ACTO

ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

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Summary of 2016 results

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SUMMARY

In 2016, the Ministry of Health issued 897 approvals to conduct clinical trials, which is 11.6% more than in 2015 and second only to 2012, when 915 approvals were issued. Approvals for all types of trials have increased in comparison with 2015, but the biggest growth, by 57.7%, was for local foreign-sponsored trials (82 approvals versus 52 approvals in the previous year). The number of approvals to conduct local Russian-sponsored trials increased by 18% (197 versus 167), and the number of Russian-sponsored bioequivalence studies increased by 11.1% (170 versus 153). The number of approved foreign-sponsored bioequivalence studies grew by only 2.1% (146 versus 143). Overall, more approvals for both foreign- and Russian- sponsored local trials were issued in 2016 than ever before and the year also set a new record for the number of approvals of foreign-sponsored bioequivalence studies.

Unfortunately, results for international multicentre clinical trials (IMCTs) in 2016 were less impressive. The number of approvals for such trials (302) increased by a modest 4.5% from the previous year (289), and remained far short of the 2011 record, when 370 IMCTs were approved. Substantial growth of other types of trials meant that the share of IMCTs in the overall market structure declined again, to 33.7% (35.9% in 2015 and 59.6% before implementation of the Law "On Circulation of Medicines").

This issue of the ACTO Newsletter looks in detail at key indicators of the current state of the Russian clinical research market: structure of the local trials sector, distribution of IMCTs by phases, structure of the market by therapeutic areas, the most popular medicinal products for manufacture of generics, etc.

For the second consecutive year, the Newsletter contains detailed statistics on the distribution of IMCTs across Russia's administrative regions. The three leaders in 2016 were the cities of Moscow and St. Petersburg, and Tatarstan. However, the distribution is different if we measure by the number of IMCTs per million inhabitants. In this case Yaroslavl Region takes first place, followed by St. Petersburg, and then Smolensk Region. Moscow is not even in the top 10.

A separate section of the Newsletter deals with companies active on the clinical trials market, including a rating of sponsors and contract research organizations for IMCTs and local trials.

We look at the time required to obtain approval documents. Average times were almost unchanged in 2016 compared with 2015: 99 versus 98 days to obtain approvals to conduct trials, 14 versus 13 days for the approvals for the import of medicinal products, and 18 versus 19 days for approvals for the export of biological samples. There was some increase in the time required to obtain additional permits: 29 versus 24 days for the extension of trials and the inclusion of new centers and patients. However, applications to make amendments to a trial protocol were approved more quickly (44 versus 52 days). Approval times are quite satisfactory overall.

The single biggest bureaucratic process in 2016 was the extension of expired accreditation certificates for medical institutions to conduct trials. Throughout the year 518 institutions underwent this procedure. The task proved challenging both for the industry and for the regulator, the Russian Ministry of Health of Russia, but it was successfully completed.

The final section of the bulletin focuses on the new statistical data for the Russian IMCT market: volumes of import of medicines to Russia for clinical trials.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

In 2016, the Ministry of Health issued 897 clinical trial approvals, which is 11.6% more than in the previous year (Table 1). At the end of November, representatives of the FGBU "Scientific Center for Expert Evaluation of Medicinal Products" of the Ministry of Health (FGBU) even predicted that 2016 would set a new record and that over 1000 approvals for conducting clinical trials would be issued by the end of the year. This did not happen, as can be seen from Figure 1, but more approvals were issued in 2016 than in any year except for 2012.

Approvals for all types of trials grew in comparison with 2015, but the biggest growth, by 57.7%, has been for the local foreign-sponsored trials (82 approvals in 2016 versus 52 in the previous year). The number of approvals for international multicentre clinical trials (IMCTs) increased by 4.5% (302 versus 289).

ACTO measurement of IMCT approvals requires clarification, as our classification of trials does not always coincide with that in the Russian Ministry of Health registry. We only treat a trial as an IMCT if we find it in the American or European registers. If a trial is not included in those registries or if there is some other reason to doubt its international status, we classify it as a local trial, even if it is listed in the Ministry of Health registry as an IMCT. There have been many cases recently when manufacturers (particularly local manufacturers) have described a trial as international when it is carried out in Russia and one or more post-Soviet countries. However, the international registries, as a rule, contain no data on such trials, and their nature is difficult to establish. We believe that confidence in trials, which are not carried out in countries that have a developed regulatory system (and accordingly, an adequate monitoring system), is insufficient for their classification as IMCTs.

We believe this clarification is important, since in 2016 there were a quite a few trials that were declared as IMCTs in the Ministry of Health registry, but were absent from the internationally recognized registries. According to www.grls.rosminzdrav.ru, 319 trials had international status, but we only classified 302 as IMCTs. Hence there is some discrepancy between the data in the Ministry of Health registry and in the ACTO statistics.

Table 1

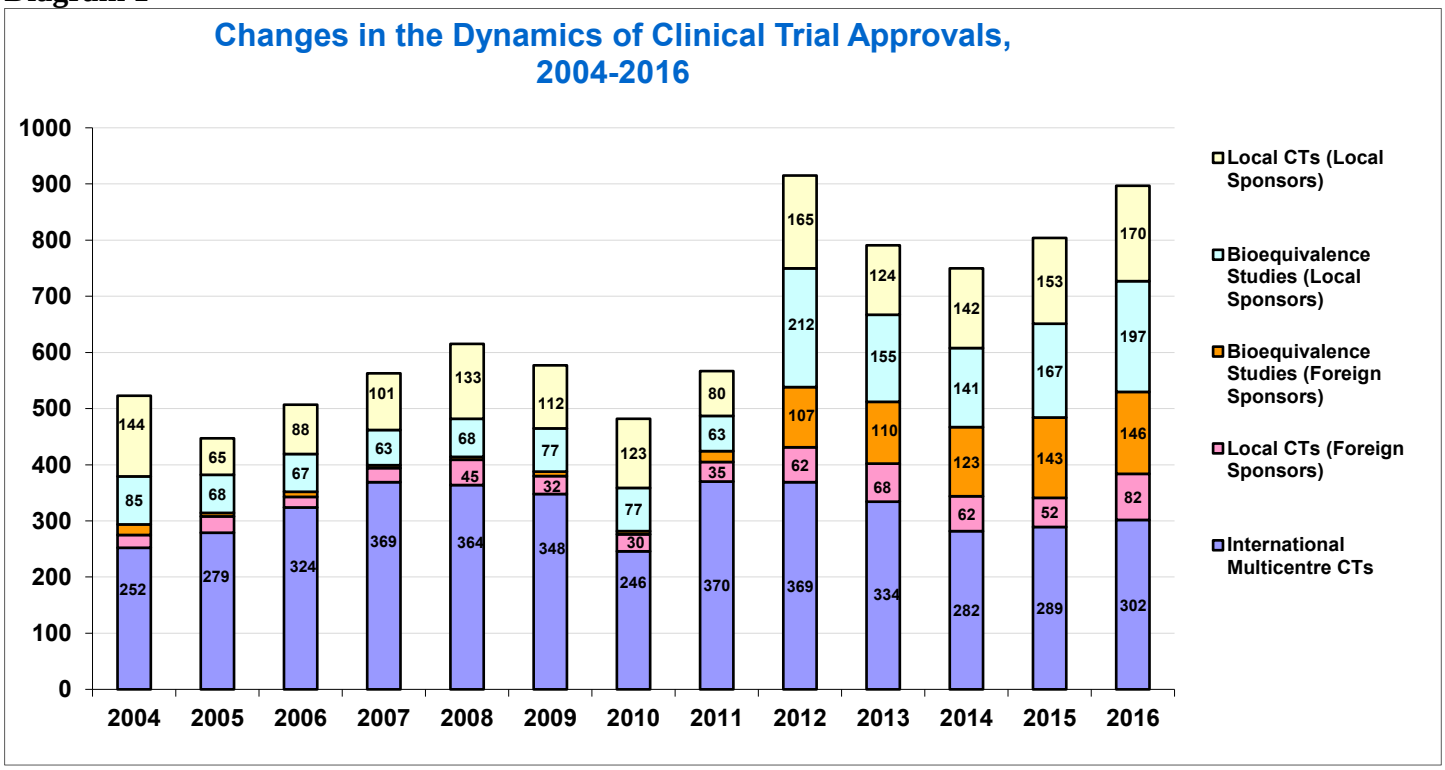
Clinical Trial Approvals: 2016 vs. 2015						
Year	**Total**	**International Multicenter CTs**	**Local CTs (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CTs (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
2016	897	302	82	146	197	170
2015	804	289	52	143	167	153
2016 vs. 2015, %	11.6%	4.5%	57.7%	2.1%	18.0%	11.1%

Data from www.grls.rosminzdrav.ru

Diagram 1 shows the development of the Russian clinical trials market by years. Setbacks in 2010 were associated with the transfer of the approval issuing function from Roszdravnadzor to the Ministry of Health, which put the system out of action for a whole quarter. All subsequent years were affected by the consequences of the new Law "On Circulation of Medicines", which made it obligatory to provide the registration dossier of the new medicinal product with the data of clinical trials partially conducted in Russia, and by the state policy to encourage import substitution. It can be seen that more approvals for both foreign- and Russian-sponsored local trials and for foreign-sponsored bioequivalence studies were issued in 2016 than ever before.

The number of IMCT approvals, which fell to the level of 2005 in 2014, went back up to the above 300 approvals mark in 2016.

Diagram 1

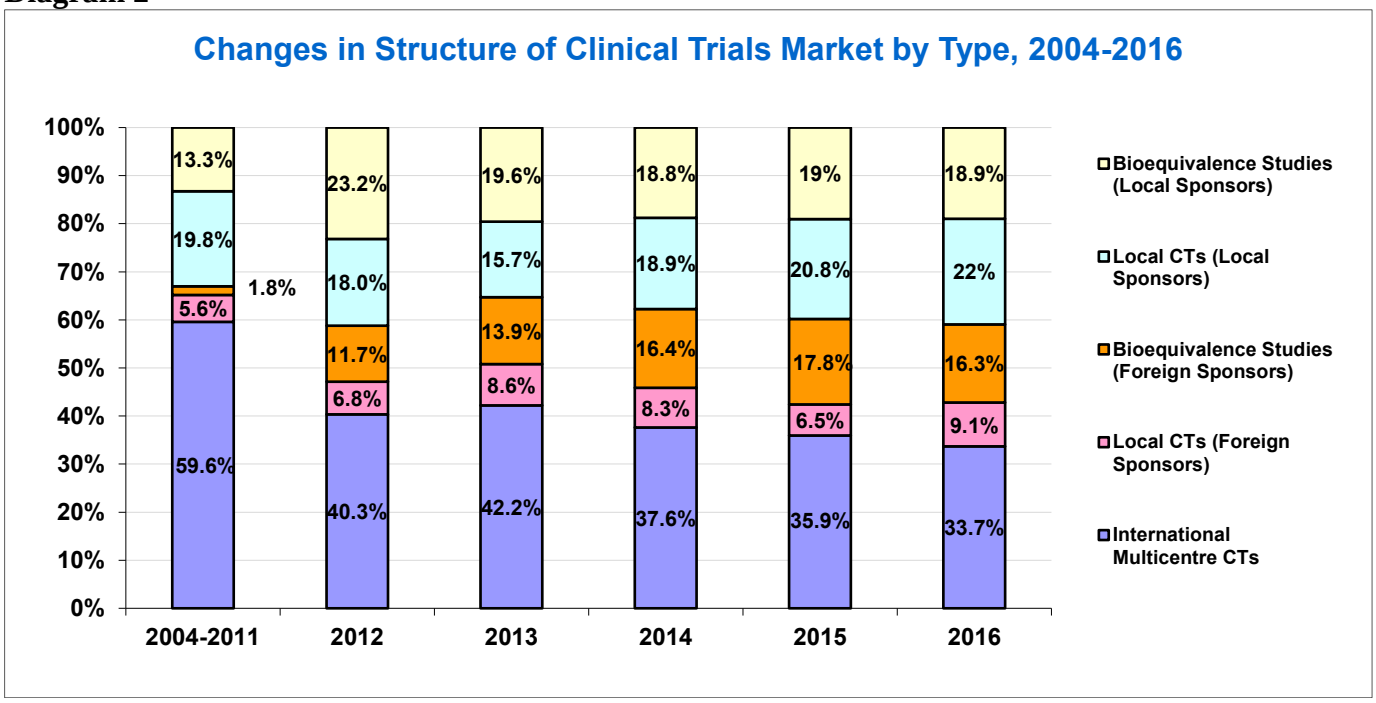


Data from www.grls.rosminzdrav.ru, www.roszdravnadzor.ru

STRUCTURE AND DYNAMICS OF THE CLINICAL TRIALS MARKET BY TYPE

Diagram 2 shows changes in the market structure by the type of trials. There was little change in ratios between different types of clinical trials from 2004 to 2011, so the Figure shows average values for this period.

Diagram 2



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

It can be seen, first, that the share of IMCTs in overall market structure has continued to decline in the years after implementation of the Law "On Circulation of Medicines", due to an increase in the share of other types of trials. By 2016 the IMCT share had decreased to 33.7%.

It can also be seen that the shares of Russian- and foreign-sponsored local trials reached record levels in 2016 (22% and 9.1%, respectively). We can find no clear explanations of the increase in foreign-sponsored trials. On the contrary, we expected their decrease after January 1, 2016 when amendments to the Law "On Circulation of Medicines" came into force, by which therapeutic equivalence trials for certain generic pharmaceutical forms were no longer required.

