Clinical Trials in Russia
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Executive Summary – English

The Ministry of Health of the Russian Federation approved 897 new clinical trials of all types, including local and bioequivalence studies, during 2016. This represents a 12% increase over 2015.

The main contribution into the total number of studies in 2016 was made by multinational multi-center clinical trials (MMCT), the number of these studies is 319 and it is 3% more than in 2015. The number of bioequivalence studies (BE) increased from 292 studies in 2015 to 302 in 2016, a 3% increase from last year's figure. The number of local clinical trials (LCT) significantly increased from 200 in 2015 to 276 in 2016.

Clinical trials in Russia in 2016 were sponsored by companies from 39 countries. The maximum number of trials (373) were initiated by Russian sponsors. American sponsors with 138 new studies took the runner-up place; they are followed by Indian sponsors (80 trials), and Swiss sponsors (38 trials).

The number of Phase I clinical trials has increased from 55 studies in 2015 to 83 new studies (51% increase). The number of Phase II trials has increased from 81 studies in 2015 to 92 new studies (14% increase). The number of Phase III trials increased from 352 to 387 studies, 10% more than in 2015. The number of Phase IV trials increased in comparison with 2015 from 22 to 32 studies.

The number of subjects planned to be enrolled in Phase I-IV trials launched in 2016 is 67,385, 31% more than 2015 figure, when 51,338 subjects were planned to be enrolled.

Novartis and *Merck & Co.* are on the top of the heap of foreign pharmaceutical manufacturers in 2016 by sponsoring 20 new studies each, differentiating in number of patients. They are followed by *Bristol-Myers Squibb,* having 15 new trials, and *GlaxoSmithKline* and *Dr. Reddy's*, each with 13 new studies in 2016.

Top five domestic pharmaceutical manufacturers by the number of new studies in 2016 is headed by *Atoll,* having 24 new trials. They are followed by *Biocad* and *Pharmsyntez* with 16 new trials each, differentiating in the number of patients. Top five is concluded by companies *PharmFirma Sotex* and *Kanonpharma Production*, each having 12 new studies.

The top five Russian research sites in 2016 include: *Russian Oncological Scientific Center named after N.N. Blokhin* (90 new studies), *Kazan State Medical University* (82 studies), *First St. Petersburg State Medical University named after I.P. Pavlov* (76 studies), *First Moscow State Medical University named after I.M. Sechenov* (75 studies) and *EcoSafety Ltd.* (56 new studies).

The top five CROs in Russia are: *Quintiles* (30 new studies), *PPD Development* (16 studies), *OCT Rus* and *Parexel* (12 studies each), and *Pharmaceutical Research Associates CIS* (11 studies).

In this issue we decided to make **two new ratings**: Top 10 investigated diseases in 2016 and Studies by ICD-10 classification, 2015-2016.

The top investigated diseases in 2016 include: Asthma (21 studies), Seropositive rheumatoid arthritis (15 studies), Type 2 diabetes mellitus (12 studies), Multiple sclerosis and Gonarthrosis [arthrosis of knee] (10 studies each).

The top therapeutic areas were: Oncology (114 new studies), Neurology (67 studies), Therapy (53 studies), Rheumatology (50 studies) and Infectious diseases (49 studies).

The Center for Drug Evaluation and Research (CDER) of the FDA approved 103 new drugs during 2016, and **27** of them were (or are being) studied in clinical trials conducted in Russia.

During 2016, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 105 new drug applications[1]. **Seventy one** 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 2016 году Министерством здравоохранения Российской Федерации было выдано 897 разрешений на все виды клинических исследований (КИ), что на 12% больше, чем за 2015 год.

При этом количество новых международных многоцентровых КИ, инициированных в 2016 году, составило 319, что на 3% больше по сравнению с прошлым годом. Количество исследований биоэквивалентности увеличилось на 3% по сравнению с 2015 годом и составило 302 против 292. Количество локальных КИ, проводимых на территории России, значительно увеличилось по сравнению с 2015 годом и составило 276 исследований против 200.

Спонсорами КИ, разрешенных к проведению в России в 2016 году, выступили компании из 39 стран. На первое место вышли российские производители с 373 КИ, за ними идут американские спонсоры с 138 КИ, Индия (80 КИ) и Швейцария (38 КИ).

