



SYNERGY
ORANGE
PAPER

RESEARCH REPORT

CLINICAL TRIALS IN RUSSIA

2018 FALL

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FOREWORD

The Orange Paper is a free publication produced by Synergy Research Group for the pharmaceutical industry since 2007. It pulls together data from numerous public sources into a single brief document to aid decision makers planning to conduct clinical trials. It is produced quarterly, with an annual summary at the close of each year.



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EXECUTIVE SUMMARY

The Ministry of Health of the Russian Federation approved the initiation of 184 new clinical trials of all types in Russia, including local and bioequivalence studies with an overall year on year growth rate of 17% by number of studies.

The dominant type of clinical trials conducted in Russian sites was MMCT with 46% market share and with a year on year growth rate of 30% (from 65 studies in Q3 2017 to 85 studies in Q3 2018). The most prevalent phase of clinical trials conducted in Russian sites by number of studies was Phase III.

There is a significant level of oligopoly within the Russian Clinical trials market – whereby the top five international sponsors conduct 18% of the total number of studies conducted in this quarter and 27% of all of patients enrolled in these trials. The combined market share of top five Russian Sponsors is approximately 11% of total number of studies conducted in this quarter and 22% of all of patients enrolled in these trials. So in fact the ten largest pharmaceutical companies together account for 29% of all clinical trials conducted in Russia by number of studies and 49% of patients enrolled in these studies.

During Q3 2018 the Center for Drug Evaluation and Research (CDER) of the FDA approved 13 new drugs as new molecular entities (NME); Four of these 13 drugs were tested in clinical trials involving Russian sites.

Top domestic pharmaceutical manufacturers are *Materia Medica, Gamaleya Research Institute, Biocad, Medsyntez and Nanotek*.

The top-5 International Sponsors in Russia are: *IQVIA, Parexel, iPharma, PPD and Synergy Research Group*.

Three top tech trends in the Pharmaceuticals industry in Q3 2018 were:

- Improving quality of Patient Relationship with patient-faced services like Medication Adherence apps, Telemedicine services and In-Home Diagnostic devices;
- Improving quality, speed and cost-efficiency in clinical trials with Risk Management solutions, Study Data Analysis tools and Study Compliance systems;
- Improving speed and cost-efficiency in Clinical Practice of Healthcare Providers with AI-powered automated Diagnostic tools and voice-powered Physician's Assistant tools.





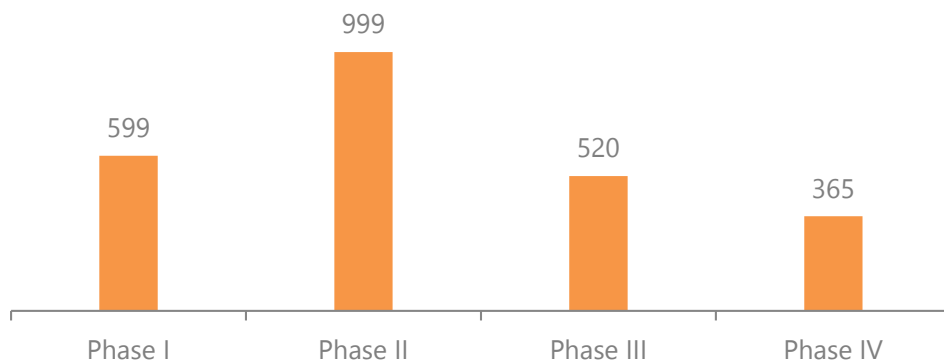
WORLDWIDE CLINICAL TRIALS

Trial Data

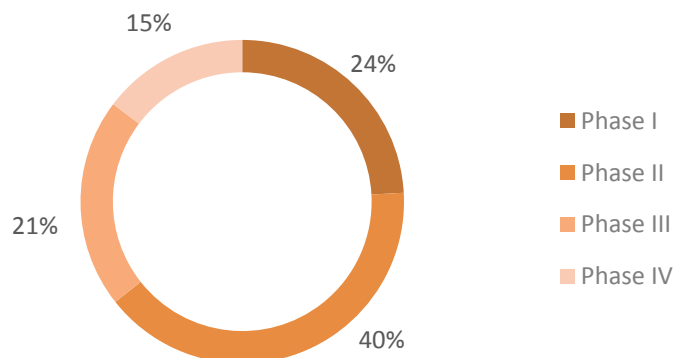
During Q3 2018 the official FDA website showed approvals for initiation of 6,396 new clinical trials of all types worldwide, including local and bioequivalence studies with an overall year on year growth rate of 19% driven in large by an increasing number of trials in developing countries.

Interventional study types identified as Phase (I- IV) were confirmed for 2,483 clinical trials. The most prevalent phase of clinical trials on a global scale was Phase II. The combined market share of USA and European countries reached 57% by the number of initiated studies; Russia accounts for only 3% of the global clinical trials market. Interventional clinical trials are the dominant type of research with 82% market share.

