ACTO

ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

ACTO NEWSLETTER № 12

Summary of 2015 results

MOSCOW 2016

CONTENTS

SUMMARY

As usual, we begin our summary of the year by looking at general statistics. In 2015 the Ministry of Health issued 804 approvals to conduct clinical trials (7.2% more than in 2014). Of these approvals, 289 were approvals for international multicentre clinical trials — IMCTs (282 in the previous year).

The increase in the number of trials is visible in almost all categories of trials. The number of bioequivalence studies of Russian generics grew by 8.5% (153 approvals compared to 141 in 2014). The number of bioequivalence studies initiated by foreign sponsors increased by 16.3% (143 approvals compared to 123). The sector for local trials by Russian sponsors also grew (167 compared to 142). The only type of trial for which the number of approvals issued is down, compared to the previous year, was the sector of local trials by foreign sponsors (52 approvals compared to 62 the previous year).

Looking at the dynamics of the market structure, we remind readers that it first changed significantly in 2012 with the adoption of the law "On Circulation of Medicines". This was first seen as a significant growth (from 1.8% in the pre-reform period up to 17.8% in 2015) in the share of bioequivalence studies by foreign sponsors. This growth is due to the requirement to conduct local trials in order to register a medicinal product in Russia. The growth is actually not that significant in the share of other types of local trials and bioequivalence trials. All of this together led to a significant decline in the percentage of IMCTs. While in the pre-reform period international trials accounted for nearly 60% of the market, by 2015 this sector had diminished to 35.9%.

The next subject of this edition is the analysis of the market structure by therapeutic areas. Almost one-third (32.3%) of approvals in 2015 for IMCTs were for oncological medicinal products. First place among trials for generics and biosimilars went to medicinal products intended to treat infectious diseases (22.1% in foreign-sponsored trials and 19.7% in Russian-sponsored trials).

In this edition of the newsletter we have also analysed how IMCTs are distributed across Russia. The first place out of all regions of the Russian Federation in terms of number of approvals in 2015 for IMCTs went to St. Petersburg (254 IMCTs). The second place went to Moscow (231 IMCTs), and the third — to the Republic of Tatarstan (102 IMCTs). The ranking of Russian regions by their active participation in IMCTs per 1 million inhabitants was rather different. In the first place was the Yaroslavl region (54.3 IMCTs per 1 million population). St. Petersburg took the second (48.9) place, and the third place went to the Smolensk region (46.6). By this reckoning, Moscow was only in the 16th place (18.9 IMCTs per 1 million inhabitants).

In the next section of the newsletter we looked at the relationship between the trials conducted by sponsors themselves and those for which a contract research organisation (CRO) has been contracted. In this section we present a ranking of the most active pharmaceutical companies and CROs in individual market sectors.

By tradition, in a separate section of this newsletter we highlight the waiting periods for Russian Ministry of Health issuance of various approval documents essential for conducting clinical trials. The average timeline to obtain approval to conduct clinical trials was 98 days (95 in 2014), approval to import medicinal products was 13 days, and approval to export biological samples was 19 days. In general, we can note that for all types of document issuance with the exception of approval to conduct a trial, the situation with timelines improved over the year.

We wrap up the newsletter with what is almost a detective story. Having heard the loud announcement about development of a Russian vaccine against Ebola virus, we decided to look into what this all means.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

In 2015 the Ministry of Health issued 804 approvals to conduct clinical trials. This was up 7.2% from 2014 (Table 1).

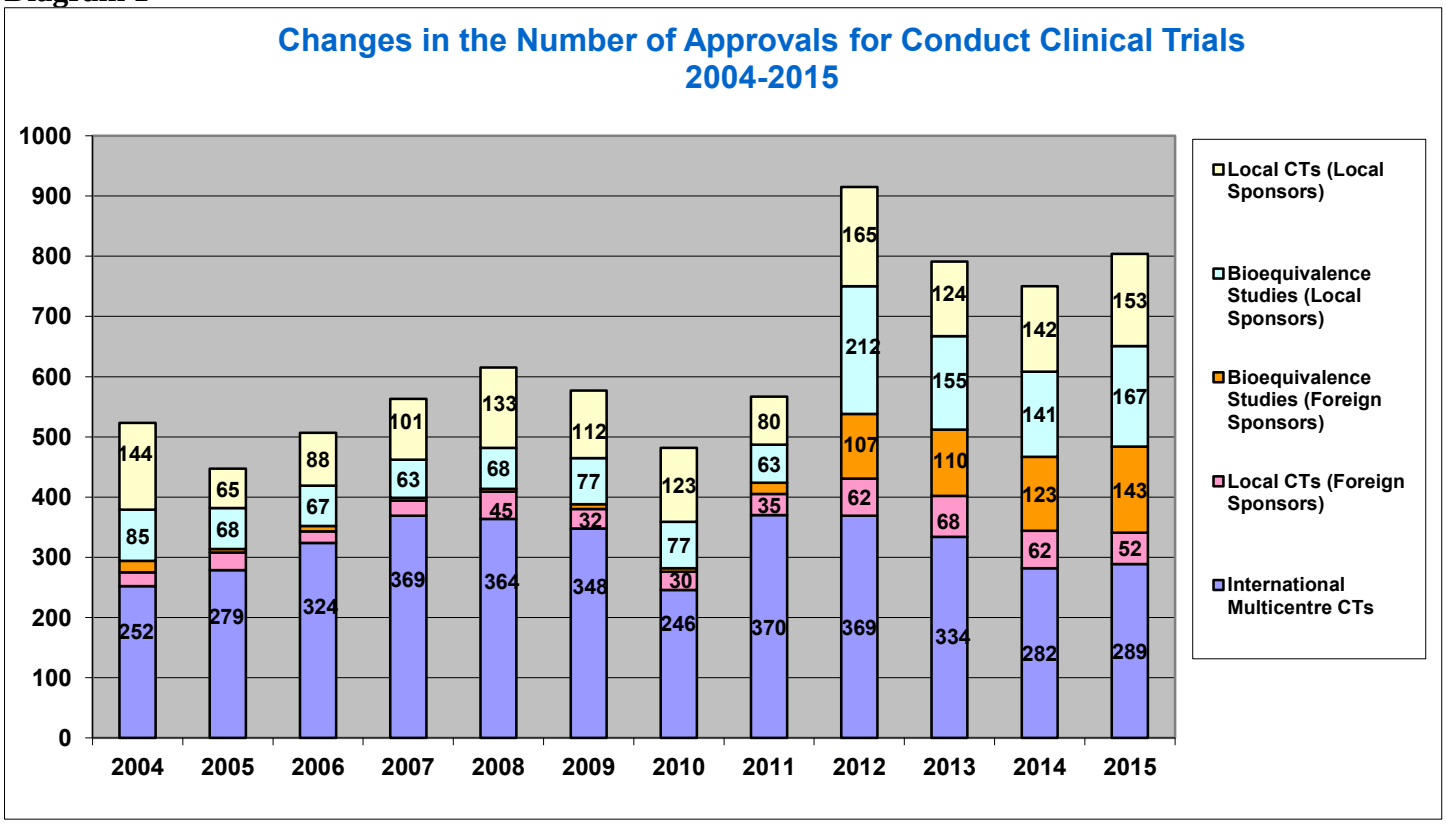
The increase was seen in almost all sectors. However, growth was minimal in the IMCT sector – just 2.5% (289 approvals compared to 282 in the previous year). The number of approvals for bioequivalence studies initiated by Russian sponsors grew by 8.5% (153 compared to 141 in 2014). Even greater was the 16.3% growth in the number of bioequivalence studies of foreign generics (143 approvals compared to 123). The top growth of 17.6% was in the sector of local trials of efficacy and safety conducted by Russian sponsors (167 compared to 142). Only in the case of local trials by foreign sponsors did we see a drop in the number of approvals issued. The difference between 2015 and 2014 was 10 approvals, or 16.1% (52 compared to 62).

Table 1

Approvals for Conduct Clinical Trials: 2015 vs. 2014						
Year	**Total**	**International Multicenter CTs**	**Local CTs (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CTs (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
2015	**804**	**289**	**52**	**143**	**167**	**153**
2014	**750**	**282**	**62**	**123**	**142**	**141**
2015 vs. 2014, %	**7,2%**	**2,5%**	**-16,1%**	**16,3%**	**17,6%**	**8,5%**

Data from www.grls.rosminzdrav.ru

Diagram 1



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

In Diagram 1 we show the dynamics of the Russian clinical trials market over the past 12 years.

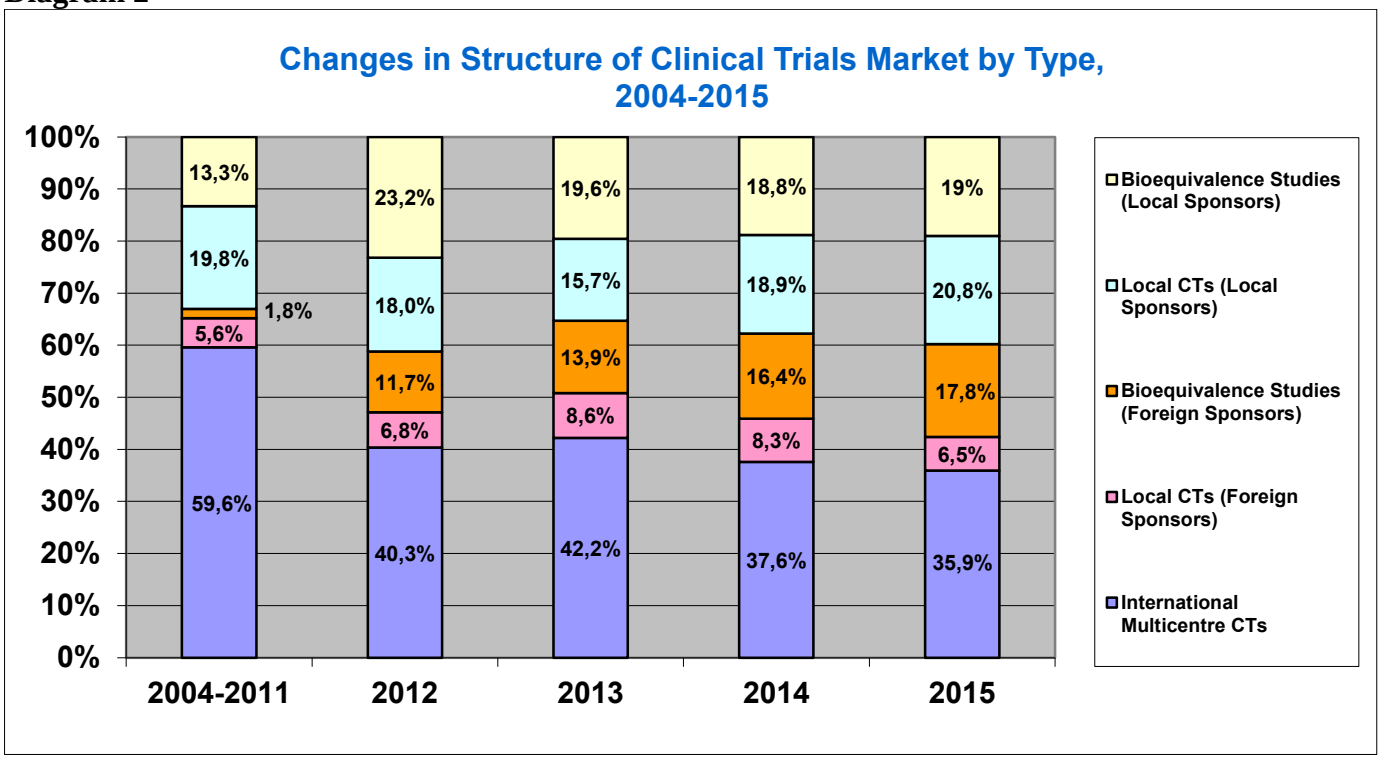
We remind readers that the drop in the number of projects in 2010 was as a result of the adoption of the law “On Circulation of Medicines”. At that time, due to the transfer of approval issuing authority from Roszdravnadzor to the Ministry of Health and Social Development, the system was not functioning for an entire quarter.

The sharp growth in the total number of trials in 2012 (in the first place due to the increasing share of local trials and bioequivalence studies) was a result of adoption of the aforementioned law, and the announcement in the country of the focus on substituting imports. True, in the following two years the total number of trials once again fell. In 2014 this hit first of all the international projects. That year saw the biggest drop (excluding the previously mentioned 2010) in numbers of IMCTs – by 15.5%. As a result of this fall, the Russian IMCT market fell back to 2005 levels. Last year, 2015, showed a slight improvement in the situation. However, the number of approvals granted last year for IMCTs still fell short of the 300 trial mark.

STRUCTURE AND DYNAMICS OF THE CLINICAL TRIALS MARKET BY TYPE

We draw your attention to the changes in the structure of the market by type of trial (Diagram 2). Up to 2012, the relationship between various types of clinical trials was fairly stable, therefore the graph shows the average figures for the period 2004 up to 2011. The first significant changes in the market structure came in 2012, when the market felt the full effect of the changes brought on by the law "On Circulation of Medicines". In the first place, this was seen as significant growth in the share of bioequivalence studies by foreign sponsors (from 1.8% in the pre-reform period up to 17.8% in 2015). This growth is due entirely to the implementation of requirements to conduct local trials in order to register a medicinal product in Russia. Also demonstrating growth, though not as significant, were the shares of other types of local trials and bioequivalence studies. All of this together lead to a decline in the share of IMCTs. Therefore, while in the pre-reform period international trials accounted for almost 60% of the market, by 2015 this sector had declined to 35.9%.

Diagram 2



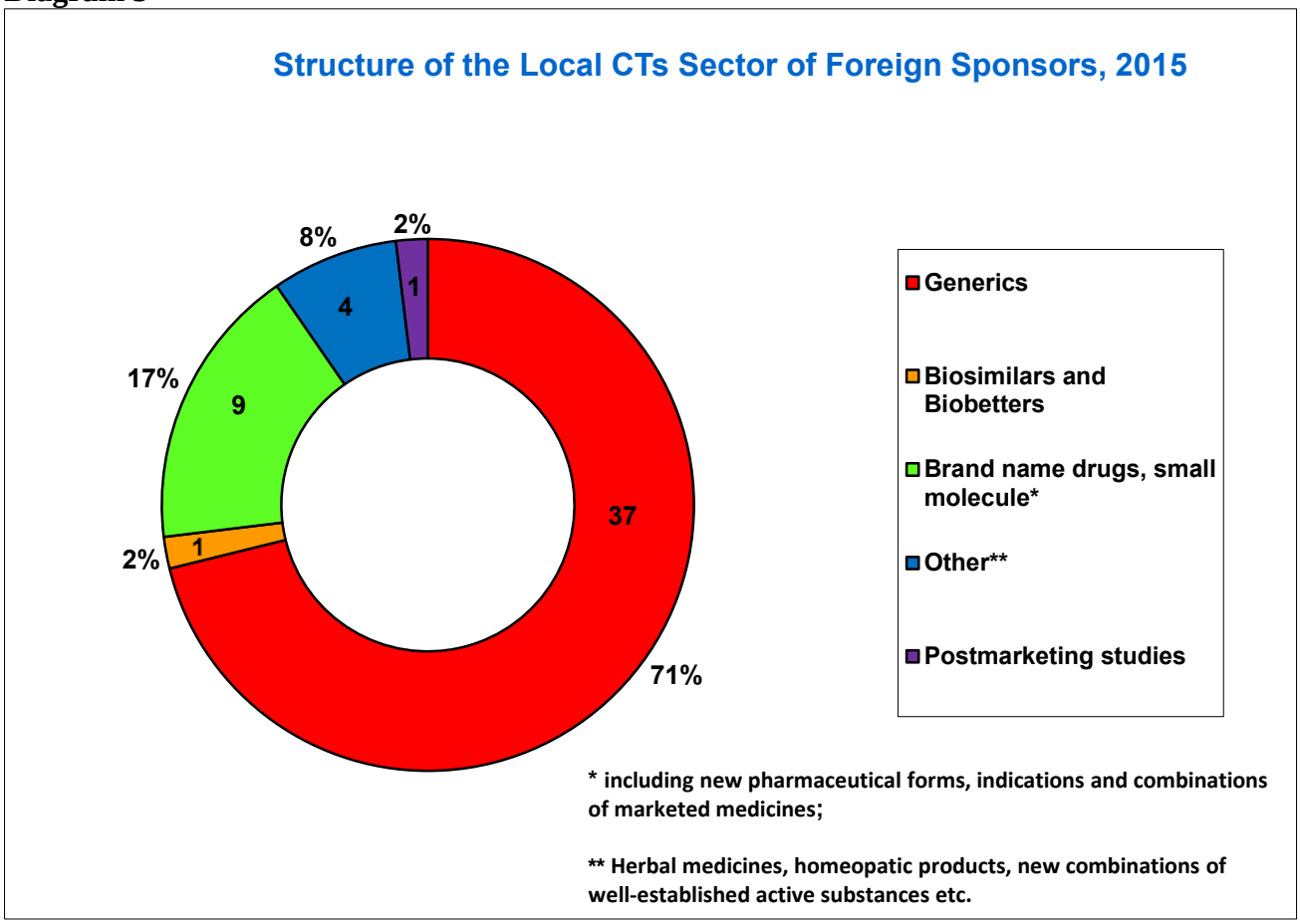
Data from www.grls.rosminzdrav.ru, www.roszdravnadzor.ru

A year ago after the adoption of further amendments to the law "On Circulation of Medicines", we forecasted a decrease in the share of local trials by both foreign and domestic sponsors. Our basis for this was the change due to come into force on January 1, 2016, to the requirement to conduct local trials of so-called "therapeutic equivalence" for a range of generic medicinal products for which it was not possible to conduct bioequivalence studies. We expected that several manufacturers would put their projects on hold earlier, and we can see a drop already in the numbers for 2015. However as we can see, a small decrease came only in the sector of local trials by foreign sponsors (6.5% compared to 8.3% last year). Moreover, that, as we will see further on, is due to the drop in the number of local trials for the original medicinal products, but not for generics.

The share of local trials by domestic sponsors has even grown somewhat (20.8% compared to 18.9% in 2014). However, in the end, the changes to the law have only just come into force. We will have to observe the process going forward.

Now we will turn to look at the structure of local trials approved in 2015. In Diagram 3 we present the structure of trials by foreign sponsors.