В 2016 году было инициировано 83 новых КИ I фазы, что на 51% больше, чем в 2015 году (55 КИ). Количество исследований II фазы (92 новых исследования) увеличилось на 14% по сравнению с 2015 годом (81 КИ). Количество КИ III фазы увеличилось с 352 до 387, что на 10% больше по сравнению с прошлым годом. Количество исследований IV фазы увеличилось по сравнению с 2015 годом с 22 до 32 исследований.

Количество субъектов для участия в исследованиях I-IV фаз в 2016 году составило 67 385, что на 31% больше, чем в 2015 году, когда планировалось участие 51 338 субъектов.

В 2016 году лидирующие позиции среди иностранных производителей по количеству новых исследований заняли компании *Novartis* и *Merck & Co.,* каждая с 20 новыми исследованиями, но с разным количеством пациентов. Далее следуют компании *Bristol-Myers Squibb* с 15 новыми КИ, а также *GlaxoSmithKline* и *Dr. Reddy's*, каждая с 13 новыми КИ.

Список пяти лидирующих отечественных производителей по количеству новых исследований в 2016 году возглавила компания *Атолл* с 24 исследованиями. Далее следуют компании *Биокад* и *Фармсинтез* (16 исследований каждая), а затем компании *Сотекс* и *Канонфарма продакшн* (12 исследований каждая).

В пятерку передовиков по исследованиям в 2016 году вошли следующие центры: *Российский онкологический научный центр имени Н.Н. Блохина* (90 новых исследований), *Казанский государственный медицинский университет* (82 исследования), *Первый Санкт-Петербургский государственный медицинский университет им. акад. И.П. Павлова* (76 новых КИ), *Первый Московский государственный медицинский университет им. И.М. Сеченова* (75 КИ) и *ООО «НИЦ Эко-безопасность»* (56 КИ).

Пятерка лидеров среди КИО в России: *Quintiles* (30 новых КИ), *PPD Development* (16 КИ), *OCT Rus* и *Parexel* (по 12 КИ), *Pharmaceutical Research Associates CIS* (11 КИ).

В этом выпуске мы составили **два новых рейтинга**: Десятка наиболее часто изучаемых заболеваний в 2016 году и Классификация исследований по МКБ-10 в 2015-2016.

В список лидирующих исследуемых заболеваний в 2016 году вошли следующие нозологии: астма (21 исследование), серопозитивный ревматоидный артрит (15 КИ), сахарный диабет 2 типа (12 КИ), рассеянный склероз и артроз коленного сустава (по 10 КИ).

Наибольшее количество исследований проведено в следующих областях: онкология – 114, неврология – 67, терапия – 53, ревматология – 50 и инфекционные заболевания – 49 новых КИ.

FDA одобрено в 2016 году 103 новых лекарственных препарата, по **27** из которых в России проводились (или проводятся) КИ. EMA одобрено в 2016 году 105 новых лекарственных препаратов, по **71** из которых в России проводились (или проводятся) КИ.

Clinical Trials by Type and Manufacturing Country

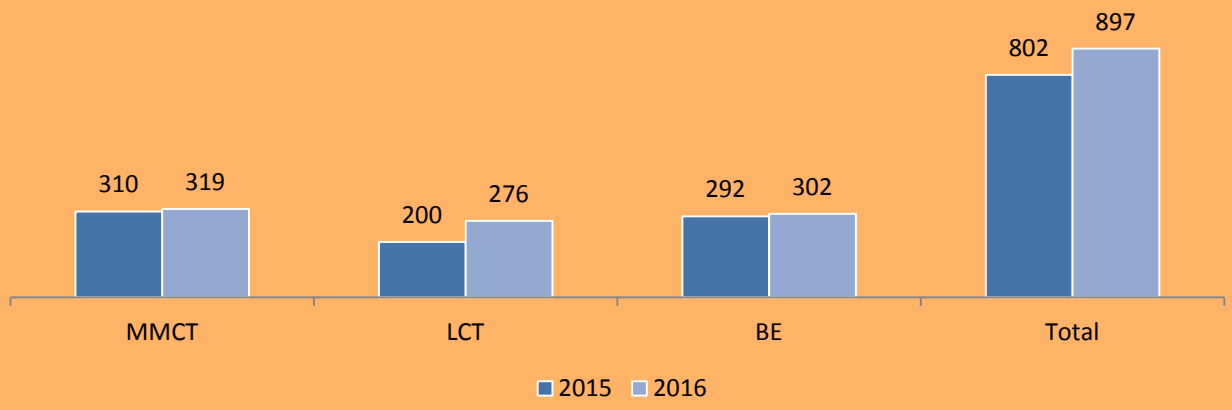
The Russian MoH approved 897 new clinical trials of all types including local and bioequivalence studies during 2016, demonstrating a 12% increase in comparison with the same point of the last year.

