ACTO

ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

ACTO NEWSLETTER №6

Summary of 2012 results

MOSCOW 2013

CONTENTS

SUMMARY

First of all we would like to apologise to our readers for having slightly delayed this newsletter publication. However, the 2012 results relating to Russian clinical trials market have turned out to be quite interesting and hopefully you will not be disappointed.

Let us remember that the year 2012 was marked by further changes of the Russian pharmaceutical industry. The Ministry of Health and Social Development was reconfigured into two separate ministries – the Ministry of Health and the Ministry of Labour. The Ministry of Health is headed by Veronika Skvortsova. The subsequent staffing reshuffles gave a cause for hope for positive changes with regards to legislation of the pharmaceutical sector. To see if these hopes were well-founded, read in the section on Legislative Initiatives.

In 2012 the Ministry of health issued 915 approvals to conduct clinical trials, which is more than 60 % excess over the 2011 rate. This was also an absolute record for the entire period of keeping records. Evaluating the results of the year according to this indicator, we could have called them spectacular. However there was one huge interfering factor – significant structural changes in the market, and the reasons therefor.

The significant growth in the number of approvals issued was primarily due to a real boom in bioequivalence studies. The number of this kind of studies of foreign medicines increased by a factor of nearly six, totalling 107 approvals set against just 19 in 2011. The number of bioequivalence studies by Russian sponsors also grew by nearly three times (212 compared to 63). The number of local efficacy and safety trials by local sponsors grew by more than two times (165 compared to 80); the number of local trials by foreign sponsors was up 1.8 times (62 compared to 35). At the same time, the number of approvals for international multicentre clinical trials (IMCTs) stayed the same – 369 approvals in 2012 compared to 370 in 2011.

As a result the total share of IMCTs in 2012 dropped from 60 % (the average for the preceding eight years) to 40 %. And the share of bioequivalence studies reached 35 % compared to the previous average of 15.1 %. The share of local efficacy and safety trials remained practically unchanged – 7 % against the average indicator of 5.6 % for foreign sponsors and 18 % against 19.8 % for local sponsors.

An analysis of the local efficacy and safety trials sector revealed that the majority of the trials were those of generics. On the whole it can be concluded that the Russian market for clinical trials previously indisputably innovative, has over the course of one year veered sharply towards generics. In our opinion, these structural changes on the market are the result of the law “On Circulation of Medicines” passed in 2010.

The next item of this issue is an analysis IMCTs distribution across Russia. The leading areas were, as expected, St. Petersburg and Moscow. The third place, rather surprisingly for us, went to the Yaroslavl Region.

As usual we summed up the year’s results of monitoring of the waiting times for the approval documentation issuing. The average period to obtain approval to conduct clinical trials in 2012 was 116 days, which is 14 days less than in 2011. The wait times for other types of approvals also improved. The average period for issuing a permit for import of medicinal products was 18 days compared to 30 days in 2011, and for import/export of biological samples was 20 days set against 34 days in 2011.

In a separate section of this issue we consider the quality of IMCTs conducted in Russia. Evaluation was based on the data from FDA inspections results.

One more item of this newsletter is the expert review prepared as part of the project by the European Commission on a comparative analysis of EU and Russian legislation in the area of clinical trials.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

In 2012 the Ministry of Health issued 915[1] approvals to conduct clinical trials, which is more than 60 % higher than the number of approvals issued in 2011 (Table 1). This is also an absolute record for the entire period of records keeping, since 2004. However the number of approvals for international multicentre clinical trials (IMCTs) remained unchanged – 369 approvals in 2012 compared to 370 in 2011.

Which sectors of the market saw such significant growth in the number of approvals issued? First of all it should be noted that the number of bioequivalence studies by foreign sponsors grew six fold compared to the previous year (107 in 2012, 19 in 2011). The number of approvals issued for the same type of studies by Russian sponsors more than tripled (212 against 63). The number of local efficacy and safety trials by local sponsors more than doubled (165 compared to 80), and the number of local trials by foreign sponsors was up 1.8 times (62 compared to 35).

Table 1

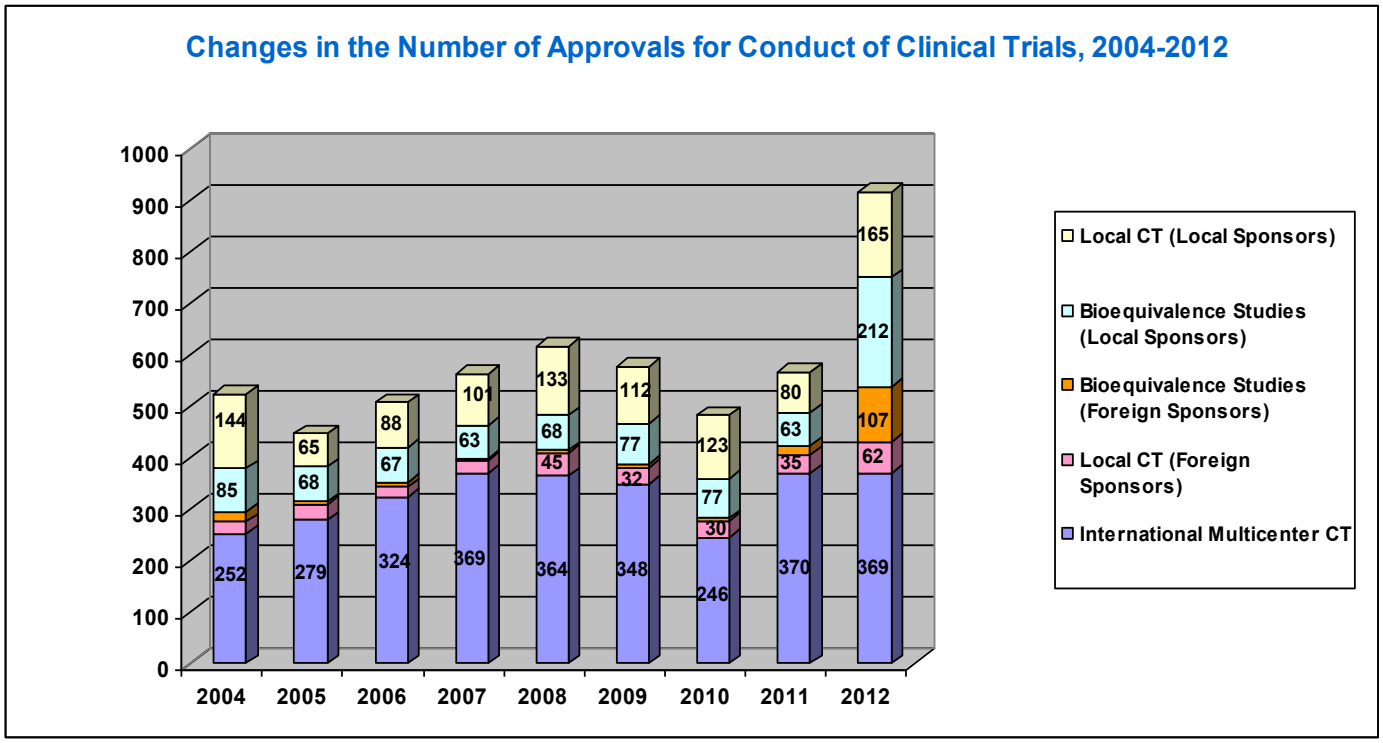
Approvals for Conduct of Clinical Trials: 2012 vs. 2011						
	Total	**International Multicenter CT**	**Local CT (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CT (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
2012	**915**	**369**	**62**	**107**	**165**	**212**
2011	**567**	**370**	**35**	**19**	**80**	**63**
2012 vs. 2011, %	**61,4%**	**-0,3%**	**77,1%**	**463,2%**	**106,3%**	**236,5%**

