ACTO

Association of Clinical Trials Organizations

ACTO NEWSLETTER № 16

Summary of 2017 results

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SUMMARY

The Newsletter opens with an overview of key indicators. The past year was characterized by a notable reduction in the number of clinical trial approvals. In 2017 the Ministry of Health granted 700 approvals, which is the lowest indicator in the recent six years. Compared to 2016, the reduction was 22%. International multicenter clinical trials (IMCT) were least affected (281 approvals versus 302 in 2016, down 7%), whereas local trials by foreign sponsors suffered the most (71 versus 146, down 51.4%, for bioequivalence studies, and 48 versus 82, down 41.5% for efficacy and safety studies). The number of trials by local sponsors also markedly decreased: efficacy and safety studies – by 24.4% (149 vs 197); bioequivalence studies – by 11.2% (151 vs 170). As a result of non-uniform contraction in various sectors, the share of IMCT approvals among all approvals in 2017 proved larger than in 2014-2016, standing at 40.1% versus 33.7% a year earlier. The surmised reasons for the decline in the sector of local trials and changes in the market structure can be found in the first and second sections of the Newsletter.

Presented further are IMCT market layers by phases of trials (phase III being traditionally prevalent) and by therapeutic areas. Taking the lead in IMCT is oncology (68 trials, 24.2% of all IMCT; together with oncohemotology, this makes for the total of 90 trials or 32%), followed by rheumatology (28 trials, 10%) and neurology (24 trials, 8.5%). Presented in the same section of the Newsletter is a breakdown by therapeutic fields for local studies.

The IMCT distribution by regions of Russia in 2017 reveals an interesting pattern: while we do not see any radical shifts in the ratings, there is a certain tendency towards decentralization – due to some leading regions, such as the Siberian and Ural federal districts. On the contrary, the number of new IMCTs went down in Moscow and St. Petersburg. You may find detailed statistics in the respective section.

Traditionally, the ACTO reviews the activity of certain market players. During the past year the number of companies participating in international trials increased by four sponsor companies and by one CRO. In the market of local trials, however, the number of players decreased by 40 foreign and 30 national sponsors as well as by two CROs.

Reviewing the deadlines for clinical trial approvals is another regular column. In this area the year 2017 differed little from previous years, with minor fluctuations observed against the backdrop of the generally stable picture.

Since 2016, ACTO has been reviewing the statistics of medicines import for clinical trials. We have estimated that the total value of drug supplies increased in 2017 by 23% year-on-year, being worth RUB 13.5 billion. In the USD equivalent the growth stood at 42.1% ($232 million versus $163 million).

In addition to the traditional columns, this Newsletter also includes a review of the situation with the trials of HIV, hepatitis C and tuberculosis medicines. An approximate assessment shows that on all three ICD diseases in quantitative (number of trial approvals) and qualitative (presence of newest medicines in the local market) terms, clinical trials in Russia harbor growth potential.

Reviewing the results for 2017 would be incomplete without a narrative on ACTO counteracting the attempts by Moscow Healthcare Department (MHD) to establish administrative control over the conduct of clinical trials in its subordinate institutions. We suppose that MHD was responsible for reducing the number of IMCTs in clinics under the Department's jurisdiction.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

Last year the Ministry of Health issued 700 clinical trial approvals, down 22% compared to 2016, when 897 trials were approved (Table 1). All studies types were affected. The sector of international multicenter clinical trials (IMCT) saw the least reduction of 7% (281 approvals vs 302 a year before). It should be borne in mind, though, that the ACTO classification does not always coincide with the one in the register of approvals issued by the Ministry of Health. We do not classify trials as IMCTs unless we can find them in the US or European databases and get more detailed information on conditions of their conduct. Thus, there are 291 IMCT approvals for 2017 in the Ministry of Health's register, whereas we assigned 10 less trials to this category.

Table 1

Clinical Trial Approvals: 2017 vs. 2016						
Year	**Total**	**International Multicenter CTs**	**Local CTs (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CTs (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
2017	700	281	48	71	149	151
2016	897	302	82	146	197	170
2017 vs. 2016, %	-22.0%	-7.0%	-41.5%	-51.4%	-24.4%	-11.2%

Data from www.grls.rosminzdrav.ru

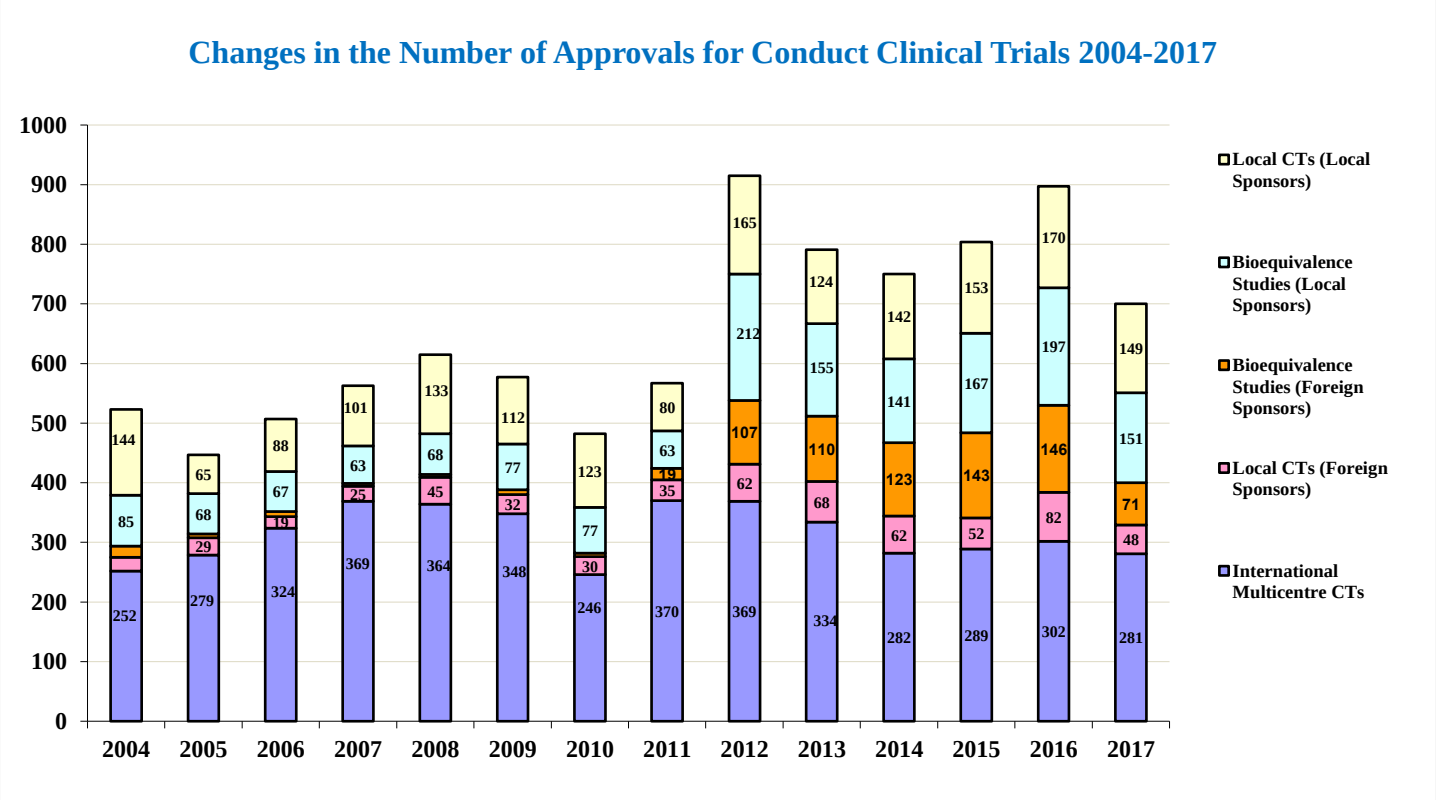
The sharpest fall was observed in the bioequivalence studies of foreign generics – by 51.4% (71 approvals vs 146 in 2016). Dwindling slightly less but still quite notably (by 41.5%) was the number of issued approvals for local trials of efficacy and safety of foreign medicines. The downward trend did not bypass the studies of Russian sponsors either. Thus the number of local trials by domestic developers contracted almost by a fourth – 24.4% (149 approvals vs 197 in 2016), whereas the number of bioequivalence studies – by 11.2% (151 approvals vs 170).

See Diagram 1 for the dynamics of the Russian market of clinical trials by years. The graphically shown reduction of 2017 is impressive. What caused this slump? To gain an insight we should look back to recent years.

We remember that the fall of 2010 was related to the new Federal Law "On Circulation of Medicines": the regulatory system just did not work in the last quarter of that year (the function of issuing approvals was then being transferred from the Federal Service for Surveillance in Healthcare to the Ministry of Health and Social Development). Throughout 2011 the market was readjusting, getting used to the new rules. In 2012 it rebound forcefully, to make up for the previous period. We see a rapid growth of local trials for several reasons: enforcement of the new requirement (submitting the results of clinical trials partly made in Russia, for new drugs to be registered), the policy of import substitution and the support of domestic manufacturers, the expiration of patents for a large number of blockbusters. A similar pattern of booming local clinical trials was repeated in the following four years up to 2017, but then suddenly we witnessed a sharp decline in the sector of local trials, by foreign sponsors in the first place. Yet the slump affected domestic projects as well. For all that, the IMCT count has been fluctuating insignificantly in the last four years, remaining roughly at the same level. How can we explain this pattern?

Relative to the key factor of the slump in the number of local trials by foreign sponsors, the experts we polled were unanimous in their assessments. They blamed the requirement to provide results of an inspection of the manufacturing site, conducted by the Russian inspectorate, before a new drug can be registered. This requirement was enacted at the turn of 2016. As a result, the registration of foreign drugs in 2017 dropped by 43% against the previous year. This could not but take a toll on the market of local trials. Why conduct trials if registration is uncertain?

Diagram 1



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

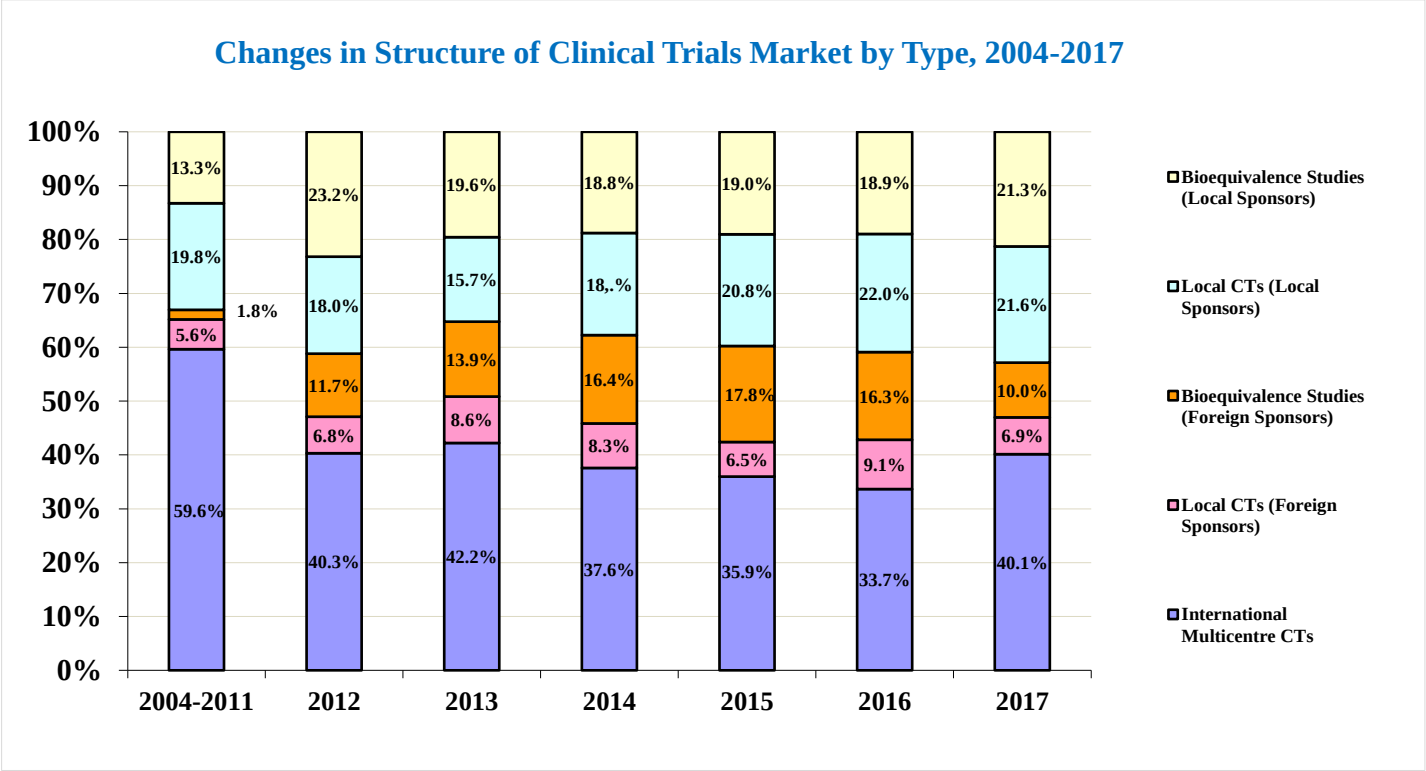
This perfectly explained the dwindling number of local trials of foreign drugs. But the sector of domestic sponsors also contracted, even if not so dramatically. At first we tried to explain this trend by the fact that some "homemade" drugs are only packaged in Russia, the major stages of their production cycle located abroad, which means they also fall to the requirement to produce the Russian inspection results. We even made this assumption in the previous issue of this Newsletter. Yet we were confounded by the profundity of the drop that in the segment of local trials by local sponsors reached 24.4%, just to remind. Have Russian developers run out of money? This could certainly be one of the factors, given that the national economy is going through turbulent times indeed. Yet we had a feeling that we had overlooked something else.

When we found the explanation, though, we were amazed at how simple it was. The answer turned out to be under our very nose, but we totally neglected it! Amendments to the law "On Circulation of Medicines" that were passed in late 2014 repealed the requirement to produce the results of so-called "therapeutic equivalence" studies for a number of generic pharmaceutical forms: various types of water solutions for parenteral administration, oral solutions, gases and some others. The amendments were to come into force on the 1 January 2016. And starting in late 2014, in five (!) consecutive issues of the Newsletter, ACTO kept predicting the upcoming reduction in the number of local trials, with the persistence of loony Cassandra. The predictions failed year after year, though: both in 2015, when we believed manufacturers should have started preparations for changes in the registration rules, and in 2016, when the amendments took effect. Moreover, in 2016 we saw the growing number of all types of local trials to such an extent that the shares of local trials by both Russian and foreign sponsors even reached their historic maximums! Ultimately, we got so much frustrated to see our own forecast failing that we totally forgot about it in 2017. Yet at this point the market finally took a nosedive, to our sheer astonishment. We could never expect to see the market players being so inert. Of course, the cost of local trials is way lower than that of IMCT trials. But these are costs to be incurred nonetheless: did not our pharma companies take note of the rules' change that favored them? Yet other factors could be at play too, as many expected the introduction of the "substitutability" system that had long been lobbied by FAS. This concept was reflected in the law, but it's still not quite clear, when and how this system must work in reality. Fearing that some generics won't be recognized as substitutable, their manufacturers might have preferred to be on the safe side and continue with local trials. Yet this version is rather questionable. Anyway the changes that occurred in 2017 could not but affect the structure of the market.

STRUCTURE AND DYNAMICS OF THE CLINICAL TRIALS MARKET BY TYPE

Changes in the shares of various types of trials that we've seen in recent years are shown in Diagram 2. It's apparent that after the market got adapted to the terms of the Law "On Circulation of Medicines" the share of IMCTs in the total volume of trials conducted in Russia was successively going down, reaching the level of 33.7% in 2016, almost twice less than prior to the reform, when it had averaged almost 60% in 2004-2011. In 2017, however, IMCT rebounded by 6.4 pct., surpassing the 40% mark. This, albeit small, revenge in IMCTs cannot but rejoice.

Diagram 2



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

We see from the Diagram that this happened at the expense of the contraction of other trial types with the exception of bioequivalence studies by local sponsors. The share of the latter increased by 2.4 pct in 2017, despite the 11% reduction in the absolute number of approvals issued for this type of trials. The most tangible contraction could be observed in the sectors of bioequivalence studies and local efficacy and safety trials by foreign sponsors, which is but logical given that their number dropped significantly.

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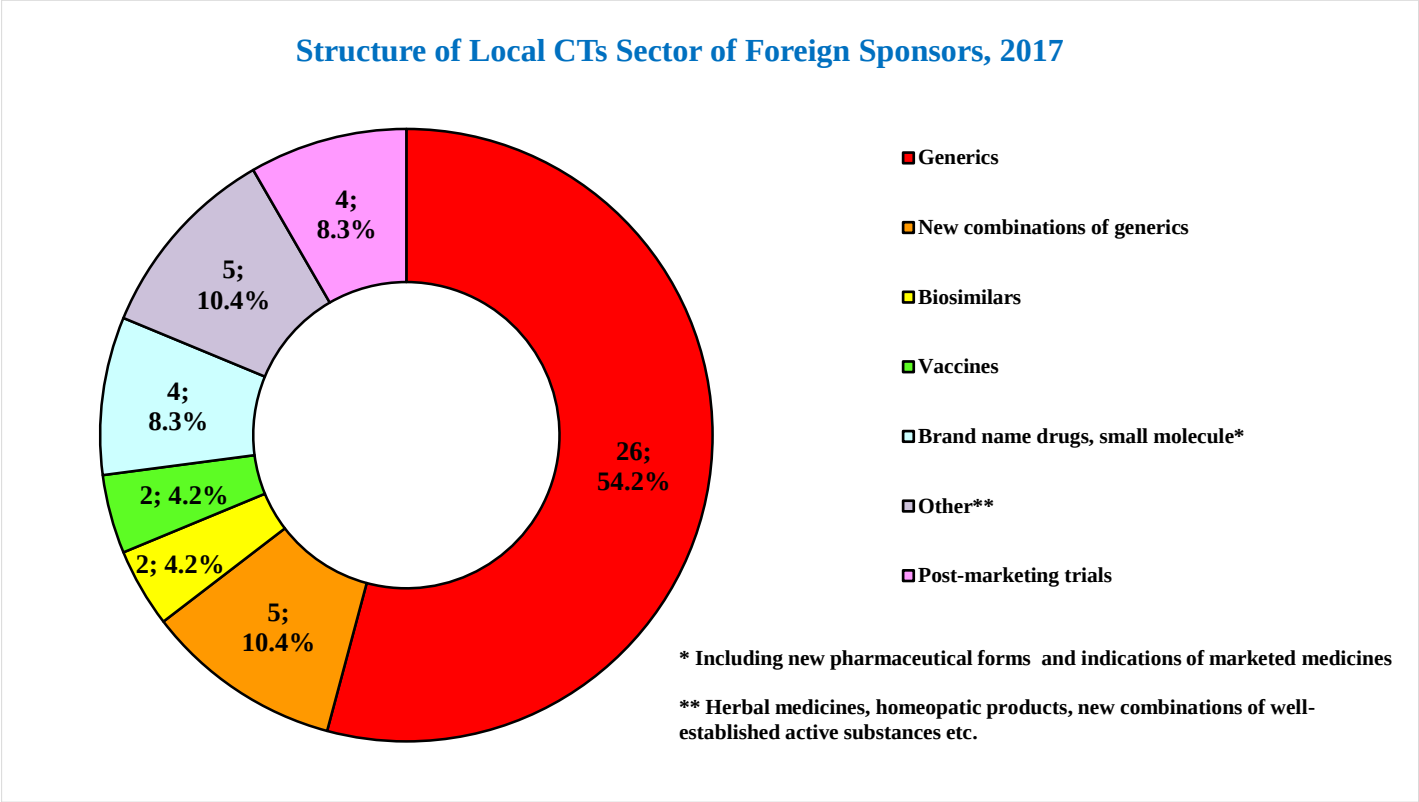
While working on the yearly issue of the Newsletter, we traditionally analyze, among other things, the structure of the local efficacy and safety trials sector (bioequivalence studies are not included). You may see in Diagram 3 what kinds of products were tested by foreign sponsors in the course of local trials.

Despite the reduction of the local trial count, the structure of this sector is still similar to the one we observed in 2016. Generics account for the highest share – 26 trials or 54.2% (there were 45 a year before, but their share also stood at 55%). New combinations of generics and "other drugs" come next in terms of their shares that stand at 10.4% (5 trials each). We included herbal or animal preparations, homeopathy and similar medical products in the latter category.

Diagram 3



Data from www.grls.rosminzdrav.ru

We categorized four trials of brand-name drugs, small molecules (8.3%) among the local studies. We are talking about Hidrasec (Racecadotril) from Abbott whose use was supposed to be studied in babies, children and teenagers with acute diarrhea; also the trial of Comtess® (Entacapone) administered to Parkinson patients and sponsored by Orion Corp. By its description this trial looked like being of international scope, but was declared as local and we failed to find it in international registers. The third one was a trial to assess the efficiency of Pirfenidone from F. Hoffmann-La Roche in patients suffering from idiopathic pulmonary fibrosis in the Russian clinical practice. The fourth one somewhat perplexed us, because it proposed to study a medicinal agent that is not quite traditional (though formally it meets the definition of the medicine, suggested in the Law "On Circulation of Medicines"). The matter regards the comparison of Custodiol-N and Custodiol® solutions used for conservation of transplanted organs (kidneys and liver), initiated by Dr. Franz Koehler Chemie.

