Clinical Trials in Russia
Orange Paper
Annual 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 700 new clinical trials of all types, including local and bioequivalence studies, during 2017. This represents a 22% decrease over 2016.

The main contribution into the total number of studies in 2017 was made by multinational multi-center clinical trials (MMCT), the number of these studies is 291 and it is 9% less than in 2016. The number of bioequivalence studies (BE) decreased from 302 studies in 2016 to 215 in 2017, a 29% decrease from last year's figure. The number of local clinical trials (LCT) significantly (by 30%) decreased from 276 in 2016 to 194 in 2017.

Clinical trials in Russia in 2017 were sponsored by companies from 39 countries. The maximum number of trials (298) were initiated by Russian sponsors. American sponsors with 116 new studies took the runner-up place; they are followed by Swiss sponsors (55 trials), and Indian sponsors (45 trials).

The number of Phase I clinical trials has decreased from 83 studies in 2016 to 46 new studies (45% decrease). The number of Phase II trials has increased from 92 studies in 2016 to 93 new studies (1% increase). The number of Phase III trials decreased from 387 to 312 studies, 19% less than in 2016. The number of Phase IV trials increased in comparison with 2016 from 32 to 34 studies.

The number of subjects planned to be enrolled in Phase I-IV trials launched in 2017 is 55,903, 17% less than 2016 figure, when 67,385 subjects were planned to be enrolled.

Novartis is on the top of the heap of foreign pharmaceutical manufacturers in 2017 by sponsoring 25 new studies. They are followed by *AstraZeneca* and *Merck & Co.,* having 17 new trials each, differentiating in number of patients, *F.Hoffmann-La Roche* with 15 new trials, and *Dr. Reddy's* with 14 new studies in 2017.

Top five domestic pharmaceutical manufacturers by the number of new studies in 2017 is headed by *Biocad,* having 18 new trials. They are followed by *North Star* with 17 new trials, *Microgen* with 14 studies and *Kanonpharma Production* with 13 trials. Top five is concluded by *Pharmasyntez* with 11 studies.

The top five Russian research sites (BE and Phase I studies) in 2017 include: *Medical Center Probiotec* (33 new studies), *Clinical Hospital N2, Yaroslavl region* (25 studies), *Bioeq Ltd.* and *Ecosafety Ltd.* (21 studies each) and *Road Clinical Hospital at the station Yaroslavl of Russian Railways* (17 new studies).

The top Russian research sites (Phase II-IV studies) include: *Russian Oncological Scientific Center named after N.N. Blokhin* (62 studies), *Kazan State Medical University* (54 studies), *First Moscow State Medical University named after I.M. Sechenov* (52 new studies) and *First St. Petersburg State Medical University named after I.P. Pavlov* (47 new studies).

The top five CROs in Russia are: *Quintiles* (27 new studies), *PPD Development* (15 studies), *IPHARMA* and *Pharmaceutical Research Associates CIS* (14 studies each), and *Synergy Research Group* (13 studies).

The top therapeutic areas were: Oncology (99 new studies), Therapy (48 studies), Hematology (47 studies) and Rheumatology and Neurology (42 studies each).

The Center for Drug Evaluation and Research (CDER) of the FDA approved 151 new drugs during 2017, and **30** of them were (or are being) studied in clinical trials conducted in Russia.

During 2017, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 94 new drug applications[1]. **Fifty eight** 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 2017 году Министерством здравоохранения Российской Федерации было выдано 700 разрешений на все виды клинических исследований (КИ), что на 22% меньше, чем за 2016 год.

При этом количество новых международных многоцентровых КИ, инициированных в 2017 году, составило 291, что на 9% меньше по сравнению с прошлым годом. Количество исследований биоэквивалентности уменьшилось на 29% по сравнению с 2016 годом и составило 215 против 302. Количество локальных КИ, проводимых на территории России, значительно (на 30%) уменьшилось по сравнению с 2016 годом и составило 194 исследования против 276.

Спонсорами КИ, разрешенных к проведению в России в 2017 году, выступили компании из 39 стран. На первое место вышли российские производители с 298 КИ, за ними идут американские спонсоры с 116 КИ, Швейцария (55 КИ) и Индия (45 КИ).

