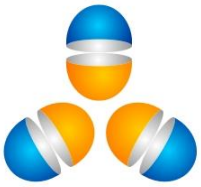


ACTO

Association of Clinical Trials Organizations

ACTO NEWSLETTER №8

Summary of 2013 results

MOSCOW 2014

CONTENTS

SUMMARY

In 2013 the Ministry of Health issued 791 approvals to conduct clinical trials. This was 13.6% fewer than in 2012. The most significant drop was in the sector for trials of Russian sponsors. And so, the number of local trials in that sector dropped by 24.8% (124 compared to 165 in 2012), and bioequivalence studies dropped by 26.9% (155 compared to 212). The number of approvals for international multicentre trials (IMCT) decreased by 9.5% (334 compared to 369). As a result the volume of this sector was down to 2006 levels.

Insignificant growth was noted only in sectors of local trials of foreign sponsors. There was a rise of 2.8% from 2012 in the number of approvals for bioequivalence studies and by 9.7% in the number of local trials of efficiency and safety.

Analysis of the structure of the market by type of trials has shown that the trends ACTO saw in 2012 have only strengthened. As of today the adoption of the law "On the Circulation of Medicines" has resulted in the following results:

- A significant contraction in the share of IMCTs (42.2% in 2013 against 59.6% in the pre-reform period) and the virtual lack of the expected growth in this sector of the market on the number of trials.
- Significant growth was observed in the share of bioequivalence studies of foreign generics, from the pre-reforms 1.8% to almost 14% in 2013.
- Insignificant growth in the number of local trials by foreign sponsors (from 5.6% to 8.6%). 77.9% of these trials are on generic medicines. This means that the majority of innovative manufacturers, coming up against the need to conduct repeat trials in Russia, have adopted a wait-and-see approach. And no one knows when new medicines, which are already on sale in other countries, might make it to Russian consumers.
- The share of local trials with Russian companies over the past year has only decreased, from 19.8% to 15.7%. 42.7% of this sector of the market is also trials for generics. And just 24.2% is trials for original developments from domestic pharmaceutical companies.

The main conclusion is that as a result of the reforms, the Russian market for clinical trials has significantly turned towards copy medicines.

Another subject in this issue is the analysis of the structure of the market by therapeutic areas. 26% of all approvals granted in 2013 for IMCTs were on cancer drugs. Out of the foreign-made generics the largest share of 26.8% went to medicines used in cardiology and cardiovascular disease. Domestic manufacturers of generic medicines are concentrated primarily on infectious diseases (22.8%).

Analysing the year's results, we decided to look at the relationship between trials conducted by pharmaceutical companies themselves, and by attracting contract research organisations (CRO). In addition, we created a rating of the most active companies by separate market sectors. We hope that this section of the newsletter will be of interest to our readers.

As usual we present the results of the annual ACTO monitoring of waiting periods for issuance of approval documents. In 2013 the Ministry of Health changed the process of reviewing applications to conduct trials. They began issuing refusals more frequently. In order to resolve the situation and continue the review process, the companies had to put in a wholly new application and full set of documents. In practice this led to the formal reduction of waiting periods, but in practice this situation only leads to longer lead-times to begin trials. As a result the average wait time for an approval decreased by 29 days (from 116 in 2012 to 87 in 2013). Without trusting too much in this improvement, we can nevertheless speak with certainty about reduced times to issue other types of approvals, where practice has remained unchanged. And so, the average time to obtain permit to import investigational product was 14 days, compared to 18 in 2012, the time to get approval of protocol amendments was 45 days compared to 64 days in 2012, and the time for other approvals (extending the trials, additional patients, and so on) was 26 days compared to 41 in 2012.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

In 2013 the Ministry of Health issued 791 approvals to conduct clinical trials. This was down 13.6% from 2012 (Table 1). Let us remember that 2012 was a record year in the number of approvals issued.

Reductions in comparison with previous year's figures were shown in nearly all market sectors, with the exception of local trials for efficacy and safety and bioequivalence studies by foreign sponsors. And so, the number of approvals for IMCTs decreased by 9.5% (334 compared to 369). Much more significantly, the number of approvals for trials by Russian sponsors was down by a quarter. And so the number of local trials for domestic manufacturers was down 24.8% (124 compared to 165), and the number of bioequivalence studies was down 26.9% (155 compared to 212). That, by and large explains the drop in the overall figures for 2013.

As we have already said, growth was seen only in the sectors of local trials by foreign sponsors. In truth, this growth was minimal – the total difference as compared to 2012 was just nine trials. There was growth of only 2.8% in the number of approvals for bioequivalence studies for foreign medicines (110 compared to 107), and of 9.7% in the number of approvals of local trials of efficacy and safety (68 compared to 62).

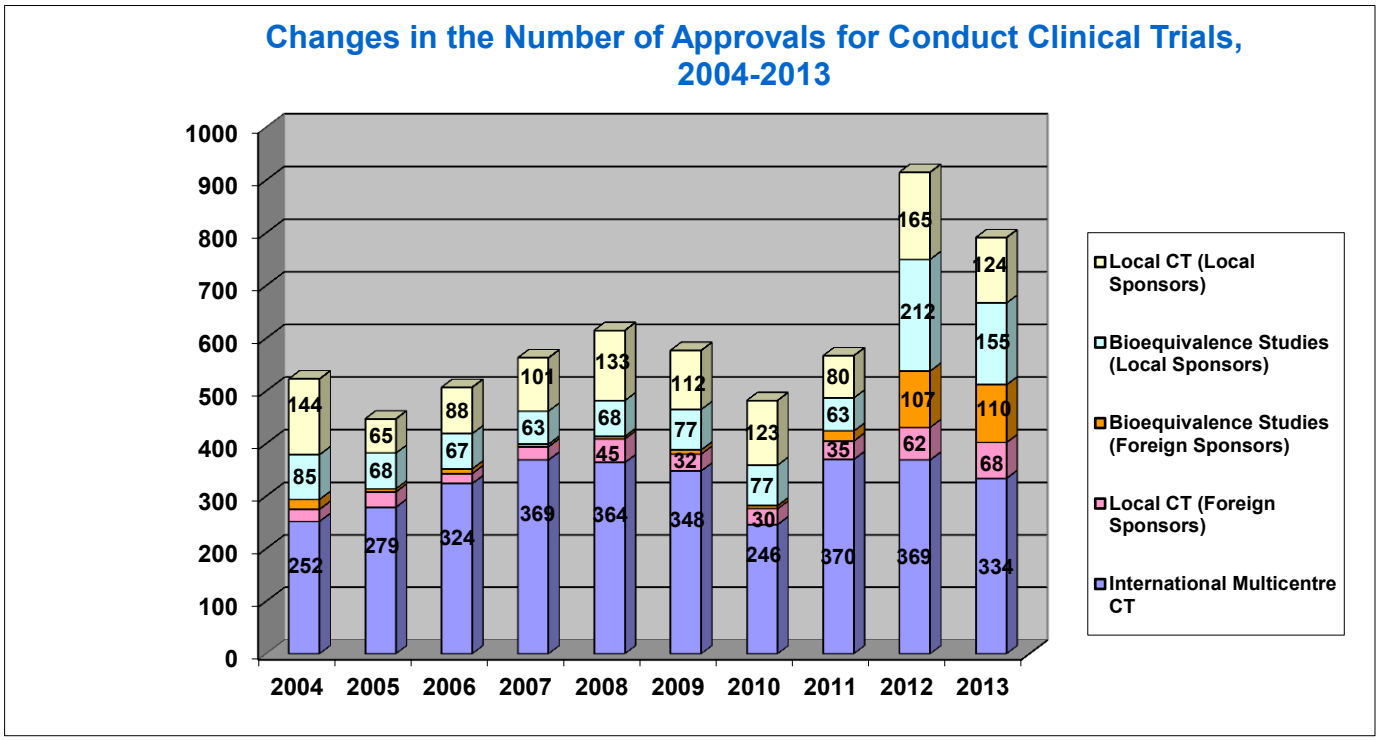
Table 1

Approvals for Conduct Clinical Trials: 2013 vs. 2012						
	Total	**International Multicentre Clinical Trials**	**Local Clinical Trials (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local Clinical Trials (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
2013	**791**	**334**	**68**	**110**	**124**	**155**
2012	**915**	**369**	**62**	**107**	**165**	**212**
2013 vs. 2012, %	**-13,6%**	**-9,5%**	**9,7%**	**2,8%**	**-24,8%**	**-26,9%**

Data from www.grls.rosminzdrav.ru

The dynamics of the Russian clinical trials market and in particular the impact of one of the most important events of recent years – the 2010 adoption of the law "On the Circulation of Medicines" – is much better explained in Diagram 1.

Diagram 1



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

After the market drop in 2010, brought about by the reform of the approval system, it took another year to recover. Then in 2012 there was significant growth – of more than 60% – in the number of approved trials. This is explained firstly by the significant jump in the number of trials in the sector for bioequivalence studies by both Russian and foreign sponsors – by a factor of three and nearly six times, respectively (*for more information see ACTO Newsletter No.6).* The number of issued approvals for IMCTs in 2012 remained at the 2011 level.

As we said, 2013 brought a reduction in the total number of approvals issued. And the number of approvals issued for IMCTs fell to 2006 levels[1].

What kind of conclusions can we draw, looking at these market dynamics? First, we cannot fail to recognise that the adoption of the law "On the Circulation of Medicines", and most importantly its requirements on the mandatory registration local trials, has had a huge impact on the clinical trials market. Second, the impact has not been entirely what we expected.

We remember that the grounds for the need to conduct registration trials were said, by bureaucrats, to be: "Let the companies come to Russia with their international trials." ACTO subsequently spoke out against this requirement, but anyway expected that it would obliquely stimulate growth in the number of IMCTs taking place in Russia. However as we see, these predictions have yet to come true. First the reform 'worked' on generics, requiring them to conduct both repeat bioequivalence studies (for foreign medicines) and 'therapeutic equivalence' trials. The latter referred to all generic medicines, regardless of their 'nationality'.

[1] Without taking into account data from the 'reform year' of 2010

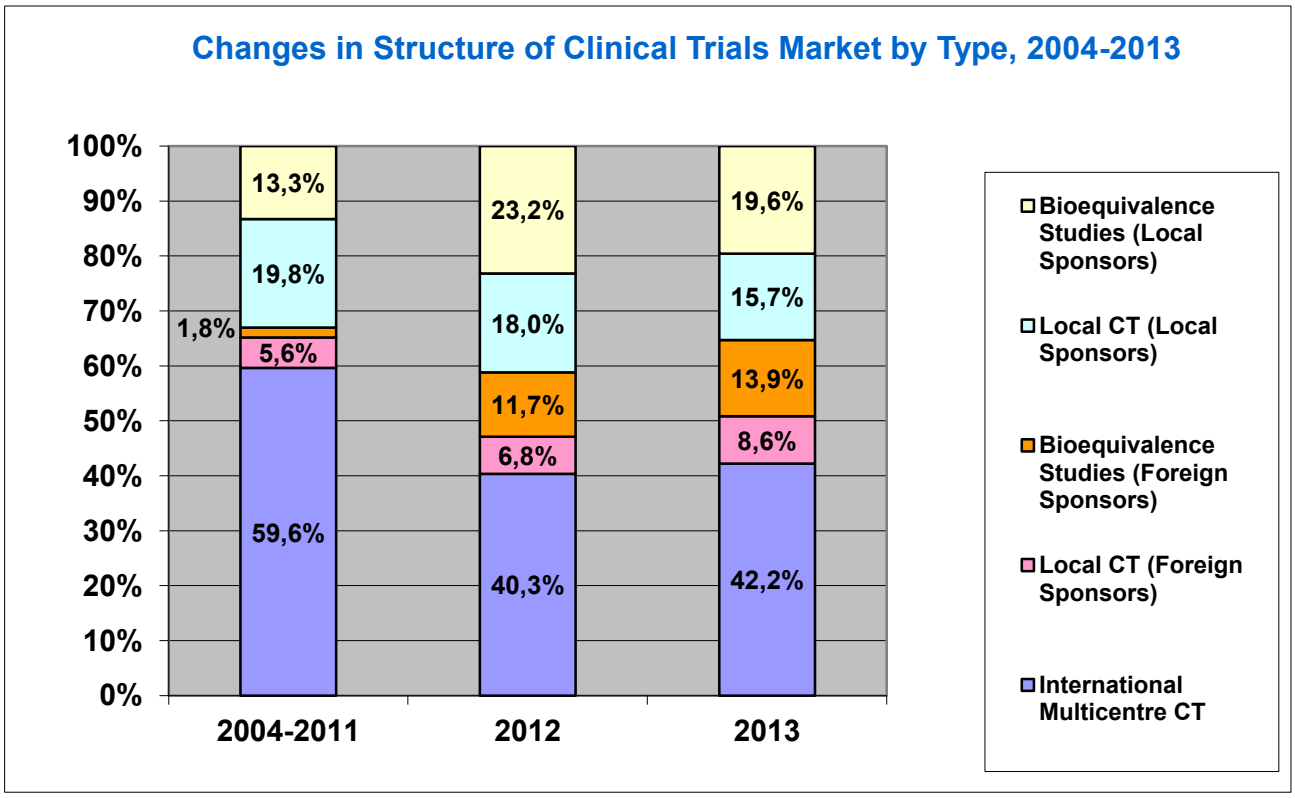
Here we must also explain that the insignificant growth in the number of local trials of efficacy and safety of foreign medicines, as we will see later, was due primarily to the impact of generics, and not at all to brand name medicines. Regarding IMCTs, that number as we have already seen increased slightly in 2011-2012, but in the last year not only did not grow, it in fact fell. The reason for this effect is not yet entirely clear. But the fact remains a fact – it would seem logical that the expected growth in international projects as a result of the adoption of the law "On the Circulation of Medicines" is not yet in evidence.