The trials of two biosimilar drugs Trastuzumab and Bevacizumab, both made by Dr. Reddy's Laboratories, and two vaccines – the combination vaccine Boostrix™ from GlaxoSmithKline Biologicals for diphtheria, tetanus and pertussis prevention, as well as the tuberculous vaccine TB/FLU-04L – were also conducted as local ones. The latter trial was reportedly sponsored by the republican state enterprise Research Institute of Biological Safety Problems under the Scientific Committee of Kazakhstan's Ministry of Education and Science, with Research Institute of Influenza as an organization involved in the trial (that also was a clinical site).

The trials of four products – Privigen (immunoglobulin) from CSL Behring; Trioginal® of Besins Healthcare; Akatinol Memantine made by Merz Pharma, and cartilage protector Alflutop® by the Romanian company Biotehnos – were attributed to the post-registration sector. The last drug's API, pursuant to the label, is "bioactive small sea fish concentrate" including anchovy and sprat. The plan called for comparing two therapeutic regimes under the intramuscular injection of various drug doses to patients suffering from knee osteoarthrosis.

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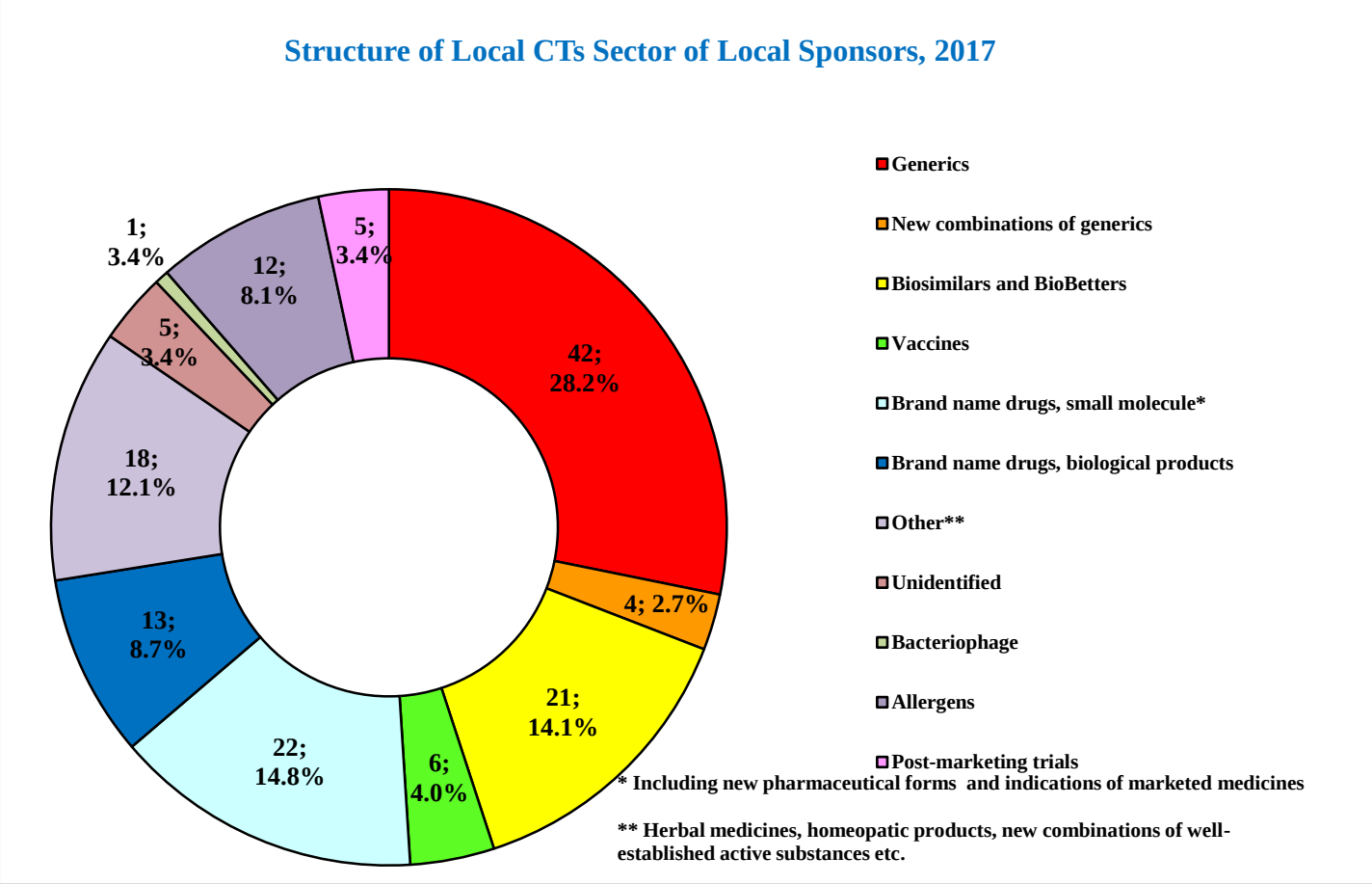
Shown in Diagram 4 is the structure of local trials by national sponsors. As usual, generics account for the main share – 28.2% (42 trials). A year earlier, it was slightly higher standing at 31% (61 trials). New combinations of generics accounted for another 2.7% (4 trials).

Diagram 4



Data from www.grls.rosminzdrav.ru

Biosimilars accounted for 14.1% of all trials (21 approvals). Taking lead here are Generium and Zavod Medsintez (five trials by each) as well as Biocad (four trials of biosimilars and one drug that we ranked among biobetters). Biocad is the undisputed leader by the number of original biological products as well, with nine out of 13 approvals granted in this category. As a matter of fact, the company declared six of its trials as international. But because we failed to find any corroboration of their international status (although Belarus was declared as participating on a par with Russia in a couple of trials), we attributed them to local ones.

The trials of brand-name drugs, small molecules, account for 14.8% (22 trials). Three trials each were initiated by R-Pharm (all three for Narlaprevir), Polysan (Remaxol drug) and ChemRar Group (CD-008-0173, CD-008-0045 and AB5080 drugs). Two other trials from this category were assigned by us to Investigator initiated studies. This is a trial of Forxiga from AstraZeneca, conducted by the Scientific Clinical Centre of Russian Railways, and a trial of Pradaxa made by Boehringer Ingelheim, and conducted by the Urals State Medical University. By the formal hallmark, these trials were ranked by us among those conducted by domestic sponsors, as Russian research institutes were are named the initiators of these clinical trials.

Six trials (4% of all local studies by domestic sponsors) were dedicated to vaccines: two for influenza prevention, two for tick-borne encephalitis, one for Meningococcal disease and another one for an Ebola prevention vector vaccine.

For the first time this year, we set allergens aside as a separate group. As we can see from Diagram 4, this group included 12 studies in 2017. And if one of these truly resembles a clinical trial (studying the safety of and

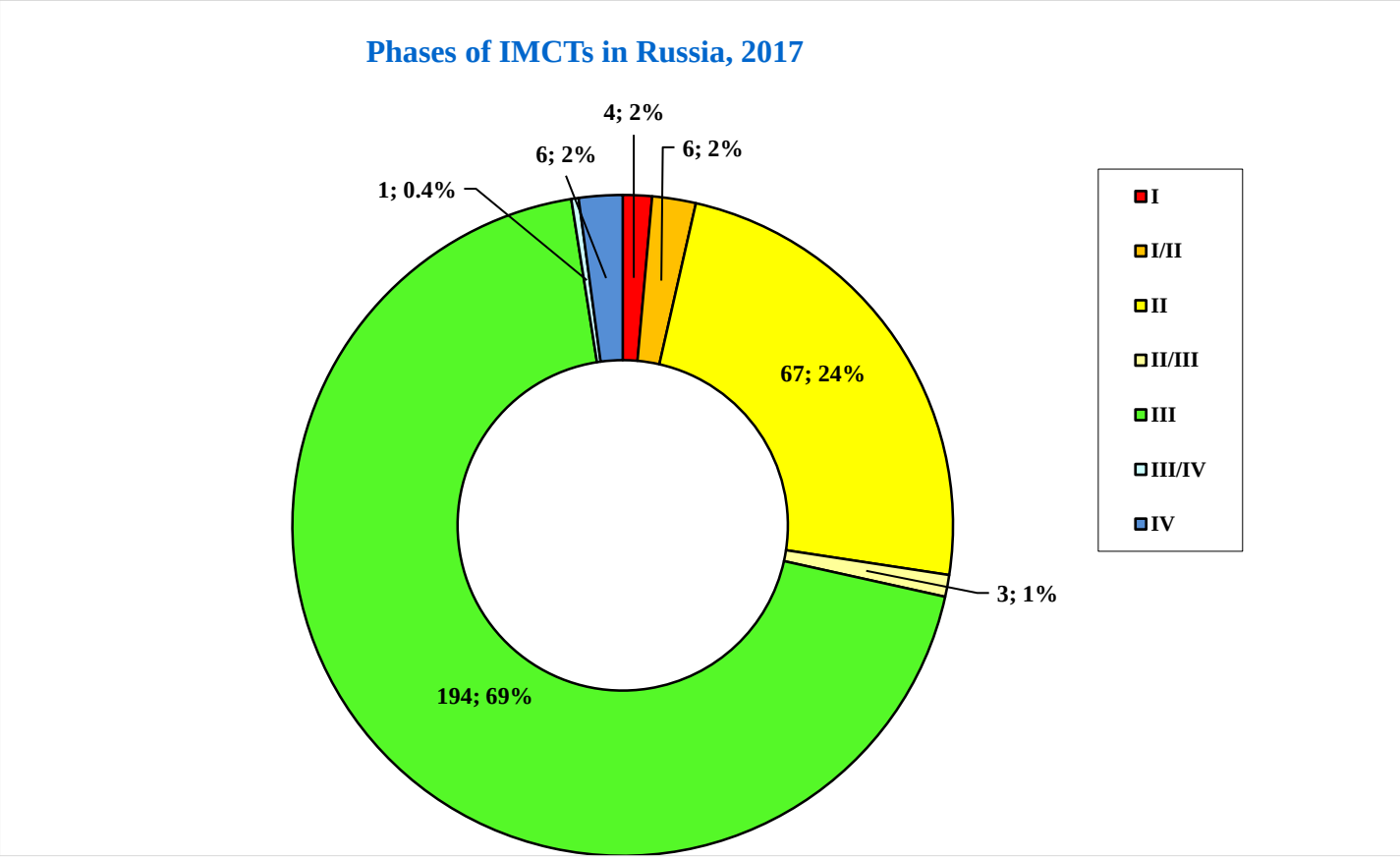
tolerance to Berpol among pollen fever patients, conducted by Petrovax Pharm), the remaining 11 baffled us. All 11 are conducted by Microgen: three are designated as III phase studies, other eight – as IV phase studies. The declared aim is studying the specific activity of different allergen types (birch pollen, ragweed, artiplex tatarica, European alder, etc.) "in keeping with the requirements of GPA "Allergens" for certification as the in-house reference standard." Aren't there any analysis methods in the world that would allow to develop reference standards without involving a human as a clinical trial subject? Especially since this does not quite match the purposes for clinical trials as per part 1 of Art. 38 of the Law "On Circulation of Medicines". One of international experts confirmed that the specific activity is studied at the stage of conducting Phase II. According to another expert, the developers could have just worded the objectives of the studies in a wrong way. This version cannot be corroborated or refuted, unless we see the protocol. And it is unclear what exactly stands behind these studies.

The "Other" section is represented by versatile flora and fauna derivatives (mostly by slaughterhouse waste, judging by the description of raw materials), homeopathy, metals treated with peptides, and other front-end prospecting by modern-day alchemists. Their total count is 18. We failed to identify the composition or even the nature of five other domestic developments.

SRTUCTURE AND DYNAMICS OF THE INTERNATIONAL MULTICENTRE CLINICAL TRIALS MARKET BY PHASE

Diagram 5 shows the breakdown of IMCTs approved in 2017, by phases. There's nothing new; on the whole, the Russian IMCT market structure by phases has been stable in recent years.

Diagram 5



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

Remedies for non-small cell lung cancer accounted for two I phase trials out of four, oncohematology – for one, hematology – for another one. In four out of six I/II phase trials oncology drugs were also studied and in two others – oncohematology drugs.

STRUCTURE OF THE CLINICAL TRIALS MARKET BY THERAPEUTIC AREAS

Table 2 shows a distribution of approved IMCTs by therapeutic areas. The top trio has not changed during the year, with oncology taking the lead (68 trials, 24.2%). Coming next is rheumatology (28 trials, 10%) and neurology (24 trials, 8.5%).

Oncohematology which we set aside from oncology and which ranked sixth a year before, now ranks fourth (22 trials, 7.8%). The total share of oncology and oncohematology in all IMCTs was 32% (28.2% in 2016).

The number of trials in hematology notably increased in 2017 – 20 vs five in 2016, which means its share grew by 5.4 pct. As a result, this therapeutic area went up from 16th to 5th position. The share of trials in cardiology and cardiovascular diseases (CVD) also rose from 3.3% to 5.3%.

Contracting, on the other hand, were the shares of psychiatry (from 5% to 2.8% – 8 IMCTs vs 15 a year earlier), HIV/hepatitis C/tuberculosis (from 3.3% to 2.1% or 6 vs 10 IMCTs) and dermatology (from 3.3% to 1.4% or 4 vs 10 IMCTs).

Table 2

Split of International Multicenter CTs by Therapeutic Areas, 2017			
Therapeutic Area	**Number of IMCTs**	**Share (%)**	**The number of planned participants**
Oncology	68	24.2%	5 141
Rheumatology	28	10.0%	2 422
Neurology	24	8.5%	2 622
Oncohaematology	22	7.8%	833
Haematology	20	7.1%	301
Endocrinology	19	6.8%	3 255
Gastroenterology	16	5.7%	1 048
Pulmonology	15	5.3%	2 700
Cardiology and CVD	15	5.3%	3 957
Infectious Diseases (except HIV/HCV/tuberculosis)	10	3.6%	744
Psychiatry	8	2.8%	673
Nephrology	8	2.8%	1 269
HIV/HCV/tuberculosis	6	2.1%	447
Dermatology	4	1.4%	167
Gynecology	4	1.4%	436
Otorhinolaryngology	4	1.4%	251
Surgery	3	1.1%	300
Ophthalmology	2	0.7%	138
Allergology	2	0.7%	155
Geriatrics	2	0.7%	140
Immunology	1	0.4%	30
TOTAL	281	100.0%	27 029

Data from www.grls.rosminzdrav.ru

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The distribution of local studies of generics and biosimilars as well as of bioequivalence studies by foreign sponsors by therapeutic areas is given in Table 3.

Table 3

Split of Local CTs and Bioequivalence Studies (Generics and Biosimilars) of Foreign Sponsors, 2017			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Cardiology and CVD	22	21.2%	1 556
Analgesic and NSAIDs	14	13.5%	1 658
Gastroenterology	8	7.7%	971
Otorhinolaryngology	8	7.7%	2 044
Infectious Diseases (except HIV/HCV/tuberculosis)	7	6.7%	595
Urology	6	5.8%	542
Gynecology	5	4.8%	424
Oncology	4	3.8%	137
Ophthalmology	4	3.8%	632
HIV	4	3.8%	230
Dermatology	4	3.8%	788
Psychiatry	3	2.9%	92
Neurology	2	1.9%	93
Pulmonology	2	1.9%	230
Endocrinology	2	1.9%	84
Rheumatology	2	1.9%	68
Oncohaematology	2	1.9%	80
Allergology	1	1.0%	56
Immunology, Transplantology	1	1.0%	44
Haematology	1	1.0%	10
Antinicotin therapy	1	1.0%	268
Stomatology	1	1.0%	100
TOTAL	104	100.0%	10 702

Data from www.grls.rosminzdrav.ru

The highest number of approvals in this sector, like in 2016, fell to the share of medicines used in cardiology and CVD – 21.2% (22 trials), followed by the studies of analgesics and non-steroid anti-inflammatory drugs (NSAID) – 13.5% (14 trials). The third and fourth positions with the share of 7.7% were split between gastroenterology (1.6% in 2016) and otorhinolaryngology (no approvals were granted in 2016).

The shares of virulent diseases and gynecology (each of the groups accounted for 8.3%) as well as oncology (7.3% in 2016) also sank year-on-year.

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The distribution of local and bioequivalence studies by therapeutic areas among domestic sponsors is given in Table 4.

Anti-infectious drugs accounted for most trials (28), their share standing at 12.8% (7.7% in 2016). Coming next are HIV, hepatitis C and tuberculosis trials set aside by us as a separate group and taking the lead in 2016 (10.1% vs 12% the year before). Neurology (9.6% vs 10.8%) ranked third.

Table 4

Split of Local CTs and Bioequivalence Studies (Generics and Biosimilars), Conducted by Local Sponsors, 2017			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Infectious Diseases (except HIV/HCV/tuberculosis)	28	12.8%	1 291
HIV/HCV/tuberculosis	22	10.1%	1 194
Neurology	21	9.6%	1 650
Cardiology and CVD	18	8.3%	842
Oncology	13	6.0%	1 084
Analgesic and NSAIDs	13	6.0%	730
Gastroenterology	13	6.0%	714
Rheumatology	12	5.5%	914
Endocrinology	11	5.0%	820
Urology	9	4.1%	352
Psychiatry	8	3.7%	330
Pulmonology	7	3.2%	307
Haematology	6	2.8%	506
Gynecology	6	2.8%	950
Allergology	6	2.8%	234
Surgery	4	1.8%	243
Dermatology	3	1.4%	362
Oncohaematology	3	1.4%	402
Anaesthesiology	3	1.4%	522
Otorhinolaryngology	3	1.4%	297
Phlebology	2	0.9%	172
Hepatology	2	0.9%	61
Nephrology	2	0.9%	336
Ophthalmology	1	0.5%	90
Anthelminthic medicines	1	0.5%	45
Toxicology, Alcoholism treatment	1	0.5%	250
TOTAL	218	100.0%	14 698

Data from www.grls.rosminzdrav.ru

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Shown in Table 5 are molecules that were in highest demand last year among generic manufacturers.

Medications used in cardiology and CVD treatment top the list. Taking the lead is rosuvastatin: eight trials of mono- and combination products on its basis (one homemade and 7 of the foreign make), followed by amlodipine used in combinations – seven trials (five foreign and two domestic ones). Valsartan (cardiology and CVD as well), ibuprofen and paracetamol (analgesics and NSAID) as well as chlorhexidine (widely used in medicine) containing drugs accounted for six trials each.

HIV medicines like atazanavir, darunavir, combination medications of lamivudine, abacavir (ABC), tenofovir (TDF), efavirenz (EFV) were very popular among the manufacturers of generics in 2017.

Meldonium was a disappointment in 2017. While a year earlier five trials of meldonium-containing drugs had been initiated, not a single one was made in 2017.

Table 5

Most Requested INN Used in Clinical Trials of Generics in 2017				
Substance	**Number of CTs of foreign generics**	**Number of CTs of local generics**	**All clinical trials to a given INN**	**Therapeutic Area**
Rosuvastatin (separately and in fixed combinations)	7	1	8	Cardiology and CVD
Amlodipine in combination	5	2	7	Cardiology and CVD
Valsartan (separately and in fixed combinations)	4	2	6	Cardiology and CVD
Ibuprofen (separately and in fixed combinations)	3	3	6	Analgesic and NSAIDs
Paracetamol (in fixed combinations)	5	1	6	Analgesic and NSAIDs
Chlorhexidine (in fixed combinations)	3	3	6	Otorhinolaryngology, Dermatology, Gynecology
Atazanavir	1	4	5	HIV
Darunavir	1	4	5	HIV
Lamivudine (in fixed combinations)	2	3	5	HIV
Perindopril (in fixed combinations)	3	2	5	Cardiology and CVD
Chondroitin sulfate (separately and in fixed combinations)	-	5	5	Rheumatology
Etoricoxib	2	3	5	Rheumatology
Abacavir (in fixed combinations)	2	2	4	HIV
Hydrochlorothiazide (in fixed combinations)	4	-	4	Cardiology and CVD
Desloratadine	-	4	4	Allergology
Dexketoprofen	-	4	4	Analgesic and NSAIDs
Dexpanthenol (in fixed combinations)	2	2	4	Otorhinolaryngology, Dermatology, Gynecology
Dutasteride (separately and in fixed combinations)	4	-	4	Urology
Lenalidomide	2	2	4	Oncohaematology
Metformin (separately and in fixed combinations)	1	3	4	Endocrinology
Moxifloxacin	1	3	4	Infectious Diseases
Oseltamivir	-	4	4	Infectious Diseases
Tadalafil	2	2	4	Urology
Tamsulosin (separately and in fixed combinations)	3	1	4	Urology
Ezetimibe (separately and in fixed combinations)	1	3	4	Cardiology and CVD
Sodium Enoxaparin	-	4	4	Surgery
Efavirenz (separately and in fixed combinations)	-	4	4	HIV
Abiraterone	1	2	3	Oncology
Valganciclovir	-	3	3	Infectious Diseases
Ketorolac	1	2	3	Analgesic and NSAIDs
Xylometazoline (in fixed combinations)	3	-	3	Otorhinolaryngology
Lidocain (in fixed combinations)	3	-	3	Otorhinolaryngology
Linezolid	-	3	3	Infectious Diseases
Nimesulide (separately and in fixed combinations)	1	2	3	Analgesic and NSAIDs
Progesterone	1	2	3	Gynecology
Simethicone (separately and in fixed combinations)	3	-	3	Gastroenterology
Tenofovir (separately and in fixed combinations)	-	3	3	HIV

Data from www.grls.rosminzdrav.ru

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The distribution of local studies of original products (biological drugs inclusive) by foreign and local sponsors is shown in Tables 6 and 7, respectively. You can see that domestic developers were most interested in infectious diseases in 2017.