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 increased from 310 studies in 2015 to 319 in 2016, a 3% increase from last year's figure.

The number of bioequivalence studies (BE) increased from 292 studies in 2015 to 302 in 2016, a 3% increase from last year's figure.

The number of local clinical trials (LCT) has significantly increased from 200 in 2015 to 276 in 2016, a 38% increase from last year's figure.

Figure 1. Clinical Trials in Russia in 2016

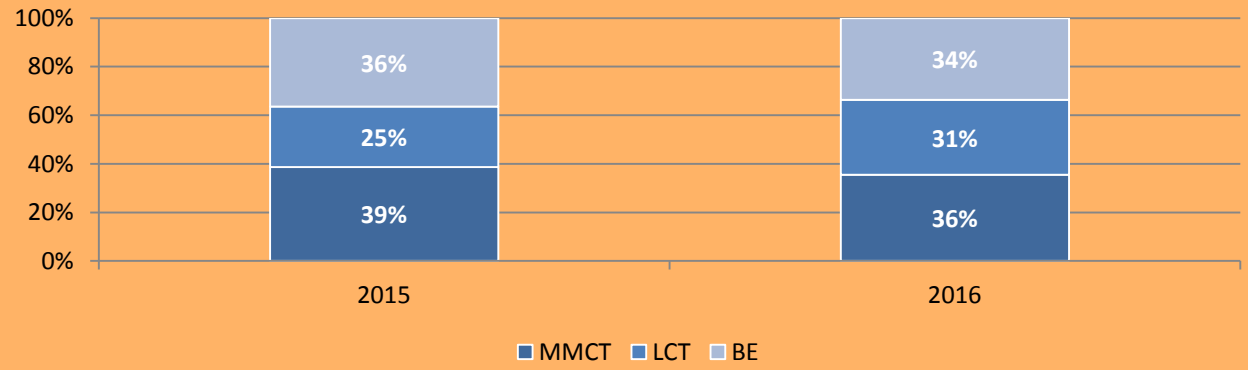


The proportions between different study types (multinational multi-center clinical trials, local clinical trials and bioequivalence studies) changed since last year (see **Figure 2**).

The share of bioequivalence studies decreased from 36% to 34% of the total number of clinical trials approved in 2016.

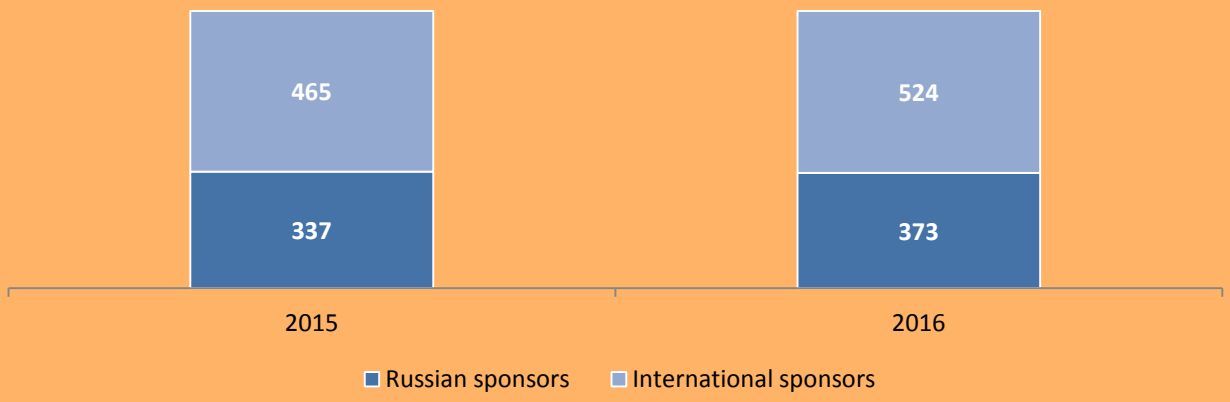
The share of the local clinical trials increased from 25% in 2015 to 31% in 2016, and the share of multinational multi-center clinical trials was 36% of the total number of trials approved during 2016 (39% in 2015).