В 2017 году было инициировано 46 новых КИ I фазы, что на 45% меньше, чем в 2016 году (83 КИ). Количество исследований II фазы (93 новых исследования) увеличилось на 1% по сравнению с 2016 годом (92 КИ). Количество КИ III фазы уменьшилось с 387 до 312, что на 19% меньше по сравнению с прошлым годом. Количество исследований IV фазы увеличилось по сравнению с 2016 годом с 32 до 34 исследований.

Количество субъектов для участия в исследованиях I-IV фаз в 2017 году составило 55 903, что на 17% меньше, чем в 2016 году, когда планировалось участие 67 385 субъектов.

В 2017 году лидирующую позицию среди иностранных производителей по количеству новых исследований заняла компания *Novartis* с 25 новыми исследованиями. Далее следуют компании *AstraZeneca* и *Merck & Co.,* каждая с 17 новыми исследованиями, но с разным количеством пациентов, *F.Hoffmann-La Roche* с 15 новыми КИ, а также *Dr. Reddy's* с 14 новыми КИ.

Список пяти лидирующих отечественных производителей по количеству новых исследований в 2017 году возглавила компания *Биокад* с 18 исследованиями. Далее следуют компании *Северная Звезда* (17 КИ), *Микроген* (14 КИ), *Канонфарма продакшн* (13 КИ) и *Фармасинтез* (11 КИ).

В пятерку передовиков по исследованиям биоэквивалентности и I фазы в 2017 году вошли следующие центры: *Медицинский центр Пробиотек* (33 новых КИ), *Клиническая больница №2 Ярославской области* (25 новых КИ), *ООО «БиоЭк»* и *ООО «НИЦ Эко-безопасность»* (по 21 КИ) и *Дорожная клиническая больница на ст. Ярославль ОАО «РЖД»* (17 новых КИ).

Лидирующие центры по исследованиям II-IV фаз: *Российский онкологический научный центр имени Н.Н. Блохина* (62 новых исследования), *Казанский государственный медицинский университет* (54 исследования), *Первый Московский государственный медицинский университет им. И.М. Сеченова* (52 КИ), *Первый Санкт-Петербургский государственный медицинский университет им. акад. И.П. Павлова* (47 новых КИ).

Пятерка лидеров среди КИО в России: *Quintiles* (27 новых КИ), *PPD Development* (15 КИ), *ООО «ИФАРМА»* и *Pharmaceutical Research Associates CIS* (по 14 КИ), а также ООО «Синерджи Ресерч Групп» (13 КИ).

Наибольшее количество исследований проведено в следующих областях: онкология – 99, терапия – 48, гематология – 47, ревматология и неврология – по 42 новых КИ.

FDA одобрен в 2017 году 151 новый лекарственный препарат, по **30** из которых в России проводились (или проводятся) КИ. EMA одобрено в 2017 году 94 новых лекарственных препарата, по **58** из которых в России проводились (или проводятся) КИ.

Clinical Trials by Type and Manufacturing Country

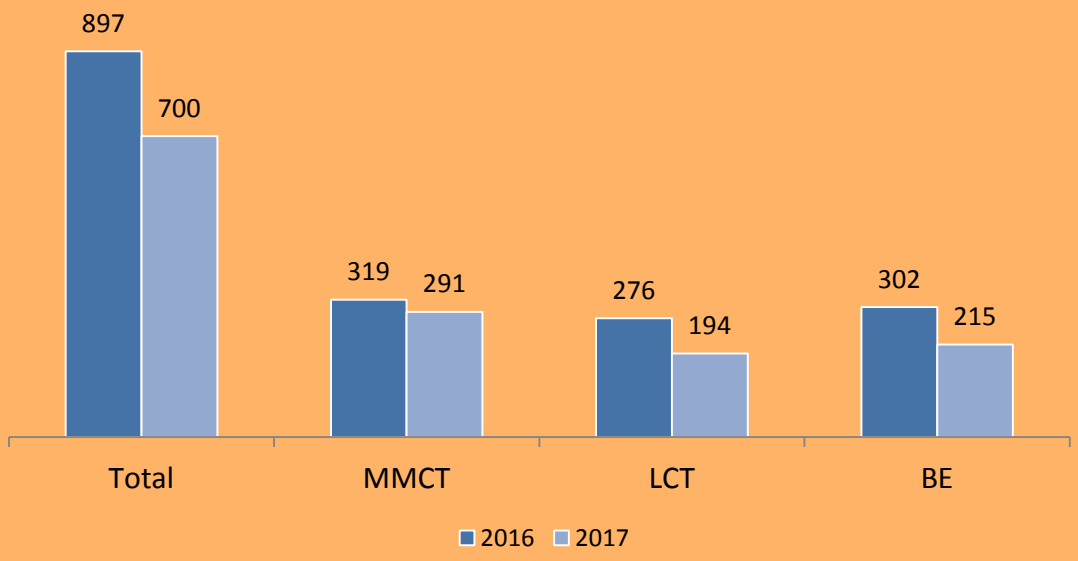
The Russian MoH approved 700 new clinical trials of all types including local and bioequivalence studies during 2017, demonstrating a 22% decrease in comparison with the same point of the last year.