Table 6

Split of Local CTs of Brand Name Drugs (including biological products) of Foreign Sponsors, 2017		
Therapeutic Area	**Number of CTs**	**Number of planned participants**
Infectious Diseases (Vaccine for the Prevention of Diphtheria, Tetanus, Whooping Cough)	1	448
Neurology	1	114
Tuberculosis (vaccine)	1	80
Gastroenterology	1	150
Pulmonology	1	78
Surgery (solution for conservation of transplanted organs)	1	165
TOTAL	6	1 035

Data from www.grls.rosminzdrav.ru

Table 7

Split of Local CTs of Brand Name Drugs (including biological products) of Local Sponsors, 2017		
Therapeutic Area	**Number of CTs**	**Number of planned participants**
Infectious Diseases, including Vaccines (except HIV/HCV/TB)	10	1 959
Oncology	5	457
HIV/HCV/tuberculosis	5	712
Neurology	5	521
Rheumatology	3	403
Psychiatry	3	161
Hepatology	3	1 107
Dermatology	2	488
Endocrinology	2	155
Gynecology	1	342
Cardiology and Cardiovascular Diseases	1	400
Toxicology, Alcoholism treatment	1	164
Allergology	1	214
TOTAL	42	7 083

Data from www.grls.rosminzdrav.ru

BREAKDOWN OF IMCT APPROVALS ACROSS RUSSIA

The distribution of approved IMCTs by Russian regions in 2017 is shown in Table 8 (*for more detail about the used criteria and calculation methods see Newsletter No. 12).*

In absolute terms in 2017, as in the previous two years, the Central Federal District was the leader, although the number of IMCTs remained the same there as in 2016 – 284, its top three leading regions being Moscow along with Yaroslavl and Ryazan regions. The Smolensk region that had ranked third in two previous years dropped down to the fourth position.

Coming next is the North-Western Federal District where St. Petersburg remains the irreplaceable leader. Third and fourth places are taken, respectively, by the Volga Federal District and the Siberian Federal District. Most active in the Volga Federal District was Nizhny Novgorod region, the Republic of Tatarstan, Samara and Saratov regions. The leaders of the Siberian Federal District are the same: Novosibirsk and Kemerovo regions (the latter outstripped Tomsk last year), Tomsk and Omsk regions.

Whereas in terms of approved IMCTs the ranking of national districts did not undergo any changes in 2017, by IMCTs per 1 million residents we see a minor rearrangement. Topping the list is the North-Western Federal District as usual (17.4 trials vs 19.3 in 2016). The Ural Federal District shot ahead to the second position (8.7 vs 7.5 the year before), leaving Siberia behind. The Siberian Federal District, even though it dropped a step down, improved its parameters (8.5 trials vs 7.7) like its rival. With the exception of these two districts, others showed worse results.

Unlike 2016, Khanty-Mansiysk, Adygeya and Mari-El as well as Tambov and Pskov regions are not represented. In the meantime, Kurgan region (two IMCTs) and Crimea (one IMCT), absent from the rating a year ago, were added.

Despite the general reduction of the IMCT count in 2017, some regions improved their parameters. We already mentioned a higher density of IMCT per capita distribution in the Urals and Siberia. The absolute number of international projects per region also increased there – by 16.3% (107 IMCTs vs 92 in 2016) and 12.2% (166 IMCTs vs 148), respectively. Better statistics in the Urals can be traced down to improved parameters of the Sverdlovsk region (62 IMCTs vs 50 a year earlier) and Chelyabinsk region (53 IMCTs vs 48). The number of medical institutions involved in trials increased in the Sverdlovsk region from 11 to 15, but decreased in the Chelyabinsk region – from 14 down to 10. Yet a real boom of IMCTs in 2017 could be observed in Siberia. Among the regions which improved their parameters are: Kemerovo (65 new trials vs 43 in 2016), Tomsk (51 vs 44) and Omsk (50 vs 42) regions as well as Altai Territory (44 vs 35). Only in Novosibirsk the number of IMCTs went down from 79 to 71, which did not hinder it from retaining the leadership in Siberia.

Among the other regions that ramped up their involvement in international projects, one cannot but mention the Kursk region where the number of new IMCTs rose 2.5 times during the year (from 8 to 20). A notable accrual was also demonstrated by Arkhangelsk (39 IMCTs vs 27 a year before) and Samara (62 IMCTs vs 50) regions. On the contrary, the number of IMCTs considerably sagged in regions such as Moscow (231 IMCTs vs 266 in 2016), St. Petersburg (236 vs 263), Tatarstan (69 vs 99), Saratov (53 vs 70), Rostov (32 vs 51), Smolensk (35 vs 48) and Stavropol (34 vs 49) regions.

Table 8

Split of IMCTs approved in 2017 by regions of the RF									
Region	**Number of IMCTs, per region**	**Number of IMCTs, per million population***	**Number of health care organizations, which approved centers for IMCTs, per region**	**How many times medical organizations of the region were involved in IMCTs (number of open centers)**	**Region**	**Number of IMCTs, per region**	**Number of IMCTs, per million population***	**Number of health care organizations, which approved centers for IMCTs, per region**	**How many times medical organizations of the region were involved in IMCTs (number of open centers)**
Central Federal District	**284**	**7.2**	**153**	**815 (847)**	**North Caucasian Federal District**	**37**	**3.8**	**12**	**43**
Moscow	231	18.7	91	490 (513)	Stavropol Territory	34	12.1	10	38
Yaroslavl Region	75	59.0	16	89	Republic of North Ossetia – Alania	4	5.7	1	4
Ryazan Region	39	34.6	6	44	Kabardino-Balkarian Republic	1	1.2	1	1
Smolensk Region	35	36.7	7	36 (38)					
Kaluga Region	33	32.5	3	33 (40)	**Siberian Federal District**	**166**	**8.5**	**72**	**417 (426)**
Voronezh Region	24	10.3	6	25	Novosibirsk Region	71	25.5	26	112
Kursk Region	20	17.8	3	20	Kemerovo Region	65	24.0	12	83
Moscow Region	18	2.4	5	19	Tomsk Region	51	47.3	7	54 (56)
Ivanovo Region	15	14.7	3	15	Omsk Region	50	25.3	6	59 (64)
Tver Region	10	7.7	2	10	Altai Territory	44	18.6	9	47 (49)
Vladimir Region	10	7.2	2	10	Krasnoyarsk Territory	37	12.9	5	39
Belgorod Region	8	5.2	2	8	Irkutsk Region	20	8.3	6	20
Lipetsk Region	6	5.2	3	6	Trans-Baikal Territory	3	2.8	1	3
Tula Region	6	4.0	1	6					
Orel Region	2	2.6	2	2	**Ural Federal District**	**107**	**8.7**	**32**	**138 (140)**
Bryansk Region	2	1.6	1	2	Sverdlovsk Region	62	14.3	15	68(70)
					Chelyabinsk Region	53	15.1	10	58
Southern Federal District	**70**	**4.3**	**25**	**93 (96)**	Tyumen Region	10	6.8	6	10
Krasnodar Territory	33	5.9	13	39 (41)	Kurgan Region	2	2.3	1	2
Rostov Region	32	7.6	8	35 (36)					
Volgograd Region	18	7.1	3	18	**Volga Federal District**	**193**	**6.5**	**87**	**435 (444)**
Republic of Crimea	1	0.5	1	1	Nizhny Novgorod Region	73	22.5	17	85
					Republic of Tatarstan	69	17.8	12	76 (82)
Northwestern Federal District	**242**	**17.4**	**136**	**721 (744)**	Samara Region	62	19.4	15	67
Saint-Petersburg	236	44.7	115	642 (664)	Saratov Region	53	21.4	10	61 (63)
Arkhangelsk Region	39	34.8	5	41 (42)	Republic of Bashkortostan	38	9.3	5	38 (39)
Republic of Karelia	11	17.5	1	11	Orenburg Region	20	10.1	3	20
Leningrad Region	10	5.6	7	13	Perm Territory	18	6.8	9	24
Murmansk Region	5	6.6	2	5	Udmurtian Republic	15	1.5	4	15
Novgorod Region	4	6.5	2	4	Kirov Region	13	10.1	4	13
Vologda Region	3	2.5	2	3	Penza Region	13	9.7	3	14
Republic of Komi	2	2.4	2	2	Republic of Mordovia	10	12.4	2	10
					Ulyanovsk Region	10	8.0	1	10
Far Eastern Federal District	**3**	**0.5**	**3**	**3**	Chuvash Republic	2	1.6	2	2
Amur Region	1	1.2	1	1					
Khabarovsk Territory	1	0.8	1	1					
Primorye Territory	1	0.5	1	1					

*We used data of Rosstat on the resident population of the region as of January 1, 2017

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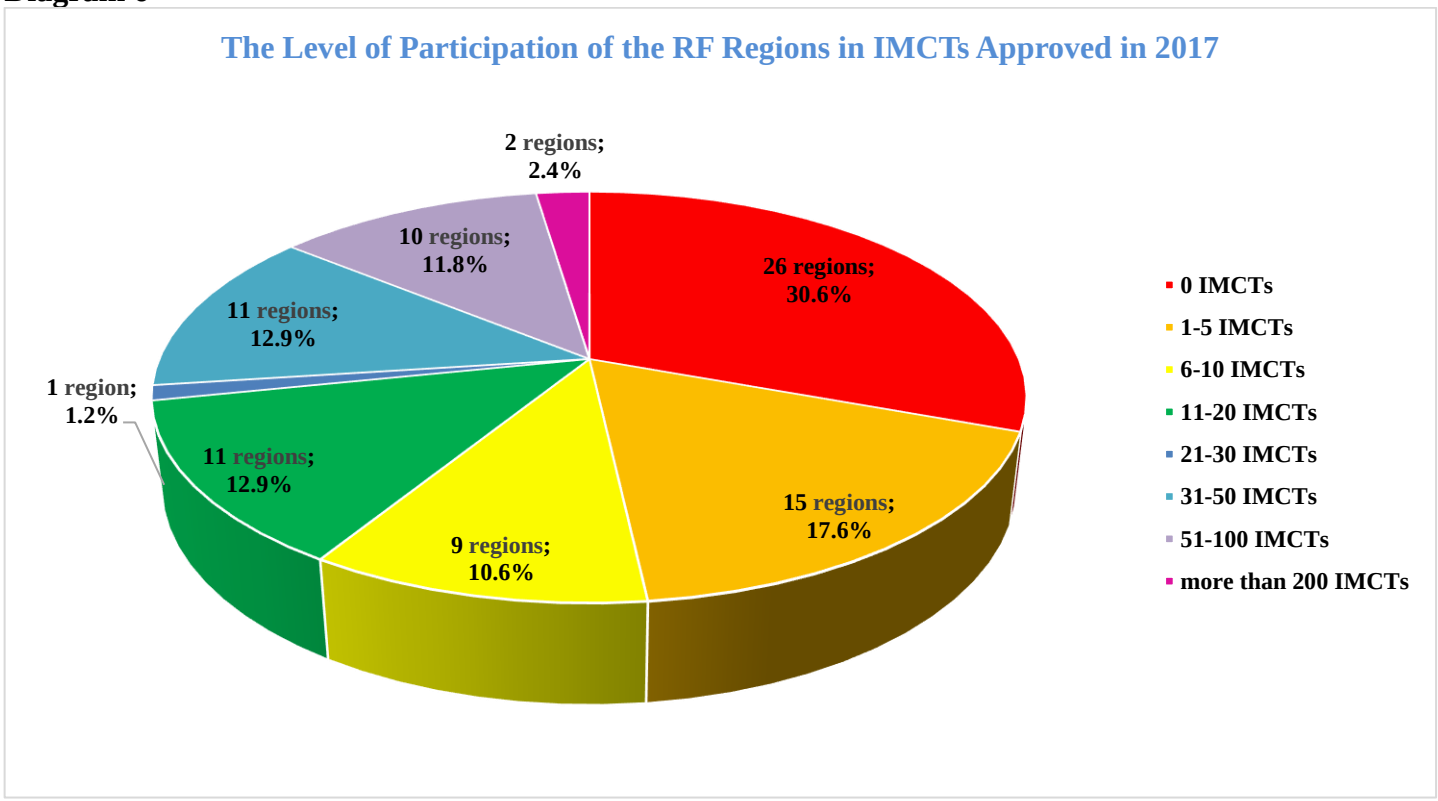
Diagram 6 helps to assess how active each of the Russian regions was in launching approved IMCTs during 2017 (by applications for them, rather than by their actual start). Nothing changed in the segment "more than 200 new IMCTs", populated by two Russian capitals. The segment "51-100 IMCTs" swelled from six regions in 2016 to 10 in 2017, with Kemerovo, Tomsk, Sverdlovsk, Chelyabinsk and Samara regions joining Yaroslavl, Novosibirsk, Nizhny Novgorod, Saratov regions and the Republic of Tatarstan. The Rostov region was there as well a year ago, but in 2017 it dropped down to the lesser activity segment "31-50 IMCTs", joining the company of Ryazan, Smolensk, Kaluga, Omsk regions, Krasnodar, Stavropol, Altai and Krasnoyarsk Territories as well as the Republic of Bashkortostan. Another newcomer to the "31-50 IMCTs" segment is the Arkhangelsk region that was earlier a member of the "21-30 IMCTs" club. The "21-30" segment was also abandoned by the Moscow, Leningrad and Orenburg regions along with the Republic of Karelia and Perm region, all sinking to the "11-20 new IMCTs" category. In the upshot, the "21-30 IMCTs" segment was only represented by the Voronezh region which climbed there from the "11-20 IMCT" segment. We do not mention the regions which could not trespass the threshold of 20 new projects. 26 regions did not declare a single center for participation in IMCTs, in 2016 their number was 23.

Diagram 6



Data from www.grls.rosminzdrav.ru

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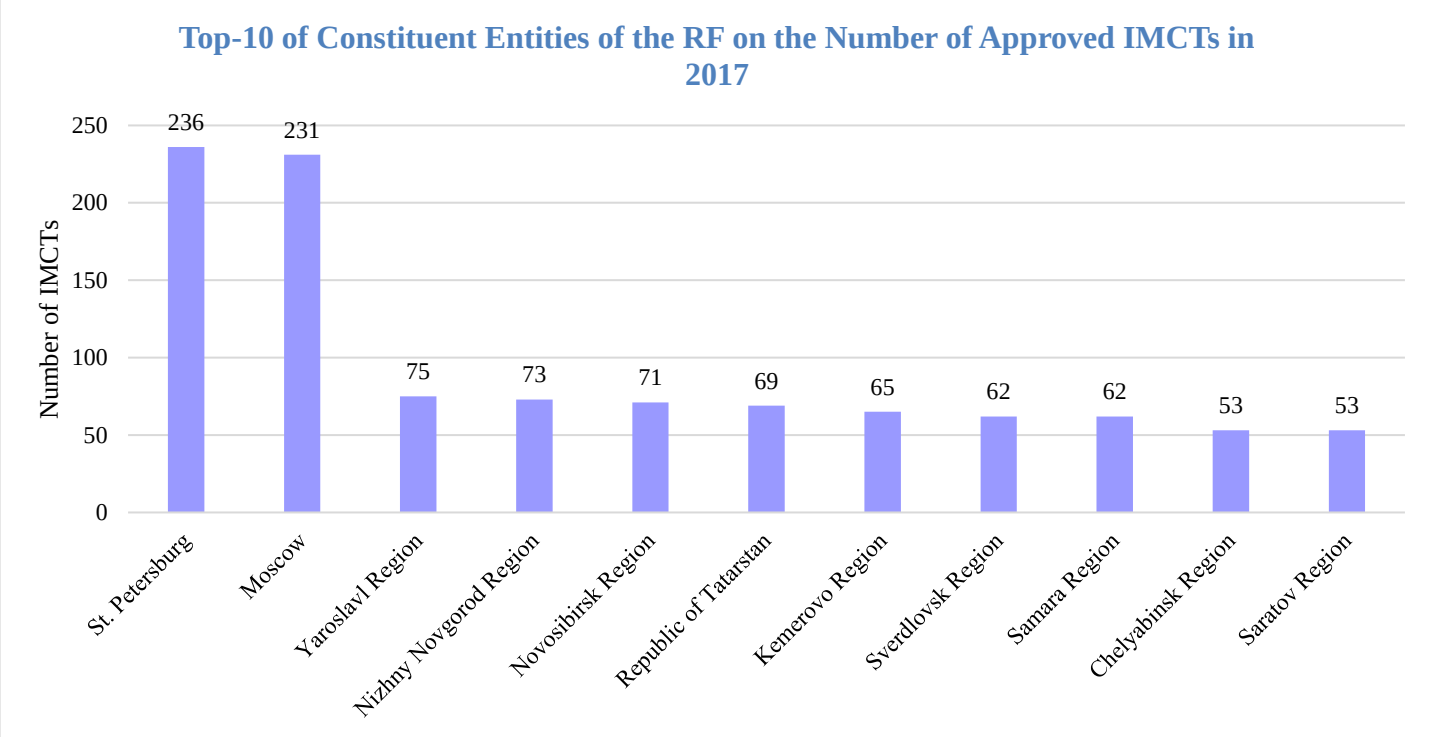
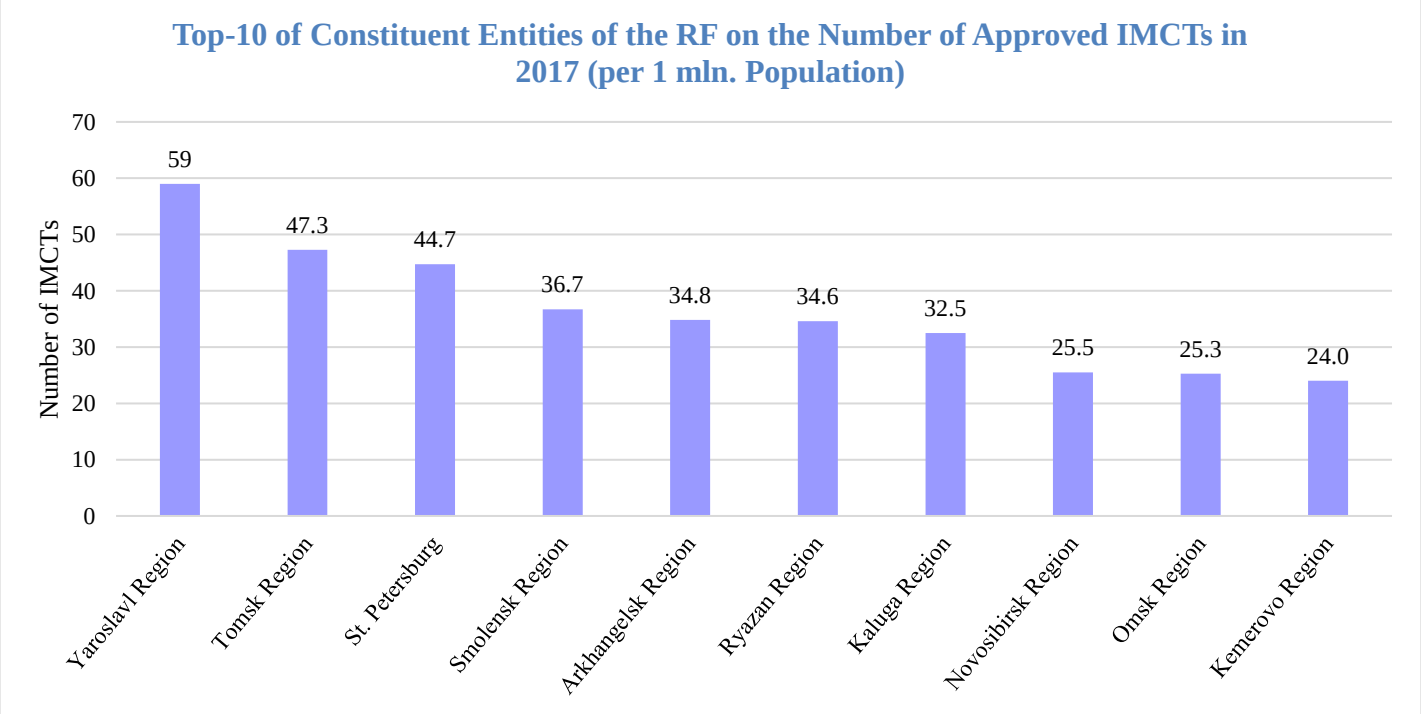
The distribution of Russian regions by activity in IMCTs differs depending on criteria used. This can well be seen from Diagrams 7 and 8. Thus, St. Petersburg, being the leader by the number of new IMCTs, ranks only third in per capita rankings. Yaroslavl region, on the contrary, ranks third by the number of international projects but first by the density of their distribution. As for Moscow, while it ranks second by the number of new IMCTs, it did not crack the top ten in terms of density, taking only the 14th position (down two steps compared to 2016).

