ACTO
ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

ACTO NEWSLETTER № 10

Summary of 2014 results

MOSCOW 2015

CONTENTS

SUMMARY

As usual, we will begin this newsletter with general statistics. In 2014 the Ministry of Health issued 750 approvals for clinical trials, which was down 5.2% compared to 2013.

The most visible decline (of 15.6%) was in international multicentre clinical trials (IMCTs): 282 approvals compared to 334 the previous year. This drop in the number of trials is unlikely to be a consequence of the increasingly difficult geopolitical situation in 2014, as this could not have had such a quick effect due to market inertia. In our opinion there is a different explanation. Studying the global data, we discovered that there was a contraction in the number of clinical trials in 2014 in the majority of countries by 14.6% compared with the previous year. In other words, almost the same as what we see in Russia. So in this sense we are in line with the international trend. Regarding the near future, our forecast is cautiously optimistic – if the IMCT market contracts this year, then it will most likely be to an insignificant degree.

The market structure by type of trials, which changed significantly after the adoption of the law "On Circulation of Medicines", has since remained relatively stable for the past three years. Having lost 20% compared to the pre-reform levels, in 2014 the share of IMCTs was 37.6% of the total market. Bioequivalence studies held almost the same share, with 35.2%. The share of other local trials reached 27.2%.

The biggest part of local trials belongs to generics (nearly 50% of such trials for foreign medicines and almost 40% for domestic products). However, we expect that the share of local trials will decrease significantly in the near future due to the coming into force of changes to the law "On Circulation of Medicines". So as a result of the changing requirements for registration of generics, the need for trials of the so-called "therapeutic equivalency" in most cases will disappear.

In this issue we have also analyzed the structure of the market by therapeutic areas. In IMCTs, first place went to oncological medicines (22.7% of the whole sector). Out of trials of generics and biosimilars conducted by foreign sponsors, first place went to the medicines used to treat infectious diseases (20.4%). Among generic medicines from Russian manufacturers, the biggest share was for trials in cardiology and cardio-vascular diseases (20.4%). The innovative developments from domestic companies were primarily aimed at the fight against infectious diseases (43.8%).

The same as in the previous year, we looked at how the market is split between the main players. We also looked at how approvals for trials were distributed between sponsors and contract research organizations in various sectors of the market.

By tradition in our annual issue we present data on waiting time for the Ministry of Health to issue approval documents. In 2014 the average waiting time to obtain approval to conduct a trial was 95 days, to obtain permit to import medicines was 14 days, and to obtain permit to import biomaterial was 23 days. Nearly all types of approval documents saw a slight increase in timeframes compared to 2013. It can be seen as non-critical, with the exception of the times to get approval for protocol amendments, which increased by 33.3% and amounted to 60 days as opposed to 45 in 2013.

Last but not least, additional subject of this newsletter is the analysis of the changes being brought to the law "On Circulation of Medicines". We present a short discourse on the history of the law, and our evaluation of the changes. The conclusion is that the updated law, although it has not solved all the problems in the sphere of clinical trials, has nevertheless improved the situation and the changes for our sector of the pharmaceutical market in general are positive.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

In 2014, the Ministry of Health issued 750 approvals for clinical trials. This was down 5.2% from 2013 (Table 1).

The most noticeable drop was in the sector for international multicentre clinical trials (IMCTs) – a drop of 15.6% (282 approvals in 2014 against 334 in 2013). The number of approvals for bioequivalence studies initiated by Russian sponsors dropped by 9% (141 approvals in 2014 compared to 155 in 2013), and approvals for local trials by foreign sponsors dropped by 8.8% (62 approvals in 2014 compared to 68 in 2013).

Growth in the number of approvals issued can be seen in two areas: the share of local trials by Russian sponsors and bioequivalence studies by foreign sponsors increased by 14.5% (142 approvals against 124 in 2013) and 11.8% (123 against 110), respectively.

Table 1

Approvals for Conduct Clinical Trials: 2014 vs. 2013						
Year	**Total**	**International Multicenter CTs**	**Local CTs (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CTs (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
2014	**750**	**282**	**62**	**123**	**142**	**141**
2013	**791**	**334**	**68**	**110**	**124**	**155**
2014 vs. 2013, %	**-5,2%**	**-15,6%**	**-8,8%**	**11,8%**	**14,5%**	**-9,0%**

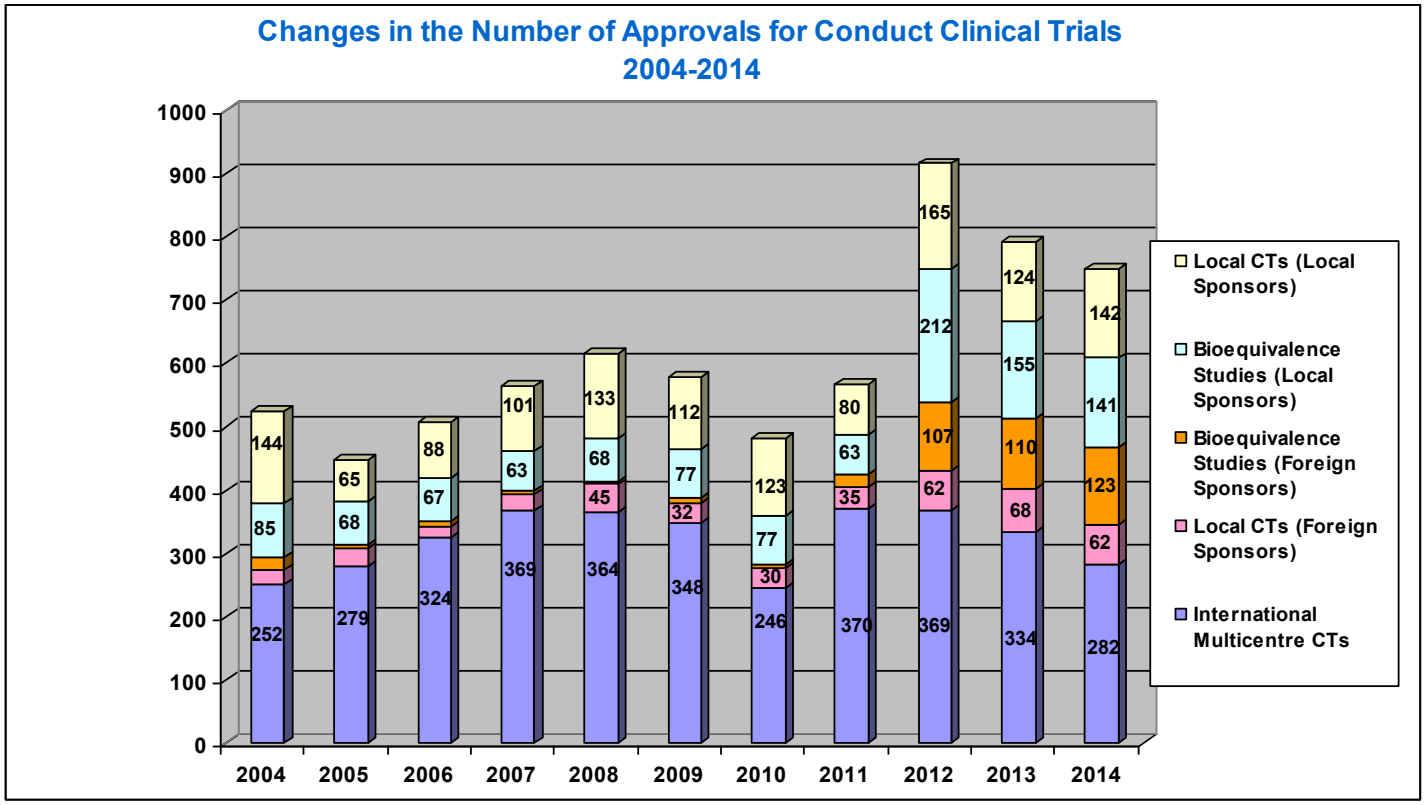
Data from www.grls.rosminzdrav.ru

Diagram 1, quite familiar to our loyal readers, demonstrates how the number of approvals issued for various types of clinical trials has changed over the years.

As we remember from the previous issues of the newsletter, the sharp increase in the number of approvals in 2012 (mostly due to bioequivalence studies and local trials of therapeutic equivalency) was attributed to two factors – the implementation of requirements for mandatory local registration trials, as well as the announced course on import substitution.

Then for two years (2013 and 2014), the total number of trials has somewhat dropped. But anyway the number of local trials and bioequivalence studies significantly exceeds the pre-reform levels.

Diagram 1



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

We are much more concerned about the decrease in the quantity of IMCTs, which last year dropped below the psychologically important level of 300 trials. Such low figures were previously seen only in 2004, 2005, and 2010.

How can we explain such a drop? We have not seen any particular reasons for this within the country. It is clear that the general geo-political situation, seriously deteriorating in early 2014, could not have helped but affect the sector for international clinical trials. And we were prepared for some amount of "contraction" in the market, first of all at the account of smaller companies without a presence in Russia that have only one or two molecules in development. This category of sponsors is understandably more sensitive to potential influence from external factors and predictably reacts to increased business risks. Our guess was confirmed by few messages from contract research organisations about temporary suspension by several smaller sponsors of the active negotiations on running trials in Russia. Regarding larger sponsors who have a long-standing presence in the Russian market and have their own representative offices in the country and therefore first-hand information, they seem to feel much more confident. We reached this conclusion via a poll of representatives of various companies, confirming the absence of any kind of panic on the part of large multi-national pharmaceutical companies.

On the other hand, there is also an economic factor today in Russia, in addition to the difficult geopolitical situation. The financial crisis which has developed in the country at the end of 2014 has led to a distinct drop in the cost of conducting clinical trials. It is clear that the market is leaning towards levelling-off and that in a certain period of time the cost will rise once again. But for now we can say that Russia has a slight economic advantage.

However, the political and economic factors having potential influence on the sphere of clinical trials could not have impacted on the data for 2014 because of the market inertia. We can see the real influence when we get the data for the current and following years.

How can we then explain the market contraction in 2014 of IMCTs by 15.6% compared to the previous year? We decided to analyze the global trends, using the resource www.clinicaltrials.gov. In particular, we

looked at the changes in the number of trials registered on the resource in a number of countries in 2013 and 2014. The selection was made purely based on interventional trials. This showed that in 2014 a contraction in the number of trials is visible in a majority of countries and on average was 14.6%, or in other words almost exactly the same as what we had in Russia (Table 2).

Table 2

Number of Interventional Clinical Trials Conducted in Different Countries, 2014 vs. 2013							
Country	**Number of CTs, 2013**	**Number of CTs, 2014**	**2014 vs. 2013, %**	**Country**	**Number of CTs, 2013**	**Number of CTs, 2014**	**2014 vs. 2013, %**
Austria	**266**	**213**	**-19,9%**	**Latvia**	**45**	**28**	**-37,8%**
Belgium	**540**	**478**	**-11,5%**	**Mexico**	**182**	**156**	**-14,3%**
Brazil	**465**	**443**	**-4,7%**	**Netherlands**	**524**	**518**	**-1,1%**
Canada	**1211**	**1112**	**-8,2%**	**Norway**	**210**	**171**	**-18,6%**
China	**872**	**858**	**-1,6%**	**Poland**	**349**	**321**	**-8,0%**
Croatia	**45**	**29**	**-35,6%**	**Portugal**	**96**	**76**	**-20,8%**
Czech Republic	**277**	**208**	**-24,9%**	**Romania**	**134**	**119**	**-11,2%**
Denmark	**416**	**412**	**-1,0%**	**Serbia**	**53**	**35**	**-34,0%**
Estonia	**44**	**33**	**-25,0%**	**Slovakia**	**98**	**71**	**-27,6%**
Finland	**173**	**116**	**-32,9%**	**Spain**	**753**	**670**	**-11,0%**
France	**1190**	**1137**	**-4,5%**	**Sweden**	**370**	**309**	**-16,5%**
Germany	**1018**	**901**	**-11,5%**	**Switzerland**	**299**	**323**	**8,0%**
Hungary	**247**	**174**	**-29,6%**	**Taiwan**	**333**	**307**	**-7,8%**
India	**199**	**161**	**-19,1%**	**Turkey**	**216**	**195**	**-9,7%**
Israel	**414**	**336**	**-18,8%**	**Ukraine**	**103**	**84**	**-18,4%**
Italy	**709**	**591**	**-16,6%**	**United Kingdom**	**984**	**995**	**1,1%**
Japan	**365**	**347**	**-4,9%**	**United States**	**6665**	**6783**	**1,8%**
Average, %							**-14,6%**

Data from www.clinicaltrials.gov

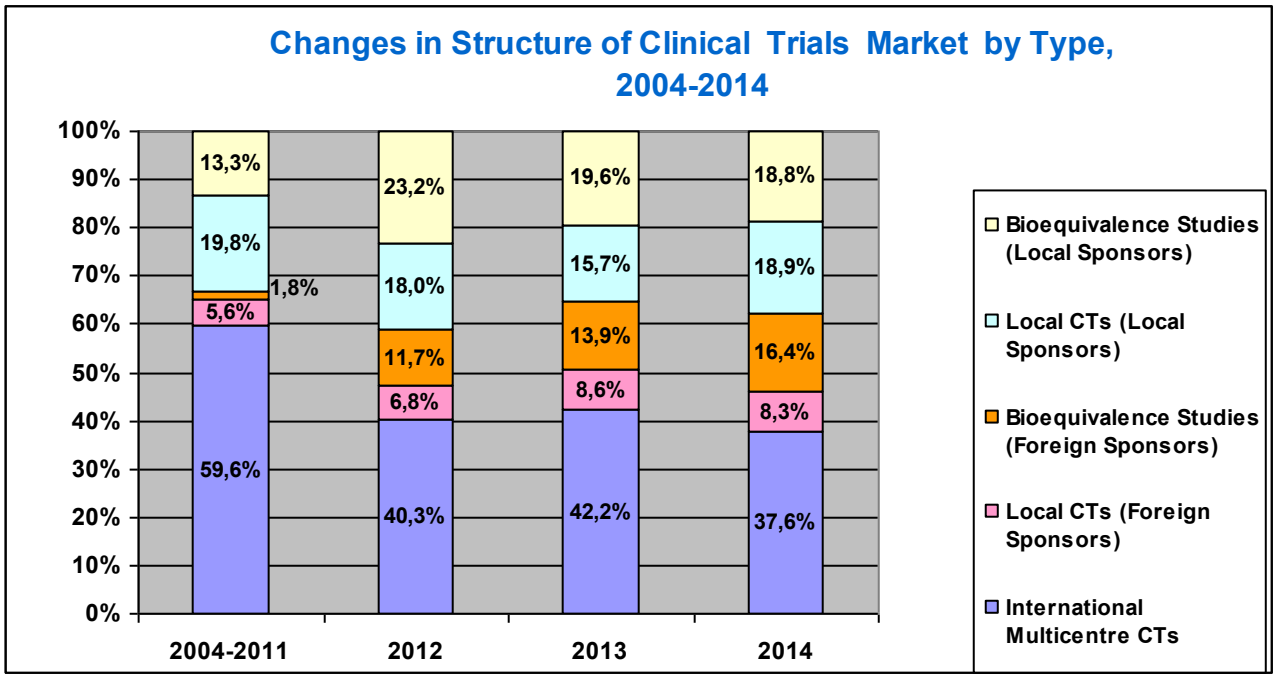
We can draw the conclusion that the drop in the number of IMCTs that we observed in 2014 in Russia reflects the global trend on the whole, and is not something specific to our country. Regarding the future of this sector of the market in the next few years, our forecast is relatively optimistic. If the IMCT market shrinks further, this will probably be to an insignificant degree. And we cannot rule out that it may grow slightly. By the way, this all holds true based on one condition – that our bureaucrats do not come up with another genius idea that could threaten the entire process of conducting trials. Although, looking back, we can say that over the past decade such threats have arisen more than once, and up to now the market has been able to successfully manage them.

