Celgene Europe Limited
01/26/2017	Synjardy (empagliflozin / metformin)	Boehringer Ingelheim GmbH
02/23/2017	Lokelma (sodium zirconium cyclosilicate)	AstraZeneca AB
02/23/2017	Natpar (parathyroid hormone)	Shire Pharmaceuticals Ireland Ltd
02/23/2017	Roteas (edoxaban)	Daiichi Sankyo Europe GmbH
02/23/2017	Darzalex (daratumumab)	Janssen-Cilag International NV
03/23/2017	Refixia (nonacog beta pegol)	Novo Nordisk A/S
03/23/2017	Keytruda (pembrolizumab)	Merck Sharp & Dohme Limited
03/23/2017	Opdivo (nivolumab)	Bristol-Myers Squibb Pharma EEIG
03/23/2017	Zebinix (eslicarbazepine acetate)	Bial - Portela & Cª, S.A.
		Source: EMA

Inspections

FDA inspections

At the moment of the Orange Paper Q1 2017 production no information about FDA inspections conducted in the Russian investigative sites was available.

Roszdravnadzor inspections

According to the Roszdravnadzor quarterly report[2], 8 inspections were conducted in institutions performing preclinical and clinical trials and located in 8 Russian cities during Q1 2017. Violations were found in 4 institutions.

[1] Positive opinions on new generic, hybrid and biosimilar medicines are not included.
[2] http://www.roszdravnadzor.ru/drugs/controllslp/documents/40010

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.