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 has decreased from 319 studies in 2016 to 291 in 2017, a 9% decrease from last year's figure.

The number of bioequivalence studies (BE) decreased from 302 studies in 2016 to 215 in 2017, a 29% decrease from last year's figure.

The number of local clinical trials (LCT) has significantly decreased from 276 in 2016 to 194 in 2017, a 30% decrease from last year's figure.

Figure 1. Clinical Trials in Russia in 2017

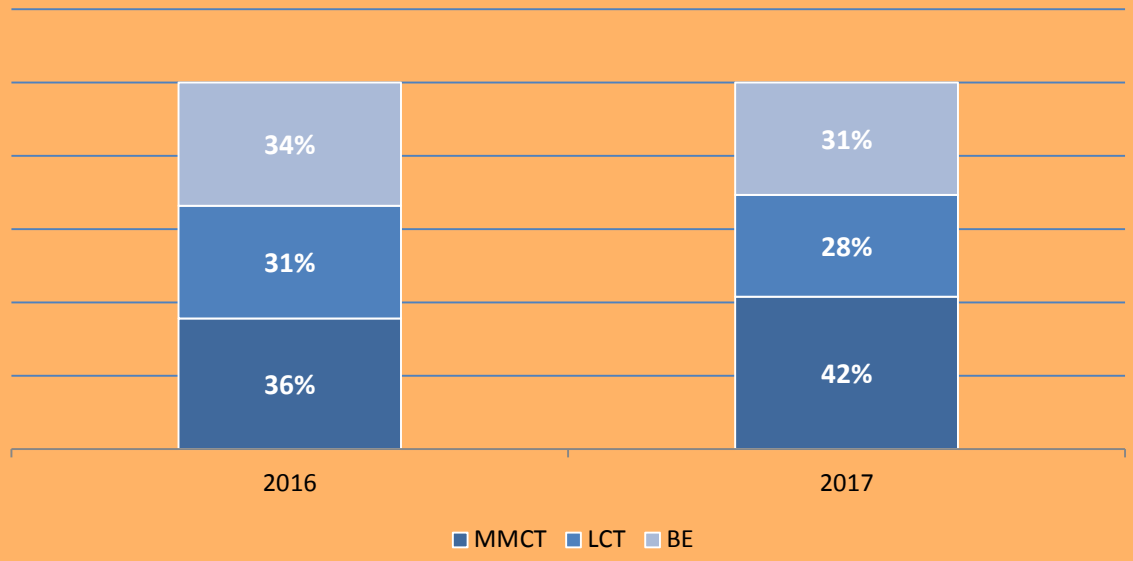


The proportions between different study types (multinational multi-center clinical trials, local clinical trials and bioequivalence studies) changed since last year (see **Figure 2**).

The share of bioequivalence studies decreased from 34% to 31% of the total number of clinical trials approved in 2017.