Breakdown of global clinical trials by Phase



Percentage breakdown of global clinical trials by Phase

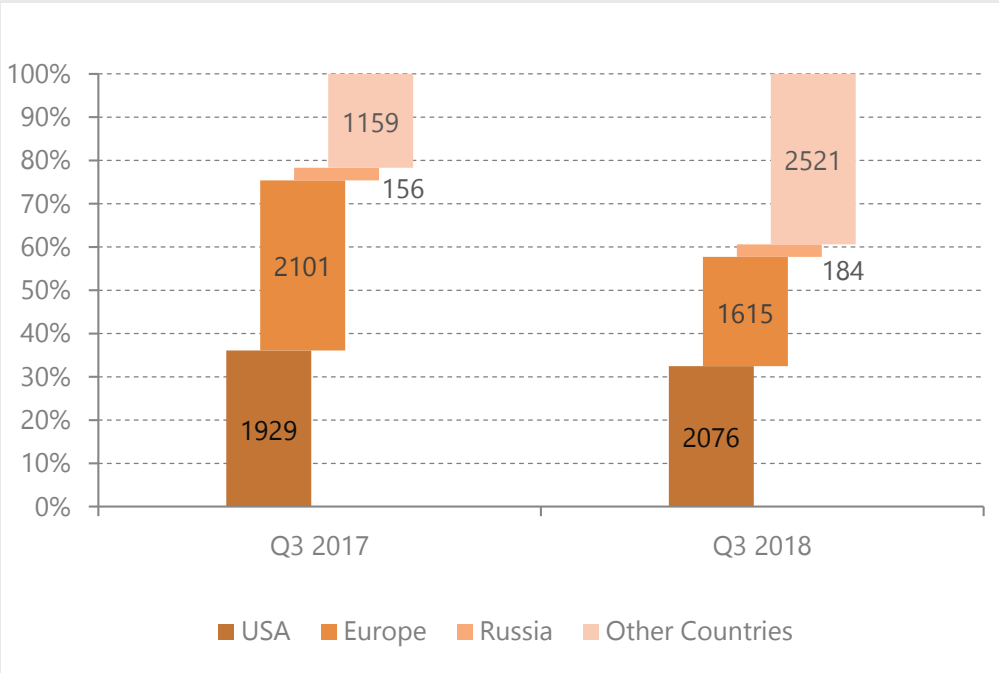




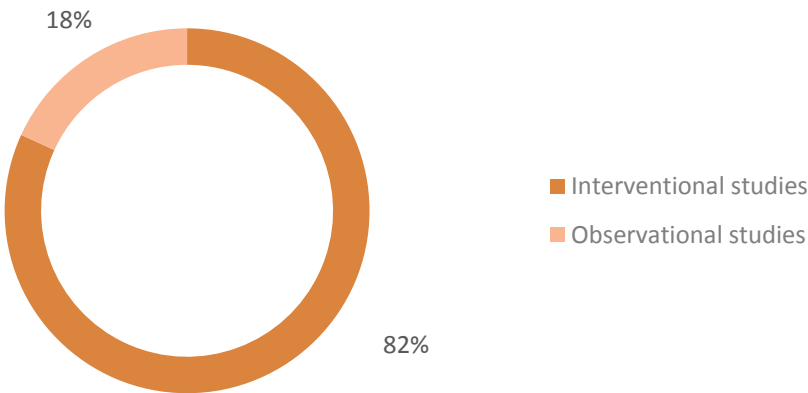
Breakdown by region of origin

The proportions between different regions (USA, Europe, Russia, Other Countries) for trials conducted in Q3 2018 changed in comparison to Q3 2017.

The share of Clinical Trials conducted in Russia stayed at 3% in comparison with Q3 2017.



Breakdown of global Clinical Trials by Type

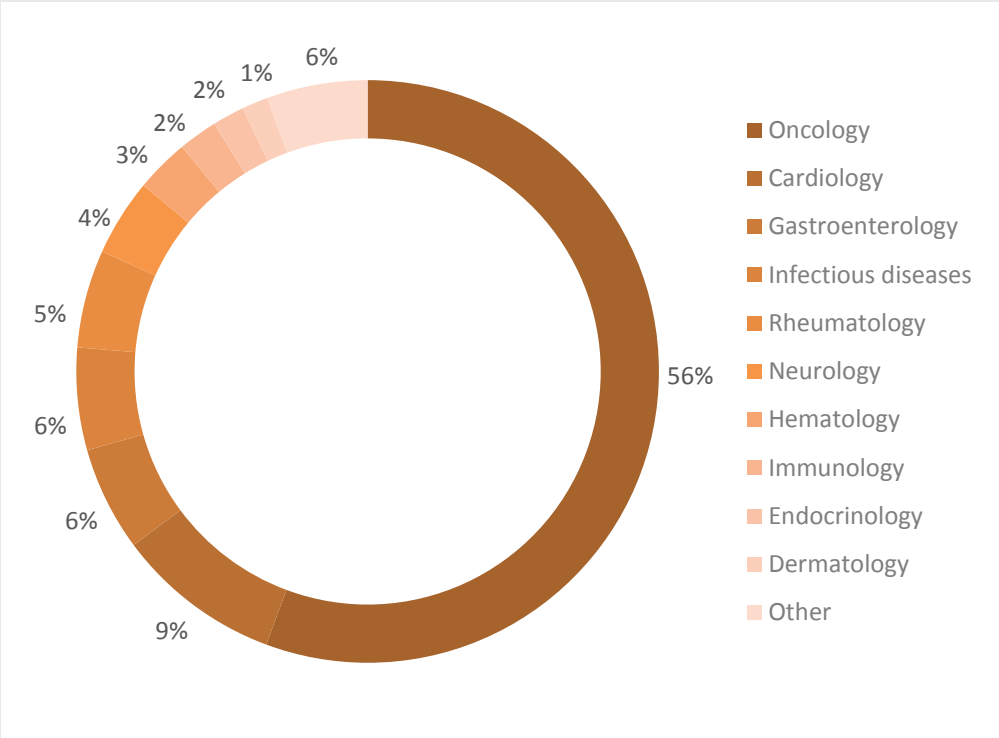




Therapeutic areas of clinical trials worldwide

The largest number of studies were initiated in Oncology (1382 studies), Cardiology (228 studies), Gastroenterology (144), Infectious diseases (141) and Rheumatology (135 studies).