THE STRUCTURE AND DYNAMICS OF THE MARKET FOR CLINICAL TRIALS BY TYPE

Let us look at how the structure of the market has changed over these years by type (Diagram 2). The picture confirms what we have already said. Up to 2011 the relationship between various types of clinical trials was relatively stable (this is why in the diagram we present the average breakdown of shares on 2004-2011 data). In 2012 the market structure changed significantly for the first time. The share of IMCTs dropped by nearly 20%. This was because of growth in the share of other types of trials – primarily bioequivalence trials by both foreign and domestic sponsors. And while in relationship to Russian medicines the growth in 2012 was reversed with a slight drop last year, for generics from foreign manufacturers the share of bioequivalence trials continues to grow, and in two years has gone from inconsequential 1.8% of the market to nearly 14%.

From the diagram we can also see that contrary to expectations, there was almost no growth in the share of local trials of efficacy and safety for foreign medicines – from 5.6% to 8.6% over two years. At the same time, as we have said, and as we see below, this growth was achieved in trials of generic medicines. Regarding the share of local trials by domestic manufacturers, this has even dropped slightly, from 19.8% to 15.7%.

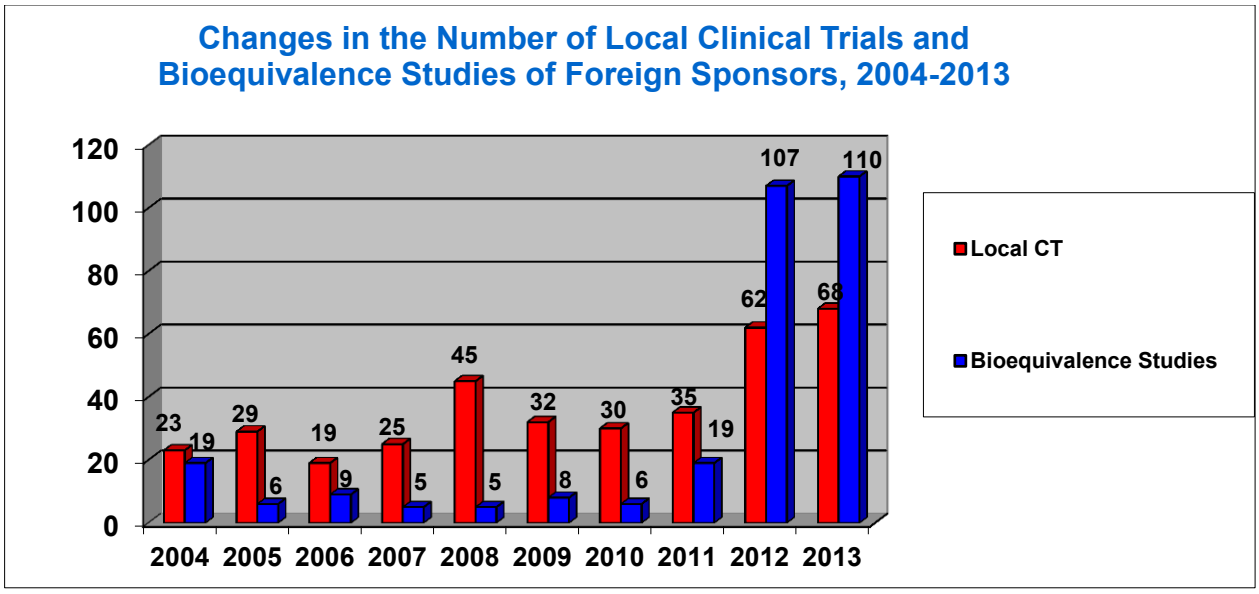
Diagram 2



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

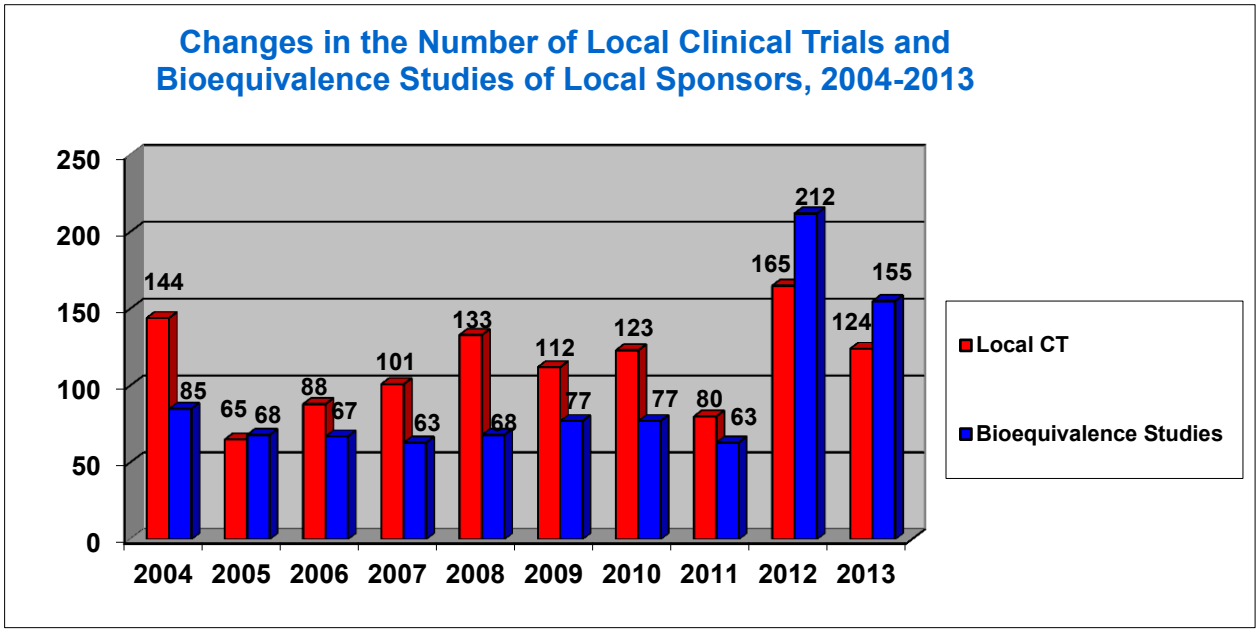
In Diagrams 3 and 4 we show the dynamics of the number of approvals for local trials of efficacy and safety, as well as bioequivalence studies by foreign and Russian manufacturers by year. We see that for both categories of sponsors up to 2012 local trials of efficacy and safety predominated. In 2012 there was a step-change – now the number of bioequivalence studies exceeded the number of local trials of efficacy and safety. The trend that we noted a year ago continued in 2013. This once again confirms our conclusion that as a result of the reforms, the clinical trials market has significantly shifted in the direction of trials on generic medicines.

Diagram 3



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

Diagram 4



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

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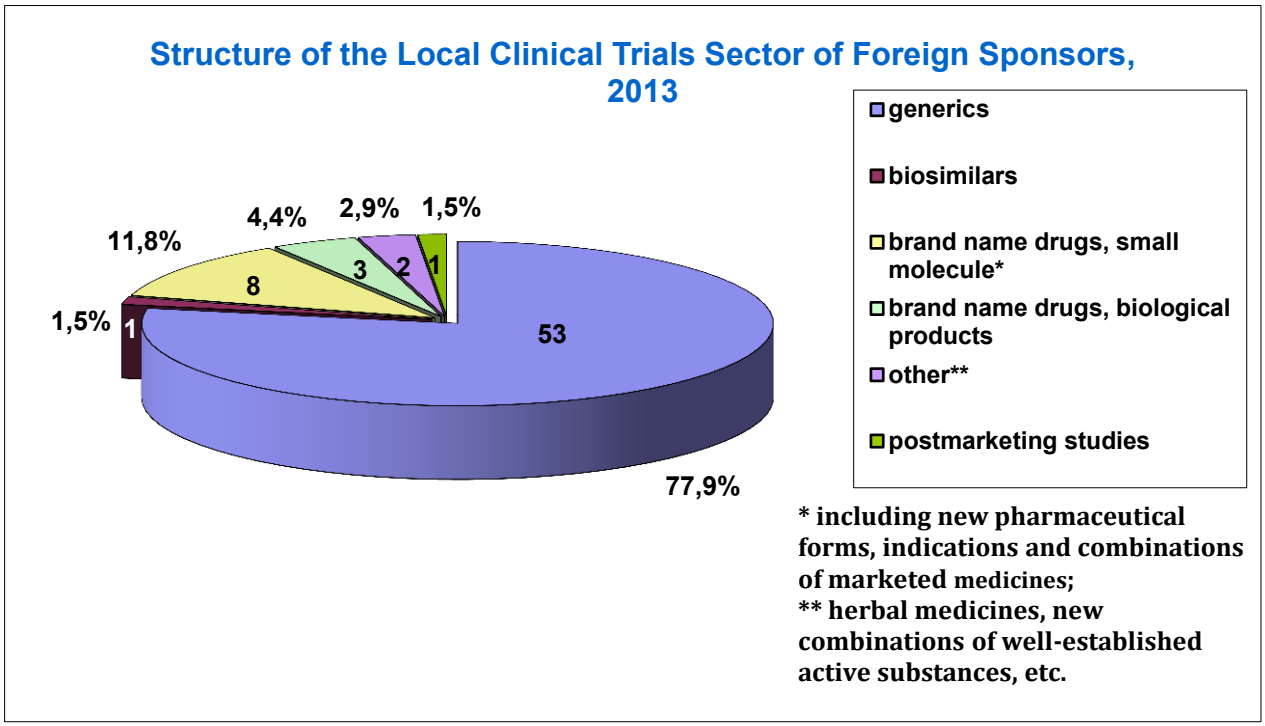
In Diagrams 5 and 6 we present the structure of the sector of local trials of efficacy and safety separately for foreign and Russian sponsors.

This year we have slightly corrected the classification we used earlier. And so, trials on brand name drugs we have broken down into two separate groups – for small molecules and for biological products. In addition, for trials by Russian sponsors we had to create another group – 'unidentified'. The issue is that we had to classify the trials ourselves, owing to the quite sparse information contained in the Ministry of Health

register. Frequently the only indicator is the name of the drug and the protocol. These data are not always enough to go on, to understand what kind of medicine is being studied.

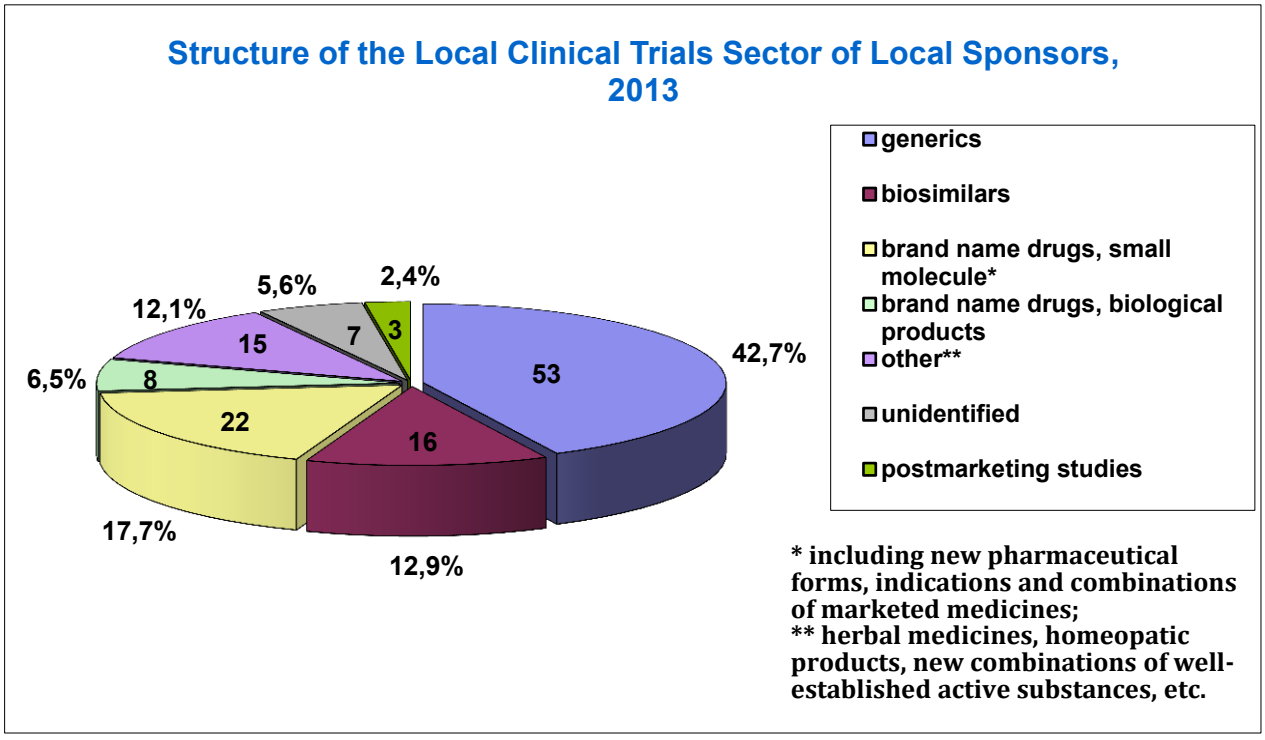
As in the previous year, we set in a separate group the postmarketing trials. By the way, the number of such trials in 2013 was quite insignificant.