THE STRUCTURE AND DYNAMICS OF THE CLINICAL TRIALS MARKET BY TYPE

The next figure that we have been tracking all these years is the structure of the market by type of trial. While before the adoption of the law "On Circulation of Medicines" this was stable, and the majority (60%) were international trials, beginning from 2012[1] the picture has changed significantly (Diagram 2). There was a significant reduction in the IMCT sector due to the increasing share of other types of trials, primarily bioequivalence studies by foreign sponsors. And so, in 2014 the share of IMCTs was 37.6%, in other words down more than 20% compared to the pre-reform levels. However, the share of bioequivalence studies initiated by foreign sponsors grew from 1.8% (the average for 2004-2011) to 16.4%.

At the same time, judging by the data of the past three years, the changes in the market structure have more or less stabilized. We are seeing year-on-year fluctuations in the share of various types of trials but we can call these insignificant.

Diagram 2



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

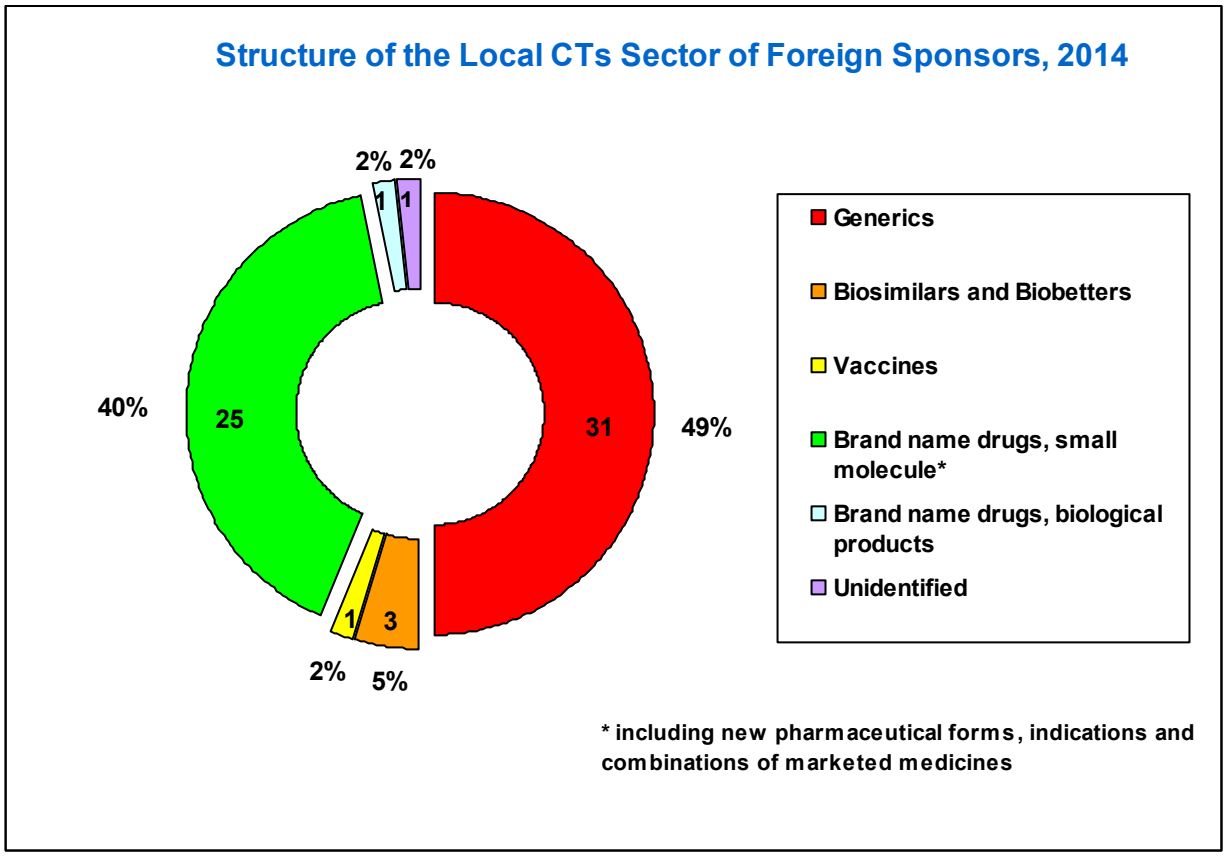
Speaking about future prospects, in the next few years we are expecting significant changes in the market structure again. These expectations are linked to the new regulations for registration of generics which came into force on January 1, 2015. In particular, now there will be no requirement for the so-called "therapeutic equivalency" trial regarding most pharmaceutical forms of medicine for which it is not possible to conduct bioequivalence studies *(for more information see the section "Changes to the law "On Circulation of Medicines" – how they influence the clinical trials market")*. The result of this should be a significant drop in the share of local trials of generic medicines by both foreign and domestic manufacturers.

The volume of the expected contraction is reflected in the next two Diagrams, where we present the structure of the sector of local trials by foreign and domestic sponsors in 2014 (Diagrams 3 and 4).

[1] Significant changes were noted beginning in 2012, and not from when the law was adopted (the end of 2010), because of market inertia. Companies needed a year to adapt to the new rules of the game: making decisions, developing documentation for trials, passing through expertise to obtain approvals and so on.

In analysing the data on local trials we used the same classification that we used in 2012 and 2013 (*for more information see Newsletters No. 6 and No. 8)*. However, this time we decided to remove vaccines from the group of original biological medicines and place them in a separate group. In addition, we changed the name of the "Biosimilars" group to "Biosimilars and BioBetters".

Diagram 3



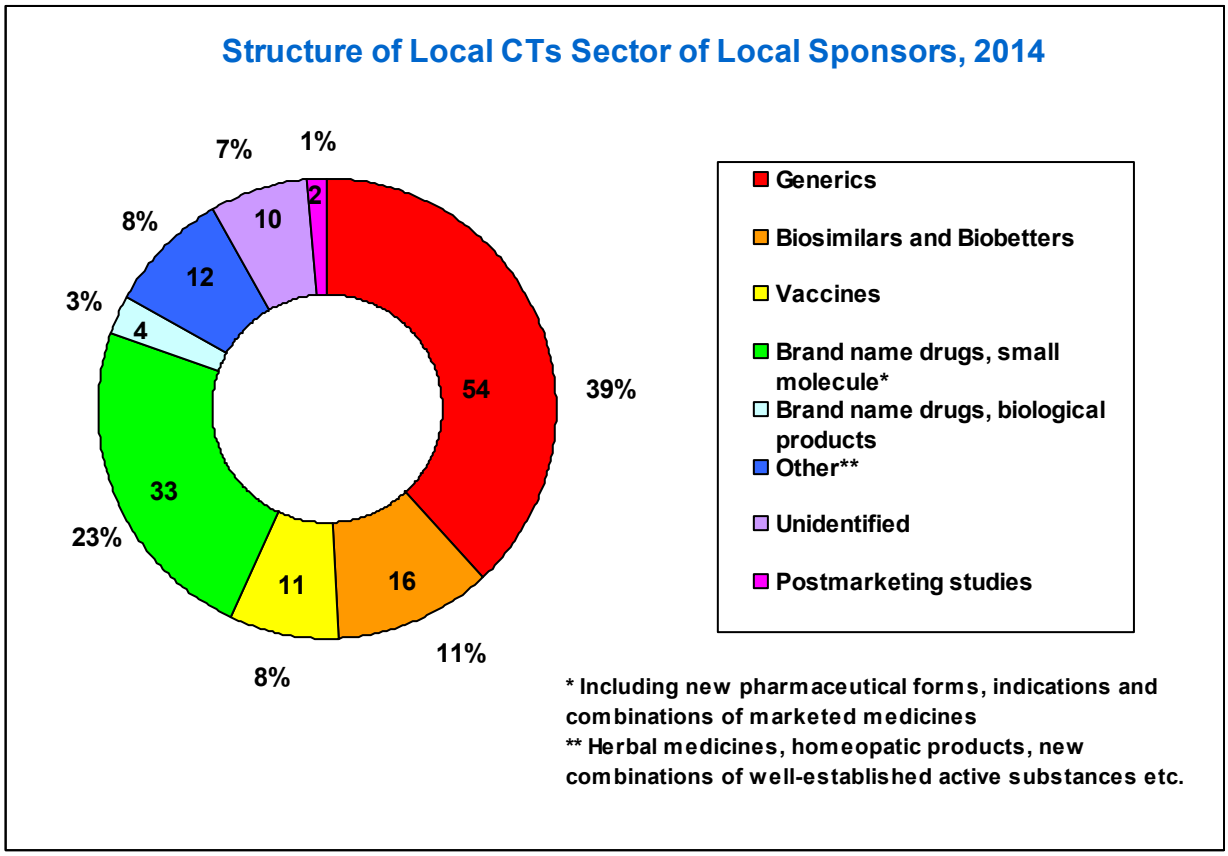
Data from www.grls.rosminzdrav.ru

Last year, as in 2012 and 2013, the biggest number of approvals issued for local trials was for generics. It is true that in comparison to the two previous years, the share of generic medicines of foreign manufacture has dropped to 49% in 2014 compared to 77.9% in 2013 and 72.6% in 2012. The share of domestic generics also dropped, but not significantly, to 39% in 2014, from 42.7% in 2013 and 40.6% in 2012.

As we expect, it is precisely this sector of the market – local trials for therapeutic equivalency of both foreign and domestic generics – that will gradually reduce to zero.

In Diagram 3 we also see the second-largest group – brand name medicines representing small molecules. This group took second place in 2013 as well, but over the last year its share rose significantly (40% in 2014 compared to 11.8% in 2013). Although we should not forget that "brand name medicines" include not only innovative ones (which are really unique), but also combinations of previously-registered medicines, and new pharmaceutical forms of medicines, and medicines being studied for new indications.

Diagram 4



Data from www.grls.rosminzdrav.ru

As we see in Diagram 4, trials of brand name medicines produced on the basis of small molecules took second place among local trials by domestic sponsors as well. In 2014 this share increased compared to the previous year, although not as significantly as for foreign products – 23% compared to 17.7% in 2013.

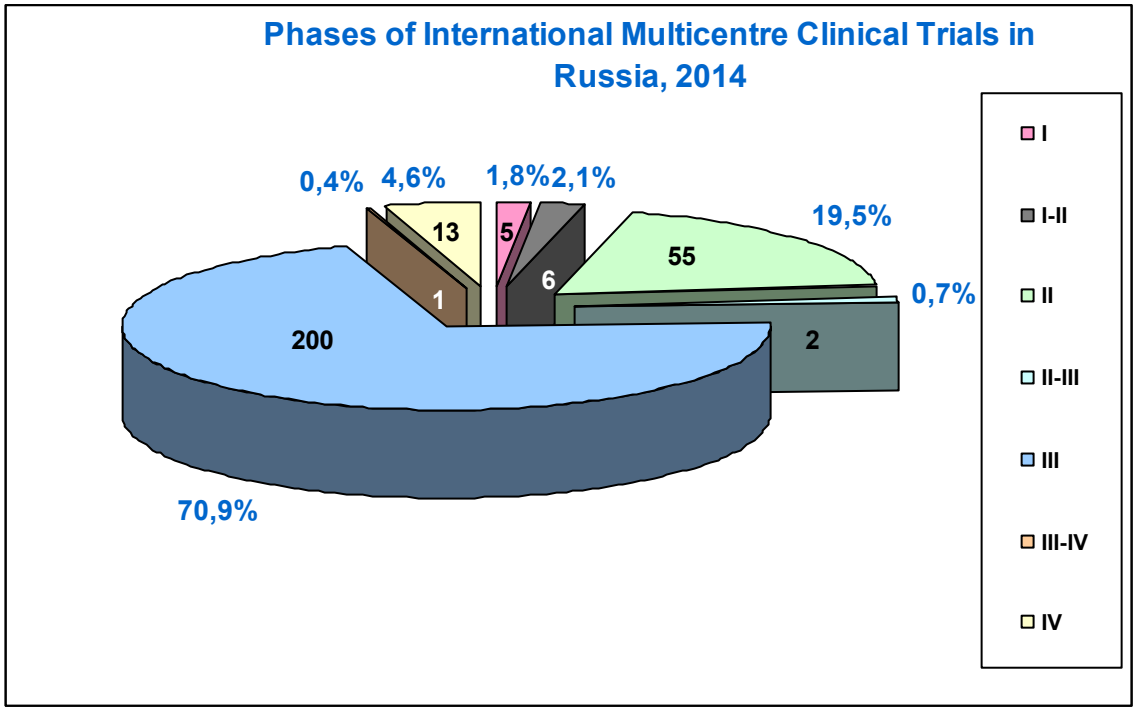
Speaking of local trials, we would like to look separately at the vaccine sector. In 2013, as we have already mentioned, we did not distinguish vaccines in their own group, but instead included them in the brand name biological products group. However, for last year the number of approvals for trials of domestic vaccines grew so much that we considered them worthy of their own group. And so, in 2014 there were 11 trials approved for domestic vaccines, 8% of the total number of local trials by Russian sponsors, when a year ago the share of trials for all brand name biological products by domestic manufacturers (including vaccines), was 6.5% (8 trials).