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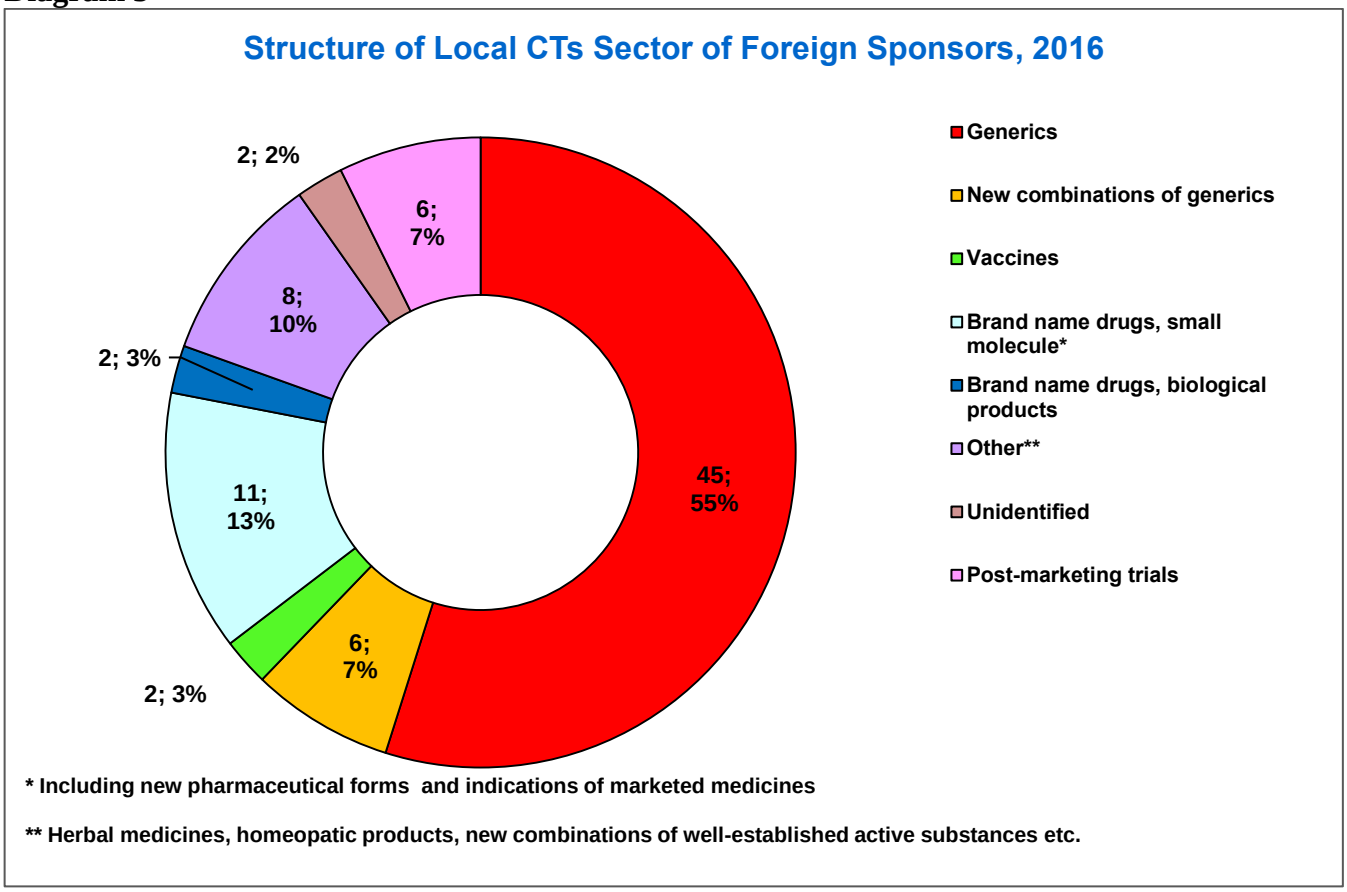
Diagram 3 shows the structure of local efficacy and safety trials initiated by foreign sponsors.

As in previous years, generics take the largest share (55% or 45 studies). We distinguished a new group this year, entitled "New combinations of generics" (we previously treated such medicines as originators – brand name products, which was theoretically correct but not always justified, particularly when the combinations were of well-known medicines used for monotherapy for many years). In total, generics and their new combinations account for 62% of foreign-sponsored local trials. Second place (13% or 11 trials) is taken by brand name medicines (small molecules).

As regular readers know, we refer post-marketing trials to a separate group. The share of foreign-sponsored post-marketing trials was 7% (6 trials) in 2016: three trials of brand name medicines, two of generic medicines, and one trial of a drug, which we referred to the group of "other drugs" (the homeopathic medicine, Oscillococcinum).

Diagram 3



Data from www.grls.rosminzdrav.ru

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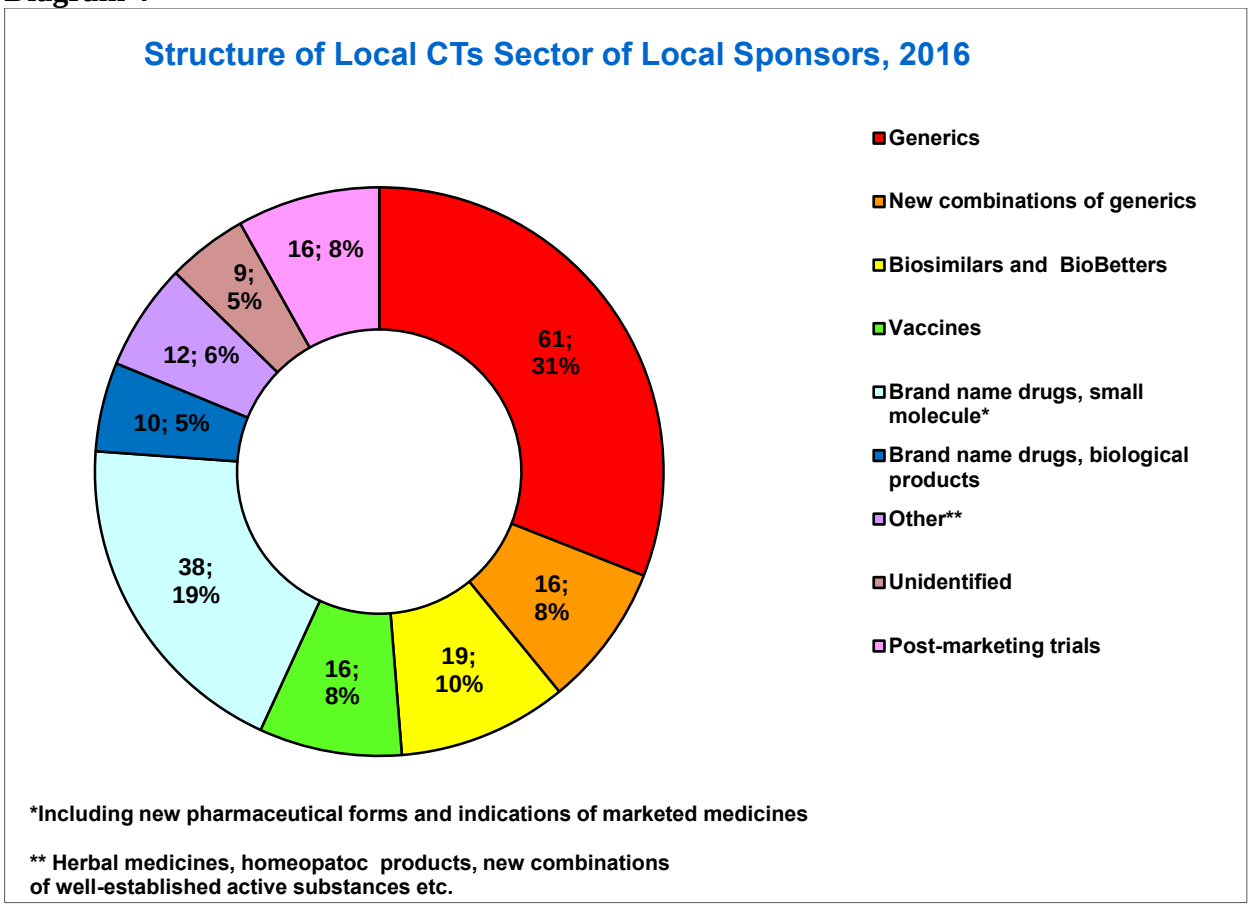
Diagram 4 shows types of drugs used in Russian-sponsored local trials. The biggest share is again taken by generics (31%, 61 trials) and the addition of new combinations of generics raises their cumulative share to 39%.

Second place among Russian-sponsored trials is taken by trials with brand name medicines based on small molecules (19%, 38 trials). Studies of biosimilars, a group absent from foreign-sponsored local trials, takes a sizeable share of 10% (19 trials).

Local post-marketing trials initiated by domestic sponsors accounted for 8%, with 16 trials, of which three were conducted with brand name products (small molecules), one with an originator biological drug, three with vaccines, five with generics and four with biosimilars.

Diagram 4

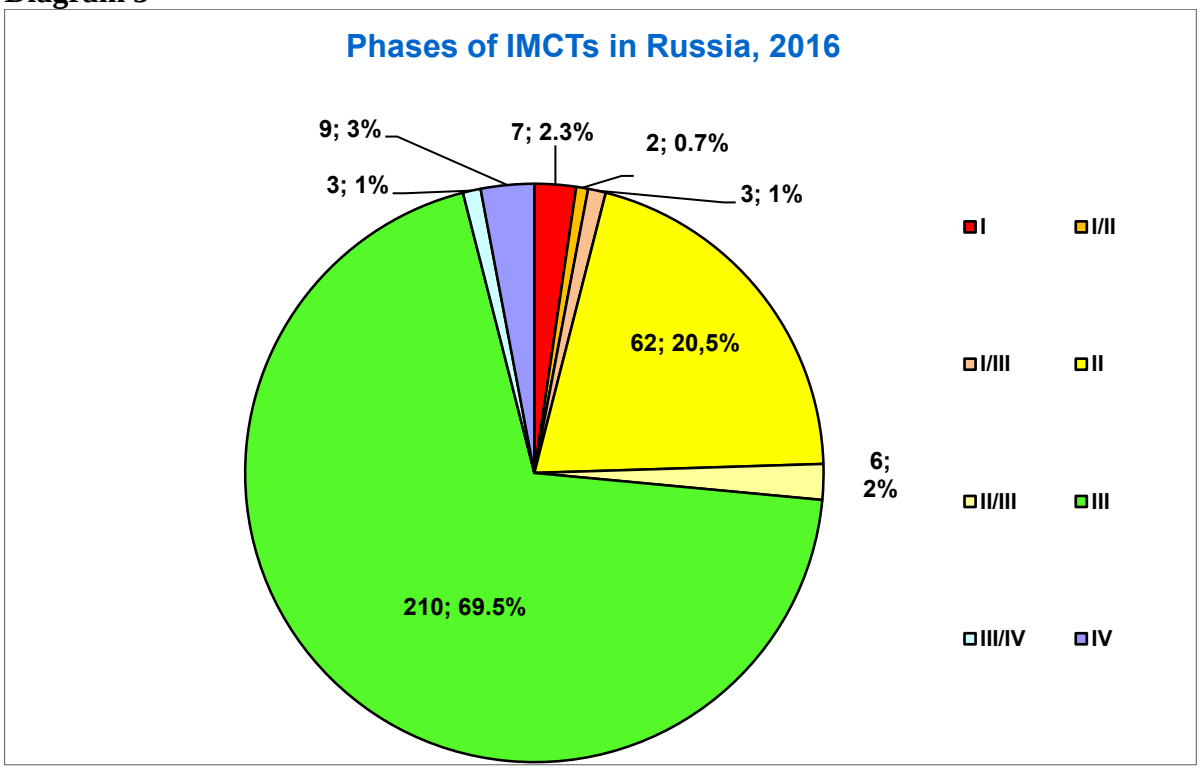


Data from www.grls.rosminzdrav.ru

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

Diagram 5 shows the distribution of IMCTs approved in 2016, by phases.

Diagram 5



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

Three of the seven international phase I trials approved in 2016 studied anti-cancer drugs and the other four referred to rheumatoid arthritis, hemophilia, gastroenterology and psychiatry.

STRUCTURE OF THE CLINICAL TRIALS MARKET BY THERAPEUTIC AREAS

We have made some changes to the tables of therapeutic areas. A new column has been introduced showing the number of study participants planned to be enrolled in Russia, according to the registry of issued approvals. In addition, HIV, hepatitis C and tuberculosis, which were previously referred to other infectious diseases, as well as oncohematology and phlebology have been allocated to distinct therapeutic areas.

Table 2 shows areas of the IMCTs, which were approved in 2016. As usual, first place is taken by cancer drugs (22.2%, 67 trials). Taken together with oncohematology (18 more IMCTs), oncology trials account for almost one third (28.2%) of the total number of IMCTs in Russia. Second place is taken by rheumatology (36 trials or 11.9% of the total, up from 7.4% in 2015), and third place is taken by neurology (28 trials or 9.3%, down from 9.1% in 2015 when neurology was in second place).

Table 2

Split of International Multicenter CTs by Therapeutic Areas, 2016			
Therapeutic Area	**Number of IMCTs**	**Share (%)**	**The number of planned participants**
Oncology	67	22.2%	4 328
Rheumatology	36	11.9%	3 389
Neurology	28	9.3%	2 778
Endocrinology	23	7.6%	2 559
Pulmonology	19	6.3%	4 185
Oncohaematology	18	6.0%	811
Gastroenterology	16	5.3%	871
Psychiatry	15	5.0%	1 367
Dermatology	10	3.3%	563
Infectious Diseases (except HIV/HCV/tuberculosis)	10	3.3%	853
HIV/HCV/tuberculosis	10	3.3%	870
Cardiology and CVD	10	3.3%	4 925
Nephrology	7	2.3%	796
Gynecology	6	2.0%	962
Ophthalmology	6	2.0%	500
Hematology	5	1.7%	122
Phlebology	5	1.7%	154
Immunology	4	1.3%	92
Allergology	3	1.0%	200
Analgesics and NSAIDs	2	0.7%	419
Urology	2	0.7%	370
TOTAL	302	100.0%	31 114

Data from www.grls.rosminzdrav.ru

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Table 3 shows therapeutic areas of local trials and bioequivalence studies initiated by foreign sponsors.

Table 3

Split of Local CTs and Bioequivalence Studies (Generics) of Foreign Sponsors, 2016			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Cardiology and CVD	40	20.7%	2 731
Analgesics and NSAIDs	23	11.9%	1 854
Gynecology	16	8.3%	1 391
Infectious Diseases (exept HIV/HCV/tuberculosis)	16	8.3%	724
Oncology	14	7.3%	733
Neurology	13	6.7%	649
Urology	12	6.2%	1 010
Ophthalmology	10	5.2%	1 378
Pulmonology	9	4.7%	873
HIV	8	4.1%	404
Endocrinology	6	3.1%	284
Allergology	5	2.6%	824
Anthelminthic medicines	3	1.6%	182
Immunology	3	1.6%	160
Gastroenterology	3	1.6%	138
Psychiatry	3	1.6%	99
Surgery, Anesthesiology, Intensive Care	2	1.0%	310
Rheumatology	2	1.0%	168
Dermatology	1	0.5%	80
Immunology, Transplantology	1	0.5%	48
Metabolic medicines	1	0.5%	36
Phlebology	1	0.5%	28
Other	1	0.5%	24
TOTAL	193	100.0%	14 128

Data from www.grls.rosminzdrav.ru

First place in 2016 was taken by drugs used to treat cardiac and cardiovascular diseases (CVD) (20.7%, 40 trials), second place was taken by studies of analgesics and nonsteroidal anti-inflammatory drugs (NSAIDs) (11.9%, 23 trials), and third and fourth places were shared by studies of drugs used in gynecology and for the treatment of infectious diseases (8.3% each, 16 trials in each area). However, the last figure does not include eight anti-HIV studies, which were allocated to a separate group. Their inclusion raises the share of infectious disease trials to 12.4%.