Figure 2. Clinical Trials by Type in 2016



The geographic origins of sponsors did not significantly change in comparison with last year. 58% of the total number of new studies in 2016 were sponsored by foreign companies which received 524 study approvals (58% in 2015). The share of studies of local manufacturers was 42% both in 2015 and 2016, and amounted to 373 studies in 2016 (**Figure 3**).

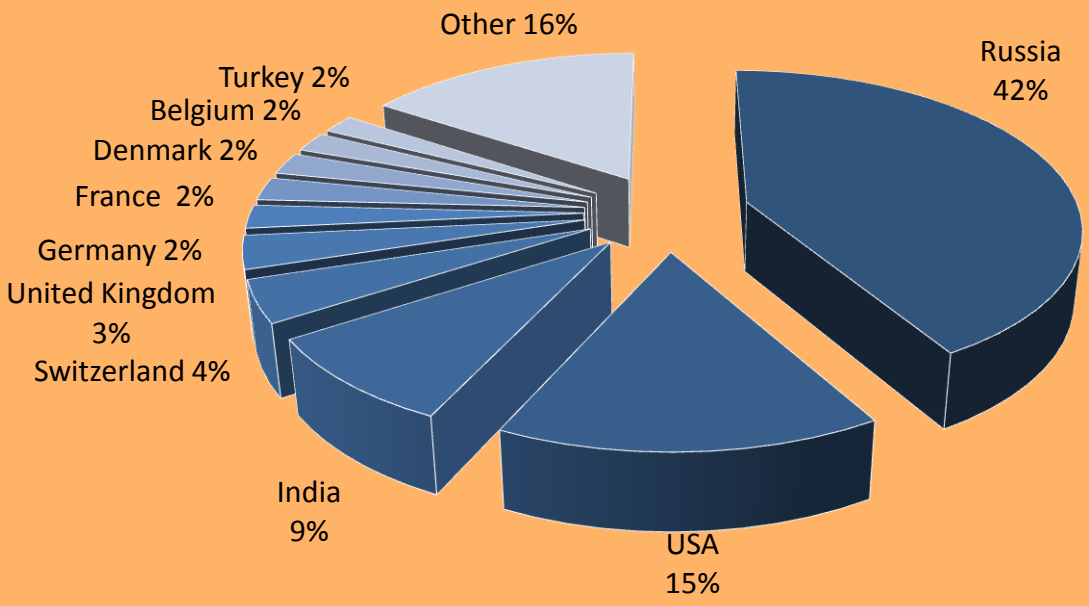
Figure 3. Russian vs International Sponsors in 2016



Clinical trials in Russia in 2016 were sponsored by companies from 39 countries. **Figure 4** indicates the geographic breakdown in sponsors' country of origin.

The maximum number of trials (373) were initiated by Russian sponsors. American sponsors with 138 new studies took the runner-up place; they are followed by Indian sponsors with 80 trials, then by Swiss sponsors with 38 new studies. The group of leaders is concluded by United Kingdom with 30 trials, France and Germany, each having 21 studies, and Danish Sponsors (20 studies).

Figure 4. Sponsors' Country of Origin for 2016 Clinical Trials in Russia



Other sponsors include: Belgium (18 studies), Turkey (17 studies), Poland (15 studies), Hungary and Israel (11 studies each), Austria and Sweden (10 studies each), Slovenia (eight studies),