Diagram 7



Data from www.grls.rosminzdrav.ru

Diagram 8



Data from www.grls.rosminzdrav.ru

If we compare the TOP-10[1] Russian regions by the number of IMCTs approved in 2017 and 2016, the following changes are noteworthy: Moscow lost to St. Petersburg, being five trials behind the northern capital. Tatarstan went down from the third to the sixth position in the rankings. Yaroslavl region climbed from the fifth to the third position, Nizhny Novgorod region soared from seventh to fourth rank, knocking down Novosibirsk to the fifth position. Saratov region moved from rank six down to the tenth-eleventh position sharing it with Chelyabinsk which was not in the TOP-10 a year ago, along with the Kemerovo region (seventh line of the rating). The tandem stability was demonstrated by Sverdlovsk and Samara regions which shared the ninth-tenth position a year before and then together climbed to the eighth-ninth position last year, having simultaneously increased the number of new IMCTs from 50 to 62. Rostov region that ranked eighth in 2016 dropped out of the TOP-10, ending the year only in the 23rd position.

Yaroslavl region still ranks first by the number of IMCTs per 1 million residents, despite the decrease in the absolute number of trials from 61.3 to 59. Tomsk region climbed from the fourth to the second position (47.3 IMCTs per 1 million people versus 40.9 a year before), dethroning St. Petersburg (44.7 vs 50.3 in 2016) and third-prize winner of the previous year – the Smolensk region (36.7 vs 50.1). The Republic of Karelia (ranked fifth in 2016), Saratov region (ex-ninth) and Tatarstan (ex-tenth) abandoned the TOP-10 as in 2017 they ranked only 18th, 12th and 17th, respectively. Meanwhile Arkhangelsk region cracked the TOP-10 (ranked fifth in 2017 and only 11th a year earlier) along with Omsk (ranked ninth in 2017 and 14th in 2016) and Kemerovo (10th vs 17th) regions. Ryazan (sixth), Kaluga (seventh) and Novosibirsk (eighth) regions retained their positions.

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Table 9 shows the TOP-20 most active clinics in terms of IMCTs. Apart from the number of international studies approved in 2017 with the medical institution involved, the Table also gives the number of centers it opened during the year as well its ranking.

The top trio remained unchanged despite their losses in the number of trials. Kemerovo Regional Clinical Hospital named after S.V. Belyaev, all of a sudden, ended up ranking fourth, having tripled the number of new IMCTs during the year from 11 to 33. In 2016, this hospital shared the rank from 60th to 66th.

Other medical institutions which stepped up their activity as compared to 2016 are also worthy of mention. Thus, Omsk Clinical Oncological Dispensary that earlier ranked 13th rose up to the sixth position, whereas Federal Almazov North-west Medical Research Centre climbed to the seventh position (from rank 22-23 in 2016). Obninsk National Medical Research Radiology Centre ranked ninth, climbing up from the 17th position. Kuzbass Scientific Research Institute of Complex Problems of Cardiovascular Diseases leaped from rank 53 to rank 12 straight off. St. Petersburg City Multiprofile Hospital No.2 markedly improved its position in the rating as well, jumping from lines 68-77 to lines 19-21 as it almost doubled the number of new IMCTs. Yet Tomsk National Research Medical Centre under the RAS made the most remarkable breakthrough, having soared from lines 167-201 to the 17th position.

Quite the opposite, losing their ground were Saratov State Medical University named after V. I. Razumovsky (ranked 10th vs 5th in 2016), N. N. Petrov Research Institute of Oncology (ranked 14-15 vs sixth in 2016), Siberian SMU (ranked 16th vs seventh in 2016), Ryazan SMU named after Academician I.P. Pavlov (went down from rank 12 to 19-21 lines of the rating). Also dropping out of the TOP-10 and sinking to lines 22-25, are Saratov Regional Clinical Hospital (ranked eighth in 2016) and Rostov Medical University (ranked 14th a year before). The Military Kirov Medical Academy that ranked ninth in 2016 and Smolensk State Medical University that ranked 19th, shared position 29-30 in the rankings for 2017.

[1] Two regions share lines 10-11 of the rating in 2017, so the number is not even.

Table 9

Top-21 Medical Organizations on the Activity of Participation in IMCTs Approved in 2017				
Place in ranking	**Name of medical organization**	**Number of IMCTs approved in 2017 with participation of this medical organization**	**Number of centers approved in 2017 for conducting IMCTs**	**Number of IMCTs and ranking of the centers (on approvals issued in 2016)**
1	N. N. Blokhin Russian Cancer Research Centre, Russian Ministry of Health, Moscow	52	64	60 (1)
2	I. P. Pavlov First St. Petersburg State medical University, Russian Ministry of Health, St. Petersburg	47	52	57 (2)
3	Kazan State Medical University, Russian Ministry of Health, Kazan	37	43	55 (3)
4	Kemerovo Regional Clinical Hospital named after S.V. Belyaev, Kemerovo	33	33	11 (60-66)
5	I. M. Sechenov First Moscow State Medical University, Russian Ministry of Health, Moscow	32	34	33 (4)
6	Clinical Oncological Dispensary, Omsk	28	32	26 (13)
7	Federal Almazov North-west Medical Research Centre, Russian Ministry of Health, St. Petersburg	28	29	20 (22-23)
8	N. A. Semashko Nizhny Novgorod Regional Clinical Hospital, Nizhny Novgorod	28	28	28 (10)
9	National Medical Research Radiology Centre, Russian Ministry of Health, Obninsk	26	32	24 (17)
10	Saratov State Medical University named after V. I. Razumovsky, Russian Ministry of Health, Saratov	26	28	32 (5)
11	St. Petersburg City Clinical Oncological Dispensary, St. Petersburg	26	27	27 (11)
12	Scientific Research Institute of Complex Problems of Cardiovascular Diseases, Kemerovo	26	26	12 (53)
13	I. I. Mechnikov North-West State Medical University, Russian Ministry of Health, St. Petersburg	24	25	20 (22-23)
14-15	N. V. Solovyev Yaroslavl region Clinical Hospital for First Medical Assistace, Yaroslavl	24	24	24 (18)
14-15	N. N. Petrov Research Institute of Oncology, Russian Ministry of Health, St. Petersburg	24	24	30 (6)
16	Siberian State Medical University, Russian Ministry of Health, Tomsk	22	23	28 (7)
17	Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk	21	22	5 (167-201)
18	Regional Clinical Hospital, Barnaul	21	21	13 (46-52)
19-21	Ryazan State Medical University named after Academician I.P. Pavlov of the Ministry of Health of Russia, Ryazan	19	19	27 (12)
19-21	St. Petersburg Clinical Practical Research Centre for Specialised Types of Medical Aid (Oncological), St. Petersburg	19	19	20 (25-26)
19-21	City Multiprofile Hospital No. 2, St. Petersburg	19	19	10 (68-77)

Source: www.grls.rosminzdrav.ru

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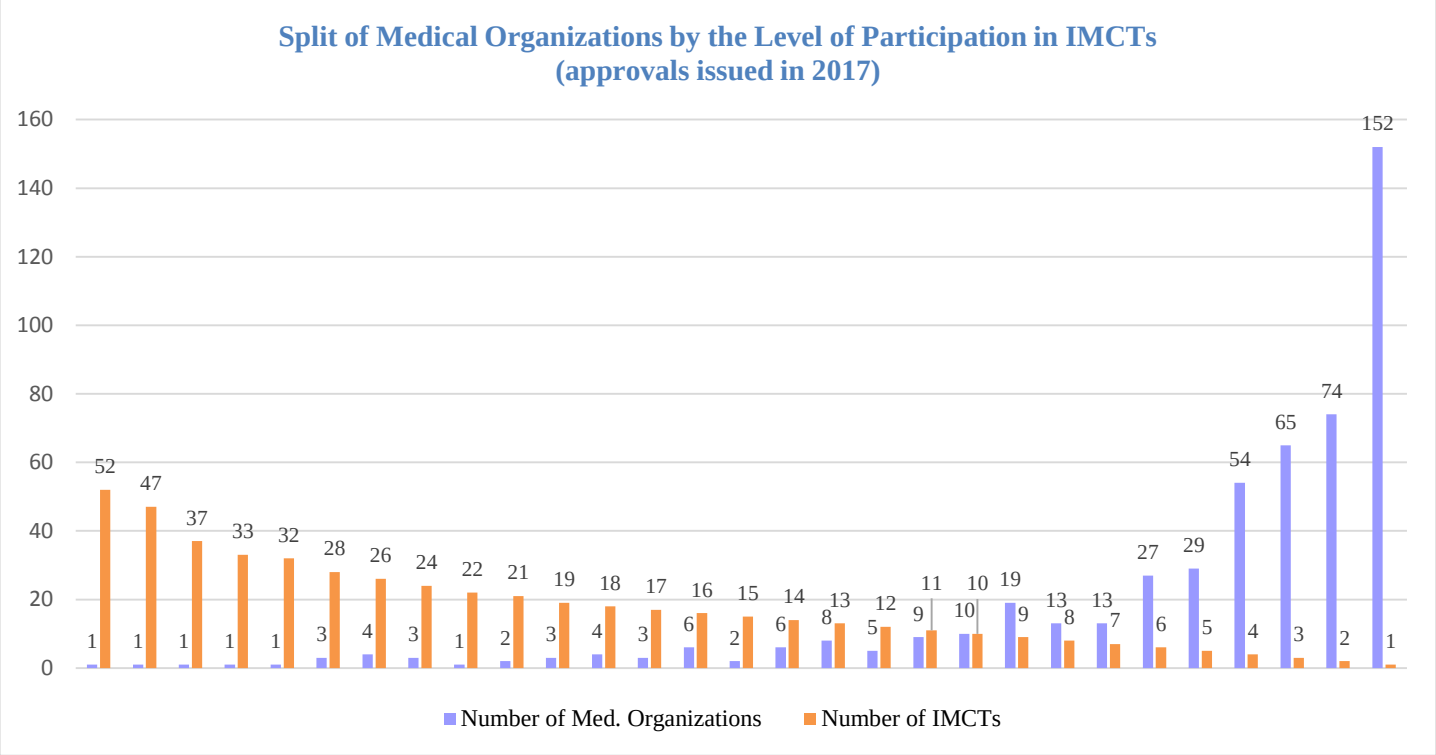
Diagram 9 shows the distribution of approved IMCTs by medical institutions where they must be conducted. More than 30 new trials fell to the share of five clinics, whereas 152 institutions declared their participation in only one international project, 74 – in two projects, etc. Overall 520 institutions were involved in new IMCTs last year, down 19 year-on-year.

Diagram 9



Data from www.grls.rosminzdrav.ru

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For the third year in a row we review the two leading regions Moscow and St. Petersburg in more detail as we analyze the regional distribution of international trials. In particular, we look at the activity of medical institutions as regards the conduct of IMCTs, depending on their subordination.

From Table 8 we remember that at the end of the year both regions decreased their results compared to the year 2016. Let's try to figure out the reasons. In Moscow (see Table 10) the highest number of IMCT centers falls to the share of medical institutions subordinate to the Russian Ministry of Health – 227 new centers in 2017, followed by clinics under the jurisdiction of the Moscow Healthcare Department (MHD) – 117 centers as well as federal departmental institutions – 110 centers. For all that, in 2017 the number of clinics involved in new IMCTs shrank by two federal departmental institutions (24 versus 26), by six institutions under the MHD jurisdiction (28 vs 34); however, institutions subordinate to the Ministry of Healthcare increased the number of trials by 5 (23 vs 18 in 2016). In the meantime, the number of IMCT centers opened in all of these institutions dwindled: by 9.2% (227 vs 250 in 2016) as regards the institutions subordinate to the Ministry of Health; by 17.9% (110 vs 134) in institutions of departmental affiliation; and by 24.5% (117 centers vs 155 the year before) for clinics under the MHD jurisdiction. A steeper decline (39.5%) was observed only in non-government health institutions. Yet the changes of relative indicators seem weightier there due to a small sampling, i.e. a generally small number of clinics participating in IMCTs and a small number of centers opened.

We believe that the main reason for such a tangible slump in the number of IMCT centers in MHD clinics (by a fourth) was the mounting of extra administrative hurdles that commenced in 2016 and peaked by mid-2017 *(for more detail see the last section of this Newsletter)*. Complicated rules of the game and deterioration of the trial terms in clinics subordinate to MHD could not but cause an outflow of IMCTs. The real situation can be even worse: we build our calculations on the statistics from the MoH register of approved trials. A center's mentioning in the approval, however, does not mean it will actually be opened. Quite likely, some of the centers were just declared on paper. Furthermore, the market inertia is to be taken into account. We assume that we'll see a deeper degradation of Moscow's parameters next year.

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 centers approved for IMCTs**			**Activity Ratio**	
	2017	**2016**	**2017**	**2016**	**2017 vs 2016, %**	**2017**	**2016**
Ministry of Healthcare of the Russian Federation	23	18	227	250	**-9.2**	9.9	13.9
Moscow Department of Healthcare	28	34	117	155	**-24.5**	4.2	4.6
Federal bodies (except Ministry of Healthcare of the RF)	24	26	110	134	**-17.9**	4.6	5.2
Non-governmental health system	12	15	26	43	**-39.5**	2.2	2.9
JSC "Russian Railways"	2	2	20	26	**-23.1**	10.0	13.0
Ministry of Healthcare of the Moscow region	2	3	13	16	**-18.8**	6.5	5.3
TOTAL	91	98	513	624	**-17.8**	5.6	6.4

Data from www.grls.rosminzdrav.ru

The number of centers opened during the year went down in St. Petersburg as well (see Table 11), though ongoing growth in the number of non-government health institutions involved in IMCTs is quite eye-catching. There were as many as 38 of these in 2017 versus 34 a year ago. This is the second largest group next only to clinics subordinate to the Health Committee of Saint Petersburg. Nevertheless, private institutions lose to public ones by the number of centers they open. Be that as it may, it's not the first year that active involvement of the non-government sector in the northern capital's IMCTs surprises us.

Table 11

The level of participation of healthcare organizations in Saint-Petersburg in IMCTs depending on subordination							
Subordinated to	**The number of medical organizations involved in new IMCTs**		**The number of centers approved for IMCTs**			**Activity Ratio**	
	2017	**2016**	**2017**	**2016**	**2017 vs 2016, %**	**2017**	**2016**
Health Committee of Saint-Petersburg	51	55	277	331	**-16.3**	5.4	6.0
Ministry of Healthcare of the Russian Federation	13	12	169	203	**-16.7**	13.0	16.9
Non-governmental health system	38	34	116	120	**-3.3**	3.1	3.5
Federal bodies (except Ministry of Healthcare of the RF)	9	11	61	78	**-21.8**	6.8	7.1
Committee of Health of the Leningrad Region	3	3	32	38	**-15.8**	10.7	12.7
JSC "Russian Railways"	1	1	9	13	**-30.8**	9.0	13.0
TOTAL	115	116	664	783	**-15.2**	5.8	6.8

Data from www.grls.rosminzdrav.ru

We can also see from Table 11 that a slump in the number of IMCT centers approved in 2017 was significant for nearly all types of medical institutions – perhaps with the exception of the non-government health system where it was only 3.3%. In clinics under the jurisdiction of St. Petersburg Health Committee the number of new centers went down by 16.3%; among those subordinate to the Russian Ministry of Healthcare – by 16.7%; in clinics subordinate to other federal departments – by 21.8%.

It only remains to add that other regions made up for Moscow and St. Petersburg decline in terms of the number of new IMCT centers, in a way. Thus, 9.4% more centers than a year ago (58 vs 53) were opened in the Chelyabinsk region; 11.1% more centers (70 vs 63) in the Sverdlovsk region; 20.8% more in the Omsk region (64 vs 53). Kuzbass retained leadership positions as the number of IMCT centers opened in the Kemerovo region during 2017 increased by the respectable 53.7% – 83 new IMCT centers versus 54 the year before. It can thus be stated that we witness a clear realignment trend in 2017, as regards IMCTs, in favor of Siberia and the Urals.

PARTICIPATION OF MEDICAL INSTITUTIONS IN BIOEQUIVALENCE STUDIES

Table 12 contains the ranking of medical institutions by their activity in bioequivalence studies. It should be noted that half of them are non-government health institutions.

Table 12

Top-16 medical organizations on the activity of participation in Bioequivalence Studies (approvals issued in 2017)					
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 center ranking on approvals issued in 2016**
1	"Medical Center Probiotech", Serpukhov	29	27	2	26 (3-4)
2	Clinical Hospital №2, Yaroslavl	26	18	8	33 (2)
3-4	Road clinical Hospital at the station Yaroslavl, JSC "Russian Railways", Yaroslavl	17	10	7	14 (7-8)
3-4	"Research Center Eco-bezopasnost", St. Petersburg	17	11	6	34 (1)
5-6	City Clinical Hospital №68, Moscow Department of Healthcare, Moscow	13	3	10	9 (11)
5-6	Federal Research and Clinical Centre of Physical-Chemical Medicine, Federal Medical-Biologicall Agency, Moscow	13	1	12	7 (14-15)
7	"BioEq", St. Petersburg	12	11	1	19 (5)
8-10	"MedFort", St. Petersburg	8	8	-	n/a
8-10	Institution of the Russian Academy of Sciences Hospital RAS, Moscow region, Troitsk	8	7	1	6 (16-19)
8-10	Kazan (Privolzhsky) Federal University, Kazan	8	7	1	3 (26-33)
11-12	"Family Doctor+ Clinic", Nizhny Novgorod	7	7	-	16 (6)
11-12	"BESSALAR Clinic", Moscow	7	-	7	13 (9)
13-14	"Scientific Clinical Center of JSC "Russian Railways", Moscow	6	3	3	1 (35-50)
13-14	Regional Institution Cardiology Clinic, Ivanovo	6	5	1	6 (16-19)
15-16	Yaroslavl Regional Clinical Drug Treatment Hospital, Yaroslavl	5	5	-	10 (10)
15-16	Yaroslavl Region Clinical Hospital № 8, Yaroslavl	5	5	-	5 (20-23)

Data from www.grls.rosminzdrav.ru

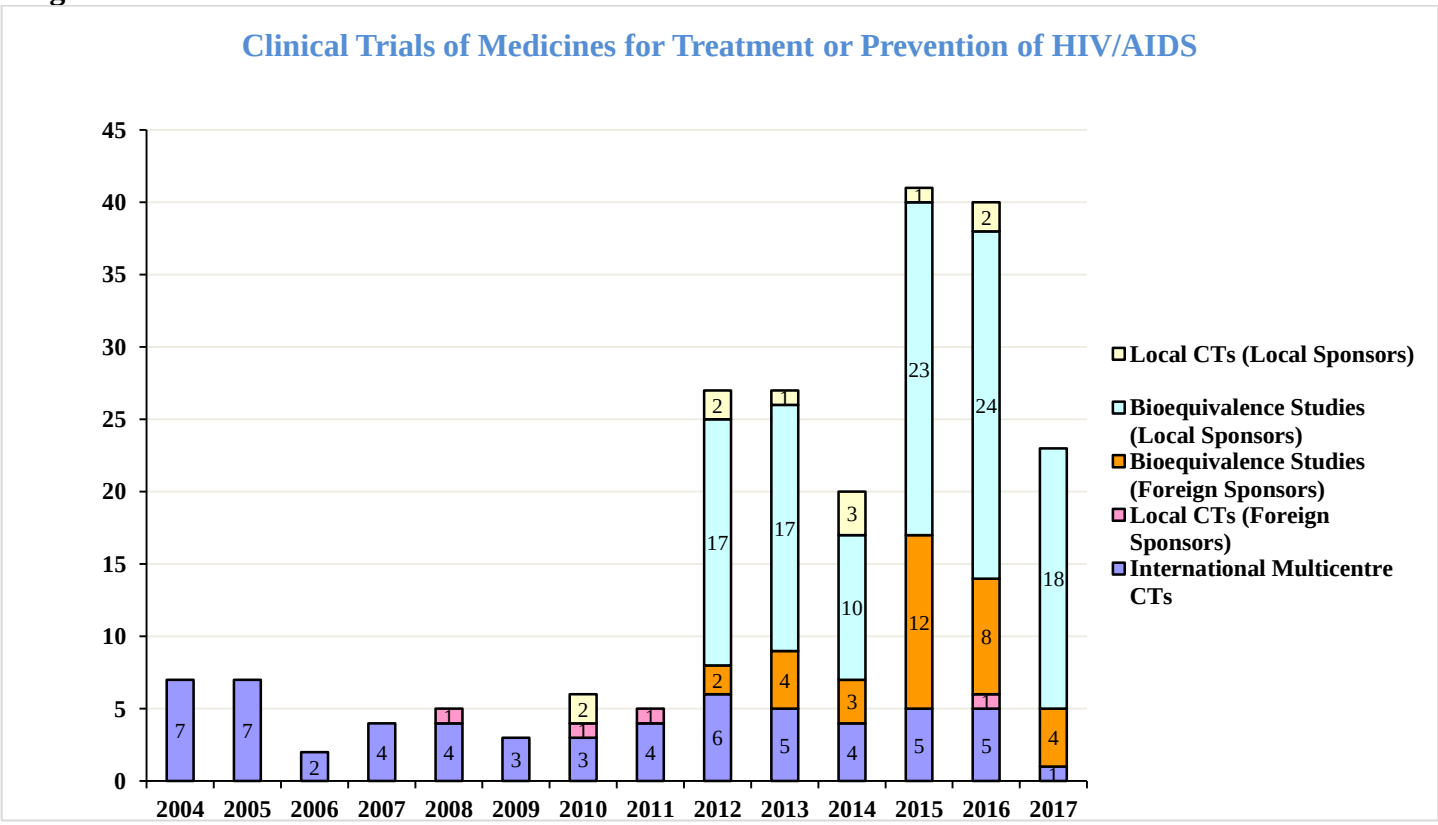
SITUATION WITH CLINICAL TRIALS OF MEDICATIONS FOR TREATMENT OF HIV/AIDS, HEPATITIS C AND TUBERCULOSIS MEDICATIONS

ACTO Newsletter No. 4 analyzes the situation with clinical trials of HIV/AIDS, hepatitis C and tuberculosis drugs (since HIV-positive patients often suffer from all three viruses) for the period 2004 – Q1 2012. In this issue we publish a sequel to this overview of the same diseases. We analyze the trials approved in Russia from 2012 to 2017 inclusive. The sampling was based on the data in the register of approvals by the Ministry of Healthcare; in cases where ICD diseases are not mentioned in trial protocols – with due regard for the proposed clinical use of the medication under review (and/or a comparator drug in bioequivalence studies) as per the State Register of Medicines register of official medications and other open sources.