More than one therapeutic area could be assigned to a trial. BE studies were not included in any therapeutic area group.





WORLDWIDE CLINICAL TRIALS

Sponsor Data

“Team members” comprising the TOP-TEN global sponsors of clinical trials worldwide has remained static for the past 5 years – this fact may be explained by the substantial and continuously rising amounts of investments required for research and development of new drugs.

It’s remarkable that the combined market power of these leading pharmaceutical corporations is about 10% of the patient population engaged in interventional clinical trials where a study phase has been identified.

Nº	Company Name	No. studies	No. patients
1	Novartis	32	7 033
2	Pfizer	23	3 302
3	Hoffman-La Roche	21	15 129
4	Abbvie	16	4 765
5	Merck	14	8 998
6	GlaxoSmithKline	14	13 045
7	Janssen	12	1 010
8	Eli Lilly	11	3 164
9	Boehringer Ingelheim	11	654
10	AstraZeneca	11	6 032
Combined market share of top-10 companies		3%	10%





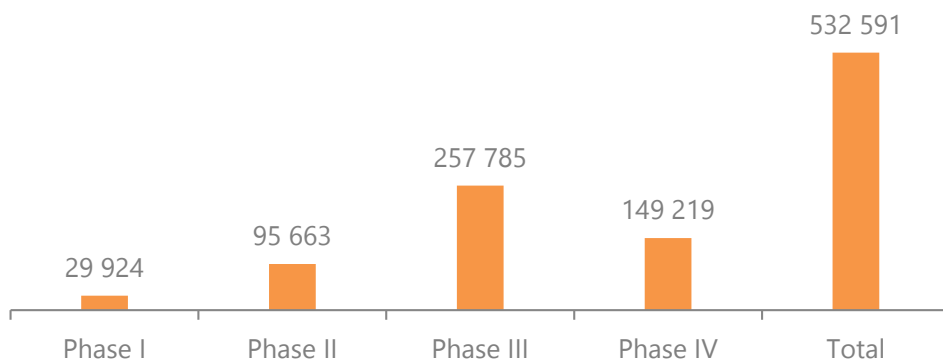
WORLDWIDE CLINICAL TRIALS

Patient Data

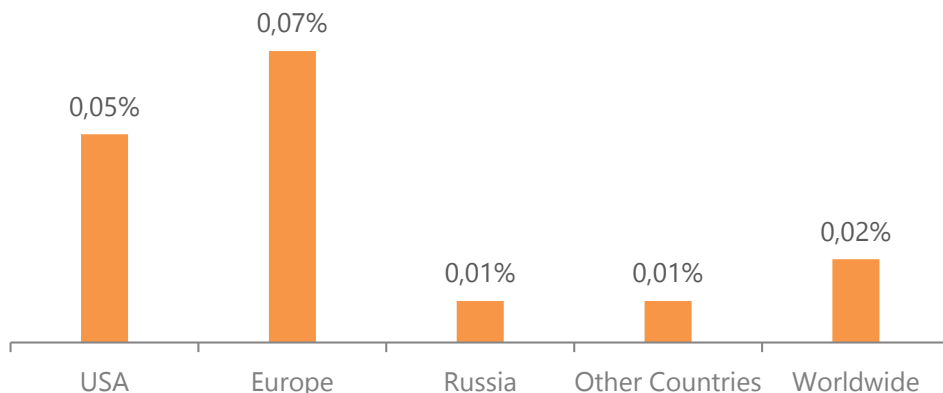
The worldwide population of patients enrolled in clinical trials of all types in Q3 2018 reached 1.2 million people. Six hundred thousand of these patients are enrolled in interventional trials with an identified study phase (I – IV). The majority of patients are enrolled in Phase III trials, with the largest growth in global patient population being in Europe.

However, the share of patients participating in clinical trials remains extremely low in comparison with the overall size of population – approximately 0,02% Worldwide and 0,01% in Russia. The prevalent therapeutic areas of clinical trials worldwide are Oncology and Cardiology.

