ACTO

Association of Clinical Trials Organizations

ACTO NEWSLETTER № 20

Summary of 2019 results

MOSCOW 2020

We publish this issue of our Newsletter in 2020 during the pandemic of the new coronavirus infection. Compared to 2019, the situation has changed drastically and the only thing left is to look at the last year's figures with nostalgia. It is already obvious that the trends emergent in 2019 and described in this issue won't develop and that both the clinical trials market and the world economy at large will suffer changes of unprecedented scale, difficult to foresee at present.

We keep track of all processes in the Russian market of clinical trials. Initial generalizations about the pandemic impact will be made already in the next issue and will be based on the data for January-June of 2020. For now we present to you the results of a rather successful and pre-crisis (as we now know) year for our industry.

CONTENTS

SUMMARY

ACTO Newsletter No. 20 presents the key parameters of the Russian clinical trials market for 2019.

In 2019 the Ministry of Health of the Russian Federation issued 746 clinical trial approvals, up 14.2% year-on-year. All types of trials demonstrated sturdy growth. The sector of local trials by foreign sponsors went up 34.6%, despite low absolute values (35 approvals against 26 a year earlier). The number of local trials by Russian sponsors rose 19.2% (155 approvals against 130 in 2018). The number of approvals for bioequivalence studies of generics made abroad (80 versus 69 a year before) and in Russia (163 versus 141) increased roughly by equal percentage (15.9% and 15.6%). The number of approvals for international multicentre clinical trials (IMCT) rose 9.1% to 313 against 287 in 2018.

Oncology accounting for 24.3% of all approvals for international projects, issued in 2019, and 76 trials - remained a traditional leader among therapeutics areas. If we add oncohaemtology, together they make for 91 trials and 29.1% of approvals, i.e. nearly one-third of all new IMCTs. Neurology with 33 trials and the share of 10.5% ranks second. Rheumatology ranks third with similar results: 29 trials and 9.3% of all approvals issued in 2019. Psychiatry ranks fourth (21 IMCTs, 6.7%). These are followed by hematology and infectious diseases (save for HIV, hepatitis C and tuberculosis which we set apart as a special group) splitting the fifth rank with 18 trials each and the market share of 5.8% each. Breaking local trials in generics/biosimilars and foreign-sponsored bioequivalence studies down by therapeutic area, endocrinology takes the lead with 20 new trials and 19.2% of approvals issued for this category. In a similar distribution for domestic sponsors, neurology tops the list (30 trials, 12.8% of all approvals).

The analysis of IMCT distribution between different territories of Russia shows that North-Western Federal District ranks first, having increased by 37 (287 versus 250 a year earlier) the number of IMCTs in whose approvals the medical organizations of the region were mentioned. In Central Federal District the growth stood only at 11 IMCTs (283 versus 272) and this region ranked second in 2019. Volga Federal District with 208 new trials (against 181 a year before) ranked third. Siberian Federal District ranked fourth, boasting 12 new projects more than in 2018 (178 against 166). Ural Federal District with 105 IMCTs (against 89 a year before) ranked fifth. Moscow and Saint-Petersburg remain the most active entities of the Russian Federation with more than 200 new IMCT sites slated for opening there. Thanks to 284 new international projects, St. Petersburg reclaimed leader’s positions in 2019, which it took in 2017 and then ceded to Moscow in 2018. With only 268 IMCT sites scheduled for opening in Moscow last year, this was not enough to claim the victory.

Besides the subjects mentioned, the Newsletter presents information about the main players of the Russian clinical trials market: ratings of sponsors and contract research organizations by the number of approvals obtained as well as the ratings of medical organizations, etc.

Traditionally we review changes in timeframes for issuing of various approval types. We publish statistics on the import of medical products into the Russian Federation for use in clinical trials.

Furthermore, we make an attempt to generalize the available information about international multicentre clinical trials involving pediatric population, limiting ourselves, like in other sections, to a review of the data on approvals issued throughout 2019.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

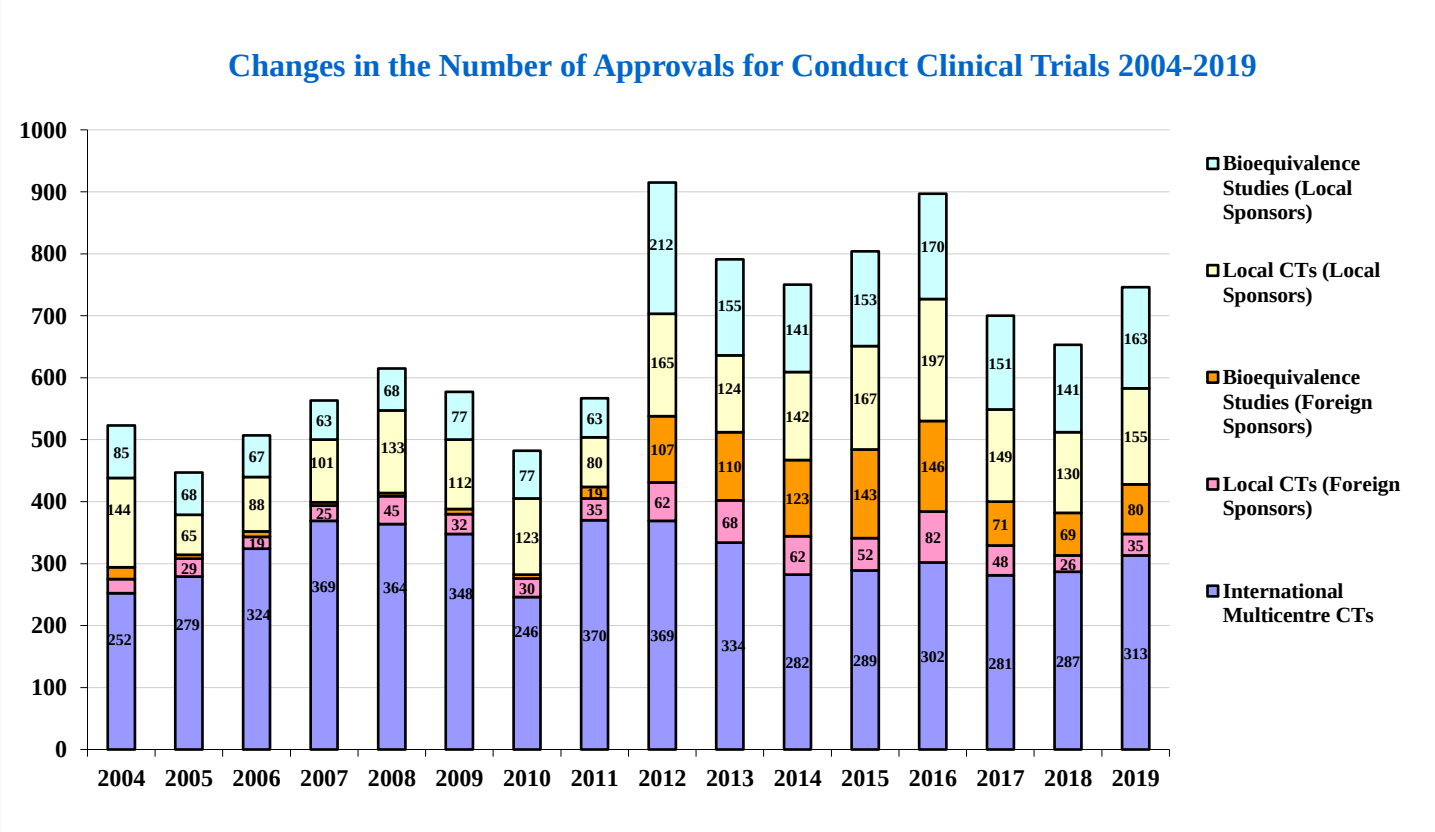
The Ministry of Health of the Russian Federation issued 746 approvals for clinical trials in 2019. This is 14.2% more than in 2018 (see Table 1). The growth can be seen for all types of trials. The highest increase of the relative indicator can be seen in the sector of local trials by foreign sponsors, which grew by a remarkable 34.6%. Such typical for this sector remarkable surges are caused by a small number of trials. Thus only 35 trials were approved in 2019 against 26 a year before. The number of local trials by Russian sponsors rose 19.2% (155 approvals against 130 in 2018). The number of approvals for bioequivalence studies of generics made abroad (80 versus 69 a year before) and in Russia (163 versus 141) increased roughly by an equal percentage (15.9% and 15.6%). Finally, the number of IMCT approvals increased by 9.1% to 313 against 287 in 2018.

Table 1

Approvals for Conduct Clinical Trials: 2019 vs 2018						
Year	**Total**	**International Multicenter CTs**	**Local CTs (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CTs (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
2019	746	313	35	80	155	163
2018	653	287	26	69	130	141
2019 vs 2018, %	14.2%	9.1%	34.6%	15.9%	19.2%	15.6%

Data from www.grls.rosminzdrav.ru

Diagram 1



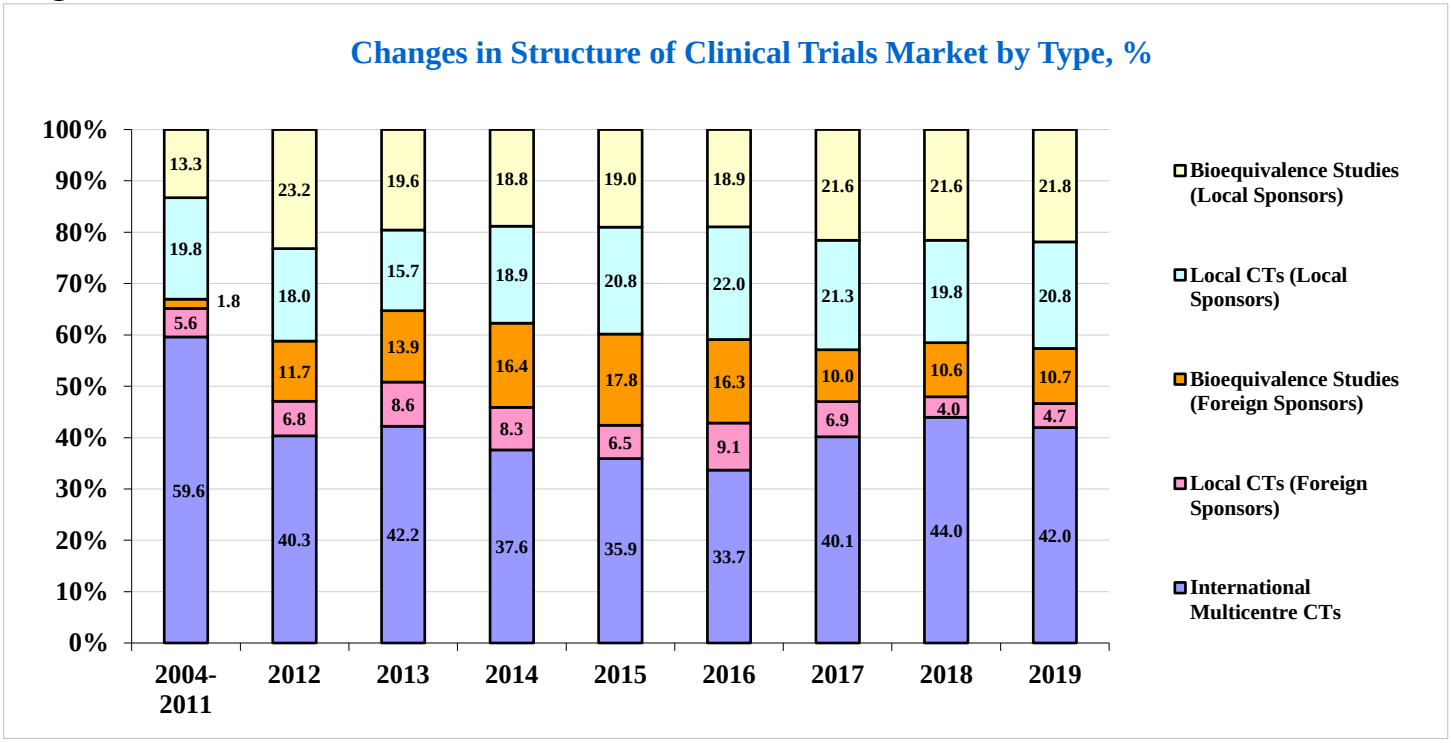
Data from www.grls.rosminzdrav.ru, www.roszdravnadzor.ru

Diagram 1 shows the changing dynamics of the total number of trials and their certain types by years. In comparison with the seven recent years of relative market stability after the pharmaceutical sector regulation reform of 2010, the past year demonstrated decent results. The IMCT count (313 approvals) is way above the average (298 approvals) for seven recent years. The number of approved bioequivalence studies and local trials by foreign sponsors is below the average (80 against 106 and 35 against 53), whereas the number of domestic-sponsored local trials is slightly higher than average in seven recent years (163 against 153 in bioequivalence studies and 155 against 152 in local studies on efficacy and safety). So on the whole 2019 is a quite successful year for the industry of clinical trials in Russia.

STRUCTURE AND DYNAMICS OF THE CLINICAL TRIALS MARKET BY TYPE

Diagram 2 shows the changing share of different type of trials by years. You can see that in 2019 IMCTs lost two percentage points compared to the previous year (42% versus 44%). Though it should be reminded that 2018 was the best year by this indicator starting from 2012. The shares of other trial types underwent even smaller fluctuations that hardly deserve a special mention.

Diagram 2



Data from www.grls.rosminzdrav.ru, www.roszdravnadzor.ru

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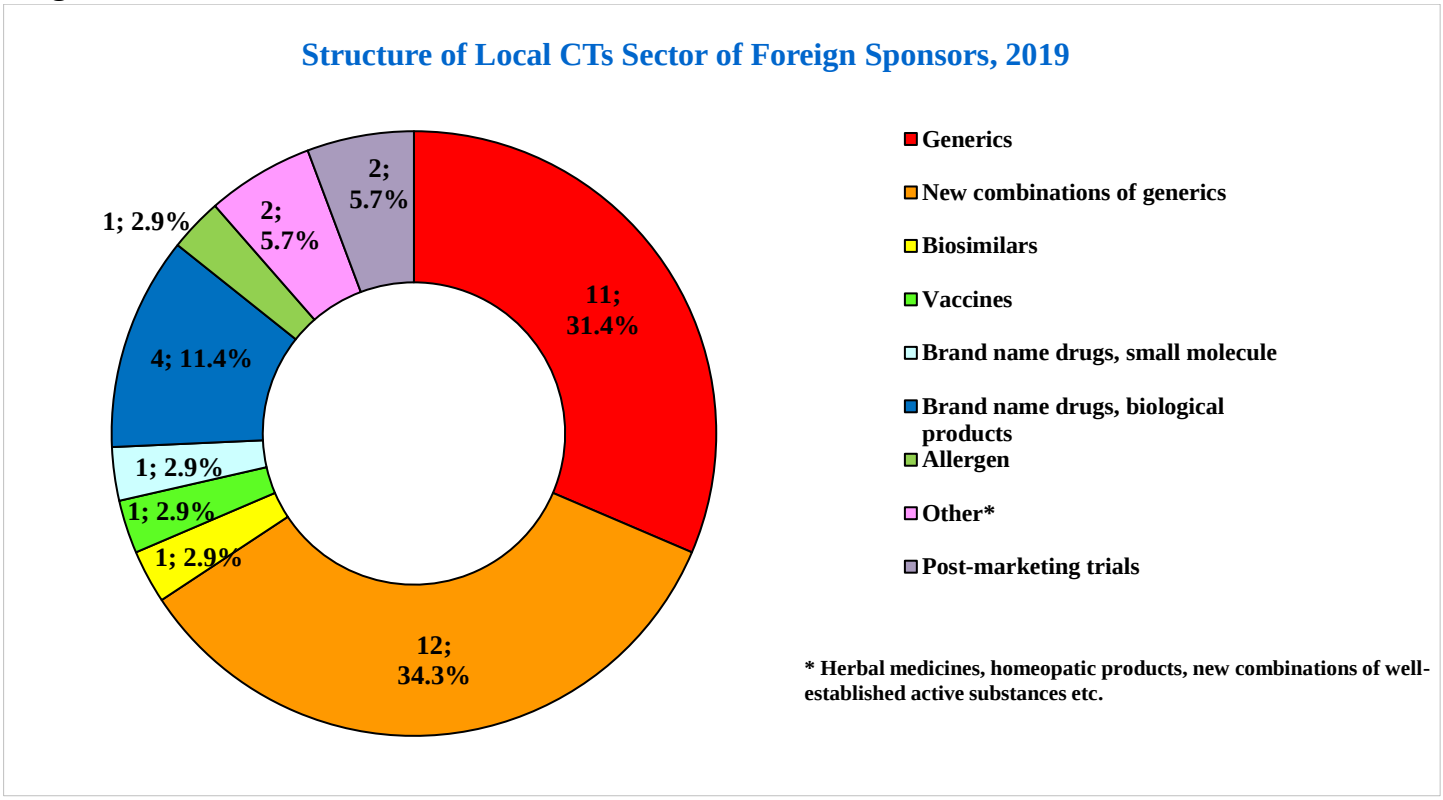
Diagram 3 shows the structure of local trials by foreign sponsors (exclusive of bioequivalence studies). The share of generics trials is weighty in this structure as usual (31.4% against 34.6% in 2018), although this time it slightly lost to the share of new combinations of generics that grew by 22.8 percentage points (from 11.5% to 34.3%) year-on-year.

The share of trials of brand-named biological products came to 11.4% (four trials). In 2018 it took only 3.8% of the market (one trial). On the other hand, the share of trials of biosimilars went down from 15.4% (four trials) in 2018 to 2.9% (one trial) last year.