HIV/AIDS

Approvals for the conduct of 178 trials of HIV/AIDS treatment and prevention drugs (see Diagram 10) were issued in 2012-2017 in Russia, seven times as many as during the previous six years from 2006 to 2011, when 25 trials were approved. And while in 2004-2011 IMCTs prevailed (80.5%), in 2012-2017 bioequivalence studies called the shots, accounting for 79.8% of all HIV/AIDS drug trial approvals. Domestic sponsors initiated 61.2% of all bioequivalence studies (109 in absolute figures), foreign sponsors – another 18.5% (33) studies.

Diagram 10



Data from www.grls.rosminzdrav.ru

We classified one study as local with a foreign sponsor: ViiV Healthcare was approved to conduct trial from November 2016 to July 2018, for the declared purpose of studying the long-term safety of dolutegravir (DTG) for those who earlier participated in IMCTs of the same company studying the same drug.

The number of local studies initiated by Russian companies rose dramatically: there were only two of these from 2006 to 2011, but the number rose to nine in the following six years from 2012 to 2017, with domestic developments studied in eight of them. The adoption in 2011 of the federal target program for the development of pharmaceutical industry for the period up to 2020, could have spurred local studies.

IMCTs slid from the main to a third group, accounting for 14.6% of the total number – 26 trials out of 178 (one of them is providing a broader access to the medication for patients who completed the study). In

absolute figures the number of IMCTs dwindled only in 2017 (one trial against the average of 4.5 in 2004-2016). In other words, a change in the ratio of IMCTs to bioequivalence studies was due to the growing number of the latter. First of all, this fits well into the general trend, regardless of the ICD code (see The Volume and Dynamics of the Clinical Trials Market in this Newsletter); and secondly, this reflects a global situation with expiration of patent protection for drugs approved from 1995 to 2004: prior to 1996 FDA had approved four drugs; in 1995-2004 – 21 drugs, and after 2004 – another 22[2]. As a rule, these drugs received patent protection before approval. Thus, the first wave of patent protection expiry rolled on in recent 6-8 years.

Of 26 IMCTs 21 are third-phase trials. The number of Russian participants involved in the trials of HIV/AIDS treatment and prevention medications in 2012-2017, as per the register, ranged from 5 to 240 people and in 80% of trials – from 24 to 80 people.

Comparing the Russian and global dynamics may cause a problem, since we lack comparable world statistics. The ICD search in the clinicaltrials.gov register brings under the category of intervention studies not only medicinal drugs, but also medical devices, tests, psychotherapy and educational impact, etc. There were 1,624 such studies for HIV/AIDS declared in the clinicaltrials.gov register for 2012-2017. To get a rough estimation of the drug trials count, we made a random sampling of 312 trials from the general population, followed by checking whether these were studies of a therapeutic medication, vaccine or cell therapy for HIV-AIDS. Such trials accounted for 37%, extended to the population, that gives us ground to assume with a 99.7% probability that the matter regards 600±120 trials of drugs in this ICD code, which is 3-4 times more than in the Russian Federation – a very rough approximation, but unfortunately, we failed to find more accurate comparison methods.

Another parameter that lends itself to comparison is objects of studies in national and international trials. By comparing the estimated drugs, we can assess the extent to which Russian patients can get access to recent developments in HIV/AIDS medication. As per the HIV-MIDReport-2017[3], only in the middle of 2017 there were 52 HIV/AIDS drugs, vaccines and therapies in clinical trials or under consideration of FDA, including 32 retroviral medications (regular and combination), 16 vaccines and four cell therapies. One of the innovative solutions is a drug disabling the virus to infect new cells and blocking its penetration through cell membranes[4]. In Russia they had been studying 48 active agents and/or their combinations as well as two domestic vaccines during the same period[5]. Table 13 lists active agents most frequently mentioned in IMCT protocols, whereas Table 14 lists the leaders of bioequivalence studies.

Table 13

Active substances, most often studied in IMCTs in Russia in 2012-2017	
INN	**Number of IMCTs**
Dolutegravir	4
Raltegravir	4
Abacavir + Dolutegravir + Lamivudine	2
Dolutegravir + Lamivudine / Tenofovir disoproxil fumarate + Dolutegravir + Emtricitabine	2
Dolutegravir + Rilpivirine	2
Cabotegravir + Rilpivirine	2

Data from www.grls.rosminzdrav.ru

[2] As of March 2018.
[3] http://phrma-docs.phrma.org/files/dmfile/HIV-MIDReport-2017.pdf
[4] Trogarzo, approved by FDA in March 2018 was never studied in Russia.
[5] CombiHIVvac and DNA-4.

Table 14

Active substances, most often studied in Bioequivalence Studies in Russia in 2012-2017				
INN	**Number of studies**	**Comparator product**	**Bioequivalence studies conducted by local sponsors**	**Bioequivalence studies conducted by foreign sponsors**
Zidovudine + Lamivudine	19	Combivir (Glaxo)	13	6
Darunavir	13	Prezista (Johnson & Johnson)	11	2
Abacavir + Lamivudine	10	Kivexa (Glaxo, ViiV Healthcare)	6	4
Atazanavir	10	Reyataz (Bristol-Myers Squibb, AstraZeneca)	9	1
Tenofovir disoproxil fumarate	9	7 Viread (Gilead), 2 Tenofovir (Hetero drugs)	6	3
Lamivudine	9	Epivir (Glaxo, ViiV Healthcare)	5	4
Tenofovir disoproxil fumarate + Emtricitabine	8	Truvada (Gilead)	6	2
Efavirenz	8	Stocrin (Merck Sharp & Dohme)	6	2
Abacavir	7	Ziagen (Glaxo, ViiV Healthcare)	6	1
Lopinavir + Ritonavir	7	Kaletra (Abbot, AbbVie)	7	
Ritonavir	7	Norvir (Abbot, AbbVie)	6	1
Nevirapine	6	Viramune (Boehringer Ingelheim Pharma)	5	1

Data from www.grls.rosminzdrav.ru

In 2012-2017, FDA approved 11 HIV drugs[6], including three new active ingredients[7] and eight combination drugs, including a prodrug of the earlier used active ingredient[8]. Out of 11 drugs approved by the American regulator, five have not been studied in Russia[9]. At the same time, two active ingredients approved by FDA in 2014 as monodrugs[10] were studied in Russia only as part of the combination[11] approved by FDA in 2012. Four other drugs approved by FDA were also studied in Russia: Stribild (STB), Tivicay, Triumeq and Juluca. Of these four only Tivicay is included in the drug register (since 2014), with ViiV Healthcare starting to launch its local production in Russia in 2017.

We pointed out in our 2012 analysis that the absence of Gilead Science, one of the key developers of HIV drugs, on the Russian market negatively affected the accessibility of modern HIV treatments. In that same year the said company entered the Russian market, but this did not lead to a dramatic rise in the number of IMCTs. Gilead Science organized three IMCTs in 2012-2017 and was ranked third in the list of international developers of HIV medications, sharing the third position with Bristol-Myers Squibb which also initiated three IMCTs. Merck ranked second with four IMCTs. Shooting far ahead is ViiV Healthcare – 13 IMCTs of HIV/AIDS drugs in six recent years. Yet Gilead is responsible for indirect impact: in 2012-2017 drugs such as Viread, Truvada, Atripla and Eviplera owned by the company and registered in Russia figured as comparators in 23 bioequivalence studies.

Hepatitis C

In 2012-2017 Russia issued approvals for 66 clinical trials of hepatitis C drugs (Diagram 11). To compare this stat with the world parameters, an approximation was made using clinicaltrials.gov. The search by key words “Hepatitis C, HCV”, exclusive of observation studies, yielded the population of 662 trials. A sampling of 243 trials was then made, where about 80% of all studies were drug trials. Extended to the population, this gives, with a 99.7% probability, 530±40 protocols. In other words, the number of similar trials recorded on clinicaltrials.gov in 2012-2017 approximately eight times exceeds the number of trials in the Russian Federation conducted over the same period.

[6] Stribild, Tivicay, Tybost, Vitekta, Triumeq, Evotaz, Genvoya, Prezcobix, Descovy, Odefsey and Juluca, see the infographics https://aidsinfo.nih.gov/understanding-hiv-aids/infographics/25/fda-approval-of-hiv-medicines

[7] Dolutegravir (tradename: Tivicay), cobicistat (Tybost) and elvitegravir (Vitekta).

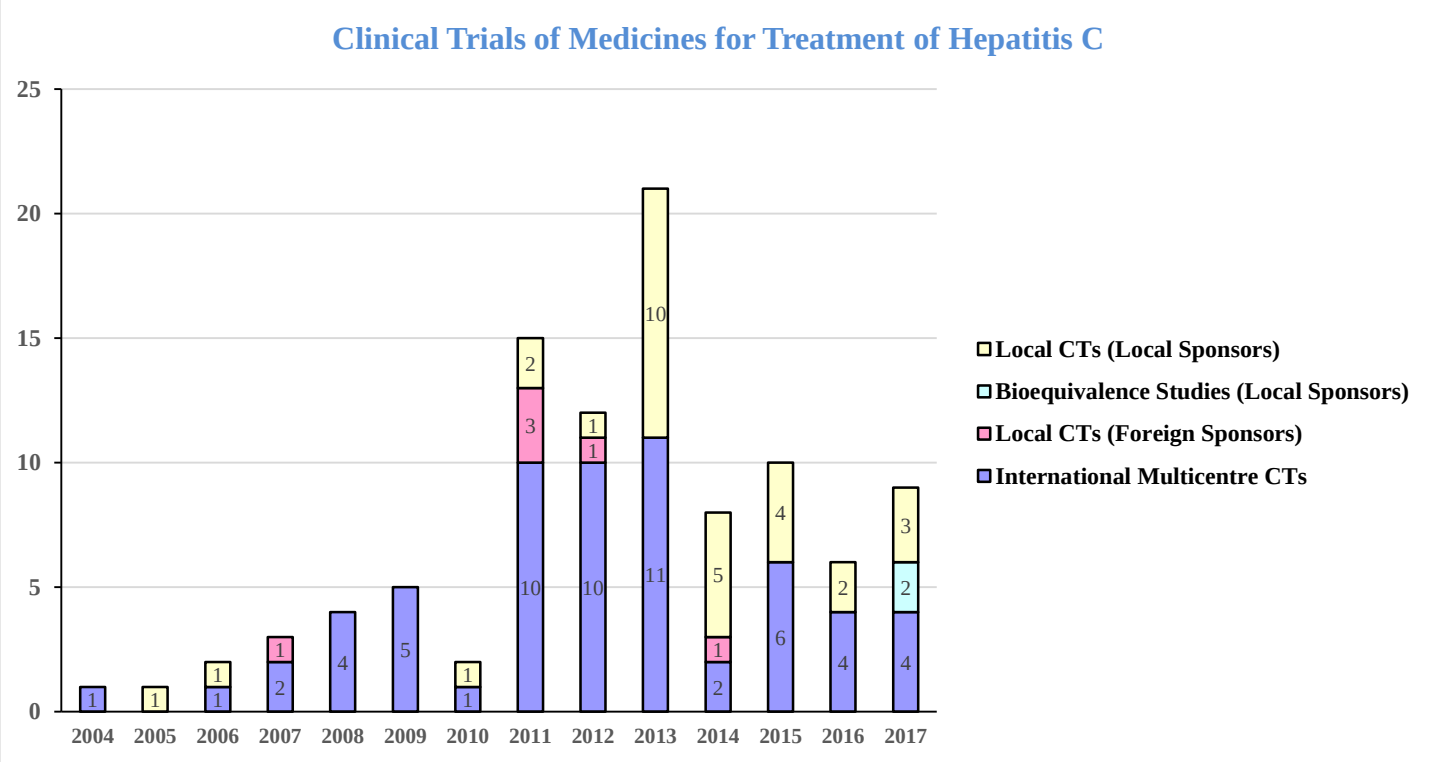
[8] Tenofovir alafenamide fumarate as an alternative to tenofovir disoproxil fumarate.

[9] Evotaz, Genvoya, Prezcobix, Descovy, Odefsey.

[10] Cobicistat and elvitegravir under the tradenames of Tybost and Vitekta.

[11] Stribild (combination formula cobicistat + tenofovir disoproxil fumarate + elvitegravir + emtricitabin), approved in 2012, was tested in Russia (2013–2017).

Diagram 11



Data from www.grls.rosminzdrav.ru

IMCTs are leaders in Hepatitis C clinical drug trials during the period under review – 56% of the total number or 37 trials. Coming next are local studies organized by Russian sponsors (38%, 25 trials). Foreign sponsors initiated two local studies in Russia (3%) matching the number of bioequivalence studies initiated by domestic sponsors[12]. There were no bioequivalence studies of hepatitis C drugs of the foreign make, as per the data of the Ministry of Health's register for 2012-2017.

Compared to the previous 6-year period, the number of hepatitis C drug trials roughly doubled: the number of trials averaged five studies in 2006-2011 and eleven – in 2012-2017. The greatest contribution to this growth was made by the largest IMCT category (the average annual IMCT count rising from 4 to 6) as well as local studies by Russian sponsors, almost imperceptible during the previous 6-year period (their average annual count rising from <1 to >4).

The increase in the number of trials in these categories parallels a surge of international activity in the development of hepatitis C drugs and the emergence of new drug generations swiftly replacing one another. The rousing interest may well be tracked via a growing number of IMCTs from 2006 to 2013. The upturn stopped in 2010, when the Law "On Circulation of Medicines" was being passed and it was difficult to get a clinical trial approval, but already in 2011 the pattern was resumed and the curve went upward again. The peak of clinical trials (2013) coincides with the key breakthrough, i.e. the advent of second-generation Direct Acting Anti-hepatitis C Virus Drugs (DAA) effective in 90-100% of all cases.

The change of drug generations was so fast that Russian sponsors went on developing interferons in 2013, which were inferior to the second-generation DAA drugs in terms of efficiency. Today interferons are no longer included in the main treatment schemes recommended by WHO, but because they are much cheaper compared to DDA drugs, they still feature in the Russian "Recommendations on Hepatitis C Adult Patients Diagnostics and Treatment." Thus, in 2013 Biocad brought out to the market its own sustained-action interferon under the tradename of Algeron, later added to the list of vital drugs.

One example of DAA study by a Russian sponsor is R-Pharm. In 2012 the company concluded an agreement with Merck to promote its drug in Russia and the CIS markets: it started studying it in 2013 and in 2016 had it registered in Russia under the brand name of Narlaprevir.

[12] In both cases the comparator was Sovaldi (sofosbuvir) manufactured by Gilead – the first second-generation DAA drug approved by FDA.

Yet the main part of DAA was studied in Russia as part of IMCTs. From 2012 to 2017 FDA approved 10 drugs[13], of which eight were studied with the involvement of Russian centers[14]. In addition, Russia participated in the trials of asunaprevir from Bristol-Myers Squibb (registered in Russia under the tradename of Sunvepra in 2015), which was soon after that approved in Canada, China and Japan.

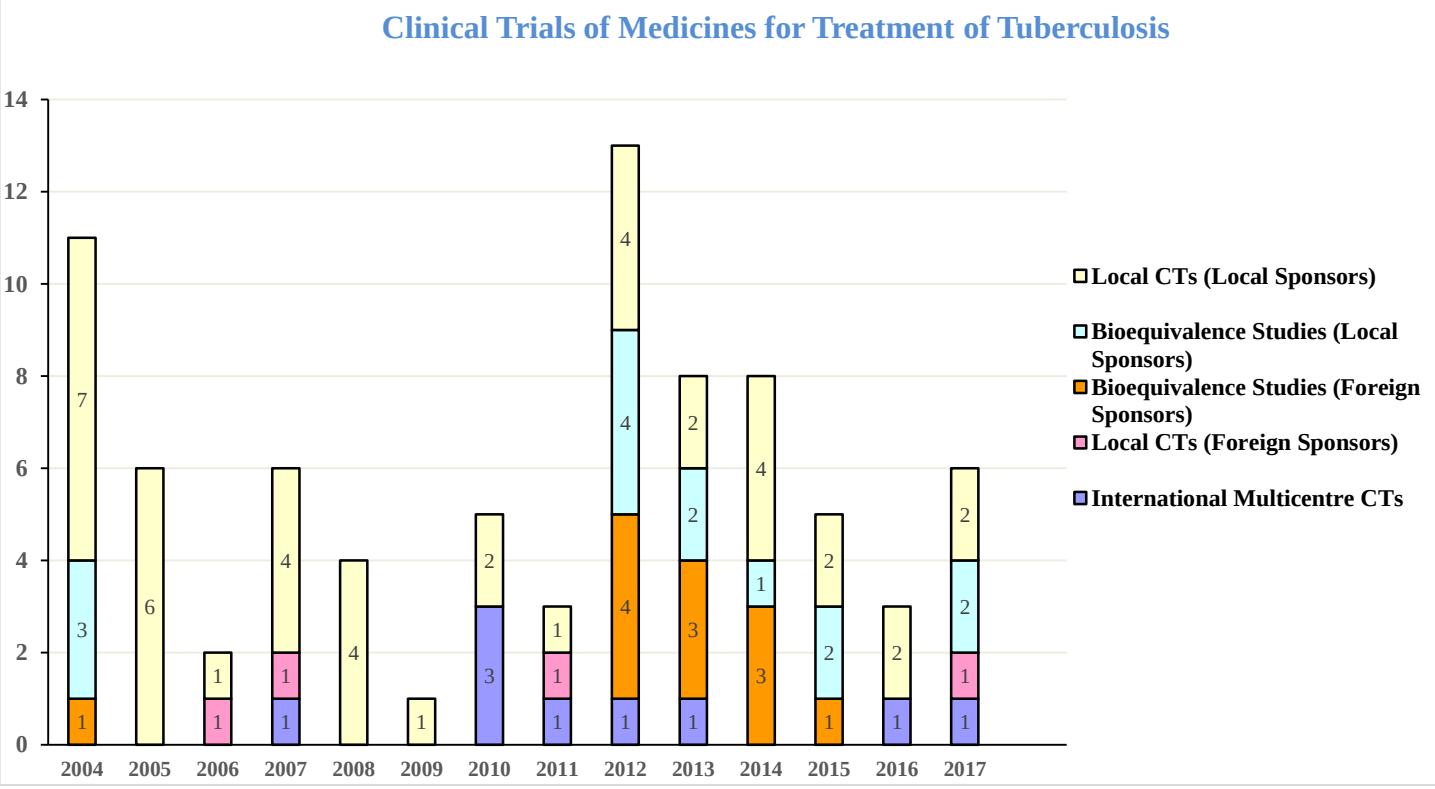
Bristol-Myers Squibb proved the leader by the number of IMCTs of hepatitis C drugs in 2012-2017, having conducted 16 trials, followed by AbbieVie with nine IMCTs, by Merck with six trials, by Gilead (4 trials) and by Janssen (2 trials).

Tuberculosis

Tuberculosis is rather uncommon now in North America and Western Europe; yet this disease remains a big problem in some regions, including in Russia. Of special concern is multi-drug resistance potentially threatening the population of prosperous countries as well. This situation is reflected in the structure and dynamics of anti-tuberculosis clinical trials in Russia: Diagram 12 shows a small share of IMCTs (compared to other ICD codes under review) as well as a notable share of trials conducted by local sponsors.

In 2012-2017 Russia provided approvals to conduct 43 anti-tuberculosis drugs, not to mention broad-spectrum antibiotics included in tuberculosis treatment schemes. This number can be roughly compared to international stats, courtesy of clinicaltrials.gov. The search by the key word "Tuberculosis", with observation studies deducted, results in the population of 286. A random sampling was then made, amounting to 164 trials. The sampling check revealed that 46% of these are the studies of medicinal drugs, exclusive of broad-spectrum antibiotics. For the general population in question, with the probability of 99.7%, this gives us 132±22 trials. This means that 3-4 times more trials of anti-tuberculous drugs, as compared to Russia, were declared on the clinicaltrials.gov resource in 2012-2017.