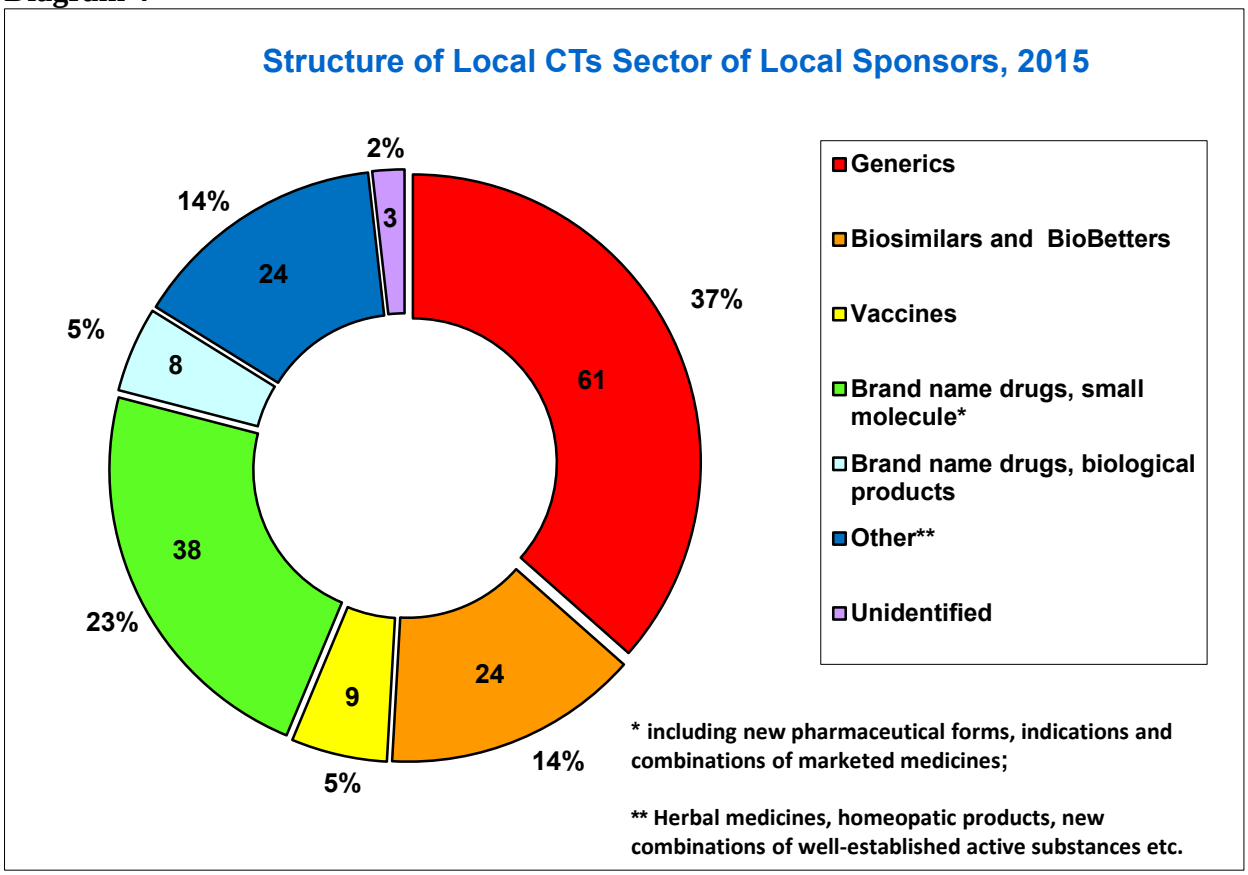
Diagram 3



Data from www.grls.rosminzdrav.ru

As in previous years, the biggest numbers of approvals have been issued in the local sector for generics. In 2014 this figure was sharply down compared to 2013 (49% against 77.9%). However, as we can see in the diagram, in 2015 this figure again rose sharply, reaching 71%. The growth of this share is not due so much to an increase in the number of generics trials (on which there were six more than in 2014), but mainly due to the drop in other sectors. In particular, there was a significant drop in the share of brand name drugs represented by small molecules – 17% (nine trials) compared to 40% (25 trials) in 2014. We remind you that we include in the "brand name drugs" category not only innovative medicinal products (of which there are generally very few), but also combinations of previously registered medicinal products, and new pharmaceutical forms, and medicinal products being studied for new indications.

Diagram 4



Data from www.grls.rosminzdrav.ru

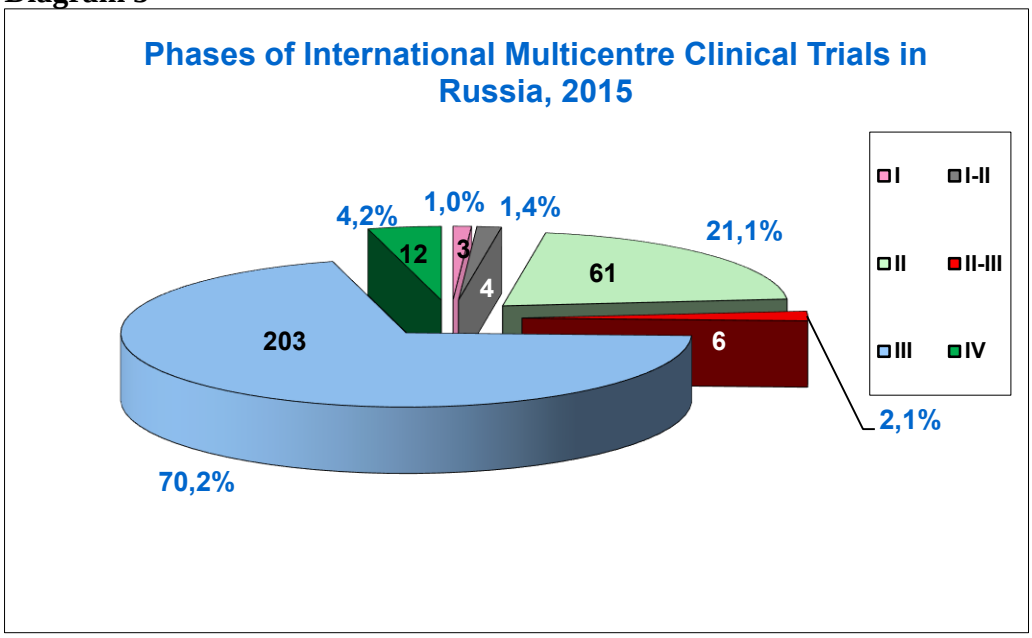
As we can see in Diagram 4, the share of local trials of domestic generics is 37%. It is insignificantly less than in 2014 when it was 39% (in fact the number actually increased slightly from 54 trials the previous year to 61). Trials of brand name drugs, small molecules are, as in the previous year, in second place and accounted for the same share – 23%. There is also an increase in the share of trials that we collectively call "other". This includes herbal medicines, homeopathy, new combinations of well-established substances, and others. The share of "others" in 2015 is 14% (24 approvals) compared to 8% (12 approvals) the previous year.

Similarly, 14% went to local trials of bio-similars and BioBetters. In 2014, these medicinal products accounted for 11% of all local trials by local sponsors.

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

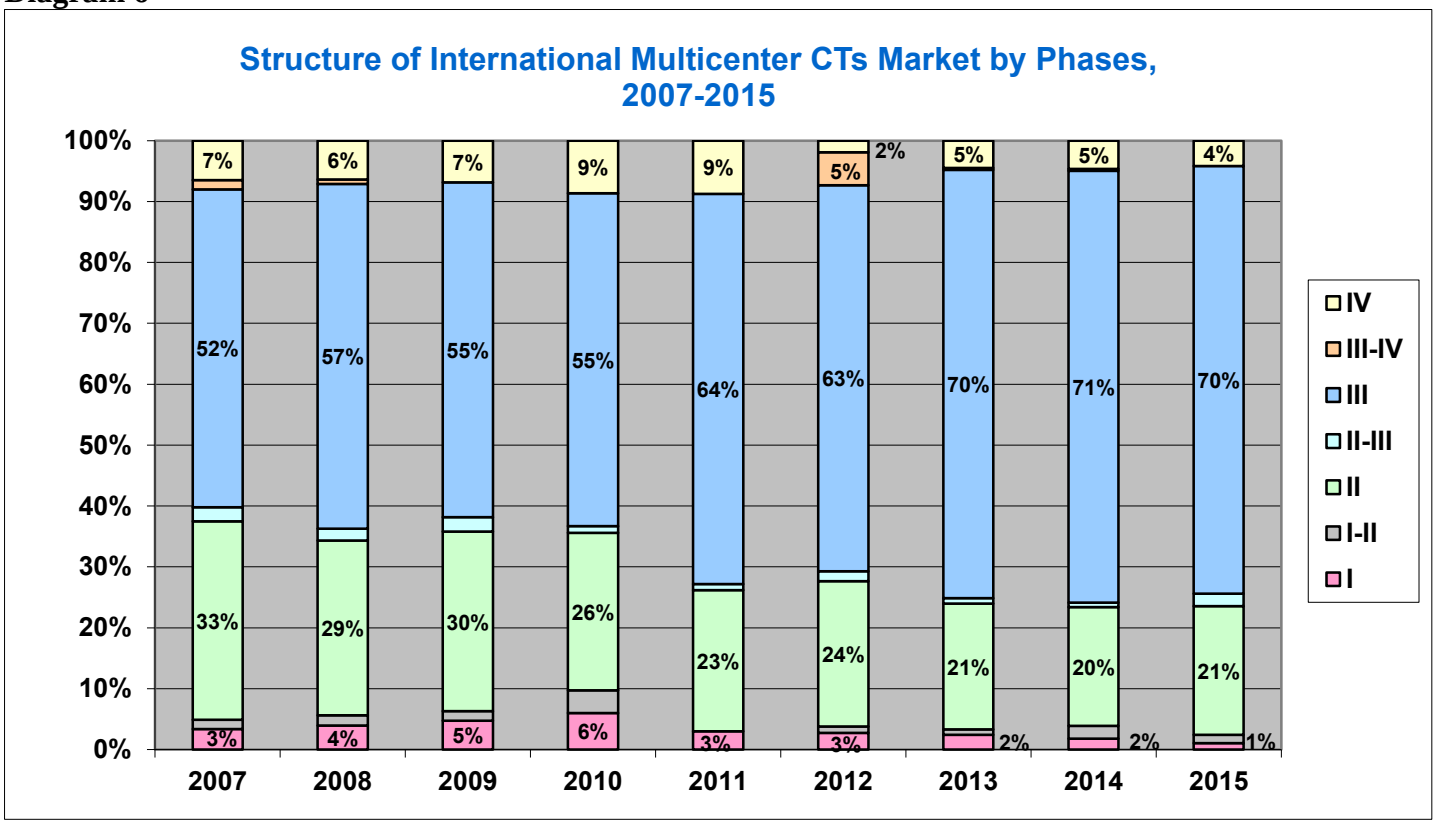
In Diagram 5 we present data on the breakdown of approvals granted in 2015 for IMCTs by phase. Diagram 6 gives a picture of how this breakdown has changed from 2007 to 2015.

Diagram 5



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

Diagram 6



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

We'll go into more detail on early phases. In 2015 three Phase I international trials were approved. All three trials were in oncology. Out of four trials marked as Phase I/II, two were in haematology, one in oncology, and another in dermatology/immunology.

STRUCTURE OF THE CLINICAL TRIALS MARKET BY THERAPEUTIC AREAS

Table 2 presents a picture of the breakdown of approvals in 2015 for IMCTs by therapeutic areas. As in previous years, first place went to oncology medicinal products with a record 92 IMCTs, or 32.3% of all IMCTs (in 2014 there were 64 trials with a share of 22.7%). Second position went to neurology with 26 IMCTs (9.1%). In third place were trials in rheumatology (21 trials, 7.4%).

Table 2

Split of International Multicenter CTs by Therapeutic Areas, 2015 vs. 2014			
Therapeutic Area	**Number of IMCTs, 2015**	**Share (%), 2015**	**Share (%), 2014**
Oncology	**92**	**32,3%**	**22,7%**
Neurology	**26**	**9,1%**	**6,0%**
Rheumatology	**21**	**7,4%**	**9,9%**
Endocrinology	**20**	**7,0%**	**11,3%**
Pulmonology	**20**	**7,0%**	**8,9%**
Infectious Diseases	**20**	**7,0%**	**5,7%**
Dermatology; Immunology	**20**	**7,0%**	**3,9%**
Gastroenterology	**15**	**5,3%**	**4,6%**
Cardiology and Cardiovascular Diseases	**12**	**4,2%**	**9,9%**
Hematology	**9**	**3,2%**	**7,1%**
Psychiatry	**6**	**2,1%**	**1,8%**
Nephrology	**6**	**2,1%**	**1,1%**
Surgery, Anesthesiology, Traumatology	**6**	**2,1%**	**0,0%**
Ophthalmology	**5**	**1,8%**	**1,8%**
Allergology	**3**	**1,1%**	**1,4%**
Gynecology	**2**	**0,7%**	**1,1%**
Urology	**2**	**0,7%**	**1,1%**
Hepatology	**0**	**0,0%**	**0,7%**
Others	**4**	**1,4%**	**1,1%**
TOTAL	**285**	**100,0%**	**100,0%**

Data from www.grls.rosminzdrav.ru

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In Tables 3 and 4 we present a breakdown by therapeutic subject of local trials and bioequivalence studies of generics and biosimilars from foreign and domestic sponsors respectively.

Medicinal products for infectious diseases take the leading position (as in the previous year) among foreign sponsors by (40 trials, or 22.1%). In a second place were medicinal products used in cardiology and in treating cardio-vascular diseases (37 trials, or 20.4%). In a third place were analgesics and anti-inflammatories (15 trials, or 8.3%).

Table 3

Split of Local CTs and Bioequivalence Studies (Generics and Biosimilars) of Foreign Sponsors, 2015 vs. 2014			
Therapeutic Area	**Number of CTs, 2015**	**Share (%), 2015**	**Share (%), 2014**
Infectious Diseases	**40**	**22,1%**	**20,4%**
Cardiology and Cardiovascular Diseases	**37**	**20,4%**	**16,6%**
Analgesic and Anti-inflammatory Medicines	**15**	**8,3%**	**5,1%**
Gynecology	**10**	**5,5%**	**7,0%**
Oncology	**9**	**5,0%**	**3,2%**
Allergology	**8**	**4,4%**	**4,5%**
Gastroenterology	**8**	**4,4%**	**5,7%**
Pulmonology	**8**	**4,4%**	**4,5%**
Psychiatry	**6**	**3,3%**	**5,7%**
Endocrinology	**6**	**3,3%**	**5,7%**
Ophthalmology	**6**	**3,3%**	**4,5%**
Neurology	**6**	**3,3%**	**3,8%**
Urology	**5**	**2,8%**	**3,2%**
Immunology, Transplantology	**4**	**2,2%**	**0,0%**
Surgery, Anesthesiology, Intensive Care	**4**	**2,2%**	**0,0%**
Rheumatology	**4**	**2,2%**	**2,5%**
Otorhinolaryngology	**2**	**1,1%**	**1,3%**
Dermatology	**2**	**1,1%**	**0,0%**
Nephrology	**1**	**0,6%**	**0,0%**
Hepatology	**0**	**0,0%**	**1,3%**
Phthisiology	**0**	**0,0%**	**2,5%**
Others	**0**	**0,0%**	**2,5%**
TOTAL	**181**	**100,0%**	**100,0%**

Data from www.grls.rosminzdrav.ru

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Among domestic sponsors, the first two positions also went to infectious diseases (47 trials, or 19.7%) and cardiology and cardiovascular diseases (29 trials, or 12.2%). In third place were trials for neurological medicinal products (24 trials, or 10.1%).

Table 4

Split of Local CTs and Bioequivalence Studies (Generics and Biosimilars), Conducted by Local Sponsors , 2015 vs. 2014			
Therapeutic Area	**Number of CTs, 2015**	**Share (%), 2015**	**Share (%), 2014**
Infectious Diseases	**47**	**19,7%**	**15,6%**
Cardiology and Cardiovascular Diseases	**29**	**12,2%**	**20,4%**
Neurology	**24**	**10,1%**	**11,4%**
Analgesic and Anti-inflammatory medicines	**21**	**8,8%**	**6,6%**
Endocrinology	**16**	**6,7%**	**3,8%**
Oncology	**15**	**6,3%**	**6,2%**
Pulmonology	**11**	**4,6%**	**2,8%**
Gynecology	**9**	**3,8%**	**0,9%**
Psychiatry	**8**	**3,4%**	**4,7%**
Urology	**8**	**3,4%**	**2,4%**
Hematology	**8**	**3,4%**	**1,4%**
Rheumatology	**8**	**3,4%**	**5,7%**
Gastroenterology	**6**	**2,5%**	**5,7%**
Allergology	**5**	**2,1%**	**1,9%**
Dermatology; Immunology	**3**	**1,3%**	**1,9%**
Anesthesiology, Surgery	**4**	**1,7%**	**0,9%**
Immunology; Transplantology	**3**	**1,3%**	**0,0%**
Otorhinolaryngology	**2**	**0,8%**	**2,4%**
Ophthalmology	**2**	**0,8%**	**1,4%**
Roentgenology, Radiology	**2**	**0,8%**	**0,0%**
Nephrology	**1**	**0,4%**	**1,4%**
Hepatology	**1**	**0,4%**	**0,0%**
Bracing Remedies	**1**	**0,4%**	**0,0%**
Others	**4**	**1,7%**	**2,4%**
TOTAL	**238**	**100,0%**	**100,0%**

Data from www.grls.rosminzdrav.ru

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In Table 5 we present the molecules used in 2015 of greatest popularity with generics developers. The most in-demand components were amlodipin in various combinations (14 trials), then lamivudin separately and in fixed combinations (12 trials). The third and fourth places (each with 10 trials) were split between moxifloxacin and metformin (the last being both in monotherapy and in combinations). The first component was most popular among foreign manufacturers, and the second with local manufacturers.