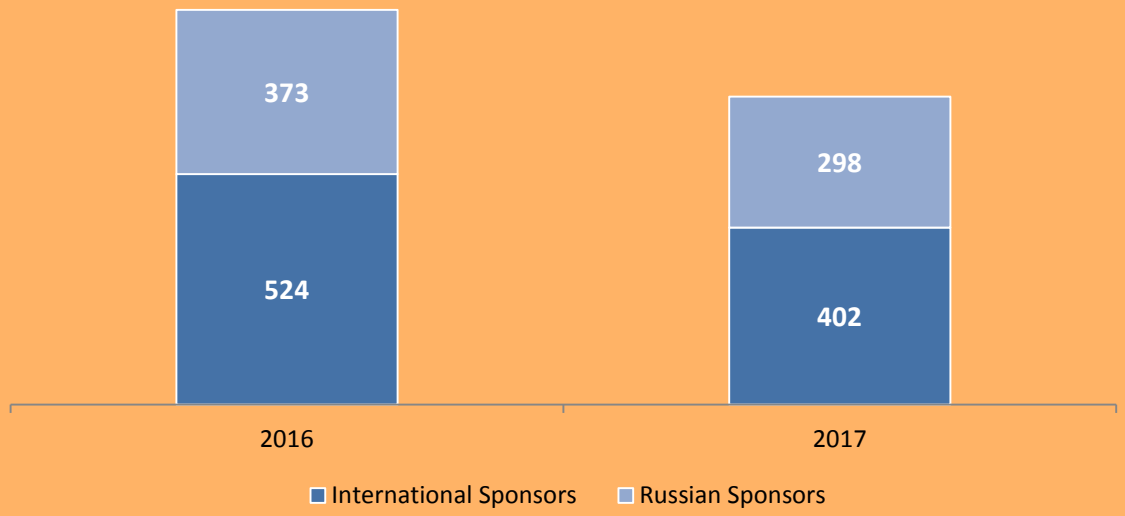
The share of the local clinical trials decreased from 31% in 2016 to 28% in 2017, and the share of multinational multi-center clinical trials was 42% of the total number of trials approved during 2017 (36% in 2016).

Figure 2. Clinical Trials by Type in 2017



The geographic origins of sponsors did not significantly change in comparison with last year. 57% of the total number of new studies in 2017 were sponsored by foreign companies which received 402 study approvals (58% in 2016). The share of studies of local manufacturers increased from 42% in 2016 to 43% in 2017, and amounted to 298 studies (**Figure 3**).

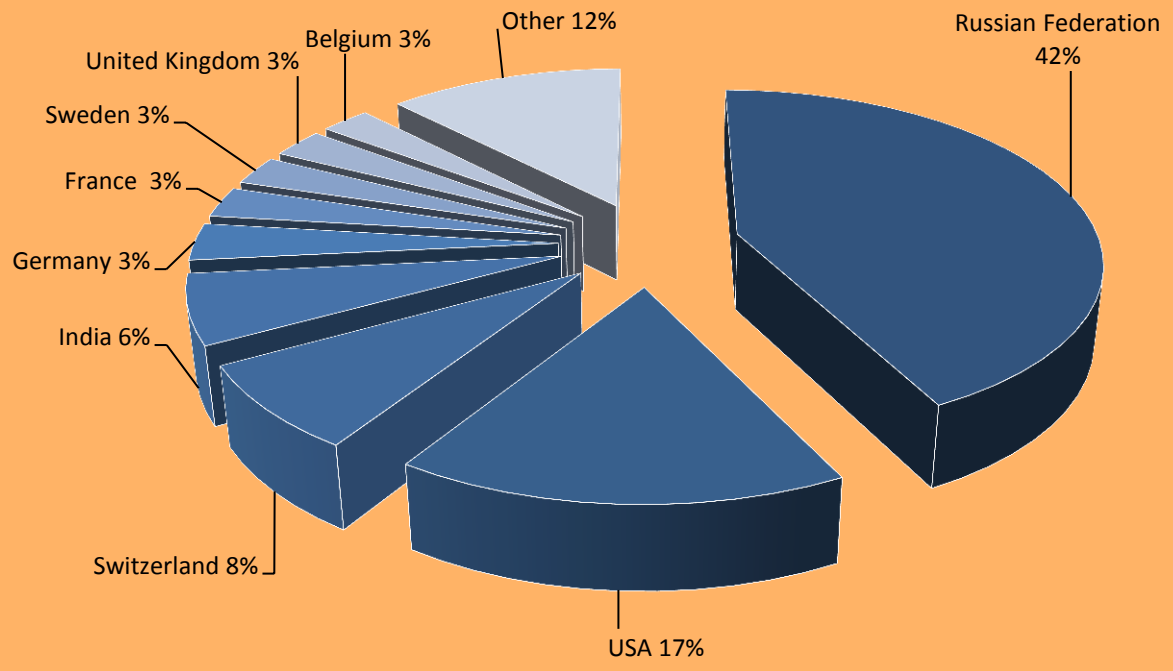
Figure 3. Russian vs International Sponsors in 2017



Clinical trials in Russia in 2017 were sponsored by companies from 39 countries. **Figure 4** indicates the geographic breakdown in sponsors' country of origin.