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Table 4 shows distribution across therapeutic areas of local trials and bioequivalence studies initiated by local sponsors. First place is taken by medicines used for the treatment of HIV/HCV/TB (12%, 31 trials), second place by neurological drugs (10.8%, 28 trials) and cardiology drugs take third place (10.4%, 27 trials).

Table 4

Split of Local CTs and Bioequivalence Studies (Generics and Biosimilars), Conducted by Local Sponsors, 2016			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
HIV/HCV/tuberculosis	31	12.0%	1 609
Neurology	28	10.8%	1 750
Cardiology and CVD	27	10.4%	1 559
Endocrinology	25	9.7%	1 232
Infectious Diseases (exept HIV/HCV/tuberculosis)	20	7.7%	1 478
Oncology	19	7.3%	1 520
Pulmonology	16	6.2%	782
Analgesics and NSAIDs	15	5.8%	899
Gastroenterology	11	4.2%	895
Urology	10	3.9%	425
Psychiatry	8	3.1%	370
Hematology	6	2.3%	326
Gynecology	6	2.3%	261
Rheumatology	5	1.9%	906
Dermatology	5	1.9%	716
Phlebology	5	1.9%	582
Oncohaematology	4	1.5%	488
Ophthalmology	4	1.5%	382
Immunology; Transplantology	3	1.2%	192
Surgery	2	0.8%	406
Immunology	2	0.8%	88
Metabolic medicines	2	0.8%	50
Hepatology	1	0.4%	24
Allergology	1	0.4%	28
Alcoholism treatment	1	0.4%	36
Nephrology	1	0.4%	45
Otorhinolaryngology	1	0.4%	182
TOTAL	259	100.0%	17 231

Data from www.grls.rosminzdrav.ru

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Table 5 shows the products, which were of greatest interest to manufacturers of generics in 2016. Metformin leads in this section with 13 approved trials of drugs based on its use (4 foreign and 9 domestic). Hydrochlorothiazide is in the second place (as sole agent and in combination) with 12 studies (mainly initiated by foreign sponsors), and third and fourth places, with 10 studies each, are shared by telmisartan (taken as a single agent and in combination) and ethinylestradiol in different combinations.

Table 5

Most Requested INN Used in Clinical Trials of Generics in 2016				
Substance	**Number of CTs of foreign generics**	**Number of CTs of local generics**	**All clinical trials to a given INN**	**Therapeutic Area**
Metformin (separately and in fixed combinations)	4	9	13	Endocrinology
Hydrochlorothiazide (separately and in fixed combinations)	10	2	12	Cardiology and CVD
Telmisartan (separately and in fixed combinations)	9	1	10	Cardiology and CVD
Ethinylestradiol in fixed combinations	7	3	10	Gynecology
Abiraterone	6	3	9	Oncology
Amlodipine in combination	6	3	9	Cardiology and CVD
Atorvastatin (separately and in fixed combinations)	7	1	8	Cardiology and CVD
Tenofovir (separately and in fixed combinations)	4	4	8	HIV
Ibuprofen (separately and in fixed combinations)	6	1	7	Analgesics and NSAIDs
Lidocain in fixed combinations	3	4	7	Analgesics and NSAIDs, Gynecology
Valsartan (separately and in fixed combinations)	4	2	6	Cardiology and CVD
Diosmin (separately and in fixed combinations)	1	5	6	Phlebology
Meloxicam	1	5	6	Analgesics and NSAIDs
Moxifloxacin	2	4	6	Ophthalmology, Infectious Diseases
Oseltamivir	3	3	6	Infectious Diseases
Rosuvastatin (separately and in fixed combinations)	5	1	6	Cardiology and CVD
Sildenafil	2	4	6	Urology, Cardiology and CVD
Abacavir (separately and in fixed combinations)	1	4	5	HIV
Azithromycin	2	3	5	Infectious Diseases
Aminophenylbutyric acid	1	4	5	Neurology
Acetylsalicylic acid (separately and in fixed combinations)	2	3	5	Cardiology and CVD, Analgesics and NSAIDs
Zidovudine (separately and in fixed combinations)	2	3	5	HIV
Losartan (separately and in fixed combinations)	4	1	5	Cardiology and CVD
Pregabalin	4	1	5	Neurology
Ritonavir (separately and in fixed combinations)	0	5	5	HIV
Fenspirid	3	2	5	Pulmonology
Emtricitabine (separately and in fixed combinations)	2	3	5	HIV
Etoricoxib	4	1	5	Analgesics and NSAIDs
Meldonium/Meldonium dihydrate	1	4	5	Metabolic medicines

Data from www.grls.rosminzdrav.ru

The analysis found surprising popularity of another substance, which had not been used in previous clinical trials: meldonium, invented as long ago as the mid-1970s and recently at the center of international doping scandals, made its entry with five approved trials (one by a Turkish sponsor and four by domestic sponsors). The interest is explained by the fact that the Ministry of Health of Tatarstan announced a call for bids last fall for purchases of meldonium with value of nearly 1 million rubles. If the drug is in such demand, why not to produce it?

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Tables 6 and 7 provide data on foreign- and Russian-sponsored local trials of brand name medicines, respectively.

Table 6

Split of Local CTs of Brand Name Drugs (including biological products) of Foreign Sponsors, 2016		
Therapeutic Area	**Number of CTs**	**Number of planned participants**
Infectious Diseases (exept HIV/HCV/TB)	4	820
Neurology	3	635
Allergology	1	310
Analgesics and NSAIDs	1	230
HIV	1	33
Gastroenterology	1	260
Immunology	1	30
Oncohaematology	1	70
Oncology	1	50
Otorhinolaryngology	1	300
Pulmonology	1	152
Surgery	1	79
Endocrinology	1	370
TOTAL	18	3 339

Data from www.grls.rosminzdrav.ru

Table 7

Split of Local CTs of Brand Name Drugs (including biological products) of Local Sponsors, 2016		
Therapeutic Area	**Number of CTs**	**Number of planned participants**
Infectious Diseases, including Vaccines (exept HIV/HCV/TB)	26	3 494
Oncology	8	541
Rheumatology	5	664
HIV/HCV/tuberculosis	4	386
Neurology	4	299
Surgery, neurosurgery	3	339
Urology	3	669
Gynecology	2	468
Dermatology	2	240
Radiology	2	175
Psychiatry	2	180
Endocrinology	2	179
Cardiology and CVD	2	248
Analgesics and NSAIDs	1	54
Anesthesiology	1	150
Toxicology, Alcoholism treatment	1	150
Oncohaematology	1	44
Ophthalmology	1	300
TOTAL	70	8 580

Data from www.grls.rosminzdrav.ru

BREAKDOWN OF IMCT APPROVALS ACROSS RUSSIA

Data on the distribution of IMCTs approved in 2016 by Russian federal macro-districts and their constituent administrative regions are presented in Table 8 (*see detailed information on the criteria used and the calculation methodology in ACTO Newsletter № 12).*

First place by absolute values (number of IMCTs approved in 2016, number of participating medical institutions and number of centres opened) is taken by the Central Federal District, where the foremost region is the city of Moscow, followed by Yaroslavl and Smolensk Regions. The North-Western Federal District comes a close second, dominated by the city of St. Petersburg. Third and fourth places are taken, respectively, by the Volga Federal District, where Tatarstan, and Saratov and Nizhny Novgorod Regions predominate, and the Siberian Federal District, where Novosibirsk, Tomsk, Omsk, and Kemerovo Regions are the main players.

Turning to IMCT distribution density (number of trials per million population), the North-Western Federal District leads by a large margin with a figure of 19.3, more than 2.5 times ahead of the Siberian (7.7), Urals (7.5) and the Central (7.3) Federal Districts.

The overall picture of IMCT distribution by territories is not much changed from 2015. Compared to 2015 we now see trials commencing in 2016 in Khabarovsk Territory, Amur and Vologda Regions, the Republic of Adygea and the Republic of Kabardino-Balkaria. Crimea and Kaliningrad dropped out of the list of regions obtaining clinical trial approvals in 2016.

We also note a reduction in the number of IMCTs in Kursk and Vladimir Regions (eight each in 2016, compared with 24 and 20, respectively, in 2016) and some growth in Stavropol Territory (49 approved IMCTs in 2016 versus 35 in 2015), Saratov Region (70 versus 56) and Irkutsk Region (17 versus 10).

Table 8

Split of IMCTs approved in 2016 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**	**7.3**	**160**	**935 (979)**	**North Caucasian Federal District**	**52**	**5.4**	**12**	**60 (62)**
Moscow	266	**21.6**	98	585 (624)	Stavropol Territory	49	**17.5**	10	54 (56)
Yaroslavl Region	78	**61.3**	15	103 (105)	Republic of North Ossetia – Alania	5	**7.1**	1	5
Smolensk Region	48	**50.1**	8	54	Kabardino-Balkarian Republic	1	**1.2**	1	1
Ryazan Region	37	**32.7**	4	39	**Siberian Federal District**	**148**	**7.7**	**76**	**354 (368)**
Kaluga Region	31	**30.7**	3	31 (34)	Novosibirsk Region	79	**28.6**	29	110
Moscow Region	28	**3.8**	7	30	Tomsk Region	44	**40.9**	8	47 (55)
Ivanovo Region	20	**19.4**	5	20	Kemerovo Region	43	**15.8**	11	53 (54)
Voronezh Region	19	**8.1**	5	19	Omsk Region	42	**21.2**	7	50 (53)
Tver Region	9	**6.9**	1	9	Altai Territory	35	**14.7**	8	42 (43)
Vladimir Region	8	**5.7**	2	8	Krasnoyarsk Territory	33	**11.5**	6	33
Kursk Region	8	**7.1**	2	8	Irkutsk Region	17	**7.1**	6	17 (18)
Tula Region	8	**5.3**	1	8	Trans-Baikal Territory	2	**1.9**	1	2
Lipetsk Region	6	**5.2**	3	6	**Ural Federal District**	**92**	**7.5**	**32**	**125 (130)**
Belgorod Region	6	**3.,9**	2	6	Sverdlovsk Region	50	**11.6**	11	58 (63)
Orel Region	5	**6.6**	2	5	Chelyabinsk Region	48	**13.7**	14	53
Tambov Region	3	**2.9**	1	3	Tyumen Region	11	**7.6**	6	11
Bryansk Region	1	**0.8**	1	1					
Southern Federal District	**79**	**5.6**	**30**	**110 (114)**	Khanty-Mansi Autonomous Area - Yugra	3	**1.8**	1	3
Rostov Region	51	**12.0**	12	55	**Volga Federal District**	**205**	**6.9**	**87**	**497 (513)**
Krasnodar Territory	32	**5.8**	12	37	Republic of Tatarstan	99	**25.6**	17	118 (126)
Volgograd Region	16	**6.3**	5	17 (21)	Saratov Region	70	**28.1**	8	86 (93)
Republic of Adygeya	1	**2.2**	1	1	Nizhny Novgorod Region	69	**21.2**	17	81
Northwestern Federal District	**268**	**19.3**	**140**	**841 (882)**	Samara Region	50	**15.6**	12	53
Saint-Petersburg	263	**50.3**	116	742 (783)	Republic of Bashkortostan	39	**9.6**	3	39
Arkhangelsk Region	27	**23.9**	5	31	Perm Territory	23	**8.7**	8	25 (26)
Leningrad Region	23	**12.9**	7	25	Orenburg Region	21	**10.5**	3	21
Republic of Karelia	23	**36.5**	3	24	Ulyanovsk Region	19	**15.1**	2	19
Republic of Komi	6	**7.0**	2	6	Udmurtian Republic	16	**10.6**	6	16
Novgorod Region	5	**8.1**	2	5	Penza Region	14	**10.4**	3	15
Vologda Region	4	**3.4**	2	4	Kirov Region	12	**9.2**	3	12
Murmansk Region	3	**3.9**	2	3	Republic of Mordovia	7	**8.7**	3	7
Pskov Region	1	**1.6**	1	1	Republic of Mari El	3	**4.4**	1	3
Far Eastern Federal District	**4**	**0.7**	**4**	**4**	Chuvash Republic	2	**1.6**	1	2
Khabarovsk Territory	2	**1.5**	2	2					
Amur Region	1	**1.2**	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, 2016

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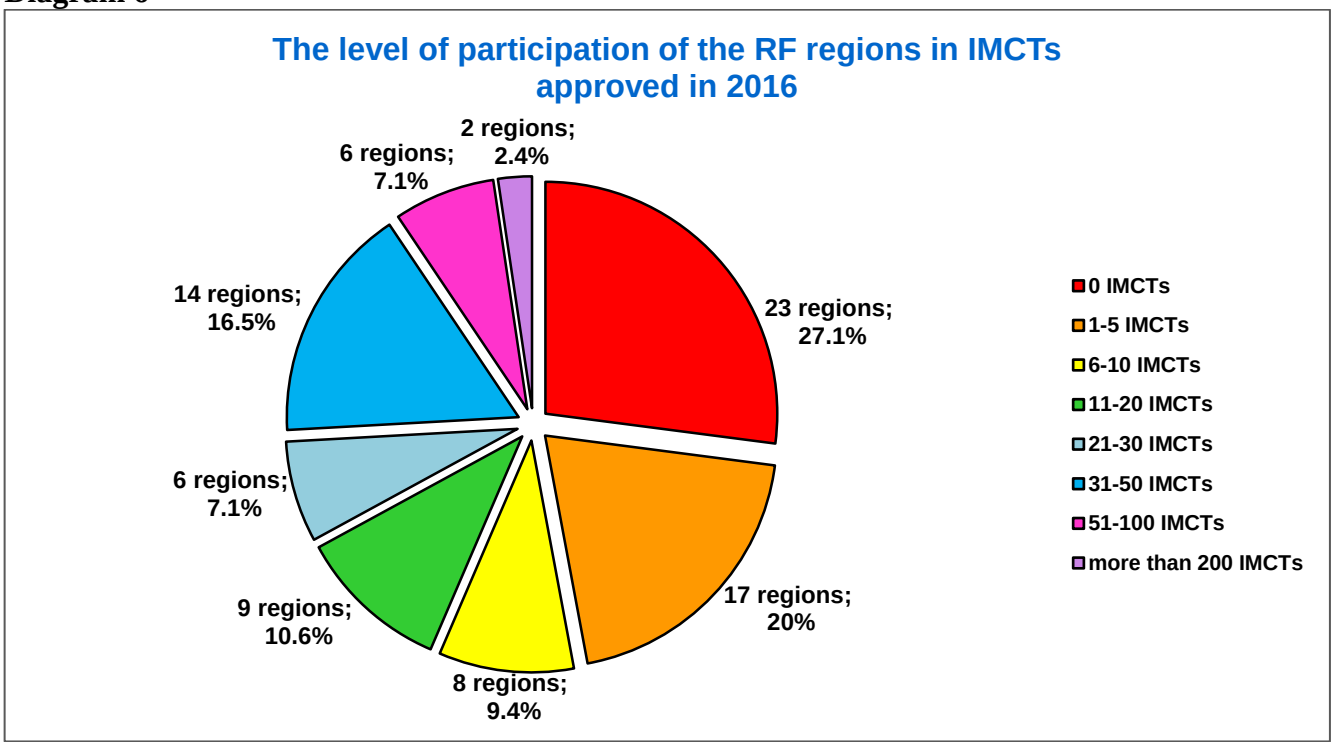
Diagram 6 reflects the picture of participation by Russian regions in IMCTs, showing that 23 of Russia's 85 regions do not participate in IMCTs at all, while two regions, the cities of Moscow and St. Petersburg, each participate in more than 200 trials.