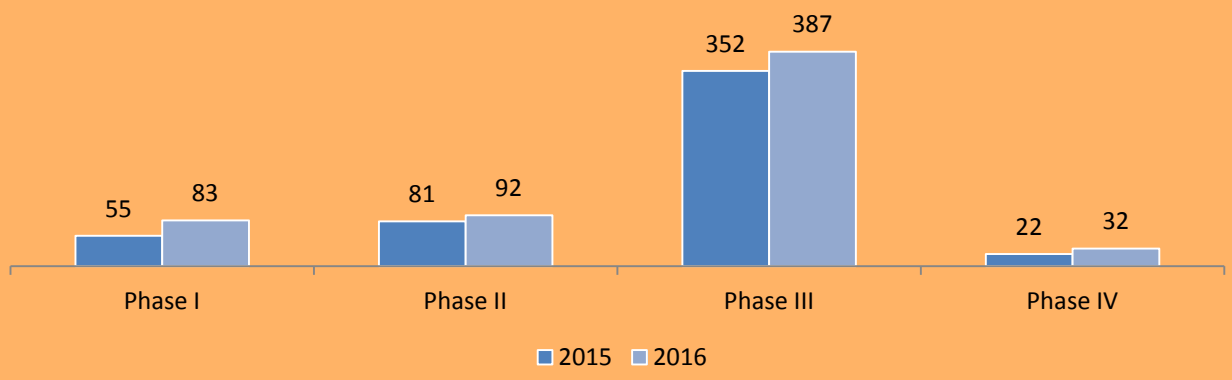
Spain, Italy, Republic of Cyprus, Netherlands (six studies each), Republic of Korea and Czech Republic (five studies each), Romania, Republic of Bulgaria, Croatia, Republic of Belarus, Republic of Macedonia, Ukraine (four studies each), Iceland (three studies), United Arab Emirates, Jordan, Republic of Moldova, China, Latvia (two studies each), and Finland, Brazil, Luxembourg, Japan and Taiwan, each started one new study in 2016.

Clinical trials by Phase

The number of Phase I clinical trials increased to 51% compared to 2015: from 55 studies to 83 new studies in 2016. The number of Phase II trials increased to 14% compared to 2015 from 81 studies to 92 new studies (**Figure 5**).

The number of Phase III trials increased from 352 to 387 studies, 10% more than in 2015. The number of Phase IV trials increased in comparison with 2015 from 22 to 32 studies in 2016 (45% increase).

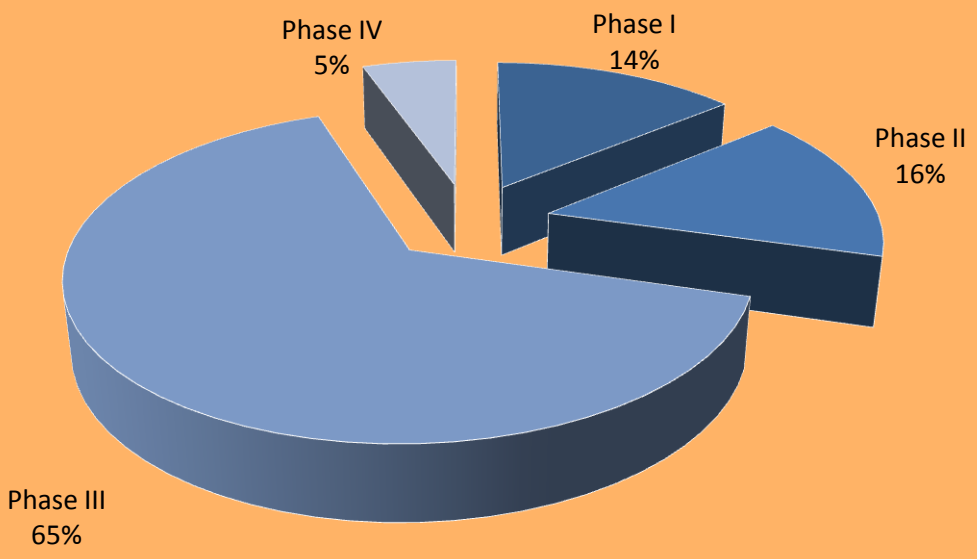
Figure 5. Clinical Trials in Russia in 2016 by Phase[1]



As shown in **Figure 6**, the share of Phase III trials in 2016 is 65% of the total number of studies, the share of Phase I trials is 14%, Phase II trials is 16% and the share of Phase IV studies accounted to 5%.

[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.