The maximum number of trials (298) were initiated by Russian sponsors. American sponsors with 116 new studies took the runner-up place; they are followed by Swiss sponsors with 55 new studies, then by Indian sponsors with 45 trials. The group of leaders is concluded by Germany with 24 trials, France with 20 studies, Sweden and United Kingdom (19 studies each).

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



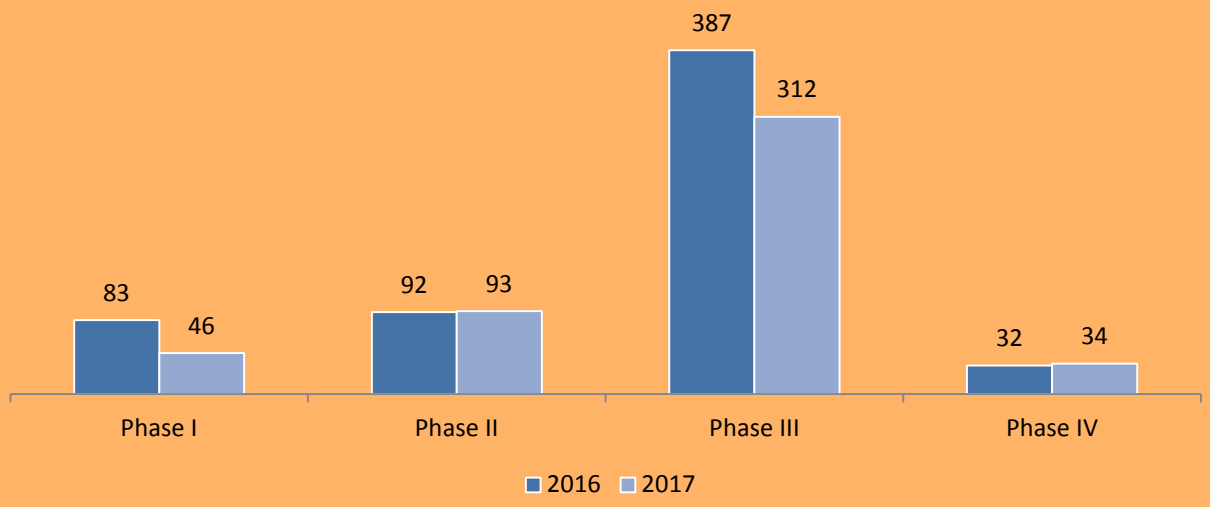
Other sponsors include: Belgium (18 studies), Israel (eight studies), Denmark (seven studies), Netherlands and Austria (six studies each), Italy (five studies), Republic of Belarus, Japan, Poland, Spain, Turkey and Republic of Cyprus (four studies each), Republic of Korea and Republic of Macedonia (three studies each), Iran, Hungary, Croatia, Canada, Portugal, Slovenia and Malta (two studies each), and Republic of Bulgaria, Bosnia and Herzegovina, Czech Republic, Finland, Luxembourg, New Zealand, Republic of Kazakhstan, Ukraine, United Arab Emirates and Jordan, each started one new study in 2017.

Clinical trials by Phase

The number of Phase I clinical trials decreased to 45% compared to 2016: from 83 studies to 46 new studies in 2017. The number of Phase II trials increased to 1% compared to 2016 from 92 studies to 93 new studies (**Figure 5**).

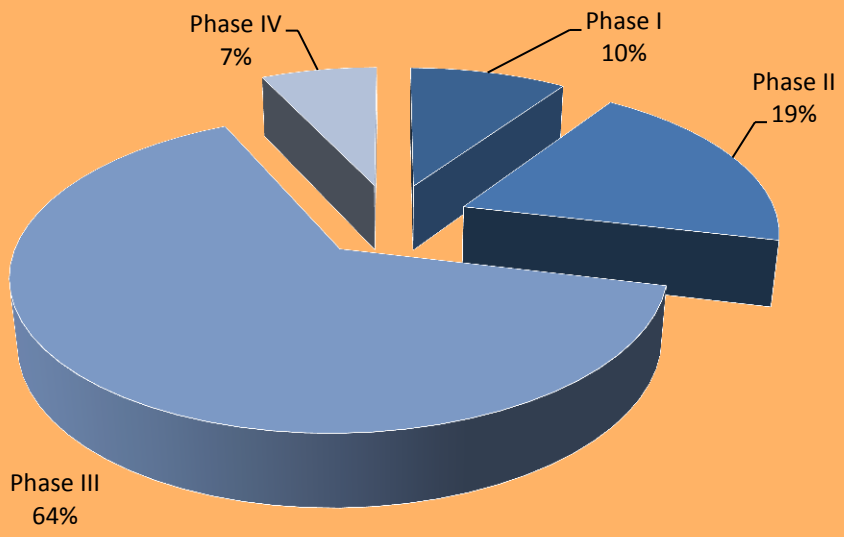
The number of Phase III trials decreased from 387 to 312 studies, 19% less than in 2016. The number of Phase IV trials increased in comparison with 2016 from 32 to 34 studies in 2017 (6% increase).