Diagram 5



Data from www.grls.rosminzdrav.ru

Diagram 6



Data from www.grls.rosminzdrav.ru

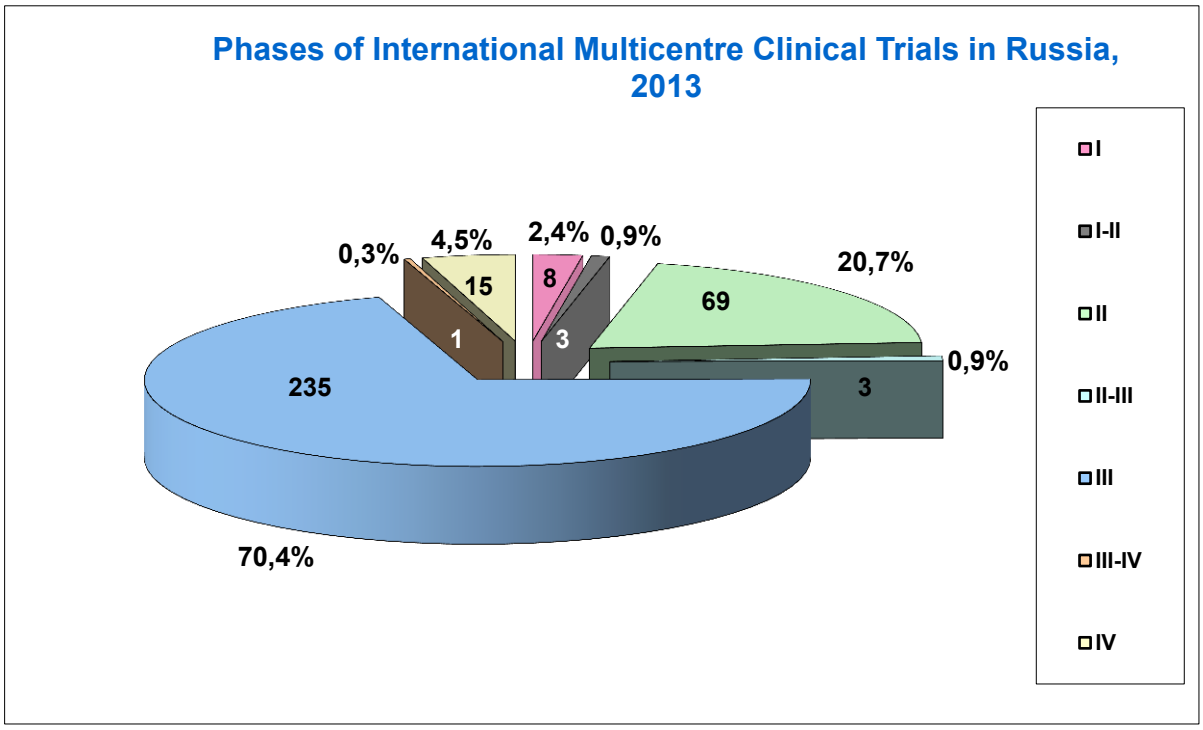
As we can see from these two diagrams, without a doubt the leading position goes to generics. This aspect of the sector for local trials we noted already last year (*see ACTO Newsletter No.6).* We can only add that in 2013 the share of generic medicines grew only slightly compared to previous year's figures, amounting for trials by Russian sponsors to 43% compared to 41% in 2012, and by foreign sponsors, 78% against 73%.

We would like to comment on one further trend, which we first noticed in our analysis of data in 2013. By all accounts, previously announced partnerships between a number of Russian companies and their western colleagues have come into the active, practical stage. And so, according to the Ministry of Health register, last year a minimum of six approvals were issued for clinical trials on brand name drugs, which were being developed by domestic companies on a partnership basis. These companies include ChemRar, R-Pharm, and NeuroMax.

THE STRUCTURE AND DYNAMICS OF THE MARKET FOR INTERNATIONAL MULTICENTRE CLINICAL TRIALS BY PHASES

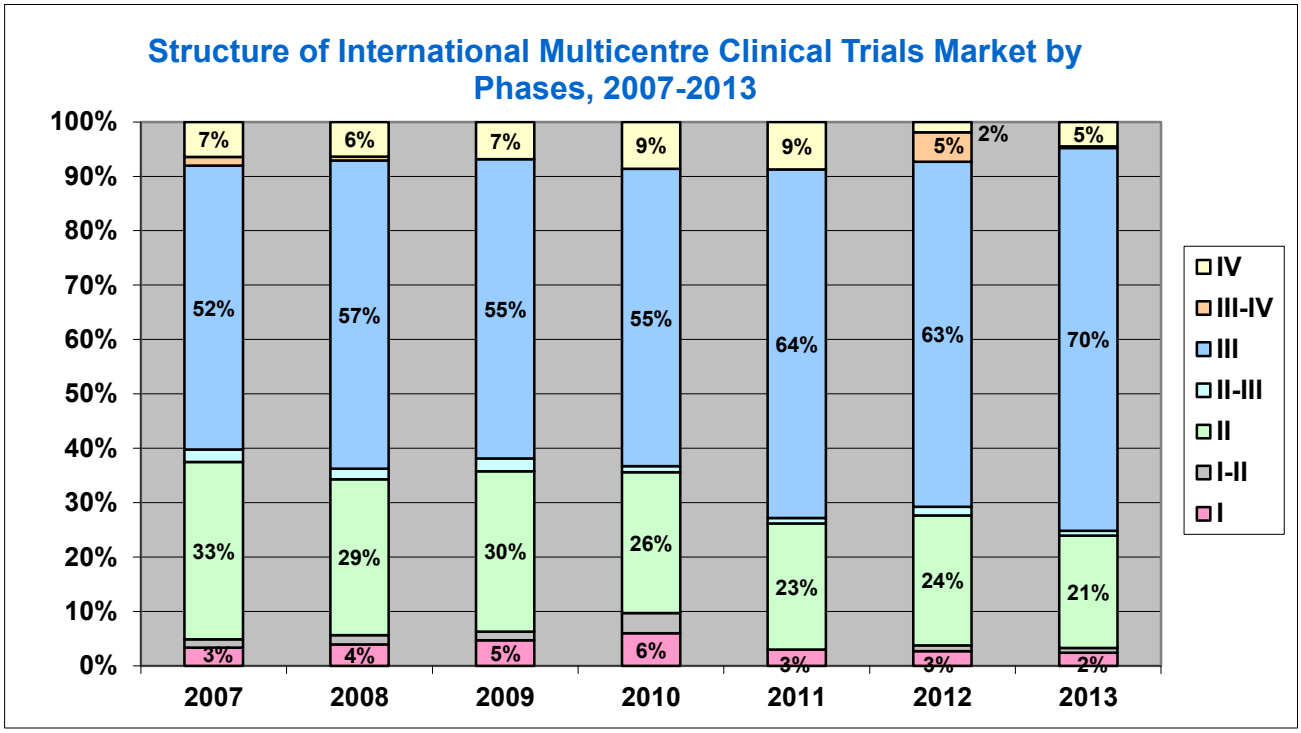
Data about the breakdown of approvals in 2013 for IMCT by phases are presented in Diagram 7. For comparison, in Diagram 8 we present the same breakdown but with dynamics by year – from 2007-2013.

Diagram 7



Data from www.grls.rosminzdrav.ru, [www.clinicaltrials.gov, www.clinicaltrialsregister.eu](http://www.clinicaltrials.gov)

Diagram 8



Data from www.grls.rosminzdrav.ru, www.rosminzdrav.ru, [www.clinicaltrials.gov, www.clinicaltrialsregister.eu](http://www.clinicaltrials.gov)

We can see that in the past three years, the share of phase III IMCT has increased in comparison with previous years. The share of trials of other phases has, in contrast, fallen.

We can only add that out of the eight approvals granted in 2013 for phase I international trials, three were to study medicines to treat cancers, two each were for the treatment of rheumatoid and idiopathic arthritis, and one was a medicine designed to treat systemic lupus erythematosus.

THE STRUCTURE OF CLINICAL TRIALS BY THERAPEUTIC AREAS

In preparing this edition, we decided to also look at the breakdown between various types of trials by therapeutic areas.

Table 2 gives an overall picture of the type of breakdown in IMCT sectors. As we can see, more than a quarter of all international trials are in the field of oncology.

Table 2

Split of International Multicentre Clinical Trials by Therapeutic Areas		
Therapeutic Area	**Number of IMCT**	**Share, %**
Oncology	**87**	**26,0%**
Rheumatology	**33**	**9,9%**
Endocrinology	**32**	**9,6%**
Cardiology and Cardiovascular diseases	**31**	**9,3%**
Infectious diseases	**28**	**8,4%**
Neurology	**28**	**8,4%**
Pulmonology; Phthisiology	**26**	**7,8%**
Psychiatry	**18**	**5,4%**
Hematology	**16**	**4,8%**
Dermatology; Immunology	**11**	**3,3%**
Nephrology	**7**	**2,1%**
Gastroenterology	**5**	**1,5%**
Ophthalmology	**4**	**1,2%**
Urology	**3**	**0,9%**
Others	**5**	**1,5%**
TOTAL	**334**	**100,0%**

Data from www.grls.rosminzdrav.ru

In Tables 3 and 4 we present data on trials of generics and biosimilars by both foreign and domestic sponsors. And so, the leading position among foreign sponsors goes to trials in the fields of cardiology and

cardiovascular disease (26.8%), second place goes to trials on generics used for infectious diseases (17.1%). Among domestic sponsors, in contrast, first place goes to trials in the field of infectious diseases (22.8%), and second to cardiology and cardiovascular disease (16.5%).

Table 3

Split of Local Clinical Trials and Bioequivalence Studies (Generics and Biosimilars) of Foreign Sponsors		
Therapeutic Area	**Number of CT**	**Share, %**
Cardiology and Cardiovascular diseases	**44**	**26,8%**
Infectious diseases	**28**	**17,1%**
Neurology	**16**	**9,8%**
Pulmonology; Phthisiology	**15**	**9,1%**
Analgesic and Anti-inflammatory medicines	**8**	**4,9%**
Rheumatology	**7**	**4,3%**
Allergology	**6**	**3,7%**
Gastroenterology	**6**	**3,7%**
Oncology	**6**	**3,7%**
Hepatology	**4**	**2,4%**
Ophthalmology	**4**	**2,4%**
Endocrinology	**4**	**2,4%**
Anesthesiology, Surgery, Intensive care	**3**	**1,8%**
Urology	**3**	**1,8%**
Others	**10**	**6,1%**
TOTAL	**164**	**100,0%**

Data from www.grls.rosminzdrav.ru

Table 4

Split of Local Clinical Trials and Bioequivalence Studies (Generics and Biosimilars) of Local Sponsors		
Therapeutic Area	**Number of CT**	**Share, %**
Infectious diseases	**51**	**22,8%**
Cardiology and Cardiovascular diseases	**37**	**16,5%**
Pulmonology; Phthisiology	**19**	**8,5%**
Neurology	**19**	**8,5%**
Oncology	**18**	**8,0%**
Analgesic and Anti-inflammatory medicines	**15**	**6,7%**
Endocrinology	**10**	**4,5%**
Rheumatology	**9**	**4,0%**
Psychiatry	**8**	**3,6%**
Urology	**7**	**3,1%**
Gastroenterology	**7**	**3,1%**
Hematology	**6**	**2,7%**
Allergology	**5**	**2,2%**
Dermatology; Immunology	**4**	**1,8%**
Otorhinolaryngology	**3**	**1,3%**
Others	**6**	**2,7%**
TOTAL	**224**	**100,0%**

Data from www.grls.rosminzdrav.ru

Data on local trials of brand name drugs are presented in Tables 5 and 6 (for foreign and domestic manufacturers, respectively). Since the number of such trials was limited, we considered a not entirely accurate to count the percentage of shares conducted in a given field of therapy.

Table 5

Split of Local Clinical Trials of Brand Name Drugs of Foreign Sponsors	
Therapeutic Area	**Number of CTs**
Infectious diseases	**4**
Cardiology and Cardiovascular diseases	**3**
Analgesic and Anti-inflammatory medicines	**1**
Nephrology	**1**
Ophthalmology	**1**
Gastroenterology	**1**
TOTAL	**11**

Table 6

Split of Local Clinical Trials of Brand Name Drugs of Local Sponsors	
Therapeutic Area	**Number of CTs**
Infectious diseases	**11**
Oncology	**5**
Neurology	**3**
Cardiology and Cardiovascular diseases	**2**
Gastroenterology	**1**
Dermatology; Immunology	**1**
Narcology	**1**
Nephrology	**1**
Psychiatry	**1**
Pulmonology	**1**
Rheumatology	**1**
Radiology	**1**
Endocrinology	**1**
TOTAL	**30**

Data from www.grls.rosminzdrav.ru

WHO'S WHO: THE MAJOR PLAYERS ON THE RUSSIAN CLINICAL TRIALS MARKET

In this edition we also decided to look at how approvals break down by sponsor companies and contract research organisations (CROs). This was made possible thanks to the Ministry of Health registry, which has separate categories for "organisation conducting the clinical trial" (trial sponsor) and "organisation engaged by the developer of the medicine" (as a rule, CRO). If in the second field, the register lists the same company as in the first field, then we counted that as the trial being conducted by the company itself. Of course we recognise that this is not always the case – work on clinical trials is multi-faceted and sometimes a CRO is engaged not for all tasks, but only separate parts of the process. And in this case, especially if the tasks transferred are not connected with regulatory aspects (for example, data management), the sponsor is not required to declare this in the application, and this means that it would not appear in the database. And in this sense the register is not a full and accurate reflection of the reality of the situation. However even such data as there are quite interesting to study.