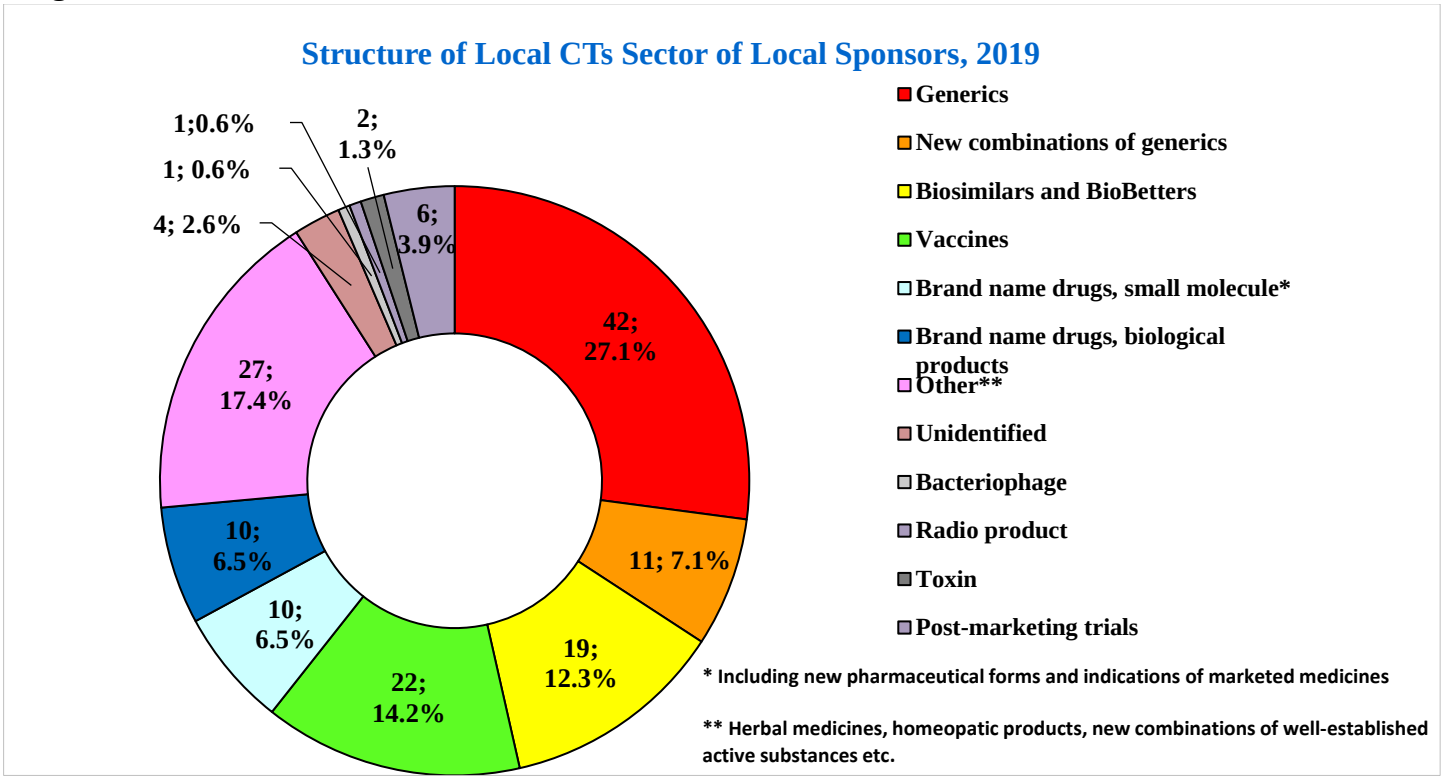
Diagram 3



Data from www.grls.rosminzdrav.ru

Diagram 4 shows local trials for which approvals were obtained in 2019 by domestic sponsors. Generics accounted for the highest share of 27.1% (42 trials), whereas a year before their share stood at 16.2%. New combinations of generics accounted for another 7.1% (11 trials). The sector of biosimilars and BioBetters is represented by 19 trials (12.3% of the total local trials numbers). Most popular among biosimilars were eculizumab (three trials), insulin aspart (also three trials), trastuzumab and bevacizumab (two trials each).

Diagram 4



Data from www.grls.rosminzdrav.ru

Vaccines accounted for 14.2% (22 trials). Influenza vaccines are tested in most cases (12 trials). The plan also called for the testing of Middle East respiratory syndrome preventing vaccines in two trials. Other protocols deal with rotavirus, pneumococcus, polio, natural smallpox, dysentery, haemophilus influenza, hepatitis B vaccines as well as a combined vaccine against diphtheria, tetanus and pertussis.

Brand name drugs, small molecules as well as biological products accounted for 10 trials each or 6.5% of all local trials each (19.2% or 25 trials and 5.4% or 7 trials a year before, respectively).

The sector of post-marketing trials notably sagged. In 2019 its share stood at 3.9% (six trials), whereas in 2018 its share was as high as 16.9% (22 trials). Bewildered by such a massive spread of post-marketing trials in 2018, we were even forced to break them down by types of products. This year the numbers have got back to normal, though, and do not require any additional breakdown.

Meanwhile the "other" sector, where we traditionally include homeopatic medicines, herbal and animal extracted products and suchlike, accounted for 17.4% of all trials in 2019 (27 trials). This group is mostly represented by various peptides mainly extracted from different cattle organs (e.g. swine embryo brains). And here the fantasy of developers is unrestrained both in respect of preparations' composition and the design of trials.

But perhaps MedInvest, LLC that conducted four trials via the contract research organization MDA kicked it up a notch. The name of one where Testonorm was studied in the third phase with 120 people involved reads: *"Multicentre, prospective, double-blind, placebo-controlled, randomized, in parallel groups trial of efficiency and safety of Testonorm^{R} - a lyophilisate to prepare a solution for intramuscular injection of 5 mg (Samson-Med, LLC, Russia) for men with spermatogenesis disorder.* Suppose the placebo effect can indeed be observed in spermatogenesis as well. Who are we to question the golden standard of clinical trials? As for three more trials by the same sponsor, they totally baffled us. All three are phase I and involve 42 participants each. We could never get the clue of what the investigation products (Nephropept, Langopept, Corapept) actually are; the only thing we realized is that the matter regards some peptides. Therapeutics areas declared by the sponsor include nephrology, pulmonology and cardiology, as was easy to guess by the names of those products. Yet the design of trials, as follows from the names of respective protocols, befuddled us completely: *"Double-blind, randomized, placebo-controlled study of the safety and tolerance of single and multiple ascending intramuscular dose of IMP*[1] *in healthy volunteers".* This must have been a real advance in the approach to studying medicines. Or how else can you explain, why they also used placebo control (for comparison) in the first phase of the trial with healthy volunteers involved, where ascending drug doses were studied? Perhaps this is a question for our expert institutions that approved the given trials from both ethical and scientific perspectives.

And finally one protocol (0.6%) each in the structure of local trials of domestic medicinal products fell to the share of bacteriophage and radiopharmaceutical product and in two trials were tested toxins (1.3%). We failed to crack the puzzle of drug origin in four other trials and so they were categorized as UMO (unidentified medicinal objects).

[1] Nephropept, Langopept or Corapept depending on the protocol.

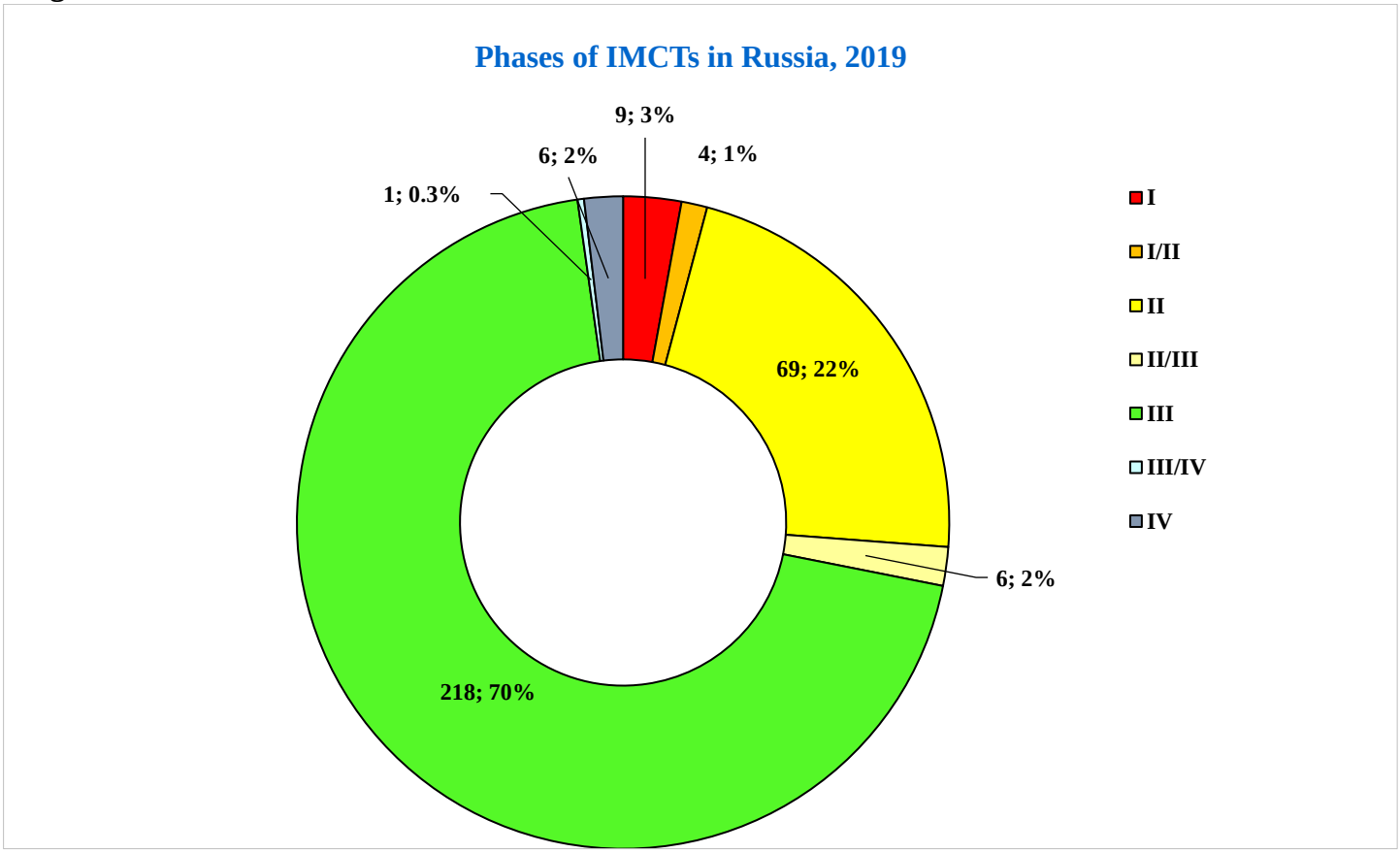
STRUCTURE OF THE IMCT MARKET BY PHASE

The distribution by phases of approvals for IMCTs issued in Russia in 2019 is shown in Diagram 5. This distribution is perhaps the most stable indicator of all we review. The past year brought nothing essentially new to it. Traditionally the phase III of trials was the most massive of all: 70% of the total IMCTs volume (218 approvals) against 67% (192 approvals) a year before. Following next is the phase II: 22% (69 approvals) against the same 22% (63 approvals) in 2018; phase IV accounted for 2% in 2019 (six approvals) against 3% (10 approvals) in 2018.

Further it makes sense to dwell on earlier phases in greater detail. Phase I IMCTs accounted for 3% (nine trials) against 2% (five trials) in 2018. Five out of nine protocols fell to the share of testing drugs against oncological diseases (melanoma, squamous cell skin, head and neck cancer, carcinoma, prostate cancer, advanced hepatocellular cancer and other malignant tumors), one per each trial in hematology (hemophilia), infectious diseases (nosocomial pneumonia), psychiatry (mental disorders) and endocrinology (diabetic nephropathy). It should also be noted that trials of medicinal products against nosocomial pneumonia and mental disorders were designed for participation of children (2-7 years of age) and teenagers (12-18 years of age), respectively.

And finally in four trials of phases I-II they studied medicinal products to be used in oncology (urothelial cancer) and oncohaematology (T-cell lymphoma, marrow fibrosis as well as the dose-ranging protocol in treating the chronic graft-versus-host disease in children).

Diagram 5



Data from www.grls.rosminzdrav.ru, www.clinicaltrials.gov, www.clinicaltrialsregister.eu

STRUCTURE OF THE CLINICAL TRIALS MARKET BY THERAPEUTIC AREAS

Oncology accounting for 24.3% of all approvals for international projects, issued in 2019, and 76 trials - remained a traditional leader among therapeutics areas. If we add oncohaemtology, together they make for 91 trials and 29.1% of approvals, i.e. nearly one-third of all new IMCTs.

In other cases the upper lines of Table 2 were renewed. Compared to 2018, notably more IMCT approvals were issued in psychiatry (its share grew by five percentage points or 16 IMCTs), rheumatology (by 4.8 percentage points and also 16 IMCTs in absolute figures), neurology (4.2 p.p., 15 trials), endocrinology and ophthalmology (each field added 2.7 p.p., nine trials). On the contrary, the shares of gastroenterology (by 7.5 p.p. or by 20 IMCTs) and cardiology with CVD (by 4.4 p.p. or 12 IMCTs) that ranked second and third in a similar table for 2018 shrank.

Table 2

Distribution of International Multicenter CTs by Therapeutic Areas, 2019			
Therapeutic Area	**Number of IMCTs**	**Share (%)**	**Planned number of participants**
Oncology	76	24.3%	5 688
Neurology	33	10.5%	1 836
Rheumatology	29	9.3%	2 306
Psychiatry	21	6.7%	2 216
Haematology	18	5.8%	413
Infectious Diseases (except HIV/HCV/tuberculosis)	18	5.8%	2 204
Gastroenterology	17	5.4%	1 396
Endocrinology	16	5.1%	1 637
Oncohaematology	15	4.8%	719
Ophthalmology	15	4.8%	707
Dermatology	12	3.8%	746
Pulmonology	10	3.2%	1 223
Cardiology and CVD	9	2.9%	1 737
Allergology	4	1.3%	320
Urology	4	1.3%	715
Nephrology	4	1.3%	307
Hepatology	3	1.0%	120
Obstetrics and Gynecology	2	0.6%	165
Immunology	2	0.6%	270
HIV/HCV	2	0.6%	25
Surgery	2	0.6%	900
Otorhinolaryngology	1	0.3%	360
TOTAL	313	100.0%	26 010

Data from www.grls.rosminzdrav.ru

The year 2019 proved most successful for IMCTs in neurology and psychiatry during the time of ACTO monitoring, i.e. since 2013. The previous record - 28 neurological and 15 psychiatric IMCTs with their shares

standing at 9.3% and 5% respectively - was set in 2016[2]. The growth in 2019 strikes the eye as it contrasts with the previous year when these therapeutics areas' indicators drew very close to minimum during the time of our monitoring: 18 neurological and 5 psychiatric IMCTs with shares standing at 6.3% and 1.7%, respectively. Below are only the results for 2014: 17 IMCTs in neurology (6% of new approvals), five IMCTs in psychiatry (1.8%).

In psychiatry the activity was largely maintained by several sponsor companies: Acadia Pharmaceuticals with seven Pimavanserin[3] IMCTs, Sunovion with four IMCTs of antipsychotic agent SEP-363856[4], Alkermes with two trials of ALKS 3831[5] and Janssen Pharmaceutica with two trials of different medications used to treat a major depressive disorder (MDD). That said, we do not see any buildup of other psychic disorders in IMCTs with remedies for schizophrenia, MDD and bipolar disorders still calling the shots almost in all trials.

In neurology we have a different picture: new diagnoses that ACTO has never come across during the time of monitoring have been added to the list of indications - e.g. GM2-gangliosidosis. What's more, the global trend of higher focus on developing new remedies for migraine and myasthenia gravis made itself felt in Russia as well. The Russian Ministry of Health issued five approvals in 2013-2018 and six approvals in 2019 for four sponsors to study antimigraine medications. We have the following situation with myasthenia gravis: five new IMCTs by three sponsors in 2019 preceded by two approvals in 2015 (two more trials never kickstarted in Russia in the same year 2015, since recruitment had been over before the approval was issued[6]). The list of neurological disease sponsors more than doubles from nine companies in 2018 to 19 in 2019.

As regards two more burgeoned areas, rheumatology and endocrinology, they both shrank in 2017-2018 and now they are making up for that contraction. Rheumatology - due to a longer list of diseases (IMCTs of medicinal products used in the treatment of lupus nephritis, Sjorgen's syndrome, giant cell arteritis etc.). Endocrinology - not only due to longer lists of diseases and sponsors, but also due to a larger number of IMCTs for a certain drug group, anti-diabetic (nine approvals against four a year before) as well as the high activity of Novo Nordisk that received six out of 16 approvals for IMCTs in endocrinology in 2019.

We need to look into the growth of one more therapeutics area: the number of ophthalmological IMCTs grew from six in 2018 to 15 in 2019, while their share grew by 2.7 p.p. If in 2018 they tested medications for indications such as diabetic macular edema (three IMCTs), glaucoma/ocular hypertension (two IMCTs) and preventing inflammation after eye surgery (one IMCT), in 2019 protocols mentioned neovascular age-related macular degeneration (five IMCTs), glaucoma/ocular hypertension (four IMCTs), macular edema (three IMCTs), retinopathy of prematurity (two IMCTs) and dry eye syndrome (one IMCT).

We'll briefly comment on the situation with therapeutics areas that dwindled in comparison with the previous year. The contracting share of gastroenterology reflects its return to normal typical of 2014-2016, followed by a boom in 2018 when a dozen of sponsors started testing more than a dozen medications for ulcerative colitis and Crohn disease in Russia. On the contrary, the results are extraordinary for cardiology. This area went down to a minimum since 2013, retaining only most popular diagnoses (cardiac insufficiency, hypercholesteremia, pulmonary hypertension and others), with the list of sponsors shrinking from 15 in 2018 to five in 2019.

[2] For more detail see "Situation with clinical trials of medicinal products to treat neurological and psychiatric diseases" in the ACTO Newsletter No. 19.
[3] A medical drug to treat hallucinations and delirium related to the psychotic condition of Parkinson's disease was approved by FDA in 2016. Now the developer is testing it as an antipsychotic agent for other disorders.
[4] It is tried in Russia with the participation of schizophrenia patients.
[5] Also meant for schizophrenia patients.
[6] See the Database of the IMCTs lost for Russia on the ACTO website.

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In the distribution by therapeutics areas for local trials and bioequivalence studies of biosimilars and generics by foreign sponsors, in comparison with 2018, we see the highest growth of the endocrinology share (by 8.7 p.p. or 11 trials, which assured this therapeutics area the top spot in Table 3 above cardiology with its indicators close to those in the last year but one), ophthalmology (by 4.4 p.p. and by five trials) and urology (by 3.2 p.p. and four trials). The shares of neurology and infectious diseases sagged more notably than other areas (both sank by 5.5 p.p. or by four trials each). For neurology and psychiatry as a single therapeutics area for the time of ACTO monitoring since 2013, by the number of local trials and bioequivalence studies initiated by foreign sponsors, only 2017 with two neurological and three psychiatric trials by foreign sponsors was less successful[7].

Table 3

Distribution of Local CTs and Bioequivalence Studies (Generics and Biosimilars) of Foreign Sponsors, 2019			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Planned number of participants**
Endocrinology	20	19.2%	914
Cardiology and CVD	19	18.3%	1238
Ophthalmology	7	6.7%	1194
Urology	7	6.7%	300
Analgesic and NSAIDs	6	5.8%	624
Neurology	4	3.8%	836
Pulmonology	4	3.8%	670
Gynecology	4	3.8%	572
Allergology	4	3.8%	444
Gastroenterology	4	3.8%	332
HIV	4	3.8%	260
Infectious Diseases (except HIV/HCV/tuberculosis)	4	3.8%	170
Rheumatology	4	3.8%	155
Coloproctology	2	1.9%	380
Otorhinolaryngology	2	1.9%	298
Psychiatry	2	1.9%	118
Oncohaematology	2	1.9%	114
Haematology	1	1.0%	500
Anesthesiology	1	1.0%	170
Cosmetology	1	1.0%	110
Oncology	1	1.0%	46
Dermatology	1	1.0%	40
TOTAL	104	100.0%	9 485

Data from www.grls.rosminzdrav.ru

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In a distribution by therapeutics area of local trials and bioequivalence studies of generics and biosimilars by domestic sponsors changes are insignificant as compared to 2018: in most cases shares changed within one

[7] Compare: “Situation with clinical trials of medicinal products to treat neurological and psychiatric diseases” in the ACTO Newsletter No. 19.

percentage point. The only exception is infectious diseases which sagged by six percentage points (17 trials in 2018 and only seven in 2019) and rheumatology whose share went down by 3 p.p. (eight trials in 2019 and 12 a year before). Gastroenterology and psychiatry grew slightly by seven and six trials accordingly - both by 2 p.p.