Diagram 6

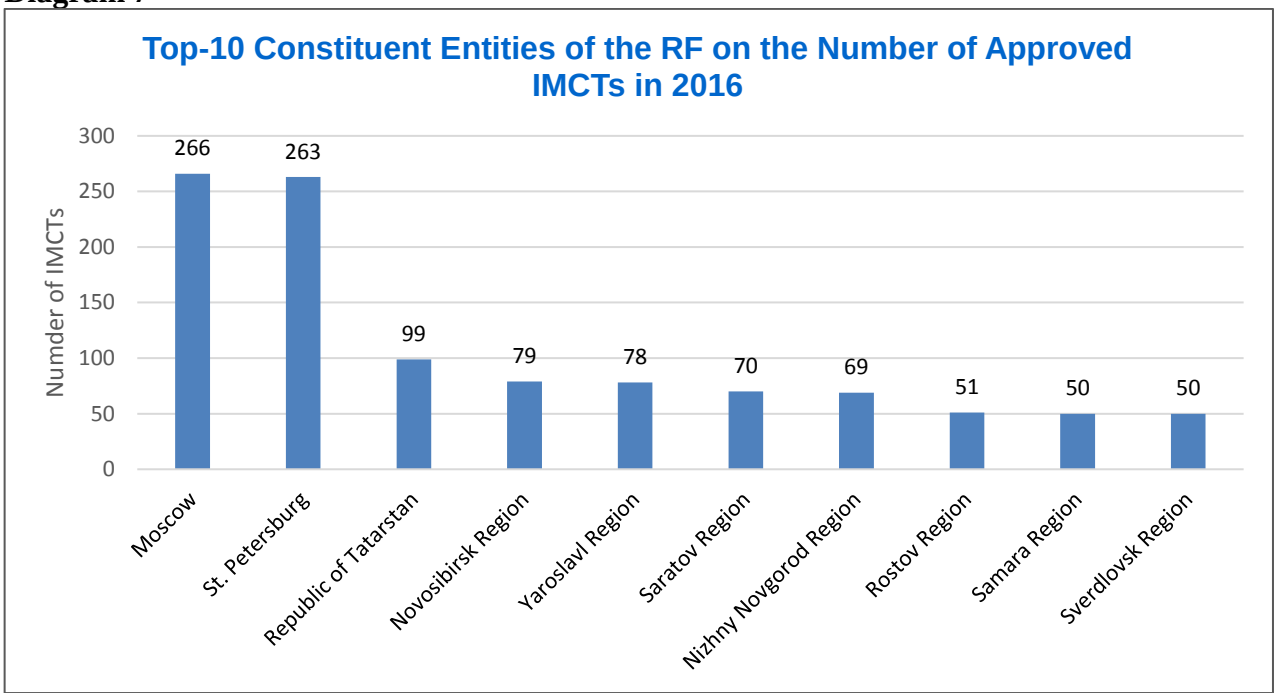


Data from www.grls.rosminzdrav.ru

The next two diagrams show the top 10 regions by the absolute number of IMCT approvals and by approvals per one million population. Moscow and St. Petersburg lead by a large margin on the first parameter (Diagram 7), followed by Tatarstan.

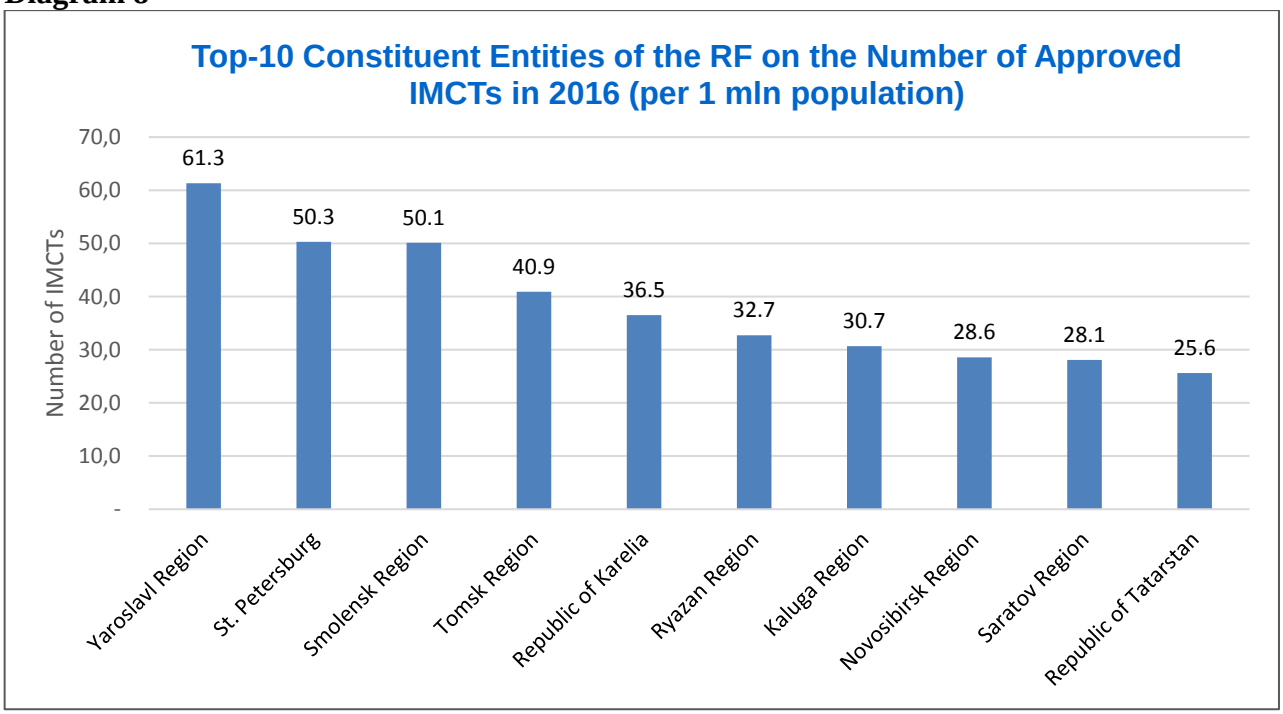
The picture presented by number of IMCTs per million inhabitants (Diagram 8) is quite different. First place, as in 2015, is taken by Yaroslavl Region, which improved its score from 54.3 to 61.3 IMCTs per million population. Second place goes to St. Petersburg (50.3 versus 48.9 in 2015) just ahead of Smolensk Region (50.1 versus 46.6 in the previous year). Moscow, with 21.6 trials per million, again failed to enter the top 10, standing 12th in the ranking.

Diagram 7



Data from www.grls.rosminzdrav.ru

Diagram 8



Data from www.grls.rosminzdrav.ru

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Table 9 shows the top 20 medical institutions participating in IMCTs. It shows both the number of IMCTs approved in 2016 with participation of the institutions as well as the total number of the institution's centers approved over the year. For comparison purposes, the right-hand column gives the number of IMCTs and (in parentheses) the institution's place in the rating in 2015. It can be seen that there was little change in the previous year's leaders (the first four lines).

Several institutions made strong progress in 2016. Saratov State Medical University jumped from 34th to 5th place. The Siberian State Medical University and the Saratov City Regional Clinical Hospital rose from 20th and 21st to the 7th and 8th places, respectively. Ryazan State Medical University advanced from 28th-33rd place to 12th. The biggest advance was by Bashkir State Medical University, which soared from the bottom of the list (87th-100th place in 2015) directly to 15th place.

Table 9

Top-20 medical organizations on the activity of participation in IMCTs approved in 2016				
Place in ranking	**Name of medical organization**	**Number of IMCTs approved in 2016 with participation of this medical organization**	**Number of centres approved in 2016 for conducting IMCTs**	**Number of IMCTs and ranking of the centers (on approvals issued in 2015)**
1	N. N. Blokhin Russian Cancer Research Centre, Russian Ministry of Health, Moscow	60	70	53 (2)
2	I. P. Pavlov First St. Petersburg State medical University, Russian Ministry of Health, St. Petersburg	57	63	65 (1)
3	Kazan State Medical University, Russian Ministry of Health, Kazan	55	61	44 (4)
4	I. M. Sechenov First Moscow State Medical University, Russian Ministry of Health, Moscow	33	42	52 (3)
5	Saratov State Medical University named after V. I. Razumovsky, Russian Ministry of Health, Saratov	32	36	16 (34-39)
6	N. N. Petrov Research Institute of Oncology, Russian Ministry of Health, St. Petersburg	30	31	40 (6)
7	Siberian State Medical University, Russian Ministry of Health, Tomsk	28	31	22 (20)
8	"Regional Clinical Hospital", Saratov	28	30	22 (21)
9	S. M. Kirov Military-Medical Academy, Russian Ministry of Defense, St. Petersburg	28	29	42 (5)
10	N. A. Semashko Nizhny Novgorod Regional Clinical Hospital, Nizhny Novgorod	28	28	28 (8)
11	St. Petersburg City Clinical Oncological Dispensary, St. Petersburg	27	29	39 (7)
12	Ryazan State Medical University named after academician I.P.Pavlov, Russian Ministry of Health, Ryazan	27	27	17 (28-33)
13	Clinical Oncological Dispensary, Omsk	26	29	24 (18)
14	Rostov State Medical University, Russian Ministry of Health, Rostov-on-Don	26	26	27 (10)
15-16	Bashkir State Medical University, Russian Ministry of Health, Ufa	25	25	8 (87-100)
15-16	Regional Clinical Hospital, Yaroslavl	25	25	18 (25-27)
17	National Medical Research Radiology Centre, Russian Ministry of Health, Obninsk	24	27	22 (19)
18	N. V. Solovyev Yaroslavl region Clinical Hospital for First Medical Assistace, Yaroslavl	24	25	27 (11)
19	Smolensk State Medical University, Russian Ministry of Health, Smolensk	23	23	27 (12-14)
20	Republican Hospital named after V.A. Baranov, Petrozavodsk, Karelia	21	21	21 (22)

Source: www.grls.rosminzdrav.ru

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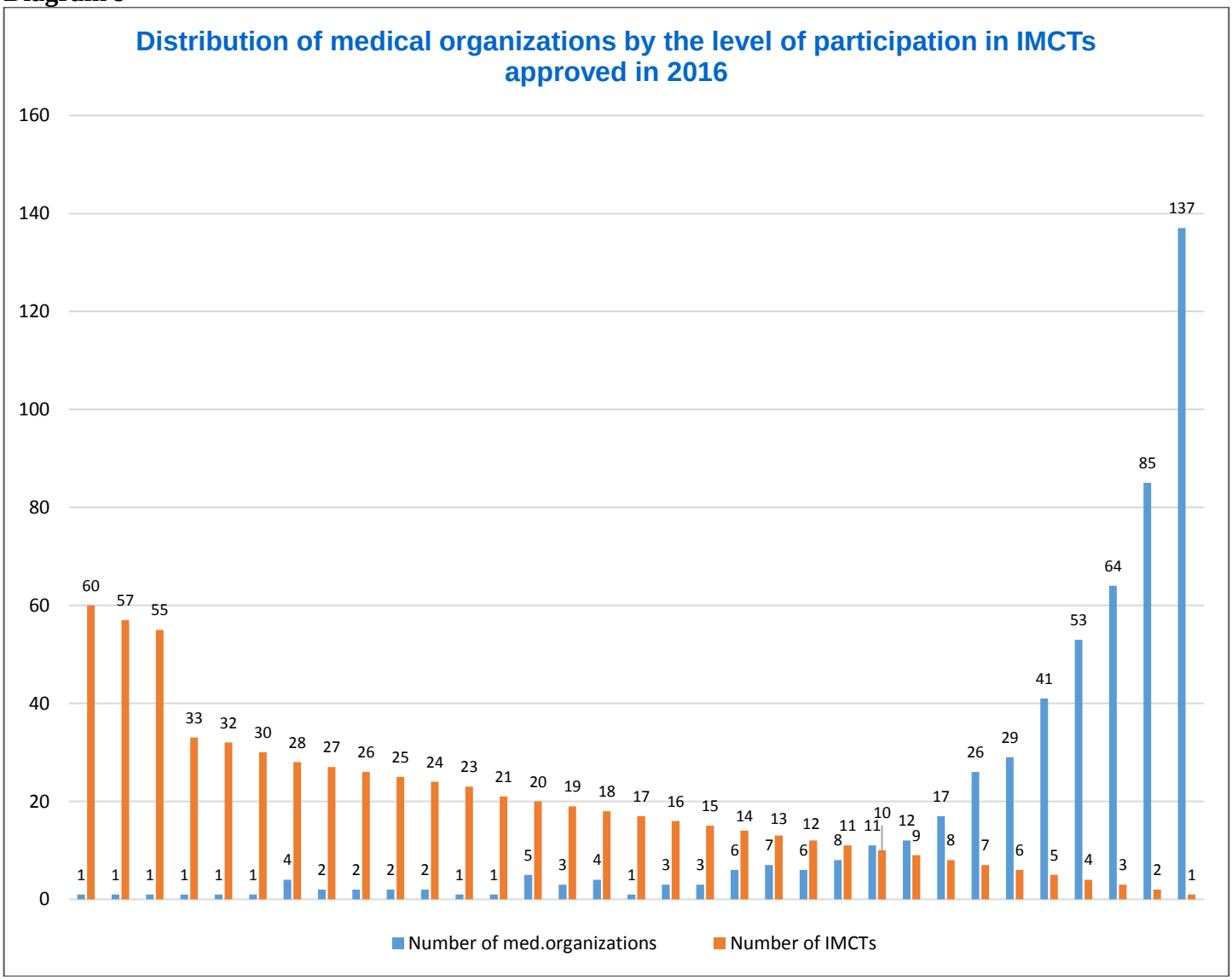
Diagram 9 shows how IMCTs are distributed between Russian medical institutions. The orange columns indicate the number of IMCTs per institution and the blue columns indicate the number of medical institutions, which received a particular number of IMCTs. So the left of the Diagram shows individual institutions, each of which had 60, 57, 55, etc. IMCTs, while the right part shows that 137 medical institutions were only involved in one IMCT, 85 in two, 64 in three, etc.