Sponsors and CROs, General Structure of Breakdown

We decided to analyse the separate types of trials, traditionally broken down into five categories: IMCTs, local trials of efficacy and safety (separate for domestic and foreign sponsors), as well as bioequivalence studies (also in two sponsor categories). As the results show, this breakdown makes sense – the share of engaging contract research organisations turned out to be different in the different types of trials.

In processing the data, first on local trials by foreign sponsors, we came up against one problem. The column "organisation engaged by the developer of the medicine" in the Ministry of Health registry in a number of cases showed an organisation which was clearly not a CRO in the classical understanding. Going on the information we obtained about these companies from accessible Internet sources, we are referring most likely to representatives of interests of groups of foreign companies in Russia across a wide range of activities, including market launch, promotion, and distribution. The services of such 'authorised representatives', as a rule, are used only by relatively small pharmaceutical companies, without their own official representation in Russia.

In all honesty we could not with a clear conscience assign such companies to the contract research organisation category. In terms of their wok they are clearly not organisations specialised in conducting clinical trials, but rather more likely were brought into the process against their will, as the need arose to run local registration trials.

We could not assign them to pharmaceutical companies, although they were listed as official representation – such organisations, despite their similarities to the latter in terms of function, work on a contract basis and represent the issues of not one, but simultaneously several companies. Therefore we decided to separate this group of organisations out into their own section, naming it 'other representatives'.

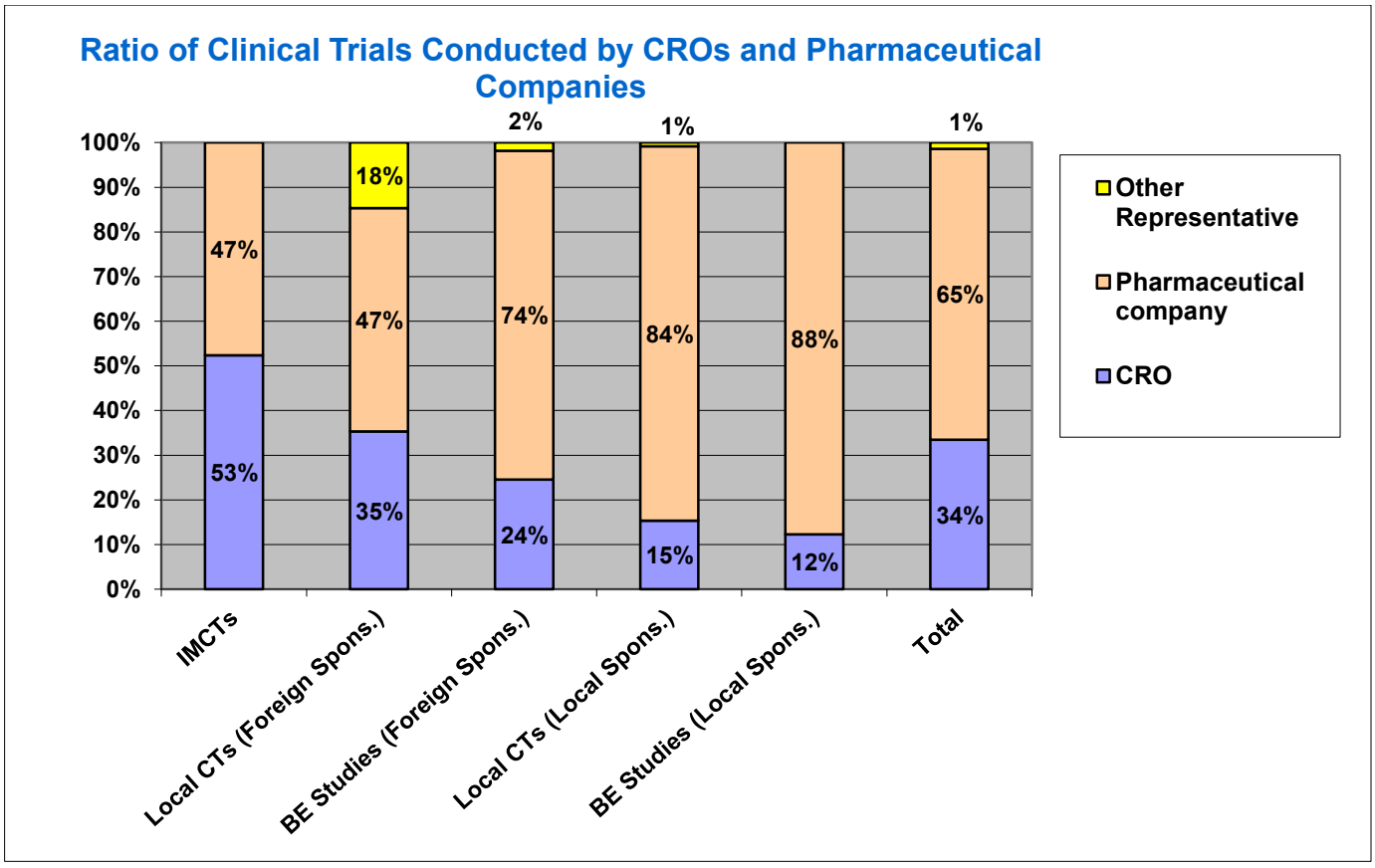
The results are presented in Table 7 and Diagram 9.

Table 7

Split of Clinical Trials Approved in 2013 by Type of Company						
	International Multicentre Clinical Trials	Local Clinical Trials (Foreign Sponsors)	Bioequivalence Studies (Foreign Sponsors)	Local Clinical Trials (Local Sponsors)	Bioequivalence Studies (Local Sponsors)	TOTAL
CRO	159	34	81	104	136	515
Pharmaceutical Company	175	24	27	19	19	265
Other Representative	-	10	2	1	-	11
TOTAL	334	68	110	124	155	791

Data from www.grls.rosminzdrav.ru

Diagram 9



Data from www.grls.rosminzdrav.ru

As we can see from these data, the largest share of CROs in conducting trials (53%) was in IMCTs. This is quite logical, since on the whole it reflects the world-wide trend – delegating the process of organising clinical trials to an independent sphere and creating a specialised sector of services is a trend that has come to us from the west. And, to tell the truth, we expected this share in IMCTs to be bigger. Here of course we must comment on the already-mentioned correction that the register does not fully reflect all cases of engaging

CROs. But all the same, the share of international trials conducted by the companies themselves (by R&D departments with the companies themselves) remained quite high at 47%.

Much lower was the share of participation of CROs in local trials and bioequivalence studies of foreign sponsors (35% and 24% respectively). At the same the share of participation of 'other representatives' was higher – at 18% – in conducting local trials of efficacy and safety of foreign manufactures (it was almost non-existent in other sectors). And the smallest share of trials, conducted by engaging CROs, was in the sector of local trials (15%) and bioequivalence studies (12%) of domestic sponsors.

International Multicentre Clinical Trials, Sponsors

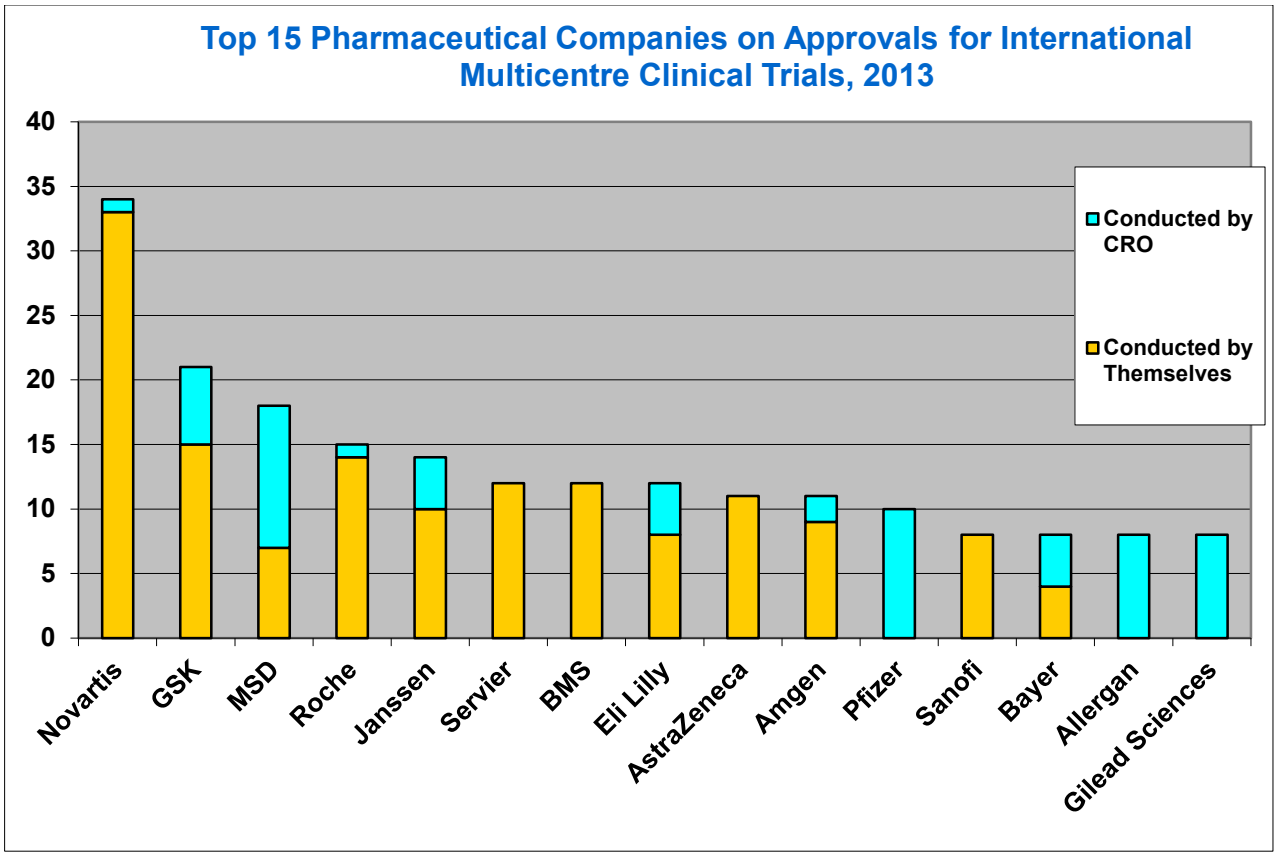
In Table 8 and Diagram 10 we present the Top 15 sponsors by number of approvals for IMCTs issued in 2013. In creating this rating, by one company we meant all the companies which are part of the same group. All trial approvals were broken down into two groups – conducted by companies (and their Russian representation) themselves, and those which according to the Ministry of Health register were conducted by CROs.

Table 8

Top 15 Pharmaceutical Companies on Approvals for International Multicentre Clinical Trials, 2013				
Ranking	**Company (including separate companies associated in group of companies)**	**Conducted by themselves**	**Conducted by CRO**	**Total**
1	Novartis	33	1	34
2	GlaxoSmithKline	15	6	21
3	Merck & Co.	7	11	18
4	F. Hoffmann-La Roche	14	1	15
5	Janssen Pharmaceutica	10	4	14
6-8	Servier	12	-	12
6-8	Bristol-Myers Squibb	12	-	12
6-8	Eli Lilly	8	4	12
9-10	AstraZeneca	11	-	11
9-10	Amgen	9	2	11
11	Pfizer	-	10	10
12-15	Sanofi	8	-	8
12-15	Bayer	4	4	8
12-15	Allergan	-	8	8
12-15	Gilead Sciences	-	8	8

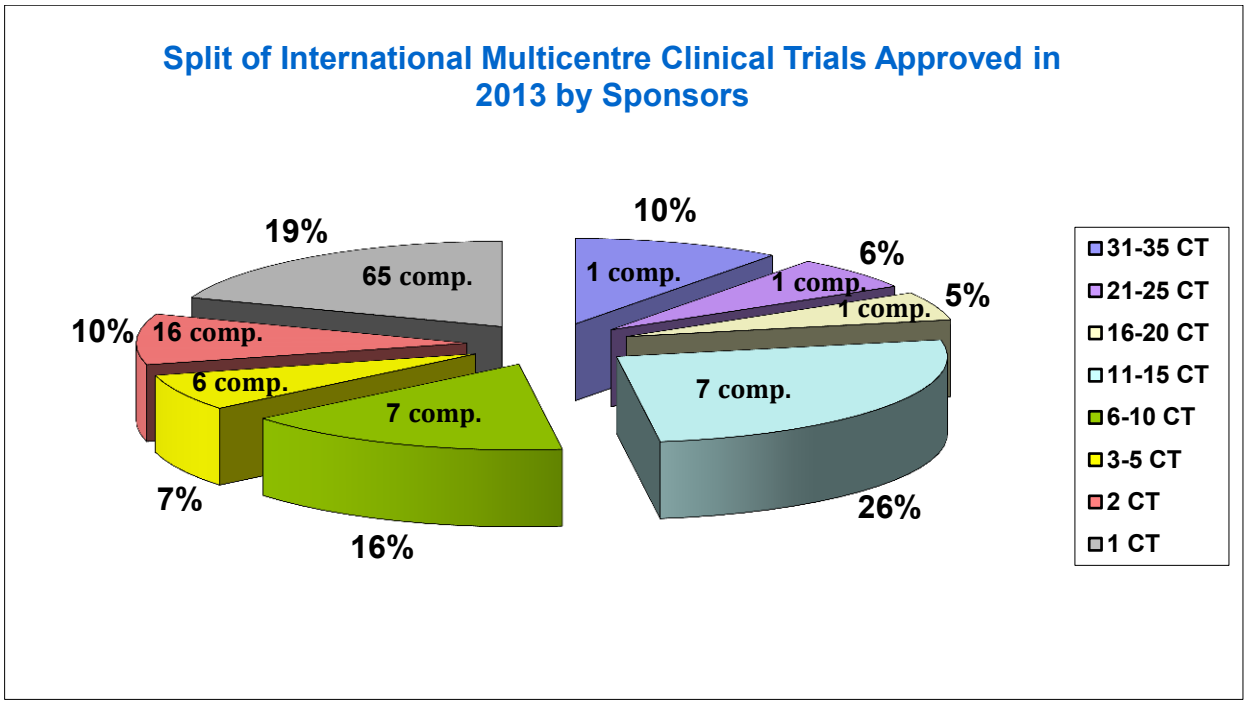
Data from www.grls.rosminzdrav.ru

Diagram 10



In order to look at the breakdown by sponsors on issued approvals for IMCTs, we broke companies into separate groups depending on their activity in initiating trials in Russia – those which were running one trial, two trials, from six to ten trials, and so on. Further, we looked at the market share overall for each group. The results are presented in Diagram 11.