Table 4

Distribution of Local CTs and Bioequivalence Studies (Generics and Biosimilars), Conducted by Local Sponsors, 2019			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Planned number of participants**
Neurology	30	12.8%	2 000
Oncology	22	9.4%	1 964
Cardiology and CVD	22	9.4%	1 013
Endocrinology	19	8.1%	1 704
HIV/tuberculosis	19	8.1%	893
Gastroenterology	15	6.4%	857
Psychiatry	12	5.1%	1 307
Analgesic and NSAIDs	11	4.7%	1 252
Gynecology	11	4.7%	1 131
Rheumatology	8	3.4%	670
Otorhinolaryngology	7	3.0%	1 311
Infectious Diseases (except HIV/HCV/tuberculosis)	7	3.0%	412
Oncohaematology	7	3.0%	344
Urology	6	2.6%	222
Surgery	5	2.1%	682
Immunology	5	2.1%	530
Haematology	5	2.1%	282
Pulmonology	5	2.1%	196
Hepatology	4	1.7%	302
Transplantology/Immunology	3	1.3%	162
Nephrology	2	0.9%	665
Dermatology	2	0.9%	309
Phlebology	2	0.9%	220
Ophthalmology	2	0.9%	174
Narcology	2	0.9%	60
Others	2	0.9%	114
TOTAL	235	100.0%	18 776

Data from www.grls.rosminzdrav.ru

The therapeutics area HIV/ Hepatitis C/Tuberculosis deserves a special mention[8]. It is domestic sponsors who are focused on this area more than their foreign peers, which is expressed in 19 trials (15 trials of medications against HIV and four against tuberculosis), whereas foreign sponsors held only four local trials in this area (see Table 3), with two more being international projects (Table 2). But we should probably make a caveat that in all of their 19 trials domestic sponsors studied medicinal products as well as their copies that hit the world market in 2006 and earlier (with one exception: Pharmasyntez received an approval for studying a combination of Lamivudine and Tenofovir, which was approved by FDA in 2018 for HIV treatment under the trade mark of

[8] There was a special article on this subject in the ACTO Newsletter No. 16.

Cimduo)[9]. In bioequivalence studies by foreign sponsors these are medications approved by FDA in 2007[10] and 2008[11], whereas in IMCTs - only recent approvals: in 2017[12] and 2019[13]. The medication Pretomanid approved by FDA in 2019 for treating Drug Resistant Tuberculosis was also tested in Russia as part of the IMCTs that were approved in 2017 and 2018.

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In Table 5 you can find molecules that figured more often than others in protocols of generics and biosimilar trials for 2019. This time Metformin (separately and in combinations) having the blood sugar reducing effect and used for diabetes treatment proved most popular, mainly among foreign sponsors - 13 trials. Combinations with estradiol (hormonal drugs, gynecology) rank second - nine trials. The third position is split between two more agents reducing the level of blood sugar: vildagliptin and sitagliptin, each of them separately and in combinations - in seven protocols.

However, popularity of the said anti-diabetic medications did not allow endocrinology to become a leader by the number of trials of generic drugs. If we take into account less popular molecules not included in Table 5, in 2019 there were 45 generics/biosimilars used in endocrinology were studied. Cardiology and CVD with 50 such trials are still at the top of the list. The trials of neurological generic drugs (30) rank third.

Among the most popular biosimilars are 16 drugs that entered the US, Canadian and Japanese markets after 2000. These are drugs such as

- Tenofovir (approved in the US since 2001),
- Gefitinib (in Japan since 2002),
- Tadalafil (in the US since 2003),
- Rosuvastatin (in Europe since 2003),
- Cinacalcet (in the US and EU since 2004),
- Sertaconazol (in USA since 2004),
- Lenalidomide (in USA since 2005),
- Nitisinone (in Europe since 2005),
- Sitagliptin and Darunavir (both in USA since 2006),
- Eculizumab (in USA since 2007; in 2010 it was the world's most expensive drug according to Forbes[14]),
- Vildagliptin (in Europe since 2008),
- Rivaroxaban (in Canada since 2008),
- Dabigatran etexilate (in EU and Canada since 2008),
- RAD001 or Everolimus (in USA since 2009),
- Dimethyl fumarate (in USA since 2013).

[9]In addition to the exception mentioned in the text, HIV medications were studied: darunavir approved in 2006 - three trials; the tenofovir/emtricitabine/efavirenz combination approved in 2006 - one trial; atazanavir approved in 2003 - two trials; fosamprenavir approved in 2003 - one trial; the lopinavir/ritonavir combination approved in 2000 - two trials; abacavir (ABC) and EFV, both approved in 1998 - one trial each; lamivudine and sacvinavir, both approved in 1995 - one trial each; phosphazide used in the Russian Federation since 1990s - one trial; as well as four trials of three antituberculotics: PAS, terizidone and protionamide that have been used for more than three dozens of years.

[10] Raltegravir, a HIV medication.

[11] Etravirine, a HIV medication.

[12] Glecaprevir, Pibrentasvir whose combination is used to treat Hepatitis C.

[13] Dolutegravir/lamivudine – a combination for HIV treatment.

[14] See https://www.forbes.com/2010/02/19/expensive-drugs-cost-business-healthcare-rare-diseases.html#b2d8fb5e1070

Table 5

Most Requested INN Used in Clinical Trials of Generics in 2019				
Substance	**Number of CTs of foreign generics**	**Number of CTs of local generics**	**All clinical trials to a given INN**	**Therapeutic Area**
Metformin (separately and in fixed combinations)	11	2	13	Endocrinology
Estradiol (in fixed combinations)	2	7	9	Gynecology
Vildagliptin (separately and in fixed combinations)	6	1	7	Endocrinology
Sitagliptin (separately and in fixed combinations)	7	–	7	Endocrinology
Ibuprofen (separately and in fixed combinations)	4	2	6	Analgesic and NSAIDs, gynecology, neurology
Rivaroxaban	5	1	6	Cardiology and CVD
Cinacalcet	1	5	6	Endocrinology
Everolimus	–	6	6	Immunology, transplantology, oncology
Dexketoprofen	1	4	5	Analgesic and NSAIDs
Etoricoxib	2	3	5	Rheumatology
Itopride	–	4	4	Gastroenterology
Pirindopril (separately and in fixed combinations)	1	3	4	Cardiology and CVD
Trimebutine	–	4	4	Gastroenterology
Cetylpyridinium chloride (in fixed combinations)	–	4	4	Otorhinolaryngology
Ethyl methyl hydroxypyridine succinate	–	4	4	Neurology, psychiatry
Azitromicine	1	2	3	Ophthalmology, infectious diseases
Acidum acetylsalicylicum (separately and in fixed combinations)	–	3	3	Cardiology and CVD
Bisoprolol (separately and in fixed combinations)	1	2	3	Cardiology and CVD
Gefitinib	1	2	3	Oncology
Gramicidin C (in fixed combinations)	–	3	3	Otorhinolaryngology
Dabigatran etexilate	2	1	3	Cardiology and CVD
Darunavir	–	3	3	HIV
Dimethyl fumarate	1	2	3	Neurology
Drospirenon (in fixed combinations)	1	2	3	Gynecology
Inosine pranobex	–	3	3	Immunology
Insulin aspart	–	3	3	Endocrinology
Lenalidomide	–	3	3	Oncohaematology
Melatonin (in fixed combinations)	–	3	3	Neurology
Nitisinone	–	3	3	Endocrinology
Oseltamivir	1	2	3	Infectious Diseases
Paracetamol (in fixed combinations)	2	1	3	Analgesic and NSAIDs, infectious diseases
Rosuvastatin (separately and in fixed combinations)	–	3	3	Cardiology and CVD
Sertaconazole	–	3	3	Gynecology, dermatology
Tadalafil	–	3	3	Urology
Tenofivir (separately and in fixed combinations)	1	2	3	HIV
Tolperisone	1	2	3	Neurology
Ursodeoxycholic acid	–	3	3	Hepatology
Esomeprazole	1	2	3	Gastroenterology
Eculizumab	–	3	3	Haematology

Data from www.grls.rosminzdrav.ru

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The following two tables present the distribution of local trials for brand name drugs by foreign (Table 6) and Russian (Table 7) sponsors.

The following developments stand behind the stingy figures of Table 6: Staloral drug "Wormwood Pollen Allergen" developed by Stallergenes, chickenpox vaccine Varivax developed by MSD, monoclonal antibody with antitumor activity brentuximab vedotin developed by Takeda, preventive medication for inhibitory forms of haemophilia (bleeding sickness) emicizumab developed by Roche, TISSIL Lio (human fibrinogen/synthetic aprotinin/human thrombin) as a hemorrhage prevention medication used in surgery and developed by Baxter Healthcare, and finally progesterone in capsules for premature delivery prevention developed by Besins Healthcare.

Table 6

Distribution of Local CTs of Brand Name Drugs (including biological products) of Foreign Sponsors, 2019		
Therapeutic Area	**Number of CTs**	**Planned number of participants**
Allergology	1	120
Infectious Diseases (except HIV/HCV/tuberculosis)	1	150
Oncohaematology	1	101
Haematology	1	50
Surgery	1	140
Obstetrics	1	370
TOTAL	6	931

Data from www.grls.rosminzdrav.ru

Drugs for the treatment of infectious diseases are especially popular among domestic sponsors, so we'll dwell in more detail on these. In all 22 trials mainly influenza vaccines are studied (12 trials) as well as vaccines from Middle East respiratory syndrome (two trials) as well as diseases and causative agents, such as dysentery, pneumococcus, hepatitis B, smallpox, polio, Haemophilus influenzae, rotavirus (one trial for each) and a triple vaccine for diphtheria, tetanus and pertussis (also one trial). Two more trials are also related to the development of medications against contagious matter, though formally we set these apart as a separate therapeutics area: HIV/hepatitis C/tuberculosis. In 2019 approvals were issued for Viriom to study phase I of a drug to be used in HIV therapy as well as for Japan-based Otsuka to study a medication for lung tuberculosis with multiple drug resistance. Otsuka also signed agreements with the Russian company R-Pharm for registration and commercialization of its development in Russia.

Table 7

Distribution of Local CTs of Brand Name Drugs (including biological products) of Local Sponsors, 2019		
Therapeutic Area	**Number of CTs**	**Planned number of participants**
Infectious Diseases (Vaccines)	22	7 066
Oncology	7	1 251
Neurology	4	902
Rheumatology	3	757
Cardiology and CVD	2	335
Pulmonology	2	134
HIV/Tuberculosis	2	85
Urology	1	350
Gynecology	1	258
Antiseptic	1	80
Allergology	1	58
TOTAL	46	11 276

Data from www.grls.rosminzdrav.ru

DISTRIBUTION OF IMCT APPROVALS ACROSS RUSSIA

One can get acquainted with the methods of calculating IMCT distribution across Russia in ACTO Newsletter No. 12 and with the final results for 2019 - in Table 8 of this issue.

In the rating based on the indicator of IMCTs' number per region two reshuffles took place as compared to 2018. The North-Western Federal District overtook the Central Federal District and can be seen at the top (287 new IMCTs against 250 a year before). In the Central Federal District the growth turned out to be not that high (283 new IMCTs against 272 in 2018). As a result the Central Federal District dropped from the first to the second position. Two more federal districts swapped places: the Ural Federal District (16 new projects more than in 2018, 105 against 89, fifth spot in 2019) and the Southern Federal District (22 IMCTs less, 83 versus 105, sixth spot).

Among the federal districts which have not been mentioned so far, the Volga Federal District showed the highest growth: 27 IMCTs more against 2018 (208 versus 181) - it still ranks third by IMCT count per region. The Siberian Federal District had 12 IMCTs more than a year before (178 against 166) and it retained the fourth position. Clinics in the North Caucasus District were less frequently involved in IMCTs in 2019 as compared to 2018 (55 new projects versus 62); this district ranks seventh. Far the Eastern Federal District is at the bottom of the list: its activity also went down as compared to the previous year (three new IMCTs versus four in 2018).

Let's dwell on the trio of leaders in greater detail. The performance of Saint-Petersburg and the Leningrad region underwent most drastic changes in the North-Western District. The number of new trials in St. Petersburg grew by 38 against 2018 (284 versus 246, a 15% growth) This number could be even higher unless two medical organizations changed their legal address and "domicile" from Saint-Petersburg to the Leningrad region. As a result, the activity of the Leningrad region increased mainly thanks to these two clinics: 32 IMCTs more than a year before (40 versus 8, a fivefold growth). Among other changes inside the region we'd mention the activity flagging in the Murmansk region from 14 new IMCTs in 2018 to six in 2019, i.e. more than by half.

In the Central Federal District the growing activity in comparison with 2018 was demonstrated by the Yaroslavl region (72 versus 51, a growth by 41% or 21 IMCTs in absolute figures), Moscow (268 against 249, up 8% or 19 IMCTs) and Smolensk region (42 versus 34, a growth of 24% or by eight IMCTs). Most notable reductions in the Central Federal District were recorded in the Ivanovo region (13 versus 24 - 11 IMCTs or 46% less) and Kursk region (16 versus 25 - nine IMCTs or 36% less).

In the Volga Federal District some regions drastically improved their statistics by the number of international protocols: the Nizhny Novgorod region (65 against 47 - 18 trials or 38% more), Saratov region (59 versus 46 - 13 IMCTs or 28% more) and Samara region (74 versus 64 - 10 IMCTs or 16% more). The activity in the Republic of Tatarstan markedly flagged: from 88 new IMCTs in 2018 to 71 in 2019, i.e. by 17 IMCTs or 19% of their number in 2018.

Noteworthy beyond the leading federal districts is firstly a surge of activity in international projects by medical organizations of the Tomsk region (by 10 from 42 to 52 IMCTs, a 24% growth) and the Omsk region (by 9 from 61 to 70, a 16% growth) of the Siberian Federal District; secondly, a decrease in new IMCTs' number in the Rostov region (by 22 from 58 to 36, a 38% decrease) and Krasnodar Territory (by 13 from 57 to 44, a 23% decrease) of the Southern Federal District as well as in the Irkutsk region of the Siberian Federal District (by 9 from 12 to 3, a 75% decrease).

Table 8

Distribution of IMCTs approved in 2019 by regions of the RF									
Region	**Number of IMCTs, per region**	**Number of IMCTs, per million population***	**Number of health care organizations, which approved sites for IMCTs, per region**	**How many times medical organizations of the region were involved in IMCTs (number of open sites)**	**Region**	**Number of IMCTs, per region**	**Number of IMCTs, per million population***	**Number of health care organizations, which approved sites for IMCTs, per region**	**How many times medical organizations of the region were involved in IMCTs (number of open sites)**
Central Federal District	**283**	**7,2**	**160**	**839 (883)**	**North Caucasian Federal District**	**55**	**5.6**	**17**	**68**
Moscow	268	21.3	97	539 (573)	Stavropol Territory	52	18.6	13	63
Yaroslavl Region	72	55.4	17	90 (91)	Republic Of North Ossetia-Alania	2	2.9	2	2
Smolensk Region	42	46.7	7	44 (46)	Kabardino-Balkarian Republic	2	2.2	2	3
Kaluga Region	35	35.0	3	36 (39)					
Moscow Region	30	4.0	6	31 (32)	**Siberian Federal District**	**178**	**10.4**	**67**	**363 (365)**
Ryazan Region	23	20.9	5	23 (26)	Novosibirsk Region	85	30.4	25	107
Kursk Region	16	14.6	3	16	Omsk Region	70	36.8	9	70 (71)
Ivanovo Region	13	13.0	4	13	Tomsk Region	52	47.3	8	54 (55)
Voronezh Region	10	4.4	5	10	Kemerovo Region	46	17.0	7	49
Tver Region	7	5.4	4	7	Krasnoyarsk Territory	41	14.1	8	43
Tula Region	7	4.7	2	7	Altai Territory	36	15.7	8	37
Lipetsk Region	6	5.5	2	6	Irkutsk Region	3	1.3	2	3
Vladimir Region	6	4.3	1	6					
Tambov Region	5	5.0	1	5	**Ural Federal District**	**105**	**8.5**	**37**	**134**
Belgorod Region	4	2.5	1	4	Sverdlovsk Region	53	12.3	17	57
Kostroma Region	1	1.7	1	1	Chelyabinsk Region	48	13.7	11	50
Bryansk Region	1	0.8	1	1	Tyumen Region	22	14.7	6	23
					Kurgan Region	2	2.5	1	2
Southern Federal District	**83**	**5.0**	**24**	**108**	Khanty-Mansi Autonomous Area	2	1.2	2	2
Krasnodar Territory	44	7.7	11	47					
Rostov Region	36	8.6	8	36 (37)	**Volga Federal District**	**208**	**7.1**	**86**	**453 (458)**
Volgograd Region	24	9.6	5	24	Samara Region	74	23.1	13	80
					Republic of Tatarstan	71	18.2	14	73 (74)
Northwestern Federal District	**287**	**20.5**	**154**	**868 (898)**	Nizhny Novgorod Region	65	20.3	15	75
Saint-Petersburg	284	52.6	125	736 (765)	Saratov Region	59	24.6	11	75 (79)
Leningrad Region	40	21.1	11	45 (46)	Republic of Bashkortostan	30	7.3	5	30
Arkhangelsk Region	31	28.2	5	32	Ulyanovsk Region	21	17.5	2	21
Republic of Karelia	26	43.3	2	26	Perm Territory	19	7.3	6	19
Kaliningrad Region	8	8.0	4	8	Udmurtian Republic	18	12.0	5	18
Vologda Region	7	5.8	3	7	Orenburg Region	18	9.0	4	18
Murmansk Region	6	7.5	2	6	Kirov Region	17	13.1	5	17
Republic of Komi	5	6.3	1	5	Penza Region	16	12.3	2	16
Novgorod Region	3	5.0	1	3	Republic of Mordovia	9	11.3	3	9
					Mari El Republic	2	2.9	1	2
Far Eastern Federal District	**3**	**0.4**	**2**	**3**					
Khabarovsk territory	3	2.3	2	3					

*We used data of Rosstat on the resident population of the region as of January 1, 2019

In addition to the absolute figures, the number of IMCTs per million population is shown in table 8. Here the TOP-3 looks quite traditional: the Northwestern Federal District with 20.5 new IMCTs per million population, the Siberian District with 10.4 and the Ural District with 8.5. All leading federal districts built up their figures: in 2018 similar figures for the same federal districts looked thus: 17.9, 8.6 and 7.2. The most drastic growth of IMCTs' number per million population on a year-on-year basis was recorded in the Leningrad region (from 4.4 to 21.1 - mainly because of two clinics that changed their legal address if you remember), Yaroslavl region (from 39.2 to 55.4), Tomsk region (from 38.2 to 47.3), Smolensk region (from 34 to 46.7) and Saint-Petersburg (from 45.6 to 52.6). The deepest fall by this indicator can be seen in the Ivanovo region (from 24 in 2018 to 13 in 2019), Murmansk region (from 17.5 to 7.5), Kursk region (from 22.7 to 14.6) and Ryazan region (from 27.3 to 20.9) as well as in the Republic of Mordovia (from 20 to 11.3).