Table 5

Most Requested INN Used in Clinical Trials of Generics and Biosimilars in 2015				
Substance	**Number of CTs of foreign generics and biosimilars**	**Number of CTs of local generics and biosimilars**	**All clinical trials to a given INN**	**Therapeutic Area**
Amlodipine in fixed combinations	12	2	14	Cardiology and Cardiovascular diseases
Lamivudine (separately and in fixed combinations)	4	8	12	Infectious diseases
Moxifloxacin	6	4	10	Infectious diseases
Metformin (separately and in fixed combinations)	4	6	10	Endocrinology
Zidovudine (separately and in fixed combinations)	3	6	9	Infectious diseases
Valsartan (separately and in fixed combinations)	5	4	9	Cardiology and Cardiovascular diseases
Paracetamol (separately and in fixed combinations)	2	6	8	Analgesic and Antiinflammatory medicines
Ethinylestradiol in fixed combinations	6	1	7	Gynecology
Linezolid	4	3	7	Infectious diseases
Ibuprofen (separately and in fixed combinations)	5	2	7	Analgesic and Antiinflammatory medicines
Rosuvastatin (separately and in fixed combinations)	4	2	6	Cardiology and Cardiovascular diseases
Indapamide (separately and in fixed combinations)	3	3	6	Cardiology and Cardiovascular diseases
Tenofovir (separately and in fixed combinations)	3	3	6	Infectious diseases
Voriconazole	5	1	6	Infectious diseases
Citicoline	2	3	5	Cardiology and Cardiovascular diseases
Telmisartan (separately and in fixed combinations)	3	2	5	Cardiology and Cardiovascular diseases
Mycophenolate mofetil	3	2	5	Immunology; Transplantology
Levocetirizine (separately and in fixed combinations)	4	1	5	Allergology; Pulmonology
Fluticasone (separately and in fixed combinations)	2	3	5	Allergology; Pulmonology
Sildenafil	2	2	4	Urology
Perindopril in fixed combinations	2	2	4	Cardiology and Cardiovascular diseases
Lidocain in fixed combinations	1	3	4	Analgesic and Antiinflammatory medicines
Abacavir (separately and in fixed combinations)	0	4	4	Infectious diseases
Lisinopril in fixed combinations	3	1	4	Cardiology and Cardiovascular diseases
Emtricitabine in fixed combinations	2	2	4	Infectious diseases
Efavirenz (separately and in fixed combinations)	2	2	4	Infectious diseases
Formoterol (separately and in fixed combinations)	3	1	4	Pulmonology
Glimepiride (separately and in fixed combinations)	1	3	4	Endocrinology
Thioctic acid	1	3	4	Neurology
Quetiapine	1	3	4	Psychiatry
Esomeprazol	3	1	4	Gastroenterology
Montelukast (separately and in fixed combinations)	4	0	4	Pulmonology

Data from www.grls.rosminzdrav.ru

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In Table 6 we present data on local trials of original medicinal products by foreign sponsors. The number of these sorts of trials was so insignificant that there was no point in showing the percentage relationships of the separate therapeutic subjects.

Table 6

Split of Local CTs of Brand Name Drugs of Foreign Sponsors, 2015	
Therapeutic Area	**Number of CTs**
Gastroenterology	**4**
Analgesic and Anti-inflammatory Medicines	**2**
Neurology	**1**
Urology	**1**
Otorhinolaryngology	**1**
TOTAL	**9**

Data from www.grls.rosminzdrav.ru

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In Table 7 we can see for which therapeutic subjects local manufacturers are working on original medicinal products. In the first place were medicinal products intended for treating infectious diseases (12 trials). For comparison, we note that in the previous year, this subject was also in the first position, but with 21 trials and a big break from the other positions. As in a previous year, the second place (and with the same number of trials – 8) was oncology.

Table 7

Split of Local CTs of Brand Name Drugs of Local Sponsors, 2015	
Therapeutic Area	**Number of CTs**
Infectious Diseases	**12**
Oncology	**8**
Neurology	**4**
Pulmonology	**3**
Surgery	**3**
Dermatology; Immunology	**2**
Otorhinolaryngology	**2**
Gynecology	**2**
Roentgenology, Radiology	**2**
Cardiology and Cardiovascular Diseases	**1**
Psychiatry	**1**
Analgesic and Anti-inflammatory Medicines	**1**
Hematology	**1**
Antidote; Detoxifying agent	**1**
Ophthalmology	**1**
Endocrinology	**1**
Urology	**1**
TOTAL	**46**

Data from www.grls.rosminzdrav.ru

BREAKDOWN OF IMCT APPROVALS ACROSS RUSSIA

In this edition of the newsletter, we decided to analyse how IMCTs are distributed across the Russian Federation. For this, we used the data from the Ministry of Health registry about which medical organisations were referenced in applications for approval to conduct international clinical trials in 2015.

The consolidated data by Russian region are presented in Table 8. We provide a brief explanation on the figures and on how we calculated these results:

- The data on the numbers of IMCTs taking place in a given region (second column). We remind readers that in 2015 a total of 289 IMCTs were approved. If the same trial was on record as taking place at the medical organisations in different regions, it was counted in each region. By this logic, we calculated the number of IMCTs taking place in a federal district. Therefore, if you add up all the data by region you will have a mistake – the figure will exceed the real total of approved trials. Therefore, when studying the data as we present them, please remember that they reflect the picture only for the trials approved in 2015. We cannot know from this data the total number of current trials underway in a region, including those which were initiated in previous years;
- The number of IMCTs per 1 million inhabitants (third column). In making this calculation, we used data from Rosstat on the number of permanent inhabitants in a region as of January 1, 2015;
- In the fourth column we show the number of medical organisations in a given region of the Russian Federation which, according to the register of trials approved in 2015, were indicated as conducting IMCTs;
- The fifth column includes data about how many times in 2015 medical organisations in the region have been included in IMCTs, and also about the total number of medical centres open for this (data on centres is in parentheses). Allow us to explain the difference, from our point of view, between a medical centre and a medical organisation. By medical organisation we mean a specific legal entity – a hospital or an educational institution. However, as we know, the same medical organisation can host several clinical bases. For example, different departments in medical educational institutions are often located at hospital bases. In addition, within the framework of one trial a medical organisation (that same educational institution) may open several centres (places at which the clinical trial is conducted). Each of these centres will have its own principal investigator, although the trial itself, and the head organisation with whom they have an agreement, are the same. Let us return to the table. In the event that the number of medical organisations taking part in an IMCT and the number of centres do not differ, then one number is presented in the corresponding graph. If a medical organisation has several centres within the framework of a single trial, we present two numbers: the data on participation of medical organisations and in parentheses, the number of open centres.

In order to make it clearer, we will look at the example of the Rostov region. From the table we can see that in 2015, the region took part in 38 IMCTs (second column). Eight medical organisations were brought in to these trials (fourth column). However, since several medical organisations were taking part in the same trials simultaneously, and in several of them there were several centres open, for these 38 IMCTs, the region's medical organisations were involved about 40 times (and there were 42 medical centres open).

For convenience, we have brought in data not only by Russian region, but also by federal district. From the table we can see that on numbers of IMCTs just as on the number of medical organisations attracted, the Central Federal District leads, as it includes active regions such as Moscow, Yaroslavl, and the Smolensk region. Just a tad behind the leader comes the North-West Federal District, primarily of course due to St. Petersburg. Slightly further behind is the Volga Federal District, including regions popular for IMCTs such as the Republic of Tatarstan, Nizhny Novgorod, and the Saratov region, and then the Siberian Federal District with centres in Novosibirsk, Kemerovo, and Tomsk.

Таблица 8

Split of IMCT approved in 2015 by regions of 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	**269**	**6,9**	**163**	**893 (939)**	North Caucasian Federal District	**36**	**3,7**	**10**	**46**
Moscow	231	**18,9**	94	541 (580)	Stavropol Region	35	**12,5**	9	41
Yaroslavl Region	69	**54,3**	12	94	Republic of North Ossetia-Alania	5	**7,1**	1	5
Smolensk Region	45	**46,6**	6	45	Siberian Federal District	**143**	**7,4**	**65**	**344 (355)**
Ryazan Region	36	**31,7**	4	36 (38)	Novosibirsk Region	76	**27,7**	20	103 (108)
Kaluga Region	26	**25,7**	4	28 (34)	Kemerovo Region	55	**20,2**	14	68
Moscow Region	31	**4,3**	7	32	Tomsk Region	39	**36,3**	7	51 (56)
Kursk Region	24	**21,5**	5	24	Omsk Region	40	**20,2**	5	42 (43)
Voronezh Region	18	**7,7**	7	20	Altai Krai	33	**13,8**	7	35
Vladimir Region	20	**14,2**	3	20	Krasnoyarsk Krai	31	**10,8**	6	32
Ivanovo Region	16	**15,4**	5	16	Irkutsk Oblast	10	**4,1**	5	10
Tver Region	7	**5,3**	4	8	Zabaykalsky Krai	3	**2,8**	1	3
Lipetsk Region	6	**5,2**	3	6	Ural Federal District	**87**	**7,1**	**31**	**126 (127)**
Belgorod Region	6	**3,9**	3	6	Sverdlovsk Region	58	**13,4**	13	64 (65)
Tambov Region	6	**5,6**	1	6	Chelyabinsk Region	43	**12,3**	12	50
Tula Region	4	**2,6**	1	4	Tyumen Region	11	**7,7**	5	11
Bryansk Region	3	**2,4**	2	3	Khanty-Mansi Autonomous District – Yugra	1	**0,6**	1	1
Orel Region	3	**3,9**	2	3	Volga Federal District	**186**	**6,3**	**84**	**425 (434)**
Southern Federal District	**77**	**5,5**	**23**	**99 (102)**	Republic of Tatarstan	102	**26,5**	16	123 (127)
Rostov Region	38	**9,0**	8	40 (42)	Nizhny Novgorod Region	67	**20,5**	18	79 (80)
Krasnodar Krai	37	**6,8**	10	39	Saratov Region	56	**22,5**	10	60 (64)
Volgograd Region	21	**8,2**	5	20 (21)	Samara Region	45	**14,0**	10	47
Northwestern Federal District	**258**	**18,6**	**124**	**808 (830)**	Republic of Bashkortostan	30	**7,4**	4	30
Saint-Petersburg	254	**48,9**	102	708 (730)	Orenburg Region	22	**11,0**	2	22
Arkhangelsk Region	42	**36,8**	6	43	Kirov Region	15	**11,5**	4	15
Republic of Karelia	22	**34,8**	2	22	Penza Region	14	**10,3**	3	14
Leningrad Region	10	**5,6**	5	16	Perm Region	12	**4,6**	7	12
Republic of Komi	9	**10,4**	3	9	Ulyanovsk Region	10	**7,9**	2	10
Novgorod Region	4	**6,5**	2	4	Udmurt Republic	7	**4,6**	3	7
Murmansk Region	3	**3,9**	2	3	Republic of Mordovia	4	**4,9**	3	4
Pskov Region	2	**3,1**	1	2	Republic of Mari El	1	**1,5**	1	1
Kaliningrad Region	1	**1,0**	1	1	Chuvash Republic	1	**0,8**	1	1
Far Eastern Federal District	**2**	**0,3**	**2**	**2**	Crimean Federal District	**2**	**0,9**	**1**	**2**
Primorsky Krai	2	**1,0**	2	2	Republic of Crimea	2	**1,1**	1	2

*We used data of Rosstat on the resident population of the region as of January 1, 2015

If we look at the data on numbers of trials by number of inhabitants, we get a rather different picture. In the first place we would have the North-West district, then the Siberian, and finally the Urals Federal District. The Central Federal District, in this ranking, would come in at fourth place.

The last thing we would like to say about this table is to mention the effect on the map of the Russian IMCT market of the new Russian region, the Republic of Crimea. As we can see, in 2015 there were two clinical trials approved which brought in the S. I. Georgievsky Crimean State Medical University, located in Simferopol. The first was an extension study of the medicinal product for treating epilepsy sponsored by Bial-Portela Ca.S.A. The trial in Russia was under contract to Scope International AG. The second trial assessing a medicinal product for treatment of rheumatoid arthritis, is sponsored by Sanofi (the trial in Russia is being carried out by the company itself).

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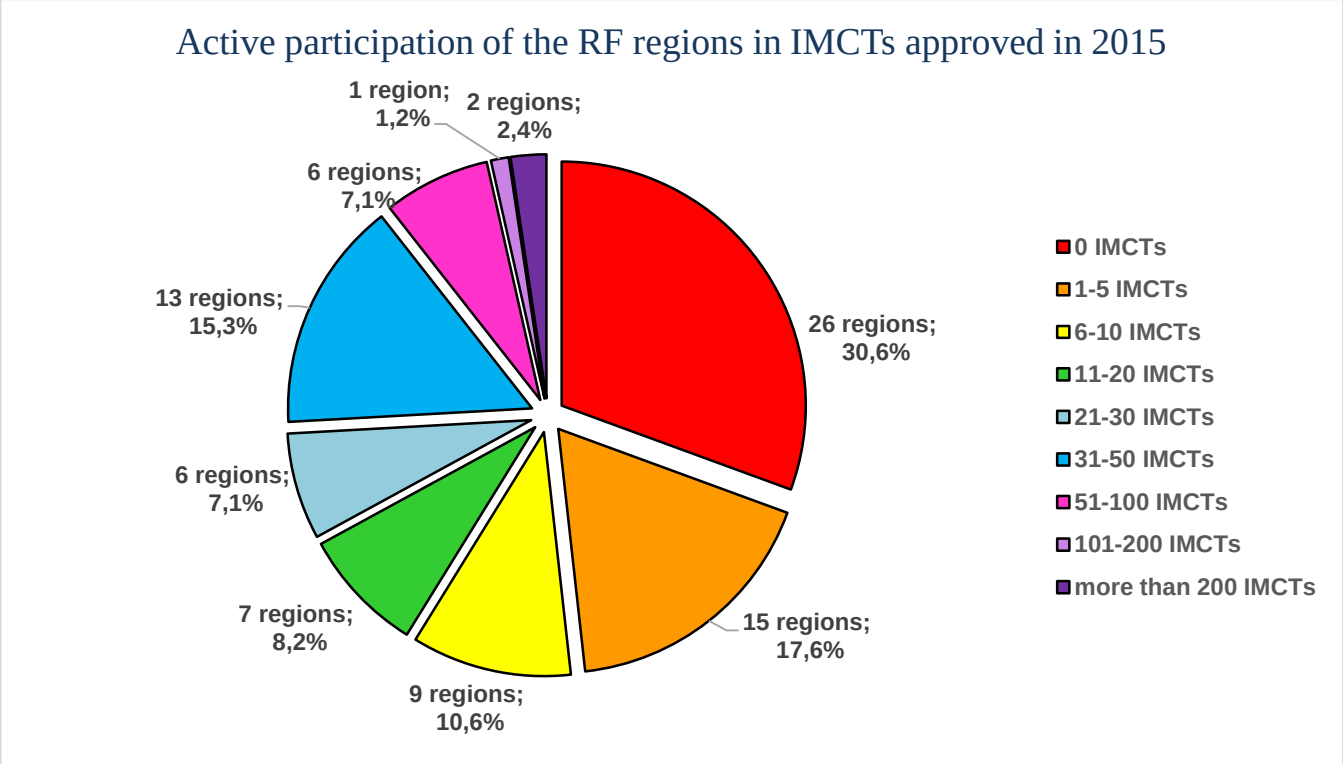
For better clarity and an improved picture of results, we decided to build several separate graphs on the basis of these tables.

So, in Diagram 7 we present the data on active participation of Russian regions in IMCTs approved in 2015.

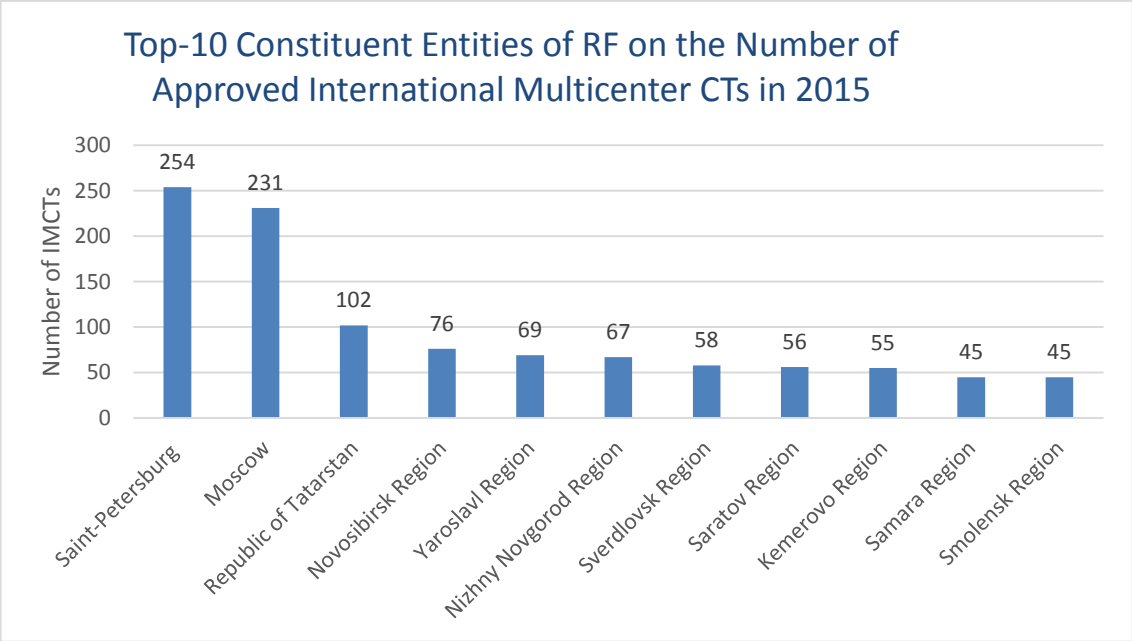
Diagram 7



Data from www.grls.rosminzdrav.ru

In Diagrams 8 and 9 we can see the changes of leading regions depending on which parameters we use for the evaluation. In the first diagram we use the number of IMCTs in which a region is participating as the basis for ranking the regions. In the second diagram, we grade them taking into the account regional population (counted in millions of inhabitants).