Number of patients enrolled worldwide by Phase



Breakdown of Number of Patients Enrolled as a % of Population



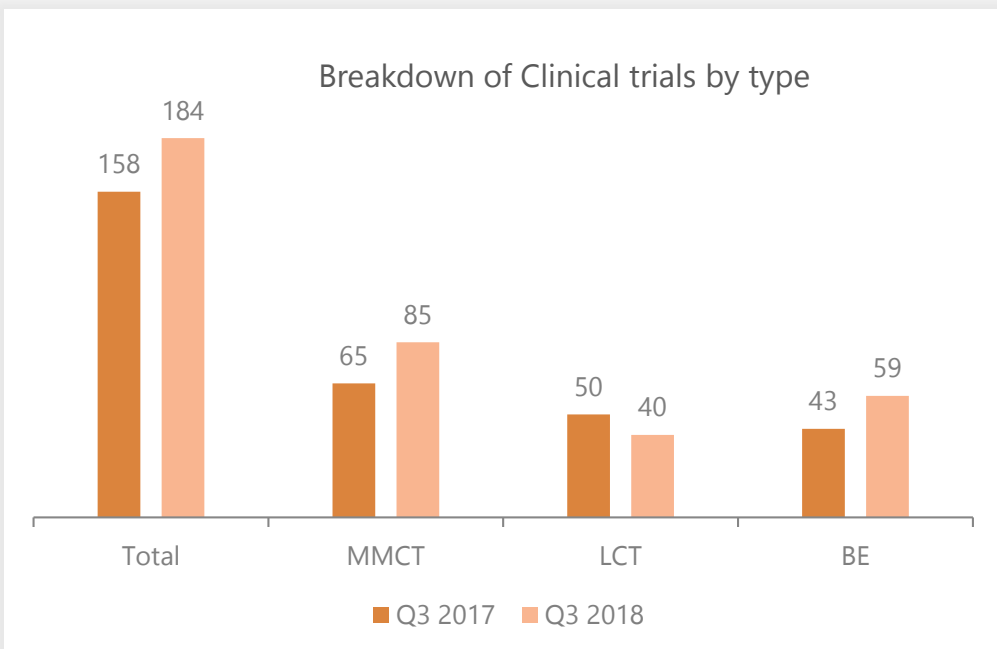


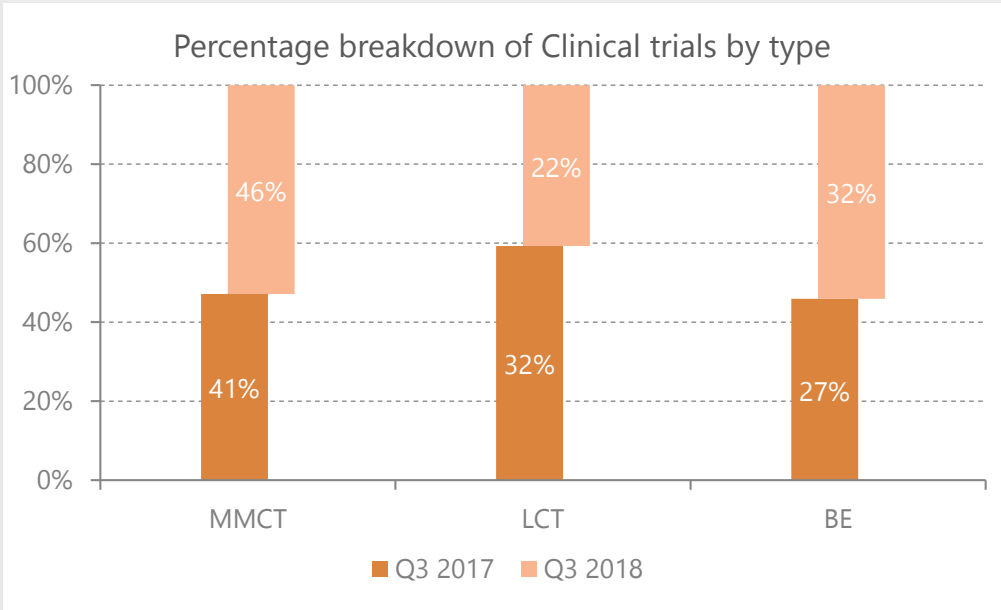
CLINICAL TRIALS IN RUSSIA

Trial Data

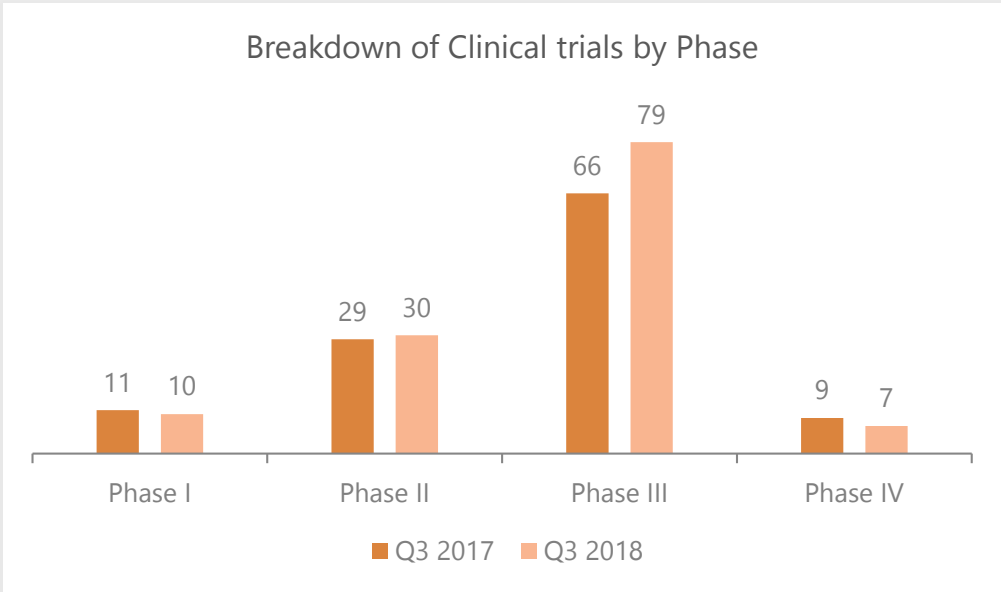
During Q3 2018 the Russian Ministry of Health approved the initiation of 184 new clinical trials of all types in Russia, including local and bioequivalence studies with an overall year on year growth rate of 17%. The most prevalent type of clinical trials conducted across Russian sites was MMCT (multinational multi-center clinical trials) with 46% market share and with a year on year growth rate of 30% (from 65 studies in Q3 2017 to 85 studies in Q3 2018).