Data from www.grls.rosminzdrav.ru

A more vivid picture of the changes on the market in 2012 can be gleaned by comparing the data on the number of approvals issued for various types of trials from 2004 to 2012 (Diagram 1).

[1] There was one more approval that was not included because it referred not to a clinical trial but to provision of a medicine prior to its registration in Russia for patients who had previously participated in the clinical trial.

Diagram 1



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

The Diagram demonstrates that from 2005 to 2008 the total number of approvals grew steadily, while the share of various types of trials stayed more or less the same. There was a slight drop in 2009, apparently as a consequence of the global economic crisis – in that year there was a drop in the number of clinical trials all over the world. In 2010 in Russia the law "On Circulation of Medicines" was passed, and in the resulting reshuffle of the regulatory system, work on issuing approvals for clinical trials was halted for nearly the whole quarter. This was the cause of the drop in the total number of approvals issued in 2010. In 2011 the system was sorted out and the figures came back up to pre-reform levels.

The year 2012 differs markedly from the general picture thanks to the significant growth in the total number of approvals issued. The Diagram also shows that this growth was primarily due to the unprecedented high rate of bioequivalence studies by both Russian and foreign sponsors. For a more in-depth understanding, let's look at the way the structure of the market has changed.

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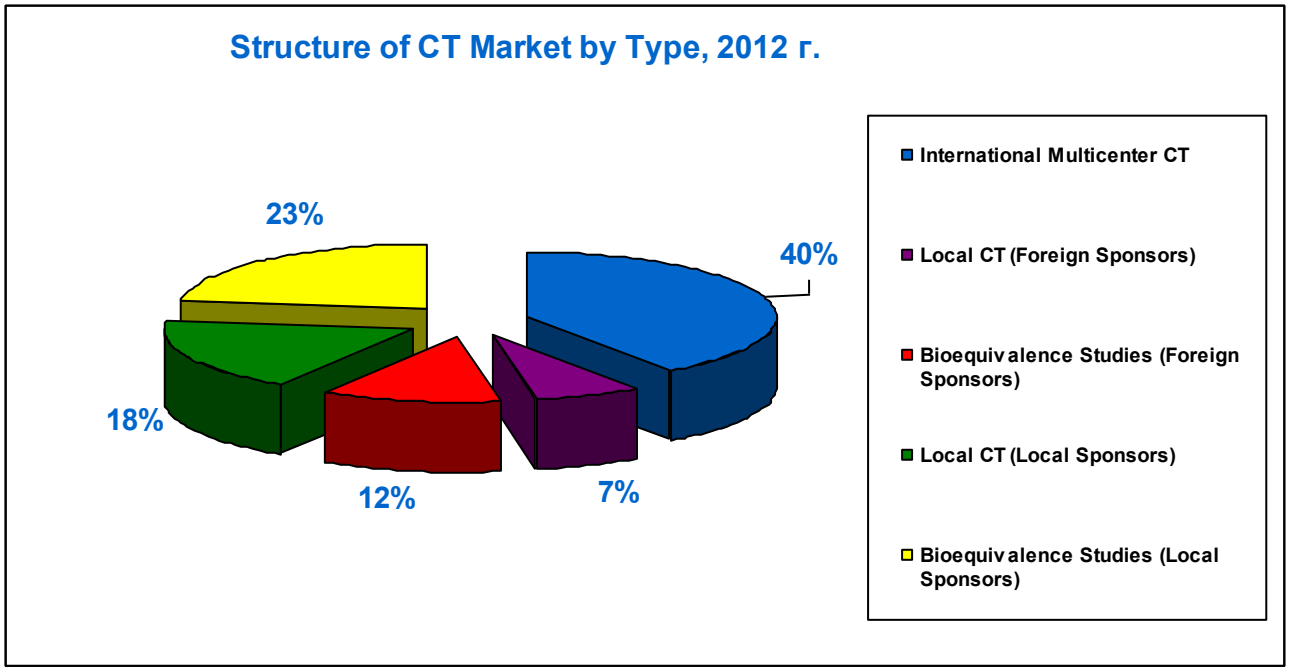
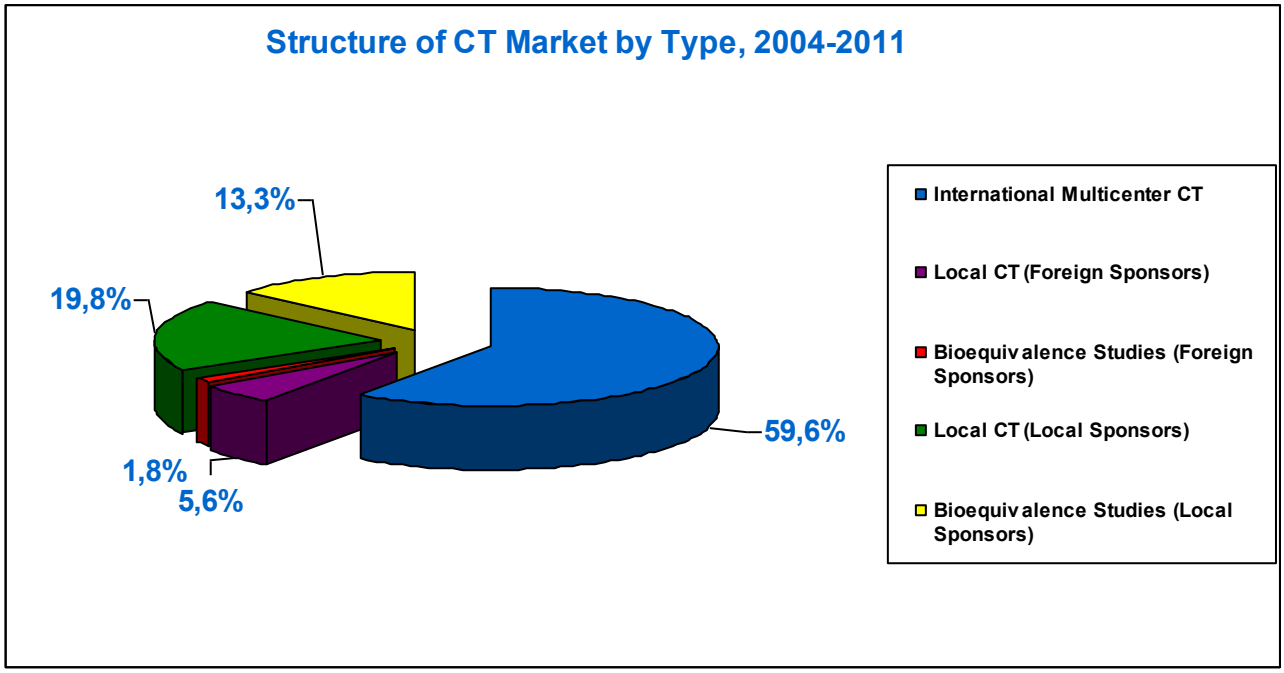
Diagram 2 shows the structure of the clinical trials market based on 2012 results. For comparison Diagram 3 is provided, reflecting the average relative shares of various types of trials on the market for 2004-2011, when the relative shares remained quite stable.