Finally, we would like to comment on the data on local trials by domestic sponsors – developments carried out within the framework of partnership with western companies. We first noted the appearance of such trials in 2013. Then, six such programs were identified. In 2014 we counted seven trials of medicines developed within the frameworks of partnership. The sponsors from the Russian side were, as in the previous year, the ChemRar group of companies and the R-Pharm company. These two leaders of domestic innovative production were joined by Nanolek, which obtained a license to manufacture a polio vaccine from Bilthoven Biologicals, the Dutch Company.

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

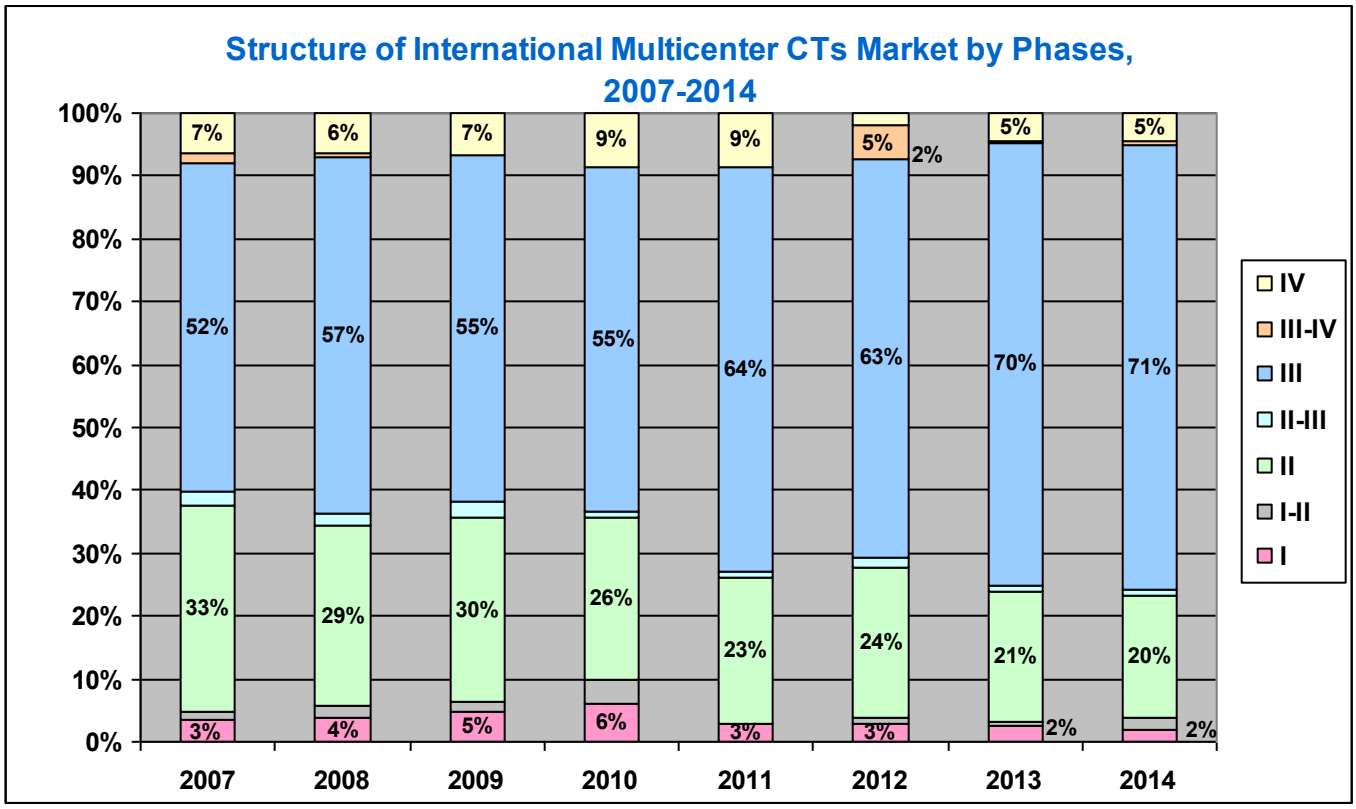
Diagram 5 shows the breakdown of 2014 approvals for IMCTs by phase.

Diagram 5



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

Diagram 6



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

Diagram 6, in turn, demonstrates the dynamics of the breakdown of international trials by phase over the past few years. It must be said that the structure of this breakdown has remained a stable figure, changing little

in the process of tectonic shifts that have happened on the market as a result of the adoption of the law "On Circulation of Medicines". We can only note the continuing growth in the share of Phase 3 trials alongside with slight drops in the share of all other types.

So, the only remaining item is our traditional listing of Phase 1 trials – the smallest number, although they are vitally important in developing medicines. In 2014, five Phase 1 IMCTs were approved. Two of them were for trials of medicines for oncological diseases, one was for hemophilia, one was for lupus nephritis, and one was for polyarticular and systemic juvenile idiopathic arthritis. We can also add that out of six protocols designated as Phase 1/2 trials, five were to study oncological medicines, and the sixth was to treat patients with Fabry's Disease.

THE STRUCTURE OF THE CLINICAL TRIALS MARKET BY THERAPEUTIC AREAS

The breakdown of approvals in 2014 for IMCTs by therapeutic areas is reflected in Table 3. Same as a year ago, oncological medicines are in the lead – over the year, 64 trials were approved, 22.7% of all IMCTs. Second place went to trials of medicines used in endocrinology (32 protocols or 11.3%). Third and fourth places were shared by trials of medicines used for treating rheumatological diseases and cardiological and cardio-vascular diseases (28 trials or 9.9% of the total volume of IMCTs).

The position of psychiatry has become catastrophic – just five protocols (1.8% of all IMCTs) were approved in 2014 compared to 18 in 2013. We have predicted this situation many times, unsuccessfully trying to draw attention to the problem (*see Newsletters No. 2, No. 5, No. 7 and No. 9).* We see the root of the problem in the position of the lead expert of the Ethics Council, holding, as far as we can tell, a course to limit the launch of new anti-psychotics in the Russian market.

Table 3

Split of International Multicenter CTs by Therapeutic Areas, 2014 vs. 2013

Therapeutic Area	Number of IMCTs, 2014	Share (%), 2014	Share (%), 2013
Oncology	64	22,7%	26,0%
Endocrinology	32	11,3%	9,6%
Rheumatology	28	9,9%	9,9%
Cardiology and Cardiovascular Diseases	28	9,9%	9,3%
Pulmonology	25	8,9%	7,8%
Hematology	20	7,1%	4,8%
Neurology	17	6,0%	8,4%
Infectious Diseases	16	5,7%	8,4%
Gastroenterology	13	4,6%	1,5%
Dermatology	11	3,9%	3,3%
Psychiatry	5	1,8%	5,4%
Ophthalmology	5	1,8%	1,2%
Allergology	4	1,4%	0,0%
Gynecology	3	1,1%	0,6%
Nephrology	3	1,1%	2,1%
Urology	3	1,1%	0,9%
Hepatology	2	0,7%	0,3%
Others	3	1,1%	0,6%
TOTAL	282	100,0%	100,0%

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Tables 4 and 5 show the breakdown by therapeutic areas of local trials and bioequivalence studies for generics and biosimilars.

In these groups of trials, conducted by foreign sponsors (Table 4) in 2014 the leaders were medicines used to treat infectious diseases (32 trials, or 20.4%), followed by those used to treat cardiological and cardio-vascular diseases (26 trials, 16.6%). Trials for gynaecological medicines (11 trials, 7%) took the third place.

Table 4

Split of Local CTs and Bioequivalence Studies (Generics and Biosimilars) of Foreign Sponsors, 2014 vs. 2013			
Therapeutic Area	**Number of CTs, 2014**	**Share (%), 2014**	**Share (%), 2013**
Infectious Diseases	**32**	**20,4%**	**17,1%**
Cardiology and Cardiovascular Diseases	**26**	**16,6%**	**26,8%**
Gynecology	**11**	**7,0%**	**1,2%**
Gastroenterology	**9**	**5,7%**	**3,7%**
Psychiatry	**9**	**5,7%**	**1,2%**
Endocrinology	**9**	**5,7%**	**2,4%**
Analgesic and Anti-inflammatory Medicines	**8**	**5,1%**	**4,9%**
Pulmonology	**7**	**4,5%**	**6,7%**
Allergology	**7**	**4,5%**	**3,7%**
Ophthalmology	**7**	**4,5%**	**2,4%**
Neurology	**6**	**3,8%**	**9,8%**
Oncology	**5**	**3,2%**	**3,7%**
Urology	**5**	**3,2%**	**1,8%**
Rheumatology	**4**	**2,5%**	**4,3%**
Phthisiology	**4**	**2,5%**	**2,4%**
Hepatology	**2**	**1,3%**	**2,4%**
Otorhinolaryngology	**2**	**1,3%**	**0,0%**
Others	**4**	**2,5%**	**1,8%**
TOTAL	**157**	**100,0%**	**100,0%**

Data from www.grls.rosminzdrav.ru

For domestic sponsors (Table 5), the situation is mirrored: first place went to trials of generics used in cardiology and the treatment of cardio-vascular diseases (43 trials, 20.4%), and second place was for medicines used to treat infectious diseases (33 trials, 15.6%). Third place in 2014 went to trials of neurological medicines (24 trials, 11.4%).

Table 5

Split of Local CTs and Bioequivalence Studies (Generics and Biosimilars), Conducted by Local Sponsors , 2014 vs. 2013			
Therapeutic Area	**Number of CTs, 2014**	**Share (%), 2014**	**Share (%), 2013**
Cardiology and Cardiovascular Diseases	**43**	**20,4%**	**16,5%**
Infectious Diseases	**33**	**15,6%**	**22,8%**
Neurology	**24**	**11,4%**	**8,5%**
Analgesic and Anti-inflammatory medicines	**14**	**6,6%**	**6,7%**
Oncology	**13**	**6,2%**	**8,0%**
Rheumatology	**12**	**5,7%**	**4,0%**
Gastroenterology	**12**	**5,7%**	**3,1%**
Psychiatry	**10**	**4,7%**	**3,6%**
Endocrinology	**8**	**3,8%**	**4,5%**
Pulmonology; Phthisiology	**6**	**2,8%**	**8,5%**
Urology	**5**	**2,4%**	**3,1%**
Otorhinolaryngology	**5**	**2,4%**	**1,3%**
Dermatology; Immunology	**4**	**1,9%**	**1,8%**
Allergology	**4**	**1,9%**	**2,2%**
Ophthalmology	**3**	**1,4%**	**0,0%**
Nephrology	**3**	**1,4%**	**0,4%**
Hematology	**3**	**1,4%**	**2,7%**
Gynecology	**2**	**0,9%**	**0,9%**
Anesthesiology, Surgery, Intensive Care	**2**	**0,9%**	**0,9%**
Others	**5**	**2,4%**	**0,4%**
TOTAL	**211**	**100,0%**	**100,0%**

Data from www.grls.rosminzdrav.ru

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Analysing the data on the number of trials of generics and biosimilars, we also decided to look at which medicines were most often copied by generics manufacturers (Table 6).

The most in-demand were ethynilestradiol used in various combinations and moxifloxacin (10 trials each). The next most popular was hydrochlorothiazide, also in various combinations (nine trials), and then rosuvastatin (eight trials).

Table 6

Most Requested INN Used in Clinical Trials of Generics and Biosimilars in 2014				
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**
Moxifloxacin	**8**	**2**	**10**	**Infectious diseases**
Ethinylestradiol in fixed combinations	**9**	**1**	**10**	**Gynecology**
Hidrochlorothiazide in fixed combinations	**5**	**4**	**9**	**Cardiology and Cardiovascular diseases**
Rosuvastatin	**4**	**4**	**8**	**Cardiology and Cardiovascular diseases**
Paracetamol (separately and in fixed combinations)	**3**	**4**	**7**	**Analgesic and Anti-inflammatory medicines**
Imatinib	**3**	**4**	**7**	**Oncology**
Memantine	**4**	**2**	**6**	**Psychiatry**
Metformin (separately and in fixed combinations)	**4**	**2**	**6**	**Endocrinology**
Sildenafil	**3**	**3**	**6**	**Urology**
Glucosamine (separately and in fixed combination)	**1**	**5**	**6**	**Rheumatology**
Chondroitin sulfate (separately and in fixed combinations)	**0**	**6**	**6**	**Rheumatology**
Linezolid	**4**	**1**	**5**	**Infectious diseases**
Amlodipine in combination	**4**	**1**	**5**	**Cardiology and Cardiovascular diseases**
Enoxaparin sodium	**1**	**4**	**5**	**Cardiology and Cardiovascular diseases**
Mebeverine	**1**	**4**	**5**	**Gastroenterology**
Lamivudine (separately and in fixed combinations)	**1**	**3**	**4**	**Infectious diseases**
Levofloxacin	**2**	**2**	**4**	**Infectious diseases**
Perindopril (separately and in fixed combinations)	**3**	**1**	**4**	**Cardiology and Cardiovascular diseases**
Bisoprolol in combination	**2**	**2**	**4**	**Cardiology and Cardiovascular diseases**
Candesartan	**1**	**3**	**4**	**Cardiology and Cardiovascular diseases**
Valsartan (separately and in fixed combinations)	**3**	**1**	**4**	**Cardiology and Cardiovascular diseases**

Ursodeoxycholic acid	**2**	**2**	**4**	**Gastroenterology**
Rabeprazole	**3**	**1**	**4**	**Gastroenterology**
Escitalopram	**1**	**3**	**4**	**Psychiatry**
Desloratadine	**2**	**2**	**4**	**Allergology**
Latanoprost	**4**	**0**	**4**	**Ophthalmology**
Pregabalin	**3**	**1**	**4**	**Neurology**

Data from www.grls.rosminzdrav.ru

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Table 7 shows the therapeutic areas of the local trials of brand name medicines of foreign manufactures, approved in 2014. Since the total number is not large, we have not indicated the percent shares.