Diagram 12



Data from www.grls.rosminzdrav.ru

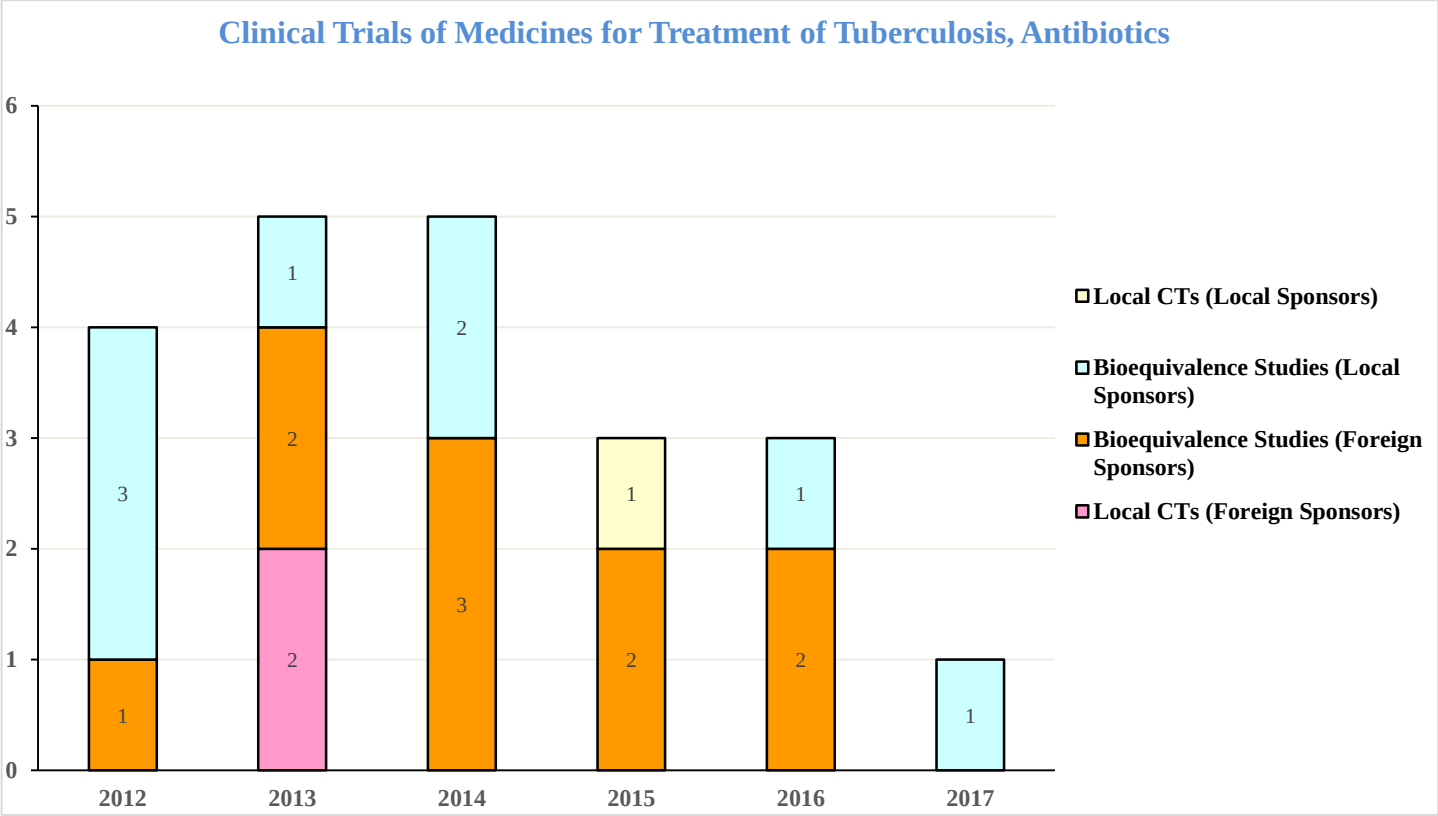
[13] Sovaldi (INN sofosbuvir), Olysio (simeprevir), Viekira Pak (ombitasvir, paritaprevir, ritonavir, dasabuvir), Harvoni (ledipasvir, sofosbuvir), Technivie (ombitasvir, paritaprevir, ritonavir), Daklinza (daclatasvir), Zepatier (elbasvir, grazoprevir), Epclusa (sofosbuvir, velpatasvir), Mavyret (glecaprevir, pibrentasvir), Vosevi (sofosbuvir, velpatasvir, voxilaprevir).

[14] Sovaldi, Harvoni and Epclusa from Gilead, Viekira Pak, Technivie and Mavyret from AbbieVie, Daklinza from Bristol-Myers Squibb and Zepatier from Merck.

Half of all trials approved in Russia from 2012 to 2017 (22 out of 43) were bioequivalence studies[15], of which 11 were initiated by foreign sponsors and another 11 – by Russian sponsors, and 16 projects (37% of 43) were represented by local studies of domestic sponsors. Another local study was initiated by a foreign sponsor[16]. Only about one tenth of the total number of approvals (four trials) fell to the share of IMCTs. The total number of trials doubled as compared to the previous six-year period: from the average 3.5 studies per year (2006-2011) to 7 (2012-2017). This growth was largely triggered by bioequivalence studies, which fits into the general trend, regardless of ICD codes.

On the quality side, we may talk about progress in global trials of anti-tuberculosis drugs, though the number of new molecules used in this therapeutic area is not as high as in case of HIV and hepatitis C. Only two new anti-tuberculous drugs were given the nod in the world in the last six years, but these are the first approvals since the late 1950s. Janssen's bedaquiline was approved in the US and Otsuka's delamanid was authorized in EU and a number of other countries from 2012 to 2017. Bedaquiline as a monodrug had been studied by Russian centers prior to 2012, whereas in 2017 it was studied in a combination with linezolid and pretomanid. Delamanid was not studied in Russia. Russian sponsors promoted their own developments as well: thus in spring 2017 Infectex announced a successful clinical trial of IIb-III phases of SQ109 drug with the mode of action similar to the well-known anti-tuberculous drug ethambutol (EMB). Besides anti-tuberculosis drugs proper, Russia hosted the clinical trials of broad-spectrum antibiotics used in tuberculosis treatment schemes (levofloxacin or Lfx, cycloserine or Cs, sparfloxacine). Diagram 13 shows the number of approvals provided for these drugs' trials in 2012-2017.

Diagram 13



Data from www.grls.rosminzdrav.ru

[15] Most popular comparators: Terizidon and PASA from different manufacturers.
[16] SRI under the Science Committee of Kazakhstan's Education Ministry studied the anti-tuberculous vaccine.

MAIN PLAYERS ON THE RUSSIAN CLINICAL TRIALS MARKET – 2017

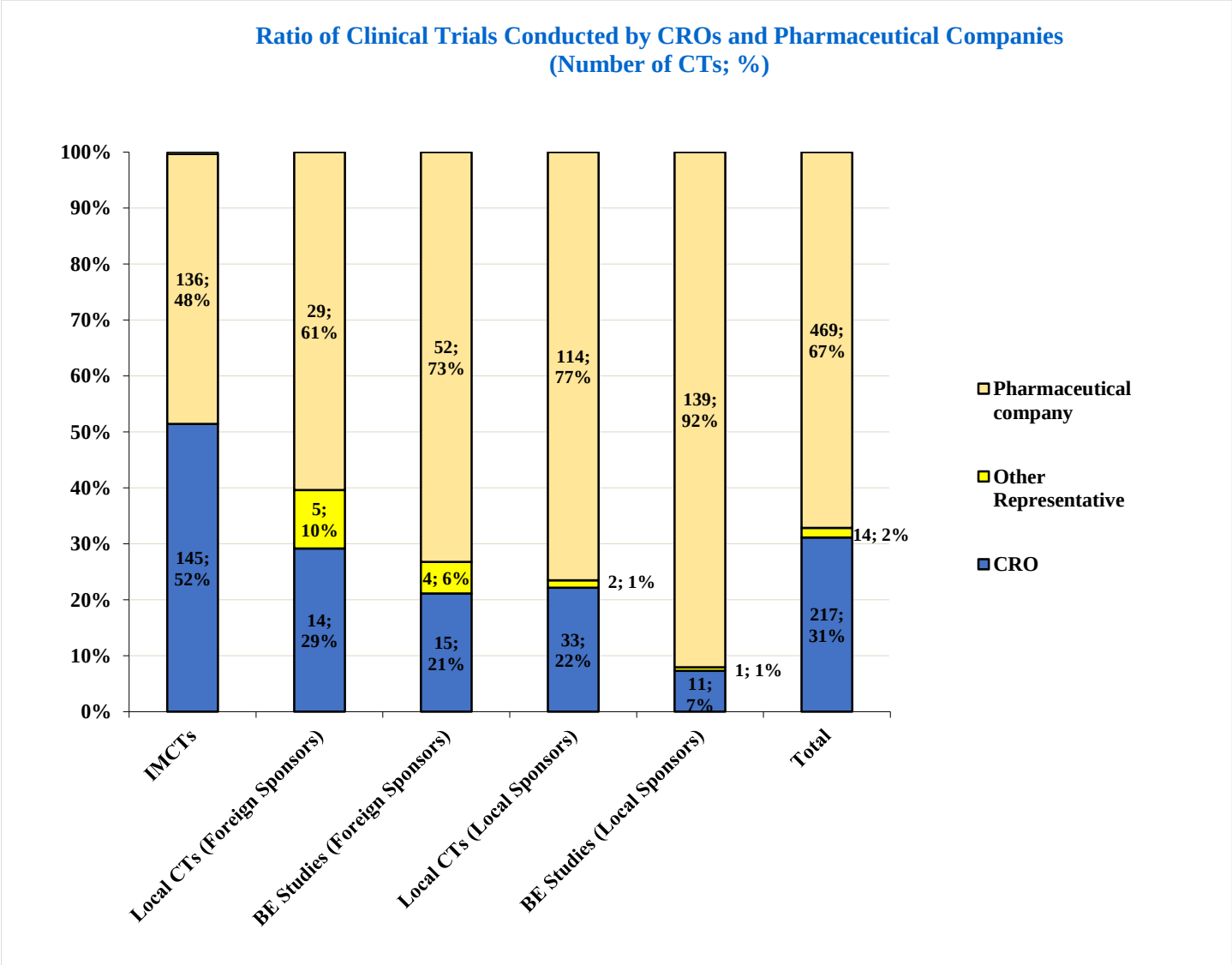
Sponsors and CROs, general structural breakdown

In this section of the Newsletter we'll focus on the main participants of the clinical trials market in 2017. The breakdown of trials by companies conducting them is shown in Diagram 14.

In accordance with the established practice, we conventionally divided the market participants into three groups: sponsors, contract research organizations (CRO) and "other representatives". Under the latter we mean companies which do not solely specialize in the conduct of clinical trials, i.e. they are not classical CROs. Most often the matter regards organizations that proceed with the drug marketing, including its registration and distribution (*for more detail about the criteria used for the given classification see Newsletters No. 12 and 14*).

What's more, we'd like to make a caveat that the clinical trials register of the Russian Ministry of Health does not always fully reflect the information on sponsors engaging CROs. Unless a CRO is involved in getting a clinical trial approval, its participation may not be reflected in the register, so when analyzing data, one should remember that CROs are most likely responsible for a greater share of trials.

Diagram 14



Data from www.grls.rosminzdrav.ru

As we compare the general picture with the one in 2016, we can notice that in the IMCT segment the distribution of trials conducted by sponsors independently or with the involvement of CROs has not changed much: 48% and 52%, respectively, versus 47% and 52%[17] in 2016. It also remained practically unchanged in the

[17] Slightly less than 1% in 2016 fell to the share of studies with the involvement of "other representatives".

sector of bioequivalence studies by Russian sponsors: 92% of all trials were conducted by pharmaceutical companies, whereas in 2016 their share stood at 91%.

As for other types of trials, the ratio has changed. Thus in the local studies of foreign sponsors the share of projects delivered by sponsors independently, went up from 52% to 61%. Concurrently, the share of these trials conducted by CROs increased from 23% to 29%. Accordingly, the percentage of trials with the involvement of "other representatives" went down from 24% to 10%. A similar situation was observed in the segment of bioequivalence studies by foreign sponsors. Thus, the share of trials conducted by companies themselves rose by 16 pct from 57% to 73%. The share of projects with CROs involved also increased from 12% to 21%. On the other hand, the involvement of "others" markedly dropped down from 31% to 6%. We do not know exactly why. To find an answer, it is necessary to analyze changes in the composition of participants and the structure of trials. It should be noted that the share of "other representatives" only kept rising in previous years, reaching its historical maximum in 2016 (when the maximum number of local studies by foreign sponsors was also recorded). But in 2017 their share suddenly plummeted. This could be the logical consequence of the general numerical contraction of such studies by foreign sponsors. If our version is correct (that the key factor of the said contraction was the requirement for production facilities to be audited by Russian inspectorate became the "bottleneck" in the registration of foreign drugs) then this would mean that the number of applications to companies we rank among "other representatives", i.e. companies providing package drug marketing services, must have dwindled as well.

As for local studies by Russian sponsors, changes were of a somewhat different nature here: the share of trials handed over to CROs rose from 13% to 22% during the year (prior to that the maximum of 18% had been observed in 2014).

Interestingly enough, such fluctuations inside certain types of trials did not much affect the general distribution. The share of trials conducted by sponsors independently actually remained at the previous level – 67% vs 66% in 2016, though their distribution between the companies involved somewhat changed: the share of classic CROs grew from 25% to 31%, whereas the share of "other representatives" sank from 8% to 2% due to their exodus from local trials by foreign sponsors.

International multicentre clinical trials, sponsors

Table 15 shows the TOP-15 IMCT sponsors. For comparison, we also show the number of IMCTs and a company's position in the Rating 2016 in the last column.

Table 15

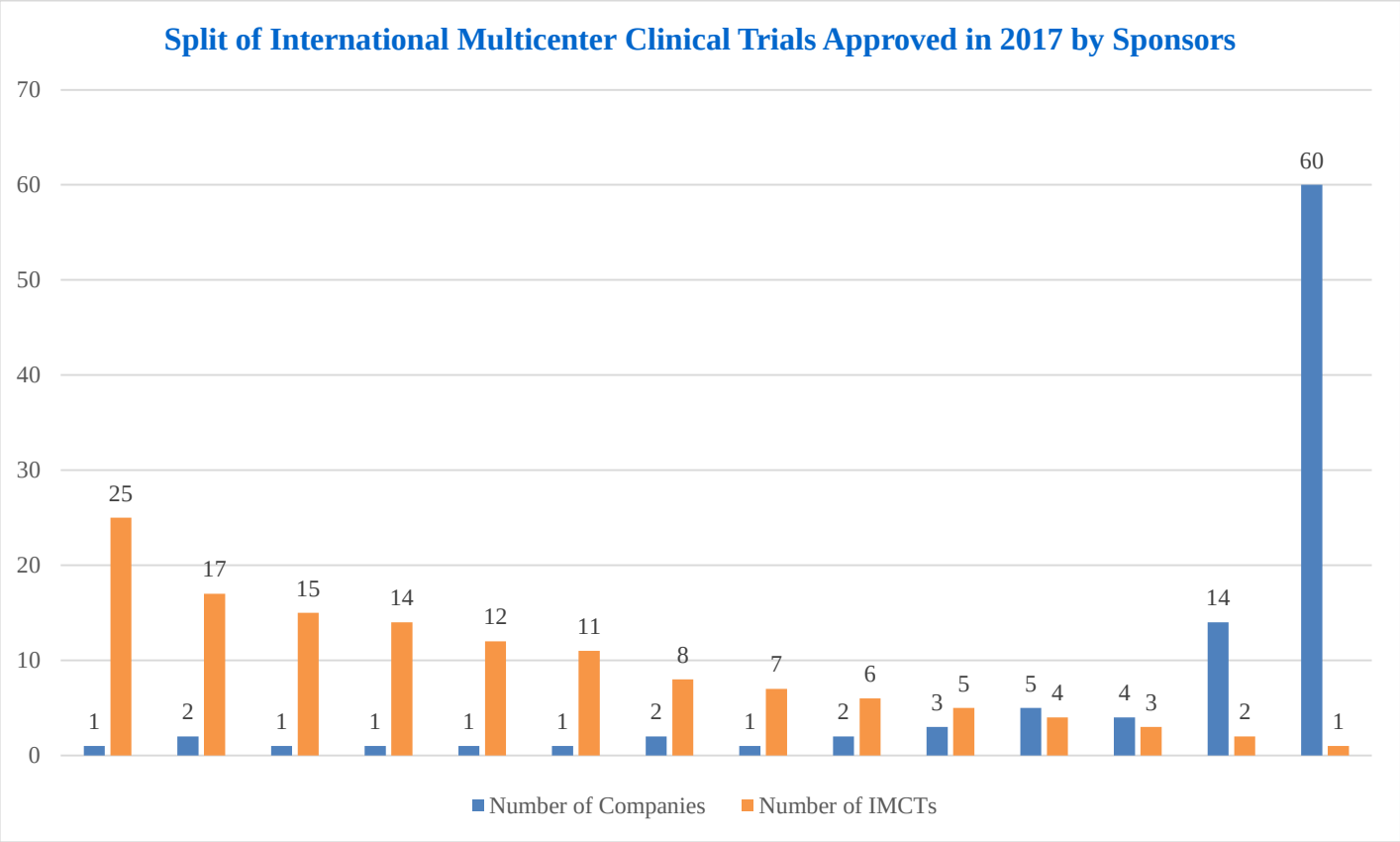
Top-15 Pharmaceutical Companies on Approvals for International Multicenter CTs, 2017					
Rating position in 2017	**Company (including separate companies, associated in group of companies, as well as independent divisions of the company)**	**Conducted by themselves**	**Conducted by CRO**	**Total**	**Number of IMCTs; Ranking in 2016**
1	Novartis	24	1	25	21 CTs; 1
2-3	Merck & Co.	16	1	17	18 CTs; 2
2-3	AstraZeneca	14	3	17	12 CTs; 7-8
4	F. Hoffmann-La Roche	15	-	15	15 CTs; 4-5
5	Sanofi	14	-	14	7 CTs; 12-13
6	GlaxoSmithKline	10	2	12	16 CTs; 3
7	AbbVie	11	-	11	12 CTs; 7-8
8-9	Bristol-Myers Squibb	7	1	8	15 CTs; 4-5
8-9	Janssen Pharmaceutica	6	2	8	13 CTs; 6
10	Eli Lilly	5	2	7	7 CTs; 12-13
11-12	Gilead Sciences	-	6	6	5 CTs; 14-17
11-12	Bayer	4	2	6	n/a
13-15	Pfizer	-	5	5	11 CTs; 9
13-15	Celgene Corporation	1	4	5	4 CTs; 18-22
13-15	Octapharma AG	-	5	5	n/a

Data from www.grls.rosminzdrav.ru

Novartis, the ACTO rating's irreplaceable leader, was granted the highest number of approvals for IMCT in 2017, followed by the previous year's silver prizewinner Merck & Co. which shared the second-third position with Astra Zeneca that climbed up to it from the seventh-eighth line it took a year ago. GlaxoSmithKline that ranked third a year earlier sank to the sixth position. F. Hoffmann-La Roche was ranked fourth, followed by Sanofi that climbed up seven positions to the fifth position, having doubled the number of IMCT approvals (ranked 12-13 in 2016). The TOP-15 also includes some sponsors that were absent from the rating in 2016 – Bayer (ranked 11-12) and Octapharma AG (rank 13-15).

The distribution of IMCTs conducted among the sponsor companies is shown in Diagram 15. As can be seen, seven companies were responsible for ten or more new IMCTs, whereas 60 sponsors were granted a single clinical trial approval each. Overall 98 companies initiated IMCTs in 2017. In 2016 there were 94 of these; in 2015 – 91.

Diagram 15



Data from www.grls.rosminzdrav.ru

International multicentre clinical trials, CROs

Now let's look at the TOP-15 most active CROs involved in IMCTs last year (see Table 16).