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



As shown in **Figure 6**, the share of Phase III trials in 2017 is 64% of the total number of studies, the share of Phase I trials is 10%, Phase II trials is 19% and the share of Phase IV studies accounted to 7%.

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.

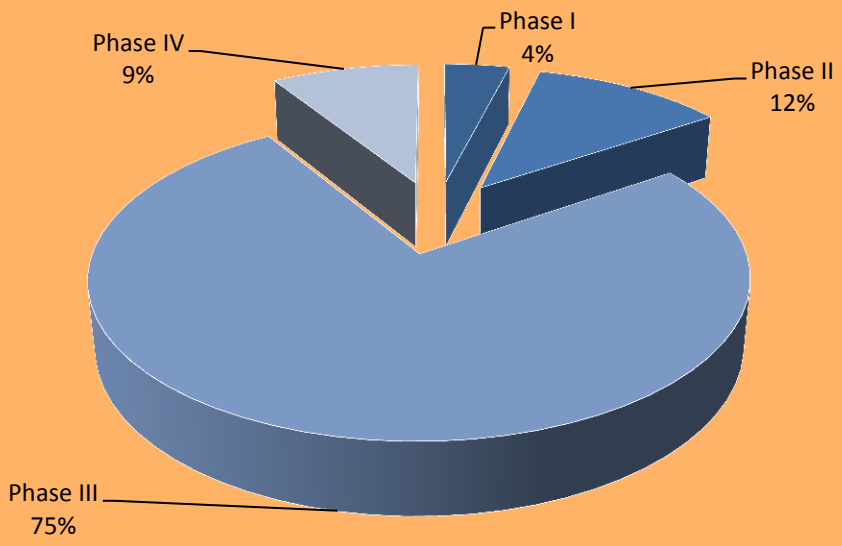
The number of subjects planned to be enrolled in Phase I-IV trials launched in 2017 is 55,903, 17% less than 2016 figure, when 67,385 subjects were planned to be enrolled.

2,191 subjects in Phase I trials; 6,501 – in Phase II trials; 42,230 – in Phase III studies and 4,981 subjects will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is one, the maximum number is 1,100.

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 2017 by Study Phase



The Top Five: Sponsors, Sites and CROs

Table 1. Top-5 International Study Sponsors in 2017

№	*Company Name*	*No. studies*[1]	*No. patients*
1	Novartis	25	2008
2	AstraZeneca	17	4664
3	Merck & Co.	17	1750
4	F.Hoffmann-La Roche	15	796
5	Dr. Reddy's	14	1663

Table 2. Top-5 Russian Study Sponsors in 2017

№	*Company Name*	*No. studies*	*No. patients*
1	Biocad	18	2253
2	North Star	17	670
3	Microgen	14	945
4	Kanonpharma Production	13	480
5	Pharmasyntez	11	1177

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

№	*Site Name*	*City*	*No. studies*
1	Medical Center Probiotec	Serpukhov, Moscow region	33
2	Clinical Hospital N2, Yaroslavl region	Yaroslavl	25
3	Bioeq Ltd.	Saint-Petersburg	21
4	Ecosafety Ltd.	Saint-Petersburg	21
5	Road Clinical Hospital at the station Yaroslavl of Russian Railways	Yaroslavl	17

[1] Excluding BE studies.