Diagram 11

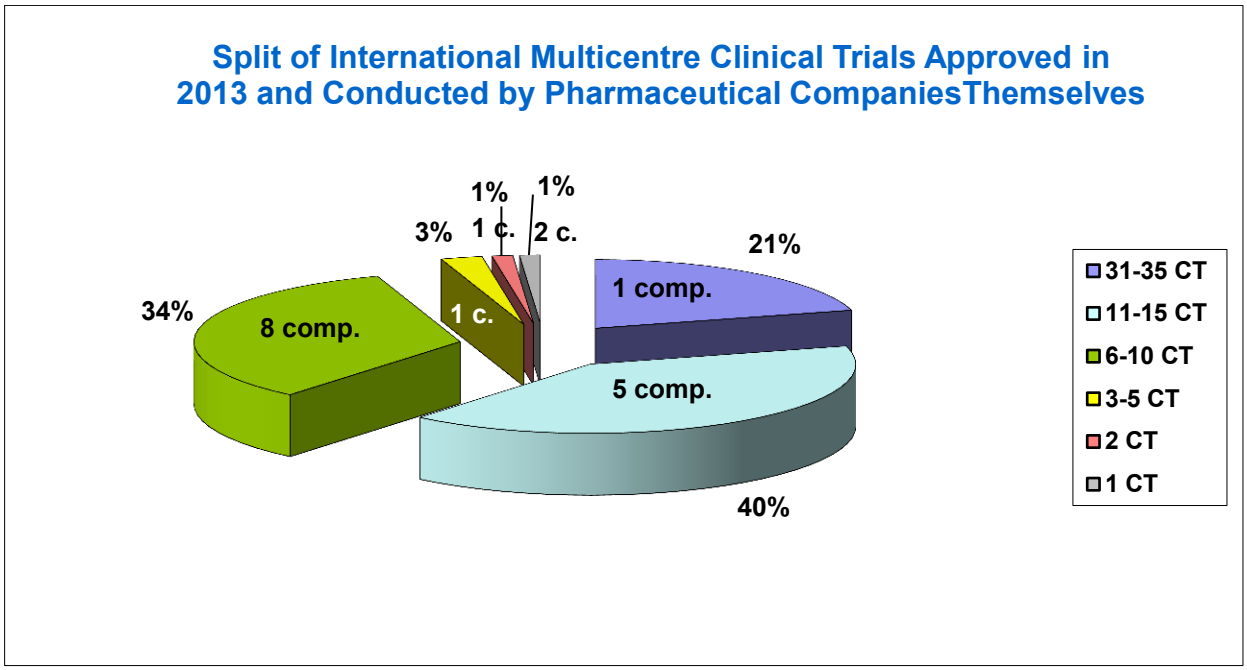


Data from www.grls.rosminzdrav.ru

The three most active companies got 21% of all approvals in 2013 for IMCTs (10%, 6%, and 5%, respectively). The following seven companies, each initiating between 11 and 15 IMCTs, took 26%. A further seven companies, each obtaining between six and ten approvals for IMCTs, took 16%. Six companies (7% of the IMCT market) initiated between three and five protocols. Sixteen companies (10% of the market) got approvals for two studies. And the largest group – 65 companies – had just one approval each. This group had 19% of all IMCTs approved in 2013. In all, according to data from the Ministry of Health register, in 2013 the number of IMCT sponsors totaled 104 pharmaceutical companies.

But in addition to the fact that all approved IMCTs were broken down by sponsor, we were also interested in how they broke down among pharmaceutical companies which were conducting the trials themselves. Data about this is presented in Diagram 12. The leader (from Table 8 we know that this is Novartis, with 33 trials), took 21% of all IMCTs approved in 2013 and conducted by the company itself. Next there is a group of five companies, whose share (totaling 40%) came from 11-15 approved protocols. Eight companies had 6-10 trials, and this group amounted to 34%. Just one company was in the group of 3-5 trials (and it had a 3% share of self-run IMCT trials). One more company (1%) had two trials. And two companies (also 1%) had one IMCT protocol each.

Diagram 12



Data from www.grls.rosminzdrav.ru

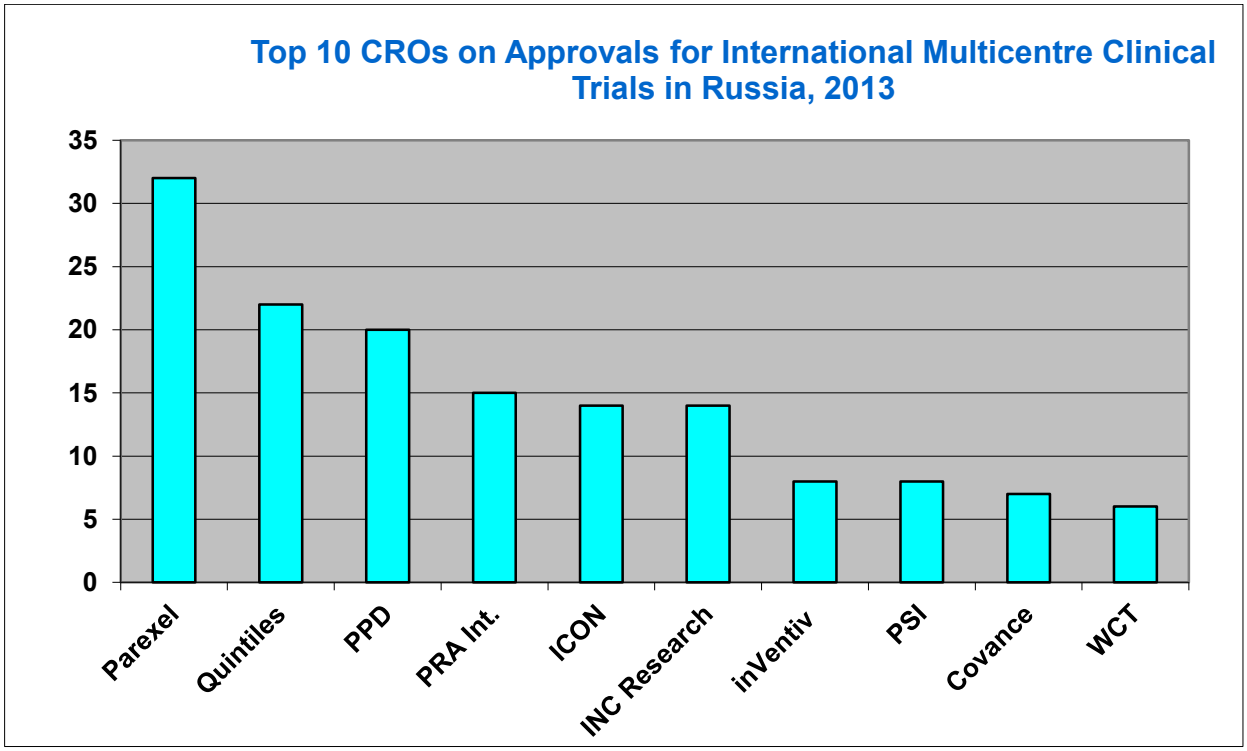
International Multicentre Clinical Trials, CROs

In Table 9 and Diagram 13 we present the Top 10 CROs by number of approvals for IMCTs issued in 2013. Table 9 also contains data on the number of sponsors whose trials are being conducted by a given CRO.

Table 9

Top 10 CROs on Approvals for International Multicentre Clinical Trials, 2013			
Ranking	**Company**	**Number of Clinical Trials**	**Number of Sponsors**
1	**Parexel**	**32**	**14**
2	**Quintiles**	**22**	**15**
3	**PPD**	**20**	**15**
4	**PRA International (incl. ClinStar)**	**15**	**8**
5-6	**ICON**	**14**	**6**
5-6	**INC Research**	**14**	**10**
7-8	**inVentive Health Clinical (incl. PharmaNet and i3)**	**8**	**7**
7-8	**PSI**	**8**	**8**
9	**Covance**	**7**	**5**
10	**Worldwide Clinical Trials**	**6**	**6**

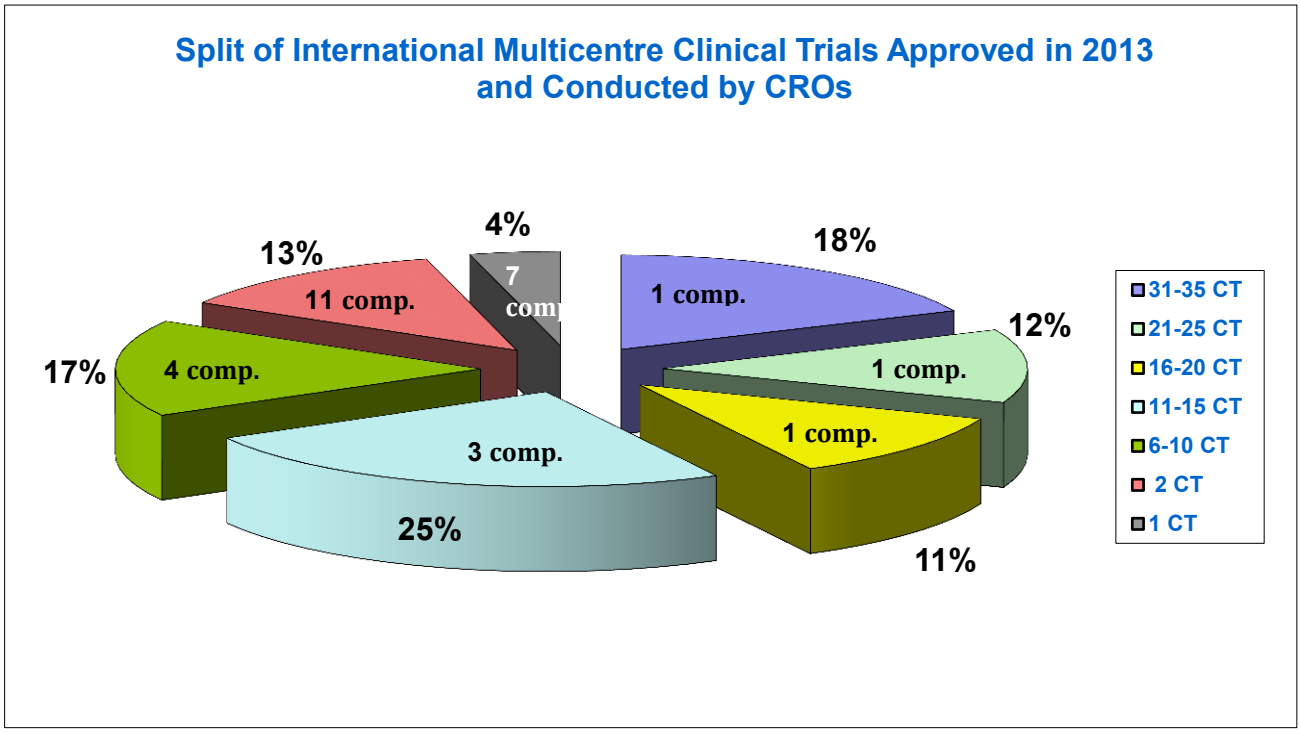
Diagram 13



Data from www.grls.rosminzdrav.ru

In order to look at the breakdown for approvals for IMCTs which were run by CROs by company, as well as in the case of sponsors, we grouped all contract research organisations by the number of trials they conducted. The results are presented in Diagram 14.

Diagram 14



Data from www.grls.rosminzdrav.ru

And so it is clear that the first trio of companies have a total of 42% of all approvals obtained in 2013 (18%, 13%, and 11%). Next we look at a group of three companies whose average number of approvals for the year was in the 11-15 range. The total share of these companies was 24% of the total of approvals obtained. A further four companies, obtaining 6-10 trials per year, took 17% of the market. Eleven companies got two approvals each, and their total market share was 13%. And just 4% of the market went to companies whose share was just one approved international project each (just seven companies).

In total, according to data from the Ministry of Health registry, 28 CROs were engaged to conduct IMCTs in 2013.

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In addition to IMCTs, we also wanted to look at the most active players on the market for local trials. We decided to combine trials of efficacy and safety with bioequivalence studies. This approach was dictated by the fact that trials of efficacy and safety, as we have already said several times previously, are most often conducted with regards to generic medicines.