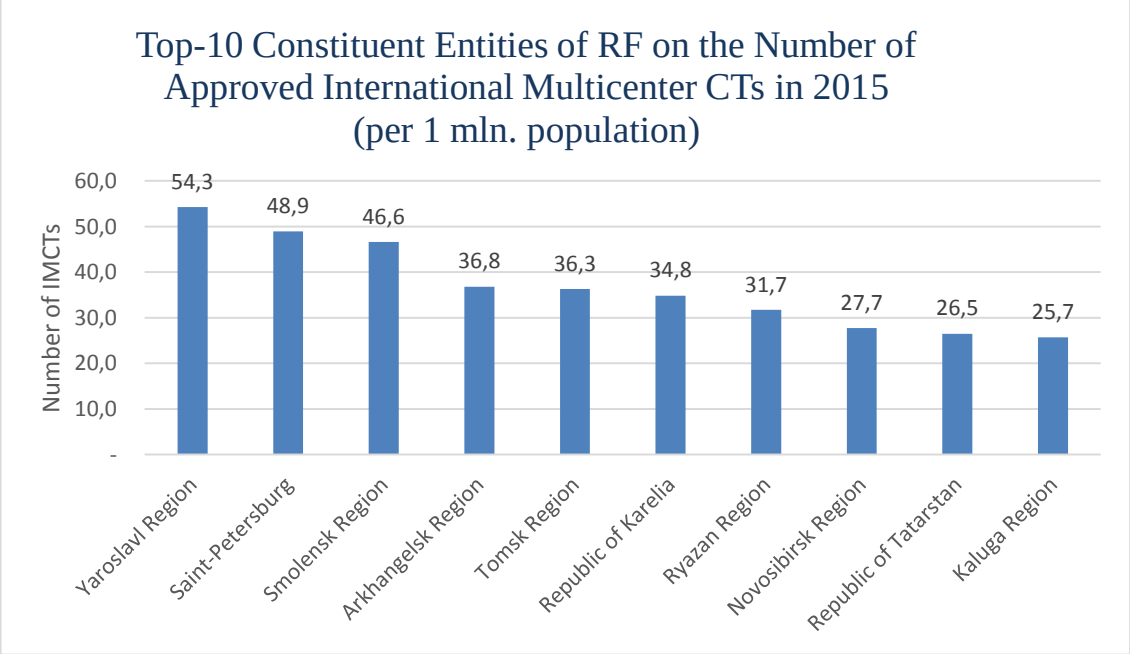
Diagram 8



Data from www.grls.rosminzdrav.ru

The Yaroslavl region, taking just the fifth place in the absolute list of IMCTs it hosted in 2015 (69 trials), was the incontestable leader when calculating how many trials it hosted per 1 million inhabitants (54.3). St. Petersburg, taking the first place on number of IMCTs (254 trials), was in the second place based on trials per inhabitant (48.9 IMCTs per 1 million inhabitants). The Smolensk region didn't do badly at all, sharing the 10th place with the Samara region on number of IMCTs (45 trials each), and shot to the third place on number of trials relative to population (46.6 IMCTs per 1 million). Moscow, just behind St. Petersburg on number of trials (231), was far outside the top ten when ranked relative to population, taking just the 16th place (18.9 IMCTs per million).

Diagram 9



Data from www.grls.rosminzdrav.ru

In Table 9 we present the top 20 medical organisations by activity of participation in IMCTs. As in the case with Table 8, the data presented reflects the number of IMCTs approved in 2015 with participation of a given organisation and also for the number of centres opened in that period.

As a comment to this data we would like to add that out of Moscow medical educational institutions, only the I. M. Sechenov First Moscow State Medical University was in the top twenty, in the esteemed third place (the institution was named in 52 IMCTs approved in 2015). "Third Medical" (A. I. Yevdokimov Moscow State University of Medicine and Dentistry), with 20 IMCTs, was in the 23rd place. The "second" medical institution (N. I. Pirogov Russian National Research Medical University) was way back below the 40th place with just 15 IMCTs.

Table 9

Top 20 medical organisations by active participation in IMCTs approved in 2015			
Place in ranking	**Name of medical organisation**	**Number of IMCTs approved in 2015 with participation of this medical organisation**	**Number of centres approved in 2015 for conducting IMCTs**
1	I. P. Pavlov First St. Petersburg State medical University, Russian Ministry of Health, St. Petersburg	**65**	**71**
2	N. N. Blokhin Russian Cancer Research Centre, Russian Ministry of Health, Moscow	**53**	**64**
3	I. M. Sechenov First Moscow State Medical University, Russian Ministry of Health, Moscow	**52**	**62**
4	Kazan State Medical University, Russian Ministry of Health, Kazan	**44**	**47**
5	S. M. Kirov Military-Medical Academy, Russian Ministry of Defense, St. Petersburg	**42**	**42**
6	N. N. Petrov Research Institute of Oncology, Russian Ministry of Health, St. Petersburg	**40**	**45**
7	St. Petersburg City Clinical Oncological Dispensary, St. Petersburg	**39**	**43**
8	N. A. Semashko Nizhny Novgorod Regional Clinical Hospital, Nizhny Novgorod	**28**	**29**
9	Arkhangelsk region Arkhangelsk Clinical Oncological Dispensary, Arkhangelsk	**28**	**28**
10	Rostov State Medical University, Russian Ministry of Health, Rostov-on-Don	**27**	**29**
11	N. V. Solovyev Yaroslavl region Clinical Hospital for First Medical Assistace, Yaroslavl	**27**	**28**
12–14	Republic Clinical Oncological Dispensary of the Ministry of Health of the Republic of Tatarstan, Kazan	**27**	**27**
12–14	Smolensk State Medical University, Russian Ministry of Health, Smolensk	**27**	**27**
12–14	St. Petersburg Clinical Practical Research Centre for Specialised Types of Medical Aid (Oncological), St. Petersburg	**27**	**27**
15	Novosibirsk State Medical University, Russian Ministry of Health, Novosibirsk	**26**	**31**
16	Leningrad region Clinical Hospital, St. Petersburg	**26**	**26**
17	I. I. Mechnikov North-West State Medical University, Russian Ministry of Health, St. Petersburg	**25**	**26**
18	Clinical Oncological Dispensary, Omsk	**24**	**25**
19	National Medical Research Radiology Centre, Russian Ministry of Health, Obninsk	**22**	**28**
20	Siberian State Medical University, Russian Ministry of Health, Tomsk	**22**	**24**

Source: www.grls.rosminzdrav.ru

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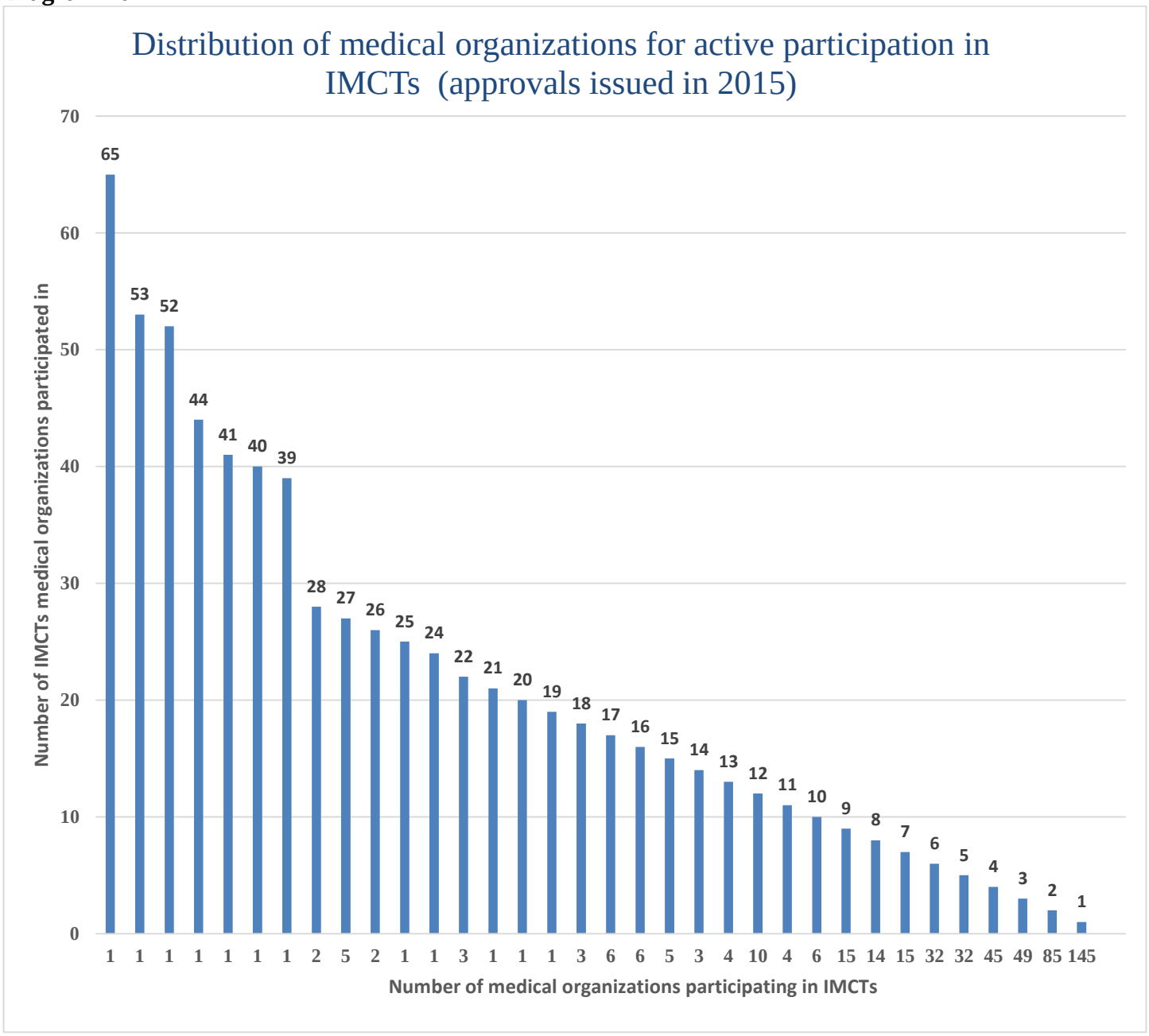
In Diagram 10 we present a breakdown of medical organisations by active participation in IMCTs. From this we can see how many organisations are participating in a given number of international trials approved in 2015. As in the previous year, 145 medical organisations were attracted to participate in at least one IMCT, 85 were involved in two, 49 were involved in three, and so on.

Diagram 10



Data from www.grls.rosminzdrav.ru

It's clear that this graph reflects the stark reality, and we are forced to compare on the same level the huge state educational institutions (which in addition to their own patient beds often have a well-developed clinical network based at affiliated hospitals), and modest municipal clinics. Which, in all honesty, is probably not entirely fair.

Therefore, we decided to look at an evaluation of centres' activity from yet another point of view. We decided to analyse how medical organisations under various different types of ownership and authority were being recruited into IMCTs. In this analysis we limited ourselves to just two Russian regions – Moscow (Table 10) and St. Petersburg (Table 11).

Classification by authority over the medical organisations we carried out in the following way. At the federal level were organisations under the Russian Ministry of Health or other federal bodies (Federal Agency for Scientific Organisations, Federal Medical and Biological Agency, Department of Presidential Affairs, Rospotrebnadzor, the Ministry of Defence, and so on). At the Russian regional level were organisations under regional health authorities. In Moscow this is either the Department of Health of the City of Moscow, or the Ministry of Health of the Moscow region. In St. Petersburg this is the Department of Health of St. Petersburg or the Department of Health of the Leningrad region. Finally, we had a separate category for medical organisations belonging to the Russian Railways, as well as under the private healthcare system (LLCs, non-profits, and others).

In calculating the number of medical organisations in each group that were listed for participating in IMCTs in 2015, we also looked at the number of centres that were approved at these medical organisations. In addition, with these two figures, we were able to work out the relationship between the two, calling the resulting parameter the "activity ratio".

Table 10

Active 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 2015 for IMCTs**	**Activity Ratio**
Moscow Department of Healthcare	**33**	**136**	**4,1**
Ministry of Healthcare of the Russian Federation	**24**	**251**	**10,5**
Federal bodies (except Ministry of Healthcare of the RF)	**23**	**133**	**5,8**
Non-governmental health system	**8**	**13**	**1,6**
JSC "Russian Railways"	**3**	**27**	**9,0**
Ministry of Healthcare of the Moscow region	**3**	**20**	**6,7**
Total	**94**	**580**	**6,2**

Data from www.grls.rosminzdrav.ru

In Moscow, the majority of medical organisations taking part in IMCTs were under the Department of Health of the City of Moscow (33 organisations). However, the number of clinical centres opened by these medical organisations in 2015 was just 136. At the same time, institutions taking part in IMCTs and operating under the authority of the Russian Ministry of Health, of which there were 24 in Moscow, opened a total of 251 centres. Accordingly, the activity ratio of institutions under the Russian Ministry of Health was 10.5 (the highest for the capital), whereas for clinics under the Department of Health of the City of Moscow it was just 4.1 (the fifth result, ahead only of organisations in the private healthcare sector).

In St. Petersburg the picture is somewhat different. The majority of medical organisations taking part in IMCTs were, as in Moscow, under the authority of the city Department of Health (54). In second place were, surprisingly, private healthcare sector clinics, of which there were 25. And only after that there were institutions under the Russian Ministry of Health (12). Although looking at the number of centres approved in 2015, we see that the most active (with a ratio of 19.5) were the clinics under the Department of Health of the Leningrad region (although there were only two of these). The activity ratio of clinics under the Department of Health of the City of St. Petersburg was just 5.9 (the fourth result by region). The ratio of institutions under the Russian Ministry of

Health was nearly as high (16.8), and moreover significantly outweighed the same number from Moscow clinics operating under the same governmental authority.

But as a whole we can see that the average activity ratio in the northern capital was higher than in Moscow (7.2 compared to 6.2). We remind readers that also on other parameters (on the total number of organisations participating in IMCTs, as well as the number of IMCTs per 1 million inhabitants), St. Petersburg is ahead of Moscow.

Table 11

Active 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 2015 for IMCTs**	**Activity Ratios**
Saint-Petersburg Department of Healthcare	**54**	**318**	**5,9**
Non-governmental health system	**25**	**86**	**3,4**
Ministry of Healthcare of the Russian Federation	**12**	**201**	**16,8**
Federal bodies (except Ministry of Healthcare of the RF)	**8**	**82**	**10,3**
Ministry of Healthcare of the Leningrad Region	**2**	**39**	**19,5**
JSC "Russian Railways"	**1**	**4**	**4,0**
Total	**102**	**730**	**7,2**

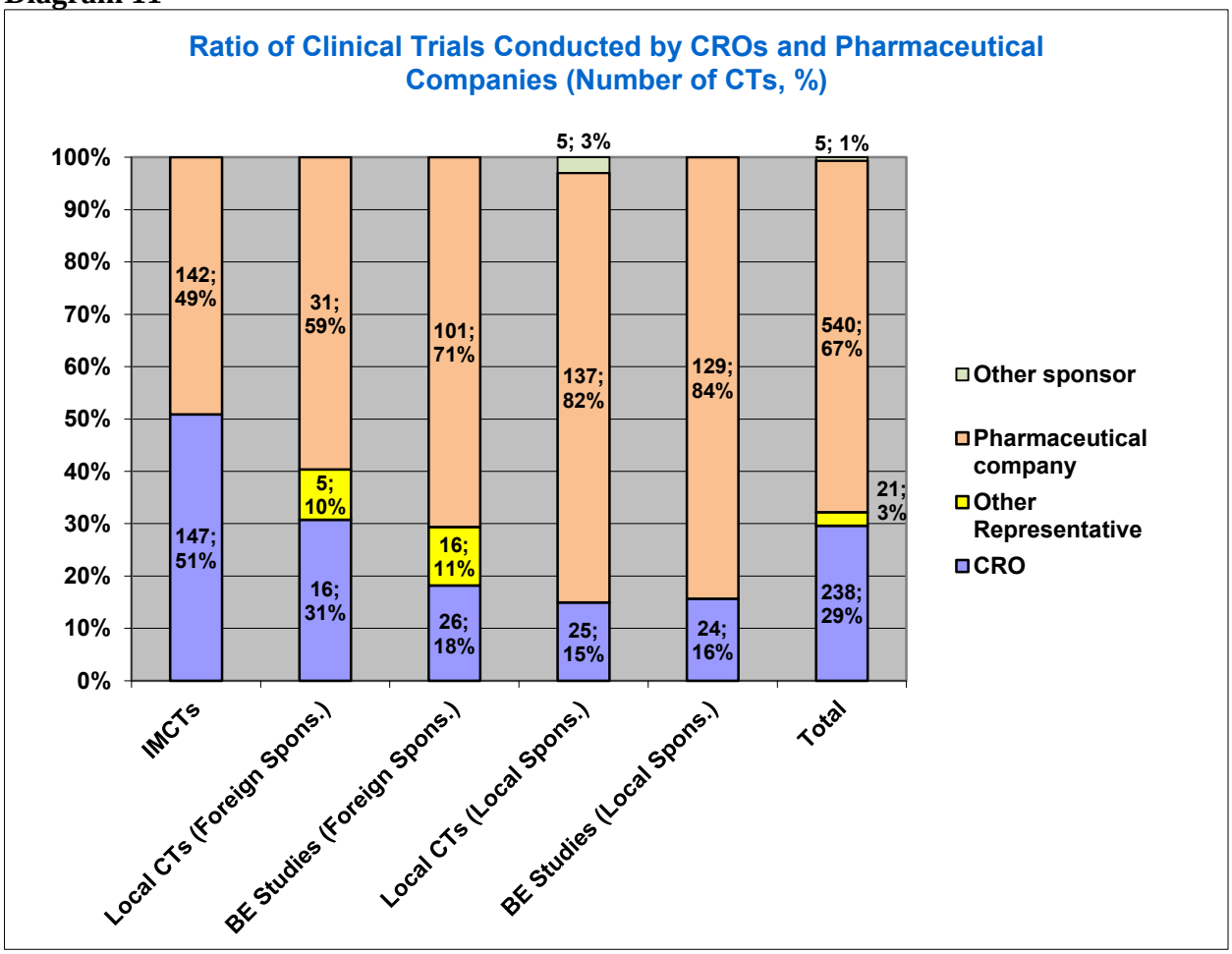
Data from www.grls.rosminzdrav.ru

MAIN PLAYERS ON THE RUSSIAN CLINICAL TRIALS MARKET – 2015

Sponsors and CROs, general structural breakdown

Diagram 11 gives a picture of what proportion of trials approved in 2015 are being conducted by the sponsors themselves, and what proportion are being run by third parties.

Diagram 11



Data from www.grls.rosminzdrav.ru

Before we look at our analysis, we remind readers that the data on participation in various trials by contract research organisations (CROs) was obtained from the registry of approved clinical trials. Not all cases of CROs being involved with trials have been noted in this registry. If a contract organisation is working on areas that as a rule are not under regulatory oversight, its participation in the trial may not be reflected in the registry. Therefore, the share of participation by CROs in the process of conducting clinical trials is in fact slightly higher than what we see in this graph.

The second thing we need to clarify is the distinction of a separate category for 'other representatives'. By this we mean organisations contracted by sponsors to the conduct of the trials, but not as contract research organisations, whose main speciality is organising the process of conducting clinical trials. As such, in the category of 'other representatives' we included companies engaged in market access, distribution, and marketing of foreign medicinal products for pharmaceutical companies that do not have their own representatives in Russia.

As we can see from this data, the biggest share of CROs involved in the process (50.5%), were as usual on IMCTs. True, this has dropped slightly compared to 2014, when the ratio was 53% to 47% in favour of CROs *(see Informational and analytical Newsletter No. 10).*

There was a significant increase compared to last year's figure for the share of trials conducted using a CRO both in the sector for local trials by foreign sponsors (31% compared to 23%), and in the sector for bioequivalence trials by domestic manufacturers (16% compared to 7%). There was a slight increase (18% compared to 16%) in bioequivalence studies of generics by foreign manufacturers. And in the sector of local trials by Russian sponsors there was a slight drop, 15% of trials conducted used a CRO compared to 18% a year earlier.