Diagram 9



Data from www.grls.rosminzdrav.ru

Tables 10 and 11 present data on level of participation of various medical organizations in Moscow and St. Petersburg in IMCTs, based on the subordination of the clinics.

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 IMCTs**	**The number of centres approved in 2016 for IMCTs**	**Activity Ratio**
Ministry of Healthcare of the Russian Federation	18	250	13.9
JSC "Russian Railways"	2	26	13.0
Ministry of Healthcare of the Moscow region	3	16	5.3
Federal bodies (except Ministry of Healthcare of the RF)	26	134	5.2
Moscow Department of Healthcare	34	155	4.6
Non-governmental health system	15	43	2.9
TOTAL	98	624	6.4

Data from www.grls.rosminzdrav.ru

Table 11

The level of participation of healthcare organizations in Saint-Petersburg in IMCTs depending on subordination			
Subordinated to	**Number of medical organizations involved in IMCTs**	**Number of centres approved in 2016 for IMCTs**	**Activity Ratios**
Ministry of Healthcare of the Russian Federation	12	203	16.9
JSC "Russian Railways"	1	13	13.0
Ministry of Healthcare of the Leningrad Region	3	38	12.7
Federal bodies (except Ministry of Healthcare of the RF)	11	78	7.1
Saint-Petersburg Department of Healthcare	55	331	6.0
Non-governmental health system	34	120	3.5
TOTAL	116	783	6.8

Data from www.grls.rosminzdrav.ru

It can be seen from the fourth columns of the tables that groups of clinics are ranked in the same order in both Moscow and St. Petersburg. Medical institutions of the Russian Ministry of Health are most popular, and clinics in the non-state healthcare system attract the least demand. Overall, the rate of participation is higher in the northern capital than in Moscow for all groups of clinics, with the exception of clinics affiliated with Russian Railways, which perform equally well in both cities.

Considerable growth in the number of private clinics participating in IMCTs was already noticeable in 2015 and continued in 2016. In Moscow eight non-state healthcare clinics were included in the calculation in 2015 when they opened a total of 13 IMCT centers. In 2016, the number of such clinics increased to 15 and their number of centers to 43. In St. Petersburg 25 private clinics with 86 centers were registered in 2015, increasing to 34 with 120 centers in 2016.

PARTICIPATION OF MEDICAL INSTITUTIONS IN BIOEQUIVALENCE STUDIES

Table 12 shows the top 15 medical institutions rated by their participation in bioequivalence studies.

Table 12

Top-15 medical organizations on the activity of participation in Bioequivalence Studies (approvals issued in 2016)					
Ranking	**Name of medical organization**	**Total number of bioequivalence studies**	**Number of bioequivalence studies, local sponsors**	**Number of bioequivalence studies, foreign sponsors**	**Number of bioequivalence studies and ranking of the centre, 2015**
1	"Research Center Eco-bezopasnost", St. Petersburg	34	13	21	15 (8)
2	Clinical Hospital №2, Yaroslavl	33	15	18	32 (2)
3-4	Clinical Hospital №3, Yaroslavl	26	16	10	43 (1)
3-4	"Medical Center Probiotech", Serpukhov	26	23	3	11 (11)
5	"BioEq", St. Petersburg	19	12	7	24 (4)
6	"Family Doctor+ Clinic", Nizhny Novgorod	16	14	2	27 (3)
7-8	Road clinical Hospital at the station Yaroslavl, JSC Russian Railways, Yaroslavl	14	6	8	3 (17-22)
7-8	Research Institute of Pharmacology and Regenerative Medicine named after E.D. Goldberg, Tomsk	14	10	4	22 (5)
9	"BESSALAR Clinic", Moscow	13	3	10	2 (23-27)
10	Yaroslavl Regional Clinical Drug Treatment Hospital, Yaroslavl	10	4	6	10 (10)
11	City Clinical Hospital №68, Moscow Department of Healthcare, Moscow	9	0	9	1 (28-38)
12-13	National Research Center for Preventive Medicine of the Ministry of Healthcare of the Russian Federation, Moscow	8	3	5	7 (14)
12-13	City Clinical Hospital № 15 named after O. M. Filatov, Moscow Department of Healthcare, Moscow	8	4	4	3 (17-22)
14-15	Federal Research and Clinical Centre of Physical-Chemical Medicine, Federal Medical-Biological Agency, Moscow	7	0	7	n/a
14-15	Russian National Research Medical University named after N.I. Pirogov, Russian Ministry of Health, Moscow	7	3	4	2 (23-27)

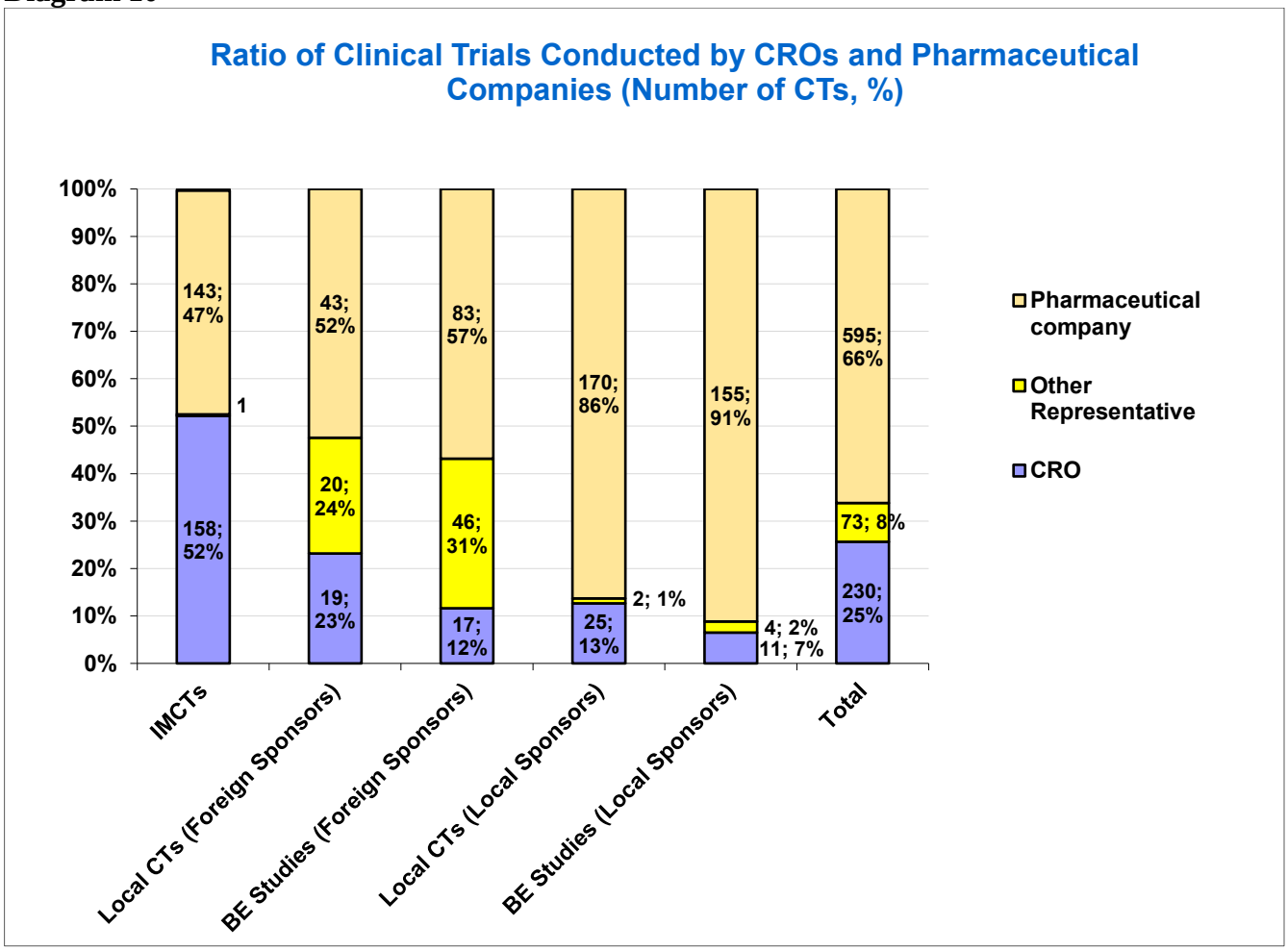
Data from www.grls.rosminzdrav.ru

MAIN PLAYERS ON THE RUSSIAN CLINICAL TRIALS MARKET – 2016

Sponsors and CROs, general structural breakdown

Diagram 10 shows the share of trials approved in 2016, which sponsors conducted themselves or used the services of third parties. We emphasize again that the statistics need to be taken with a bias correction of measurement, since they use data of the Ministry of Health register, which do not always capture the fact that trials were carried out using the services of external organizations. So the real share of such trials is somewhat higher.

Diagram 10



Data from www.grls.rosminzdrav.ru

The classification of groups of market participants also requires comment. The definition of sponsors and contract research organizations (CROs) is obvious, but the exact meaning of "other representatives" may be less so.

ACTO realized the need to classify this group separately when we started analyzing data on market participants in 2013. We noticed then, in some foreign-sponsored local trials, that certain companies mentioned in the register as "organizations contracted by the developer for the conduct of the trial" were not classic CROs, and their function mainly consisted in bringing products to market, often including distribution. Smaller foreign pharmaceutical manufacturers with no representative offices in Russia often use the services of such companies.

Later, the "other representatives" group was expanded to include companies offering specialized services for product registration. Such companies sprang up in large numbers after approval of the law "On Circulation of Medicines." Some of them eventually specialized, and we began to classify these as CROs, while others remained in the "other representatives" group. So our distinction here is, to some extent, arbitrary.

Finally, the 2016 analysis revealed another group (as yet still small), which we also included in "other representatives": companies declaring their main activity as "strategic consulting" or something similar. One and

the same activity can be given different names, and “assistance in entering the market” and “strategic consulting” may mean essentially the same thing. But this reinforces our point about the relatively arbitrary nature of the “other representatives” group.

The preceding comments seem important to make due to a gradual increase in the share of “other representatives” from just 1% of the clinical research market in 2013 to 3% in 2014 and 2015, and then to 8% in 2016. The services of such representatives are mainly used by foreign pharmaceutical manufacturers, but they are gradually beginning to play a role in clinical research work by domestic manufacturers.

International multicentre clinical trials, sponsors

Table 13 shows the top 10 sponsors, according to approvals issued for conduct of IMCTs in 2016.

Table 13

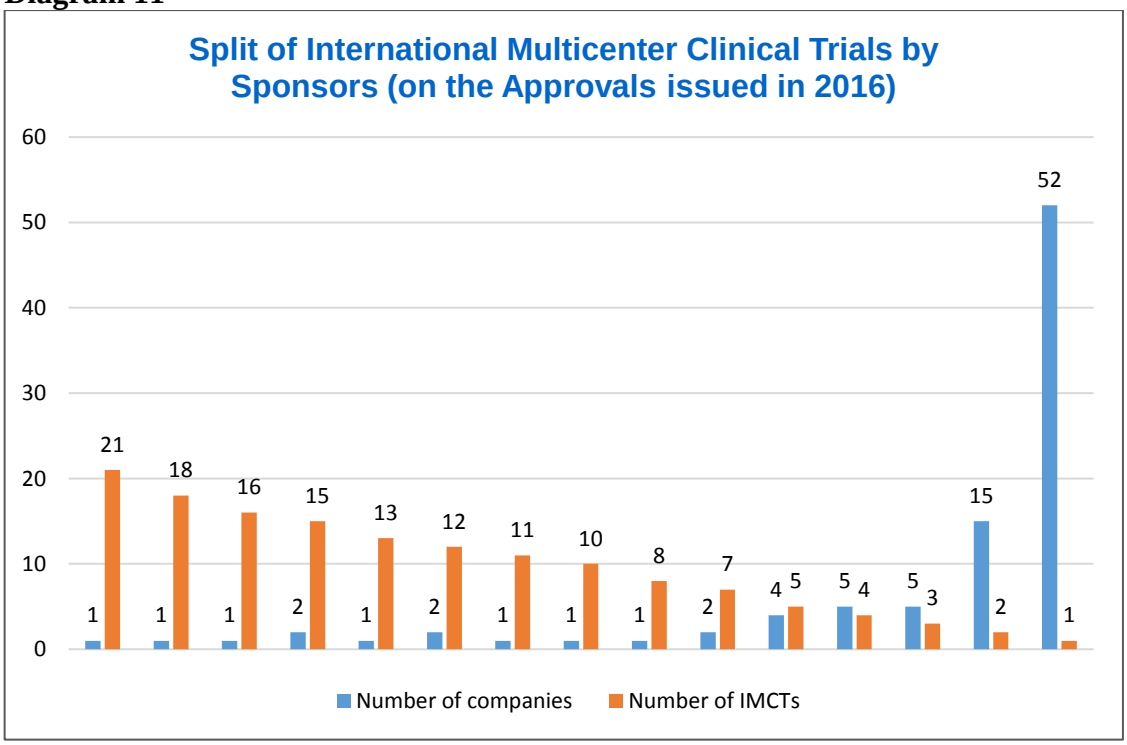
Top-10 Pharmaceutical Companies on Approvals for International Multicenter CTs, 2016					
Ranking	**Company (including separate companies, associated in group of companies, as well as independent divisions of the company)**	**Conducted by themselves**	**Conducted by CRO**	**Total**	**The Number of CTs; ranking in 2015**
1	Novartis	21	–	21	22 CTs; 1
2	Merck & Co.	18	–	18	20 CTs; 3
3	GlaxoSmithKline	9	7	16	7 CTs; 12-13
4-5	Bristol-Myers Squibb	15	–	15	13 CTs; 5
4-5	F. Hoffmann-La Roche	13	2	15	21 CTs; 2
6	Janssen Pharmaceutica	9	4	13	17 CTs; 4
7-8	AbbVie	12	0	12	4 CTs; 16-17
7-8	AstraZeneca	8	4	12	11 CTs; 6-7
9	Pfizer	–	11	11	5 CTs; 15
10	Novo Nordisk	10	–	10	8 CTs; 10-11

Data from www.grls.rosminzdrav.ru

The table, inter alia, gives an idea of changes in the group of leaders compared with 2015. Novartis has retained pole position since 2013, when we first began to analyze these statistics, and Merck & Co., F. Hoffmann-La Roche, Janssen Pharmaceutica, and AstraZeneca have never left the top 10 over the four years. The positions of other companies have varied more from year to year. In 2016, GlaxoSmithKline, AbbVie, and Pfizer returned to the top 10, while Boehringer Ingelheim (11th place), Sanofi (12th-13th), and Bayer, which received only one approval for a trial together with another sponsor, left the table.