Diagram 2



Data from www.grls.rosminzdrav.ru

Diagram 3



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

These Diagrams demonstrate that the share of IMCTs on the market in 2012 dropped by nearly 20 % (from 59.6 % to 40 %). At the same time the share of local efficacy and safety trials by both foreign and local

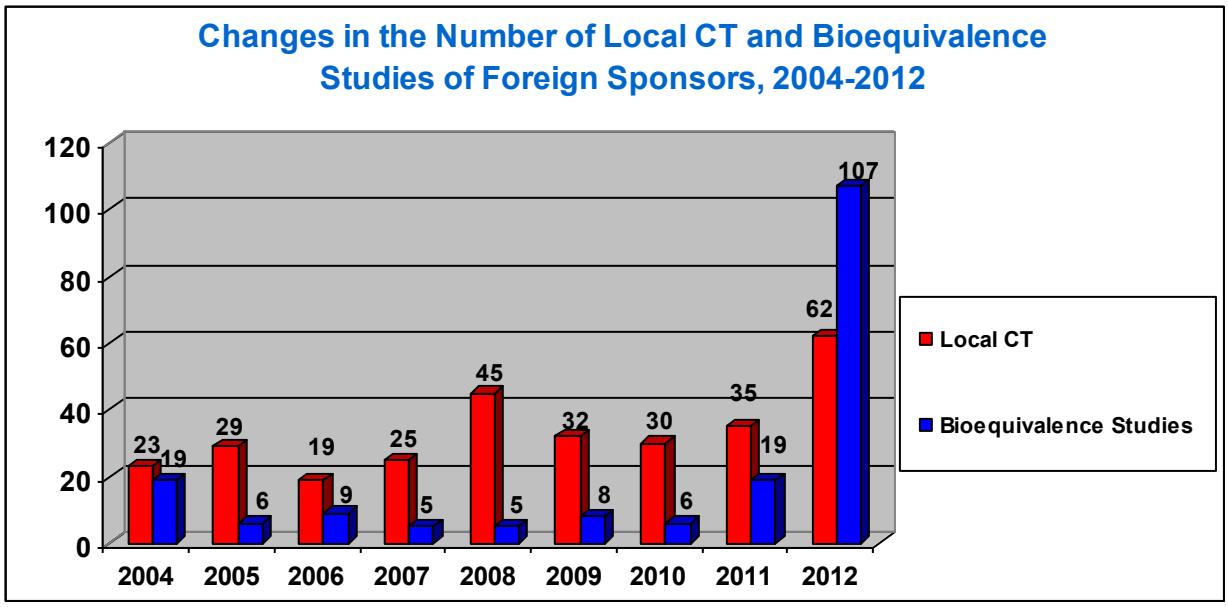
sponsors remained practically unchanged – 7 % compared to 5.6 % for foreign sponsors and 18 % compared to 19.8 % for local sponsors.

Therefore, the 20 % drop in IMCTs took place against the backdrop of significant growth in the two remaining sectors – bioequivalence studies by foreign and local sponsors. For local medicinal products, these types of studies were 23 % of the market compared to previous years' average of 13.3 %. The share of bioequivalence studies by foreign sponsors also increased markedly from 1.8 % to 12 %. As a result, the total share of bioequivalence studies reached 35 % compared to a previous average of 15.1 %.

How can one explain such significant growth in this type of studies? There are at least two obvious factors. The first one is the patent cliff promised in 2012 for the global pharmaceutical industry. The second factor is the direct consequence of the 2010 law "On Circulation of Medicines", under which in order to register a medicine in Russia it is necessary to submit the results of trials with the participation of Russian centres. The very embodiment of this is seen primarily in the generics sector. As a result, our country has literally been hit with a wave of bioequivalence studies.

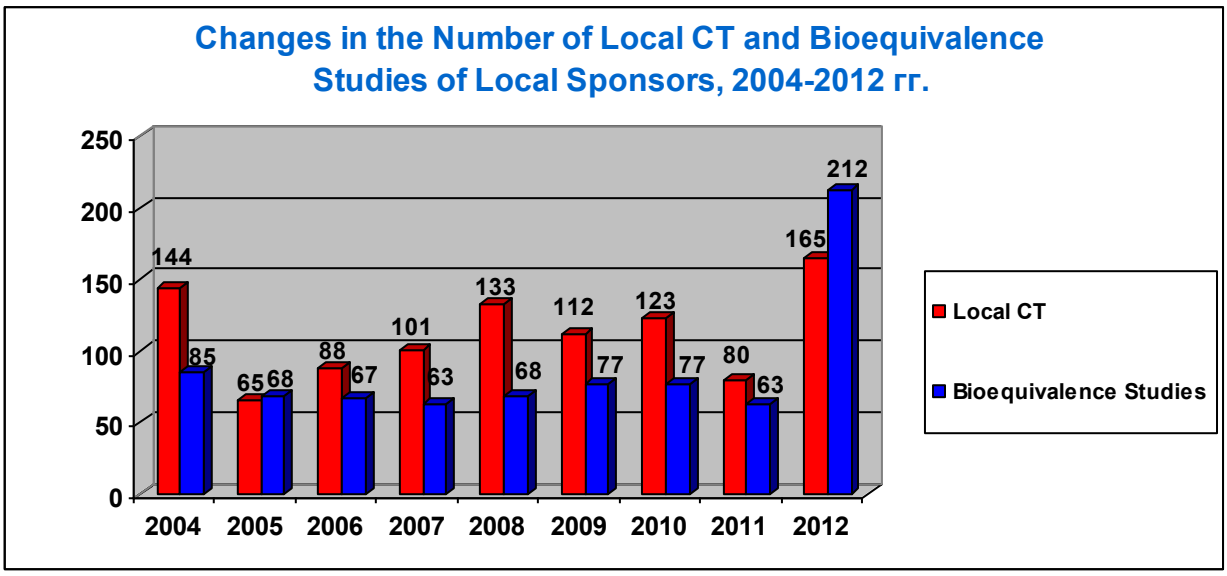
Diagrams 4 and 5 show the movement in the issuing of approvals for local efficacy and safety trials, and for bioequivalence studies by foreign and local sponsors from 2004 to 2012. It is clear that while before 2012 in the local research sector, efficacy and safety trials predominated, the picture has changed over the last year. Now the number of bioequivalence studies exceeds the number of local efficacy and safety trials by both foreign and Russian manufacturers.