The total breakdown by all types of trials corresponds with the figures for 2014. The trials conducted by CROs both last year and a year earlier came up to 29%, while the share of 'other representatives' remained 3% for both years.

Comparing data with the previous year, it is also important to look at the new category that we have added this time, 'other sponsors'. Analysing the data by companies that initiated local clinical trials in in 2015, we turn to five cases in which the sponsor was not a pharmaceutical company, but another kind of organisation – a research institution, educational institution, or even a civic organisation. This requires a little bit of explanation. On its own, the status of a research or educational institution doesn't tell us anything, and the practice is fairly widespread for such organisations to hold the license to manufacture a medicinal product and register the medicinal product in their own name. As an example we can look at the N. F. Gamaleya Research Institute for Immunology and Microbiology, or the N. N. Blokhin Russian Cancer Research Centre, which hold both the license for production, and the registration in their name, of relevant medicinal products. In these cases we included the applicant with pharmaceutical manufacturers. But organisations which attracted our attention this year we were not able to find either in the registry of registration holders, or in the registry of enterprises with a license to manufacture medicines. And we decided that it would be worth putting them in a separate category – 'other sponsors'. Below, in Table 12, we list these organisations, and also the medicinal products that they are developing.

Table 12

Organisation initiating the trial	**Medicinal product**
Regional state budgetary educational institution for continuing professional education "Institute of Higher Qualifications for Healthcare Specialists", Ministry of Health of the Khabarovsk region	Fluorodeoxyglucose, 18F (Fluorodeoxyglucose [18F])
All-Russian NGO "Russian Narcotics League"	Sulfalong® (Disulfiram)
Federal budgetary science institution "State Research Centre for Applied Microbiology and Biotechnology", Federal service for supervision in the field of consumer rights protections and human rights	Molecular microencapsulated plague vaccine (Prophylactic plague vaccination)
Federal budgetary science institution "V. N. Orekhovich Scientific Research institute of Biomedical Chemistry"	Phospholipovit
Federal state budgetary educational institution of higher education "Lomonosov Moscow State University", Department of fundamental medicine	Innervin

Data from www.grls.rosminzdrav.ru

International Multicentre clinical trials, sponsors

In Table 13 and in Diagram 12 we present the top 15 pharmaceutical companies by number of approvals issued in 2015 to conduct clinical trials.

Table 13

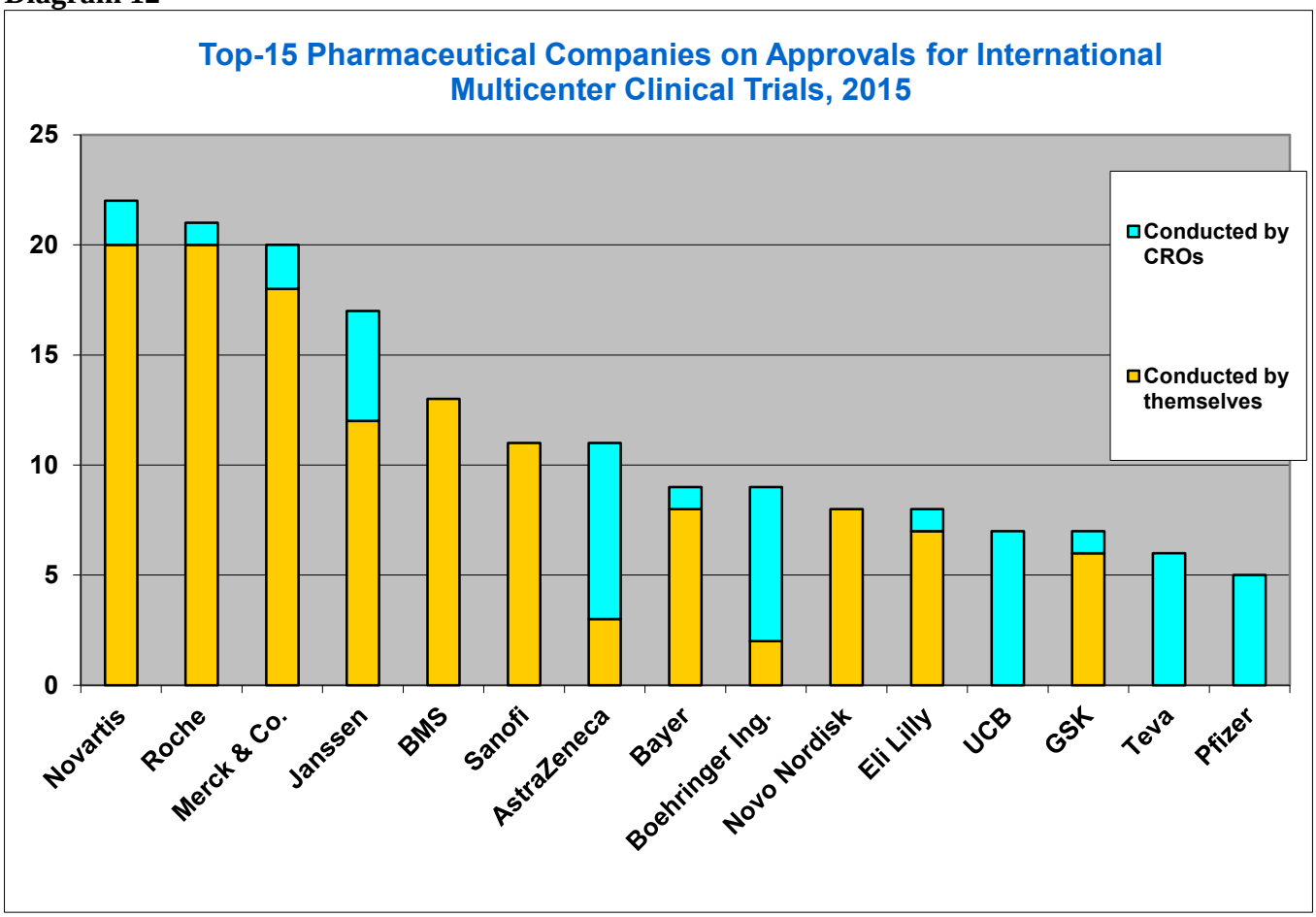
Top-15 Pharmaceutical Companies on Approvals for International Multicenter CTs, 2015						
№	Company (including separate companies associated in group of companies, as well as independent divisions of the company)	Conducted by Themselves	Conducted by CROs	Total	Position in rating, 2015	The Number of CTs; position in rating 2014
1	Novartis	20	2	22	1	27 CTs; 1
2	F. Hoffmann-La Roche	20	1	21	2	14 CTs; 3
3	Merck & Co.	18	2	20	3	9 CTs; 9
4	Janssen Pharmaceutica	12	5	17	4	12 CTs; 5-6
5	Bristol-Myers Squibb	13	-	13	5	3 CTs; 20-23
6	Sanofi	11	-	11	6-7	10 CTs; 8
7	AstraZeneca	3	8	11	6-7	12 CTs; 5-6
8	Bayer	8	1	9	8-9	7 CTs; 11-12
9	Boehringer Ingelheim	2	7	9	8-9	6 CTs; 13-14
10	Novo Nordisk	8	-	8	10-11	6 CTs; 13-14
11	Eli Lilly	7	1	8	10-11	2 CTs; 24-36
12	UCB Pharma	-	7	7	12-13	n/a
13	GlaxoSmithKline	6	1	7	12-13	20 CTs; 2
14	Teva	-	6	6	14	5 CTs; 15-16
15	Pfizer	-	5	5	15	11 CTs; 7

Data from www.grls.rosminzdrav.ru

From the table we can see how the group of leaders has changed compared to 2014. Novartis, leading in the number of trials a year earlier, kept the top position in 2015. GSK took the second place in 2014 with 20 trials, but fell 11 points down to the 13th position. Not entirely lucky was the year for Pfizer, dropping from the seventh to the 15th position. The position of Merck & Co, Inc improved considerably (from the ninth up to the third place), as did the position of Bristol-Meyers Squibb (which shot up from the 20-23rd place to the fifth). It wasn't a bad year for Eli Lilly, which skyrocketed from the end of the list (the 24-36th place in 2014) to the 11th position. UCB, which had no approvals in 2014, started 7 IMCTs in 2015, making it into the top 15, in the 12th place.

Unfortunately, based on last year's results, Amgen and AbbVie (which had shared the 16-17th place) dropped out of the top 15, as did Merck KGaA and AB Science (on the 18-24th place).

Diagram 12

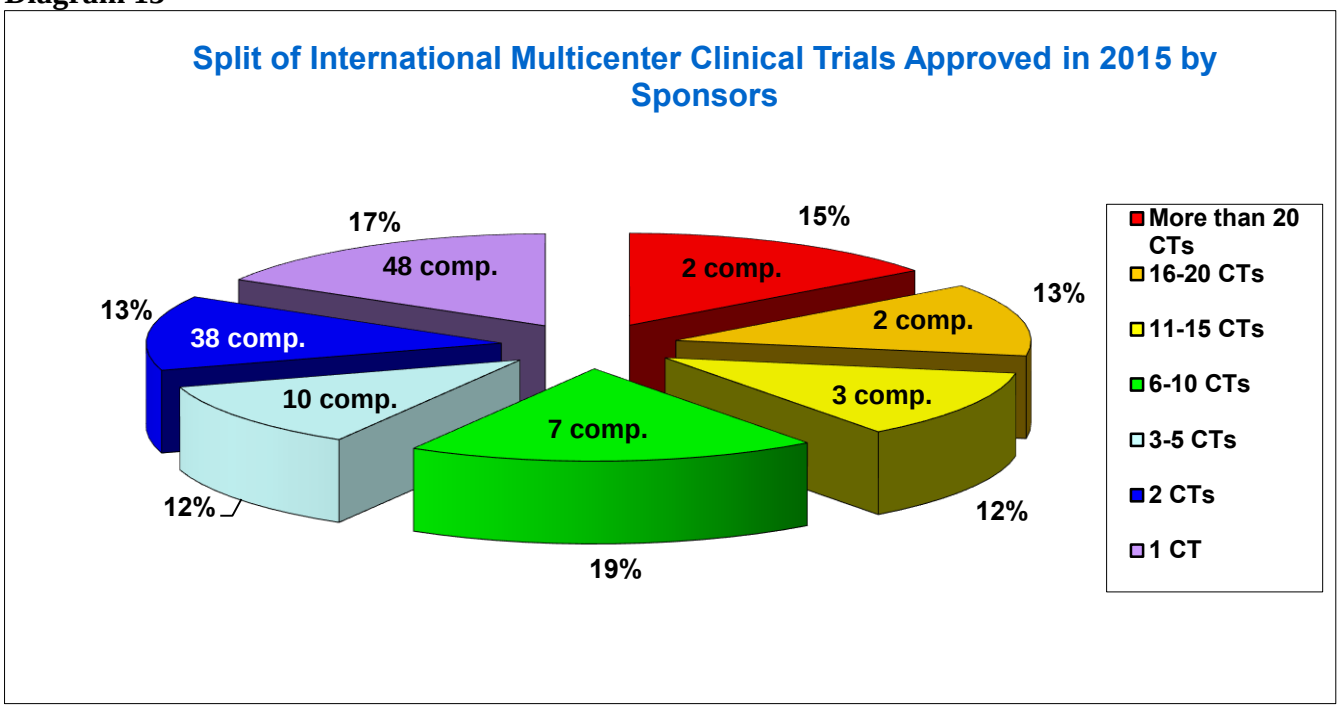


Data from www.grls.rosminzdrav.ru

In order to demonstrate the breakdown of IMCT approval by sponsor more clearly, we divided the companies into groups based on how many trials they were conducting.

In Diagram 13 we can see that the seven most active companies had 40% of all IMCT approvals issued. So, 15% of the market goes to Novartis and F. Hoffman-La Roche (with 22 and 21 trials, respectively), and 13% to Merck & Co and Janssen Pharmaceutica (20 and 17 trials, respectively). In total according to the data from the Ministry of Health register for 2015, there were 91 companies sponsoring IMCTs, exactly as many as in 2014. And this means that in the last year, which was so difficult for the Russian economy as a whole, there was no loss in the numbers of foreign sponsors of international trials.

Diagram 13



Data from www.grls.rosminzdrav.ru

International multicentre clinical trials, CROs

The top 10 contract research organisations, based on the number of IMCTs approved in 2015 in which they were involved, are presented in Table 14 and in Diagram 14.

Table 14

Top-10 CROs on Approvals for International Multicenter CTs, 2015					
№	Company	Number of CTs	Number of Sponsors	Ranking in 2015	Number of CTs; Ranking in 2014
1	Quintiles	29	20	1	27 CTs; 1
2	PPD	16	13	2	15 CTs; 3
3	PRA Health Sciences	15	6	3	12 CTs; 4
4	Parexel	11	6	4	11 CTs; 5-6
5	PSI	7	7	5	11 CTs; 5-6
6	ICON	6	6	6-7	16 CTs; 2
7	MB Quest	6	6	6-7	7 CTs; 8-10
8	INC Research	5	3	8-10	10 CTs; 7
9	InVentiv Health Clinical	5	4	8-10	4 CTs; 11-13
10	WCT	5	5	8-10	2 CTs; 14-18

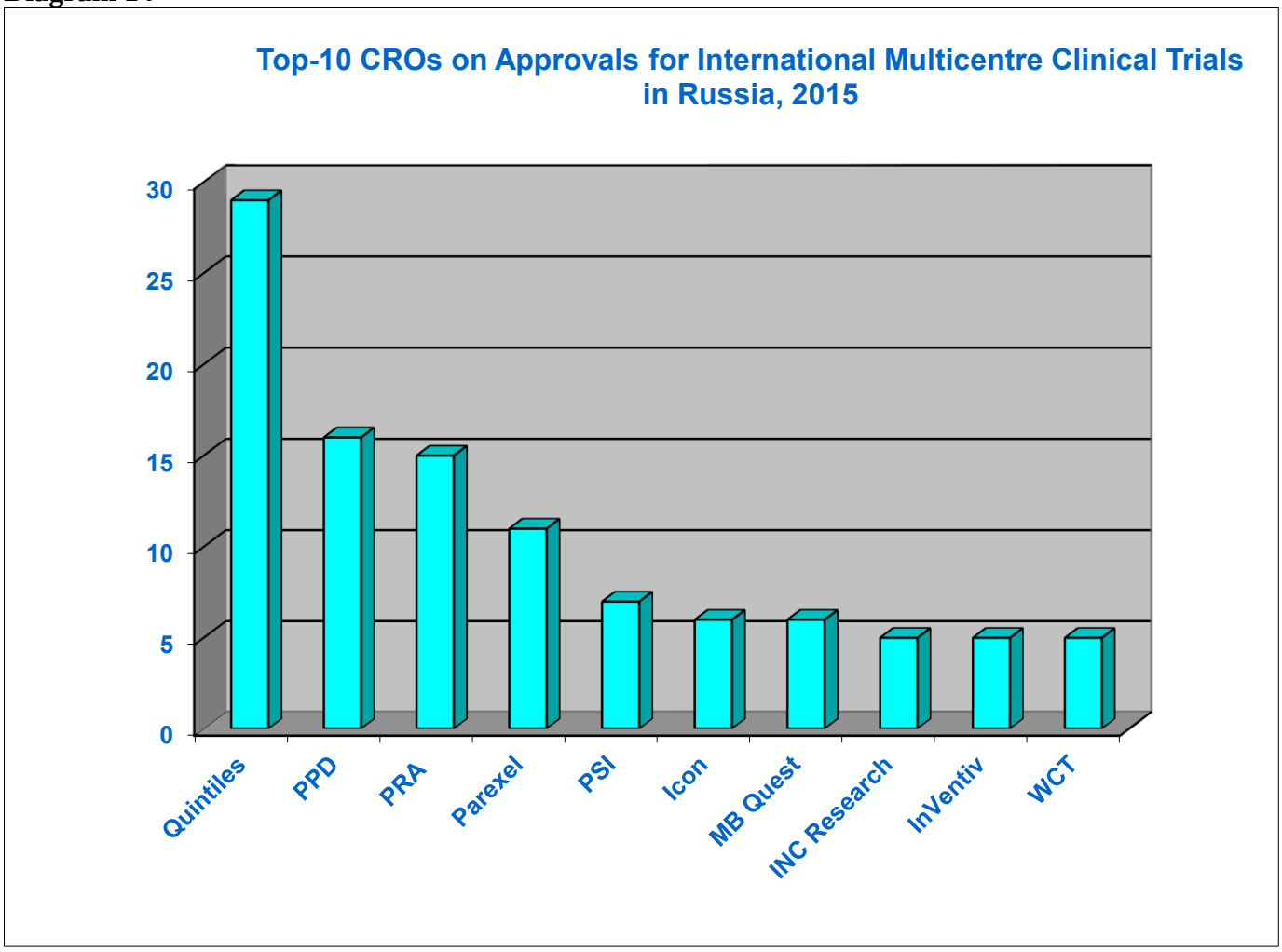
Data from www.grls.rosminzdrav.ru

We should note that the ranking of contract research organisations was more stable than the ranking of sponsors. And so, the majority of leading CROs from 2014 kept their positions in 2015, with a minimum of movement within the top 10. The most significant change in position was for ICON. In 2015 the company dropped four slots, from second to sixth in the ranking (which has a lot to do with the corresponding improvement in

position of several competitors). It is possible that this result goes some way to explaining the loss in position for Pfizer, one of ICON's main clients.

There were insignificant changes to be seen at the end of the top 10 also. Covance dropped out (the eighth place in 2014, down to the 17th-21st in 2015) as did Sinergy Research Group (ninth in 2014 down to the 11-14th in 2015). And inVentiv Health Clinical and Worldwide Clinical Trials (WCT) joined the top ten.