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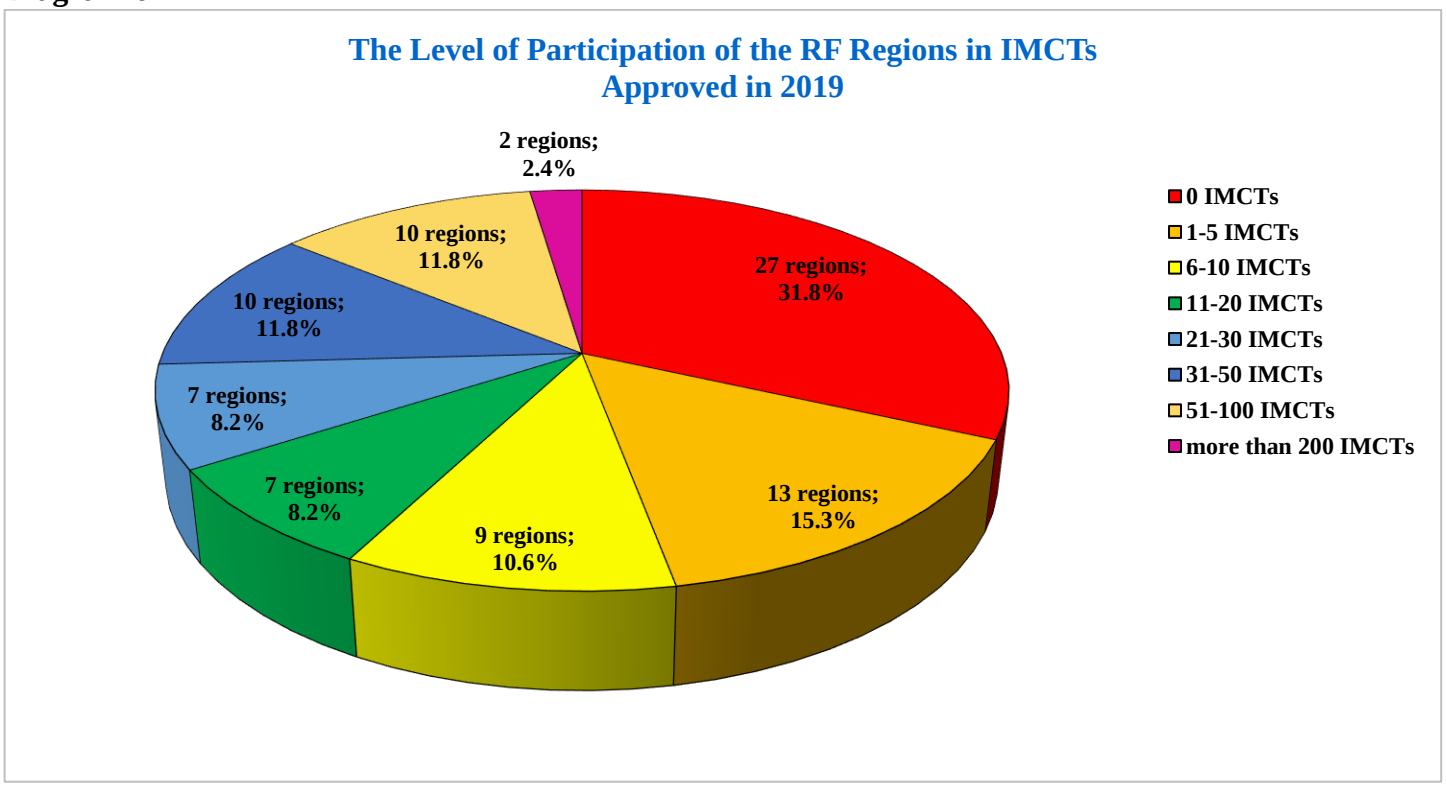
A regional distribution by number of new IMCTs announced can be assessed using Diagram 6.

Traditionally only Moscow and Saint-Petersburg landed in "more than 200 IMCTs" segment.

The 51-100 IMCTs segment grew from eight to ten regions year-on-year and still includes the Novosibirsk, Omsk, Samara and Yaroslavl regions as well as the Republic of Tatarstan and the Stavropol Territory. The Krasnodar Territory and Rostov region were excluded because of lower activity, but in the meantime the Saratov, Sverdlovsk and Tomsk regions entered that segment.

The 31-50 IMCTs segment shrank from 11 to 10 regions. The Arkhangelsk, Kaluga, Kemerovo, Smolensk and Chelyabinsk regions as well as the Krasnoyarsk Territory retained their positions. The Nizhny Novgorod, Saratov, Sverdlovsk and Tomsk regions moved up to the segment of higher activity, whereas the Republic of Bashkortostan moved down to the segment of lesser activity. The Leningrad and Rostov regions, Altai and the Krasnodar territories are newcomers in this segment.

Diagram 6



Data from www.grls.rosminzdrav.ru

In the 21-30 IMCTs segment there are seven regions like a year before. The Republic of Karelia as well as the Volgograd, Moscow and Ryazan regions remained there. The Altai Territory moved up to the segment of higher activity; the Ivanovo and Kursk regions moved down to the segment of lesser activity. Their spots were filled by the Republic of Bashkortostan, the Tyumen and Ulyanovsk regions.

The 11-20 IMCTs segment shrank from 11 to seven regions. Like a year before, it includes the Perm Territory, the Udmurt Republic, the Orenburg and Penza regions. The Tyumen and Ulyanovsk regions ramped up their activity and moved up. Five regions lowered their activity and left this segment: the Republic of Mordovia, the Irkutsk, Kaliningrad, Murmansk and Tver regions. The Ivanovo, Kirov and Kursk regions joined the 11-20 IMCTs segment in 2019.

The number of regions in the 6-10 IMCTs segment grew from six to nine. The Vologda and Voronezh regions retained their spots. The Kirov and Leningrad regions moved up to higher activity segments, while the Belgorod and Novgorod regions moved down to the lesser activity segment. The Republic of Mordovia, the Kaliningrad, Murmansk and Tver regions moved down from the higher activity segment to the 6-10 IMCTs segment, whereas the Vladimir, Lipetsk and Tula regions came here from the lesser activity segment.

The 1-5 IMCTs grew from 10 to 13 regions. The Bryansk and Tambov regions, the Kabardino-Balkar Republic and the Komi Republic are left in this segment. The Vladimir, Lipetsk and Tula regions moved up to the higher activity segment, whereas the Amur region, the Trans-Baikal Territory and the Primorsky Territory moved down. Less active in 2019, as compared to 2018, the Belgorod, Irkutsk and Novgorod regions and more active the Kostroma and Kurgan regions, the Mari El and the Northern Ossetia-Alania republics, the Khanty-Mansi Autonomous Area Yugra and the Khabarovsk Territory left this segment.

Fewer regions did not plan new IMCTs at all in 2019, as compared to 2018: 27 versus 30.

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The top 10 entities of the Russian Federation by number of IMCTs approved in 2019, in absolute and relative terms, are shown in diagrams 7 and 8 respectively.

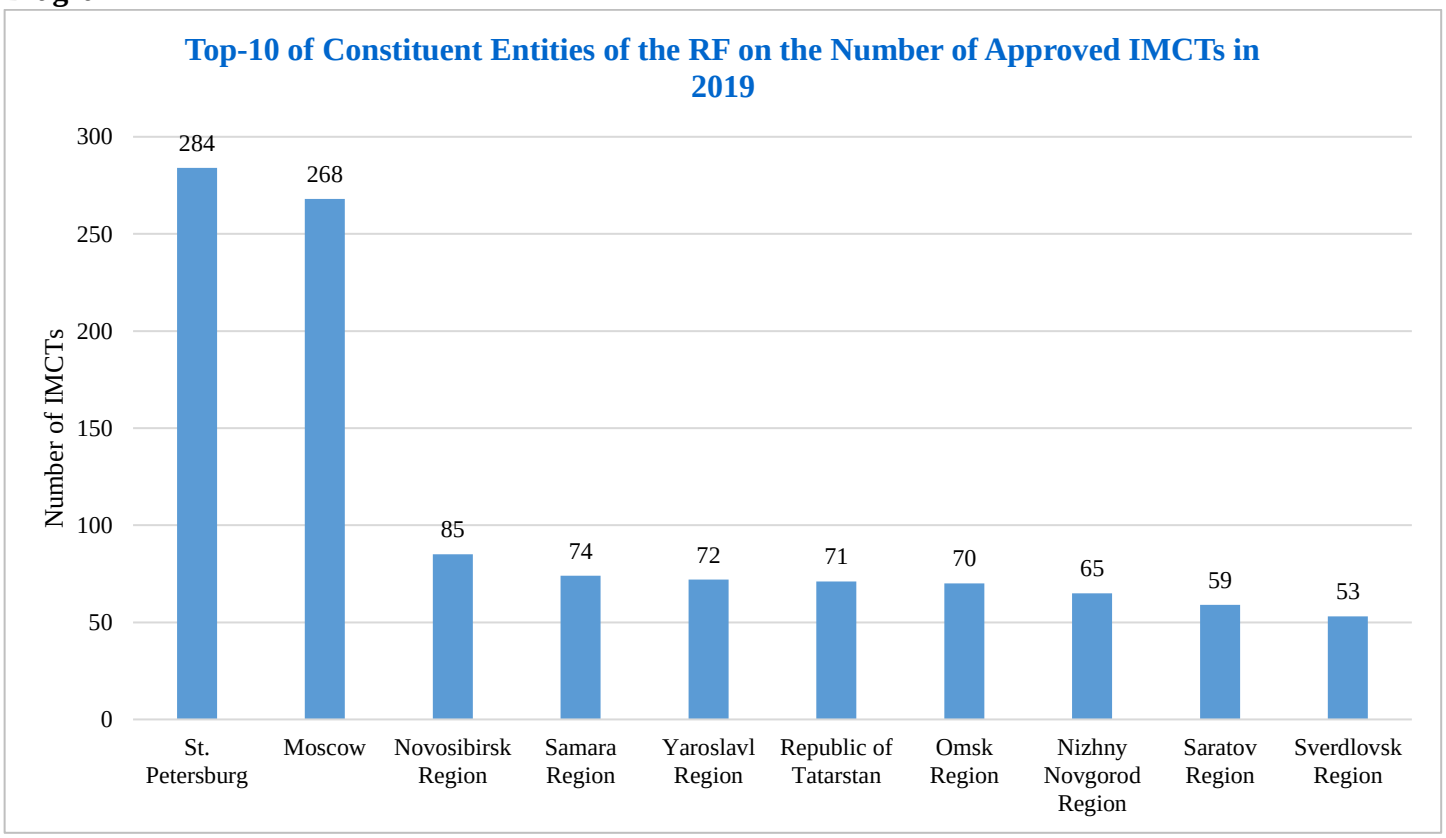
The following changes can be seen in Diagram 7 if we compared it with a similar diagram for 2018. Moscow and Saint-Petersburg swapped places once again: the latter was able to reclaim the leader's laurels which it temporarily lost in 2018 after winning the race in 2017. The gap between the two capital cities does not traditionally exceed 10% of all new projects where regional clinics are supposedly involved. This time the gap is 16 new IMCTs.

In addition to the capital cities, the Republic of Tatarstan, Novosibirsk, Samara, Omsk and Yaroslavl regions retained their spots in the TOP-10 list by the number of new international projects. The Stavropol Territory, Rostov region and Krasnodar Territory lost their places among the TOP-10 leaders. The Nizhny Novgorod, Saratov and Sverdlovsk regions filled the vacant positions. The latter three regions have been annually included in the TOP-10 by IMCTs' number since the beginning of respective monitoring by ACTO, i.e. since 2015, and they temporarily left it only in 2018.

The Yaroslavl region reclaimed the top spot by the number of IMCTs per million population. It had taken this spot since 2015 and ceded it to St. Petersburg only in 2018. Saint-Petersburg ranked second in 2019. Almost all regions shown in Diagram 8 retained their positions in TOP-10 by IMCTs' number per million population with only one exception: the Saratov region replaced the Ryazan region in the tenth position. Almost all regions in the TOP-10 improved their performance which is no wonder given a general increase in the number of IMCTs' approvals in 2019 as compared to 2018. The only regions that showed poorer performance were the Kaluga region (39 IMCTs per million residents in 2018 and only 35 in 2019), the Novosibirsk region (32.1 versus 30.4) and the

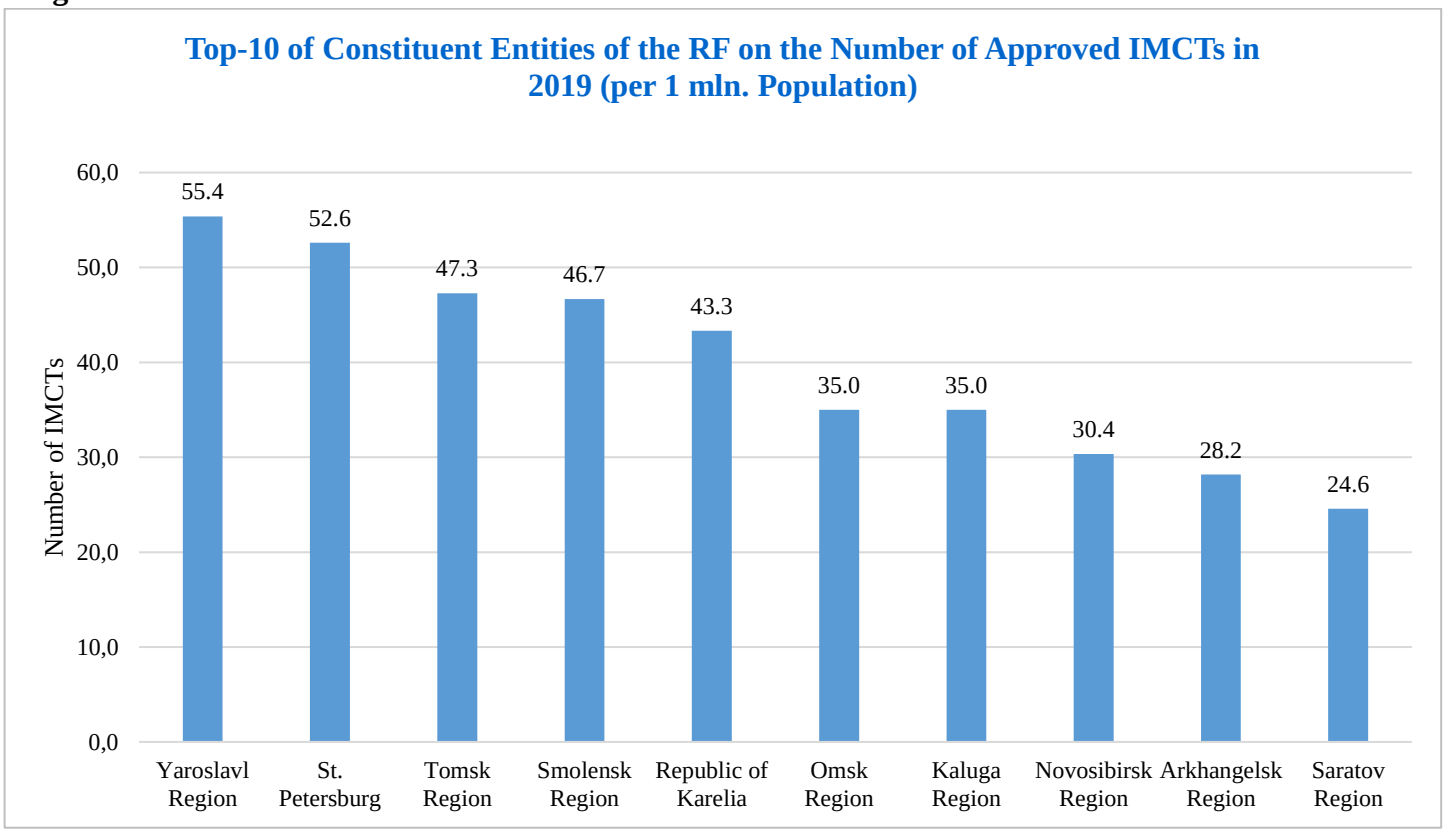
Arkhangelsk region (30 versus 28.2) The highest growth was demonstrated by the Yaroslavl region (from 39.2 in 2018 to 55.4 in 2019), the Smolensk region (from 34 to 46.7) and the Tomsk region (from 38.2 to 46.7).

Diagram 7



Data from www.grls.rosminzdrav.ru

Diagram 8



Data from www.grls.rosminzdrav.ru

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Table 9 lists 20 medical organizations that were most often involved in new IMCTs as per the approvals issued in 2019.

A dozen of these retained their spots in TOP-20. These are:

- N.N. Blokhin Russian Cancer Research Center in Moscow (ranked first in 2016-2018)
- I.P. Pavlov First Saint-Petersburg SMU (ranked first in 2015, second in subsequent years and first again in 2019);
- Omsk Clinical Oncological Dispensary (successively ranked 18th, 16th, sixth, then fourth in 2018 and now ranks third);
- I.M. Sechenov First Moscow State Medical University (successively third, fourth, fifth, split 11-13 positions in 2018, but ranked fifth in 2019);
- National Medical Research Radiological Center in Obninsk (successively 19th, 17th, ninth and once again 17th in 2018, but sixth in 2019).
- M.F. Vladimirsky Moscow Regional Research and Clinical Institute (since the beginning of ACTO monitoring effort in 2015 it cracked the TOP-20 for the first time in 2018 sharing 11-13 positions, but rose to rank 7-8 in 2019);
- City Clinical Oncology Dispensary in St. Petersburg (seventh in 2015, 11th in 2016 and 2017, eighth in 2018 and currently sharing rank 7-8);
- N.N. Petrov Research Institute of Oncology in Saint-Petersburg (sixth in 2015-2016, shared 14-15 positions in 2017, ranked seventh in 2018 and ninth in 2019).
- V.I. Razumovsky Saratov SMU (cracked the TOP-20 only in 2016 when it ranked fifth, in 2017 it ranked tenth, in 2018 - 18th and in 2019 - tenth again);
- I.I. Mechnikov North-Western SMU (ranked 17th in 2015, dropped out of TOP-20 in 2016, came back in 2017 to the 13th rank, ranked third in 2018, but shared 14-15th positions in 2019);
- Saint-Petersburg Clinical Practical Research Centre for Specialised Types of Medical Aid (Oncological) (ranked 12-14 in 2015, dropped out of TOP-20 in 2016; reappeared in 2017 splitting 19-21 positions, ranked 15th in 2018 and 17th in 2019);
- Kazan State Medical University (fourth in 2015, third in 2016 and 2017, fifth in 2018 and only 18th in 2019).

Temporarily absent institutions returned to the TOP. These are:

- Leningrad Regional Clinical Hospital (ranked 16th in 2015; failed to make it into the TOP-20 during other years, and reappeared in the fourth position in 2019);
- Siberian State Medical University in Tomsk (ranked 20th in 2015, seventh in 2016, 16th in 2017 and 11th in 2019);
- V. A. Baranov Republican Hospital in Petrozavodsk (ranked 20th in 2016, failed to crack TOP-20 in other years, split 12-13 positions in 2019);
- Kemerovo S.V. Belyaev Regional Clinical Hospital (ranked fourth in 2017, did not hit the TOP-20 in other years, split 12-13 position in 2019);
- N.A. Semashko Regional Clinical Hospital in Nizhny Novgorod (16th spot in 2015, tenth in 2016, eighth in 2017, outside of TOP-20 in 2018 and a split 14-15 position now).