Table 7

Split of Local CTs of Brand Name Drugs of Foreign Sponsors, 2014	
Therapeutic Area	**Number of CTs**
Infectious Diseases	**5**
Allergology	**4**
Cardiology and Cardiovascular Diseases	**3**
Gastroenterology	**3**
Analgesic and Anti-inflammatory Medicines	**2**
Neurology	**2**
Urology	**2**
Oncology	**2**
Gynecology	**2**
Endocrinology	**1**
Hepatology	**1**
TOTAL	**27**

Data from www.grls.rosminzdrav.ru

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Table 8 presents a breakdown by therapeutic areas of local trials of brand name medicines from domestic manufacturers. During the year, 48 such trials were approved. The first place with a wide margin took the medicines to treat infectious diseases (21 trials), and the second - developments in cancer treatment (eight trials). Further down were medicines for phythisiology, as well as cardiology and cardio-vascular diseases (three trials each). The other therapeutic areas had one trial each.

Table 8

Split of Local CTs of Brand Name Drugs of Local Sponsors, 2014	
Therapeutic Area	**Number of CTs**
Infectious Diseases	**21**
Oncology	**8**
Cardiology and Cardiovascular Diseases	**3**
Phthisiology	**3**
Neurology	**1**
Gastroenterology	**1**
Immunology	**1**
Narcology	**1**
Psychiatry	**1**
Otorhinolaryngology	**1**
Pulmonology	**1**
Traumatology	**1**
Rheumatology	**1**
Transplantology	**1**
Roentgenology, Radiology	**1**
Endocrinology	**1**
Not identified	**1**
TOTAL	**48**

Data from www.grls.rosminzdrav.ru

MAIN PLAYERS ON THE RUSSIAN CLINICAL TRIALS MARKET – 2014

The first analysis of the breakdown of the approved trials by sponsor companies and contract research organisations (CROs) we conducted when we prepared the annual Newsletter for 2013. This experience seemed successful, and so we decided to repeat it this year. We will not describe the approach we used to analyse the data again (*for more information see Newsletter No. 8)*, we will just note a few key moments that we must remember when looking at the results:

- the results presented do not fully reflect the participation of CROs in conducting trials, since this data is not always included in the primary sources used – the Ministry of Health register of issued approvals for clinical trials. So, if the function transferred to the CRO does not impact the regulatory process, the CRO's participation won't necessarily be noted in the register;
- in addition to the pharmaceutical companies themselves and CROs, we also had to distinguish another group of organisations taking part in the research process which we called "other representatives". These companies are not CROs in the classical sense as they were not engaged in conducting clinical trials at a professional level. As a rule, these are the organisations which took on the functions of launching the drug on the Russian market, promotion and distribution of medicinal products from foreign companies whenever those companies did not have their own representatives in the country.

Sponsors and CROs, General Structure of Breakdown

The general data presented in Diagram 7 shows the ratio of clinical trials based on who conducted them. The biggest share of participation by CROs (53%) was seen as expected in the IMCT sector. We note that according to 2013 data, the breakdown in this sector was exactly the same – 47% of IMCTs were run by sponsors and 53% by CROs.

For practically all other types of trials, the share of participation of CROs last year dropped in comparison to the data of 2013. So, for local trials of foreign medicines this share dropped from 35% in 2013 to 23% in 2014. At the same time, the percentage of participation by "other representatives" also dropped (from 18% to 6%). As a result, the share of local trials conducted by the pharmaceutical companies themselves grew in 2014 to 71% from 47% in 2013.

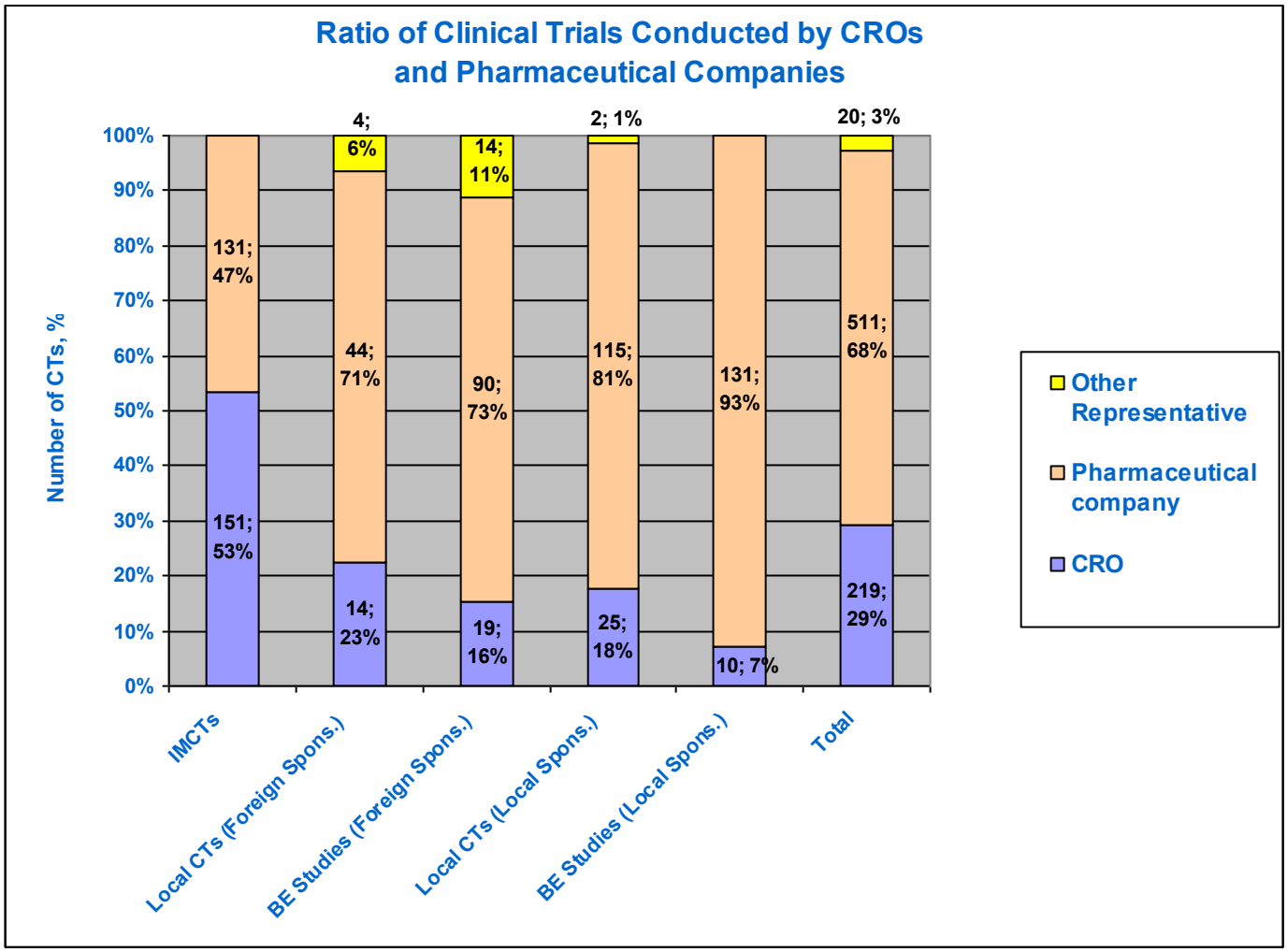
In the sector of bioequivalence studies of foreign generics, the picture is a bit different. The share of this type of trials with participation of CROs also dropped somewhat compared to the previous year – 16% compared to 24% in 2013. However, the share of trials conducted by "other representatives" grew, from 2% in 2013 to 11% in 2014. As a result, the percentage of bioequivalence studies conducted by foreign pharmaceutical companies themselves remained practically unchanged (73% last year compared to 74% the year before).

The share of CRO participation in bioequivalence studies for domestic medicines also dropped, to 7% in 2014 from 12% in 2013.

The only type of trials where the share of CRO participation increased was local trials by domestic sponsors. So, in 2014 this share was 18%, compared to 15% the year before. Trials conducted with the participation of "other representatives" remained at 1%. Accordingly, the share of such trials conducted by the domestic manufacturers themselves was down 3% compared to 2013 (81% from 84%).

As a result, the breakdown of all types of trials is not significant, but it has moved towards trials conducted by the pharmaceutical companies themselves – 68% compared to 65% in 2013. At the same time, the share of trials conducted with the participation of "other representatives" grew from 1% to 3%. The share of trials conducted with CRO participation on the other hand, dropped from 34% to 29%.

Diagram 7



Data from www.grls.rosminzdrav.ru

International Multicentre Clinical Trials, Sponsors

Table 9 and Diagram 8 present the Top 15 pharmaceutical companies based on the number of approvals granted in 2014 for clinical trials.

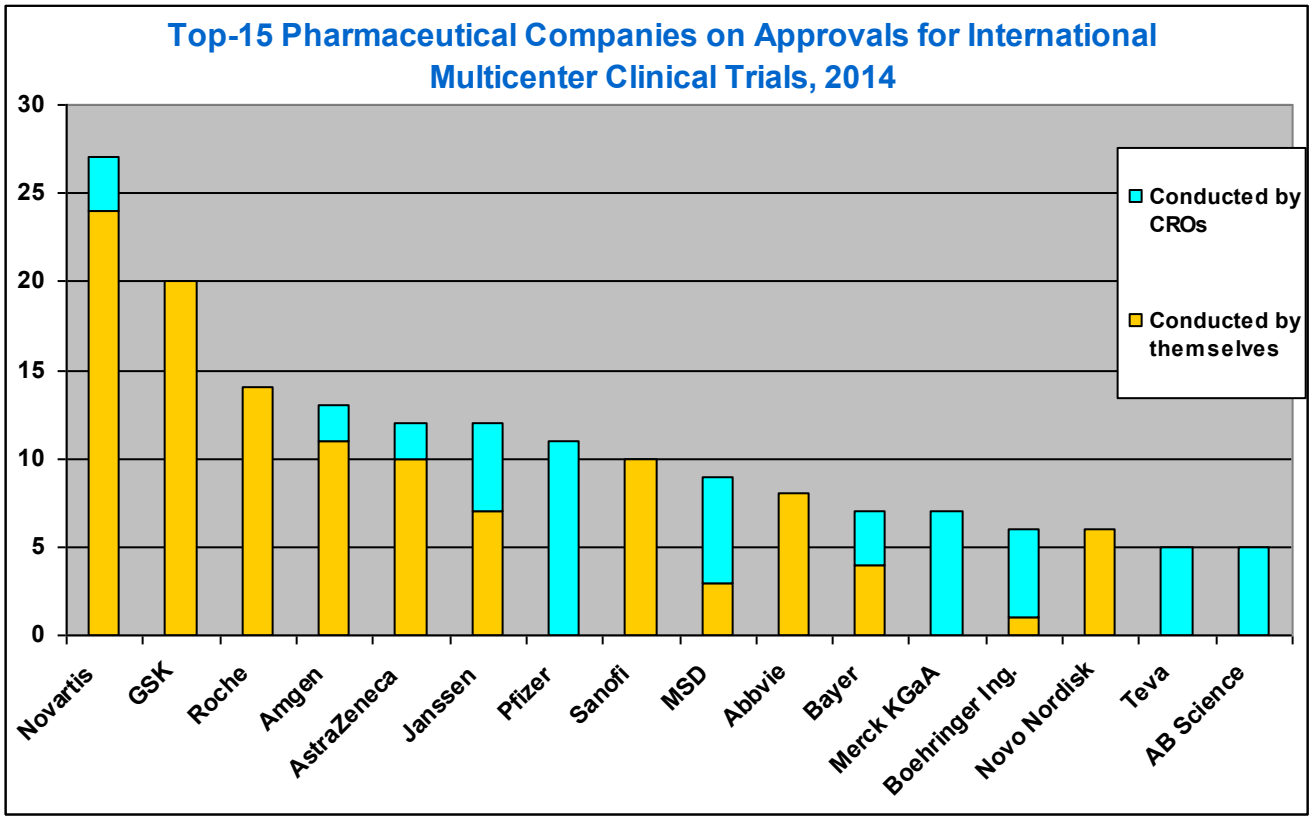
Table 9

Top 15 Pharmaceutical Companies on Approvals for International Multicenter CTs, 2014						
№	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, 2014	The Number of CTs; position in rating 2013
1	Novartis	24	3	27	1	34 CTs; 1
2	GlaxoSmithKline	20	-	20	2	21 CTs; 2
3	F. Hoffmann-La Roche	14	-	14	3	15 CTs; 4
4	Amgen	11	2	13	4	11 CTs; 9-10

5	AstraZeneca	10	2	12	5-6	11CTs; 9-10
6	Janssen Pharmaceutica	7	5	12	5-6	14 CTs; 5
7	Pfizer	-	11	11	7	10 CTs; 11
8	Sanofi	10	-	10	8	8 CTs; 12-15
9	Merck & Co.	3	6	9	9	18 CTs; 3
10	Abbvie	8	-	8	10	6 CTs; 16-17
11	Bayer	4	3	7	11-12	8 CTs; 12-15
12	Merck KGaA	-	7	7	11-12	2 CTs; 24-39
13	Boehringer Ingelheim	1	5	6	13-14	5 CTs; 18-19
14	Novo Nordisk	6	-	6	13-14	6 CTs; 16-17
15	Teva	-	5	5	15-16	2 CTs; 24-39
16	AB Science	-	5	5	15-16	n/a