Figure 6. Percentage Breakdown of Russian Clinical Trials by Phase



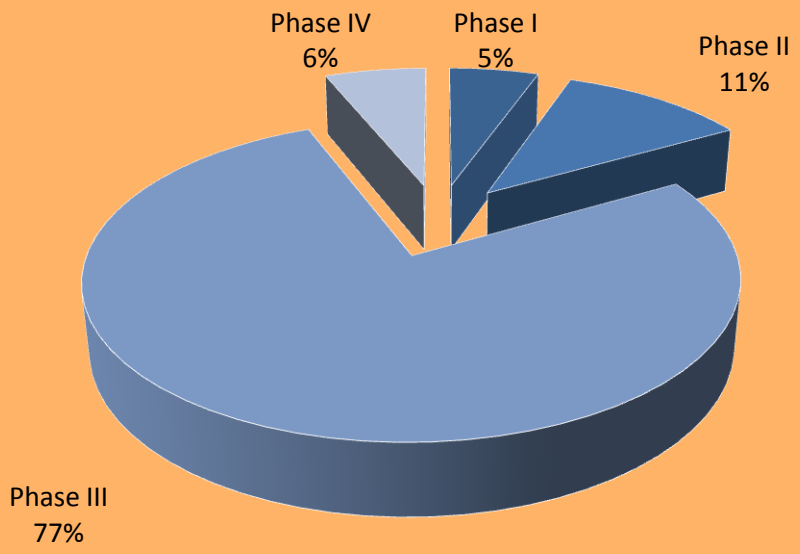
The number of subjects planned to be enrolled in Phase I-IV trials launched in 2016 is 67,385, 31% more than in 2015, when 51,338 subjects were planned to be enrolled.

3,655 subjects in Phase I trials; 7,655 – in Phase II trials; 51,924 – in Phase III studies and 4,151 subjects will be enrolled in Phase IV studies.

The minimal number of subjects in a single study is two, the maximum number is 1,910.

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 2016 by Study Phase



The Top Five: Sponsors, Sites and CROs

Table 1. Top-5 International Study Sponsors in 2016

№	*Company Name*	*No. studies*[1]	*No. patients*
1	Novartis	20	3504
2	Merck & Co.	20	2720
3	Bristol-Myers Squibb	15	437
4	GlaxoSmithKline	13	2186
5	Dr. Reddy's	13	1503

Table 2. Top-5 Russian Study Sponsors in 2016

№	*Company Name*	*No. studies*	*No. patients*
1	Atoll	24	1030
2	Biocad	16	1327
3	Pharmsyntez	16	1121
4	PharmFirma Sotex	12	1202
5	Kanonpharma Production	12	588

Table 3. Top-5 Russian Research Sites in 2016

№	*Site Name*	*City*	*No. studies*
1	N.N. Blokhin Russian Oncological Scientific Center	Moscow	90
2	Kazan State Medical University	Kazan	82
3	I.P. Pavlov First St.Petersburg State Medical University	Saint-Petersburg	76
4	I.M. Sechenov First Moscow State Medical University	Moscow	75
5	EcoSafety Ltd.	Saint-Petersburg	56

[1] Excluding BE studies.

Table 4. Top-CROs in Russia in 2016

№	*CRO Name*	*No. studies*
1	Quintiles	30
2	PPD Development	16
3	OCT Rus	12
4	Parexel	12
5	Pharmaceutical Research Associates CIS	11

Therapeutic Areas of Russian Clinical Trials in 2016

The largest number of studies were initiated in Oncology (114 studies); and is followed by Neurology (67 studies), Therapy (53 studies), Rheumatology (50 studies), Infectious diseases (49 studies), Pulmonology (40 studies), Hematology (35 studies), Allergology and immunology (32 studies) and Gastroenterology (31 studies).