The following institutions were included in the TOP-20 for the first time during the ACTO monitoring:

- V.M. Bekhterev Psychoneurological Research Institute in Saint-Petersburg (16th spot in 2019);
- Pirogov Russian National Research Medical University (split 19-20 position);
- Ulyanovsk Regional Clinical Hospital (also a split 19-20 position).

The following institutions increased their activity in conducting new international trials more than others: V.M. Bekhterev Psychoneurological Research Institute (from five in 2018 to 21 new IMCTs in 2019); I.P. Pavlov First Saint-Petersburg SMU (from 49 to 63) and Leningrad Regional Clinical Hospital (from 19 to 31). Leaders in terms of this activity reduction was Kazan SMU (from 39 to 20), I.I. Mechnikov North-Western SMU (from 42 to 23) and N.N. Blokhin Russian Cancer Research Center (from 56 to 46).

Table 9

Top-20 Medical Organizations on the Activity of Participation in IMCTs Approved in 2019				
Place in ranking	**Name of medical organization**	**Number of IMCTs approved in 2019 with participation of this medical organization**	**Number of sites approved in 2019 for conducting IMCTs**	**Number of IMCTs and ranking of the sites (on approvals issued in 2018)**
1	I. P. Pavlov First St. Petersburg State Medical University, Russian Ministry of Health, St. Petersburg	63	63	49 (2)
2	N. N. Blokhin Russian Cancer Research Centre, Russian Ministry of Health, Moscow	46	50	56 (1)
3	Clinical Oncological Dispensary, Omsk	44	45	41 (4)
4	Leningrad Regional Clinical Hospital, St. Petersburg	31	31	19 (26–28)
5	I. M. Sechenov First Moscow State Medical University, Russian Ministry of Health, Moscow	29	33	28 (11–13)
6	National Medical Research Radiological Center, Obninsk	29	32	25 (17)
7–8	Moscow Regional Research and Clinical Institute (MONIKI) named after M. F.Vladimirsky, Moscow	29	29	28 (11–13)
7–8	St. Petersburg City Clinical Oncological Dispensary, St. Petersburg	29	29	31 (8)
9	N. N. Petrov Research Institute of Oncology, Russian Ministry of Health, St. Petersburg	27	27	36 (7)
10	Saratov State Medical University named after V. I. Razumovsky, Russian Ministry of Health, Saratov	25	28	24 (18)
11	Siberian State Medical University, Tomsk	25	25	18 (29–30)
12–13	Kemerovo Regional Clinical Hospital named after S. V. Belyaev, Kemerovo	24	24	18 (29–30)
12–13	Republican Hospital named after V.A. Baranov, Petrozavodsk	24	24	19 (26–28)
14–15	Nizhny Novgorod Regional Clinical Hospital named after N. A. Semashko, Nizhny Novgorod	23	23	17 (32–35)
14–15	I. I. Mechnikov North-Western State Medical University, Russian Ministry of Health, St. Petersburg	23	23	42 (3)
16	St.Petersburg Psychoneurological Research Institute named after V.M. Bekhterev, St. Petersburg	21	37	5 (149)
17	St. Petersburg Clinical Practical Research Centre for Specialised Types of Medical Aid (Oncological), St. Petersburg	21	21	26 (15)
18	Kazan State Medical University, Russian Ministry of Health, Kazan	20	21	39 (5)
19–20	Ulyanovsk Regional Clinical Hospital, Ulyanovsk	20	20	17 (32–35)
19–20	Pirogov Russian National Research Medical University, Moscow	20	20	21 (22–24)

Source: www.grls.rosminzdrav.ru

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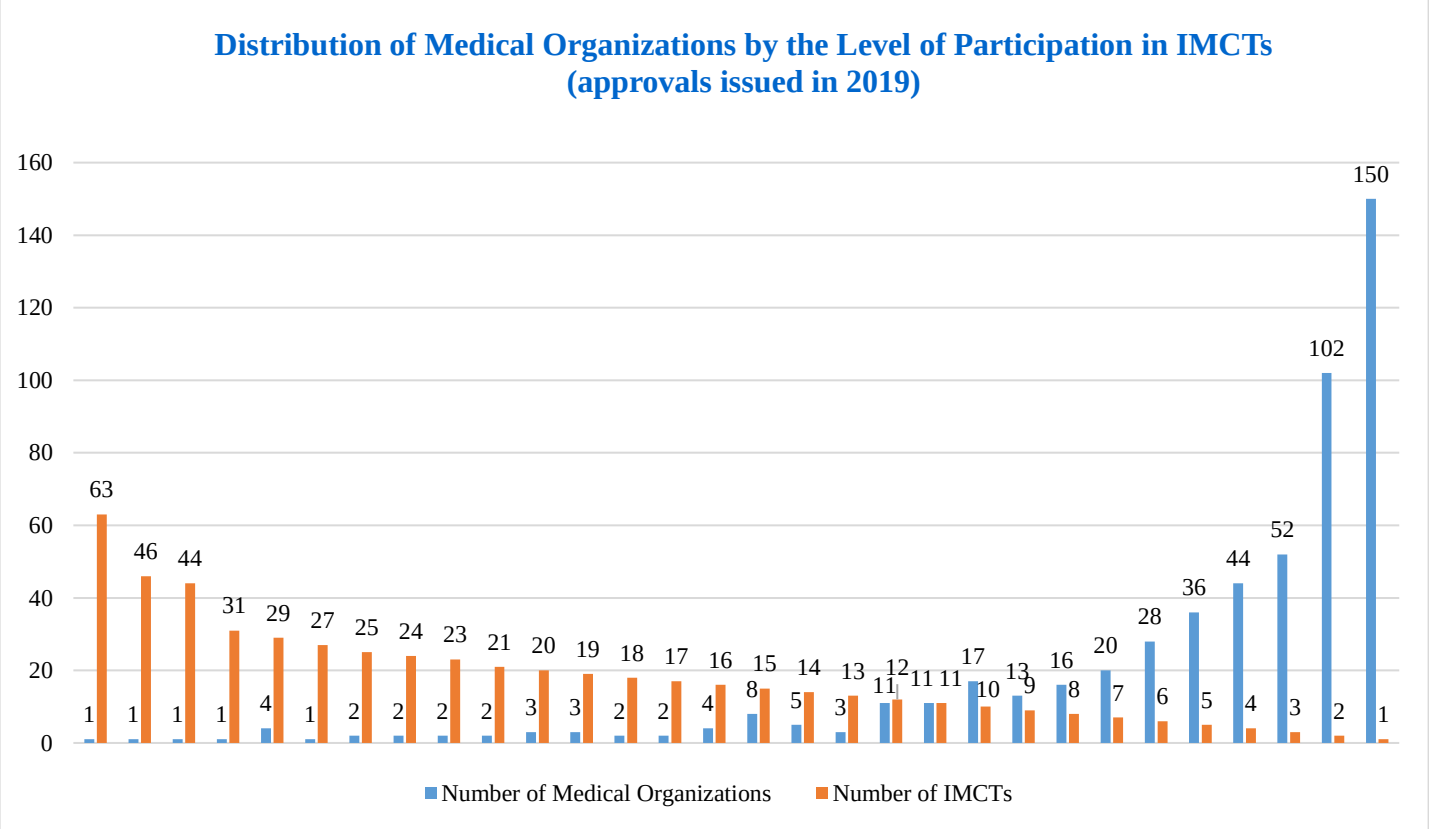
Diagram 10 shows the distribution of IMCT approvals in 2019 by medical organizations. Four clinics were involved in conducting more than 30 new trials, 13 conducted from 21 to 30 IMCTs, 52 - from 11 to 20, 94

- from 6 to 10 trials, 132 - from 3 to 5 and 252 - less than three IMCTs. All in all 547 institutions were involved in IMCTs in 2019, 44 more than a year before.

Diagram 9



Data from www.grls.rosminzdrav.ru

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Traditionally we describe in greater detail the involvement in IMCTs of most active regions, Moscow and Saint-Petersburg, analyzing the distribution of projects by medical organizations of various departmental subordinations. Tables 10 and 11 reveal what categories of clinics stood behind the dynamics in each of the regions.

In Moscow the number of medical organizations involved in IMCTs grew by seven clinics during the year, from 90 to 97. The highest growth can be seen among clinics subordinate to the Moscow Healthcare Department (from 25 to 33 institutions). The number of clinics subordinate to the Moscow Region's Ministry of Health and the JSC "Russian Railways", where sites for international trials were to open, increased by two (from two to four and from one to three, respectively). The number of Moscow non-government clinics involved in IMCTs increased by one (21 versus 20 a year before). The number of Moscow clinics involved in IMCTs and amenable to the Russian Ministry of Health went down (from 21 in 2018 to 20 in 2019) and to other federal authorities (from 21 to 16).

By the number of study sites in Moscow the segment of the "Russian Railways" clinics underwent most drastic changes: the number of sites approved for IMCTs grew by 57%, from 7 to 11. The average 15% growth by the number of sites involved in IMCTs was demonstrated by clinics of the Moscow Region Healthcare Ministry's clinics (from 29 to 34), clinics of federal subordination (save for the Ministry of Health of the Russian Federation) (from 76 to 86) and clinics attached to the Moscow Healthcare Department (from 120 to 139). The number of sites approved for IMCTs in the non-government healthcare system decreased by 17% (from 66 to

55). The number of sites in medical organizations attached to the Russian Ministry of Health remained unchanged (248).

By the activity coefficient calculated as a ratio of sites approved for IMCTs to the number of clinics participating in new IMCTs, institutions subordinate to the Ministry of Health of the Russian Federation took the lead in Moscow in 2019. Because the number of clinics engaged in new IMCTs went down by one, while the number of approved sites matched the last-year number, under the minimal change of absolute indicators the relative one (activity) that already was the highest in the region slightly grew again (from 11.8 to 12.4). For institutions subordinate to the Moscow Region's Ministry of Health the activity factor went down significantly (from 14.5 to 8.5), which can be explained by a twofold growth of the clinic number with the number of sites increased only by 17%. We see a similar situation in the segment of the "Russian Railways" clinics: a threefold growth of clinics involved in IMCTs "diluted" the increase in sites; as a result, the activity coefficient decreased (from 7 to 3.7). The activity growth (from 3.6 to 5.4) of clinics with a federal subordination (save for those attached to the Ministry of Health of the Russian Federation) ensured reduction in the number of engaged medical organizations with simultaneous increase in the number of approved sites. A decrease in the activity coefficient of clinics in the jurisdiction of the Moscow Healthcare Department can be explained by the fact that growth in the number of clinics involved in IMCTs notably overtook growth in the number of sites approved in those clinics. In the nongovernment healthcare system - the only segment where the number of approved sites contracted - this reduction further increased as a result of involving one clinic more than a year before in IMCTs. As a result, the activity coefficient dropped from 3.3 to 2.6.

Table 10

The level of participation of healthcare organizations in Moscow in IMCTs depending on subordination						
Subordinated to	**The number of medical organizations involved in new IMCTs**		**The number of sites approved for IMCTs**		**Activity Coefficient**	
	2019	**2018**	**2019**	**2018**	**2019**	**2018**
Ministry of Healthcare of the Russian Federation	20	21	248	248	**12.4**	11.8
Ministry of Healthcare of the Moscow region	4	2	34	29	**8.5**	14.5
Federal bodies (except Ministry of Healthcare of the RF)	16	21	86	76	**5.4**	3.6
Moscow Department of Healthcare	33	25	139	120	**4.2**	4.8
JSC "Russian Railways"	3	1	11	7	**3.7**	7.0
Non-governmental health system	21	20	55	66	**2.6**	3.3
TOTAL	97	90	573	546	**5.9**	6.1

Data from www.grls.rosminzdrav.ru

In Saint-Petersburg the nongovernment healthcare system takes the lead by the number of medical organizations involved in IMCTs: the number of clinics engaged in international projects grew from 37 to 47. A small growth was observed among the institutions in the jurisdiction of the St. Petersburg Healthcare Committee and federal authorities (apart from the Ministry of Health) and in the Ministry of Health's jurisdiction (by three from 51 to 54; by two from 9 to 11; and by one from 10 to 11, respectively). As for medical organizations of regional subordination involved in IMCTs, the number of such clinics dropped by two (one versus three in 2018). Like a year earlier, only one medical organization of the "Russian Railways" was involved in IMCTs in St. Petersburg.

In the only clinic of the "Russian Railways" five IMCT sites more were approved in 2019 than in 2018 (a 38% growth from 13 to 18). It ensured its activity coefficient growth by the same five percentage points. In the

nongovernment healthcare system of St. Petersburg growth in the number of approved sites from 143 to 173 (i.e. by 21%) could not keep up with growth in the number of clinics, so the activity coefficient eventually slightly dropped (from 3.9 to 3.7). Medical organizations in the Ministry of Health's jurisdiction demonstrated a growing number of approved sites from 187 to 207 (11%); but because the number of clinics involved in IMCTs also grew, the activity coefficient remained almost unchanged (18.7 in 2018 and 18.8 in 2019). In the clinics of the Saint-Petersburg Healthcare Committee the number of approved sites grew by 6% from 264 to 279, but because the number of medical organizations involved in IMCTs grew by the same share, the activity coefficient remained at the same level of 5.2. The number of sites in clinics attached to federal authorities (apart from the Ministry of Health) went down by 17% (from 69 to 57), but because the number of institutions engaged in IMCTs grew in parallel, the activity coefficient in this segment dropped from 7.7 to 5.2. The number of sites in clinics attached to the Healthcare Committee of Leningrad Region dropped deeper than anywhere else - by 30% from 44 to 31, but because the number of medical organizations engaged in IMCTs dropped threefold, the activity coefficient rose dramatically from 14.7 to 31.

Table 11

The level of participation of healthcare organizations in Moscow in IMCTs depending on subordination						
Subordinated to	**The number of medical organizations involved in new IMCTs**		**The number of sites approved for IMCTs**		**Activity Coefficient**	
	2019	**2018**	**2019**	**2018**	**2019**	**2018**
Committee of Health of the Leningrad Region	1	3	31	44	**31.0**	14.7
Ministry of Healthcare of the Russian Federation	11	10	207	187	**18.8**	18.7
JSC "Russian Railways"	1	1	18	13	**18.0**	13.0
Federal bodies (except Ministry of Healthcare of the RF)	11	9	57	69	**5.2**	7.7
Health Committee of Saint-Petersburg	54	51	279	264	**5.2**	5.2
Non-governmental health system	47	37	173	143	**3.7**	3.9
TOTAL	125	111	765	720	**6.1**	6.5

Data from www.grls.rosminzdrav.ru

PARTICIPATION OF MEDICAL ORGANIZATIONS IN BIOEQUIVALENCE STUDIES

Table 12 provides a ranking of medical organisations by their level of participation in bioequivalence studies.

Most institutions remained in TOP-15 since 2018 with only three new names added in 2019: Yaroslavl Regional Clinical Narcology Hospital, X7 Clinical Research Center in St. Petersburg and Cardiology Dispensary in Ivanovo.

Table 12

Top-15 medical organizations on the activity of participation in Bioequivalence Studies (approvals issued in 2019)					
Place in ranking	**Name of medical organization**	**Total number of bioequivalence studies**	**Number of bioequivalence studies conducted by local sponsors**	**Number of bioequivalence studies conducted by foreign sponsors**	**Number of bioequivalence studies and sites ranking on approvals issued in 2018**
1	Medical Center Probiotech, Serpukhov	28	23	5	17 (2)
2	Clinical Hospital № 2, Yaroslavl	23	19	4	31 (1)
3–4	Research Center Eco-bezopasnost, St. Petersburg	17	11	6	13 (6)
3–4	N.P. Bekhtereva Institute of Human Brain of the Russian Academy of Sciences, Saint Petersburg	17	9	8	7 (8–11)
5	Yaroslavl Regional Clinical Narcology Hospital, Yaroslavl	16	15	1	3 (19–23)
6–7	Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk	13	6	7	15 (4)
6–7	Federal Research and Clinical Centre of Physical-Chemical Medicine, Federal Medical-Biologicall Agency, Moscow	13	4	9	6 (12–14)
8–9	Clinical Hospital № 3, Yaroslavl	12	9	3	7 (8–11)
8–9	X7 Clinical Research, St. Petersburg	12	7	5	3 (19–23)
10–11	Cardiology Dispensary, Ivanovo	10	7	3	3 (19–23)
10–11	North-West Public Health Research Center, St. Petersburg	10	10	–	9 (7)
12–13	City Clinical Hospital named after V. P. Demihov, Moscow	9	1	8	14 (5)
12–13	Family Doctor+ Clinic, Nizhny Novgorod	9	8	1	7 (8–11)
14	Road clinical Hospital at the station Yaroslavl, JSC Russian Railways, Yaroslavl	8	6	2	16 (3)
15	Kazan (Privolzhsky) Federal University, Kazan	6	6	–	6 (12–14)

Data from www.grls.rosminzdrav.ru

MAIN PLAYERS ON THE RUSSIAN CLINICAL TRIALS MARKET – 2019

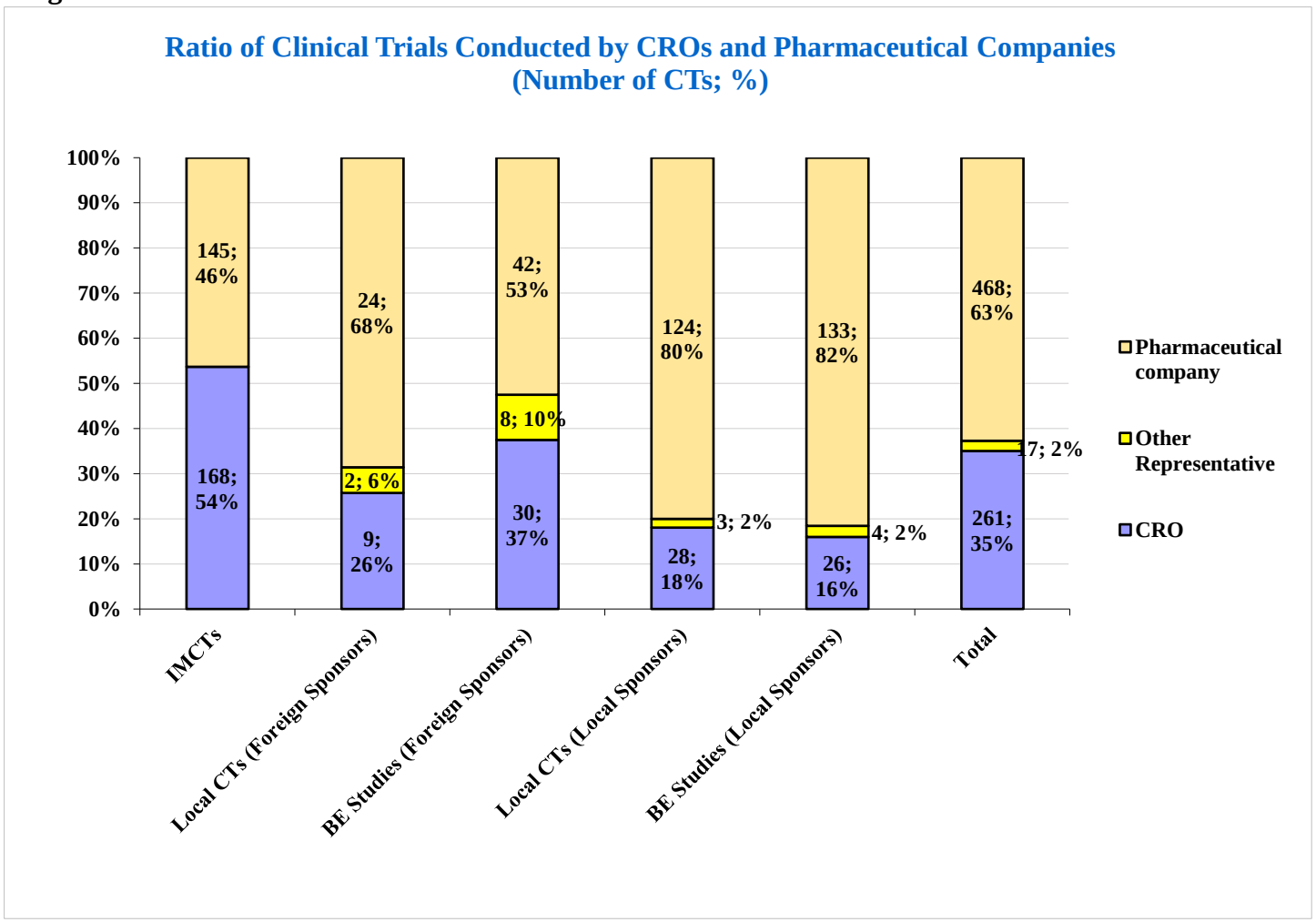
Presented below is the description of activity by main market players in different types of clinical trials. The taxonomy applied is described in more detail in respective sections of ACTO Newsletters No. 14 and 12.