Data from www.grls.rosminzdrav.ru

Diagram 8



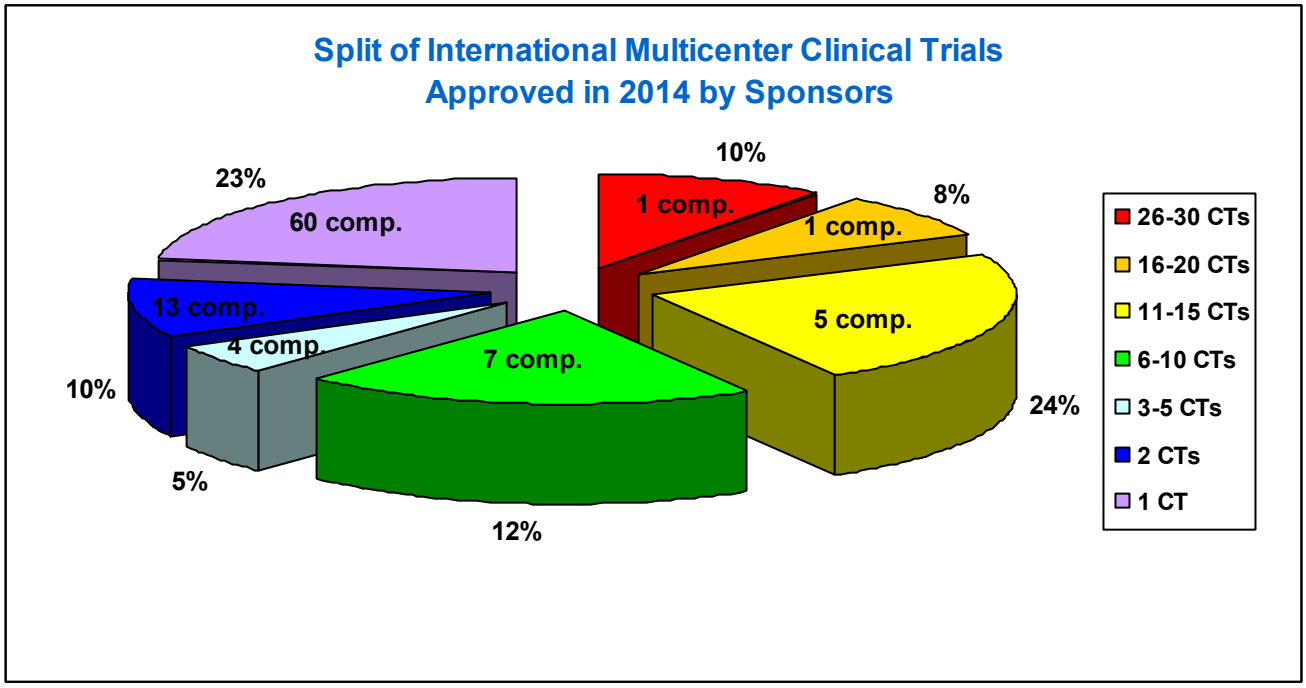
Data from www.grls.rosminzdrav.ru

From Diagram 9, we can see that the lion's share of the IMCT market (42%) in 2014 was controlled by just seven sponsor companies. And the first two sectors with volumes of 10% and 8% went to two companies (As we see in Table 9, these are Novartis and GlaxoSmithKline). 24% went to other five leading sponsors (each with 11-15 approved trials).

12% of IMCTs were distributed between seven companies (each with 6-10 trials). 5% of the market went to four companies, who initiated 3-5 trials in 2014. Thirteen companies (10% of the market) obtained approval for two trials each. And finally, 23% of all IMCTs went to the group of 60 companies who had only one approved trial each last year.

Altogether, according to the Ministry of Health register, 91 companies acted as sponsors of international trials in 2014, which is 13 fewer than in 2013.

Diagram 9



Data from www.grls.rosminzdrav.ru

International Multicentre Clinical Trials, CROs

Table 10 and Diagram 10 present the Top 10 CROs by number of IMCTs approved in 2014 with their participation.

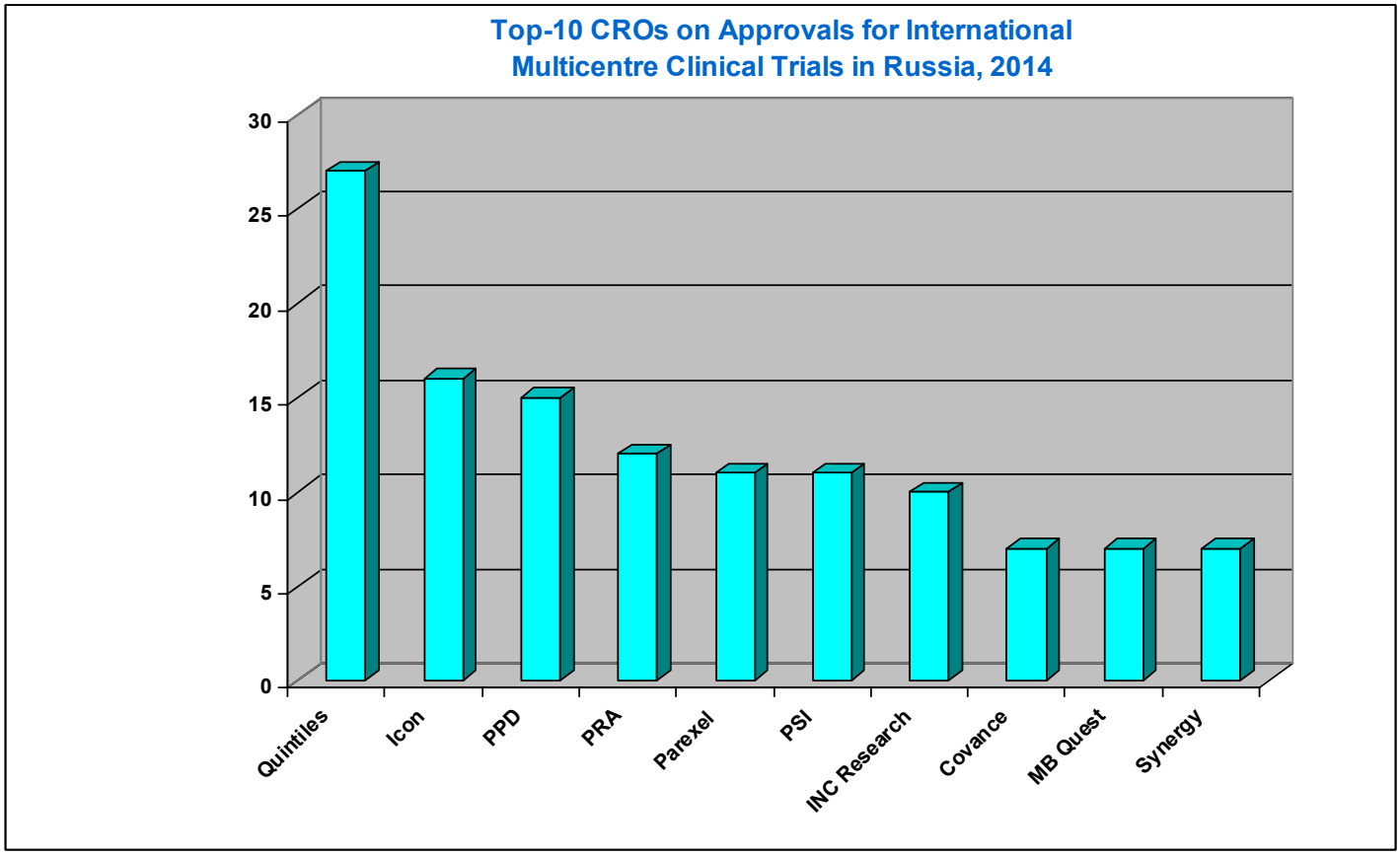
Table 10

Top-10 CROs on Approvals for International Multicenter CTs, 2014					
№	**Company**	**Number of CTs**	**Number of Sponsors**	**Ranking in 2014**	**Number of CTs; Ranking in 2013**
1	**Quintiles**	**27**	**15**	**1**	**22 CTs; 2**
2	**Icon**	**16**	**8**	**2**	**14 CTs; 5-6**
3	**PPD**	**15**	**12**	**3**	**20 CTs; 3**

4	PRA International (incl. ClinStar)	12	8	4	15 CTs; 4
5	Parexel	11	6	5-6	32 CTs; 1
6	PSI	11	10	5-6	8 CTs; 7-8
7	INC Research	10	8	7	14 CTs; 5-6
8	Covance	7	4	8-10	7 CTs; 9
9	MB Quest	7	6	8-10	2 CTs; 11-21
10	Synergy Research Group	7	3	8-10	n/a

Data from www.grls.rosminzdrav.ru

Diagram 10



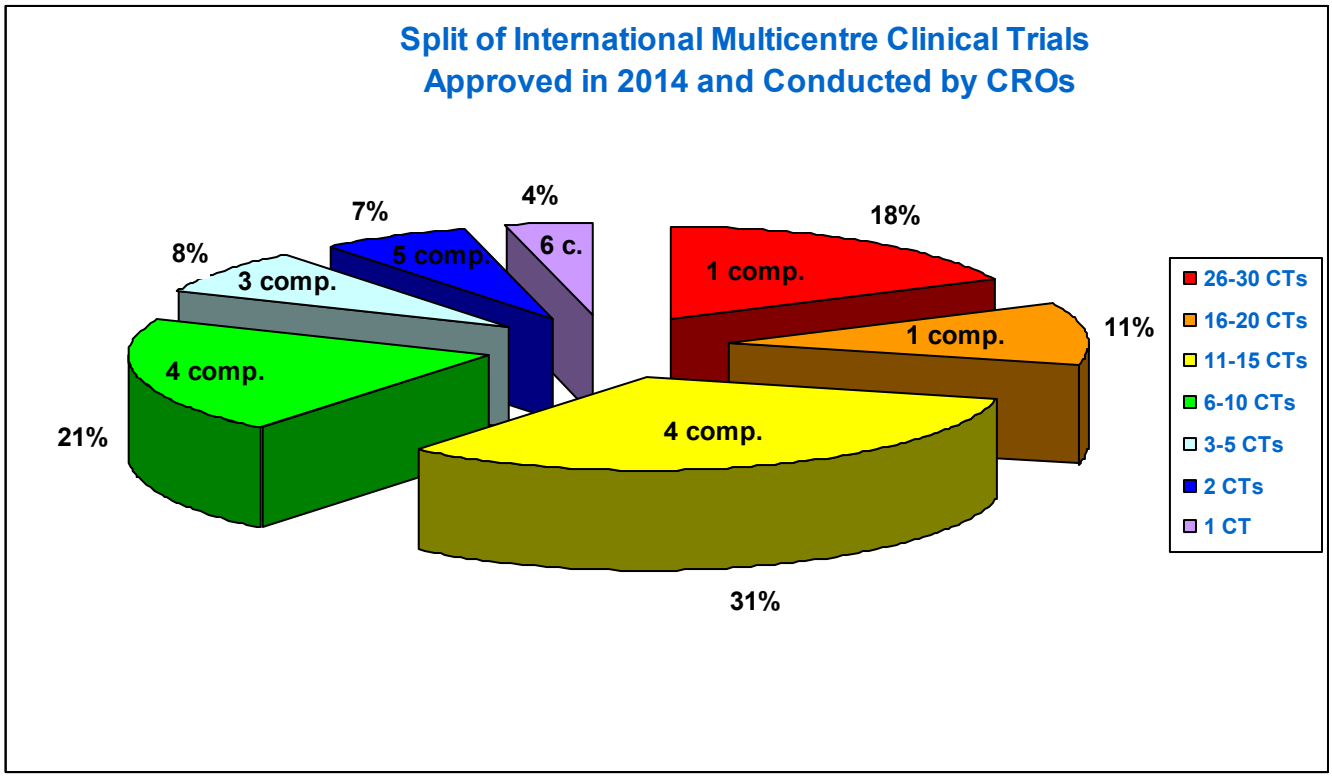
Data from www.grls.rosminzdrav.ru

By Diagram 11, we can see the breakdown for 2014 of IMCTs by CRO. Here we can see even more distinctly than in the case with sponsors, that the largest part of trials is going to the big players – 60% of all trials conducted with CRO participation went to six companies. In particular, 18% of all approved IMCTs were planned with the participation of one company (as we recall from Table 10, this is Quintiles, with 27 trials). 11% of new protocols in 2014 went to Icon. A further 31% of trials were split between four more CROs, each with 11-15 protocols.

Four companies who got 6-10 trials each per year, held 21% of the market. 8% went to three companies with three trials each, and a further 7% went to five CROs (with two protocols each). Finally, six companies who had just one trial each, held just 4% of this market segment.

In total, based on approvals in 2014 for IMCTs, according to the data from the Ministry of Health register, there were 24 CROs involved, against 28 in 2013.