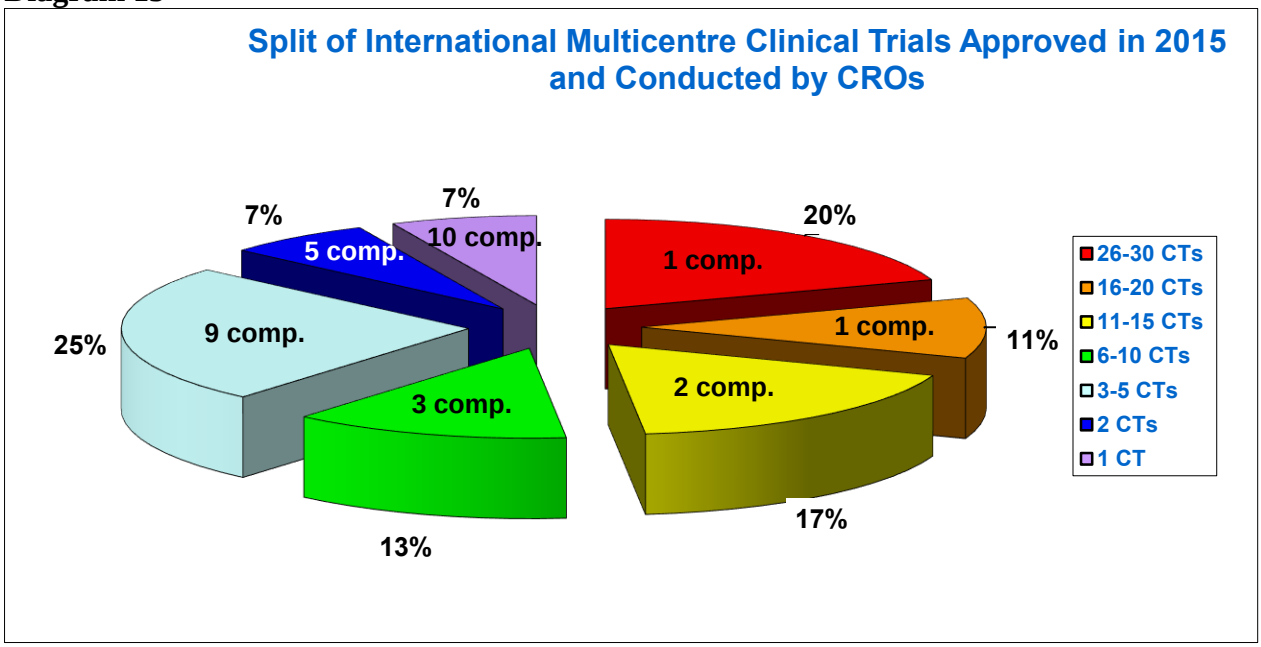
Diagram 14



Data from www.grls.rosminzdrav.ru

The results of the breakdown of IMCTs approved in 2015 by CRO are presented in Diagram 15.

Diagram 15



Data from www.grls.rosminzdrav.ru

We can see that almost one half of all IMCTs approved in 2015 that included a CRO (20%, 11%, and 17%), were split between just four companies.

On the whole, 30 CROs were involved in IMCTs approved in 2015, according to data from the Ministry of Health register, which is six companies more than in 2014.

Local Trials and bioequivalence studies, foreign sponsors

Table 15 and Diagram 16 give a picture of the leading foreign sponsors who in 2015 initiated local trials and bioequivalence studies. As in the case of the IMCTs, the trials were divided based on whether they were conducted by the companies themselves, or by involving a CRO.

Here we can see an even more significant change in the rankings, even more so than among sponsors of international trials. Stability was seen only by KRKA which maintained its position in second place. Actavis and Teva swapped places (the 1st and the 5th, respectively).

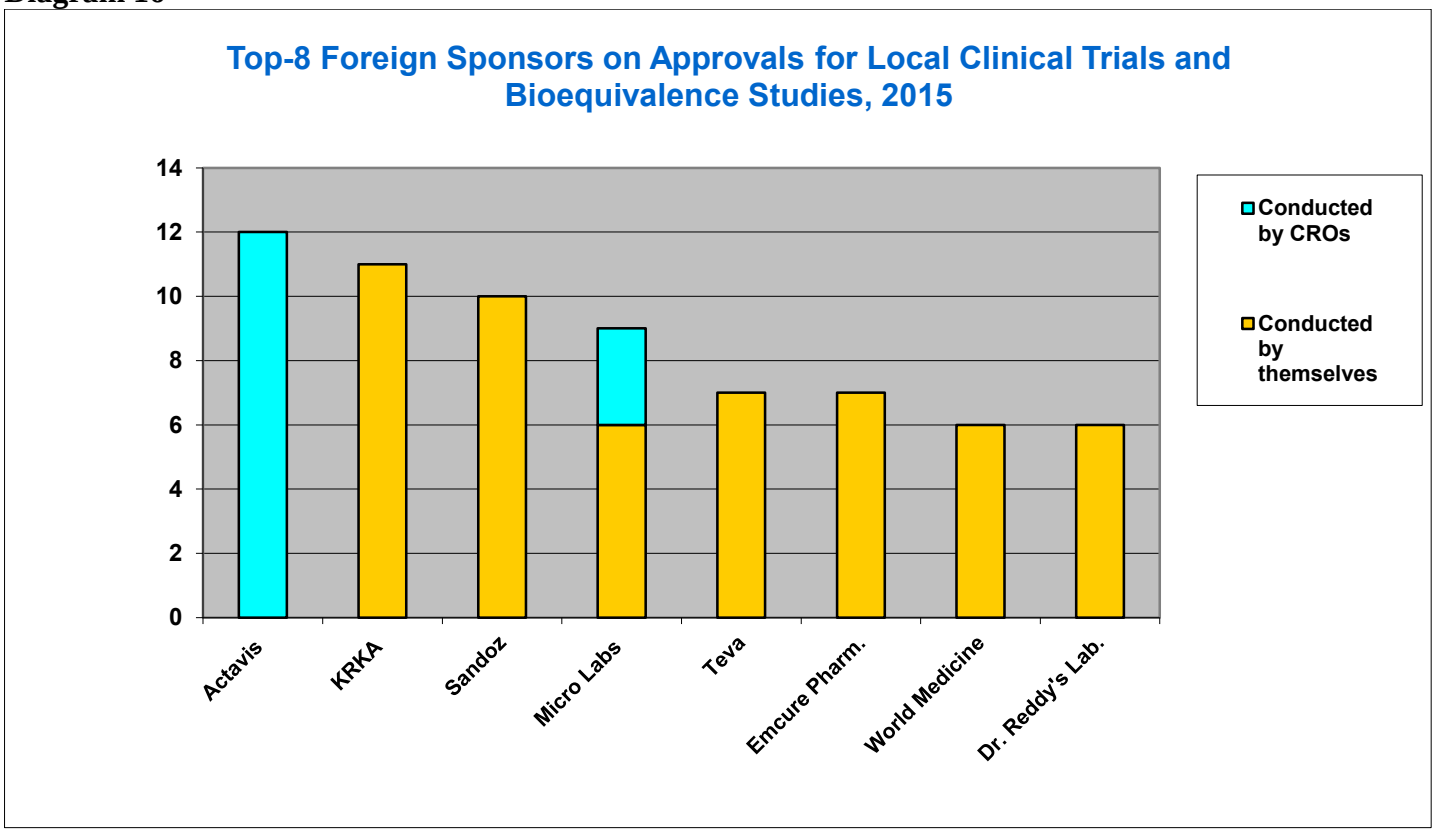
Rocketing up the chart were Sandoz, Micro Labs, Emcure Pharmaceuticals, and World Medicine. Dropping out of the top eight were Rowtech, Belupo, Sanofi, and Glenmark.

Table 15

	Top-8 Foreign Sponsors on Approvals for Local CTs and Bioequivalence Studies, 2015					
№	Company	Conducted by themselves	Conducted by CROs	Total	Ranking in 2015	Number of CTs; Ranking in 2014
1	Actavis	-	12	12	1	6 CTs; 5
2	KRKA	11	-	11	2	10 CTs; 2
3	Sandoz	10	-	10	3	3 CTs; 16-22
4	Micro Labs	6	3	9	4	3 CTs; 16-22
5	Teva	7	-	7	5-6	16 CTs; 1
6	Emcure Pharm.	7	-	7	5-6	n/a
7	World Medicine	6	-	6	7-8	1 CT; 41-78
8	Dr. Reddy's Lab.	6	-	6	7-8	7 CTs; 4

Data from www.grls.rosminzdrav.ru

Diagram 16



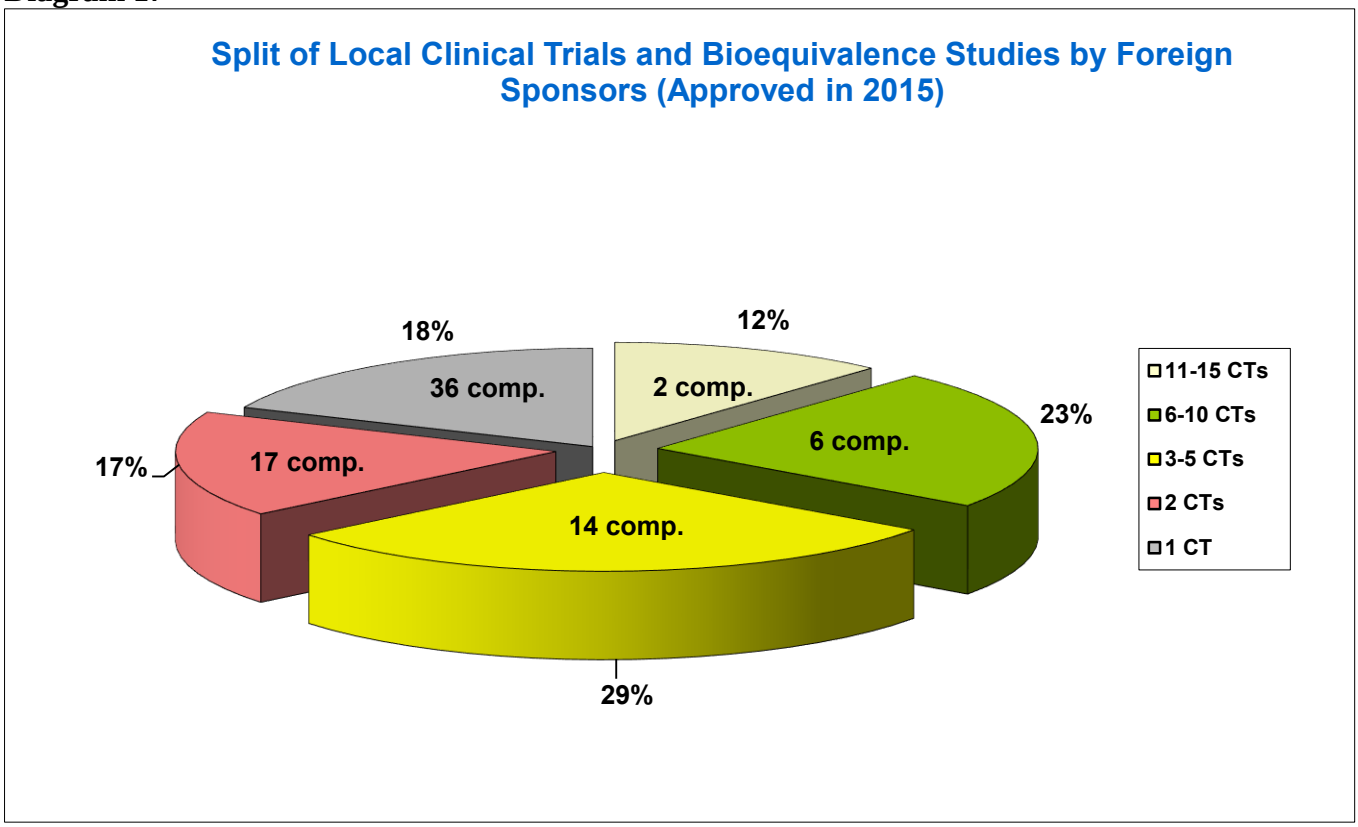
Data from www.grls.rosminzdrav.ru

In Diagram 17 we present a breakdown of local trials of efficacy and safety approved in 2015, as well as bioequivalence studies by foreign sponsors.

The leading companies last year were Actavis (12 trials) and KRKA (11 trials), with 12% of this segment of the market. Six companies initiated between six and ten trials (23% of the total number of trials in this segment of the market). Nearly a third – 29% - were conducted by 14 companies, with 3-5 trials approved each. Seventeen sponsors (17%) had two trials each, and 36 companies (18%) had one each.

Altogether, there were 75 foreign companies in the market for local trials and bioequivalence studies in 2015 (78 in 2014).

Diagram 17



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies of foreign medicinal products, CROs

In Table 16 we present a ranking of CROs that were involved in local trials and bioequivalence studies of foreign medicinal products in 2015. Since such CROs number are far fewer than the ones working on IMCTs, we listed all of them. Meanwhile, if we return to Table 14 (the top 10 CROs in IMCTs), we don't see any cross-over with participants of the local trials market. By the way, two companies that we see in Table 16, Dokumeds LLC and Sinergy Research Group LLC, do also take part in IMCTs, but based on 2015 results they were not in the top 10, and so were not reflected in our ranking of the leading companies.

Table 16

CROs on Approvals for Local CTs and Bioequivalence Studies of Foreign Sponsors, 2015

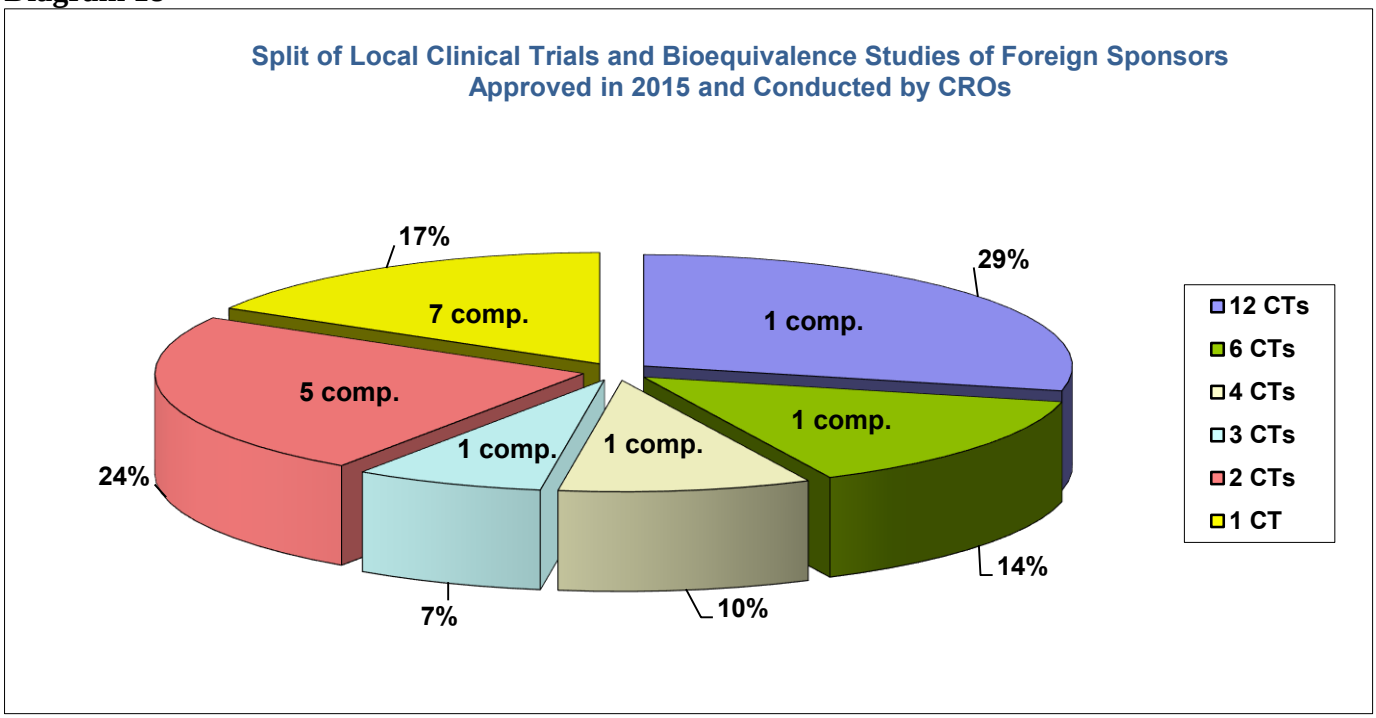
№	Company	Number of CTs	Number of Sponsors	Ranking in 2015	Number of CTs; Ranking in 2014
1	Medical Development Agency (MDA)	12	1	1	7 CTs; 1
2	PharmaReg	6	3	2	3 CTs; 4-5
3	Pharmtime	4	3	3	n/a
4	Solyur-pharma	3	1	4	6 CTs; 2
5	Solyurpharm	2	2	5-9	n/a
6	Expert & Legal Centre for Pharmaceuticals and Medical Devices	2	1	5-9	1 CT; 8-13
7	Agency for Registration Support of Medicines	2	1	5-9	n/a
8	Solyur Pharmaceuticals Group	2	2	5-9	n/a
9	RegExpert	2	1	5-9	n/a
10	ClinPharmInvest	1	1	10-16	2 CTs; 6-7
11	Ligand Research	1	1	10-16	1 CT; 8-13
12	Dokumeds	1	1	10-16	n/a
13	Synergy Research Group	1	1	10-16	n/a
14	ARS	1	1	10-16	n/a
15	R&D PHARMA	1	1	10-16	n/a
16	RUSCLINIC	1	1	10-16	n/a

Data from www.grls.rosminzdrav.ru

In Diagram 18 we see that more than half (53%) of local trials of foreign medicinal products conducted with CRO participation were conducted by just three companies. The leader in this sector of the market, MDA, was involved in 12 trials (MDA was also in first position in 2014, but with just 7 protocols).

There are in total 16 CROs working on local trials and bioequivalence trials on foreign medicinal products in 2015 (in 2014 there were 13).