The number of bioequivalence clinical trials also increased with a 32% market share and a year on year growth rate of 37% (from 43 studies in Q2 2017 to 59 studies in Q3 2018). The number of local clinical trials declined with 22% market share and a year on year reduction to 20% (from 50 studies in 2017 to 40 studies in Q3 2018).



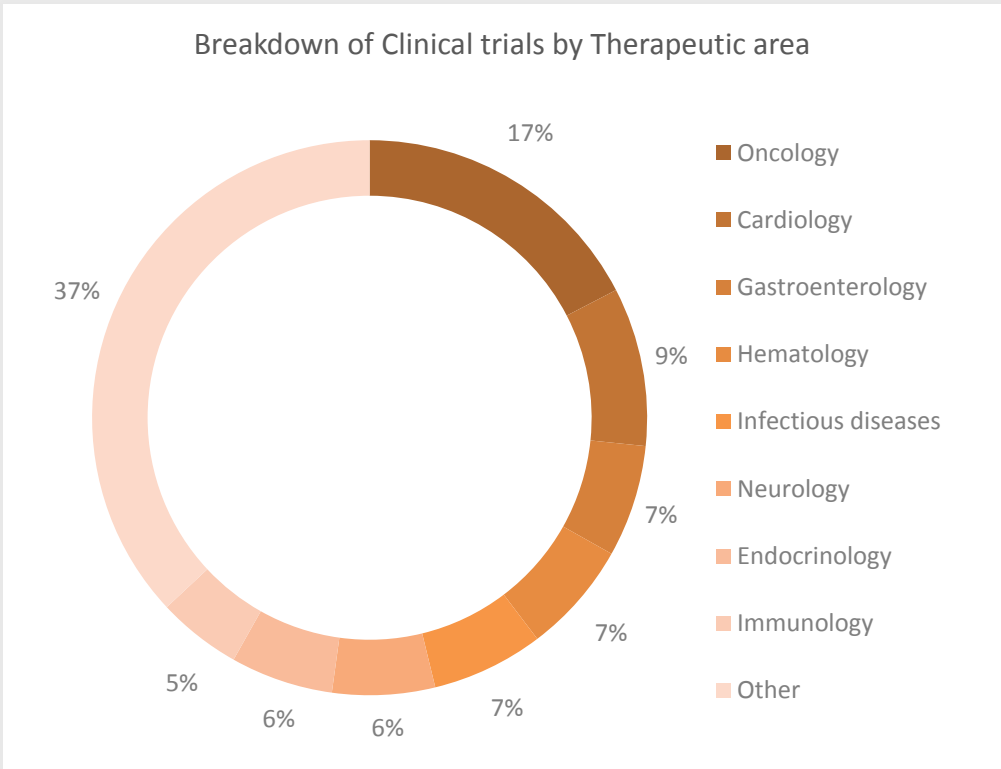


The most prevalent phase of clinical trials conducted across Russian sites by number of studies was Phase III. The number of Phase III trials increased from 66 in Q3 2017 to 79 in Q3 2018.



The largest number of clinical trials initiated in Russia in Q3 2018 were related to Oncology (32 studies), Cardiology (17 studies), Gastroenterology, Hematology and Infectious Diseases (12 studies each). Other popular areas include Neurology, Endocrinology (11 studies each), and Immunology (9 studies).

More than one therapeutic area could be assigned to a trial. BE studies were not included in any therapeutic area group.





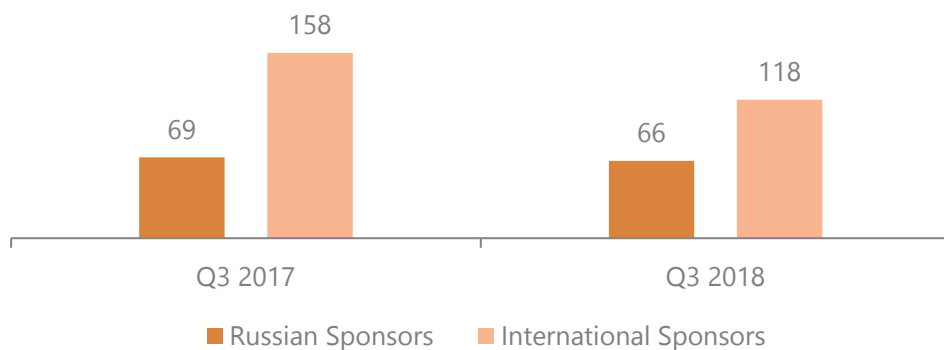
CLINICAL TRIALS IN RUSSIA

Sponsor Data

Clinical trials initiated in Russia in Q3 2018 were sponsored by pharmaceutical companies from 25 countries. The most prevalent sponsor's country of origin were Russia (66 studies), USA (32 studies) and Switzerland (21 studies).

The market share of international pharmaceutical companies in the Russian clinical trials market strengthened with a year on year growth rate of 20% (from 44% in Q3 2017 to 64% in Q3 2018) – due in part to an increasing number of clinical trials initiated with multi-national sponsors with a year on year growth rate of 33% (from 89 studies in Q3 2017 to 118 studies in Q3 2018).