Diagram 4



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

Diagram 5



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

While in bioequivalence studies everything is more or less clear – these are studies of generic medicines conducted in order to register them, the situation with the category that we call local efficacy and safety trials is much more complicated. This category includes trials of various groups of medicines: brand name drugs, generics (for pharmaceutical forms that could not be tested under bioequivalence studies), biosimilars, homeopathic medicines, new combinations of well-established active substances, and so on. These may be trials conducted both in order to register, and in the post-marketing period.

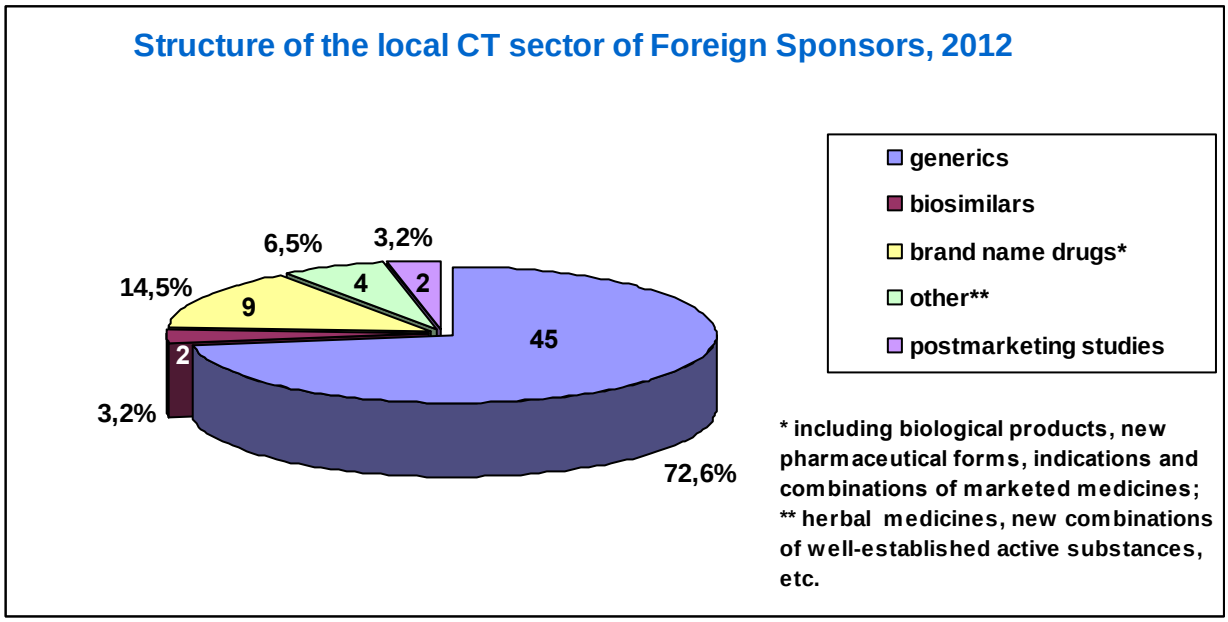
The Ministry of Health register does not contain a clear classification of approved trials, therefore we decided to classify them ourselves and analyse the structure of the sector of local efficacy and safety trials.

First of all we separated the post-marketing phase IV trials, not including in that group those which were conducted with a marketed medicine for a new application, form, or dosage. For brand name drugs, we refer to trials of both pure 'chemical' medicines (also known as small molecules) and biologicals, as well as trials on new pharmaceutical forms, dosages, and indications. For the rest – trials of homeopathic medicines, new combinations of well-established substances, medicines derived from plant or animal sources and other similar substances. We also separated generic medicines and biosimilars into distinct groups.

The resultant data on local trials by foreign and local sponsors are presented in Diagrams 6 and 7 respectively.

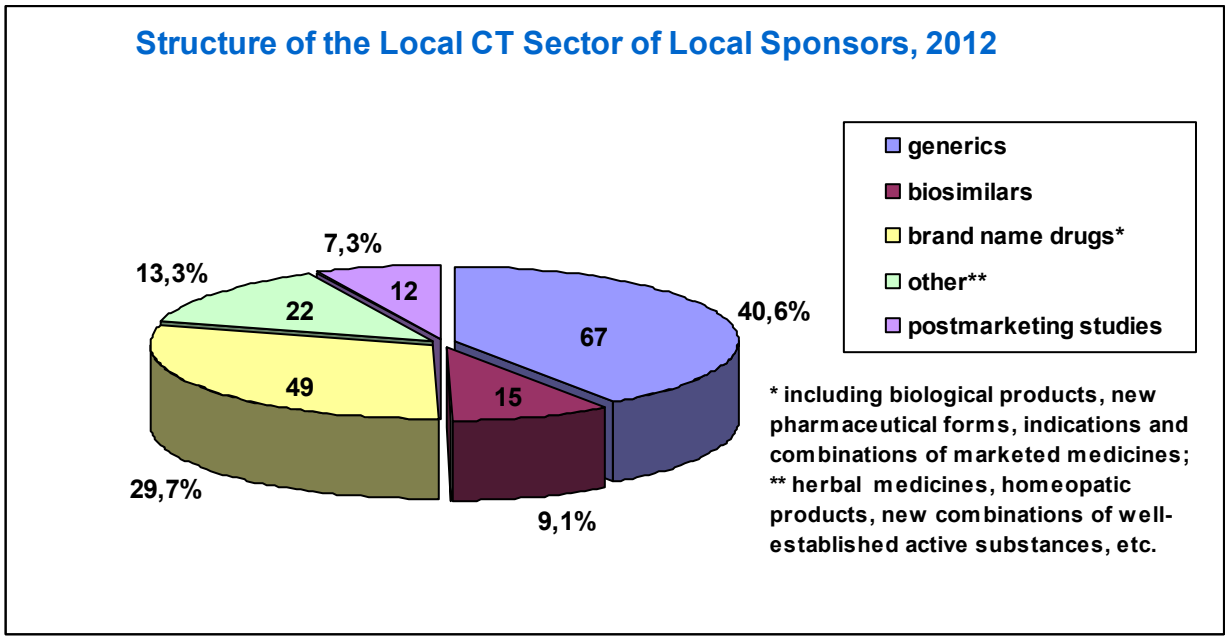
We are aware that our classification is not without flaws and that it is relatively subjective. We also encountered difficulties in trying to classify several Russian-made medicines, since based on just the protocol and the medicine name (provided to us by the Ministry of Health), in a number of cases it was not easy to determine the medicine under study. But even knowing that, it was not easy to determine if the medicine should be included under 'brand name drug' or 'others', taking into account its nature. Therefore it is quite possible that the relationship between the two sectors is a bit different. However on the whole these data give us a pretty good idea about the processes that are currently at work in the sector for local clinical trials.