Sponsors and CROs, general structural distribution

Diagram 10 shows what part of approvals issued in 2019 figures in the Ministry of Health's Register as approvals for the conduct of trials by sponsors themselves, and which ones permit trials with third parties involved.

Overall 63% of approved trials in 2019 were conducted by sponsors themselves, which is a minimum number for the entire time of ACTO monitoring (69% in 2018, 67% in 2017 and 2015, 66% in 2016). On the other hand, for CROs the factor of 35% is maximum (30% for 2018, 31% for 2017, 25% for 2016 and 29% for 2015). But it should be mentioned that a change can be caused not only by higher activity of CROs, but also by a more accurate reflection of their involvement in the Ministry of Health Register of Approved Trials which serves as a source of data for us[15]. A simultaneous impact of these factors cannot be excluded either.

Diagram 10



Data from www.grls.rosminzdrav.ru

[15] We pointed out in our previous issues that the activity of CROs could actually be higher because the Ministry of Health register of approved trials does not always reflect full information about involvement of the contract research organizations.

Traditionally IMCTs are evenly split between trials conducted by sponsors themselves and those where CROs are involved. The main proportions are preserved for other types of trials as well. The only thing that catches the eye of those studying the stats for 2019 is a growing activity of "other representatives" [16] - from eight approvals in 2018 to 17 in 2019 (i.e. from 1% to 2% of all approvals in that year), especially in bioequivalence studies by foreign sponsors (four approvals and a share of 6% in 2018 against eight approvals and 10% in 2019).

International multicentre clinical trials, sponsors

Table 13 shows Top-10 sponsors who obtained most approvals for IMCTs in 2019.

Most of these companies were present in the rating in previous years as well. In 2019 Pfizer, AstraZeneca and AbbVie dropped out of the TOP-10 leaders. After a two-year break Novo Nordisk came back. Amgen cracked the TOP-10 for the first time since 2015. Merck & Co. built up the number of approvals from 13 in 2018 to 29 in 2019, whereas Novartis obtained nine approvals less than a year before. As a result, for the first time since ACTO started its monitoring, Novartis ceded the top spot to the company that ranked only fifth-sixth in 2018. F. Hoffmann-La Roche showed the most notable fall as compared to 2018: this company dropped down from second to seventh position because of twofold reduction of the number of approvals for IMCTs obtained during the year.

Table 13

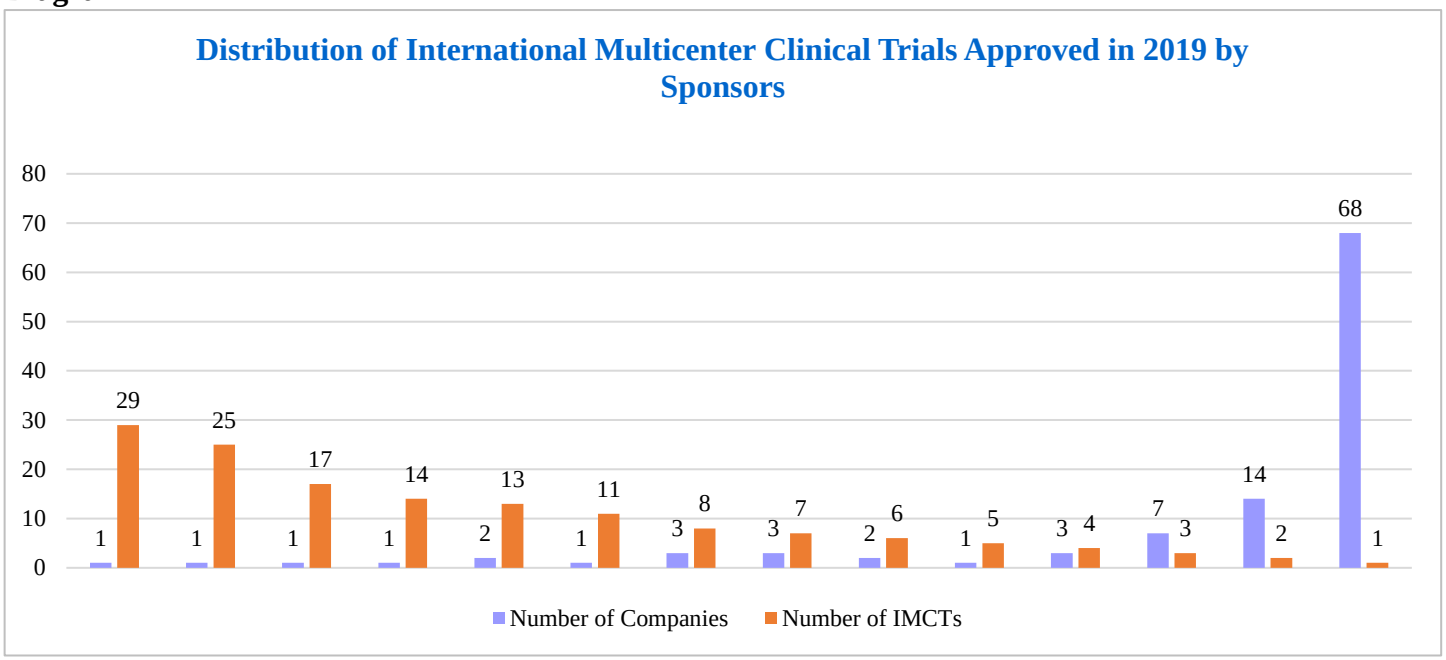
Top-10 Pharmaceutical Companies on Approvals for International Multicenter CTs, 2019					
Rating in 2019	**Company (including separate companies, associated in group of companies, as well as independent divisions of the company)**	**Conducted by themselves**	**Conducted by CRO**	**Total**	**Number of IMCTs; Ranking in 2018**
1	Merck & Co.	29	–	29	13 CTs; 5–6
2	Novartis (incl. Hexal)	23	2	25	32 CTs; 1
3	Janssen Pharmaceutica (incl. Actelion)	16	1	17	15 CTs; 3–4
4	Bristol-Myers Squibb (incl. Celgen и Impact Biomedicines)	6	8	14	12 CTs; 7–8
5–6	Eli Lilly	13	–	13	8 CTs; 10–11
5–6	Sanofi (incl. Sanofi Pasteur and Genzyme Corporation)	10	3	13	9 CTs; 9
7	F. Hoffmann-La Roche	10	1	11	23 CTs; 2
8–10	Allergan	–	8	8	8 CTs; 10–11
8–10	Amgen	8	–	8	2 CTs; 23–32
8–10	Novo Nordisk	8	–	8	3 CTs; 20–22

Data from www.grls.rosminzdrav.ru

Diagram 11 shows a distribution of approvals for IMCTs issued in 2019 among sponsors. Out of 108 companies two obtained more than 20 approvals each, five - from 11 to 20 approvals, eight - from six to ten. Less than five approvals obtained 93 sponsors of whom 68 sponsors got only one approval. The total number of sponsors who obtained approvals for IMCTs in 2019 (108) grew by 14 compared to 2018 (94).

[16] These are understood to be organizations for which conducting clinical trials is not a primary business activity, but nevertheless they may well assume this responsibility. For example, the most typical case is a launching a medicinal product to the market, including registration for which Russian legislation requires local trials.

Diagram 11



Data from www.grls.rosminzdrav.ru

International multicentre clinical trials, CROs

The TOP-10 CROs who more frequently involved in IMCTs than others as per the approvals provided in 2019 are presented in Table 14.

IQVIA ranked first again, as usual, while the last year's leader Parexel went back to the fifth position which it took in 2017. Other members of the TOP-10 also moved slightly, but their list remained almost unchanged, if not for Worldwide Clinical Trials that claimed the ninth spot, replacing Medpace and Synergy Research Group that ranked 9-11 a year before.

Table 14

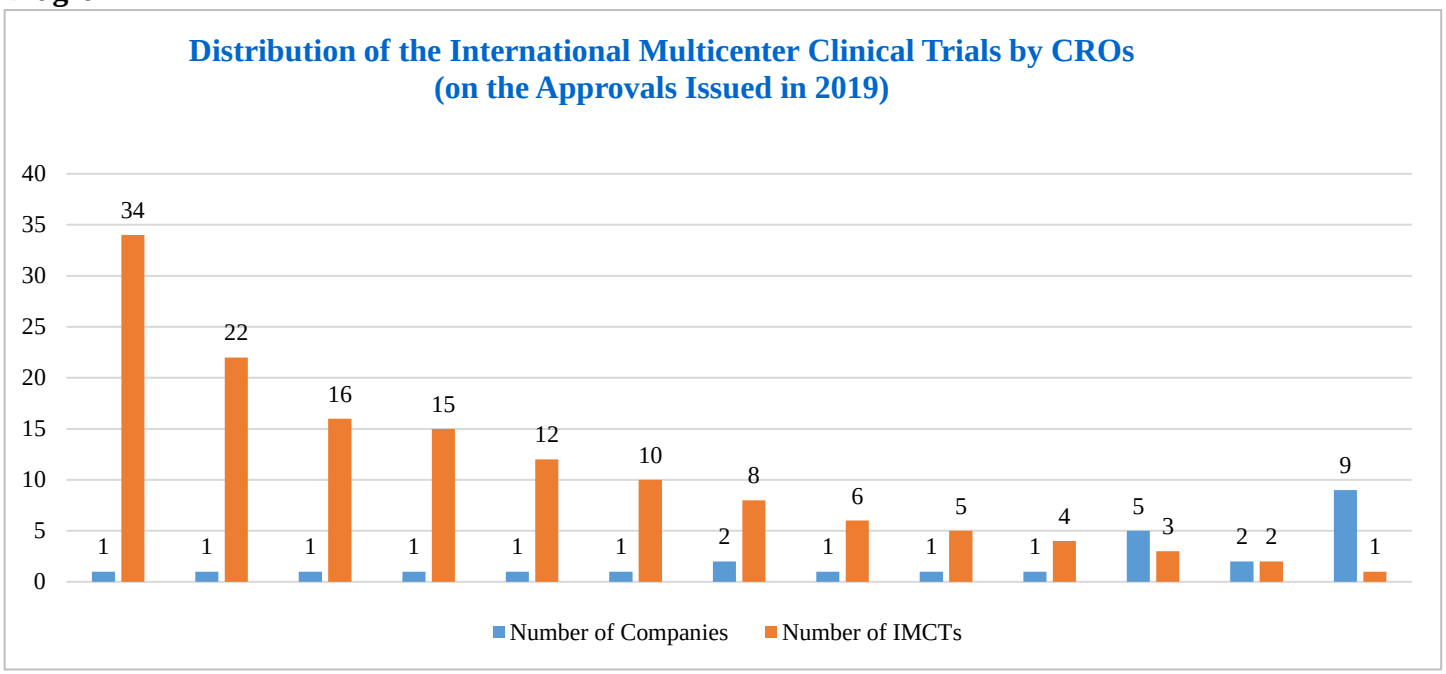
Top-10 CROs on Approvals for International Multicenter CTs, 2019				
Ranking in 2019	**Company**	**Number of IMCTs**	**Number of Sponsors**	**Number of IMCTs; Ranking in 2018**
1	IQVIA	34	20	11 CTs; 5
2	Syneos Health (INC Research + inVentiv Health Clinical)	22	13	17 CTs; 2–3
3	PRA Health Clinical	16	9	6 CTs; 7–8
4	PPD	15	11	17 CTs; 2–3
5	Parexel	12	6	22 CTs; 1
6	ICON	10	8	10 CTs; 6
7–8	Covance	8	6	6 CTs; 7–8
7–8	PSI	8	5	13 CTs; 4
9	Worldwide Clinical Trials	6	2	2 CTs; 11–19
10	MB Quest	5	5	3 CTs; 9–11

Data from www.grls.rosminzdrav.ru

Diagram 12 shows the distribution of new IMCTs among contract research organisations.

Out of the total number of 27 CROs (three less than in 2018) five were involved in more than 10 IMCTs, four - in six to ten trials, and 18 - for participation in five or fewer international projects.

Diagram 12



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies, foreign sponsors

Table 15 shows information about foreign sponsors who obtained most approvals for local trials and bioequivalence studies.

Table 15

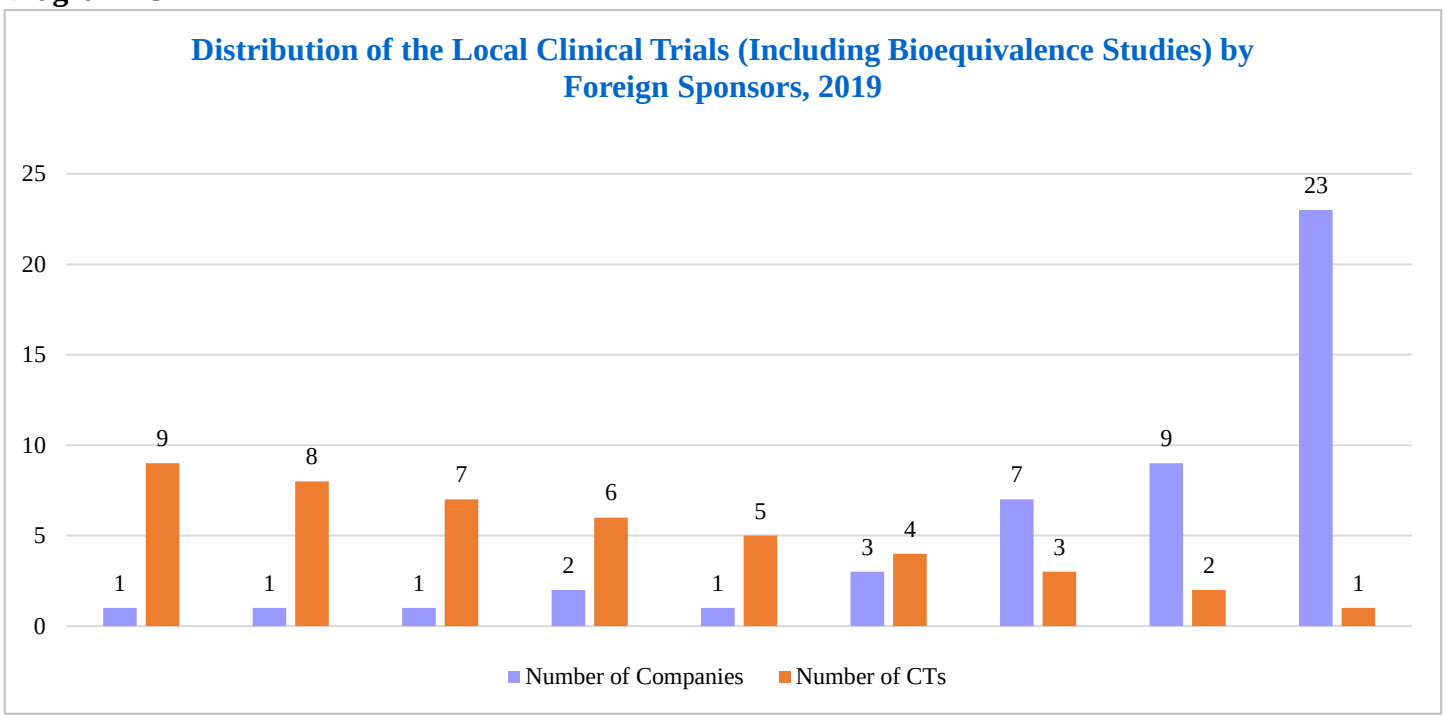
Ranking of Leading Foreign Sponsors on Approvals for Local CTs and Bioequivalence Studies, 2019					
Ranking in 2019	**Company**	**Conducted by themselves**	**Conducted by CROs/other representatives**	**Total**	**Number of CTs; Ranking in 2018**
1	Hetero Labs	9	–	9	9 CTs; 1
2	Gedeon Richter	–	8	8	n/a
3	KRKA	7	–	7	6 CTs; 3
4–5	Berlin-Chemie	–	6	6	n/a
4–5	Dr. REDDY's Lab.	6	–	6	3 CTs; 7–8
6	Rompharm Company	5	–	5	2 CTs; 9–16
7–9	Pharmland	–	4	4	1 CT; 17–47
7–9	Polpharma (incl. Medana Pharma)	4	–	4	7 CTs; 2
7–9	Xantis Pharma	–	4	4	2 CTs; 9–16

Data from www.grls.rosminzdrav.ru

Hetero Labs retained the first place, KRKA - third place. Dr. REDDY’s Lab that climbed several lines up and Polpharma that was worse off than in the previous year - can also be found in the list of leaders like in 2018. But on the whole this rating is prone for renewal more than the above-listed rating of IMCT sponsors, since five companies in Table 15 were not included in the TOP based on the results for 2018.

The distribution of new local trials and bioequivalence studies among foreign companies is shown in diagram 13. In our Newsletter for 2018 we mentioned the tendency towards the reduction in the number of sponsors of these types of trials, but in 2019 this tendency slowed down: in 2016 approvals were issued for 99 companies, in 2017 - for 59 companies, in 2018 - for 47 and in 2019 - for 48.

Diagram 13



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies, domestic sponsors

Table 16 introduces Russian sponsors leading by the number of approvals for local trials and bioequivalence studies in 2019.