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

Figure 8. Clinical Trials in Russia in 2016 by Therapeutic Area

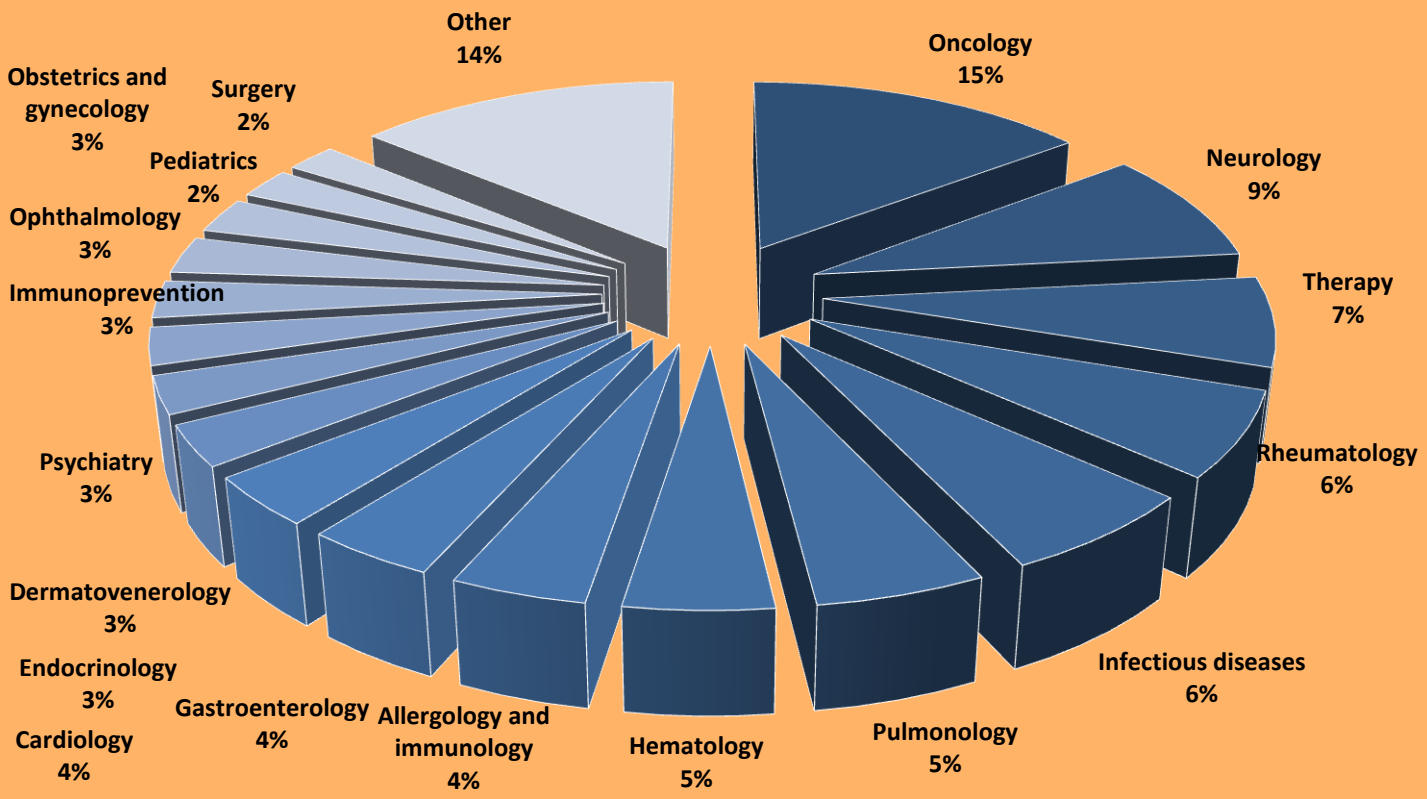


Table 5. Top 10 Investigated Diseases in 2016

№	*ICD-10 Name*	*No. Studies*	*No. Patients*
1	Asthma	21	3410
2	Seropositive rheumatoid arthritis	15	2219
3	Type 2 diabetes mellitus	12	1732
4	Multiple sclerosis	10	1433
5	Gonarthrosis [arthrosis of knee]	10	1320
6	Influenza due to other identified influenza virus	7	1174
7	Heart failure	4	1160
8	Malignant neoplasm of bronchus and lung	12	1130
9	Malignant neoplasm of breast	11	1126
10	Acute upper respiratory infections of multiple and unspecified sites	4	1117