Diagram 11



Data from www.grls.rosminzdrav.ru

Local Clinical Trials and Bioequivalence Studies of Foreign Medicines, Sponsors

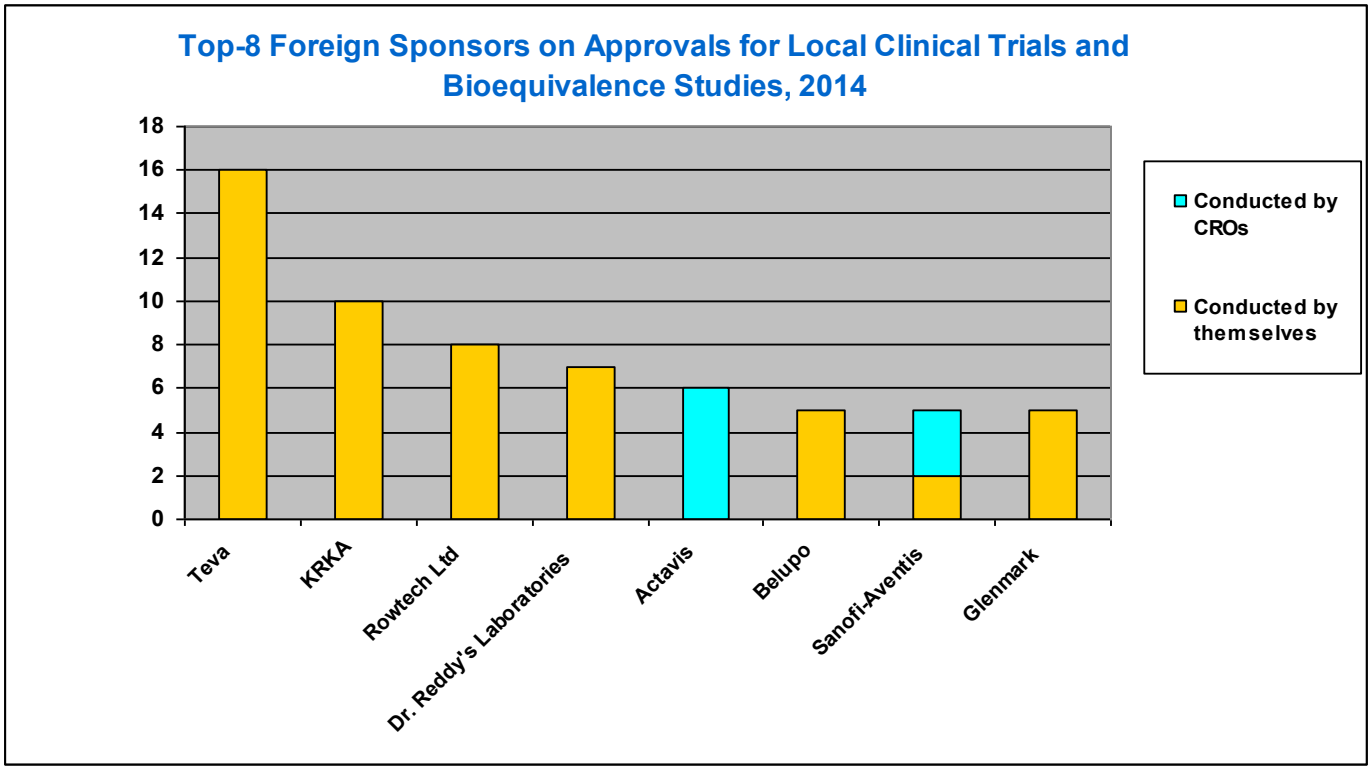
Table 11 and Diagram 12 present data about the Top 8 foreign sponsors regarding the number of approvals obtained for local clinical trials and bioequivalence studies.

Table 11

Топ 8 Foreign Sponsors on Approvals for Local CTs and Bioequivalence Studies, 2014						
№	Company	Conducted by themselves	Conducted by CROs	Total	Ranking in 2014	Number of CTs; Ranking in 2013
1	Teva	16	-	16	1	18 CTs; 1
2	KRKA	10	-	10	2	8 CTs; 2-4
3	Rowtech Ltd	8	-	8	3	n/a
4	Dr. Reddy's Laboratories	7	-	7	4	n/a
5	Actavis	-	6	6	5	6 CTs; 7-8
6	Belupo	5	-	5	6-8	4 CTs; 11-15
7	Sanofi-Aventis	2	3	5	6-8	2 CTs; 19-34
8	Glenmark	5	-	5	6-8	1 CT; 35-73

Data from www.grls.rosminzdrav.ru

Diagram 12

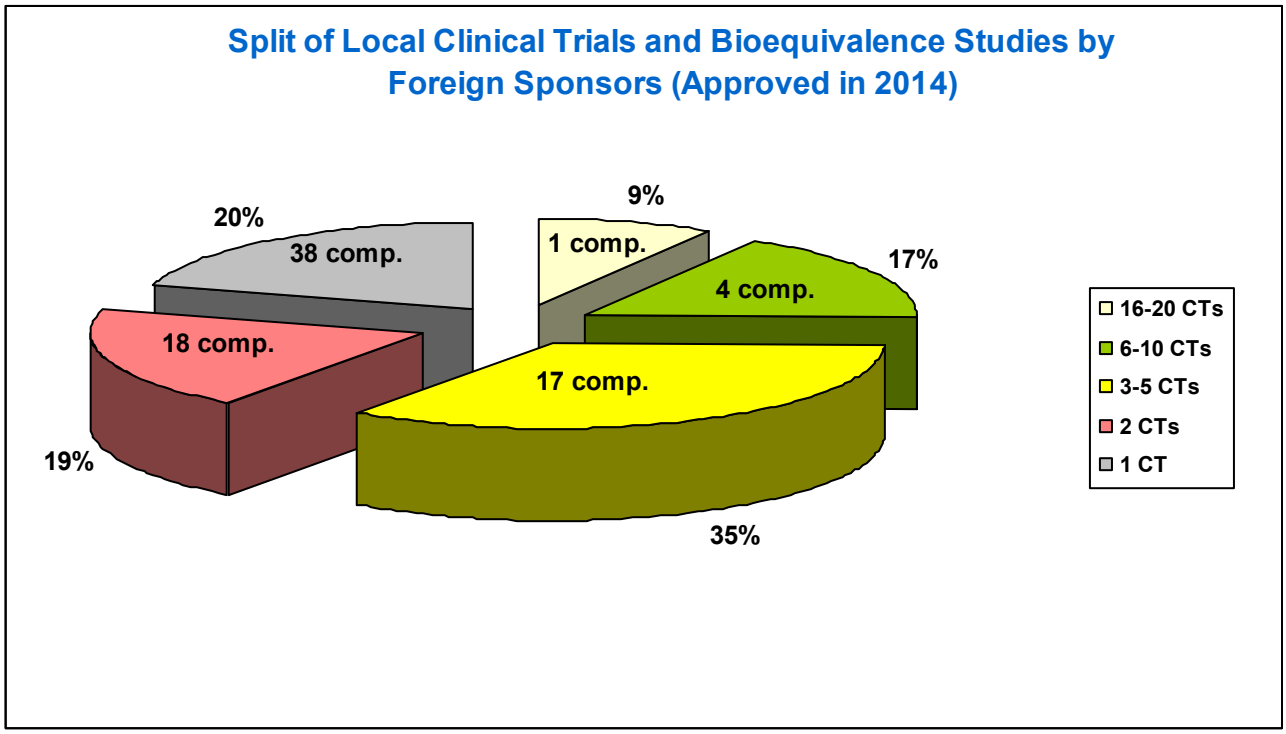


Data from www.grls.rosminzdrav.ru

Diagram 13 helps to evaluate the breakdown of local trials and bioequivalence studies by foreign sponsors. The leading position, with 9% of this market segment, went to one company – Teva, as we can see from Table 11. 17% of approvals for trials went to four companies (each with 6-10 protocols), 35% of trials were distributed among 17 companies (each with 3-5 trials). A further 19% of the market was distributed between 18 companies (each with two protocols). The remaining 21% of the market went to 38 companies with one trial apiece.

In total, 78 foreign companies participated in the local clinical trials market in 2014 (compared to 73 in 2013).

Diagram 13



Data from www.grls.rosminzdrav.ru

Local Clinical Trials and Bioequivalence Studies of Foreign Medicines, CROs

Table 12 presents a rating of CROs involved, according to the Ministry of Health register, in conducting local trials and bioequivalence studies of foreign medicines for which approval was granted in 2014. If we compare this list with the top ten CROs involved in IMCTs, we don't see any overlap.

Table 12

CROs on Approvals for Local CTs and Bioequivalence Studies of Foreign Sponsors, 2014					
№	Company	Number of CTs	Number of Sponsors	Ranking, 2014	Number of CTs; Ranking 2013
1	Medical Development Agency LLC. (MDA)	7	2	1	9 CTs; 1
2	Solyurpharma LLC.	6	2	2	3 CTs; 4-8
3	OCT Russia	4	4	3	4 CTs; 3
4	Ltd. Probiotech	3	3	4-5	5 CTs; 2
5	Ltd. PharmaReg	3	3	4-5	1 CT; 15-20
6	LLC ClinPharmInvest	2	2	6-7	2 CTs; 9-14
7	Raifarm LLC.	2	2	6-7	2 CTs; 9-14

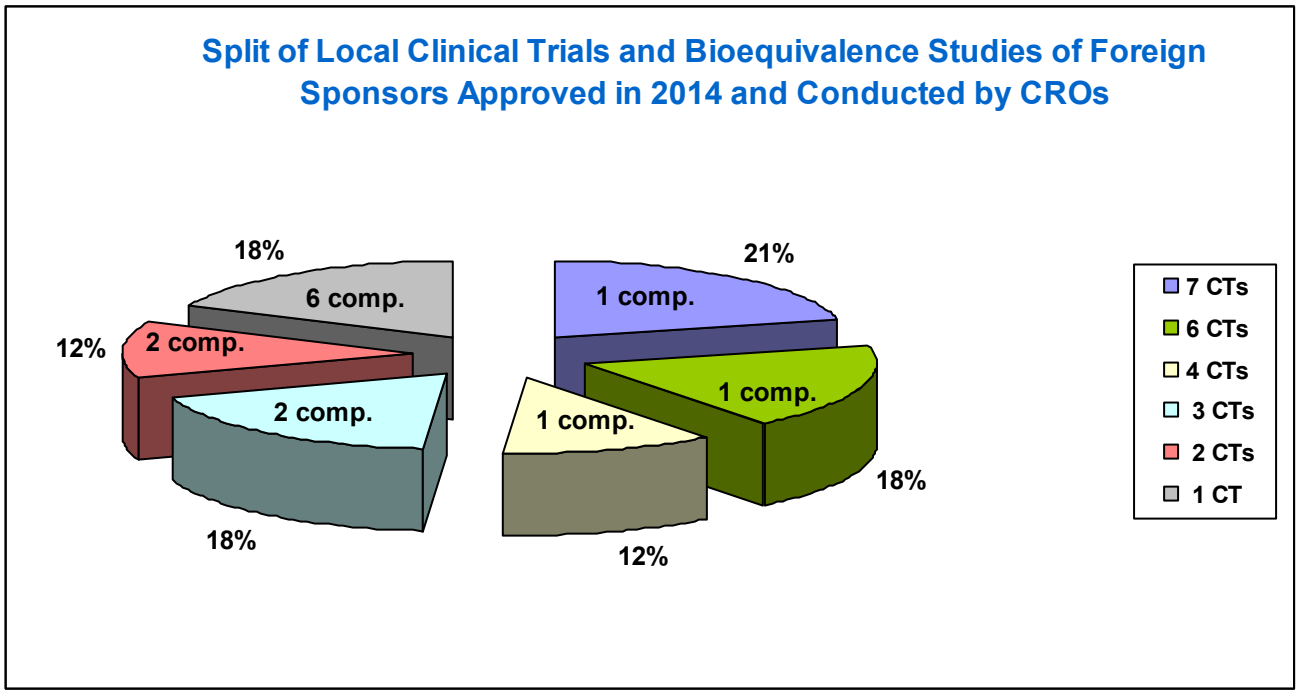
8	Ascent CRS	1	1	8-13	3 CTs 4-8
9	Atlant Clinical Ltd.	1	1	8-13	n/a
10	Expert & Legal Centre for Pharmaceuticals and Medical Devices LLC	1	1	8-13	3 CTs; 4-8
11	Ligand Research LLC	1	1	8-13	2 CTs; 9-14
12	Pharmregs	1	1	8-13	2 CTs; 9-14
13	RCT-global LLC	1	1	8-13	n/a

Data from www.grls.rosminzdrav.ru

In Diagram 14 we see that 51% of the market of local clinical trials of foreign medicines went to three CROs (with between four and seven protocols each). 18% of trials were split between two companies, each of which had three trials. A further two companies had two protocols each (12%). And other six companies had one trial each (18%).

In 2014, a total of 13 contract research organisations (data for 2013 showed 20 companies) were involved in local trials and bioequivalence studies of foreign medicines.

Diagram 14



Data from www.grls.rosminzdrav.ru

Local Clinical Trials and Bioequivalence Studies of Domestic Medicines, Sponsors

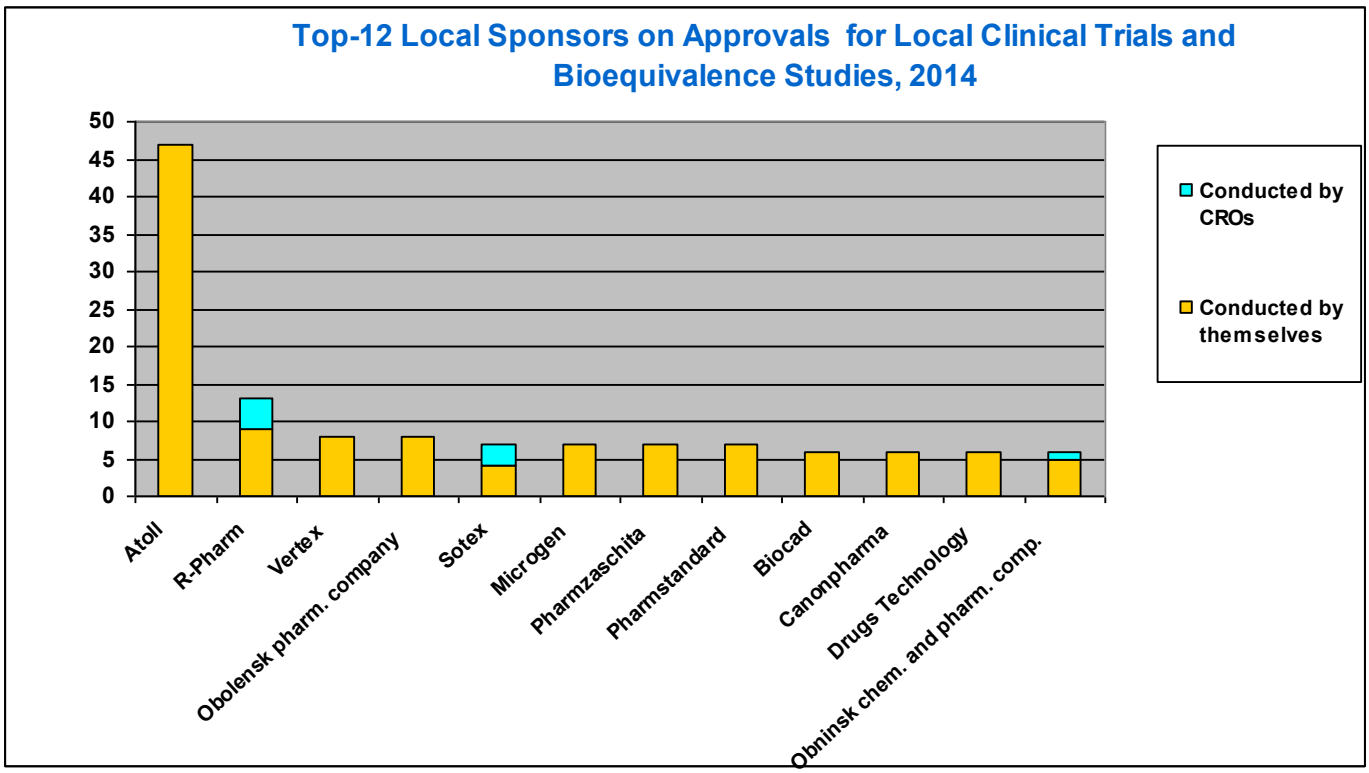
Table 13 and Diagram 15 present the data on the Top 12 Russian manufacturers based on the number of approvals obtained for local trials and bioequivalence studies.