Table 16

Top-15 Pharmaceutical Companies on Approvals for International Multicenter CTs, 2017				
Ranking in 2017	**Company**	**Number of IMCTs**	**Number of Sponsors**	**Number of IMCTs; Ranking in 2016**
1	IQVIA (formerly Quintiles IMS)	27	19	30 CTs; 1
2-3	PPD	14	13	16 CTs; 2
2-3	PRA	14	8	15 CTs; 3
4	INC Research	11	8	12 CTs; 5
5-6	Parexel	9	8	13 CTs; 4
5-6	PSI	9	8	8 CTs; 9
7	Covance	8	7	9 CTs; 6-8
8	InVentiv	7	5	9 CTs; 6-8
9-10	ICON	6	4	9 CTs; 6-8
9-10	Medpace	6	5	2 CTs; 13-20
11	Chiltern	5	5	2 CTs; 13-20
12-15	MB Quest	3	3	5 CTs; 11
12-15	KCR	3	2	2 CTs; 13-20
12-15	Premier Research	3	2	2 CTs; 13-20
12-15	Ergomed Clinical Research	3	2	n/a

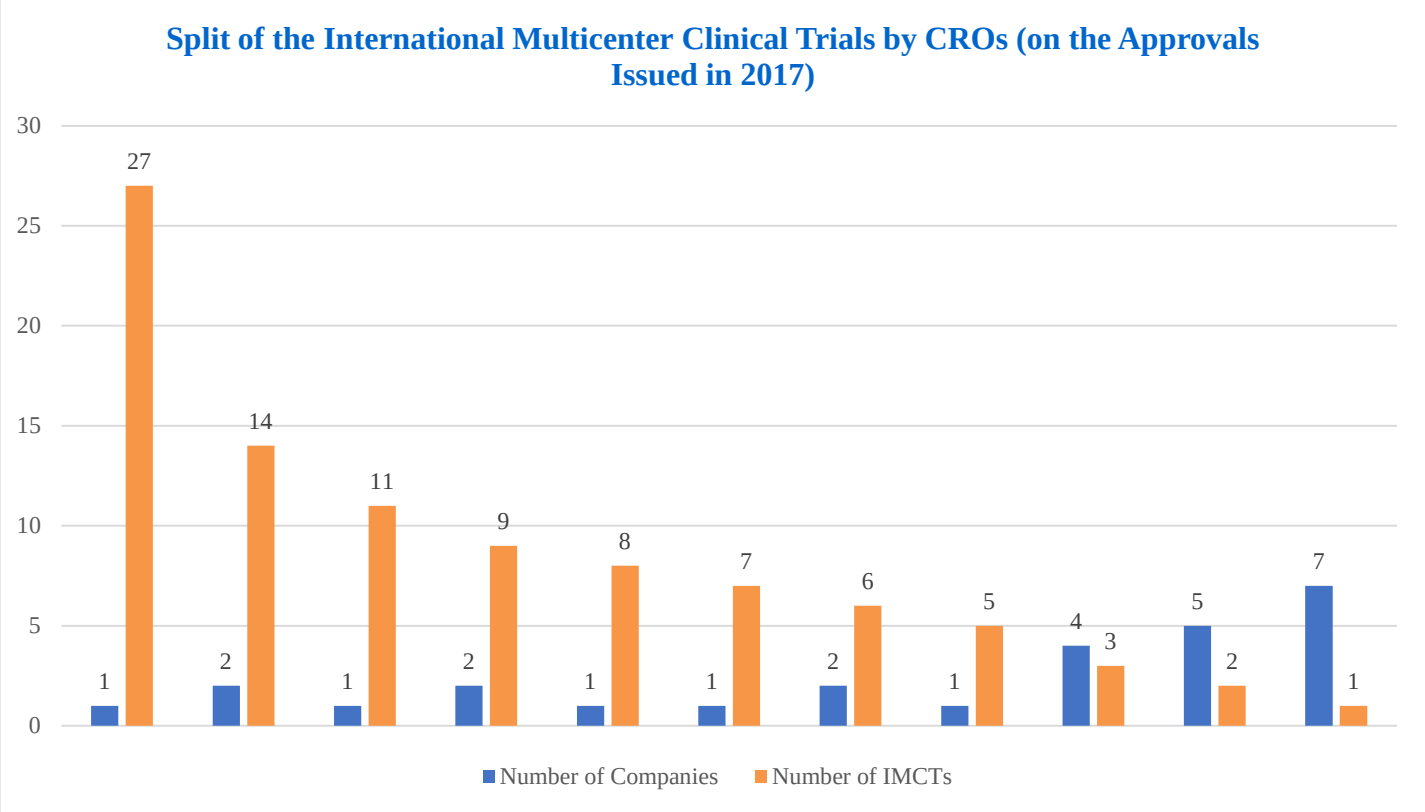
Data from www.grls.rosminzdrav.ru

For the fourth year in a row IQVIA (renamed from QuintilesIMS) remains the leader. Only in 2013 it yielded leadership to Parexel. The rivalry between PPD and PRA Health Sciences that finished two consecutive years in the second and third positions, respectively, reached maximum intensity in 2017: both companies drew level by the number of IMCT approvals, splitting the second and third ranks. INC Research that climbed one step up during the year was ranked fourth. Parexel, on the contrary, sank from fourth to fifth-sixth position, sharing it with PSI. The latter improved its standing by four positions, climbing up from rank nine. Medpace (rank 9-10) and Chiltern (rank 11) also improved their standings (they ranked 13th to 20th a year ago).

In 2018 we expect a significant reshuffle in the wake of INC Research and inVentiv Health, as well as Covance and Chiltern mergers.

Diagram 16 shows a distribution of CROs in terms of IMCT approvals in 2017. During this period 27 CROs were contracted by sponsors for the delivery of international projects, one more than in 2016.

Diagram 16



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies, foreign sponsors

Table 17 shows leading foreign sponsors who initiated the highest number of local and bioequivalence studies in 2017[18]. Like a year before, the list is topped by Dr. REDDY's Lab, followed by Hetero Labs that shared the second-fourth positions with Teva and Polpharma a year earlier. Teva ended the last year in the fourth place, whereas Polpharma, represented by Medana (part of the Group), got only one approval and ended up at the very bottom of the list (21-59 positions). The third position was taken by Sun Pharmaceutical Industries which climbed up there from the 12th position in the 2016 rating.

Table 17

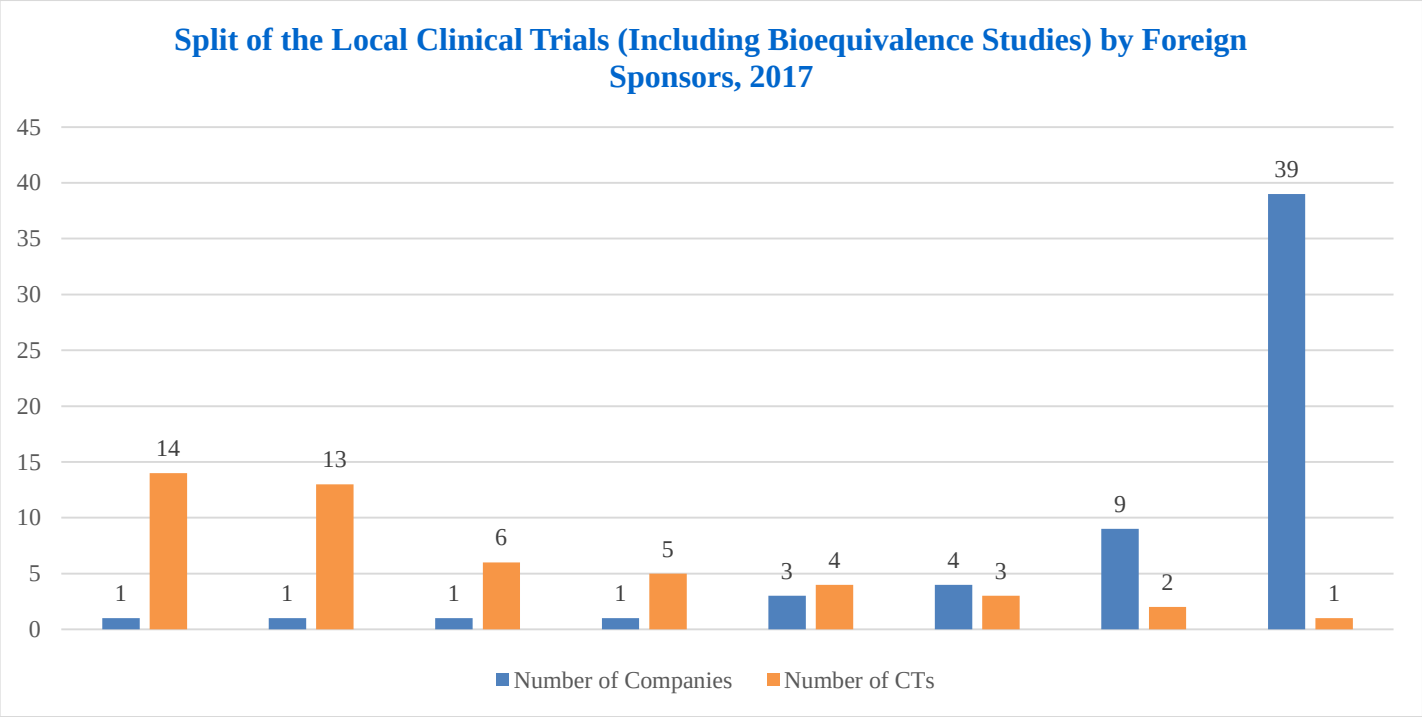
Ranking of Leading Foreign Sponsors on Approvals for Local CTs and Bioequivalence Studies, 2017					
Ranking in 2017	**Company**	**Conducted by themselves**	**Conducted by CROs/other representatives**	**Total**	**Number of CTs; Ranking in 2016**
1	Dr. REDDY's Lab.	12	2	14	14 CTs; 1
2	Hetero Labs Limited	13	-	13	10 CTs; 2-4
3	Sun Pharmaceutical Industries Limited	4	2	6	5 CTs; 12
4	Teva	5	-	5	10 CTs; 2-4
5-7	Alvogen	4	-	4	1 CT; 43-99
5-7	Johnson & Johnson / Janssen Pharmacy HB / McNeil AB	1	3	4	1 CT; 43-99
5-7	Xantis	4	-	4	1 CT; 43-99
8-11	KRKA	3	-	3	6 CTs; 9-11
8-11	Sentiss Pharma Pvt. Ltd.	3	-	3	1 CT; 43-99
8-11	Laboratorios Leon Farma, S.A	3	-	3	n/a
8-11	Pharmtechnology LLC	-	3	3	n/a

Data from www.grls.rosminzdrav.ru

[18] Four companies shared ranks 8-11 so the TOP-10 is not quite even.

Diagram 17 shows the distribution of local and bioequivalence studies, for which approvals were granted in 2017, between foreign sponsors. It's noteworthy that the number of the latter dwindled by 40% compared to 2016 (from 99 to 59).

Diagram 17



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies, domestic sponsors

The TOP-10 domestic sponsors by local and bioequivalence study approvals obtained in 2017 is shown in Table 18. Compared to the previous year, the rating underwent remarkable changes. Thus Atoll, the irreplaceable leader since 2013 (when we first began keeping track of this stat), suddenly dropped down to the bottom of TOP-10, with only nine new trials, while during the four previous years this sponsor averaged 32.8 trials. The maximum of 47 trials was reached in 2014.

With the longstanding leader ceding its positions, Biocad that was only third in 2016 topped the list. Unlike Atoll, Biocad has a large number of its own developments plus biological medications in its portfolio. Therefore, it is not going to radically cut the number of its trials. It should be noted for the sake of justice that some of the company's trials were designated in the register as international, though we could not classify them in this category, no offence meant.

Severnaya Zvezda that shared the sixth to eighth position a year earlier ranked second last year. Microgen that ranked third climbed up from rank 21-24 in the last year's rating due to an increase in the number of new trials from 5 to 14. It should be made clear that this "surge" of Microgen was possible due to those 11 trials of allergens "for certification as an in-house reference standard" that amazed us as we analyzed the market structure by types of trials.

Canonpharma production retained its fourth line in the rating, whereas Pharmasyntez dropped down from the second to the fifth position. Ranks 6-8 were split between Obolensky Pharmaceutical Company, Akrikhin and Promo-med RUS, having increased the number of trials from 7-8 in 2016 to 11 in 2017. This trio is followed by Sotex Pharm Firm which went down from ranks 4-5 to the ninth position, the last in the TOP-10 being Atoll.

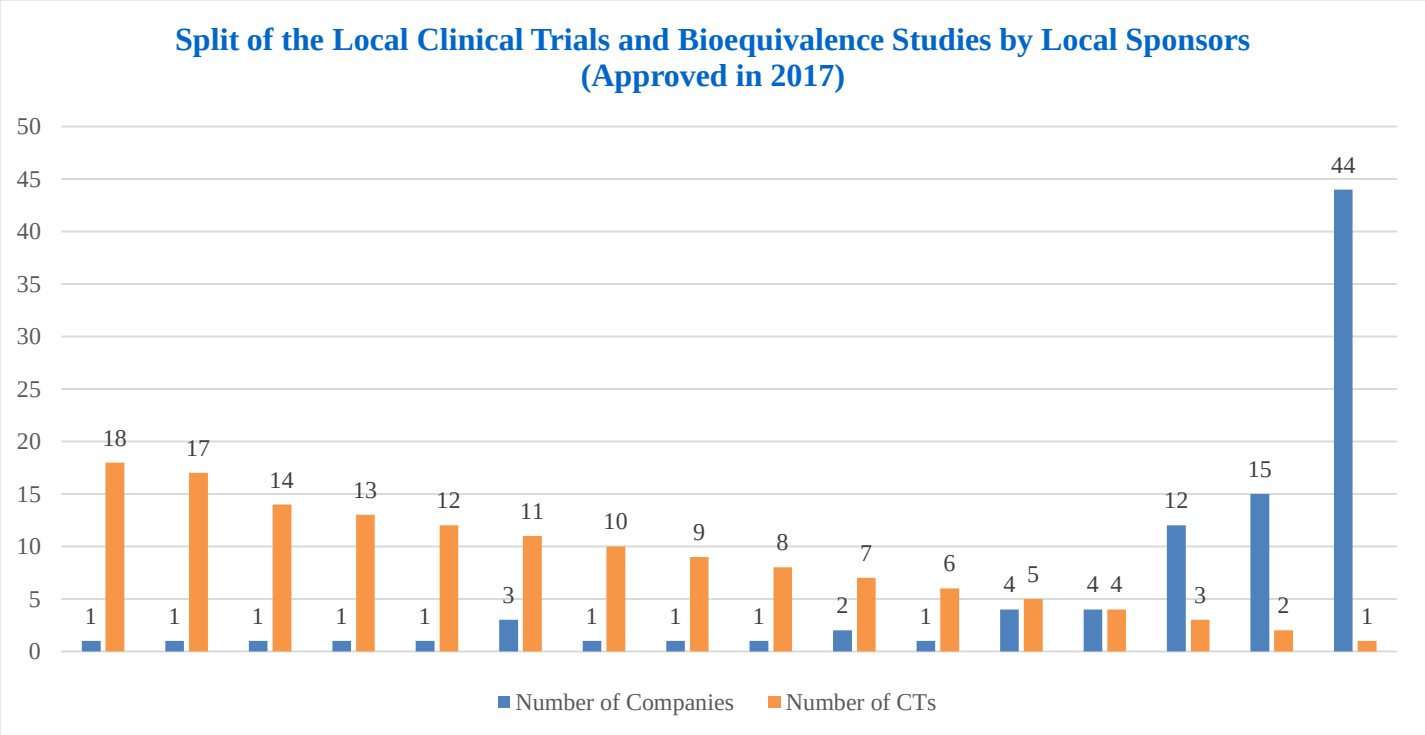
Table 18

Ranking of Local Sponsors on Approvals for Local Clinical Trials and Bioequivalence Studies, 2017					
Ranking, 2017	**Company**	**Conducted by themselves**	**Conducted by CRO**	**Total**	**Number of CTs; Ranking, 2016**
1	Biocad	18	-	18	16 CTs; 3
2	Severnaya Zvezda	17	-	17	10 CTs; 6-8
3	Microgen	14	-	14	5 CTs; 21-24
4	Canonpharma Production	13	-	13	12 CTs; 4-5
5	Pharmasyntez (incl.Pharmasyntez-Tyumen)	12	-	12	22 CTs; 2
6-8	Promo-med RUS	11	-	11	8 CTs; 9-13
6-8	Obolensky Pharmaceutical Company (OBL Pharm)	11	-	11	8 CTs; 9-13
6-8	Akrikhin	11	-	11	7 CTs; 14-16
9	Sotex Pharm Firm	10	-	10	12 CTs; 4-5
10	Atoll	9	-	9	24 CTs; 1
1	Biocad	18	-	18	16 CTs; 3
2	Severnaja Zvezda	17	-	17	10 CTs; 6-8

Data from www.grls.rosminzdrav.ru

Diagram 18 shows the distribution of local and bioequivalence studies between domestic sponsors in 2017. During the period under review, approvals for these trials were granted to 93 companies, down 24.4% year-on-year – in 2016 their number stood at 123.

Diagram 18



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies, CROs

Now let's have a look at the distribution of local and bioequivalence study approvals in 2017 among the most active CROs in this segment (Table 19). We do not have an orderly TOP-10 here either, because six companies with an equal number of trials shared positions 6 to 11.

Table 19

CROs Involved in the Local CTs and Bioequivalence Studies (on Approvals Issued in 2017)						
Ranking	**Company**	**Number of CTs of foreign sponsors**	**Number of CTs of local sponsors**	**Total number of local CTs, 2017**	**Number of sponsors**	**Number of CTs; Ranking, 2016**
1	IPHARMA	5	10	15	8	8 CTs; 2
2	Synergy Research Group	6	6	12	6	3 CTs; 10
3	OCT	3	3	6	4	9 CTs; 1
4	Smooth Drug Development		5	5	2	2 CTs; 11-13
5	Medical Center Probiotech		4	4	2	4 CTs; 7-9
6-11	Atlant Clinical	1	2	3	2	7 CTs; 3
6-11	ARS PharmRussia (formerly - "Agency for Registration Support of Medicines")	2	1	3	2	6 CTs; 4-5
6-11	Medical Development Agency (MDA)	1	2	3	3	6 CTs; 4-5
6-11	Rusclinic	2	1	3	2	2 CTs; 11-13
6-11	Almedis		3	3	1	1 CT; 14-23
6-11	ClinFarmInvest	3		3	2	1 CT; 14-23

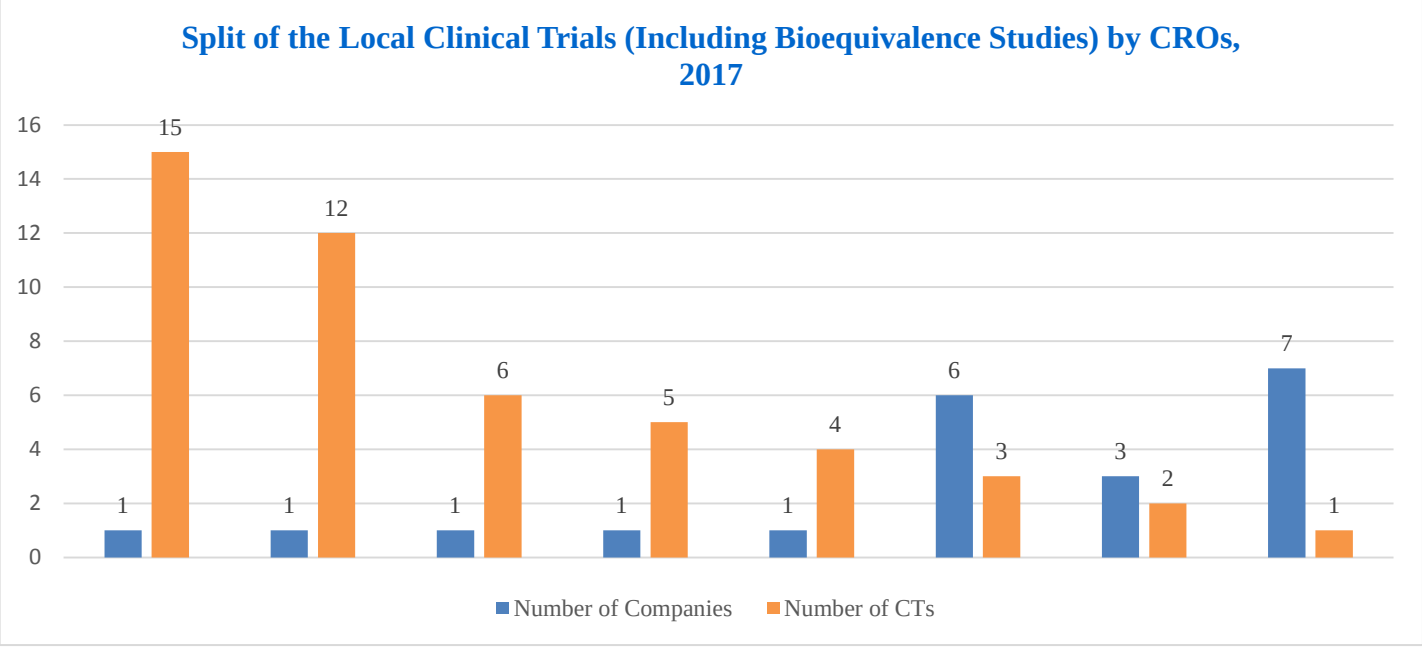
Data from www.grls.rosminzdrav.ru

IPHARMA ranked second in 2016 topped the list, followed by Synergy Research Group that was ranked tenth a year before. OST – the winner of 2016 (by local trials) lost two positions and ranked third.

Diagram 19 shows a distribution of local trials by CROs. Overall 21 CROs took part in local studies, two companies less than a year ago.

In conclusion, we can point out that during the year the number of companies participating in the market of international trials slightly increased (by four sponsor companies and one CRO); on the contrary, the number of companies involved in local trials decreased (by 40 foreign and 30 domestic sponsors as well as by two CROs).

Diagram 19



Data from www.grls.rosminzdrav.ru

TIMEFRAMES FOR OBTAINING APPROVALS

For the second year in a row ACTO monitors the deadlines for approvals together with AIPM (The Association of International Pharmaceutical Manufacturers). Participating in the 2017 survey were 34 pharmaceutical firms and CROs, members of ACTO and AIPM. The sampling for clinical trials approvals counted 252 applications (i.e. it included 90% of all IMCT approvals granted in Russia during the year). Table 20 shows the summary data.