Diagram 11 shows the distribution of IMCTs by sponsors in 2016. Leaders are shown on the left (each having 21, 18, 16, etc., trials). On the right are shown organizations that received one or two IMCT approvals (52 and 15 companies, respectively). Overall, 94 companies acted as IMCT sponsors in 2016 (91 companies in 2015).

Diagram 11



Data from www.grls.rosminzdrav.ru

International multicentre clinical trials, CROs

Table 14 shows the top 10 contract research organizations by the number of IMCTs approved with their participation in 2016. The rating is headed by QuintilesIMS (formerly Quintiles), in pole position for the third consecutive year with almost double the score of its nearest competitor. Quintiles was only once beaten (in 2013, by Parexel). As can be seen, the top 10 CROs are more stable than the top 10 sponsors, with the first four lines unchanged from 2015. Covance and Synergy returned to the top 10 in 2016, while MB Quest (11th) and Worldwide Clinical Trials (13th-20th) dropped out.

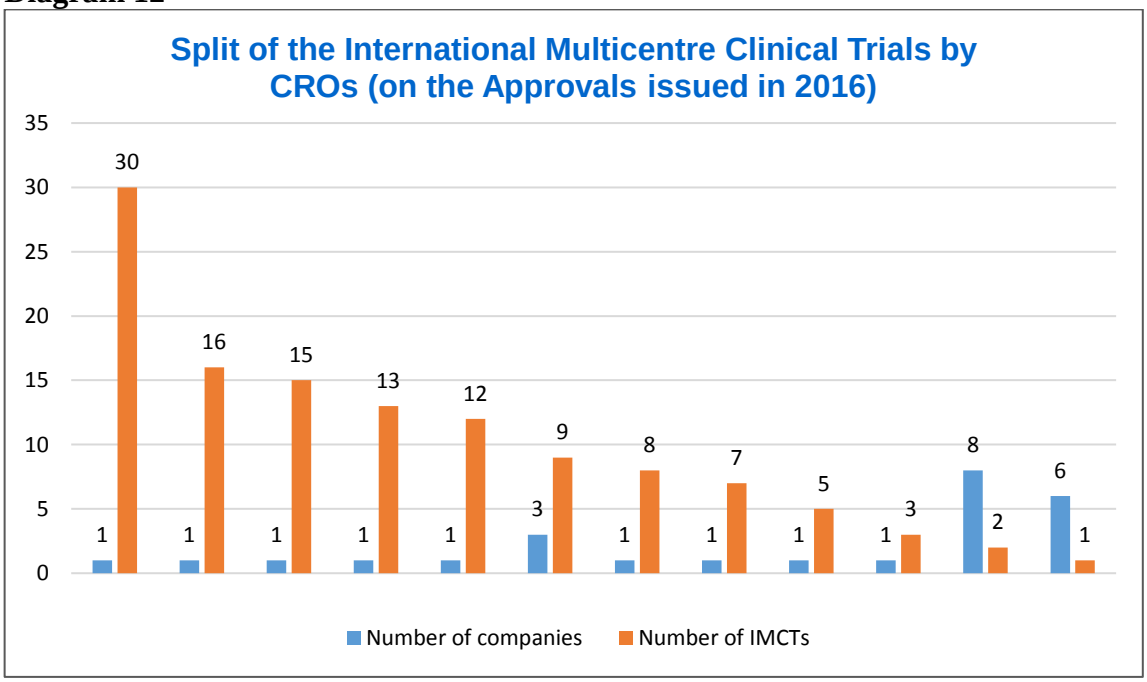
Table 14

Top-10 CROs on Approvals for International Multicenter CTs, 2016				
Ranking	**Company**	**Number of IMCTs**	**Number of Sponsors**	**Number of IMCTs; Ranking in 2015**
1	QuintilesIMS	30	20	29 CTs; 1
2	PPD	16	12	16 CTs; 2
3	PRA Health Sciences	15	7	15 CTs; 3
4	Parexel	13	8	11 Ts; 4
5	INC Research	12	10	5 CTs; 8-10
6-8	Covance	9	9	2 CTs; 17-21
6-8	ICON	9	6	6 CTs; 6-7
6-8	InVentiv Health Clinical	9	2	5 CTs; 8-10
9	PSI	8	7	7 CTs; 5
10	Synergy Research Group	7	3	4 CTs; 11-13

Data from www.grls.rosminzdrav.ru

Diagram 12 shows distribution of IMCTs approved in 2016 between CROs. On the left, we see QuintilesIMS with 30 projects. On the right are companies, which received one and two trial approvals (respectively six and eight CROs). A total of 26 CROs were involved in new IMCTs in 2016 (down from 30 CROs in the previous year).

Diagram 12



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies, foreign sponsors

There was no clear top 10 of foreign sponsors that initiated local trials and bioequivalence studies in 2016 as 9th-11th positions were taken by three companies at once (Table 15). The 2015 leader, Actavis, started only three studies in 2016 and tumbled out of the top 10, which is unsurprising in view of its recent acquisition by Teva and integration into the business of the latter. We expect to consider them together in 2017.

Another point to notice is that Sanofi and Teva — both also active participants of the Russian IMCT market — have been among the leading sponsors of local trials in recent years. Sanofi was 6th in the rating of international sponsors in 2015, and Teva was 14th. In 2016 they fell back to 12th-13th (Sanofi) and 14th-17th (Teva).

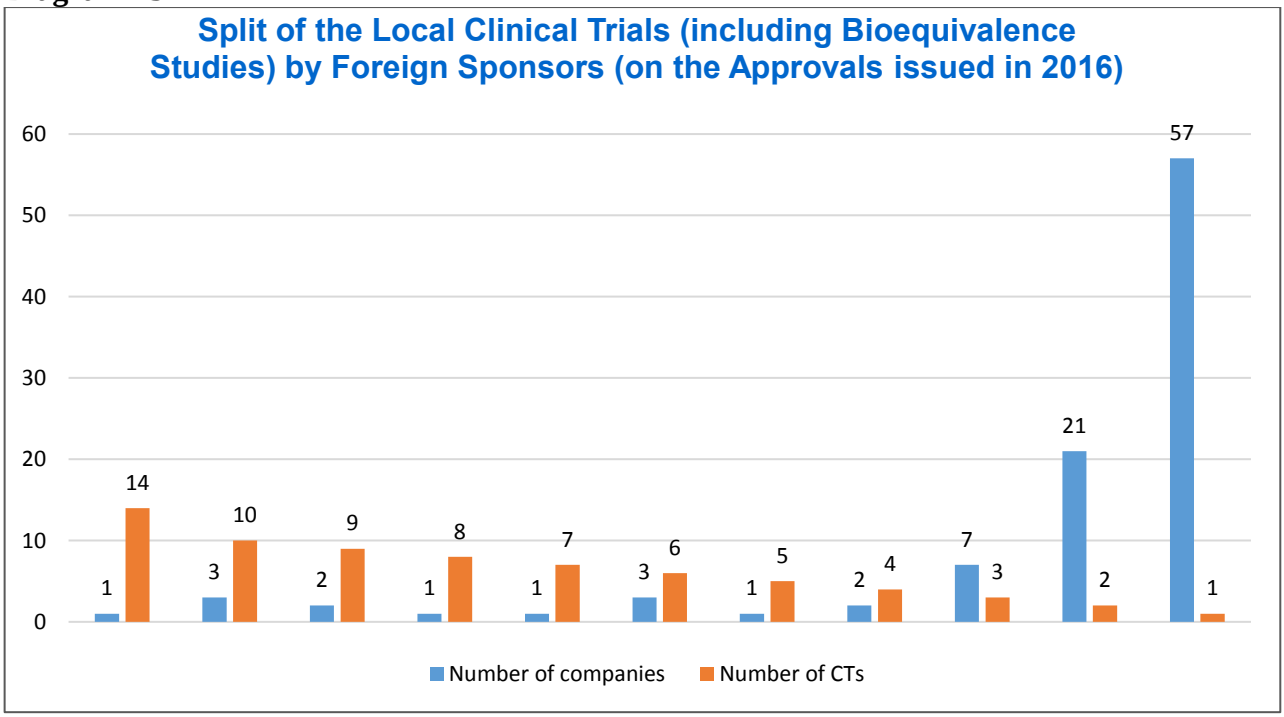
Table 15

Ranking of Leading Foreign Sponsors on Approvals for Local CTs and Bioequivalence Studies, 2016					
Ranking	**Company**	**Conducted by themselves**	**Conducted by CROs/other representatives**	**Total**	**Number of CTs; Ranking in 2015**
1	Dr. REDDY's Lab.	14	–	14	6 CTs; 7-8
2-4	Teva	10	–	10	7 CTs; 5-6
2-4	Hetero Labs Limited	10	–	10	5 CTs; 9-14
2-4	Polpharma	–	10	10	5 CTs; 9-14
5-6	Sanofi group	9	–	9	4 CTs; 15-17
5-6	World Medicine	–	9	9	6 CTs; 7-8
7	Gedeon Richter	8	–	8	3 CTs; 18-23
8	Simpex Pharma	–	7	7	2 CTs; 24-40
9-11	KRKA	6	–	6	11 CTs; 2
9-11	Micro Labs.	4	2	6	9 CTs; 4
9-11	Lupin Limited	–	6	6	2 CTs; 24-40

Data from www.grls.rosminzdrav.ru

Diagram 13 shows distribution in 2016 of approved local trials (including bioequivalence studies) with foreign sponsors. A total of 99 foreign companies were involved (75 in 2015).

Diagram 13



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies, domestic sponsors

The rating of Russian companies that initiated the most local trials, including bioequivalence studies, in 2016 is presented in Table 16. Atoll retains first place and the runners-up are also unchanged from 2015 (JSC Pharmasintez, CJSC Biocad and CJSC Canonfarma Production, although the latter shares 4th-5th place with Sotex).

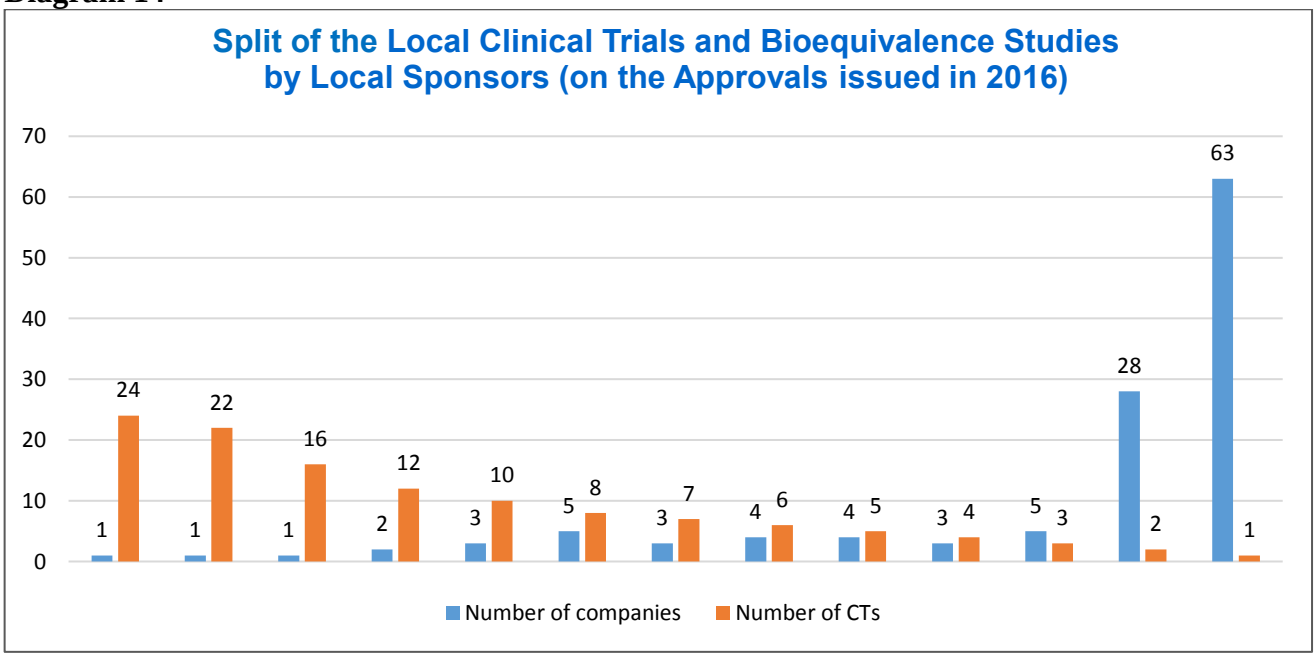
Table 16

Ranking of Leading Local Sponsors on Approvals for Local Clinical Trials and Bioequivalence Studies, 2016					
Ranking	**Company**	**Conducted by themselves**	**Conducted by CRO**	**Total**	**Number of CTs; Ranking, 2015**
1	Atoll	24	–	24	29 CTs; 1
2	Pharmasyntez (incl.Pharmasyntez-Tyumen, Pharmasyntez-Nord and RCI Syntez)	21	1	22	21 CTs; 2
3	Biocad	16	–	16	17 CTs; 3
4-5	Canonpharma Production	11	1	12	13 CTs; 4
4-5	Sotex Pharm Firm	11	1	12	3 CTs; 24-28
6-8	Nativa	10	–	10	4 CTs; 18-23
6-8	Rus Biopharm	10	–	10	2 CTs; 29-52
6-8	Severnaja Zvezda	10	–	10	4 CTs; 18-23
9-13	GEROPHARM (including GEROPHARM-Bio)	8	–	8	3 CTs; 24-28
9-13	Medisorb	8	–	8	2 CTs; 29-52
9-13	Obolensky Pharmaceutical Company (OBL Pharm)	8	–	8	8 CTs; 6-9
9-13	Promo-med RUS	8	–	8	n/a
9-13	Pharmstandard	8	–	8	5 CTs; 13-17

Data from www.grls.rosminzdrav.ru

Diagram 14 shows local trials by Russian sponsors. In 2016, such trials were initiated by 123 companies, which is one more than in the previous year.