Local Clinical Trials and Bioequivalence Studies of Foreign Medicines, Sponsors

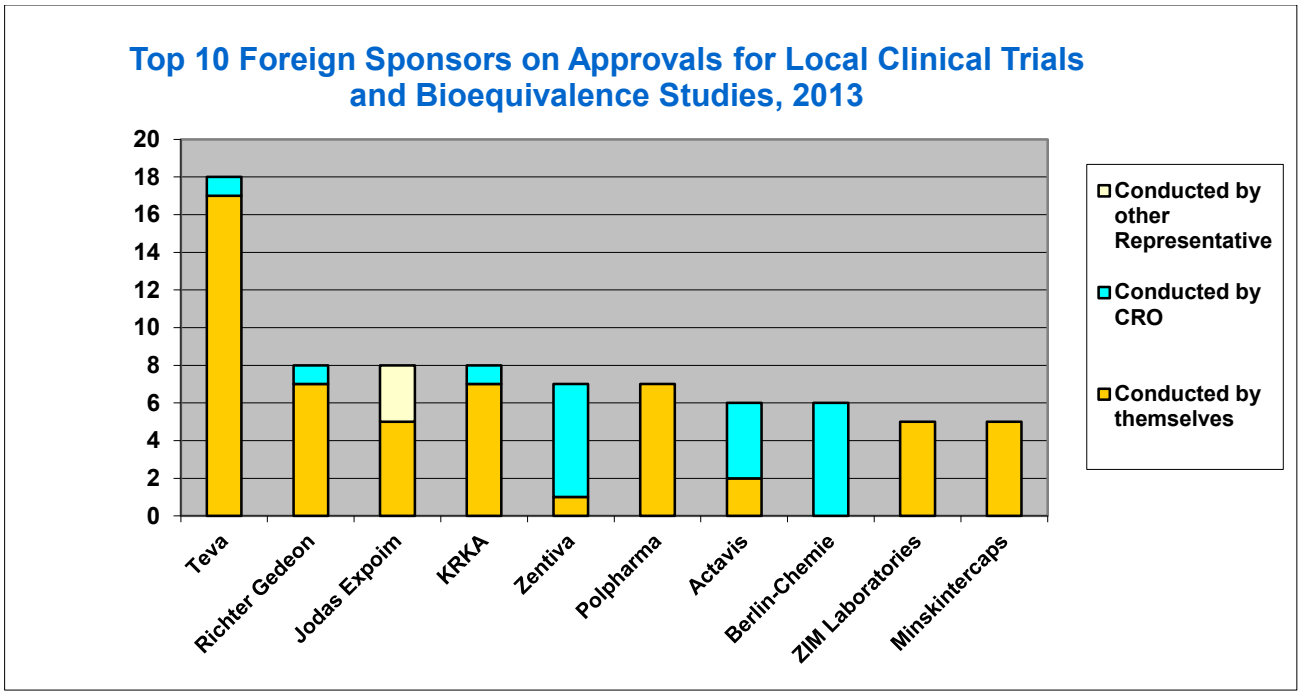
Table 10 and Diagram 15 give a picture of the main foreign sponsors who in 2013 initiated local trials and bioequivalence studies. As in the case of IMCTs, we separated the trials depending on whether they were conducted, according to the state register, by the sponsors themselves or by CROs. But in this sector, as we have already said above, we found cases of trials conducted by engaging companies other than classical CROs. In fairness, out of the companies in the Top 10, only one – Jodas Expoim – used the services of such a company.

Table 10

Top 10 Foreign Sponsors on Approvals for Local Clinical Trials and Bioequivalence Studies, 2013					
Ranking	**Company**	**Conducted by themselves**	**Conducted by CRO**	**Conducted by other Representative**	**Total**
1	**Teva**	**17**	**1**	**-**	**18**
2-4	**Richter Gedeon**	**7**	**1**	**-**	**8**
2-4	**Jodas Expoim**	**5**	**-**	**3**	**8**
2-4	**KRKA**	**7**	**1**	**-**	**8**
5-6	**Zentiva**	**1**	**6**	**-**	**7**
5-6	**Polpharma**	**7**	**-**	**-**	**7**
7-8	**Actavis**	**2**	**4**	**-**	**6**
7-8	**Berlin-Chemie AG**	**-**	**6**	**-**	**6**
9-10	**ZIM Laboratories Ltd**	**5**	**-**	**-**	**5**
9-10	**Minskintercaps**	**5**	**-**	**-**	**5**

Data from www.grls.rosminzdrav.ru

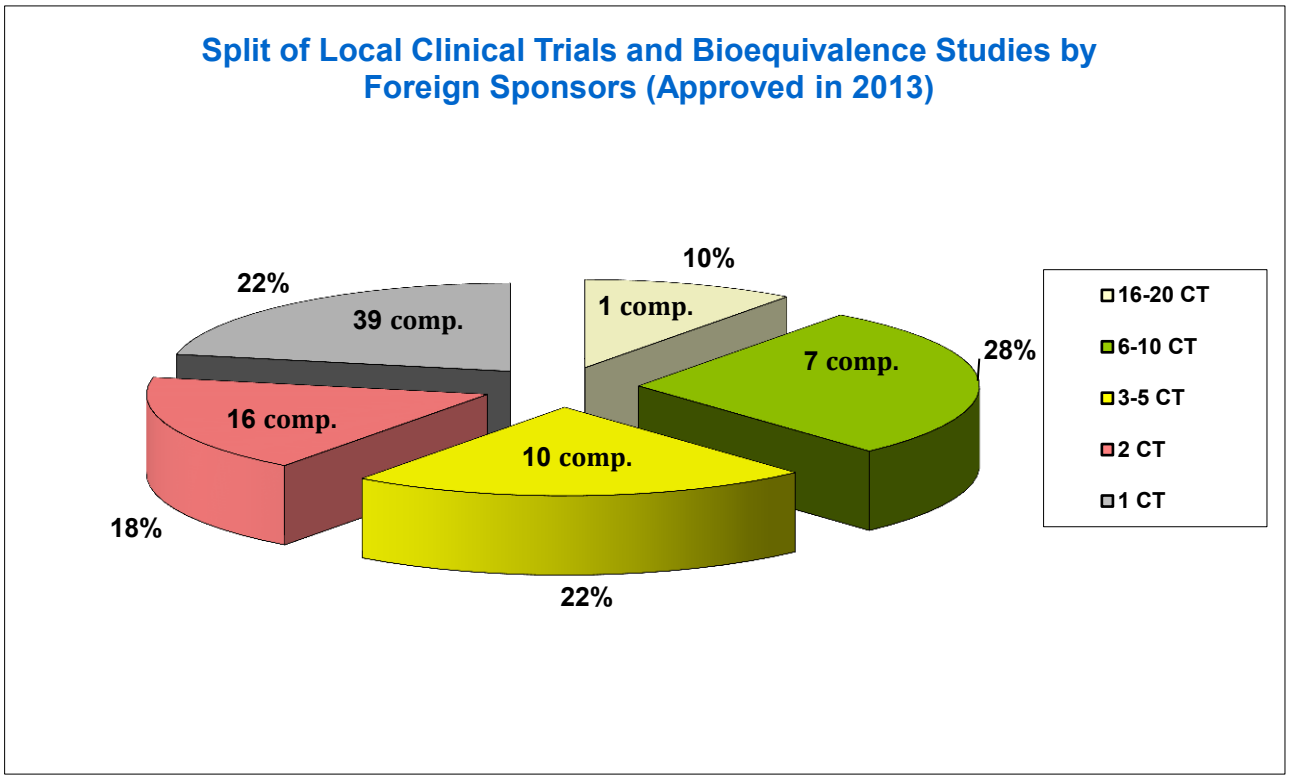
Diagram 15



Data from www.grls.rosminzdrav.ru

In Diagram 16 we present a breakdown of approvals in 2013 for local trials of efficacy and safety, as well as bioequivalence studies by foreign sponsors.

Diagram 16



Data from www.grls.rosminzdrav.ru

As we can see, the leading position and a share of 10% of the total of such trials goes to one company (from Table 10 we know that this is Teva, with 18 trials). The next share on 28% goes to a group of seven

companies, each initiating 6-10 trials over the course of the year. 22% goes to 10 companies with 3-5 trials each. Sixteen companies (18% of the total) were listed with two each, and 39 companies (22%) had one trial each.

Altogether there were 73 foreign companies taking part in the local trials market in 2013.

Local Clinical Trials and Bioequivalence Studies of Foreign Medicines, CROs

In Table 11 we look at the Top 8 contract research organisations on the number of approvals issued in 2013 for local trials of efficacy and safety and bioequivalence studies of foreign sponsors. We had to stop with the first eight companies, because subsequently there was a large number of CROs with only one or two protocols each.

Just as in the case with IMCTs, we looked not only at the number of protocols, but at the number of sponsors whose trials are being conducted by each CRO.

Table 11

Top 8 CROs on Approvals for Local Clinical Trials and Bioequivalence Studies of Foreign Sponsors, 2013			
Ranking	**Company**	**Number of CT**	**Number of Sponsors**
1	**Medical Development Agency (MDA)**	**9**	**3**
2	**Probiotech Medical Center**	**5**	**5**
3	**OCT Russia**	**4**	**3**
4-8	**Ascent CRS**	**3**	**1**
4-8	**Vita Aeterna**	**3**	**1**
4-8	**Expert and Legal Center for medicines and products for medical use**	**3**	**2**
4-8	**R&D Pharma**	**3**	**3**
4-8	**Solyurpharm**	**3**	**2**

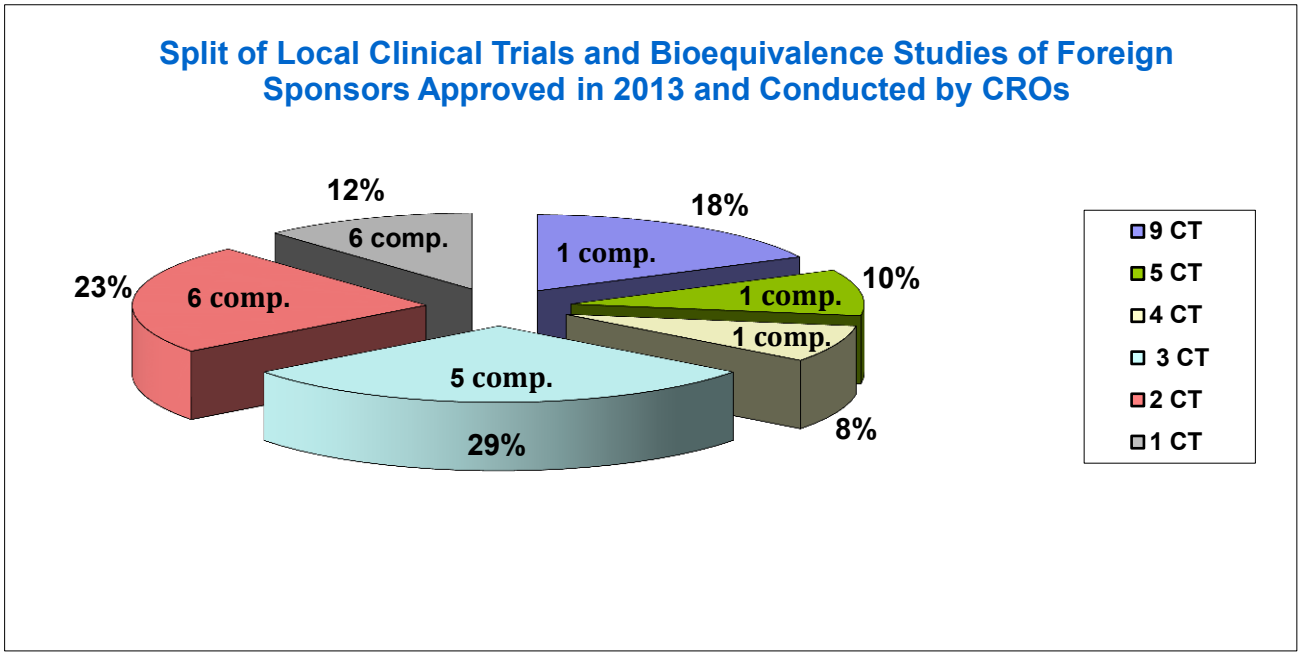
Data from www.grls.rosminzdrav.ru

In Diagram 17 we show the breakdown by contract organisations of approvals in the past year for local trials of efficacy and safety, as well as bioequivalence studies of foreign sponsors. The first three companies (9, 5, and 4 trials respectively) have 36% of approved protocols. Next come five companies, each with three trials

(28%). Six companies obtained two approved protocols each (24%). And a further six companies had one each (12%).

In total 20 CROs were engaged to conduct this type of trials in 2013.

Diagram 17



Data from www.grls.rosminzdrav.ru

As we can see from this rating, CRO participants on the market of local trials are quite different than IMCT market participants. In addition, based on the results of studying the entire list of contract research organisations conducting a given sort of trial, we were able to find only four companies declared as conducting both IMCTs and local trials. Therefore we can conclude that the Russian clinical trials market is composed of relatively distinct segments. Companies specialising in international protocols (and these are as a rule the older and more experienced market players), do practically no work in the local trials segment. Readers can draw their own conclusions as to the reasons behind this division.

Local Clinical Trials and Bioequivalence Studies of Domestic Medicines, Sponsors

In Table 12 and Diagram 18 we present the Top 10 Russian sponsors on the number of approvals obtained in 2013 for local trials of efficacy and safety, as well as for bioequivalence studies.