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

№	*Site Name*	*City*	*No. studies*
1	Russian Oncological Scientific Center named after N.N. Blokhin	Moscow	62
2	Kazan State Medical University	Kazan	54
3	First Moscow State Medical University named after I.M. Sechenov	Moscow	52
4	First St. Petersburg State Medical University named after I.P. Pavlov	Saint-Petersburg	47
5	Kemerovo Regional Clinical Hospital named after S.V. Belyaev	Kemerovo	35
6	Regional Clinical Oncological Dispensary	Omsk	35

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

№	*Site Name*	*City*	*No. studies*
1	Russian Oncological Scientific Center named after N.N. Blokhin	Moscow	70
2	First Moscow State Medical University named after I.M. Sechenov	Moscow	61
3	Kazan State Medical University	Kazan	55
4	First St. Petersburg State Medical University named after I.P. Pavlov	Saint-Petersburg	48
5	Ecosafety Ltd.	Saint-Petersburg	40

Table 6. Top-CROs in Russia in 2017

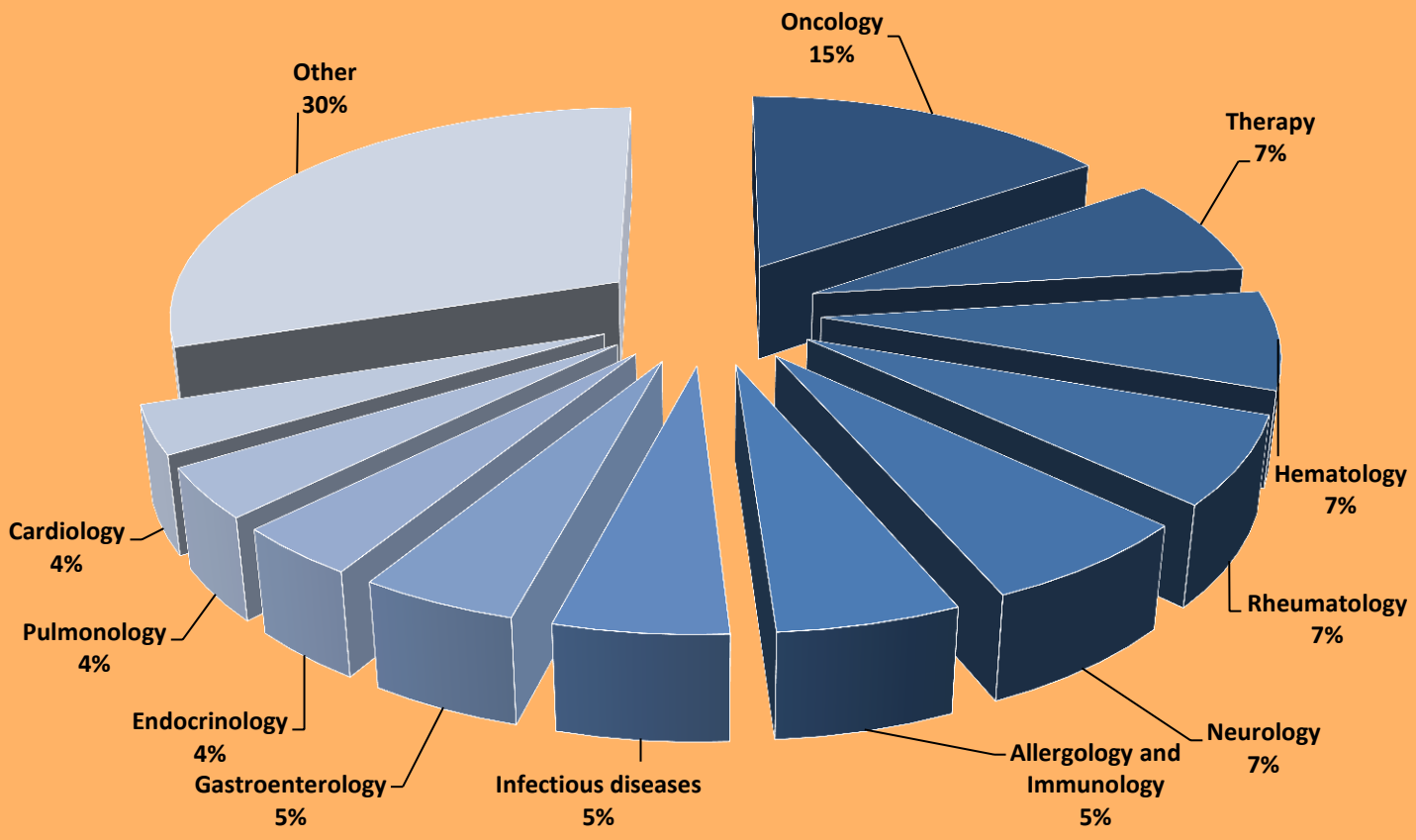
№	*CRO Name*	*No. studies*	*No. patients*
1	Quintiles	27	3008
2	PPD Development	15	1128
3	IPHARMA	14	1241
4	Pharmaceutical Research Associates CIS, LLC	14	872
5	Synergy Research Group	13	1369