Diagram 14



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies, CROs

In our previous analysis of CROs specializing in local trials, we ranked them in separate ratings based on the sponsors of such trials (domestic or foreign). This year we have decided to unite such CROs into a single group, as the companies involved are mainly the same. However, Table 17 shows the number of trials conducted in 2016 by foreign and Russian sponsors separately.

We note that Synergy Research Group, which takes 10th place in the rating of CROs by local trials was also in 10th place among organizations participating in IMCTs. So the company once again showed outstanding versatility, as only very few CROs can successfully meet the very different data quality requirements of IMCTs and local trials.

We also draw attention to Probiotec Medical Centre, which shared the 7th-9th lines of the rating with two other companies. This company was also a leader among medical institutions specializing in bioequivalence studies, where it took 3rd-4th place. The company does indeed position itself both as a medical center and as a CRO. A check in the Ministry of Health register showed that one of four trials involving Probiotec as a CRO was conducted at the same center. It would be interesting to know how monitoring was performed and whether there was any conflict of interest in this instance. However, this is a matter for regulatory bodies.

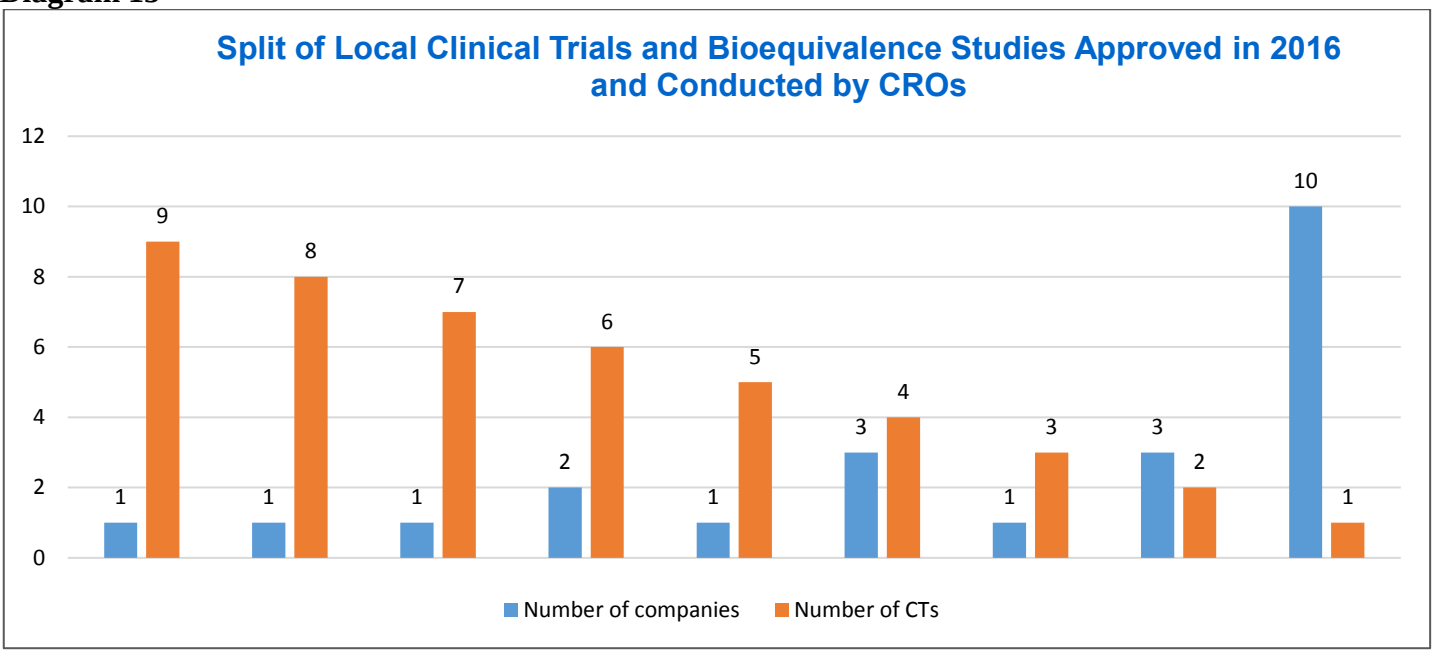
Table 17

Top-10 CROs Involved in the Local CTs and Bioequivalence Studies (on Approvals Issued in 2016)						
Ranking	**Company**	**Number of CTs of foreign sponsors**	**Number of CTs of local sponsors**	**Total number of local CTs, 2016**	**Number of sponsors**	**Number of local CTs, 2015**
1	OCT	2	7	9	8	3
2	IPHARMA	3	5	8	7	8
3	Atlant Clinical	5	2	7	3	2
4-5	ARS PharmRussia (formerly - «Agency for Registration Support of Medicines»)	6	–	6	4	3
4-5	Medical Development Agency (MDA)	5	1	6	4	18
6	R&D PHARMA	–	5	5	2	1
7-9	PharmaReg	4		4	3	7
7-9	Expert & Legal Centre for Pharmaceuticals and Medical Devices	3	1	4	4	2
7-9	Medical Center Probiotech	–	4	4	4	14
10	Synergy Research Group	1	2	3	2	1

Data from www.grls.rosminzdrav.ru

Diagram 15 shows the distribution of local trials among CROs. In total, according to the Ministry of Health register, 23 contract research organizations were involved in such trials in 2016.

Diagram 15



Data from www.grls.rosminzdrav.ru

TIMEFRAMES FOR OBTAINING APPROVALS

ACTO has conducted monitoring of the time required for obtaining approval documents since it has beed founded. For the year 2016 this monitoring was for the first time carried out jointly with the Association of International Pharmaceutical Manufacturers (AIPM). A total of 35 companies — sponsors and CROs — took part in the survey. The sample for clinical trials was 295 applications and the sample for all other types of approvals was 2,246 applications.

The overall results are presented in Table 18. For more details on the results, including the duration of each procedure by individual steps, please see the ACTO website.

Table 18

Timeframes for Obtaining Approvals, 2016					
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	99	39	326	295
To Import Medicines	8/12	14	3	36	446
To Import/Export Biosamples	13/19	18	4	59	751
To Make Amendments to the Protocol	34/48	44	7	90	416
Other Approvals (to Prolong Clinical Trials, to Include New Sites, to Enroll Additional Patients, etc.)	25/35	29	7	98	633
Total Time to Obtain Approvals to Conduct Clinical Trials and to Import/Export	54/76	117	–	–	–

Data from timeframes monitoring of ACTO and AIPM

We should note that the average time for obtaining approval to conduct a trial, shown in Table 18 (99 days), was calculated for all applications included in the survey, regardless of whether or not consideration of an application involved requests from expert institutions for further information, and the time for such a request to be made and for the company to reply to it was included in the calculation. Officials of the Ministry of Health have expressed doubts and objections regarding the calculation methodology, since they generally exclude from such calculations the time required for the applicant to reply to a request. This is quite logical from the point of the Ministry of Health, which is only interested in the duration of its actions. However, the industry needs to know the total time required to obtain an approval, as the start the trial depends on it. To avoid further disputes over the correctness of the calculation methodology, we make the calculation in four different ways (for the second consecutive year):

– 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 required to reply to the request;

– average time calculated for all applications, excluding time required to reply to expert requests;

– average time calculated for all applications regardless of whether or not they received expert requests, including the time required to reply. This is the average time given in the above table, and it is the time we use to analyze changes from year to year, since it is our original method of calculation.

The results of all four calculation methods are given in Table 19.

Table 19

Method for calculation of average time	Average time	Sample size	Comment
Time for applications, which received no expert requests	66	127	127 CT applications (43.1%) were dealt with without requests or critical remarks, but 10 of these (3.4%) were refused without requests or critical remarks. 168 applications (56.9%) received one or two requests and/or critical remarks
Time for applications, which received expert requests *(time to reply to the request is included)*	123	168	
Time for obtaining approvals for all applications *(in case of an expert request, the time required to reply is excluded from the calculation)*	73	295	
Time for obtaining approvals for all applications *(in case of an expert request, the time required to reply is included in the calculation)*	99	295	

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

Analysis of the results shows little change from 2015 (Table 20). The average time for obtaining approvals for the conduct of trials remained almost the same (99 days versus 98 days in 2015). The time for obtaining permits for import of medicinal products increased by one day (14 versus 13), whereas the time for obtaining permits for export of biological samples decreased by one day (18 versus 19). In 2016 applicants had to wait a little longer to obtain approval for the extension of trials, enroll additional patients and to obtain other additional permits (29 days versus 24 days in 2015). The time for approving amendments to a clinical trial protocol was reduced by eight days in 2016 (44 versus 52).

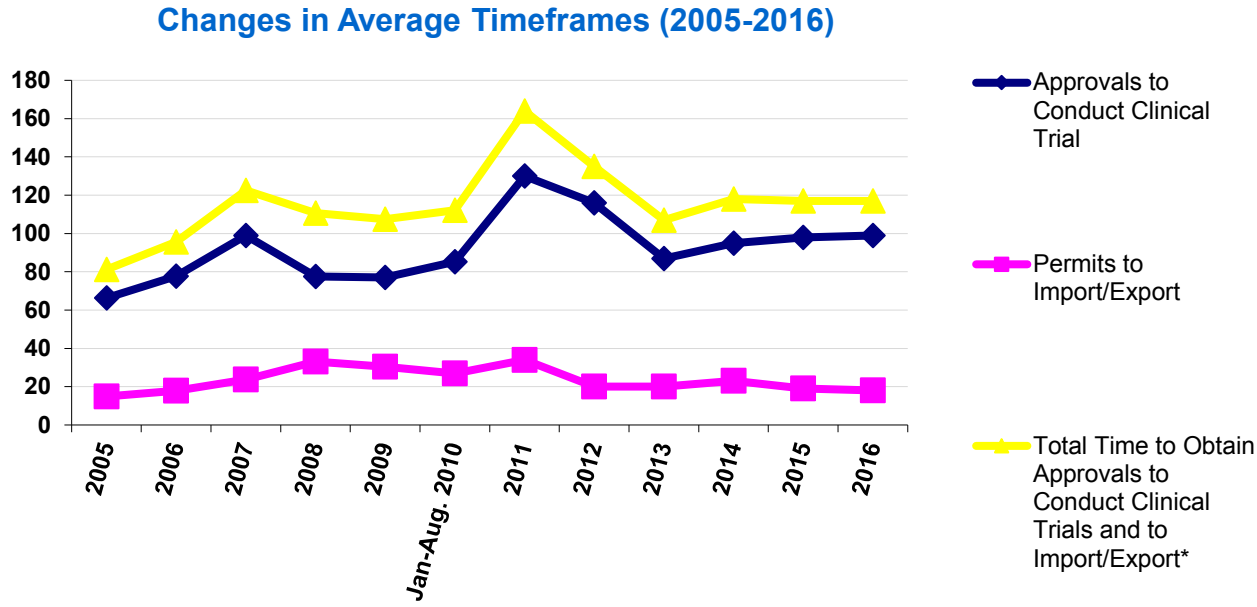
Table 20

Average Timeframes for Obtaining Approvals, 2016 vs. 2015			
Type of approval	**2016**	**2015**	**2016 vs. 2015, %**
To Conduct Clinical Trials	99	98	1.0%
To Import Medicines	14	13	7.1%
To Import/Export Biosamples	18	19	-5.6%
To Make Amendments to the Protocol	44	52	-18.2%
Other Approvals (to Prolong Clinical Trials, to Include New Sites, to Enroll Additional Patients, etc.)	29	24	17.2%

Data from timeframes monitoring of ACTO and AIPM

Diagram 16 shows changes in the time required for obtaining main approval documents to start a trial.

Diagram 16



*It's the sum of average timeframes for issuing approvals to conduct clinical trials and average timeframes for issuing permits to import/export biological materials or to import drugs (the highest number was taken into account)

Data from timeframes monitoring of ACTO

Table 21 presents detailed statistics on overruns of the legally established time for obtaining approval documents.

Table 21

Violations of Timeframes, 2016 vs. 2015								
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	2016 г.	19.7%	80.3%	73.2%	4.7%	1.6%	0.8%	0.0%
	2015 г.	8.2%	91.8%	67.2%	20.9%	3.7%	0.0%	0.0%
To Import Medicines	2016 г.	42.2%	57.8%	34.1%	20.9%	2.7%	0.2%	0.0%
	2015 г.	59.1%	40.9%	22.4%	14.5%	2.5%	1.2%	0.3%
To Import/Export Biosamples	2016 г.	65.2%	34.8%	29.2%	5.2%	0.3%	0.1%	0.0%
	2015 г.	57.2%	42.8%	33.1%	7.6%	1.9%	0.2%	0.0%
To Make Amendments to the Protocol	2016 г.	60.6%	39.4%	34.1%	5.3%	0.0%	0.0%	0.0%
	2015 г.	47.3%	52.7%	42.6%	9.1%	0.9%	0.0%	0.0%
Other Approvals (to Prolong CTs, to Include New Sites, to Enroll Additional Patients, etc.)	2016 г.	86.9%	13.1%	11.5%	0.8%	0.8%	0.0%	0.0%
	2015 г.	92.1%	7.9%	6.7%	1.0%	0.2%	0.0%	0.0%

Data from timeframes monitoring of ACTO and AIPM

We should explain that, when calculating the time necessary for issuing the main approval for conducting a clinical trial, only those applications were included, which did not receive expert requests (i.e. the average time was calculated using the first method and was 66 days).

For comparison, the table also shows data for 2015. It can be seen that the situation has improved overall. In 2016, there were no applications, consideration of which took more than four times the legally established limit and very few applications were considered for more than three times longer than the limit.

The number of approvals for conducting trials that were issued within the legal limit more than doubled (19.7% versus 8.2%). However, this percentage remains disappointingly low. The situation for all other types of approvals is much better.

EXTENSION OF ACCREDITATION OF MEDICAL INSTITUTIONS TO CONDUCT CLINICAL TRIALS

The accreditation certificates of a very large number of clinics (more than 700) to conduct clinical trials expired in 2016. Most of the expiries were during the summer, which is a vacation period. So last year was highly challenging for the Russians regulatory system.

The accreditation system established by the Law "On Circulation of Medicines", became effective in 2011. In total, 735 medical institutions were accredited by the Ministry of Health in that year and most of them (468 clinics) received their certificates in August 2011. The accreditation validity period is 5 years, after which a renewal is required. So a large number of certificates needed renewal in the summer of 2016.