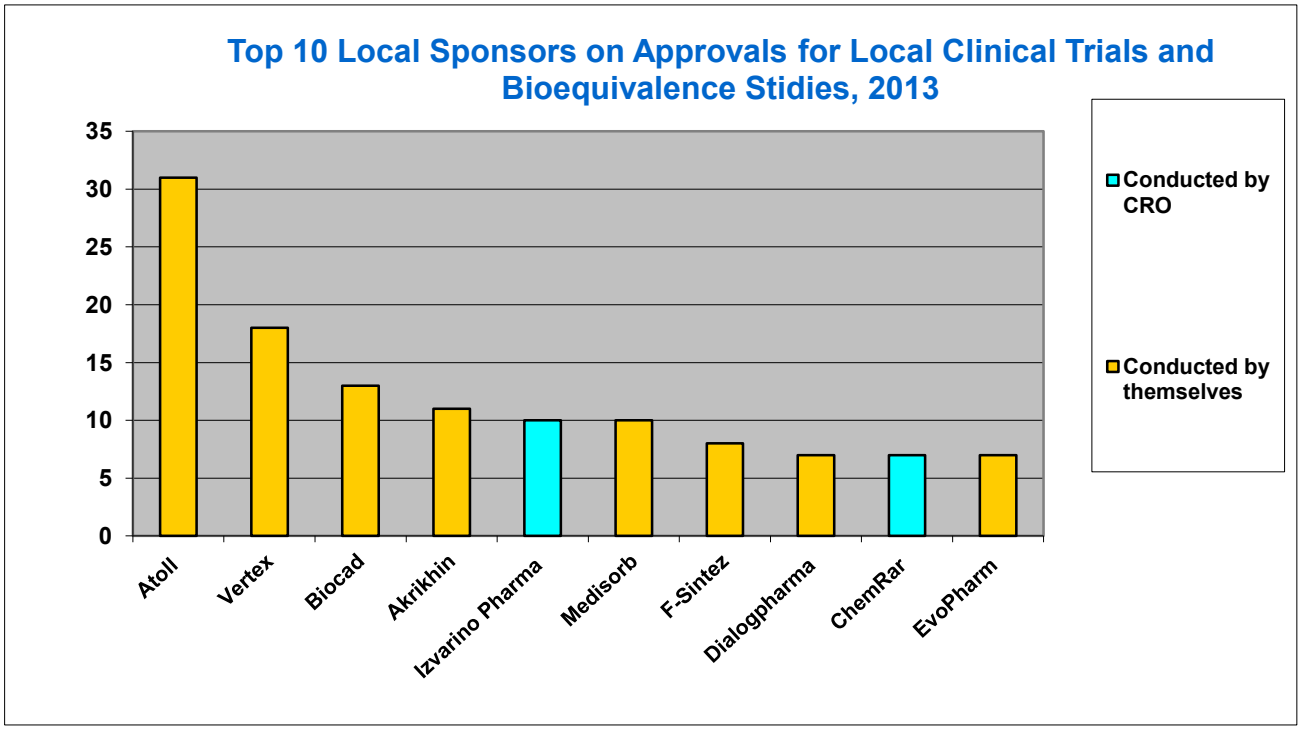
The only commentary that we would like to add to the data regards the ChemRar group. As we see in the table, the trials they initiated we have marked as conducted by a CRO. They are in fact conducted by the contract research organisation IPHARMA. But that is in turn part of the ChemRar group, but specialised in the organisation and conducting of trials. Therefore we have considered these trials as being conducted by a CRO.

Table 12

Top 10 Local Sponsors on Approvals for Local Clinical Trials and Bioequivalence Studies, 2013				
Ranking	**Company**	**Conducted by themselves**	**Conducted by CRO**	**Total**
1	**Atoll**	**31**	**-**	**31**
2	**Vertex**	**18**	**-**	**18**
3	**Biocad**	**13**	**-**	**13**
4	**Akrikhin**	**11**	**-**	**11**
5-6	**Izvarino Pharma**	**-**	**10**	**10**
5-6	**Medisorb**	**10**	**-**	**10**
7	**F-Sintez**	**8**	**-**	**8**
8-10	**Dialogpharma**	**7**	**-**	**7**
8-10	**ChemRar High-Tech Center**	**-**	**7**	**7**
8-10	**EvoPharm**	**7**	**-**	**7**

Data from www.grls.rosminzdrav.ru

Diagram 18



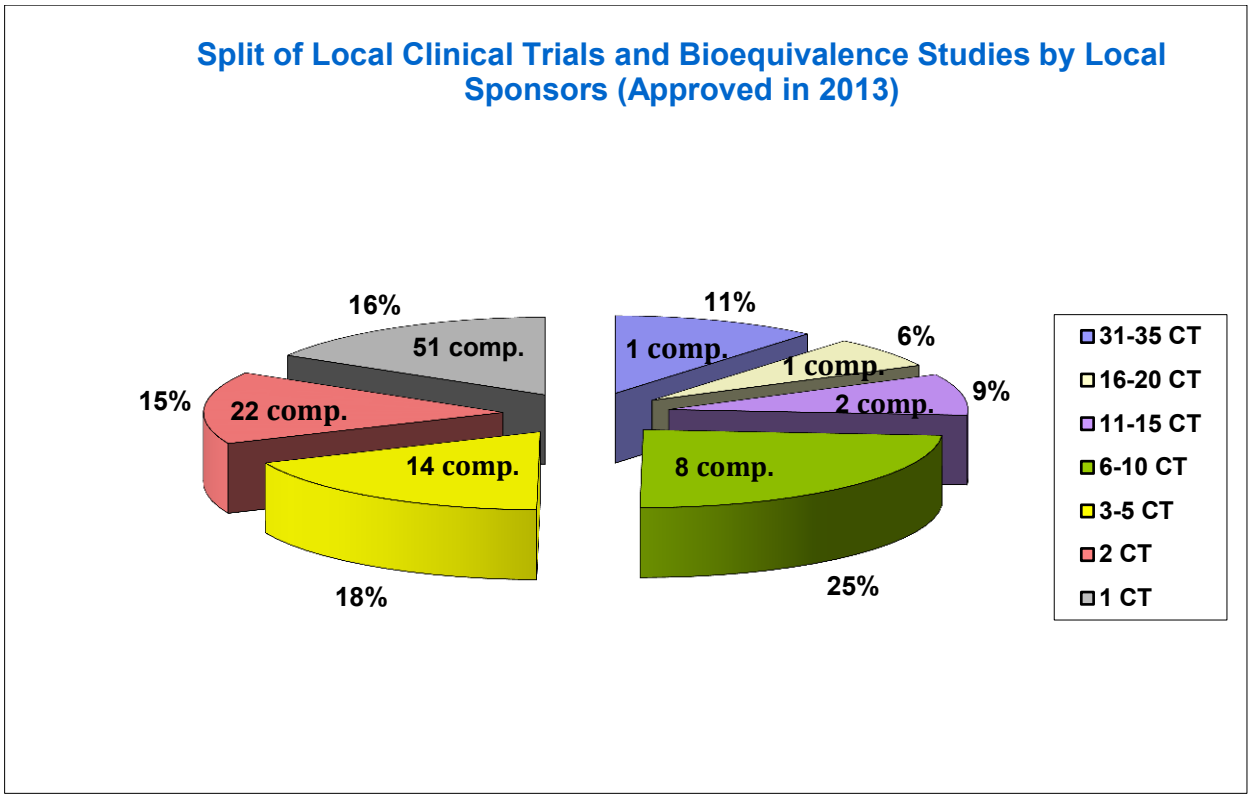
Data from www.grls.rosminzdrav.ru

Diagram 19 reflects the breakdown of approvals in 2013 for local trials and bioequivalence studies by domestic sponsors. Here, 11% of the market belongs to one company. From Table 12 we can see that this is Atoll, with 31 trials. Another company with 18 trials is in second place, holding 6% of the market. Further we have two companies, each of which in 2013 launched 11-15 clinical trials. This share of the sector was 9%. A

quarter of the market for domestic local trials went to a group of eight companies, whose activity amounted to 6-10 protocols per year. 18% went to a group of sponsors each with 3-5 trials (14 companies). Twenty-two companies (15% of the market) obtained in 2013 two approvals each. And 51 companies got one approval each (16% of the market).

Altogether, according to data from the Ministry of Health register, in 2013 there were 99 companies acting as domestic sponsors for local trials and bioequivalence studies.

Diagram 19



Data from www.grls.rosminzdrav.ru

Local Clinical Trials and Bioequivalence Studies of Domestic Medicines, CROs

In Table 13 we present data on contract research organisations working in the sector of local trials of efficacy and safety and bioequivalence studies of Russian sponsors. The number of these as included in the register of approved trials in 2013 was just nine companies. Therefore they all made it into this rating.

In first place with 12 trials was the Probiotech Medical Centre. We remember that this also held first place in the rating of local trials of foreign sponsors (5 protocols). Second place with seven trials was IPHARMA – the contract research organisation of the ChemRar/ChemDiv group of companies. In third place was OCT Russia (6 protocols), also taking third place in the rating of local trials of foreign sponsors (4 protocols).

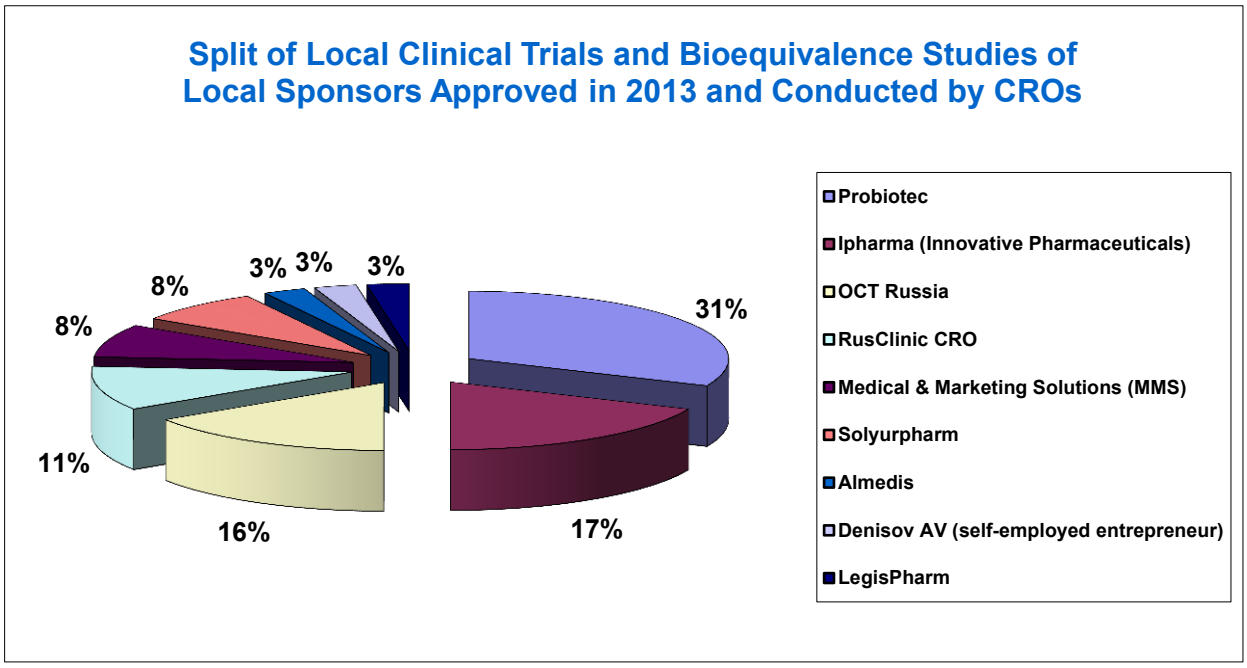
Table 13

CROs on Approvals for Local Clinical Trials and Bioequivalence Studies of Local Sponsors, 2013			
Ranking	**Company**	**Number of CT**	**Number of Sponsors**
1	**Probiotech Medical Center**	**12**	**2**
2	**Ipharma (Innovative Pharmaceuticals)**	**7**	**6**
3	**OCT Russia**	**6**	**3**
4	**RusClinic CRO**	**4**	**2**
5	**Medical & Marketing Solutions (MMS)**	**3**	**1**
6	**Solyurpharm**	**3**	**2**
7-9	**Almedis**	**1**	**1**
7-9	**Denisov A.V. (self-employed entrepreneur)**	**1**	**1**
7-9	**LegisPharm**	**1**	**1**

Data from www.grls.rosminzdrav.ru

The breakdown of all trials of efficacy and safety, as well as bioequivalence studies of Russian sponsor by CROs is presented in Diagram 20.

Diagram 20



Data from www.grls.rosminzdrav.ru

TIMEFRAMES FOR ISSUANCE OF APPROVALS

To carry out monitoring we had to slightly change the methodology of calculating waiting times for issuing main approvals to conduct clinical trials. This was due to the fact that in 2013 the Ministry of Health changed the process of reviewing applications for these types of approvals. Whereas previously when questions arose from the experts, the applicant could respond to them in the course of the review, in other words the single process itself continued without interruption (it just went on hold while the question was answered), from about halfway through last year the practice was changed. If there were questions or comments from the experts, the applicants began to get refusals. In order to resolve the situation and continue the review process, the company had to put in a wholly new application and full set of documents.

Clearly, such a change could not help but have an effect on waiting times. For the officials, it was an improvement, since each new application means that the waiting time is now counted from the beginning as well. For the applicants, it was deterioration, since all going through all procedures again just means more time passes before the trial can begin.