Table 13

Top-12 Local Sponsors on Approvals for Local Clinical Trials and Bioequivalence Studies, 2014						
№	**Company**	**Conducted by themselves**	**Conducted by CROs**	**Total**	**Ranking, 2014**	**Number of CTs/Ranking 2013**
1	**Atoll**	**47**	**-**	**47**	**1**	**31 CTs; 1**
2	**R-Pharm**	**9**	**4**	**13**	**2**	**2 CTs 27-48**
3	**Vertex**	**8**	**-**	**8**	**3-4**	**18 CTs; 2**
4	**Obolensk Pharmaceutical Company**	**8**	**-**	**8**	**3-4**	**1 CT; 49-99**
5	**Pharmaceutical company Sotex**	**4**	**3**	**7**	**5-8**	**6 CTs; 10-12**
6	**Microgen**	**7**	**-**	**7**	**5-8**	**3 CTs 19-26**
7	**Pharmzaschita**	**7**	**-**	**7**	**5-8**	**2 CTs; 27-48**
8	**Pharmstandard**	**7**	**-**	**7**	**5-8**	**4 CTs; 16-18**
9	**Biocad**	**6**	**-**	**6**	**9-12**	**13 CTs; 3**
10	**Canonpharma Production**	**6**	**-**	**6**	**9-12**	**5 CTs; 13-15**
11	**Drugs Technology**	**6**	**-**	**6**	**9-12**	**4 CTs; 16-18**
12	**Obninsk Chemical and Pharmaceutical Company**	**5**	**1**	**6**	**9-12**	**n/a**

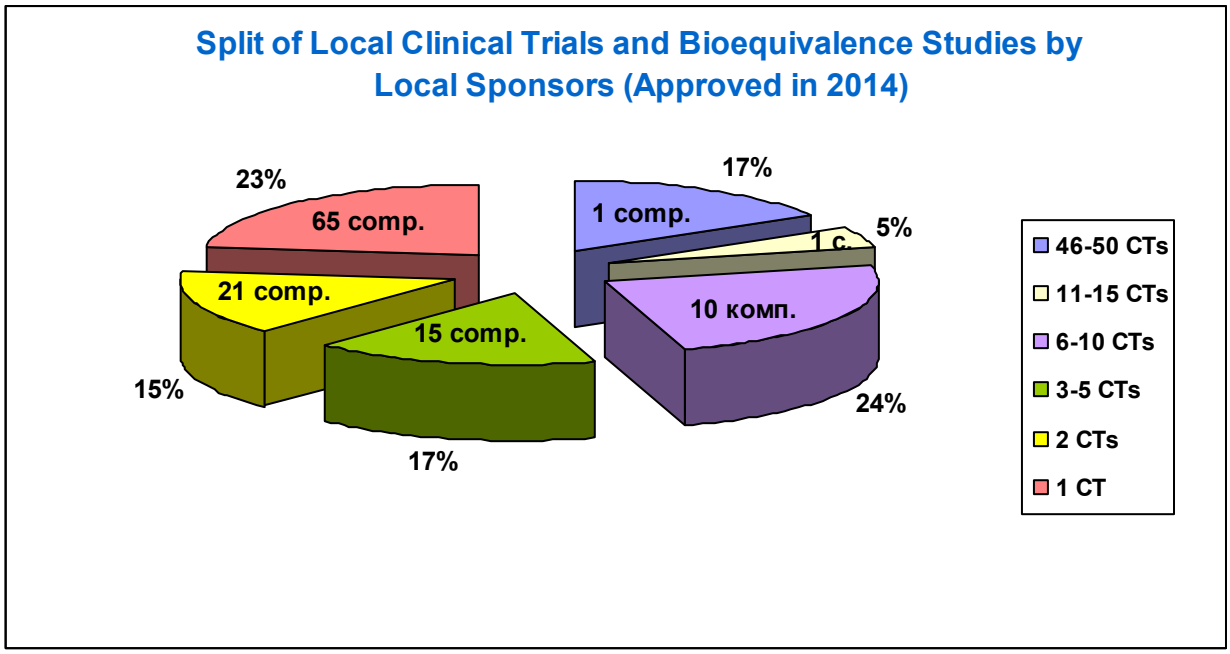
Data from www.grls.rosminzdrav.ru

Diagram 15



Data from www.grls.rosminzdrav.ru

Diagram 16



Data from www.grls.rosminzdrav.ru

Diagram 16 shows the breakdown for local trials and bioequivalence studies between Russian sponsors.

A 17% share of these types of trials goes to one company (as we can see from Table 13, this is Atoll, with 47 approvals). A further 5% of the market also goes to one player (R-Pharm with 13 protocols). 24% of all approvals obtained were split between 10 companies, each initiated between 6 and 10 trials. The next group of 15 companies, with 3-5 protocols per year per company, had a 17% market share. A further 15% of trials were split between 21 companies, each obtained two approvals in 2014. And finally, 65 companies had one approved protocol each (23%).

Altogether in this market sector in 2014 the Ministry of Health register recorded activity from 113 domestic sponsors (99 in 2013).

Local Clinical Trials and Bioequivalence Studies of Domestic Medicines, CROs

Data about the participation of CROs in conducting local trials and bioequivalence studies for domestic medicines approved in 2014 are presented in Table 14. There are only 13 such companies, that is why we decided to list them all as we did last year.

Table 14

CROs Involved in Local Clinical Trials and Bioequivalence Studies Conducted by Local Sponsors (on Approvals Issued in 2014)					
№	**Company**	**Number of CTs**	**Number of Sponsors**	**Ranking, 2014**	**Number of CTs/Ranking, 2013**
1	**Ltd. Probiotech**	**11**	**7**	**1**	**12 CTs; 1**
2	**Ipharma (Innovative Pharmaceuticals)**	**9**	**9**	**2**	**7 CTs; 2**
3	**Synergy Research Group**	**3**	**2**	**3**	**n/a**
4	**LLC Pharm-Solyur**	**2**	**1**	**4-5**	**n/a**
5	**Ascent CRS**	**2**	**1**	**4-5**	**n/a**
6	**OCT Russia**	**1**	**1**	**6-13**	**6 CTs 3**
7	**Medical & Marketing Solutions (MMS)**	**1**	**1**	**6-13**	**3 CTs; 5-6**
8	**LLC CTR Pharma**	**1**	**1**	**6-13**	**n/a**
9	**Medical Development Agency LLC. (MDA)**	**1**	**1**	**6-13**	**n/a**
10	**Expert & Legal Centre for Pharmaceuticals and Medical Devices LLC**	**1**	**1**	**6-13**	**n/a**
11	**Almedis**	**1**	**1**	**6-13**	**1 CT; 7-9**
12	**PharmRegS**	**1**	**1**	**6-13**	**n/a**
13	**R&D Pharma**	**1**	**1**	**6-13**	**n/a**

Data from www.grls.rosminzdrav.ru

We can only add that according to register data for 2014 the pool of CROs working in conducting local trials for domestic sponsors increased by four companies (13 compared to 9 in 2013). And the make-up of players changed drastically – the register for 2014 did not include four companies which had been on the list the previous year, and at the same time there were eight new CROs included.

TIMEFRAMES FOR ISSUANCE OF APPROVALS

Traditionally, in the annual review we present data on the waiting times to obtain approval documents from the Ministry of Health. This time we again had to correct the methodology of calculating timeframes for approval for clinical trials, returning to the usual method from which we had deviated last year (*see Newsletter No. 8).* The reason for this return to the previous algorithm was that the Ministry of Health changed its practice of sending questions from the part of expert organisations to the method of "stopping the clock", while in 2013 such cases were mainly refused and the applicant had to re-submit all the documents again. For the other types of approvals, as before, we used the same long-standing method of calculation.

The results for all types of approvals are presented in Table 15.

Table 15

Timeframes for Issuing Approvals, 2014[2]					
Type of approval	**Timeframes according to legislation (workdays/ calendar days)**	**Average timeframes (calendar days)**	**Minimum timeframes (calendar days)**	**Maximum timeframes (calendar days)**	**Sampling**
To Conduct Clinical Trials	**41/57**	**95**	**30**	**244**	**165**
To Import Medicines	**8/12**	**14**	**3**	**48**	**350**
To Import/Export Biosamples	**13/19**	**23**	**2**	**62**	**645**
To Make Amendments to the Protocol	**34/48**	**60**	**7**	**105**	**324**
Other Approvals (to Prolong Clinical Trials, to Include New Sites, to Enroll Additional Patients, etc.)	**25/35**	**27**	**6**	**109**	**634**
Total Time to Obtain Approvals to Conduct Clinical Trials and to Import/Export	**54/76**	**118**	**-**	**-**	**-**

Data from timeframes monitoring of ACTO

From Table 16 we can see how the average approval waiting times changed in 2014 compared with 2013. As we can see, for practically all types of approvals, with the exception of a permit to import medicines, we see a slight increase in timeframes. The biggest increase (33.3%) was in the waiting time to obtain approval for protocol amendments. There was a 15% increase in the time to obtain permits for import/export of biosamples. But this difference is not noticeable in practice, since it is a matter of only three days. The increase in waiting times to obtain approval to conduct a trial was also not so critical – 95 days compared to 87 (an increase of 9.2%). We assume that this difference arose as a result of the difference method of calculation – the approach we used last year seems to have slightly reduced the calculated waiting times as compared to real practice.

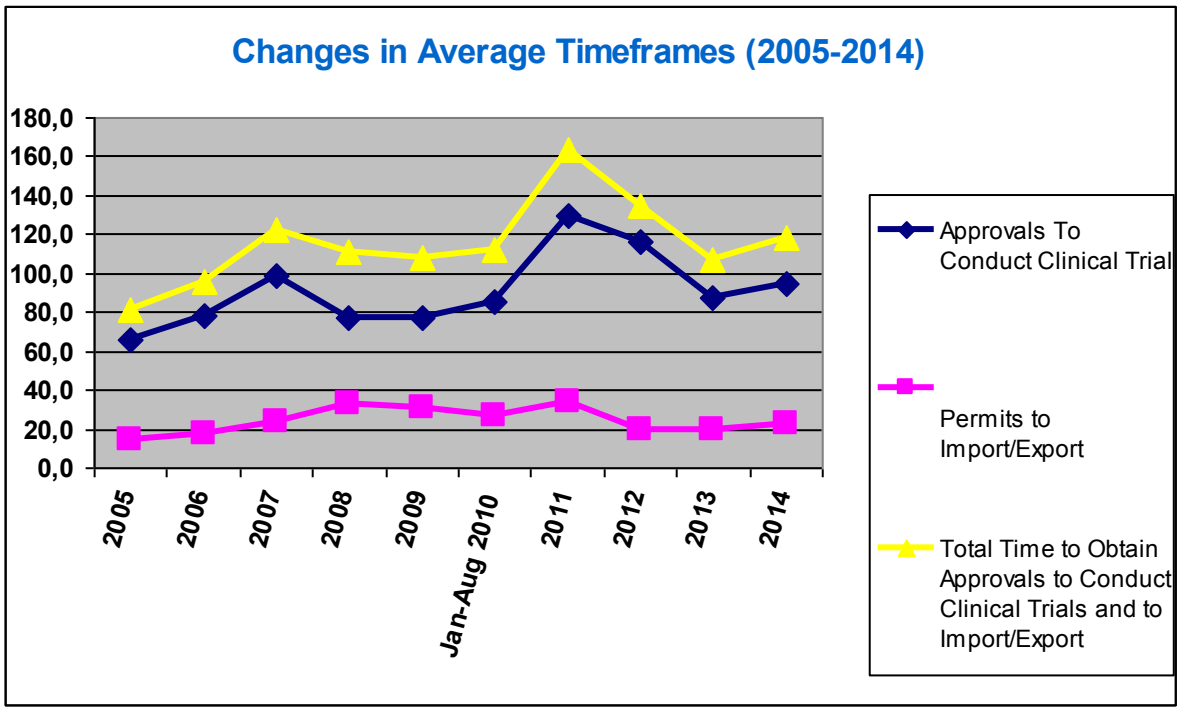
[2] During the calculating of legislative timeframes we were translating the workdays to calendar days, and adding from 1 to 4 days (depending on the kind of submission) for the registration of the application and awarding of ready document to the applicant, despite the fact that in law these stages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

Table 16

Average Timeframes for Issuing Approvals, 2014 vs. 2013			
Type of approval	**2013**	**2014**	**2014 vs. 2013, %**
To Conduct Clinical Trials	**87**	**95**	**9,2%**
To Import Medicines	**14**	**14**	**0,0%**
To Import/Export Biosamples	**20**	**23**	**15,0%**
To Make Amendments to the Protocol	**45**	**60**	**33,3%**
Other Approvals (to Prolong Clinical Trials, to Include New Sites, to Enroll Additional Patients, etc.)	**26**	**27**	**3,8%**

Data from timeframes monitoring of ACTO

Diagram 17



Data from timeframes monitoring of ACTO

In Diagram 17 we can see how average timeframes to obtain approvals have changed over the years, from 2005 to 2014. We used three parameters – the average waiting time to obtain an approval to conduct a trial, the average waiting time to obtain a permit to import medicine or to export biosamples (mostly used), as well as the total time for both of those figures. The last parameter gives us an idea about the time that a sponsor needs to actually start a trial in Russia. In 2014 this total period was 118 days, which was 11 days worse than the figure for the previous year. But from the graphic it is clear that although last year's figure is obviously not an improvement of the overall picture, it is far from the worst figure of the preceding years.