Breakdown of Clinical trials by sponsor origin



Percentage breakdown of trials by sponsor origin

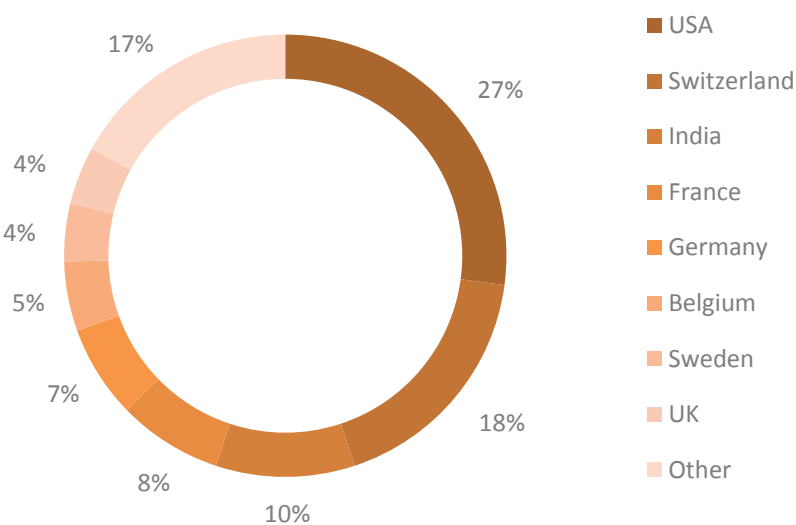


64% of clinical trials in Russia were conducted by International sponsors in Q3 2018, in comparison with 44% in Q3 2017.

66 of the trials were initiated by Russian sponsors. American sponsors with 32 new studies took the runner-up place; they are followed by Swiss sponsors with 21 trials, then by Indian sponsors with 12 new studies, then French (9 studies) and German sponsors (eight studies). The group of leaders is concluded by Belgium (six studies), Sweden and United Kingdom (five studies each).



International Sponsors' country of origin for Q3 2018



TOP-5 International Trial Sponsors in Q3 2018

Nº	Company Name	No. studies	No. patients
1	AstraZeneca	4	1 250
2	Merck & Co.	5	1 070
3	CSL Behring LLC	1	999
4	Dr. Reddy's Laboratories	1	650
5	Novartis	12	633
Combined market share of these companies		18%	27%

TOP-5 Russian Trial Sponsors in Q3 2018

Nº	Company Name	No. studies	No. patients
1	Materia Medica Holding	4	1 338
2	Gamaleya Research Institute of Epidemiology and Microbiology	3	877
3	Biocad	3	638
4	Medsyntez	3	595
5	Nanotek	1	305
Combined market share of these companies		11%	22%

Bio-Equivalence (BE) studies were not included in this ranking table.



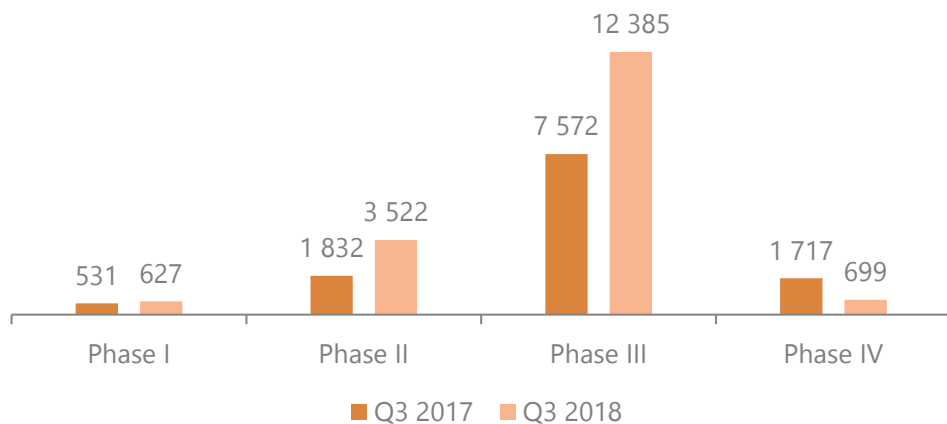


CLINICAL TRIALS IN RUSSIA

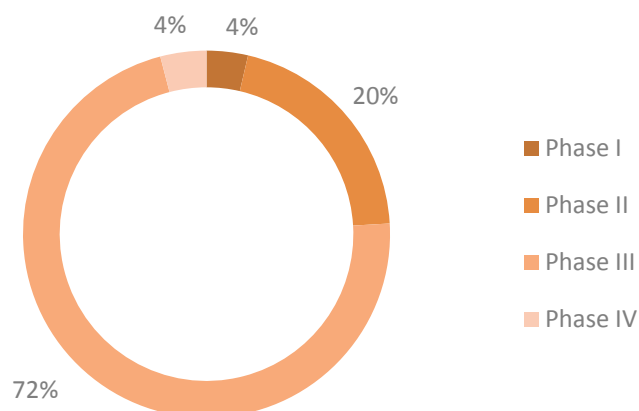
Patient Data

The overall number of patients involved in clinical trials initiated in Russia in Q3 2018 reached 17,233 people. However, this remains extremely low in comparison with the overall size of Russia's population – approximately 0,01% of the population in Russia participate in any type of clinical trial. The most prevalent phase of clinical trials by the number of participating patients is Phase III.

Breakdown of number of patients enrolled by Phase



Percentage breakdown of number of patients by phase



Study Phase	Minimum	Maximum
BE	20	144
Phase I	20	101
Phase II	4	777
Phase III	7	999
Phase IV	1	204



The minimal number of subjects in a single study is one, the maximum number is 999. The total number of patients enrolled in clinical studies in Q3 2018 increased by 48% in comparison with Q3 2017, when 11634 patients were enrolled.