Therapeutic Areas of Russian Clinical Trials in 2017

The largest number of studies were initiated in Oncology (99 studies); and is followed by Therapy (48 studies), Hematology (47 studies), Rheumatology and Neurology (42 studies each), Allergology and Immunology (35 studies), Infectious diseases (33 studies), Gastroenterology (30 studies), Endocrinology and Pulmonology (24 studies each), and Cardiology (23 studies).

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

Figure 8. Clinical Trials in Russia in 2017 by Therapeutic Area[1]



[1] More than one therapeutic area could be assigned to a trial

Clinical Trials Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 151 new drugs during 2017; 39 of them are new molecular entities (NME); other approvals concern new dosages, combinations or manufacturers. Thirty of 151 drugs were (or are being) studied in clinical trials involving Russian sites.

The **Table 7** shows the drugs which were approved by FDA in Q4 2017 that were (or are being) tested in clinical trials in Russia.

Table 7. New Drugs Approved by FDA in Q4 2017 and Tested in Russian Sites

Appr.date	*Drug (active ingredient)*	*Company*
10/11/2017	Lyrica CRNDA (pregabalin)	Pfizer Inc
10/20/2017	Bydureon Bcisenda (exenatide)	AstraZeneca AB
11/14/2017	Fasenrabla (benralizumab)	AstraZeneca AB
11/21/2017	Julucanda (dolutegravir sodium/ rilpivirine hydrochloride)	ViiV Healthcare
12/01/2017	Ogivribla (trastuzumab-dkst)	Mylan GmbH
12/05/2017	Ozempicnda (semaglutide)	Novo Nordisk Inc
12/11/2017	Admelognda (insulin lispro)	Sanofi Aventis US
12/13/2017	Ixifibla (infliximab-qbtx)	Pfizer Inc
		Source: FDA

During 2017, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 94 new drug applications[1], 21 positive recommendations on new generic medicines, two for new hybrid medicines and 13 for new biosimilar medicines. A negative opinion was adopted for 12 drugs. Fifty eight 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 Q4 2017.

Table 8. New Drugs Approved by EMA in Q4 2017 and Tested in Russian Sites

Appr. date	*Drug (active ingredient)*	*Manufacturer*
10/12/2017	Alecensa (alectinib)	Roche Registration Limited
10/12/2017	Bydureon (exenatide)	AstraZeneca AB
10/12/2017	Faslodex (fulvestran)	AstraZeneca UK Ltd
10/12/2017	Pegasys (peginterferon alfa-2a)	Roche Registration Limited
11/09/2017	Fasenra (benralizumab)	AstraZeneca AB
11/09/2017	Ocrevus (ocrelizumab)	Roche Registration Limited
11/09/2017	Genvoya (elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide)	Gilead Sciences International Limited

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

11/09/2017	Nplate (romiplostim)	Amgen Europe B.V.
12/14/2017	Ozempic (semaglutide)	Novo Nordisk A/S
12/14/2017	Herzuma (trastuzumab)	Celltrion Healthcare Hungary Kft.
12/14/2017	Taltz (ixekizumab)	Eli Lilly Nederland B.V.
		Source: EMA

Inspections

FDA inspections

According to the FDA data, six FDA inspections were conducted in the Russian investigative sites during the 2017 year: one in Ufa (on 06-Feb-2017), three in Saint Petersburg (on 20-Mar-2017, 24-Apr-2017 and 17-Jul-2017), one in Yaroslavl (on 17-Jul-2017), and one in Ryazan (on 30-Oct-2017). Five inspections ended with NAI result – no action indicated, and one inspection ended with VAI result – voluntary action indicated.

Roszdravnadzor inspections

According to the annual Roszdravnadzor report, 55 inspections were conducted in 36 institutions performing preclinical and clinical trials during 2017.

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.