Diagram 6



Data from www.grls.rosminzdrav.ru

Diagram 7



Data from www.grls.rosminzdrav.ru

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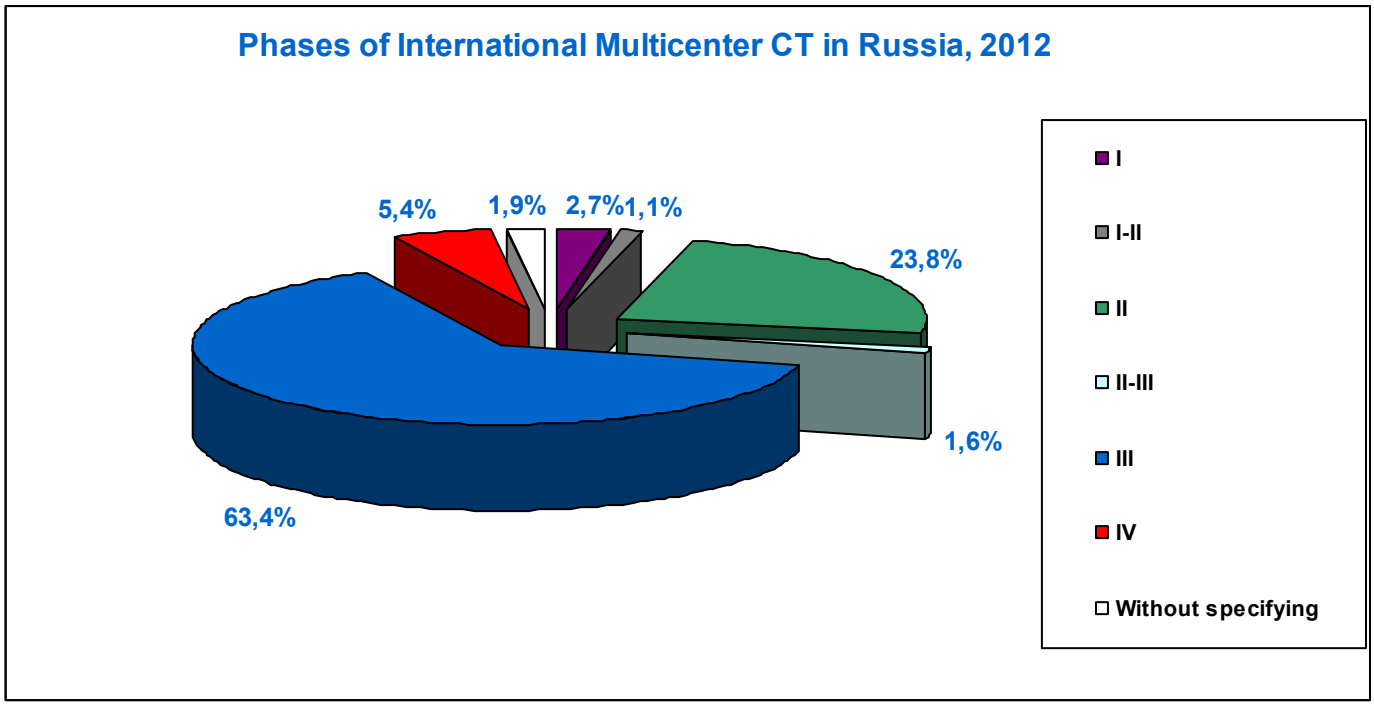
The data on IMCTs distribution based on phase are presented in Table 2 and in Diagram 8. Since the Ministry of Health registry does not currently include special designations of trial phases, and this information is not always included into the protocol name, we had to specify the corresponding data according to the American and European registers www.clinicaltrials.gov and www.clinicaltrialregister.eu.

Table 2

Phases of International Multicenter CT in Russia, 2012 г.							
	I	I-II	II	II-III	III	IV	Without specifying
Q1 of 2012	2	~	22	~	63	4	~
QII of 2012	3	2	20	2	58	7	2
QIII of 2012	3	1	24	2	60	3	2
QIV of 2012	2	1	22	2	53	6	3
Total of 2012	10	4	88	6	234	20	7

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

Diagram 8



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

Traditionally, the largest share of IMCTs conducted in Russia has been Phase III trials (63.4 %). The next largest chunk is Phase II (23.8 %). In 2012, Phase I trials accounted for 2.7 % of the market.

We would like to remind you that according to the current requirements under the law "On Circulation of Medicines", in Russia it is not possible to conduct a Phase I trial for foreign-made medicines with participation of healthy volunteers. This ban does not cover patients. According to the results of the year the number of approved IMCTs in this phase included three trials of medicines for treating cancer, three for treating rheumatoid arthritis, one each of medicines for treating Hepatitis C, schizophrenia and schizoaffective disorder, dislipidemy, and multiple sclerosis. In one of the anti-tumour medicine trials and in the trial on multiple sclerosis the focus was on participation of a specific group of patients with impaired liver function.

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In summing up the year's results, we decided to look at IMCTs distribution across Russia – throughout the federal regions and constituent entities. This analysis was possible because the Ministry of Health register now allows you to see the medical centres that are planning approved trials.

With the breakdown of the total number of approved IMCTs across the regions, we worked on the same principle used by www.clinicaltrials.gov. Eg, if the same trial is carried out in different centres located in different areas, then it is counted in each area. Therefore the total data on regions exceeds the total number of approvals issued for IMCTs in 2012 (369 approvals).

Drawing 1 shows IMCTs distribution by federal districts. Table 3 shows the same data, but by the constituent entities of the Russian Federation. The Table does not include constituent entities where there were no medical organisations taking part in IMCTs approved in 2012.