Table 6. Studies by ICD-10 classification, 2015-2016

ICD-10 classification	*2015*		*2016*	
	No. Studies	*No. Patients*	*No. Studies*	*No. Patients*
Neoplasms	196	10432	116	6986
Diseases of the musculoskeletal system and connective tissue	77	8013	79	9835
Diseases of the respiratory system	69	11871	66	11627
Diseases of the genitourinary system	24	2973	37	5691
Certain infectious and parasitic diseases	42	4434	33	3658
Diseases of the nervous system	32	2950	32	3324
Endocrine, nutritional and metabolic diseases	31	3294	30	3672
Diseases of the digestive system	26	2477	28	2747
Diseases of the circulatory system	21	3824	25	4905
Mental and behavioural disorders	16	1959	23	2529
Diseases of the skin and subcutaneous tissue	14	1072	22	2046
Diseases of the blood and blood-forming organs and certain disorders involving the immune mechanism	17	705	21	1080
Diseases of the eye and adnexa	18	1791	19	2400
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	12	1117	8	715

Injury, poisoning and certain other consequences of external causes	7	298	7	658
Factors influencing health status and contact with health services	7	875	5	850
External causes of morbidity and mortality			3	501
Diseases of the ear and mastoid process	1	60	2	560
Pregnancy, childbirth and the puerperium	1	270	1	65
Certain conditions originating in the perinatal period			1	20
Congenital malformations, deformations and chromosomal abnormalities	1	80		

Clinical Trials Results

The Center for Drug Evaluation and Research (CDER) of the FDA approved 103 new drugs during 2016; 18 of them are new molecular entities (NME); other approvals concern new dosages, combinations or manufacturers. Twenty seven of 103 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 2016 that were (or are being) tested in clinical trials in Russia.

Table 7. New Drugs Approved by FDA in Q4 2016 and Tested in Russian Sites

Appr.date	*Drug (active ingredient)*	*Company*
10/19/2016	Lartruvo (olaratumab)	Eli Lilly and Co
04/11/2016	Selzentry (maraviroc)	Viiv Healthcare
10/11/2016	Vemlidy (tenofovir alafenamide fumarate)	Gilead Sciences Inc
11/21/2016	Xultophy 100/3.6 (insulin degludec; liraglutide)	Novo Nordisk Inc
11/21/2016	Soliqua 100/33 (insulin glargine; lixisenatide)	Sanofi-Aventis Us
09/12/2016	Synjardy XR (empagliflozin; metformin hydrochloride)	Boehringer Ingelheim
		Source: FDA

During 2016, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 105 new drug applications[1], 20 positive recommendations on new generic medicines, five for new hybrid medicines and seven for new biosimilar medicines. A negative opinion was adopted for three drugs. Seventy one 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 2016.

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

Table 8. New Drugs Approved by EMA in Q4 2016 and Tested in Russian Sites

Appr. date	*Drug (active ingredient)*	*Manufacturer*
13/10/2016	Venclyxto (venetoclax)	AbbVie Ltd.
13/10/2016	Opdivo (nivolumab)	Bristol-Myers Squibb Pharma EEIG
13/10/2016	Zebinix (eslicarbazepine acetate)	BIAL - Portela & Ca, S.A.
11/10/2016	Fiasp (insulin aspart)	Novo Nordisk A/S
11/10/2016	Vemlidy (tenofovir alafenamide)	Gilead Sciences International Ltd
11/10/2016	Arzerra (ofatumumab)	Novartis Europharm Ltd
11/10/2016	Caprelsa (vandetanib)	Genzyme Europe BV
11/10/2016	Humira (adalimumab)	AbbVie Ltd
11/10/2016	Vimpat (lacosamide)	UCB Pharma S.A.
12/15/2016	Alecensa (alectinib)	Roche Registration Limited
12/15/2016	Lifmior (etanercept)	Pfizer Limited
12/15/2016	Olumiant (baricitinib)	Eli Lilly Nederland B.V.
12/15/2016	Ilaris (canakinumab)	Novartis Europharm Ltd
12/15/2016	Jardiance (empagliflozin)	Boehringer Ingelheim International GmbH
12/15/2016	Jentadueto (linagliptin/metformin)	Boehringer Ingelheim International GmbH
12/15/2016	Keytruda (pembrolizumab)	Merck Sharp & Dohme Limited
12/15/2016	Tivicay (dolutegravir)	ViiV Healthcare UK Limited
12/15/2016	Trajenta (linagliptin)	Boehringer Ingelheim International GmbH
12/15/2016	Votubia (everolimus)	Novartis Europharm Ltd
		Source: EMA

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.