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Table 17 gives us an idea of what percentage of approval documents has been issued on time or with different kinds of time-limit breaches in 2014, compared to the same data for 2013.

Table 17

Violations of Timeframes, 2014 vs. 2013								
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	2014	6,1%	93,9%	44,9%	43,0%	4,8%	1,2%	0,0%
	2013	4,0%	96,0%	51,4%	29,9%	12,4%	2,3%	0,0%
To Import Medicines	2014	42,0%	58,0%	33,4%	16,6%	7,1%	0,6%	0,3%
	2013	43,7%	56,3%	30,4%	20,0%	5,1%	0,8%	0,0%
To Import/Export Biosamples	2014	29,5%	70,5%	43,5%	24,5%	2,3%	0,2%	0,0%
	2013	53,1%	46,9%	35,8%	10,0%	1,0%	0,1%	0,0%
To Make Amendments to the Protocol	2014	25,0%	75,0%	44,7%	28,4%	1,9%	0,0%	0,0%
	2013	60,3%	39,7%	30,9%	7,4%	1,4%	0,0%	0,0%
Other Approvals (to Prolong Clinical Trials, to Include New Sites, to Enroll Additional Patients, etc.)	2014	86,8%	13,2%	10,6%	1,9%	0,5%	0,2%	0,0%
	2013	86,2%	13,8%	11,9%	1,6%	0,3%	0,0%	0,0%

Data from timeframes monitoring of ACTO

Only 6.1% of approvals for clinical trials in 2014 were issued within the statutory timeframe (this picture improved slightly from 2013, when only 4% of approvals were issued on time). We can also see slight improvement in the breakdown of the share of overdue cases by how overdue they were. So, there is a reduction in the share of overdue cases which took two to four times longer than the statutory time. However, there was a 6.5% reduction compared to 2013 in the number of approvals issued with a minimal delay (up to 1.5 times the statutory period). We can also state that the overwhelming majority of the delayed approvals were issued in approximately even shares – with a minimal delay (up to 1.5 times) or with a delay of 1.5 to twice the statutory period (44.9% and 43% respectively).

The situation with permits to import medicines is better: 42% of permits were granted on time in 2014, almost as many as in 2013 – 43.7%. The relationship between the share of overdue cases depending on the length of time overdue was also practically unchanged for these types of approvals.

It became more difficult to obtain permit for import/export of biosamples on time. In 2014, 29.5% of these permits were issued on time, though in 2013 the figure was 53.1%.

The most significant deterioration was on the average waiting times, both in the percentage of delays seen in obtaining approvals for protocol amendments. So while in 2013 60.3% of these approvals were issued on time, in 2014 this figure dropped to 25%. There was also big growth in the share of approvals obtained with a delay of 1.5-1.9 times the statutory time. In 2014 the share of such delays grew to 21% and made up 28.4% of all approvals in this group.

The timeframes to obtain other approvals (to extend the trial, to include new sites, to enroll additional patients and so on) have been followed much better and remained practically unchanged – 86.8% of these approvals were granted on time in 2014, compared to 86.2% in 2013.

In fairness we should note that having discussed these results with companies, we got feedback that in their subjective opinion, the applicants did not feel that the situation with waiting times had significantly deteriorated over the past year. The only thing they would like to draw the attention of the Ministry of Health employees to is the approval for protocol amendments. It is clear that these periods are significantly influenced by the time taken to review the materials by the Ethics Council (in cases where the amendment needs expert evaluation). Nevertheless, we would like to express the wish to adhere more closely to statutory periods for this type of approval.

Applicants had many more complaints about the quality of the expert review, first and foremost of that conducted by FGBU[3]. However we will address this issue in the next issue of the Newsletter, when we will present the results of the new poll on refusals received in the course of reviewing applications to conduct clinical trials.

[3] The Research Centre for Expertise of Medicinal Products

CHANGES MADE TO THE LAW "ON CIRCULATION OF MEDICINES" – HOW THEY INFLUENCE THE CLINICAL TRIALS MARKET

The changes to the law "On Circulation of Medicines" was probably the most significant event of 2014 for the Russian pharmaceutical market. The Ministry of Health started working on this project at the end of 2012 and it has taken two years. Finally, in December 2014 the law has been adopted. The main part of it will come into force from July 1, 2015, with separate issues being implemented later – from January 1, 2016, and from January 1, 2017. But before we start looking at the new changes in the new law, we would like to briefly return to the history of its development (*see also Newsletters No. 6 and No. 7).*

The main hallmark of the project was the lack of a clear concept throughout the whole period of working on the amendments. The need to amend the law that was adopted in 2010 has been declared by the new leadership of Ministry of Health in May 2012. However, it was never made clear what goals the proposed changes should achieve. The responsible authorities could not bring themselves to seriously criticize the existing law – the work of their predecessors – but at the same time they needed to take on this work under an onslaught of criticism. And everyone was indeed criticizing – from market players and patient groups to state authorities at all levels. Without their own concept, the Ministry of Health ended up in a difficult situation, pressured from various angles by different interested parties which often had conflicting interests. As a result the text was re-written multiple times, and proposed ideas were swapped for completely opposite ones. On one hand some loosening of the rules was proposed, on the other, much stricter control over different stages of the circulation of medicines process. Unfortunately, the finally adopted statutory wording is also too complex to be understood. Having resolved some problems of pharmaceutical market the law has simultaneously created other ones.

It appears that the clinical trials market in this sense fared better than the commercial one. The text adopted, although it does not solve a lot of the issues in the sector, still improves the situation in various ways. The main achievement is that several serious threats were successfully avoided. We list these below.

The first and one of the most serious ones was the attempt to bring in a requirement to conduct pharmaceutical testing of samples of medicines at the stage of obtaining approvals to conduct clinical trials. This initiative, which emerged at the very beginning of work on the project, puts in danger the very existence of the clinical trials market in Russia. Happily, it was avoided – the Ministry of Health finally (not immediately, but at the end) listened to the voice of reason and removed the proposed novelty from the text of the law (*for more information, see Newsletter No. 6).*

The second threat was the suggested increase in times for review of applications to obtain approval for clinical trials from 41 (under current law) to 70 working days. This was also avoided, explaining that implementing such a standard would hit Russia's competitiveness as a country taking part in international trials. As a result the waiting times for clinical trials were left unchanged, although on a number of other approval functions the Ministry of Health did increase statutory periods.

The third danger that was avoided was a regulation of non-interventional trials and limits on the number of patients participating in them. So it was proposed that this number should not exceed 10% of the number of patients diagnosed with the disease. The idea even made it into the text that passed in the first reading. However, later on, taking into account the unanimous opinion of market players, the legislators removed it.

At one of the later stages of debating the legislation, a problem arose over the incorrect use of the term "comparator (product)". For the purposes of registration of generics, developers tried to define a concept similar to the "reference product" in EC Directive 2001/83/EC. However they used "comparator" as the term and then specified that this was a registered medicine, but did not specify that it should be used only to register generics. There was a risk that in practice there could be confusion with "comparator", used in clinical trials. In

other words there was a threat of a formal ban on using unregistered products as comparators in trials. The industry's concerns were made clear to the legislators. First they confirmed that the proposed meaning of the term was used to register generics and biosimilars, and finally they replaced it with "reference product". This way the threat was removed.

The final but no less dangerous threat than implementing pharmaceutical testing of samples, was the threat that arose at the very last stage – before the second reading of the law in the State Duma. It was connected with the implementation of requirements on procedures to confirm the compliance of manufacturing facilities (both domestic and foreign) with Russian GMP rules. According to the new law, Russian manufacturers would undergo checks to obtain a license for production, and foreign manufacturers would have to undergo inspection of their production by Russian inspectors and obtain confirmation. By January 1, 2017, all foreign manufacturers would have to undergo the procedure, otherwise they would not be able to apply for registration, or make any changes to the registered file. You can imagine that this novelty would have become a serious problem with the implementation of the new law. How in the remaining time with an almost total lack of inspectorate in Russia, they will check the huge number of manufacturers, it seems no one can understand. At first the requirement was proposed for practically all levels, including obtaining approval to conduct clinical trials. This proposal was completely unacceptable for western sponsors, who would in such circumstances simply have ceased to consider Russia as a potential participant in IMCTs. The requirement was also practically impossible to implement for domestic manufacturers engaged in joint projects. But literally just before the second reading exceptions to the requirement were achieved, related to investigated medicines, leaving the conditions of mandatory confirmation of compliance with GMP of the country of manufacture.

Now let us turn to the positive changes. The most important achievement in the new law was probably the distinguishing between the processes of registration and clinical trials. The standard in place since 2010 turned the whole process of releasing new medicines onto the market on its head. Around the world, the pharmaceutical company first obtains all the proof of efficacy and safety for the future medicine, and only then brings it for authorization process, but our legislation put the cart before the horse. In order to register a medicine in Russia, the company first conducted pre-clinical trials, then somehow put together the registration dossier (including, in addition to everything else, instructions on taking the still-not-approved medicine and all its indications), and apply for registration. And only after all this, the question of conducting a clinical trial could be addressed. This was clearly absurd and was the butt of jokes throughout the pharmaceutical world. But it took five whole years to fix it. And here we would like to say thank you to the Federal Antimonopoly Service, which systematically throughout the entire period worked to obtain the necessary changes out of the Ministry of Health. Finally, from July 1 of this year, the standard bringing to order the process of releasing new medicines onto the market will come into force.

Unfortunately, attempts to implement changes to the standards on mandatory local registration trials with Russian patients were unsuccessful. Only in one case the new law does achieve recognition of the results of international trials – when registering orphan medicines. There is some hope for the others. In spring 2015, thanks again to the Federal Antimonopoly Service, there were new discussions on the need to change the standards requiring pharmaceutical companies to repeat the conduct of clinical trials, whereas such studies are totally unnecessary and scientifically unfounded. Whether these efforts will be heard or not only time can tell.

One more positive change was the removal of the requirement to conduct trials of the so-called "therapeutic equivalency" of generics, whose pharmaceutical form does not allow bioequivalence studies. We'll remind ourselves of the specifics. The law adopted in 2010 brought in the requirement for mandatory presentation of clinical trial data for all medicines. In the case of generics, bioequivalence studies were sufficient. However if they were not possible (injectable medicines, gases, creams, and so on), then "therapeutic equivalency" trials were required. These trials were as follows – the company would gather about one hundred patients (the average for domestic sponsors in 2014 was 95 patients, while for foreign sponsors it was 113), and, usually in an open-label trial, would look at something. Luckily, this standard has been changed, and from January 1, 2016 for registration of most pharmaceutical forms of generics (there are however a few exceptions), for which it is not possible to run bioequivalence studies, "therapeutic equivalency" trials will no longer be necessary.

Remarkably, some representatives of innovative companies actively fought against this standard. They naively suggested that the existing barrier was serious protection from quick market launches of generics. We chance to say that there was indeed a barrier, but its severity and efficacy were in serious doubt. And for its part, ACTO criticised this standard, understanding that in its current form it could seriously harm the clinical trials sphere – real clinical trials, conducted under GCP. These concerns were not baseless – the practice of the last few years showed what kind of quality shift (and not, clearly, for the better) the Russian clinical trials market has undergone as a result of these questionable standards (*see also Newsletter No. 9, chapter "Quality of Clinical Trials – Results of Inspections by Regulatory Bodies")*. Now after the removal of these standards, the number of such trials has begun to drop, and by early 2016 we hope that they will drop almost to zero. In truth, the problem of repeat trials for registering brand name medicines remains, but as we have already mentioned, there are positive steps towards solving this problem in the future.

The legislator did not forget about our little brothers either – now as for generics, so for combination medicines there is no need to conduct pre-clinical trials. These changes will also come into effect at the beginning of next year.

One more undoubtedly good piece of news was the relaxing of requirements for principal investigators experience. Now, in order to act as the principal investigator, a doctor must have not five, but three years of experience in clinical trials. This is a significant step, since the existing standard to a significant degree held back development in the sphere and limited the ability to attract new personnel to the field. At the regional level it was often an insurmountable barrier. Where can a clinic which has never before taken part in clinical trials find a doctor with the necessary experience? Now even if this problem has not been fully resolved, but it has been significantly eased.

In looking at the overall results, we can admit that the updated law has not solved all of the problems in the sphere of clinical trials. It has not regulated the problem of insurance (*see Newsletter No. 5).* The accreditation system for clinical sites has remained – a superfluous system which seriously complicates operations in conducting clinical trials. There are lots of other smaller issues which complicate work in the sector. There are also separate concerns connected with how this will all be enforced in practice. For any changes, even positive ones, will engender "restructuring" of the regulatory systems. And there are always problems, delays, requiring correction by some or other technical process. But on the whole we can say that the changes are for our thin slice of the pharmaceutical market, quite positive. And this gives us reason to look to the future with, albeit guarded, optimism.