Studies indicated by sponsors as Phase I-II in the applications submitted to Ministry of Health, are shown in Phase II studies group; Phase II-III – in Phase III group; Phase III-IV – in Phase IV group.





CLINICAL TRIALS IN RUSSIA

Site Data

Top-5 Russian research sites (BE and Phase I studies)

Nº	Site Name	City	No. studies
1	Clinical Hospital #2, Yaroslavl region	Yaroslavl	13
2	Clinical Hospital named after V.P. Demikhov	Moscow	10
3	Ecosafety Ltd.	Saint-Petersburg	5
4	Russian National Medical Research Center of Russian Science Academy	Tomsk	5
5	First St. Petersburg State Medical University named after I.P. Pavlov	Saint-Petersburg	2
Combined market share of these companies			19%

Top-5 Russian research sites (Phase II-IV studies)

Nº	Site Name	City	No. studies
1	Russian Oncological Scientific Center named after N.N. Blokhin	Moscow	15
2	Russian National Oncology Medical Research Center named after N.N. Petrov	Saint-Petersburg	13
3	First St. Petersburg State Medical University named after I.P. Pavlov	Saint-Petersburg	12
4	Ecosafety Ltd.	Saint-Petersburg	10
5	Russian State Clinical Oncological Health Centre	Omsk	10
Combined market share of these companies			32%



Top-5 Russian research sites (all studies)

Nº	Site Name	City	No. studies
1	Russian Oncological Scientific Center named after N.N. Blokhin	Moscow	16
2	Eco-Bezopasnost Ltd.	Saint-Petersburg	15
3	Clinical Hospital #2, Yaroslavl region	Saint-Petersburg	14
4	North-Western State Medical University named after I.I. Mechnikov	Saint-Petersburg	14
5	Clinical Hospital #2, Yaroslavl region	Yaroslavl	12
Combined market share of these companies			39%

CRO Data

Nº	CRO Name	No. studies	No. patients
1	IQVIA	7	467
2	Parexel	6	382
3	iPharma	4	263
4	PPD	4	224
5	Synergy Research Group	3	415
Combined market share of these companies		13%	10%



Regulatory Data

During Q3 2018 the Center for Drug Evaluation and Research (CDER) of the FDA approved 13 new drugs as new molecular entities (NME); other approvals concerned various improvements in existing pharmaceutical products.

Four of these 13 drugs were tested in clinical trials involving Russian sites.

Appr.date	Drug (active ingredient)	Company
07/20/2018	Tibsovonda (Ivosidenib)	Agios Pharms
07/31/2018	Mulpletanda (Lusutrombopag)	Shionogi
08/27/2018	Xeravande (Eravacycline Dihydrochloride)	Tetraphase Pharms
08/30/2018	Pifeltronda (Doravirine)	Merck

Source: FDA



During Q2 2018, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicine Agency (EMA) gave positive recommendations on 13 new drug applications, four positive recommendation on new generic medicines, four positive recommendations for new biosimilar medicines, and 18 positive opinions on extensions of therapeutic indications. A negative opinion was adopted for one drug. Eighteen of the drugs and extensions which received positive opinions were (or are being) tested in clinical trials in Russia.

The Table represents those of them which were, or are being tested in clinical trials in Russia in Q2 2018. Positive opinions on new generic, hybrid and biosimilar medicines are not included.



REGULATORY DATA

Appr. date	Drug (active ingredient)	Manufacturer
07/13/2018	Fiasp (Insulin Aspart)	Novo Nordisk
07/26/2018	Vemlidy (Tenofovir Alafenamide)	Gilead
07/27/2018	Ibrance (Palbociclib)	Pfizer
08/02/2018	Repatha (Evolocumab)	Amgen
08/03/2018	Stelara (Ustekinumab)	Janssen-Cilag
08/14/2018	Olumiant (Baricitinib)	Eli Lilly
08/24/2018	Trajenta (Linagliptin)	Boehringer Ingelheim
08/24/2018	Jentaduetto (Linagliptin/Metformin)	Boehringer Ingelheim
09/03/2018	Vimpat (Lacosamide)	UCB Pharma
09/13/2018	Humira (Adalimumab)	AbbVie
09/14/2018	Keytruda (Pembrolizumab)	Merck
09/18/2018	Pregabalin Zentiva k.s. (Pregabalin)	Zentiva k.s.

Source: EMA

Inspection Data

FDA Inspections

According to official FDA website, 2 FDA inspections were conducted at U.S. investigative sites during Q3 - 2018. One inspection resulted in a No Action Indicated (NAI) outcome, and one inspection resulted in a Voluntary Action Indicated (VAI) outcome.

Roszdraznador Inspections

According to the Roszdraznador quarterly report 17 inspections were conducted in institutions performing preclinical and clinical trials located in seven Russian cities during Q3 2018. Violations were found in ten institutions.





TECH TRENDS IN PHARMACEUTICALS AND HEALTHCARE INDUSTRIES

Patient-faced Services

Streamlined tech disruption is occurring everywhere these days. The Pharmaceuticals and Healthcare industries are no exception from this global trend, but strong state authorities' regulations in these areas create a number of difficulties for tech startups trying to improve the efficiency of patient-to-service transaction processes. Nevertheless, beginning from early 2012, there have been a multitude of ambitious and innovative tech startups aiming to improve patient experience, diagnostics and treatment efficiency, exploring new insights in data analytics and reducing transactional costs for the Pharmaceutical and Healthcare industries.