Drawing 1. Split of IMCT approved in 2012 by regions of RF

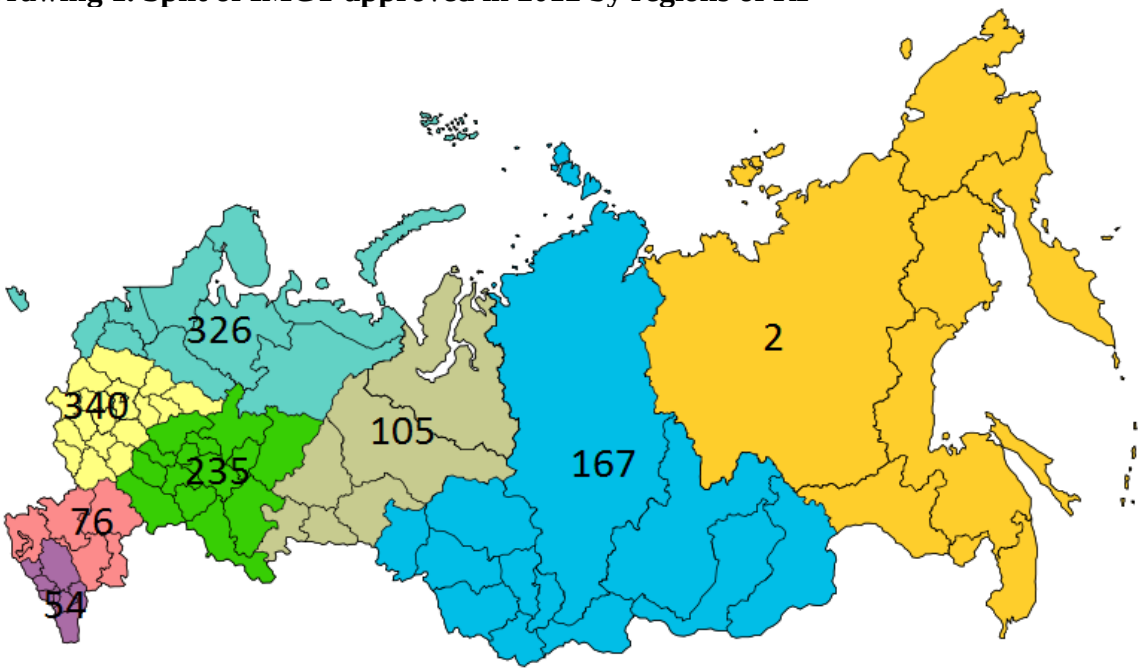


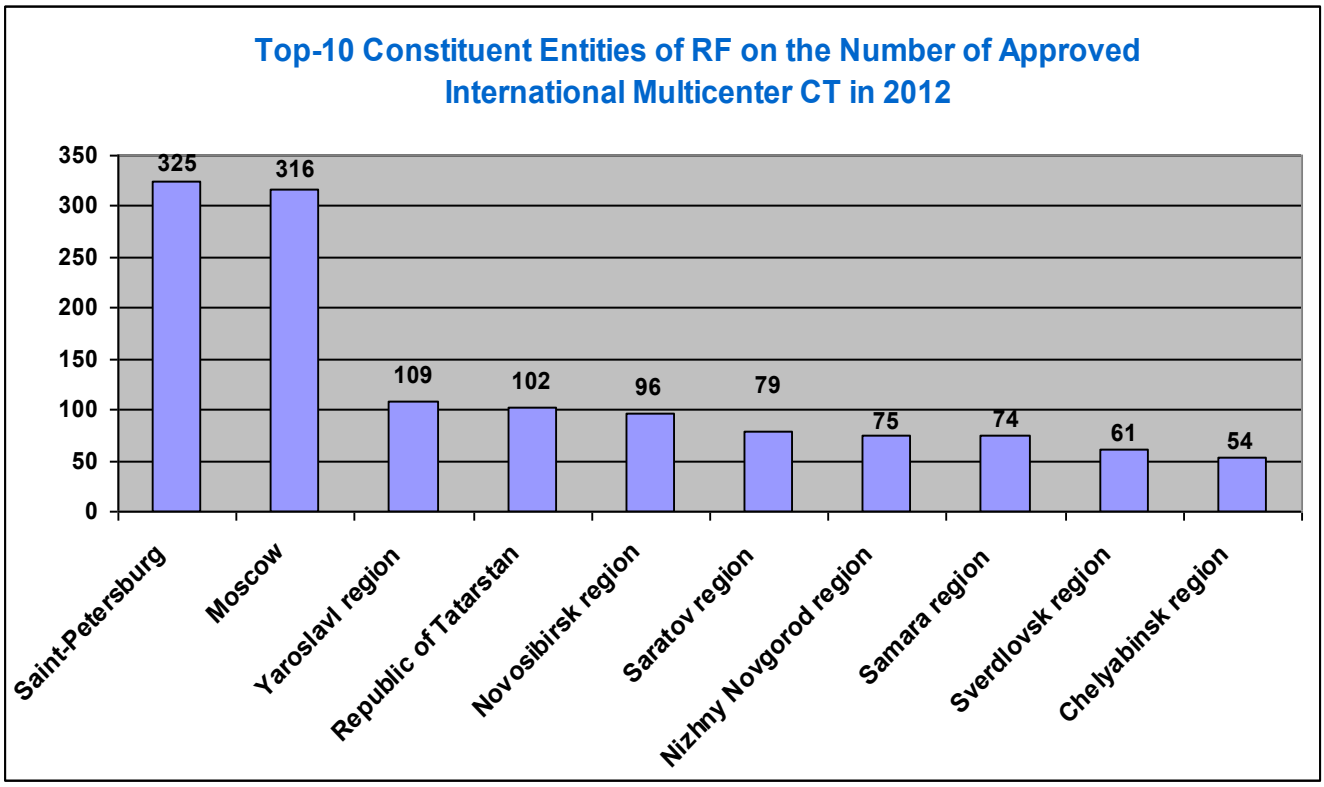
Table 3

Region	Number of Studies	Region	Number of Studies
Central Federal District	**340**	**North Caucasian Federal District**	**54**
Moscow	316	Stavropol Region	52
Yaroslavl Region	109	Republic of North Ossetia-Alania	2
Smolensk Region	46	Kabardino-Balkar Republic	1
Ryazan Region	39	**Siberian Federal District**	**167**
Tula Region	25	Novosibirsk Region	96
Lipetsk Region	24	Kemerovo Region	49
Kursk Region	23	Tomsk Region	48
Ivanovo Region	22	Altai Krai	46
Moscow Region	21	Krasnoyarsk Krai	31
Kaluga Region	16	Omsk Region	14
Voronezh Region	14	Irkutsk Oblast	13
Vladimir Region	7	Zabaykalsky Krai	7
Belgorod Region	6	**Ural Federal District**	**105**
Tambov Region	6	Sverdlovsk Region	61
Orel Region	4	Chelyabinsk Region	54
Tver Region	2	Tyumen Region	13
Southern Federal District	**76**	**Volga Federal District**	**235**
Krasnodar Krai	44	Republic of Tatarstan	102
Rostov Region	31	Saratov Region	79
Volgograd Region	18	Nizhny Novgorod Region	75
Northwestern Federal District	**326**	Samara Region	74
Saint-Petersburg	325	Republic of Bashkortostan	40
Arkhangelsk Region	41	Orenburg Region	20
Republic of Karelia	25	Perm Region	19
Leningrad Region	10	Kirov Region	10
Novgorod Region	5	Penza Region	8
Murmansk Region	2	Udmurt Republic	8
Far Eastern Federal District	**2**	Ulyanovsk Region	6
Primorsky Krai	2	Republic of Mari El	4
Amur Region	1	Republic of Mordovia	1
		Chuvash Republic	1

Data from www.grls.rosminzdrav.ru

Diagram 9 shows the Top 10 constituent entities of the Russian Federation based on the number of IMCTs conducted, for which approval was obtained in 2012. The undisputed leaders are St. Petersburg (325 trials) and Moscow (316 trials). Third place went to the Yaroslavl Region (109 trials).