Diagram 18



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies of domestic medicinal products, sponsors

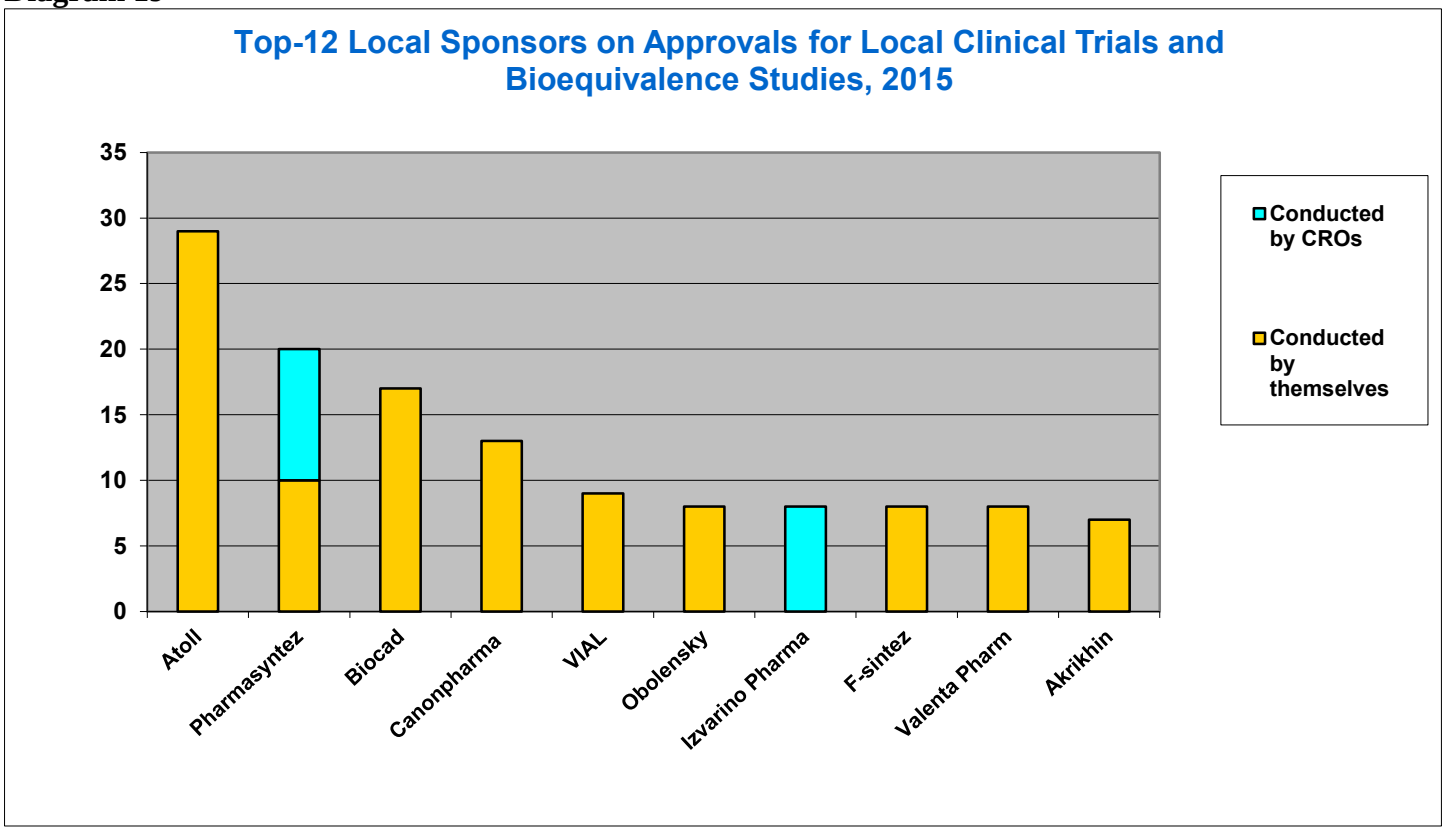
The top 12 Russian manufacturers based on the number of approvals granted for local trials and bioequivalence studies are presented in Table 17 and in Diagram 19.

Table 17

Top-12 Local Sponsors on Approvals for Local Clinical Trials and Bioequivalence Studies, 2015						
№	Company	Conducted by themselves	Conducted by CROs	Total	Ranking, 2015	Number of CTs/Ranking, 2014
1	Atoll	29	-	29	1	47 CTs; 1
2	Pharmasyntez	10	10	20	2	3 CTs; 16-27
3	Biocad	17	-	17	3	6 CTs; 9-12
4	Canonpharma Production	13	-	13	4	6 CTs; 9-12
5	VIAL	9	-	9	5	n/a
6	Obolensky Pharmaceutical Company	8	-	8	6-10	8 CTs; 3-4
7	Izvarino Pharma	-	8	8	6-10	4 CTs; 13-15
8	F-sintez	8	-	8	6-10	2 CTs; 28-48
9	Valenta Pharm	8	-	8	6-10	1 CT; 49-113
10	Akrikhin	7	-	7	6-10	3 CTs; 16-27
11	Microgen	6	-	6	11-12	7 CTs; 5-8
12	Drugs Technology	6	-	6	11-12	6 CTs; 9-12

Data from www.grls.rosminzdrav.ru

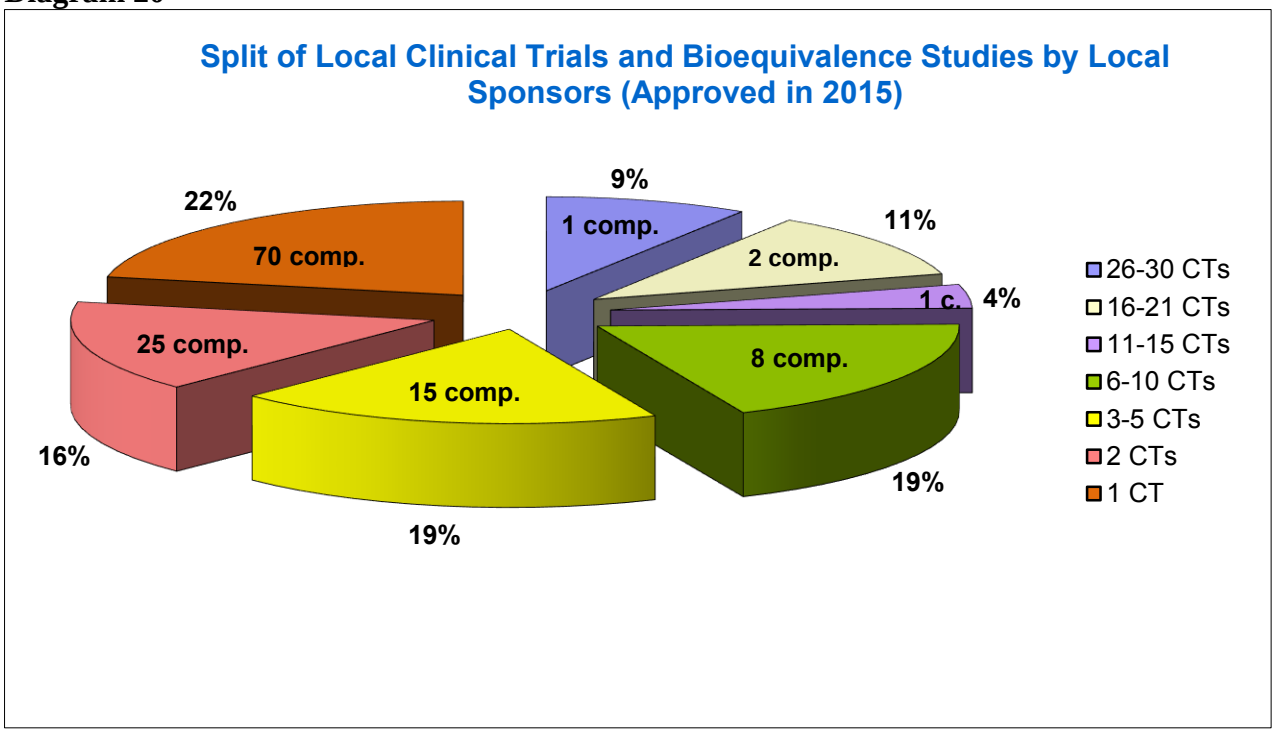
Diagram 19



Data from www.grls.rosminzdrav.ru

A breakdown of approvals for local trials and bioequivalence studies between Russian sponsors is presented in Diagram 20.

Diagram 20



Data from www.grls.rosminzdrav.ru

Compared with the previous year there was a significant decrease in the number of trials initiated by the rankings leader, Atoll. The company, which also held the top spot last year, in 2015 received approval for 29 trials (compared to 47 in 2014), which accounted for 9% of all trials by domestic manufacturers. Two companies

accounted for between 16 and 21 trials (11%), and eight companies had 6-9 trials each (19%). There were 15 companies running 3-5 trials (19%), and a further 25 companies running two trials each (16%). Finally, 70 companies received approval in 2015 to run one trial each (22%).

Altogether in 2015, 122 Russian companies initiated local trials and bioequivalence studies (in 2014, 113 did so).

Local trials and bioequivalence studies of domestic medicinal products, CROs

In Table 18 we present data on contract research organisations that worked in the sector of trials by Russian sponsors in 2015. Since there were not very many, we have listed all of them.

If we compare this list with the list of CROs running local trials on foreign medicinal products (Table 16), we see a few familiar names – MDA and PharmaReg.

Table 18

CROs Involved in Local Clinical Trials and Bioequivalence Studies Conducted by Local Sponsors (on Approvals Issued in 2015)					
№	**Company**	**Number of CTs**	**Number of Sponsors**	**Ranking, 2015**	**Number of CTs/Ranking, 2014**
1	**Probiotech**	**14**	**4**	**1**	**11 CTs; 1**
2	**SIVIlab**	**10**	**1**	**2**	**n/a**
3	**IPHARMA**	**8**	**7**	**3**	**9 CTs; 2**
4	**Medical Development Agency (MDA)**	**6**	**4**	**4**	**1 CT; 6-13**
5	**Pharm-Solyur**	**3**	**2**	**5-6**	**2 CTs; 4-5**
6	**OCT**	**3**	**3**	**5-6**	**1 CT; 6-13**
7	**Atlant Clinical**	**2**	**2**	**7**	**n/a**
8	**MDP-Group**	**1**	**1**	**8-11**	**n/a**
9	**Smooth**	**1**	**1**	**8-11**	**n/a**
10	**PharmaReg**	**1**	**1**	**8-11**	**n/a**
11	**PharmErudit**	**1**	**1**	**8-11**	**n/a**

Data from www.grls.rosminzdrav.ru

We would like to close this section with the data on active participation by medical organisations in conducting bioequivalence studies. The top 15 such organisations are presented in Table 19. This data reflects both the total number of bioequivalence trials in which an organisation participated in 2015 and the total volume of such trials that were conducted by domestic and foreign sponsors respectively.

Table 19

Top-15 medical organisations taking part in bioequivalence studies approved in 2015				
Ranking	**Name of medical organisation**	**Total**	**Domestic sponsors**	**Foreign sponsors**
1	Yaroslavl region "Clinical Hospital No. 3", Yaroslavl	43	18	25
2	Yaroslavl region "Clinical Hospital No. 2", Yaroslavl	32	10	22
3	"Clinic Family Doctor+", Nizhny Novgorod	27	26	1
4	"BioEk", St. Petersburg	24	16	8
5	"E. D. Goldberg Research Institute of Pharmacology and Regenerative Medicine", Tomsk	22	15	7
6-7	"N. I. Pirogov Moscow City Clinical Hospital No. 1", Department of Health of the City of Moscow	16	14	2
6-7	"Republic Clinical Hospital No. 2", Kazan	16	3	13
8	"Research Centre for Eco-safety", St. Petersburg	15	1	14
9	"Hospital of the Russian Academy of Sciences" (Troitsk)	13	0	13
10	"North-west Research Centre for Hygeine and Public Health", St. Petersburg	12	9	3
11	"Medical Centre Probiotech", Serpukhov	11	10	1
12	"Cardiological Dispensary", Ivanovo	9	6	3
13	Yaroslavl region "Yaroslavl regional Clinical Narcotics Hospital", Yaroslavl	8	7	1
14	"State Research Centre for Prophylactic Medicine", Russian Ministry of Health, Moscow	7	0	7
15	"S. I. Spasokukotsky City Clinical Hospital", Department of Health of the City of Moscow	6	1	5

Data from www.grls.rosminzdrav.ru

TIMEFRAMES FOR ISSUANCE OF APPROVALS

This is the part of our annual newsletter where we usually examine the timelines to obtain approval documentation necessary to conduct clinical trials. We have the ability to access the information about timelines thanks to the monitoring carried out by ACTO at the beginning of each year. This year, 24 members of the association (CROs and pharmaceutical companies) took part in the poll about the timelines, and the calculations were based on data from about 220 applications to conduct trials, and more than 2,000 other applications (to import medicinal products and export biological samples, to make amendments to the protocol, and so on).

This year we once again had to slightly modify the questionnaire regarding approvals to conduct clinical trials (the polling methodology regarding the other approval documents did not change). The need to clarify the questionnaire was due to further corrections by the Ministry of Health in the review process of applications to conduct clinical trials.

First, we included additional graphs for the stage at which the Ministry of Health reviews the completeness of documents received and makes a decision about whether to proceed to expert review. In particular, we had to include into our calculation the period of time when the "clock is stopped" in the event that the Ministry of Health has a question regarding the completeness of the set of documents. This was made necessary because from July 1, 2015, the document pack must include a certificate from the authorities in the country of manufacture confirming that the manufacturing conforms to GMP requirements. Since far from all countries' authorities are actually able to issue such documents, applicants have encountered difficulties along the lines of 'go over there, not sure where, get that, not sure what'. Accordingly, there has been a significant increase (especially in the first few months of this new rule) in the number of queries by the Ministry of Health 'to clarify information presented', and so we have been forced to analyse this stage. We can say right away that applicants lost an average of 21 days at the stage of "answering the query".

A slight digression, on the topic of queries on document packs. In the beginning the law did not directly provide for the Ministry of Health to make such a request. And since the leadership of the responsible department has taken a rather steep approach, in practice when the department received an incomplete set of documents the department simply issued a straight-forward refusal of the application. This process continued until the law has been amended to specify the ability to form a request for clarification on the information received "in the event that false information is revealed". Why the Ministry of Health is so entrapped by the idea of "false information", we can only guess. And so the applicants, if they did not include a certain document in the application or if the Ministry of Health did not accept the format it was in, began to receive queries "about false information". You can imagine the reaction of foreign companies, receiving a document from the Ministry of Health that appears to accuse them of lying to a Russian state authority! With further amendments to the law, the unfortunate wording has been improved and now the wording says "incomplete and (or) false information". But in practice the Ministry of Health, with its significant inertia, has not changed and applicants are still receiving letters with frightening "queries about false information". On the basis of these cases, we would like to turn to the leadership of the responsible department in the Ministry of Health with a request to clarify the wording of these queries, stop terrifying our foreign colleagues over such an insignificant issue.

Returning to the polling methodology regarding timelines, we must mention one further change in the process of application review, but this time a positive one. And so, since the middle of last year, the need to make a repeat application for approval has finally been brought to an end. We'll explain briefly what we mean. Because of the fact that in the beginning, the law On the Circulation of Medicines did not fully and clearly lay out the procedure for obtaining approval to conduct international trials, the Ministry of Health in practice required a repeat application for the same trial. On the basis of the initial application the expert review was initiated, and only after that review the application had to be resubmitted. Otherwise the process stalled (*for more information see Informational-analytical Newsletter No. 3, pages 13-14).* The situation was absolutely absurd, but nevertheless this practice continued for nearly five years. And now finally, first at the request of the Ministry of Economic Development and then with the force of amendments to the law, the Ministry of Health was forced to drop this obstacle, which has saved on the order of a few weeks.

The results of monitoring of timelines in general are presented in Table 20.

Table 20

Timeframes for Issuing Approvals, 2015					
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**	**98**	**50**	**263**	**220**
To Import Medicines	**8/12**	**13**	**3**	**48**	**361**
To Import/Export Biosamples	**13/19**	**19**	**6**	**57**	**694**
To Make Amendments to the Protocol	**34/48**	**52**	**7**	**103**	**342**
Other Approvals (to Prolong Clinical Trials, to Include New Sites, to Enroll Additional Patients, etc.)	**25/35**	**24**	**5**	**88**	**665**
Total Time to Obtain Approvals to Conduct Clinical Trials and to Import/Export	**54/76**	**117**	**-**	**-**	**-**

Data from timeframes monitoring of ACTO

More detailed data on each type of approval with a breakdown by stage can be found on the ACTO website at http://www.acto-russia.org/files/sroki_2015.pdf. Why do we devote so much attention to this description? The issue is that last year, representatives from the responsible department at the Ministry of Health during one of their meetings with ACTO expressed their dislike of the fact that we publish data on timelines, and also their doubts in our methodology, and even in our right to conduct such a project in principle.

Our commentary then and now is as follows: we are ready to discuss the format of our poll and the methodology of our analysis down to the tiniest detail, and we would be very glad to correct any imperfections. But the question of the project's very existence cannot be up for discussion. Perhaps the results of the analysis of timelines differ between us and the Ministry. And that is quite easily explained. The Ministry of Health looks at and considers everything "from inside", and the industry, "from outside". A bureaucrat is first and foremost occupied with ensuring that he is officially conforming to the legislated timelines for which he is personally responsible, and acts like a chess player, setting the clock to "blitz". For the applicant, the speed with which that bureaucrat works is secondary, what is of foremost importance is the overall time needed to obtain approval and get started on the trial. The different interests are the reason to different approaches.

With this in mind, we tried to take into account every nuance. And we even went so far as to calculate the results in several different formats. And so if the reader would like to look at the link provided for full calculations on timelines, he will see four average timeframes for obtaining approval to conduct clinical trials:

1) The average timeframe to obtain approval for applications on which there were no expert review queries. The result for 2015 was 75 days. This outcome, absence of expert review queries, happened in 61% of all applications
2) The average timeframe to obtain approval for applications on which there were expert review queries (the time to respond was not excluding from the question). The result for 2015 was 132 days, and this outcome (queries from the reviewers) happened in 39% of cases
3) The average timeframe to obtain approval for all applications (in the case of an expert review query the time to answer was excluded from the calculations). The result for 2015 was 78 days.

4) The average timeframe to obtain approval for all applications (in the case of an expert review query the time to answer was not excluded from the calculations). The result for 2015 was 98 days.

It is this last calculation – 98 days – that we used as the final result in Table 19, as well as to follow the dynamics by year. The Ministry of Healthy may consider this unfair, since we included all applications in this calculation, both those with expert query and those without. But since the applicants, as we already mentioned, are not interested in the time it takes a bureaucrat to fulfil his duties but rather are interested in the amount of time it will take them to obtain approval and start their clinical trials, we find this format more informative. Although, as we have already noted, calculations in other formats are also presented and can be used where necessary.

In Table 21 we present the data on changes to average timeframes for issuing various types of approval documents in 2015 as compared to 2014.

Table 21

Average Timeframes for Issuing Approvals, 2015 vs. 2014			
Type of approval	**2014**	**2015**	**2015 vs. 2014, %**
To Conduct Clinical Trials	**95**	**98**	**3,2%**
To Import Medicines	**14**	**13**	**-7,1%**
To Import/Export Biosamples	**23**	**19**	**-17,4%**
To Make Amendments to the Protocol	**60**	**52**	**-13,3%**
Other Approvals (to Prolong Clinical Trials, to Include New Sites, to Enroll Additional Patients, etc.)	**27**	**24**	**-11,1%**

Data from timeframes monitoring of ACTO

As we can see, apart from the timeframes to obtain approval to conduct clinical trials (98 days in 2015 compared to 95 in 2014), in all other categories timeframes were slightly shorter than in 2014.