The problem was aggravated by the fact that the Russian healthcare system has undergone a large number of structural reforms since 2011. Many medical institutions have had to change their organizational and legal form, as well as their name. A large number of state healthcare institutions (SHI) became budgetary (SBHI), public (SPHI), or autonomous (SAHI) state healthcare institutions. Municipal healthcare institutions (MHI) were converted to budgetary (MBHI) or autonomous (MAHI) municipal healthcare institutions. As a result of the reform of the Russian Academy of Sciences, former institutions of the Russian Academy of Medical Sciences and the Russian Academy of Sciences were transformed into Federal State Budgetary Scientific Institutions (FSBSI) or Federal State Budgetary Institutions (FSBI). The changes also affected institutions of higher education: State Educational Institutions of Higher Professional Education became Federal State Budgetary Educational Institutions of Higher Professional Education, etc. Finally, institutions whose parent organization was the Ministry of Healthcare and Social Development became institutions of the Ministry of Health of Russia.

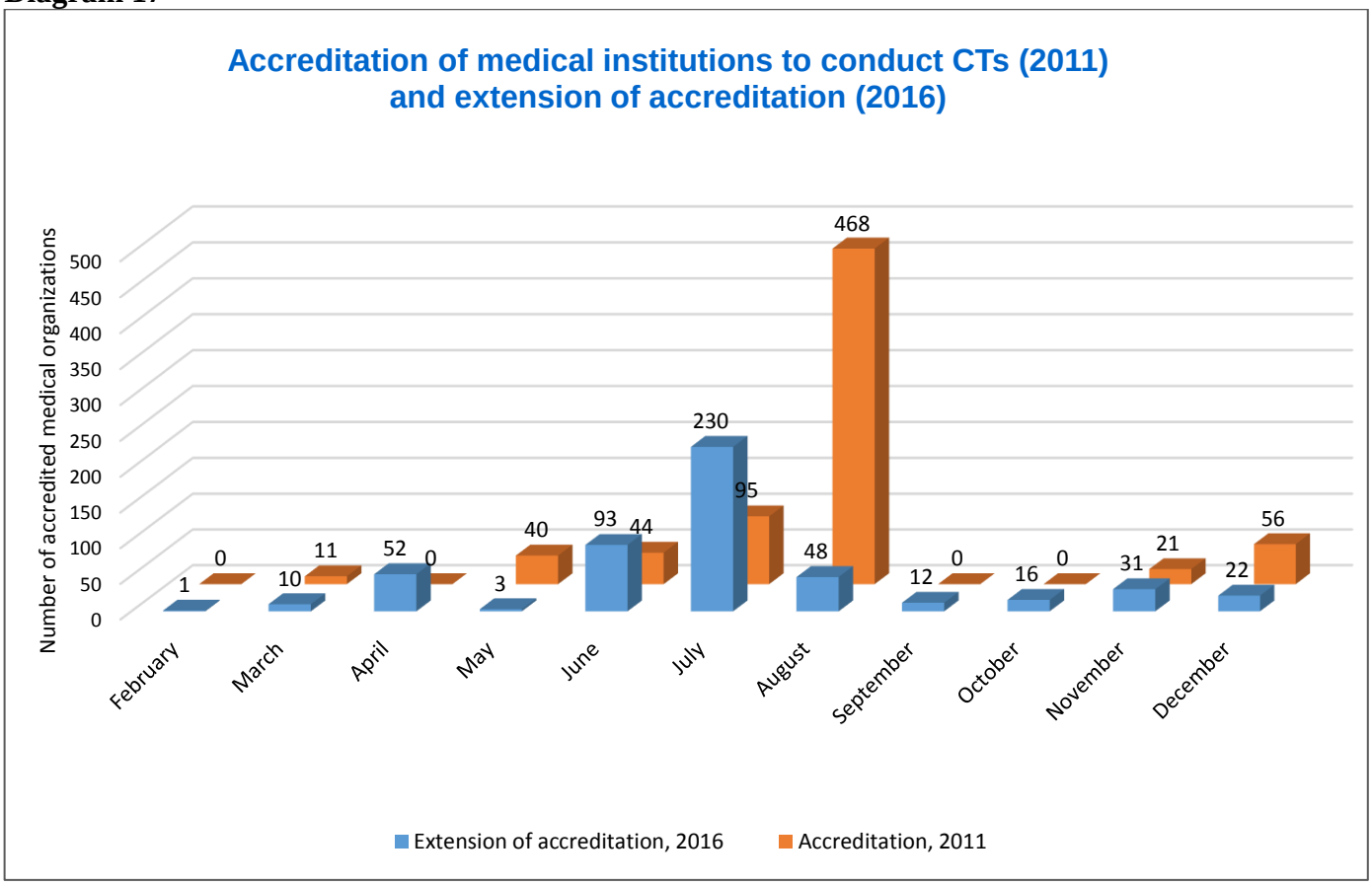
Many of the affected medical institutions asked whether these changes entailed the need for urgent changes to their accreditation certificates. This was not in fact necessary: previously issued licenses and approval documents (including accreditation certificates for the right to conduct clinical trials) were considered valid until their expiration date. Some clinics decided nevertheless to make changes to their accreditation at once, though the term of validity of existing certificates has not necessarily been extended. Most institutions preferred to deal with both matters together upon expiry of their initial accreditation period. So many clinics had to make changes to their data previously entered in the register in addition to extending the validity of their certificates.

Naturally enough, the industry was seriously concerned whether the system was prepared for such a challenge and capable of dealing with it. Details of the procedure were not clear, as the only guidelines were a resolution of the Russian Government, which stipulated the need to extend accreditation certificates five years from the date of their issue, but did not describe how this was to be done. The details were to be worked out by the Ministry of Health but no action had been taken by the beginning of 2016. After making several requests to the Ministry, in February 2016 ACTO decided to wait no longer and issued its own recommendations to medical institutions regarding accreditation extension. ACTO members, sponsors and CROs have done much work in informing clinics and carrying out follow-up to ensure that applications are submitted on time and successfully processed.

The system started to work only in March 2016 and there were instances of mismanagement. For example, the Ministry of Health initially tried to rule that applications would not be accepted earlier than 1.5-2 months before the expiry of certificates. ACTO, on the contrary, encouraged medical institutions to submit applications in advance, especially clinics, whose accreditation validity period expired in August 2016, the intention being to even out the flow of applications and thereby reduce the burden on the Ministry of Health, which was bound to increase significantly in July. All credit to the Ministry's Department of State Regulation of Circulation of Medicines, which grasped the scale of the task and made great efforts to ensure that that the system coped with this challenge to the clinical trial process. However, obstacles were created by the Ministry's legal department, approval of which was required in order for accreditations to be issued. The start of the process was therefore marred by delays in signing executed documents and by the imposition of non-statutory requirements on applicants. However, later (apparently realizing the potential consequences of attempting to dam such a fast-flowing river), the legal department liberalized its approach and the process went more quickly. A total of 159

clinics were re-accredited in June and a further 230 in July (Diagram 17). It can be fairly said that the Ministry of Health worked very hard in the summer of 2016 and met the challenge successfully.

Diagram 17



Data from: monitoring by ACTO

A total of 518 institutions obtained extension of their accreditation validity in 2016 (including those, which obtained new certificates due to change of their organizational and legal form). On the whole, the industry was pleased with the result. However, it should be recalled that 735 institutions were accredited in 2011. So what happened to the other 217? Some of them, which decided to make changes before the expiration of their certificates, managed to extend the accreditation period as early as the end of 2015. Others ceased to exist, as the reforms described above led to the merger of several institutions in some cases. A large share of the "missing clinics" simply did not apply for extension, since they had not been able to integrate into the clinical trials system and obtain projects. And there were a few, which failed to meet the time limit for filing documents, some for objective reasons, others out of negligence. These cases were the hardest to deal with, particularly if they had trials underway. Clinics, which were very late in applying, had to file for accreditation over again, submitting a full package of documents, as in primary accreditation. Some of them were only able to restore their accreditation at the beginning of 2017.

The process will certainly continue in 2017, since not all institutions were accredited for the first time in 2011. Many of them received certificates in 2012, 2013 or later and therefore have the renewal of their certificate yet to come. In total, according to the Ministry of Health register, more than 1000 institutions have been accredited in Russia. However, the peak of demand for renewal has clearly passed and, with it, a tough challenge for the Russian clinical research market. The Ministry of Health and the industry have risen to the challenge. They will have to rise to it once again in five years' time.

IMPORT OF MEDICINAL PRODUCTS FOR CLINICAL TRIALS

We conclude this issue of the Newsletter with statistics on volumes of medicinal products imported for clinical trials in Russia. These statistics were previously inaccessible for our sector of the pharmaceutical market and became available thanks to data from the analytical company, RNC Pharma.

Table 22 shows overall data for 2015 and 2016, including the shipments themselves as well as taxes and customs fees. For those readers who are not fully familiar with the clinical trials sphere, we should explain that medicinal products intended for clinical trials are non-commercial shipments, i.e., they cannot be sold or purchased and patients receive them free of charge. However, these medicinal products are considered to be commodity and have a value for purposes of customs clearance and taxation.

Table 22

Import of medicinal products to the Russian Federation for clinical trials, 2015 - 2016		
Parameter	**2015**	**2016**
Total value of shipments, rub.	9,925,263,914	10,987,235,644
VAT, rub.	1,036,827,272	1,134,482,465
Customs duties, rub.	399,507,729	343,506,764
Custom fees, rub.	12,308,655	12,232,160
VAT+ customs duties + customs fee, rub.	1,448,643,656	1,490,221,390

Source: RNC Pharma

As can be seen, Russia imported medicinal products for clinical trials to the value of almost 11 billion rubles in 2016. These are not only study drugs, but also comparator drugs and, in some cases, drugs for concomitant therapy. The industry also had to pay almost 1.5 billion rubles as taxes and fees to the Russian budget for medicinal products, which were supplied free of charge to Russian patients (most of these were advanced therapy drugs).

Table 23 and Diagram 18 show the top 10 pharmaceutical companies, whose products were supplied to Russia for clinical trials.

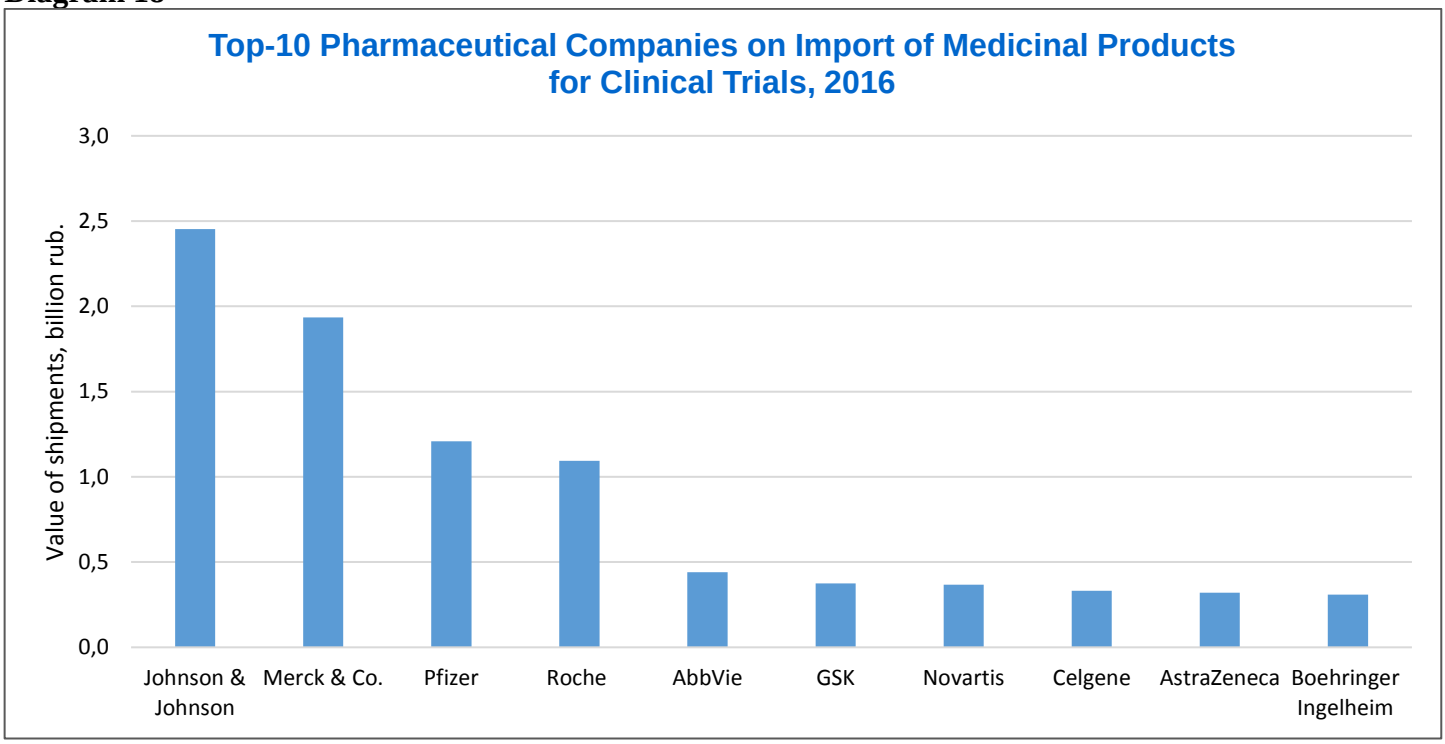
Table 23

Top-10 pharmaceutical companies on import of medicinal products for clinical trials, 2016					
Ranking	**Company**	**Value of shipments, rub.**	**Number of shipments**	**Imported by the companies themselves, %**	**Ranking, 2015**
1	Johnson & Johnson	2,453,319,013	155	45.2%	2
2	Merck Group/Merck Sharp & Dohme	1,934,254,727	163	79.5%	7
3	Pfizer	1,207,481,730	135	82.4%	1
4	Roche	1,092,992,780	225	27.2%	3
5	AbbVie	440,112,396	160	–	5
6	GSK	375,109,731	150	–	4
7	Novartis	366,888,804	157	86.9%	10
8	Celgene	331,473,626	44	–	6
9	AstraZeneca	321,037,175	109	0.1%	13
10	Boehringer Ingelheim	308,356,002	108	–	15

Source: RNC Pharma

We need to clarify here that not all these medicinal products were delivered by the companies themselves. Contract research organizations often act as the importers. Studies by competitors should also be taken into account. In such cases, a drug of company A can be used (and therefore imported) by company B as a reference drug or for concomitant therapy.

Diagram 18



Source: RNC Pharma