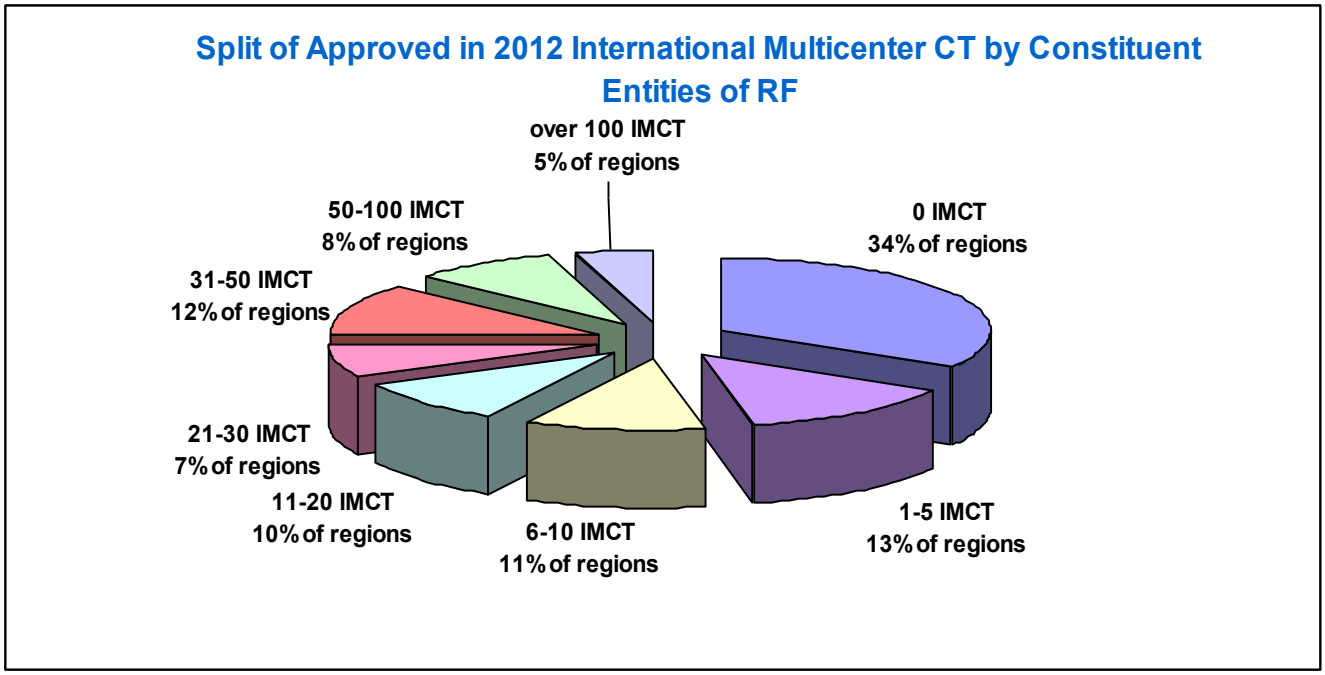
Diagram 9



Data from www.grls.rosminzdrav.ru

Diagram 10 gives a general picture of the participation of constituent entities of the Russian Federation IMCTs. 28 areas (34 %) do not take part in IMCTs, for which approval was granted in 2012. The remaining 55 constituent entities participate with a greater or lesser degree of activity.

Diagram 10



TIMEFRAMES FOR ISSUANCE OF APPROVALS

According to the data of ACTO monitoring, the average wait time to issue approval documents in 2012 was shorter compared to the same statistics for 2011 (*see Informational-analytical newsletter No.4*), confirming the trend that was first noticed in the first half of 2012 (*see Informational-analytical newsletter No.5*). However the figures on separate positions are still far off the times envisaged in the law "On Circulation of Medicines".

According to the year's results, the average period to issue approval to conduct clinical trial was 116 days (Table 4), as compared to 130 days in 2011. Let us remember that under the law this should be 41 business or 57 calendar days. The wait time to issue permit for the import of medicines was 18 days, compared to 30 days in the previous year, and the time to obtain permit for the import/export of biological materials was 20 days compared to 34 days in 2011. As a result, the total average wait time for the applicant to obtain the approvals and permits required to begin a trial was shortened by 29 days, from 164 days in 2011 to 135 days in 2012 (Table 5).

The average wait time to obtain approval for making changes in the protocol was drastically reduced from 92 days in 2011 to 64 days in 2012, as did the times for other types of approvals and permits for extending the trial, additional sites approval, increasing the number of patients, and so on (41 day in 2012 compared to 69 days in 2011).