The most promising areas of tech disruption in the Pharmaceuticals and Healthcare industries are Patient-faced services and new tech for clinical trials and healthcare providers.

Medication Adherence

Medication adherence app maker **Medisafe** has announced a partnership with **Boehringer Ingelheim** following a successful pilot program with their Pradaxa drug. A special version of Medisafe app incorporates Pradaxa-specific educational information which helps patients to comply with prescribed medication schedules.

Boehringer Ingelheim and adherence app maker **HealthPrize Technologies** announced that the digital adherence support program RespiPoints will be expanded to any patient who is taking certain **Boehringer Ingelheim** medications, including some available in the RespiMat inhaler. This experience includes free reporting of daily adherence, verifying monthly medication refills, reading educational materials as well as completing quizzes and surveys.



Telemedicine

Leading UK telemedicine provider **Babylon Health** aims to double its London team of scientists and engineers by the end of this year, targeting to expand its capabilities and apply artificial intelligence to assist patients with the management of chronic diseases. The company proved that its AI had demonstrated the ability to provide health advice "on-par with practicing clinicians" in an MRCGP assessment in June. The MRCGP exam is the final test for trainee General Practitioners (GPs), set by the UK Royal College of General Practitioners (RCGP). Trainee GPs who pass this assessment have demonstrated their competence and clinical skills to a level which is sufficiently high enough for them to undertake independent practice.

U.S. telemedicine provider **Teladoc Health** now supports more than 20 languages in corporate services for multinational customers and become available in 24-7 mode. Physicians working at Teladoc will also be equipped with the cultural background and local health system know-how necessary when taking on non-emergency cases in various regions.

In-Home Diagnostic Devices

Inui Health, formerly Scanadu, announces an FDA-cleared home urine testing platform. The smartphone-connected system can perform five different tests (protein, glucose, ketone, leukocyte and nitrite concentration in urine) that could help diagnose UTIs, diabetes, and kidney diseases

Clinical Trials

Risk Management in Clinical Trials

Quanticate, a global data-focused CRO, has announced its partnership with risk-based monitoring software vendor **CluePoints** as part of its new Data Quality Oversight service. Quanticate's new service enables risk-based centralized statistical monitoring in response to the amendments to the ICH Good Clinical Practice (GCP) E6(R2) guidelines.

By partnering with CluePoints, Quanticate will offer customers the creation of statistical analytics reports on key risk indicators and comprehensive risk signals across all clinical and operational data which enable sponsors to interpret findings to assess the integrity of their trial sites and associated data.

Leading global CRO **Iqvia** is expanding its portfolio of its clinically-focused tech solutions to automate clinical trial processes and reduce patient burden with **Salesforce** machine learning solutions.

Study Data Analytics

U.S. National Institute of Health (NIH) deals with leading big data analysis platform **Palantir** to streamline health research with a \$7M contract.

A 'subsidiary' of NIH, the National Center for Advancing Translational Sciences (NCAT) and its related groups aims to use the tech to automatically aggregate research data from public and private sources into a single interface for more streamlined analysis. This automatic platform will help the center's researchers interpret data that was previously disparate as part of a collective whole, and thereby achieve new insights.

Study Compliance

Deloitte acquires risk-based platform **QSpace** designed to manage the GxP validation life cycle of GxP and non-GxP computerized systems, manufacturing equipment, lab instruments and utility systems. It's Title 21 CFR Part 11 compliant E-signatures and configurable review workflows allow for an improved collaboration and accountability became the part of Deloitte services.

Healthcare Providers

AI Diagnostic Tools

Google DeepMind's AI can detect over 50 eye diseases as accurately as a doctor. The software is based on established principles of deep learning, which uses algorithms to identify common patterns in data and was trained on nearly 15,000 OCT scans from some 7,500 patients.

The system analyzes 3D scans of the retina, identifies dozens of common eye diseases from 3D scans and then recommends the patient for treatment. In a test where the AI's judgments were compared with diagnoses by a panel of eight doctors, the software made the same recommendation more than 94 percent of the time.

Digital pathology startup **Proscia** lands \$8.3 M in a Series A funding round. The company develops digital pathology software and AI applications for cancer diagnosis.

The use of AI in diagnosis has been on the rise. In April the FDA granted **IDx** the first De Novo clearance for an AI-based software system for the autonomous detection of diabetic retinopathy in adults who have diabetes.

Physician's Assistants

Wearable, voice-powered doctor's assistant **Notable** raises \$13.5M in a Series A funding to further develop its wearable AI voice assistant for physicians.

The platform combines AI and voice recognition technology to capture information from a doctor's visit. It can pick up on dictations and orders and can recommend the appropriate billing codes. Then the data from the visit is automatically entered into the EHR using secure robotic processing automation.

Voice-powered AI physician assistants are on the rise. In May, **Robin Healthcare**, another voice-enabled AI device designed to help doctors and clinicians write clinical notes, emerged from stealth mode. Additionally, voice-enabled doctor assistant **Suki** raised \$20 million in the spring.

About Synergy

With its unique prevolutionary mind-set, Synergy is now the World's First Agile Risk Based CRO.

Prevolution is the implementation of thoughtful premeditated change resulting from the anticipation and analysis of future trends before they happen – in other words, being 'one step ahead of evolution'.

The high recruitment rates of the emerging markets combined with innovative technology allows our clients conduct faster, cost-effective studies without sacrificing quality. We replace outdated R&D strategies by novel, more efficient approaches to clinical research.