Table 20

Timeframes for Issuing Approvals, 2017					
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**	95*	53*	401*	252
To Import Medicines	8/12	14	2	58	427
To Import/Export Biosamples	13/19	20	4	49	913
To Make Amendments to the Protocol	34/48	42	8	103	439
Other Approvals (to Prolong Clinical Trials, to Include New Sites, to Enroll Additional Patients, etc.)	25/35	26	4	112	815
Total Time to Obtain Approvals to Conduct Clinical Trials and to Import/Export	54/76	115	~	~	~

Data from timeframes monitoring of ACTO and AIPM

Like in previous years, the average time of getting trial approvals was calculated on the basis of all applications, including those which received requests from expert organizations. Accordingly, 95 days includes the time needed for the query-reply communication. The Ministry of Health uses other calculation methods that exclude the time taken by applicants for requests. To enable the comparison of results gained by using different methods, we calculate additional parameters:

– average time calculated only for applications, which did not receive expert requests;

– average time calculated only for applications, which received expert requests, including the time for the reply;

– average time calculated for all applications, with communication time in view of expert requests excluded.

All three parameters complemented with the primary one (average time calculated for all applications without excluding the time for communication in view of expert queries) are shown in Table 21.

Table 21

Method for calculation of average time	Average time	Sample size	Comment
Time for applications, which received no expert requests	69	114	114 CT applications (45.2%) were dealt with without requests or remarks. 138 applications (54.8%) received requests and/or remarks.
Time for applications, which received expert requests *(time to reply to the request is included)*	116	138	
Time for obtaining approvals for all applications *(in case of an expert request, the time required to reply is excluded from the calculation)*	74	252	
Time for obtaining approvals for all applications *(in case of an expert request, the time required to reply is included in the calculation)*	95	252	

Data from: Monitoring by ACTO and AIPM of the time for obtaining approval documents

Compared to the results of previous years, the deadlines for approvals changed insignificantly. Including the time for expert requests, the approval to conduct clinical trial was provided faster than in 2016 by four days, on average (95 days versus 99 days a year before). If the average time were separately calculated for applications on which expert requests were made and the time needed for communication in view of the requests were excluded, the situation would look even more optimistic: it took 7 days less to get an approval (116 vs 123 days in 2016). When using the method suggested by the Ministry of Healthcare (time to process all applications minus the time for expert requests), it took one day longer to get an approval (74 vs 73 days). Three more days were needed to get an approval on applications with no expert requests to follow (69 in 2016 vs 66 in 2017).

The average time of getting permits for the import/export of biological samples grew by 2 days compared to 2016. The time of getting the permit to import medicines did not change. It took 2 days less to amend the protocol in 2017 and three days less to process other applications (including approvals to prolong clinical trials, to include extra centers or to enroll additional patients, etc.). Finally, it took two days less to get the trial approval and bio-sample import/export permissions (calculated just to get an idea of how quickly one can pass the regulatory stage to actually commence a trial).

Table 22 contains data on exceeding the enacted deadlines for the issue of approvals in 2017 and 2016. Calculating the respective parameters for main clinical trial approvals, we took into account only those applications on which no expert requests were made (i.e. those that took the average of 69 days to be processed).

Table 22

Violations of Timeframes, 2017 vs. 2016								
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	2017	11.4%	88.6%	79.8%	7.0%	1.8%	0.0%	0.0%
	2016	19.7%	80.3%	73.2%	4.7%	1.6%	0.8%	0.0%
To Import Medicines	2017	38.6%	61.4%	38.9%	19.4%	2.6%	0.0%	0.5%
	2016	42.2%	57.8%	34.1%	20.9%	2.7%	0.2%	0.0%
To Import/Export Biosamples	2017	45.5%	54.5%	46.2%	7.8%	0.5%	0.0%	0.0%
	2016	65.2%	34.8%	29.2%	5.2%	0.3%	0.1%	0.0%
To Make Amendments to the Protocol	2017	75.4%	24.6%	22.6%	1.6%	0.5%	0.0%	0.0%
	2016	60.6%	39.4%	34.1%	5.3%	0.0%	0.0%	0.0%
Other Approvals (to Prolong CTs, to Include New Sites, to Enroll Additional Patients, etc.)	2017	87.2%	12.8%	12.0%	0.6%	0.0%	0.1%	0.0%
	2016	86.9%	13.1%	11.5%	0.8%	0.8%	0.0%	0.0%

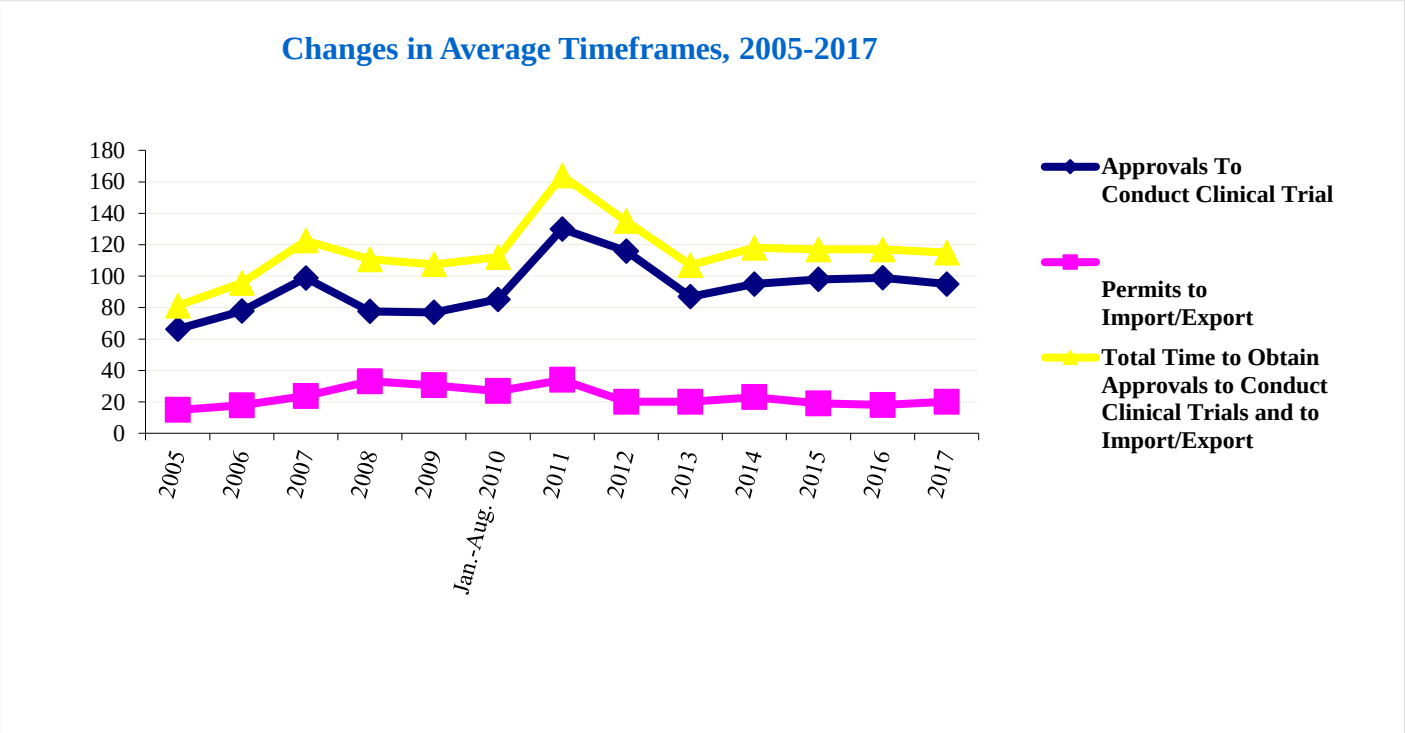
Data from timeframes monitoring of ACTO and AIPM

Here too we see minor variations, mostly negative. The percentage of clinical trials approvals provided on time decreased: 11.4% vs 19.7% in 2016. It is only gratifying that most delays (79.8%) fall within the category "less than 1.5 times".

The percentage of timely provided medicines import permits also decreased slightly: 38.6% vs 42.2% a year earlier. Permits for the import/export of bio-samples showed worse dynamics: the share of timely provided documents sank by nearly 20 pct (45.5% vs 65.2%). Things stand better with "amending the protocol" category: 75.4% of timely provided approvals versus 60.6% in 2016. Other applications also showed slightly better dynamics: 87.2% approvals without deadline violations vs 86.9% a year ago.

All these fluctuations were anything but significant. In recent years we saw the stabilization of deadlines for basic approvals needed to conduct a clinical trial. The year 2017 did not mark a turning point in this respect, which can well be seen in Diagram 20 showing all indicators starting in 2005.

Diagram 20



Data from timeframes monitoring of ACTO

The only matter of concern in 2017 was the fact that for the first time since ACTO observation, the share of applications approved without any comments from FGBU Scientific Centre for Expert Evaluation of Medical Products (79.5%, 209 applications) has increased the share of those, approved by the Council of Ethics (61.5%, 158 applications). It should be borne in mind that most criticisms made by the Council of Ethics are non-critical and imply the possibility of corrections in the way of business. Yet the very trend concerned us. Historically, applicants have always had more grudges against the FGBU expert evaluations. In recent years the situation has been changing, with an increasing number of complaints lodged by applicants in connection with decisions made by the Council of Ethics. These are preliminary data, however. We'll be able to analyze the stats in more detail and provide information on the specific content of comments made by the Council of Ethics in the next issue of the Newsletter, where we'll review the practice of expert evaluations made by both expert organizations.

IMPORT OF MEDICINAL PRODUCTS FOR CLINICAL TRIALS

In this section of the Newsletter we give the stats for import of medicinal products for clinical trials to Russia. As can be seen from Table 23, the total value of medicines imports in 2017, denominated in rubles, rose 23% year-on-year to RUB 13.5 billion. If we look at the import value in dollar terms, the growth is 42.1%.

We should remind that both drugs to be studied and comparators along with concomitant therapies (in cases they are imported) are included in our calculations. The amount of import taxes and dues rose to RUB 1.8 billion.

Table 23

Import of medicinal products to the Russian Federation for clinical trials, 2016-2017		
Parameter	**2016**	**2017**
Total value of shipments, rub.	10 987 235 644	13 524 110 010
VAT, rub.	1 134 482 465	1 397 081 825
Customs duties, rub.	343 506 764	434 360 335
Customs fees, rub.	12 232 160	15 471 988
VAT + Customs dutie + Customs fees, rub.	1 490 221 390	1 822 726 648

Source: RNC Pharma

Table 24 shows biggest pharmaceutical companies whose medicines arrived in Russia last year, as part of clinical trials. It should be borne in mind that drugs put out by any particular manufacturer can also be imported by CROs or even competing firms (whenever a given medicine was also used as a comparator or basic therapy). Therefore, it is indicated in a separate column, which share of the company's supplies was imported by this manufacturer directly (via its representatives or subsidiaries).

Table 24

Top-10 pharmaceutical companies on import of medicinal products for clinical trials, 2017					
Ranking	**Company**	**Value of shipments, rub.**	**Number of shipments**	**Imported by the companies themselves, %**	**Ranking, 2016**
1	BMS	1 852 101 483	95	99.7	13
2	Johnson & Johnson	1 848 170 478	184	50.2	1
3	Merck & Co.	1 288 799 571	184	94.1	2
4	Pfizer	1 257 505 848	117	71.2	3
5	F. Hoffmann-La Roche	815 043 424	257	74.2	4
6	Merck Group	755 892 360	49	2.1	6
7	Novartis	726 767 193	422	93.9	8
8	Kyowa Corporation	612 102 490	17	0.0	19
9	Amgen	473 239 752	136	75.7	12
10	Celgene Corporation	430 832 004	56	0.0	9

Source: RNC Pharma

Given that oncology accounts for most IMCTs in Russia (the respectable 32% if oncohematology is added), one can see how important it is for our nation to participate in IMCTs in terms of Russian patients getting access to state of the art drug therapy.

ACTO COUNTERACTING SUPERFLUOUS ADMINISTRATION OF CLINICAL TRIALS BY MOSCOW HEALTHCARE DEPARTMENT

One of the ACTO foci in 2017 was counteracting the attempts by the Moscow Healthcare Department to take clinical trials in institutions subordinate to MHD under its administrative control. You may find detailed chronology on the ACTO site (Russian version) in the section of analytic materials under the heading Moscow Clinical Trials Market Struggle Chronicle. Here we offer its short version where only the key contradictions and points of the ongoing standoff are highlighted.

The conflict of interests between the industry of clinical trials and Moscow executive authorities took shape back in 2015, but 2017 was the middle of this chess game which was launched by MHD issuing, in November 2015, a draft decree on establishing The Centre for Clinical Trials Conduct and Coordination (CCC) empowered to coordinate clinical trials in public health institutions of Moscow. ACTO sent a letter to MHD where it stated that the regulation by the Ministry of Health and Federal Service for Surveillance in Healthcare (not to mention FDA and EMA in case of IMCTs) was more than enough and additional administration might negatively affect the competitiveness of Moscow public medical institutions. MHD assured that CCC establishment would not entail any new obligations, restrictions or unjustified outlay by clinics. During the year all three points of that commitment were violated in sequence.

"New obligations" were imposed on medical institutions already in July 2016, when MHD issued Decree No. 623 binding all medical institutions of Moscow to submit to CCC detailed reports on conducting clinical trials within 3-5 business days from the start/end of the next stage. The Decree was followed by letters requesting reports which CCC was sending in July-August of 2016 to medical institutions subordinate to MHD. To the question about possible sanctions MHD replied that disobedience to the decree would entail "disciplinary liability stipulated by the Russian law", without any further clarifications.

In September 2016 ACTO submitted an application to the Moscow FAS Office for cause of the antimonopoly law violation, where it was stated that:

- first of all, CCC, pursuant to its bylaws, may conduct clinical trials, so its empowerment with regulator's functions means providing to one of the market players access to sensitive information, which means its endowment with unjustified privileges;
- secondly, as per the Russian law, it is federal rather than local authorities that are empowered to exercise clinical trials control;
- thirdly, CCC requests information already posted on the website of the Ministry of Health in the register of clinical trials; this means CCC could collect this information itself without imposing on the medical institutions responsibilities for additional information;
- finally, summing up, CCC activities may negatively affect the competitiveness of medical institutions subordinate to MHD.

Yet the Moscow FAS Office did not see any violations of the antimonopoly regulation in the activities of MHD and CCC, dismissing our complaint,

- since CCC did not conduct any clinical trials at the time when the application was under review and was not one of the market players at this level, and so the Moscow FAS Office does not see any violations in the fact that a municipal authority delegates its functions to other institutions;
- because, in the opinion of Moscow FAS Office, coordinating the activities of medical institutions does not automatically imply any possibility to influence them;
- and finally, because the Moscow FAS Office did not find any evidence that the activities of MHD and CCC brought about a decrease of clinical trials in Moscow medical institutions.

In November 2016, MHD violated the second promise "not to place new restrictions" and issued Order No. 948, whereby the Moscow Independent Ethics Committee (MIEC) was instituted, whereas all institutions subordinate to MHD were instructed to have all clinical trials they plan to conduct approved by MIEC, even when a certain institution has its in-house local ethics committee (LEC). In accordance with the effective Russian law, to obtain a clinical trial approval, an institution or center must pass a mandatory expert evaluation by the Council of Ethics under the Ministry of Health and get a LEC consent. ACTO submitted a new application to the Moscow

FAS Office where it called attention to the fact that MHD actually introduces the third mandatory level of ethical expert examination, thus mounting unwarranted restriction for the operation of the institutions subordinate to MHD and lowering their competitiveness.

While the Moscow FAS Office was reviewing this application, MHD violated the third promise in February 2017 "not to charge unjustified outlay". The CCC site has placed information that the Centre provides the service of preparing documents to be further reviewed by MIEC for a fee. For all that, documents cannot be submitted to MIEC without preliminary preparation. ACTO supplemented its recent application to the Moscow FAS Office with another complaint, calling attention to the fact that a payment is actually introduced for ethical expert evaluation by MIEC.

Considering this application, Moscow FAS Office turned to the Ministry of Health for clarifications. The Ministry of Health explained that the law does not require a mandatory consent by the Ethics Committee established by executive authorities of any Russian region; what's more, the Ministry of Health does not think it expedient to establish such ethical committees and believes that duplication of LEC functions is redundant. Following on from these clarifications, Moscow FAS Office put MHD on notice in June 2017 that it must cancel the requirement of mandatory clinical trials approval by MIEC.

Yet the protection of Moscow FAS did not allow us to fully block the assault of Moscow authorities. MHD decided on a strategic retreat and entered amendments to Order No. 948, repealing the mandatory expert evaluation of MIEC only for those jurisdictional medical institutions which have their LEC; however, the expert evaluation of MIEC for other institutions was still mandatory. In parallel, MIEC proceeded with sending letters where it suggested that institutional LECs should voluntarily forego the functions of ethical expert evaluation, handing them over to MIEC. During the same period Moscow clinics received calls from MHD, with officials insisting that they should pass expert evaluation at MIEC and sign their future contracts for clinical trials via CCC, rather than directly with their clients.

In 2017 ACTO tried to repeat its maneuver and forwarded another complaint to the Moscow FAS Office about the antimonopoly law violation, motivating their complaint by the fact that first, the amendments entered into Order No. 948, do not eliminate the violations, with MIEC expert evaluation being still mandatory for a number of entities, and, secondly, letters to LECs suggesting that they should forego an ethical evaluation mean pressure on the part of MHD.

Waiting for a reply from Moscow FAS, ACTO advanced to the next defense line and turned to FAS for explanation of the antimonopoly law:

- If a certain economic entity does not presently conduct clinical trials, though it can conduct them as per its bylaws, doesn't a prioritized submittal of information about clinical trials conducted by other institutions to this entity contradict the antimonopoly law or not?
- If a certain economic entity is empowered to coordinate other economic entities, does it mean that it acquires the capability to influence coordinated entities, or not?
- Is it admissible to endow an economic entity with functions and powers of an executive authority?
- Does the competition law apply to the relationship between public authorities and institutions under their jurisdiction?
- What is an ample ground for commencing a suit: an already established fact of restrictive business practices, or well-grounded suspicions are enough?

An exhaustive clarification, should FAS back ACTO in how it interprets the law, would allow to appeal against the dismissal of the first application by the Moscow FAS Office and unleash a new counterattack against the MHD attempts to take part in the clinical trials market under its control. Yet FAS declined to comment or clarify, just stating that the decision of Moscow FAS Office can be challenged at court. The second query in five separate letters (one per each question) and an open letter on the pages of *Pharmaceutical Herald* did not help either. So far FAS has not provided substantive clarifications in its return letters.

In parallel to its appeals to FAS, ACTO developed the second line of defense. The statistics showing that, following the endowment of CCC with coordinator functions and imposing the MIEC expert evaluations the number of clinical trials went down in institutions subordinate to MHD, would enable ACTO to apply to Moscow FAS again and insist on initiating a case upon the clear evidence of restrictive business practices. However, MHD

refused to provide information about the number of IMCTs in Moscow state clinics for 2016-2017, whereas the Moscow FAS Office turned down the ACTO petition about the expedience of requesting this information from MHD. Under these circumstances ACTO had to wait till the end of collection and processing of its own data which are revealed in this Newsletter.

In early 2018 MHD launched another offensive as Order No. 836 bound the heads of public clinics in Moscow to submit information about serious unexpected adverse reactions to Federal Service on Surveillance in Healthcare (Roszdravnadzor) and to CCC. MHD referred to Order No. 1071 of Roszdravnadzor, dated 15.02.2017, though the order bound only legal entities which received the clinical trial approval, i.e. sponsors and CROs, but not the heads of clinics, to submit this information. This did not hinder MHD from sending letters to jurisdictional institutions with reminders that they had to forward information about serious unexpected adverse reactions to CCC on a monthly basis. It became known early in 2018 that MHD made some progress, as regards the informal relations, as a number of clinics refused to sign contracts for clinical trials directly with the client and are willing to do it only via CCC.

Yet the application to Moscow FAS still threw some chill and the offensive was followed by a retreat: on 26 January 2018 MHD entered new amendments to Order No. 948. In this version, the monopoly of MIEC to ethical expert evaluation for public medical institutions of Moscow that have no their own LEC was cancelled. Five days later, based on these changes, Moscow FAS rejected the ACTO's complaint. In response, ACTO sent a new application to Moscow FAS, complaining about apparent violations in Order No. 836:

- an economic entity obtains a priority right to get safety and security information,
- MHD assumes the powers of federal authorities,
- information about serious unexpected adverse reactions must be submitted to Roszdravnadzor by legal entities that are granted clinical trial approval, rather than the administration of clinics.

The refusal to initiate legal proceedings was given a month later, on 05 March 2018. The letter stated that the actual collision between the federal (not antimonopoly) and regional legislations is not sufficient for initiating a case and it is the court rather than FAS that should get to the bottom of things. Meanwhile the Moscow FAS Office still did not see any evidence of restrictive business practices.

In the meantime, the evidence was already discernible: as per the data from the register of approved trials (without regard to how many of these have actually been launched), the number of medical institutions subordinate to MHD where companies planned IMCTs went down by 17.6% – from 34 in 2016 to 28 in 2017, while the number of IMCT centers scheduled for opening contracted by a fourth – from 155 to 117 (*for more detail see the section "Breakdown of IMCTs Approvals Across Russia"*). The "chess game" is entering the end play phase, and though both sides still have some leeway, there is a risk of MHD taking the best position on the board, though it will stay alone there after losing all chess pieces (IMCT centers). So far only Kemerovo, Chelyabinsk, Sverdlovsk and other regions of Russia have benefitted from the MHD game, since the number of trials keeps rising there.