The reason is perhaps insignificant, but why is there an increase in the approval timelines? There could be several factors to explain the increase. For example, queries both from the expert review organisations (especially the FSBI) and from the Ministry of Health (the aforementioned ‘queries about false information’). We remind readers that this period – 98 days – is calculated from the real timeframes experienced by companies to get their approvals. There could be technical hold ups at separate stages of the process. Recently applicants began to notice significant increases in the amount of time to obtain prepared documents. What do we mean by that? Establishing the time that the approval is issued is tricky as it could actually be one of two dates: the date that is indicated in this document, or the date that the document is received. These two dates almost never coincide. Employees in the department have to sign the prepared approval document, send it to the administrative department, and then the applicants must come in person to receive the document. Applicants started to complain recently that the timeframes for this final step of the process have suddenly increased. We do not know why. But the fact that the document is not actually accessible to the company does not really trouble the bureaucrats. Even less so as the difference in timeframes can always be explained by blaming the applicant, saying that they did not come and collect the approval promptly. And the company employee meanwhile has to explain himself to his boss, that he/she really isn’t negligent but that he/she cannot himself go and collect the long-awaited document if the document itself is not yet available. Here, in a word, are the different approaches to calculating the timelines.

And finally, the increase in the time to obtain approval to conduct clinical trials could be connected with the incredibly clumsy system of expert review. For example, as in the case with the ‘query about false

information' on the completeness of submitted documents, the first version of the law also lacked the ability to pause the process in the event of questions arising from the expert review organisation. Grasping the inconvenience of such a system, the Ministry of Health amended the law to add the right for the expert review organisation (FSBI) to make such a request. But they forgot the Ethics Council. And so the FSBI can request additional documentation, but the Ethics Council cannot. It can only approve or refuse the trial, but according to the opinion of the Ministry of Health, it doesn't have the right to ask any questions. Fortunately, they introduced an additional option "approve with conditions", when the applicant gets the approval but only after they make some changes to the working documentation as recommended by the Ethics Council. Very often, however, these recommendations could have been avoided at an earlier stage of the process, if the committee experts had had a chance to ask questions and receive timely answers to those questions. The very point of this situation is that questions from the FSBI are put to the applicant as part of the expert review process itself, whereas 'approval with conditions' by the Ethics Council is granted only after the expert review has been concluded. This means that a formal positive decision by the expert review can be granted only after the applicant makes the changes requested by the Ethics Council. All of this takes extra time – in practice, up to 53 days. Whenever the applicants asked that the Ethics Council be granted the same query procedure as the FSBI is using, the only answer that came from Ministry of Health bureaucrats was "not allowed". The law, you see, does not envisage such a procedure. Hard to believe that some applicant would run to challenge a query, understanding that the alternative would be a refusal and no opportunity to make another application. If the bureaucrats would only fight so hard for compliance with the law when sending applicants unreasonable, totally unfounded, and frequently simply contradictory to all logic and common sense expert conclusions such as from the FSBI! But no, the Ministry of Health in this case is more concerned with the formal side of the question, and not real efficiency in carrying out state functions.

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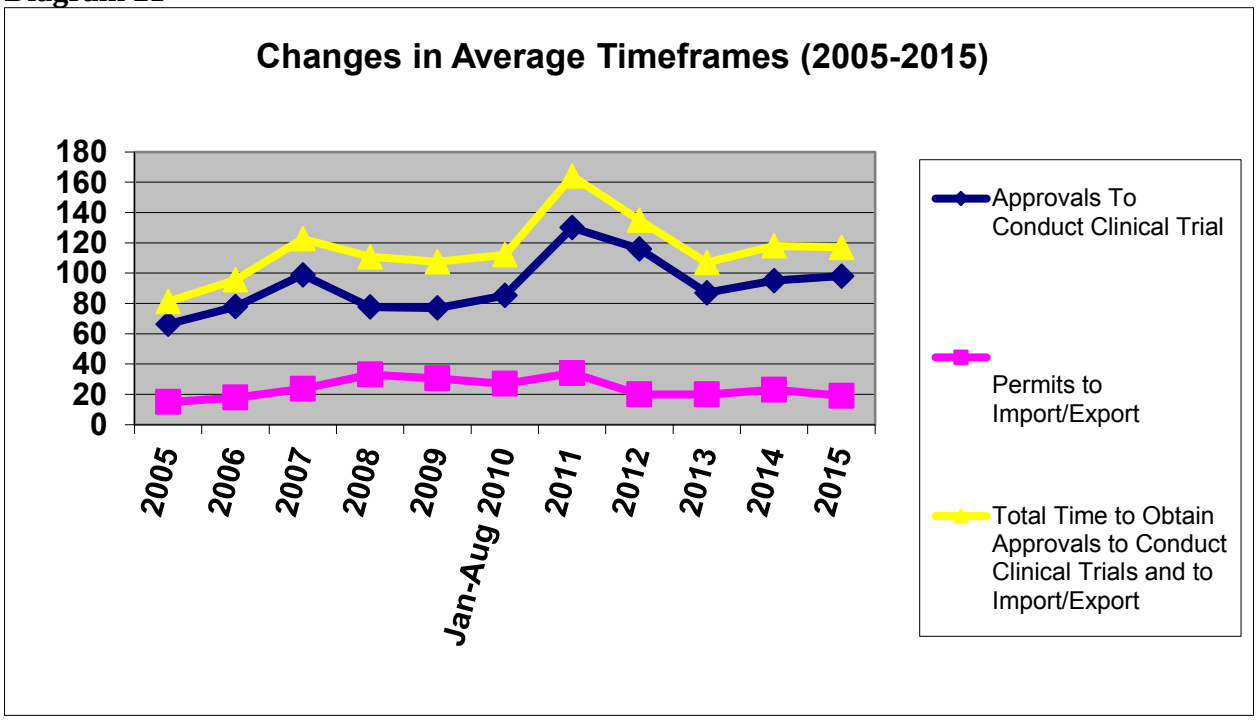
The dynamics of average timelines to issue approval documents year by year can be seen in Diagram 21.

Diagram 21



Data from timeframes monitoring of ACTO

In Table 22 we present information on how late approval documents were issued in 2015 compared to 2014.

Table 22

Violations of Timeframes, 2015 vs. 2014								
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	2015	8,2%	91,8%	67,2%	20,9%	3,7%	0,0%	0,0%
	2014	comparison is incorrect because of the changed method of calculating						
To Import Medicines	2015	59,1%	40,9%	22,4%	14,5%	2,5%	1,2%	0,3%
	2014	42,0%	58,0%	33,4%	16,6%	7,1%	0,6%	0,3%
To Import/Export Biosamples	2015	57,2%	42,8%	33,1%	7,6%	1,9%	0,2%	0,0%
	2014	29,5%	70,5%	43,5%	24,5%	2,3%	0,2%	0,0%
To Make Amendments to the Protocol	2015	47,3%	52,7%	42,6%	9,1%	0,9%	0,0%	0,0%
	2014	25,0%	75,0%	44,7%	28,4%	1,9%	0,0%	0,0%
Other Approvals (to Prolong Clinical Trials, to Include New Sites, to Enroll Additional Patients, etc.)	2015	92,1%	7,9%	6,7%	1,0%	0,2%	0,0%	0,0%
	2014	86,8%	13,2%	10,6%	1,9%	0,5%	0,2%	0,0%

Data from timeframes monitoring of ACTO

As we can see, it's a rather sad situation with obtaining primary approval to conduct clinical trials. Just 8.2% of approvals were issued on time. We did not compare this with the data from the previous year, and here's why. Earlier in calculating the share of approvals issued beyond the time limit, we used the dates on which approval was granted for all applications without exceptions (the method of calculation, described earlier as number 4, by which we calculated the average timeframe as 98 days). In order to pre-empt all questions and complaints from the regulator, this year we calculated the share of violations based on the data obtained by the method described earlier as number 1 (in other words, only using 'clean' applications, on which there were no queries from the expert review and for which the average timeframe for approval was 75 days).

In all other situations, we can see that the situation is not as bad, and over the past year has only improved, in fact rather significantly. So, the percentage of approvals to import medicinal product that were issued on time improved by 17% (59.1% in 2015 compared to 42% in 2014), and for import/export of bio-analogues, improvement was by 27.7% (57.2% compared to 29.5%).

The significant reduction in the share of delays when making changes to the protocol can only be heartening – 22.3% improvement compared to the previous year (47.3% compared to 25%). By the way, in last year's corresponding newsletter, we had expressed our wish to see the Ministry of Health conform more thoroughly to the statutory time limits for issuing these types of approvals.

Finally, a simply marvellous picture can be seen for other areas (extending trials, including other subjects, and so on), with 92.1% of these approvals issued on time.

Analysing this situation overall, we can see that historically, the worst problems with keeping to the prescribed timeframes come up with the Ministry of Health when the expert organisations are involved in the decision-making process – in obtaining approval to conduct a trial or in making changes to the protocol. The former requires involvement only from the Ethics Committee. And the picture there, as we can see, is far from catastrophic. Which is more than can be said of the timeframe to obtain primary approval where, in addition to the Ethics Committee, the FSBI is involved as an expert body.

TRIALS ON EBOLA VACCINE

In summing up the results of the past year, we can't avoid talking about a unique Russian development – a vaccination against Ebola virus. The world learned about this on January 13, 2016. The Ministry of Health announced, that Russia had developed two vaccines against Ebola, which were superior to other options, and that one of the vaccines was suitable for patients with a compromised immune system.

According to the state registry, on December 28, 2015 two vaccines were registered: "GamEvak vector Vaccine against Ebola Virus" and "GamEvak-Combi Combination Vector Vaccine against Ebola Virus". The holder of the registrations for these medicinal products is the federal Gamaleya Research Institute for Immunology and Microbiology. Of course we then checked the Ministry of Health register for an approval issued for a clinical trial on the vaccine in question. And – we found nothing.

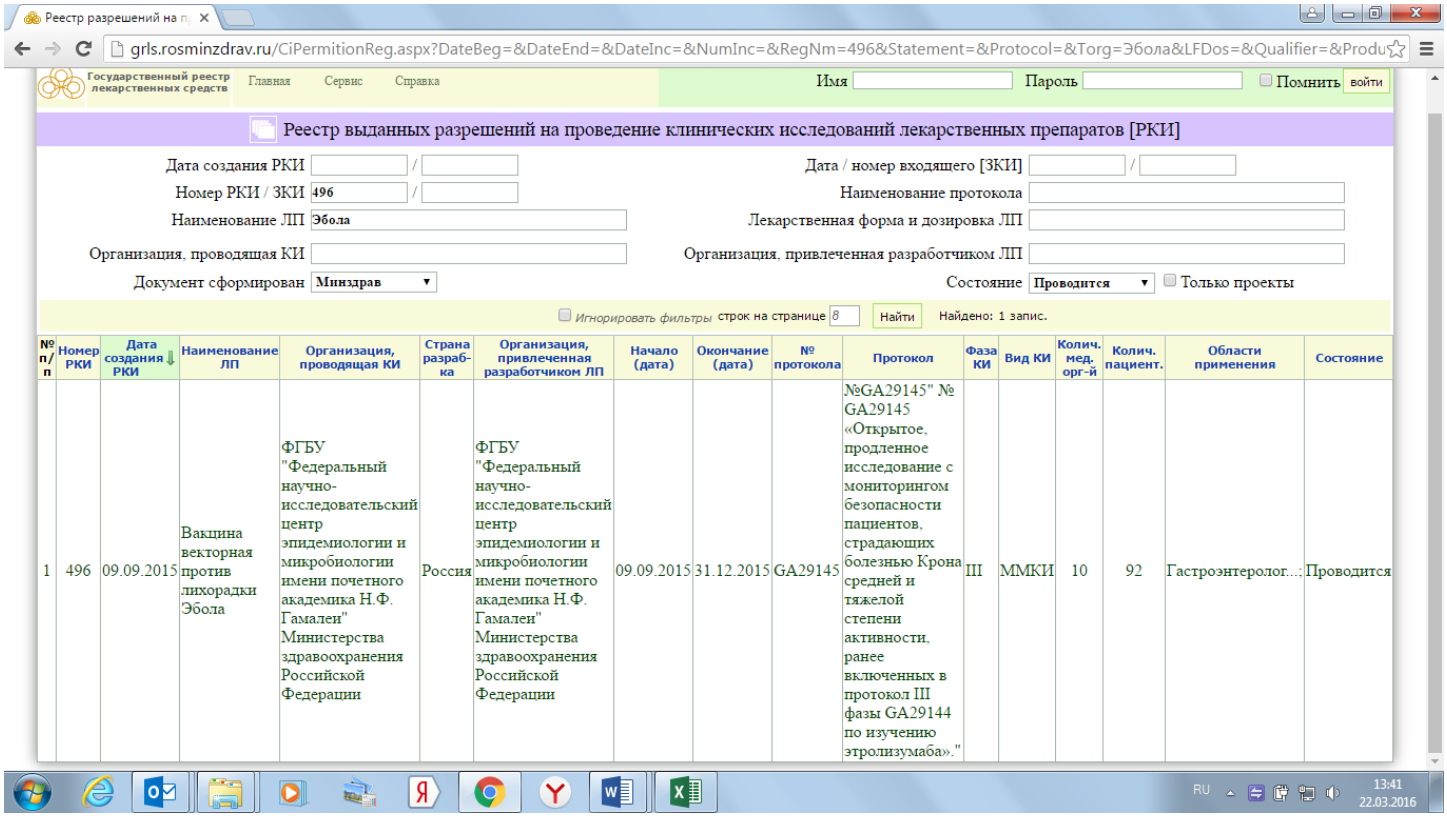
On February 15 the vaccine was presented in Geneva. The event was timed to coincide with a meeting between Russian Health Minister Veronika Skvortsova and General Director of the WHO Margaret Chen. According to announcements in the press quoting a leading employee of the Federal Gamaleya Research Institute for Immunology and Microbiology, Denis Logunov, the vaccine had shown good tolerance. A trial with 84 volunteers was mentioned.

On February 19, 2016, a new entry appeared in the Ministry of Health registry: approval for a trial under protocol No. 01-GamEvak-Combi-2016 "International multicentre trial of immunological medicinal product GamEvak-Combi Combination Vector Vaccine against Ebola Virus, 0.5 ml+0.5 ml/dose (approved by the Ethics Council on February 16, 2016). In the two-year trial (planned to be conducted between 01.03.2016 and 31.12.2017), classified as Phase III-IV, it was intended to enrol 10 patients in Russia. The trial, according to the registry entry, would be conducted in Moscow at the "Infection Clinical Hospital No. 1, Department of Health of the City of Moscow". When and where in Russia the previous phases of the trials were conducted, remains a mystery to us. On the one hand, we can't say that Eb3ola has been raging in Russia lately. On the other hand, according to Russian law, registering a medicinal product in Russia without trials in the country is not possible. How exactly the Gamaleya Research Institute for Immunology and Microbiology managed this is not clear.

On March 15 in Moscow there was a round table entitled "Russian vaccine against Ebola virus: first lessons and looking towards the future". From the press release of this event: "The Health Minister Veronika Skortsova said that the Russian Federation designated resources to conduct field trials of the new vaccine. The vaccine will be used on two thousand citizens of the Republic of Guinea. Testing is planned at Rusal's Research-Clinical Diagnostic Centre of Epidemiology and Microbiology in Guinea."

Glad for the residents of that distant country, we again had a look at the registry. And, oh what a miracle! We found an entry about a trial approved in 2015! True, the type of this entry perplexed us (and partly explains why we couldn't find it earlier). The approval was under the number 496 and was issued on September 9, 2015. Under "Medicinal product" it said "Vector vaccine against Ebola virus", and under "developer" it referenced the same Gamaleya institute. The surprise was the name of the protocol: "No GA29145 "Open-Label Extension and Safety Study for Patients With Crohn's Disease Previously Enrolled in the Etrolizumab Phase III Study GA29144". The therapeutic area, gastroenterology, was rather surprising. The goal of the study, it seems, did totally conform to expectations: "to evaluate the safety, reactogenicity and immunogenicity of the medicinal product – the vector vaccine against Ebola virus, intramuscular injection, dose/0.5 ml for healthy volunteers".

Unable to understand how to explain this discovery, we turned to our own notes (as an experienced and professionalorganisation it is typical to download and keep notes on the registry of approved studies). It turned out that under No. 496 September 9, 2015, there was in fact an approval for a trial of the Etrolizumab, by company F. Hoffmann-La Roche Ltd. (so the name of the protocol did correspond to the earlier entry). After that, the registry entry partly remained with the F. Hoffmann-La Roche Ltd. trial and partly was replaced with information about a trial on Ebola vaccine (and therefore, by the way, it was hard to find, because a search for this protocol turned up Etrolizumab). A technical glitch? But then where is the original entry for the trial?



Реестр разрешений на п

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Государственный реестр лекарственных средств | Главная | Сервис | Справка | Имя | Пароль | Помнить | войти

Реестр выданных разрешений на проведение клинических исследований лекарственных препаратов [РКИ]

Дата создания РКИ / Дата / номер входящего [ЗКИ]

Номер РКИ / ЗКИ: 496 / Наименование протокола

Наименование ЛП: Эбола / Лекарственная форма и дозировка ЛП

Организация, проводящая КИ / Организация, привлеченная разработчиком ЛП

Документ сформирован: Минздрав / Состояние: Проводится / Только проекты

Игнорировать фильтры строк на странице 8 Найти Найдено: 1 запис.

№ п/п	Номер РКИ	Дата создания РКИ	Наименование ЛП	Организация, проводящая КИ	Страна разраб-ка	Организация, привлеченная разработчиком ЛП	Начало (дата)	Окончание (дата)	№ протокола	Протокол	Фаза КИ	Вид КИ	Колич. мед. орг-й	Колич. пациент.	Области применения	Состояние
1	496	09.09.2015	Вакцина векторная против лихорадки Эбола	ФГБУ "Федеральный научно-исследовательский центр эпидемиологии и микробиологии имени почетного академика Н.Ф. Гамалеи" Министерства здравоохранения Российской Федерации	Россия	ФГБУ "Федеральный научно-исследовательский центр эпидемиологии и микробиологии имени почетного академика Н.Ф. Гамалеи" Министерства здравоохранения Российской Федерации	09.09.2015	31.12.2015	GA29145	№GA29145" № GA29145 «Открытое, продленное исследование с мониторингом безопасности пациентов, страдающих болезнью Крона средней и тяжелой степени активности, ранее включенных в протокол III фазы GA29144 по изучению этролизумаба»."	III	ММКИ	10	92	Гастроэнтеролог...;	Проводится

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In addition, we checked over the materials from the Ethics Council which, by order of the Ministry of Health, must be published on the official website within three working days after each meeting. We checked all meetings for 2015. We could not find a single decision on the trial mentioned above for a vector vaccine against Ebola virus in any Ethics Council materials[1].

How can all of this be explained? On what basis was this medicinal product registered? For now we have more questions than answers. We hope that we will have the chance to learn more about this situation.

[1] At the end of September 2015, the Ethics Council approved a conduct of a trial for a prophylactic vaccine against Ebola virus, but by a completely different manufacturer – Vektor. However, according to the state register, this trial has not yet obtained Ministry of Health approval.