As a result of the changed practice we had to differentiate and count separately – waiting times to obtain approvals in the case of a positive decision first time, and waiting times for a refusal (in the case of such), waiting times to obtain approval after a repeat application, as well as the total waiting time to obtain approval after a repeat application, from the moment of the initial submission. There were cases of repeated refusals and subsequent third, fourth, and even fifth re-submissions. But we did not include these in the count. First, because of insufficient statistical data – in any case such cases were much fewer, and this means increased discrepancies in calculation. In addition, as practice shows, with each new 'turn', meaning further delays before the trial can begin, the likelihood of the sponsor's refusal to conduct the trial in Russia increases exponentially.

For all other approvals, including permits to import medicines and export biological samples, approval of amendments to the protocol and other changes made in the course of the trials, practice and accordingly the methodology of our calculations remained unchanged.

The results of our data are presented in Table 14. As we can see, the average waiting time to obtain approval to conduct a trial 'from the first step' was 87 days. The waiting time to obtain a refusal to conduct a trial was 57 days. How can we explain the month-long discrepancy between a positive and negative result? The answer is simple – the time is run up because applicants with a positive result from expertise cannot get their approval right away. First the Ministry of Health informs them of the result of the expertise. If it is negative, the applicant gets refused right away. If it is positive, then the process continues. The applicant must write another application for approval and submit it again to the Ministry of Healthy. And only after review of this application, he will be issued with the long-awaited document. To the uninitiated reader such a situation might seem absurd. But this is how the Ministry of Health is interpreting the law. And repeated attempts by ACTO to resolve the situation have so far come to nothing (*see ACTO Newsletter No.3)*. But we have not lost hope of resolving this matter sooner or later.

The average waiting time to review a resubmission (in the case of refusal of the first application) was 81 days, in other words six days quicker than for a positive result the first time around. The difference is minimal if you take into account the fact that in a repeat submission with which the experts are already familiar it would be more logical to just concentrate on the specific issue which drew their attention the first time. How this happens in actual fact, we can only guess. The waiting times speak for themselves. The result is disappointing – if the protocol is approved the second time, the average waiting time to obtain approval, counted from the moment of submission of the first application, is 197 days.

Further is more. It becomes clear why after two or three attempts, sponsors frequently have to change their plans and refrain from conducting trials in Russia.

Table 14

Timeframes for Issuing Approvals, 2013[2]					
	Timeframes according to legislation (business/ calendar days)	Average timeframes (calendar days)	Minimum timeframes (calendar days)	Maximum timeframes (calendar days)	Sampling
To Conduct Clinical Trial	41/57	87	32	223	177
To Receive a Notification that an Approval is Refused	41/57	57	5	101	59
To Receive an Approval from the Date of the Resubmission (if the Initial Submission was Refused)	41/57	81	14	171	54
To Receive an Approval after Resubmission from the Date of the Initial Submission (if the Initial Submission was Refused)	~	197	126	289	30
To Import Medicines	8/12	14	6	43	355
To Import/Export Biosamples	13/19	20	6	62	819
To Make Amendments to the Protocol	34/48	45	3	132	350
Other Approvals (to Prolong Clinical trials, to Include New Sites, to Enroll Additional Patients, etc.)	25/35	26	3	80	682
Total Time to Obtain Approvals to Conduct Clinical Trials and to Import/Export	54/76	107	~	~	~

Data from timeframes' monitoring of ACTO

[2] During the calculation of legislative timeframes we were translating the workdays to calendar days and adding from 1 to 4 days (depending on the kind of submission) for registration of the application and awarding of a ready document to the applicant, despite the fact that in law these stages are not mentioned separately, i.e. have to be included in common term of consideration. For more detail about used system of term calculation see ACTO website www.acto-russia.org

The waiting times for different types of approvals can be better evaluated in comparison with previous periods. And so a comparison of data from 2013 and 2012 is shown in Table 15. And although a comparison of the waiting times to obtain the main document – approval to conduct clinical trials – is not entirely correct for the previously-explained reasons of changed practice, we decided to do it anyway. As a result we can show the reduced waiting times to obtain approval, down by 29 days, which is exactly a quarter less in comparison with 2012 (87 compared to 116 days).

But clearly this positive change is explained not only by the change in the process of reviewing applications. The biggest reductions in waiting times came in additional approvals (to extend trials, include additional sites, additional patients, and so on), and accounted for 36.6% (21 compared to 41 days). There was improvement of nearly 30% in the waiting times for review of applications to make amendments to the protocol (45 compared to 65 days). Reduced waiting times to import medicines were not as significant – just four days. But this waiting time itself is not long (14 days compared to 18 in 2012), and as a percentage the improvement doesn't look bad at all, at 22.2%.

The only type of approval where there was no improvement in waiting time (and in fact there was a deterioration) was permit to import and export biological samples. The average waiting time to obtain this document was 20 days, exactly the same as that found by ACTO monitoring in 2012. By the way, the figures for this type of approval in particular were set by law and then were better, so there's no reason for disappointment. On the whole we must acknowledge that the efficiency of the Russian Ministry of Health's work in this area has improved.

Table 15

Average Timeframes for Issuing Approvals , 2012 vs. 2013			
	2012	**2013**	**2013 vs. 2012, %**
To Conduct Clinical Trial	**116**	**87**	**-25%**[3]
To Import Medicines	**18**	**14**	**-22,2%**
To Import/Export Biosamples	**20**	**20**	**0%**
To Make Amendments to the Protocol	**64**	**45**	**-29,7%**
Other Approvals (to Prolong Clinical Trials, to Include New Sites, to Enroll Additional Patients, etc.)	**41**	**26**	**-36,6%**

Data from timeframes' monitoring of ACTO

A more vivid picture of the dynamics of average waiting times for approval is shown in Table 16 and Diagram 21, where we list the data of ACTO monitoring since 2005.

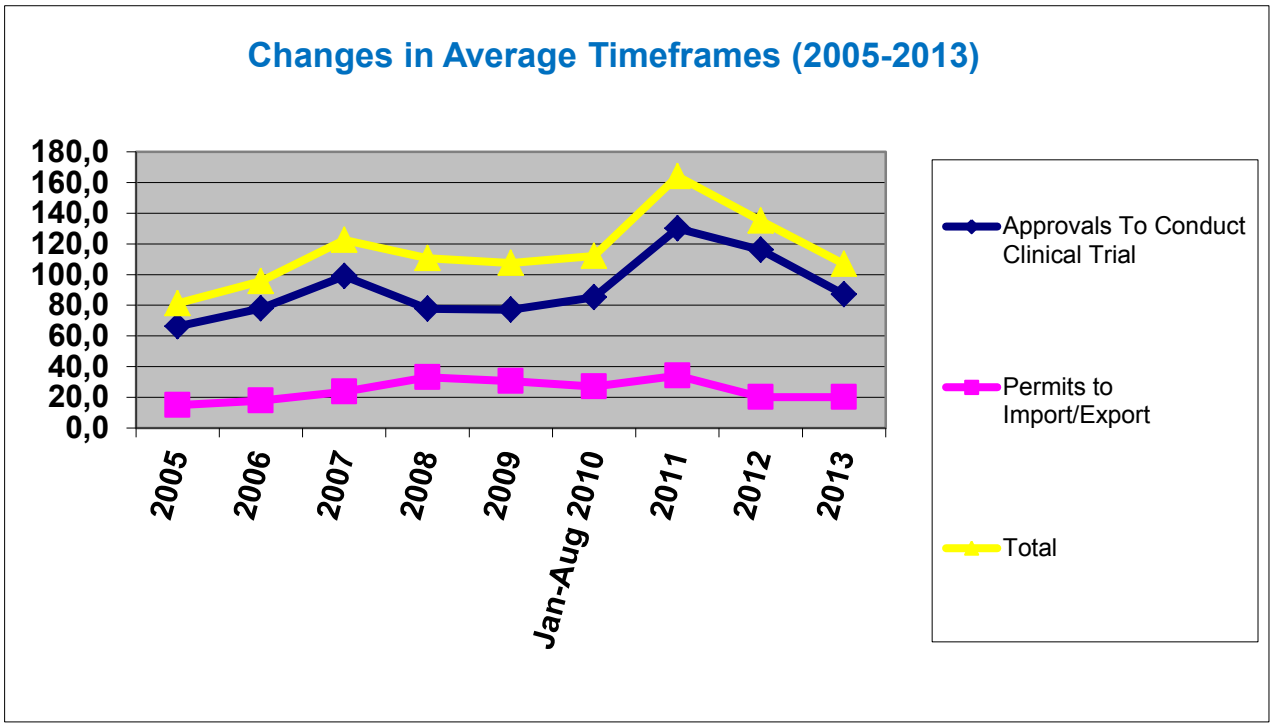
[3] Must take into account the changed practice of issuing approvals, which undoubtedly had its impact on the timing

Table 16

Changes in Average Timeframes, 2005-2013									
	2005	2006	2007	2008	2009	Jan-Aug 2010[4]	2011	2012	2013
Approvals To Conduct Clinical Trial	66,3	77,8	98,9	77,6	77,0	85,2	130,0	116,0	87,0
Permits to Import/Export	14,9	17,8	23,7	33,1	30,5	26,9	34,0	20,0	20,0
Total	81,2	95,6	122,6	110,7	107,5	112,1	164,0	135,0	107,0

Data from timeframes' monitoring of ACTO

Diagram 21



Data from timeframes' monitoring of ACTO

So as we can see the worst statistics over the entire recorded time were in 2011, when the Ministry of Health and Social Development after the adoption of the law "On the Circulation of Medicines" and the transfer to the ministry of approval functions, had only just begun this work. 2012 showed significant improvement. To be fair, waiting times to obtain approval to conduct trials had already begun to seriously deteriorate under Roszdravnadzor. At that time the waiting times for permit to import medicines and import/export biological samples were clearly better under the ministry than under its predecessor.

[4] During 2010 monitoring data was examined only through August. A new law came in force in September, and till November the work of the regulatory system was almost fully paralyzed.

2013 showed quite decent results. And so the times for obtaining permit to import medicines and import/export biological samples were for the second year in a row better under the Russian Ministry of Health than under Roszdravnadzor. On times for approval to conduct clinical trials and the total times that the applicant needed to wait to begin a trial, the Ministry of Health's figures were also up to pre-reform levels and were almost on par with those recorded in 2009. Although we cannot lose sight of the important fact that the reduced waiting times were also due to changed procedures for document review. To obtain a more objective picture we would have to analyse the dynamics of refusal figures. Unfortunately in earlier years ACTO did not keep these statistics. The first analysis was conducted only in the summer of last year, and included data for the first half of 2013. We hope to conduct similar monitoring in the middle of this year, and then we will have the chance to compare these figures with the dynamics on approval waiting times.

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In Table 17 we present data on the share of approvals in 2013 that were granted within or outside of stipulated deadlines, compared with those figures from 2012.

Table 17

Violations of Timeframes, 2013 vs. 2012								
		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 Trial	2013	4,0%	96,0%	51,4%	29,9%	12,4%	2,3%	0,0%
	2012	2,0%	98,0%	18,1%	38,2%	31,2%	7,5%	3,0%
To Import Medicines	2013	43,7%	56,3%	30,4%	20,0%	5,1%	0,8%	0,0%
	2012	28,0%	72,0%	33,2%	19,4%	14,2%	3,7%	1,5%
To Import/Export Biosamples	2013	53,1%	46,9%	35,8%	10,0%	1,0%	0,1%	0,0%
	2012	54,3%	45,7%	32,8%	10,9%	1,5%	0,3%	0,2%
To Make Amendments to The Protocol	2013	60,3%	39,7%	30,9%	7,4%	1,4%	0,0%	0,0%
	2012	34,5%	65,5%	30,4%	19,6%	13,7%	1,5%	0,3%
Other Approvals (to prolong Clinical Trials, to Include New Sites, to Enroll Additional Patients, etc.)	2013	86,2%	13,8%	11,9%	1,6%	0,3%	0,0%	0,0%
	2012	48,9%	51,1%	25,8%	15,7%	7,4%	1,7%	0,5%

Data from timeframes' monitoring of ACTO

It is remarkable that against the backdrop of improvements to the average waiting times for approval to conduct clinical trials (let us remember that the progress has been 25%), the share of approvals issued within the stipulated deadline has increased insignificantly, by just 2% (4% in 2013 compared to 2% in 2012). To be fair, there was 33.3% growth in the number of approvals issued that were over-due by less than 1.5 times (51.4% compared to 18.1%). At the same time there was a drop in the number of approvals issued further over-due.

Significantly, there was a 37.3% increase in the share of additional approvals issued on time (to extend trials, include new sites and additional patients), achieving the best out of all other types of approvals, at 86.2%. At the same time cases of over-due waiting times more than triple the deadline were nonexistent.

The significant improvement in the share of on-time approvals was also noted with amendments to protocol. It is now 60.3% compared to 34.5% in 2012. The share of such approvals, issued more than three times over the stipulated deadline, was also zero.

We noted an insignificant, in statistical terms, reduction in the percentage of permits issued on time for import/export of biological samples (53.1% compared to 54.3%). On the whole the indicators for this type of approvals were practically the same as in 2012. And they can all be called quite satisfactory.

There was a 15.7% increase in the share of permits issued on time for the import of medicine, reaching a level of 43.7%. At the same time there was a significant reduction in the percentage of permits issued significantly (more than 2-3 times) overdue.

Therefore we can conclude that the improvements in waiting times to obtain approval documentation in 2013 referred not only to average figures, but also to the share of approvals issued on time. In truth, the percentage of over-due issuance of the main document – approval to conduct clinical trials – still remains unjustifiably high.