Only Pharmasyntez (top rank again), Biocad (still second), Atoll and R-Pharm (both took lines 8-11 against 5-6 in 2018) retained their positions in the rating since last year. The rest of the list has been renewed. Among the leaders by approval growth are Amedart, Canonpharma Production and the startup Alium.

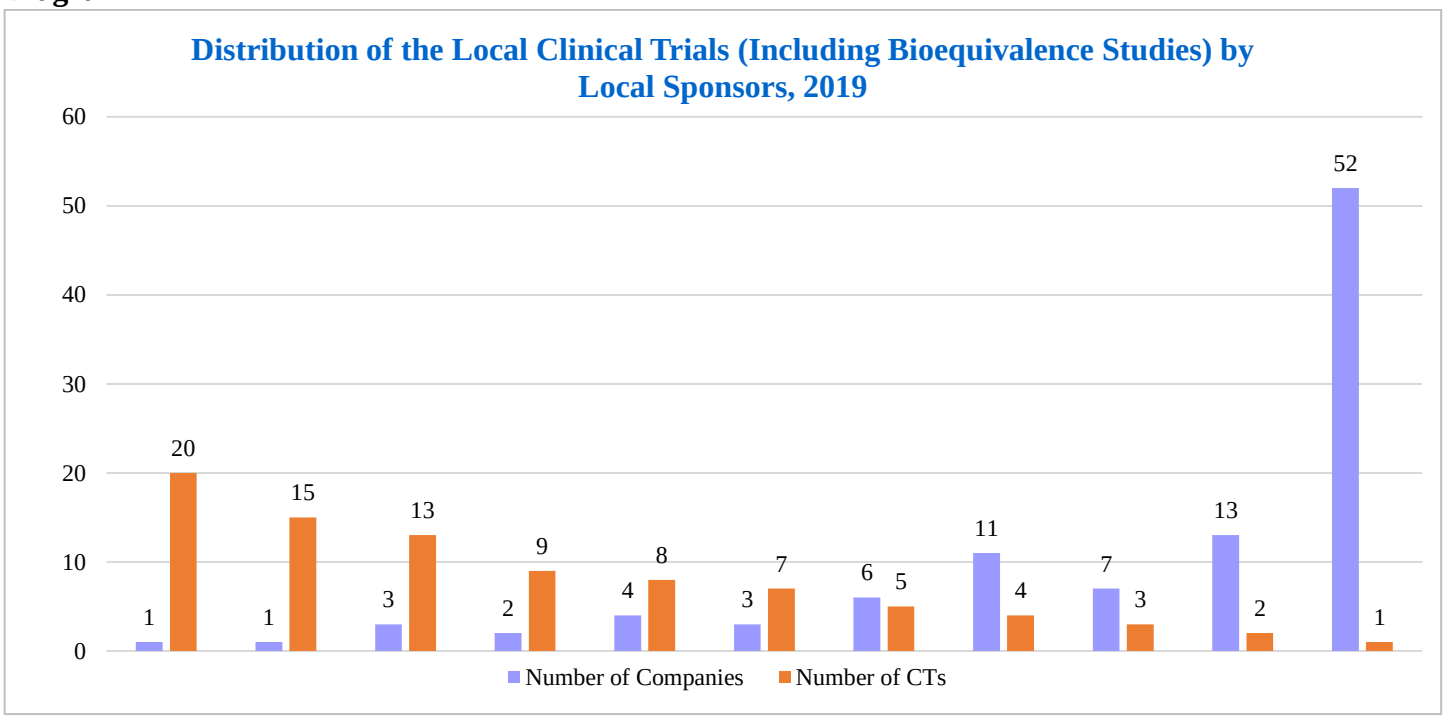
Table 16

Top-10 Local Sponsors on Approvals for Local Clinical Trials and Bioequivalence Studies, 2019					
Ranking in 2019	**Company**	**Conducted by themselves**	**Conducted by CRO**	**Total**	**Number of CTs; Ranking in 2018**
1	Pharmasyntez (incl.Pharmasyntez-Tyumen and Pharmasyntez-Nord)	20	–	20	23 CTs; 1
2	Biocad	15	–	15	13 CTs; 2–4
3–5	Alium (PE "Obolenskoe" + Binnopharm)	13	–	13	3 CTs; 21–29 – PE "Obolenskoe"; 2 CTs; 30–41 – Binnopharm)
3–5	Amedart	13	–	13	n/a
3–5	Canonpharma Production	13	–	13	5 CTs; 11–17
6–7	Generium	9	–	9	4 CTs; 18–20
6–7	Geropharm	9	–	9	3 CTs; 21–29
8–11	Atoll	8	–	8	12 CTs; 5–6
8–11	Biocom	–	8	8	n/a
8–11	MedInvest	–	8	8	1 CT; 42–94
8–11	R-Pharm	8	–	8	12 CTs; 5–6

Data from www.grls.rosminzdrav.ru

Diagram 14 shows the distribution of approvals issued in 2019 for local trials and bioequivalence studies among domestic sponsors. Approvals were provided for 103 companies, nine more than in 2018.

Diagram 14



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies, CROs

The top ranking of the CROs which participated most actively in conducting local trials and bioequivalence studies in 2019 is shown in Table 17.

Table 17

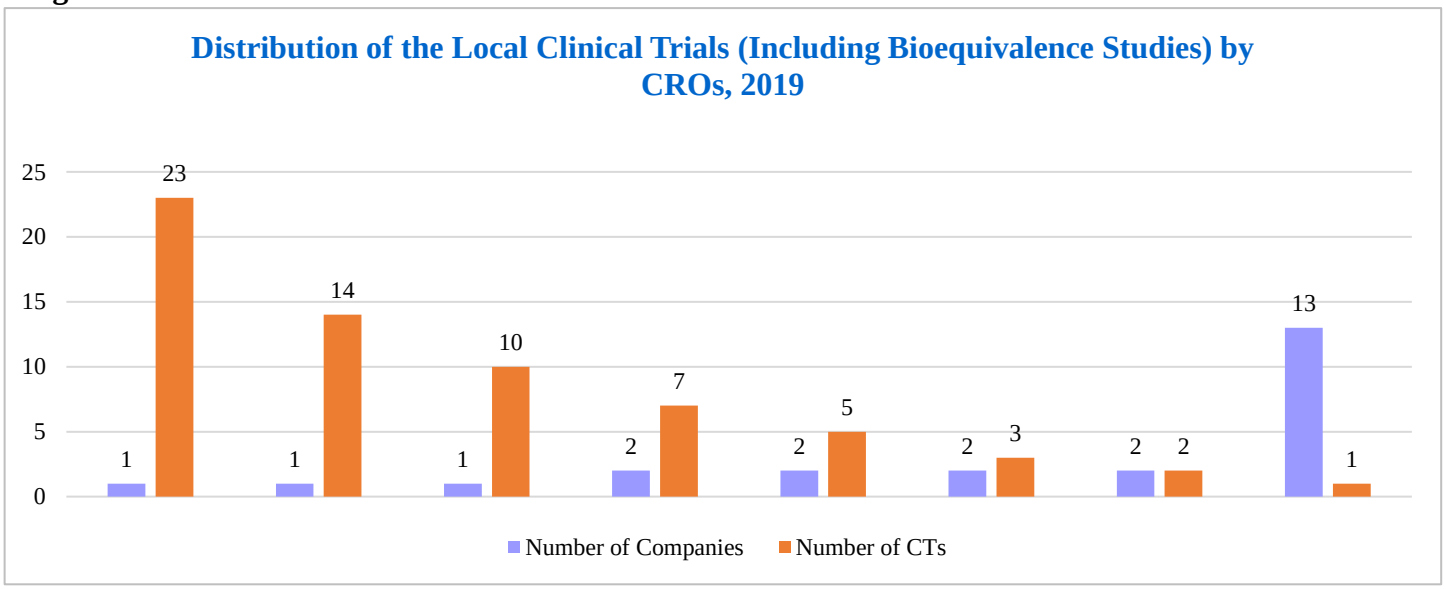
CROs Involved in the Local CTs and Bioequivalence Studies (on Approvals Issued in 2019)						
Ranking in 2019	**Company**	**Number of CTs of foreign sponsors**	**Number of CTs of local sponsors**	**Total number of local CTs, 2019**	**Number of sponsors**	**Number of CTs; Ranking, 2018**
1	Probiotech	9	14	23	8	2 CTs; 9–11
2	Medical Development Agency (MDA)	1	13	14	6	6 CTs; 3
3	Synergy Research Group	9	1	10	3	4 CTs; 5–7
4–5	IPHARMA	2	5	7	6	11 CTs; 1
4–5	R&D Pharma		7	7	4	7 CTs; 2
6–7	Biomapas	5		5	1	n/a
6–7	X7 Research	4	1	5	3	4 CTs; 5–7
8–9	Innovative Pharmacology Research (IPHAR)	3		3	1	n/a
8–9	SCT	2	1	3	3	n/a
10–11	Ligand Research		2	2	2	1 CT; 12–20
10–11	OCT		2	2	2	3 CTs; 8

Data from www.grls.rosminzdrav.ru

Last-year leaders IPHARMA and R&D Pharma dropped down to 4-5 ranks. In 2019 the rating was topped by Probiotech (that shared 9-11 positions a year before), followed by MDA that rose from the third spot and Synergy Research Group that shared 5-7 places in 2018. New names on the leaders' list include Biomapas, IPHAR, SCT and Ligand Research that demonstrated remarkable growth.

Diagram 15 shows the distribution of local trials and bioequivalence studies among contract research organisations. Overall 24 CROs were involved in this type of trials in 2019, four more than in 2018.

Diagram 15



Data from www.grls.rosminzdrav.ru

TIMEFRAMES FOR OBTAINING APPROVALS

This time 33 company members of ACTO and AIPM took part in the annual survey regarding the time of obtaining approvals needed for the conduct of clinical trials. The data of applications submitted in 2019 as well as those submitted earlier if decisions on them were made in 2019 were actually processed. See respective sections of the previous issues of ACTO Newsletter for more information about the methodological aspect of monitoring.

The results of the survey are shown in table 18. Compared to the results for 2018, the changes were insignificant. The average time of issuing an approval for conducting clinical trial is five days shorter now, 87 days instead of 92 days. It took the organizers one day longer in 2019 on average, than in 2018, to obtain licenses for importing medicinal products - 15 days instead of 14 days a year before. The average time of getting permits to make amendments to the protocol increased by one day. For other approval - by three days.

Table 18

Timeframes for Issuing Approvals, 2019					
Type of approval	**Timeframes according to legislation (workdays/calendar days)**	**Average timeframes (calendar days)**	**Minimum timeframes (calendar days)**	**Maximum timeframes (calendar days)**	**Sampling**
To Conduct Clinical Trials*	41/57**	87	51	273	257
To Import Medicines	8/12	15	5	51	428
To Import/Export Biosamples	13/19	20	4	54	974
To Make Amendments to the Protocol	34/48	48	8	84	446
Other Approvals***	25/35	29	8	142	835

Data from timeframes monitoring of ACTO and AIPM

* For all applications, regardless of the availability of requests from expert organizations or the Ministry of Health. If there is a request, the response time is not excluded from the calculation;

** In the absence of requests from expert organizations or the Ministry of Health;

*** To prolong clinical trials, to include new sites, to enroll additional patients, etc.

Table 19 shows the stats of timeframes violations in issuing approval documents. The share of approvals to conduct trials issued on time barely grew during the year (from 21.8% to 22.8%) as well as for import/export of biosamples (from 41.7% to 42.7%) and for making amendments to the protocol (from 64.4% to 64.8%). On the contrary, the shares of timely issued licenses for the import of medicinal products and especially for other approvals sank drastically (from 44.3% to 34.6% and from 91.5% to 78.9%, respectively).

Most often the actual time of providing permits exceeded the deadline set in the law by less than 1.5 time. An appreciable share of timeframes violations by 1.5-2.0 times in 2019 took place only in providing licenses for the import of medicinal products (15.7% of all permits of this type) and import/export of biosamples (7.5%). Exceeding the deadlines for granting some types of permits by more than two times took place in rare cases: 6.7% of permits for import of medicinal products; 0.7% of permits for import/export of biosamples; 0.2% of other approvals. These data roughly match the structure of issue timeframes violations on different types of approvals for 2018.

Table 19

Violations of Timeframes, 2019 vs 2018								
Type of Approval		Approvals Issued on Time	Approvals Issued in Violation of Timeframes					
			Total	Less than in 1.5 times	In 1.5–1.9 times	In 2–2.9 times	In 3–3.9 times	In 4 times and more
To Conduct Clinical Trials*	2019	22.8%	77.2%	76.5%	0.7%	0.0%	0.0%	0.0%
	2018	21.8%	78.2%	73.3%	4.9%	0.0%	0.0%	0.0%
To Import Medicines	2019	34.6%	65.4%	43.0%	15.7%	6.3%	0.2%	0.2%
	2018	44.3%	55.7%	38.8%	12.0%	4.2%	0.5%	0.2%
To Import/Export Biosamples	2019	42.7%	57.3%	49.1%	7.5%	0.7%	0.0%	0.0%
	2018	41.7%	58.3%	47.7%	9.3%	1.3%	0.0%	0.0%
To Make Amendments to the Protocol	2019	64.8%	35.2%	32.1%	3.1%	0.0%	0.0%	0.0%
	2018	64.4%	35.6%	33.3%	2.3%	0.0%	0.0%	0.0%
Other Approvals**	2019	78.9%	21.1%	19.5%	1.3%	0.0%	0.1%	0.1%
	2018	91.5%	8.5%	7.1%	1.3%	0.1%	0.0%	0.0%

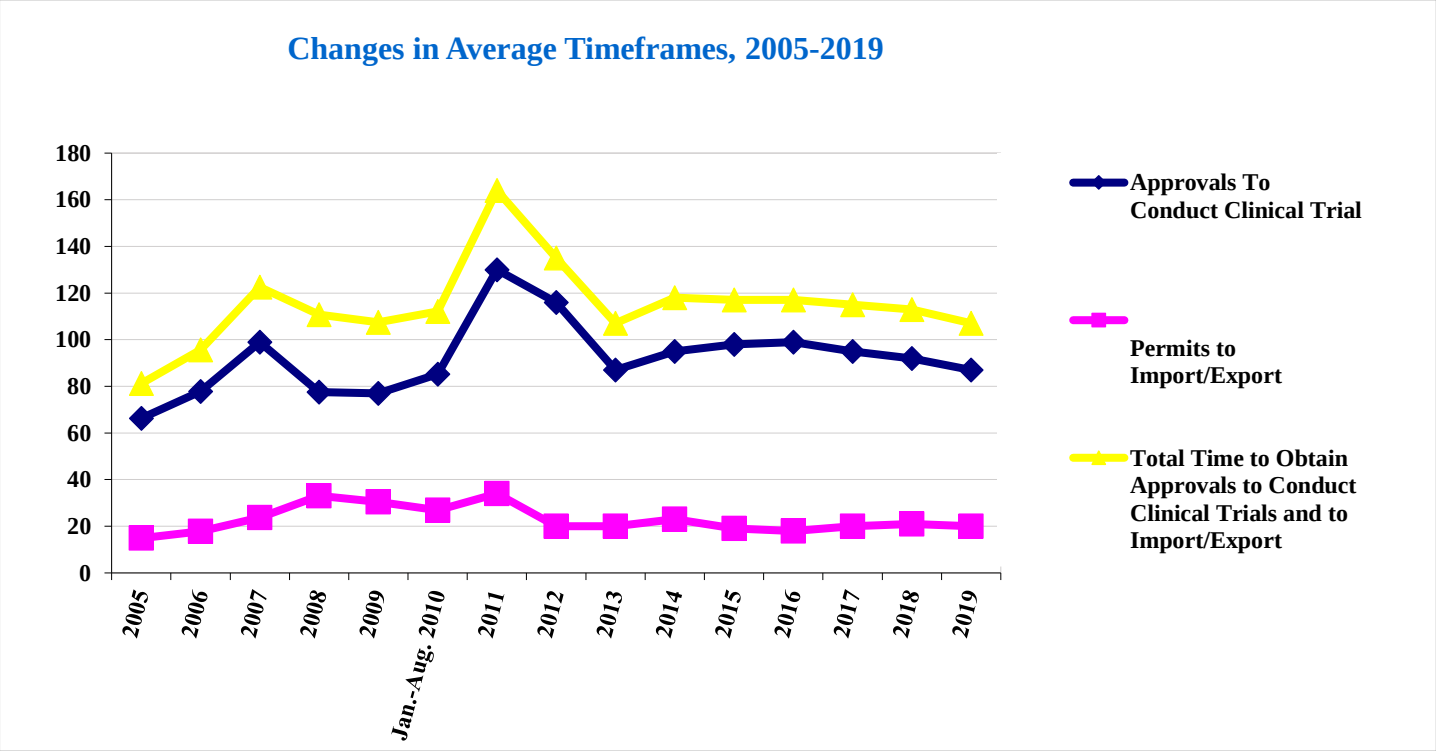
Data from timeframes monitoring of ACTO and AIPM

* The calculation of deadlines for clinical trial approvals was carried exclusively those applications where there were no requests from expert organizations or the Ministry of Health.

** To prolong clinical trials, to include new sites, to enroll additional patients, etc.

Diagram 16 lets us track a change in the time of issuing approval documents since 2005 and see the stability of these figures during seven recent years.

Diagram 16



Data from timeframes monitoring of ACTO

IMPORT OF MEDICINAL PRODUCTS FOR CLINICAL TRIALS

Given below in tables 20 and 21 are the statistics of import to the Russian Federation of medicinal products for clinical trials including comparators and concomitant treatment.

Compared to 2018, the import volume increased across all parameters analysed. The total value of medicinal products shipments to be used in clinical trials in the ruble equivalent grew by 12.3%. The growth came to 9% in dollar terms. Respective ruble growth is demonstrated by VAT amounts (12% more than in 2018) and custom duties (12.3%) as well as the VAT + Customs duties + Customs fees indicator (12.2%). The amount of customs fees grew even more - by 25.1%.

Table 20

Import of medicinal products to the Russian Federation for clinical trials, 2018–2019		
Parameter	**2018**	**2019**
Total value of shipments, rub.	14 456 760 247	16 241 047 409
Total value of shipments, $	230 850 496	251 611 534
VAT, rub.	1 492 894 044	1 672 642 159
Customs duties, rub.	435 953 057	489 490 838
Customs fees, rub.	14 909 846	18 654 524
VAT + Customs duties + Customs fees, rub.	1 943 756 947	2 180 787 522

Source: RNC Pharma

Table 21 shows the manufacturers whose medicines had the largest share in the overall volume of imported medicinal products for clinical trials in 2019. We traditionally remind that not always the below-listed companies ensure such a high volume of their medicinal products' import. CROs and competitors in need of comparators or background therapies can also import the medicines of said manufacturers. The share of supplies for which the manufacturer is in charge is indicated in a separate column of the table.

Comparison with last year's results shows that most companies are still in the TOP-10 leaders by import with the exception of GSK and Kyowa Corp. which had ranked seventh and ninth, respectively. These are replaced by Alexion Pharmaceuticals and Sanofi (they rank eighth and ninth based on the results for 2019, respectively).

Table 21

Top-10 pharmaceutical companies on import of medicinal products for clinical trials, 2019					
Ranking	**Company**	**Value of shipments, rub.**	**Number of shipments**	**Imported by the companies themselves, %**	**Ranking, 2018**
1	Novartis	2 058 268 863	438	91.2%	2
2	Merck & Co.	2 042 188 361	185	77.6%	3
3	Johnson & Johnson	1 616 469 566	189	53.8%	1
4	F. Hoffmann-La Roche	1 541 427 821	214	33.5%	4
5	BMS. incl. Celgene Corp.	930 911 331	146	24.0%	BMS - 16; Celgene - 8
6	Pfizer	708 069 095	141	48.9%	6
7	Amgen	634 605 045	188	61.4%	10
8	Alexion Pharmaceuticals	479 465 656	26	0.0%	15
9	Sanofi	398 068 857	114	92.7%	11
10	Merck Group	380 194 782	26	0.0%	5

Source: RNC Pharma

IMCTs INVOLVING CHILDREN AND YOUNG PEOPLE

While clinical trials involving pediatric population have always roused the interest of the industry representatives, this is the first time we have attempted to generalize existing information about trials with pediatric (i.e. only minors) and mixed (both younger and older than 18) population. Described below is only part of these studies, to be more exact. To begin with, we thought it sufficient to describe the trials for which approvals were provided throughout 2019; this was like a practice run. Secondly, limited sampling was caused by the fact that the age of patients is not indicated in the Ministry of Health register of approved trials so for local trials involving children and young people the key parameter, i.e. the age range of participants, remains unknown. Therefore, we have to be content with the description of international multicentre trials only.

For IMCTs it's possible to partially reconstruct the age range, relying on the data found on ClinicalTrials.gov and ClinicalTrialsRegister.eu resources. But even if on a global scale patients younger than 18 are included in a trial, Russian sites can only recruit adults for various reasons. Sometimes a sponsor decides that underage participants will be recruited at sites outside Russia and then a trial in Russia is originally declared to be designed solely for the adult population. Sometimes one of the conditions for enrollment in IMCTs is participation in a sponsor's previous trial for which children in Russia were not enrolled and, accordingly, there can be no participants younger than 18 in a new trial either. Another reason causing our special concern is that the Russian Ministry of Health can raise the lower age limit for participants, when issuing an approval for a particular trial, or even totally exclude underage patients from the trial. Therefore, an additional survey of sponsors was required to clarify the age range data.

Overall 66 approvals for IMCTs involving children and young people were issued in 2019, which accounts for 21% of all IMCTs approvals issued in 2019, including 47 IMCTs (71%) in pediatric population. Another 19 trials (29%) targeted a mixed population. In addition to the above-mentioned 66 trials, the plan called for including patients younger than 18 in at least two more IMCTs later, in 2020, using a special amendment to the protocol. In February 2020 one company managed to partially reinstate the curbed age range (the age range 1-18 was declared, but the initial submittal resulted in the age range of 12-18 to be approved[17]). Yet later they were able to obtain an approval for including children from the age of 6 via a special amendment to the protocol. The amendment to the second protocol that was reported by our members was still being prepared for submittal at the time when the given materials was being written.

The age range in all 66 IMCTs involving children and young people can be seen in Diagram 17. Each column matches a separate IMCT, whereas the column's height shows the age range of the trial's participants. The diagram also shows IMCTs with a mixed population, but for them the upper age limit is always 20 years, although in these very 19 trials the upper age limits of participants were usually way above 20 years.

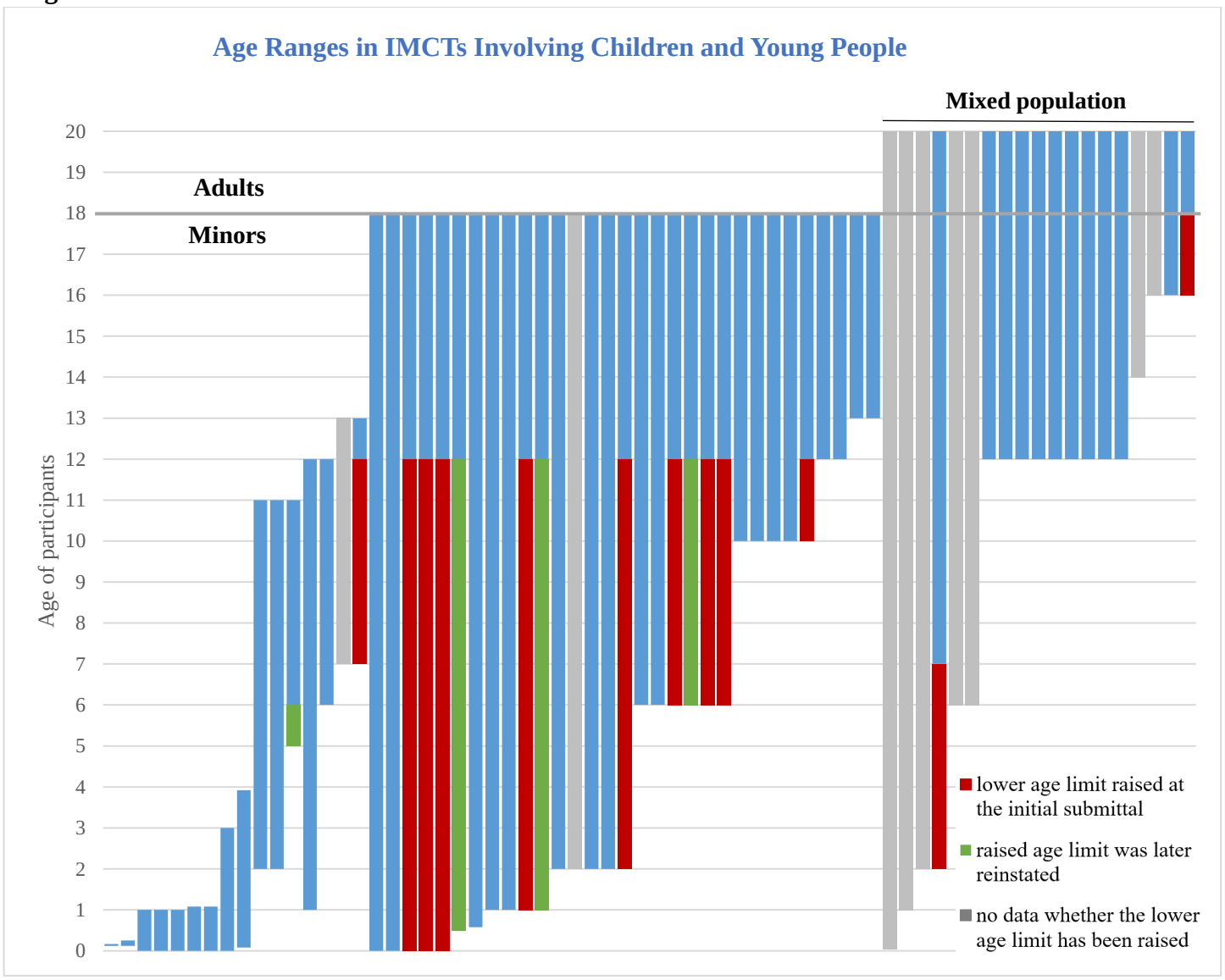
As we already mentioned, whenever the Ministry of Health issues clinical trials approvals, this department sometimes raises the lower age limit of participants (often without any prior discussion with the applicant) and information published on ClinicalTrials.gov or ClinicalTrialsRegister.eu about the age range is not always valid for Russia. This is why we had to conduct the above-mentioned survey among most sponsors of IMCTs involving children and young people that were approved in 2019. We tried to find out, whether the age range was curbed at submittal. This proved true at least in 16 cases[18] (shown in red and green on the Diagram 17); in four out of these 16 cases (green colour on the diagram) applicants later succeeded in obtaining approvals for the originally supposed age range. In at least four more out of the same 16 IMCTs sponsors have already requested or plan to request the widening of the age range that was narrowed.

[17] This is not reflected in the diagram.

[18] We could poll the sponsors of 57 out of 66 IMCTs involving children and young people, for which approvals were issued in 2019. Nine more IMCTs can potentially be "curbed" as well.

When we correlate 16 “curbed” trials with the total number of 66 IMCTs, it should be borne in mind that we could not poll all sponsors. This is how the ratio of shares looks in short form: 24% of IMCTs involving children and young people approved in 2019 (16 IMCTs) are trials where the age range was narrowed in primary approval; 14% (9 IMCTs shown in gray on the diagram) are those on which we do not have full data; and 62% (41 IMCTs) are trials where the lower age limit of participants was not raised in the process of approval.

Diagram 17



Data from www.grls.rosminzdrav.ru, www.clinicaltrials.gov, www.clinicaltrialsregister.eu, survey of sponsors

It can be seen on the diagram that most often the regulator did not allow to include children younger than 12. The age range truncation was not always accompanied by explanation of reasons[19], but when it was, the most common motivation was insufficiency of data on safety. A typical sequence of events after that: a sponsor collects safety data for the requested age group, submits them and pleads for the age range to be widened, to match the originally planned one. Unless the regulator finds any reasons for concern, the age range is widened.

At first glance, especially glance of nonspecialists, the regulator’s practice to exclude children under 12 from trials without additional safety data may seem a justified risk-reducing move. However, this view is at

[19] The following answer of the Ethics Council to a query by one of our members can hardly be viewed as rationalization: The age curbing decision “is related to the fact that consistent age gradations have long existed in pediatrics: 0-2, 2-6, 6-12, above 12 - based on the anatomical and physiological features of the child’s organism”.

variance with international guidelines on conducting trials involving pediatric population . As per the ICH E11 (R1) Guideline on Clinical Investigation of Medical Products in the Pediatric Population, *"Chronologic age alone may not serve as an adequate categorical determinant to define developmental subgroups in pediatric studies. Physiological development and maturity of organs, pathophysiology and natural history of the disease or condition, available treatment options, and the pharmacology of the investigational product are factors to be considered in determining the subgroups in pediatric studies. Further, the arbitrary division of pediatric subgroups by chronological age for some conditions may have no scientific basis and could unnecessarily delay development of medicines for children by limiting the population for study* [20]*."* In the Russian regulatory authority's practice children under 12 (12 is almost always the dividing line) are excluded from trials of various medicinal products in patients with various diseases, and that causes doubts in scientific validation of all decisions to narrow the age range.

It should be noted that even if the age range has not been narrowed, sponsors requesting the approval of pediatric trials, more often than sponsors applying for a trial with only adults involved, receive requests (including multiple) from Scientific Centre for Expert Evaluation of Medicinal Products (SCEEMP), which considerably extends the approval issue time. Furthermore, one of the sponsors pointed out in our survey that in his trial the age range was not eventually curbed, but to achieve this outcome, the sponsor had to agree to a tradeoff and to reduce the number of underage patients to be enrolled. In other words, raising the lower age limit is far from being the only risk faced by sponsors of clinical trials involving pediatric population .

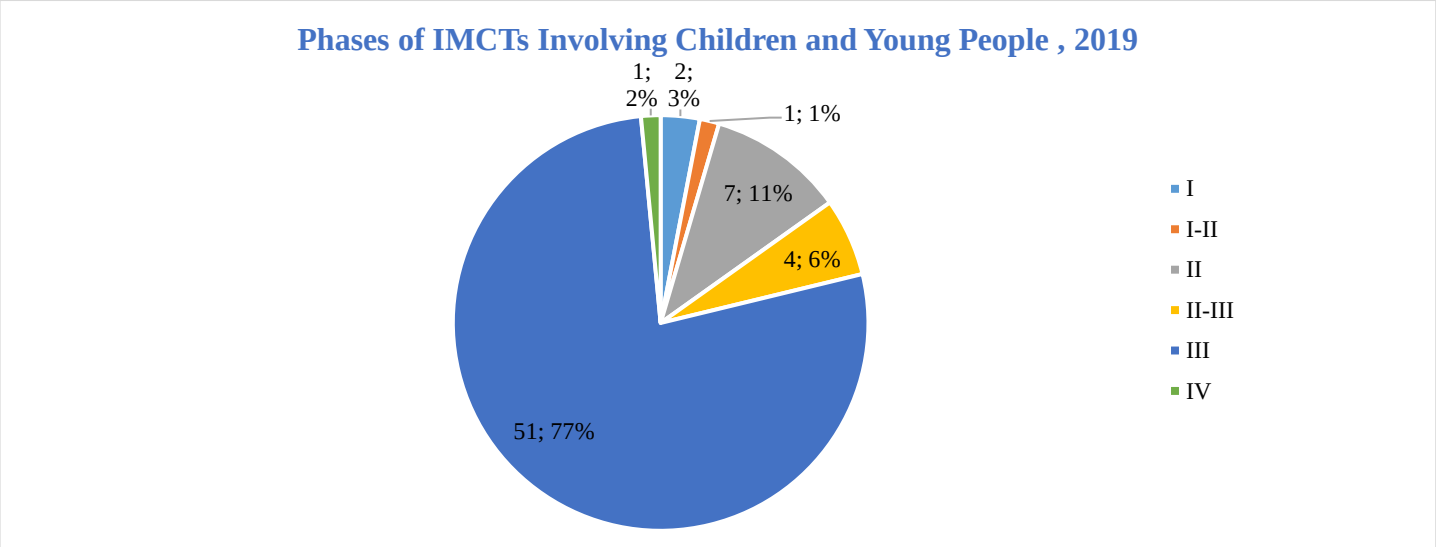
Diagram 18 reflects the distribution of IMCTs involving children and young people by phases. Let's dwell on early phases in more detail. Two trials of phase I include only the pediatric population. This is a trial of Pimavanserin in adolescents with psychic disorders initiated by Acadia Pharmaceuticals, and Ceftolozan/Tazobactam to cure children aged 0-18 from pneumonia with Merck Sharp & Dohme being a sponsor. The trial of phase I-II is conducted by Pharmacyclics LLC and aimed at studying the safety and efficacy as well as dose-ranging of ibrutinib for treatment of the chronic graft-versus-host disease in patients aged 1 to 21.

All seven IMCTs of phase II include only participants younger than 18. Three of them were conducted by Novartis: (1) dabrafenib combined with trametinib in a glioma therapy, (2) ligelizumab for urticaria fever, (3) addition of ruxolitinib to corticosteroids to prevent the graft-versus-host disease after allogeneic stem cell transplantation. Other sponsors of phase II trials, apart from Novartis, were Aeterna Zentaris (macimorelin to treat growth hormone deficiency), Merck Sharp & Dohme (posaconazole to treat invasive aspergillosis), Novo Nordisk (somapacitan in case of stunted growth), and Janssen Pharmaceutica (JNJ-53718678 in case of acute respiratory tract infection).

IMCTs of phases II-III were conducted by MedImmune (monoclonal antibody MEDI8897 to fight respiratory syncytial virus in children), Pfizer (PF-06651600 in case of alopecia in adolescents and adults), Merck Sharp & Dohme (MK-7655A to fight bacterial infection in children), Allergan (brasicumab to treat Crohn's disease in participants aged 16-80).

[20] ICH E11(R1) guideline on clinical investigation of medicinal products in the pediatric population, section 4. See a similar statement on the FDA website: https://www.fda.gov/media/101398/download.

Diagram 18



Data from www.grls.rosminzdrav.ru, www.clinicaltrials.gov

The distribution of approved in 2019 IMCTs involving children and young people by therapeutics areas is reflected in Table 22 separately for trials with pediatric and mixed populations. The planned number of Russian participants is also given for trials with pediatric population. It can be seen from the table that the TOP-3 therapeutics areas of IMCTs with only minors involved include infectious diseases (11 IMCTs), endocrinology and neurology (eight each). Haematology is far ahead of other areas among IMCTs with mixed population (seven trials).

Table 22

Distribution by Therapeutic Areas					
Therapeutic Area	IMCTs with pediatric population			IMCTs with mixed population	
	Number of IMCTs	Share (%)	Planned number of participants	Number of IMCTs	Share (%)
Infectious Diseases	11	23.4%	1385	–	–
Endocrinology	8	17.02%	350	–	–
Neurology	8	17.02%	274	1	5.26%
Rheumatology	3	6.38%	65	1	5.26%
Allergology	2	4.26%	220	–	–
Haematology	2	4.26%	26	7	36.84%
Dermatology	2	4.26%	150	2	10.53%
Oncology	2	4.26%	70	1	5.26%
Nephrology	2	4.26%	27	–	–
Ophthalmology	2	4.26%	17	–	–
Psychiatry	2	4.26%	120	1	5.26%
Pulmonology	2	4.26%	62	2	10.53%
Cardiology and CVD	1	2.13%	10	–	–
Gastroenterology	–	–	–	2	10.53%
Oncohaematology	–	–	–	1	5.26%
Otorhinolaryngology	–	–	–	1	5.26%
TOTAL	47	100%	2776	19	100%

Data from www.grls.rosminzdrav.ru

Let's dwell in more detail on specific diagnoses of most popular therapeutics areas. 11 IMCTs in the area of infectious diseases included three trials of remedies for the respiratory syncytial virus, one medication from pneumonia, aspergillosis, bacterial infection each, two trials of marboxil in the presence of flu-like symptoms, one trial of Meningococcal conjugate vaccine, and two IMCTs of 15-valent pneumococcal conjugate vaccine.

Eight endocrinological IMCTs include three trials of medications countering growth hormone deficiency or stunted growth, another three trials of drugs to treat type 2 diabetes mellitus, one for type 1 diabetes,, and one - in case of overweight and obesity.

Inside the "neurology" line diagnoses were distributed in the following way: three trials of medicinal products to treat Duchenne muscular dystrophy, two remedies for migraine[21], two for cerebral palsy, one for multiple sclerosis and another one for epilepsy. One neurological trial was a study of adjunctive Ganaxolone treatment in children and young adults (not older than 21, though) with CDKL5 deficiency disorder.

Studied in haematological trials were drugs used in bleeding sickness (4 IMCTs out of 7), Willebrand disease (2), paroxysmal nocturnal hemoglobinuria (1), heparin induced thrombocytopenia (1) and the graft-versus-host disease already mentioned in the description of the phase II IMCTs.

Concluding our overview of IMCTs involving children and young people, we'd like to introduce TOP-5 sponsors that initiated most IMCTs in Russia during 2019 with participants younger than 18, i.e. without taking into consideration trials with the mixed population. Merck Sharp & Dohme was granted the greatest number of approvals during the period under review (seven IMCTs of which five in the area of infectious diseases), followed by Eli Lilly (five IMCTs of which three in the area of rheumatology), by Amgen (four trials, two of them neurological).

Table 23

Top-5 Pharmaceutical Companies on Approvals for IMCTs with Children Participating, 2019		
Rating in 2019	**Company**	**Number of IMCTs involving children**
I	Merck Sharp & Dohme	7
II	Eli Lilly	5
III	Amgen	4
IV–V	Novartis	3
	Novo Nordisk	3
	18 more companies	***25 IMCTs in total***

Data from www.grls.rosminzdrav.ru

If the presented overview of IMCTs involving children and young people turns out rather informative for our readership and unforeseen technical difficulties do not stand in the way, we'll probably make it a regular column of the ACTO Newsletter.

[21] The studied drug Erenumab, first one from the group of CGRP receptor antagonists, was approved by FDA in 2018 and registered in Russia in February 2020.