Table 4

Timeframes for Issuing Approvals, 2012[2]					
	Timeframes According to Legislation (Business/Calendar days)	**Average Timeframes (Calendar Days)**	**Minimum Timeframes (Calendar Days)**	**Maximum Timeframes (Calendar Days)**	**Sampling**
To Conduct Clinical Trials*	**41/57**	**116**	**22**	**410**	**199**
To Import Medicines	**8/12**	**18**	**4**	**63**	**268**
To Import/Export Biosamples	**13/19**	**20**	**5**	**86**	**598**
To Make Amendments to the Protocol	**34/48**	**64**	**9**	**246**	**342**
Other Approvals (to Prolong Clinical Trials, to Include New Sites, to Enroll Additional Patients, etc.)	**25/35**	**41**	**9**	**249**	**585**
Total Time to Obtain Approvals to Conduct Clinical Trials and to Import/Export**	**54/76**	**136**	**~**	**~**	**~**

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

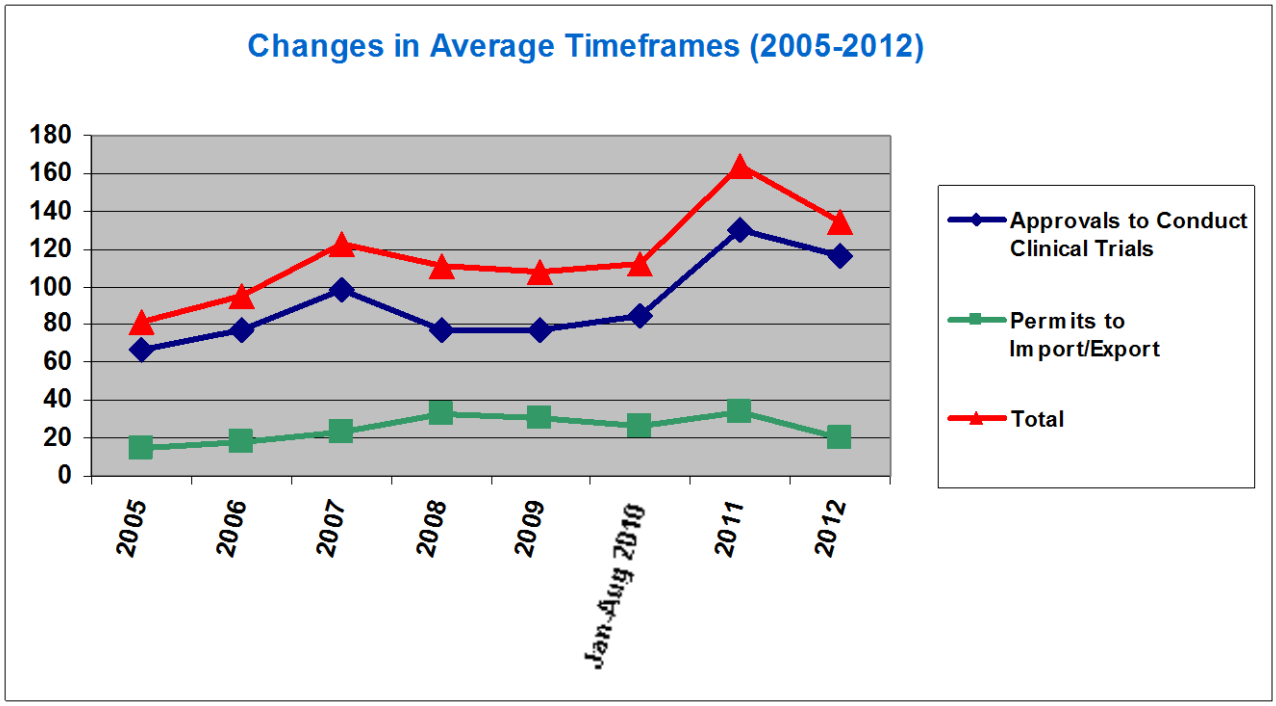
Table 5

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

Data from timeframes' monitoring of ACTO

Diagram 11 shows the dynamics in average approval issuance times from 2005 to 2012, represented more clearly. It is clear that both on the times to issue approval for trials and on the total time the applicant must wait before starting the trial, the Ministry of Health is still not working as efficiently as Roszdravnadzor. At the same time, on matters such as issuing permits for import of medicines and the import/export of biological samples, the Ministry is more efficient than its predecessor.

Diagram 11



Data from timeframes' monitoring of ACTO

[3] 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.

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The noted improvements in wait times for approval documentation can be seen not only in the average statistics, but also in the percentage of approvals issued either within the deadline or with various stages of delay. In Table 6 there are data on violations of timeframes in 2012 as compared with the same indicators for 2011.

Table 6

Violations of Timeframes, 2012 vs. 2011								
		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	2012	2,0%	98,0%	18,1%	38,2%	31,2%	7,5%	3,0%
	2011	1,8%	98,2%	4,7%	30,6%	47,1%	12,3%	3,5%
To Import Medicines	2012	28,0%	72,0%	33,2%	19,4%	14,2%	3,7%	1,5%
	2011	4,6%	95,4%	12,0%	15,9%	40,7%	17,1%	9,7%
To Import/Export Biosamples	2012	54,3%	45,7%	32,8%	10,9%	1,5%	0,3%	0,2%
	2011	13,2%	86,8%	18,6%	36,0%	24,9%	5,7%	1,6%
To Make Amendments to the Protocol	2012	34,5%	65,5%	30,4%	19,6%	13,7%	1,5%	0,3%
	2011	12,7%	87,3%	11,4%	30,0%	40,0%	4,5%	1,4%
Other Approvals (to Prolong Clinical Trials, to Include New Sites, to Enroll Additional Patients, etc.)	2012	48,9%	51,1%	25,8%	15,7%	7,4%	1,7%	0,5%
	2011	15,7%	84,3%	20,8%	19,9%	27,9%	11,5%	4,2%

Data from timeframes' monitoring of ACTO

Again the majority of violations can be seen in the wait times to obtain approval to conduct clinical trials. At the same time the most progress has been seen in the share of on-time permits for import/export of biological samples (over the year this figure improved by 41.1 % and amounted to 54.3 % of permits issued within the deadline), and other types of approvals and permits (which improved by 33.2 % and reached 48.9 % of documents issued on time). Progress also has been seen on the times for issuing other types of approval documentation.

But this tentative positive movement could soon morph back into regression. Why do we think so?

First of all, the changing practice in issuing approvals for trials. Since about the middle of the last year, applicants began to be refused permission to make changes to the submitted documents after the expert examinations within the single process of approval. Irrespective of the notes criticality the formal refusal was given, after which the applicant once again had to submit the application and the entire set of documents. By the end of the year this practice was firmly entrenched. The only thing that was not required in such a repeat submission was a second payment of the state duty. However this could also change in the future if the Ministry of Health adopts the suggested changes in the Russian Tax Code (*for more information see the section on Legislative Initiatives*).

Officials consider these changes in the practice of application oversight beneficial. The review times on applications are officially improving. When a refusal is issued, the wait time is over, and begins to be counted again from the beginning with the submission of a repeated application. What does such a scheme mean for the applicant? Formally coming in on time approvals are ultimately taking longer, and this means that the time until the trial start is increasing. What does this mean for the state? We won't look again at the aspects of benefits for the healthcare system from participating in IMCTs and the influence of approval wait times on such participation. Looking at a more basic thing – the administrative burden on the regulator. By refusing changes in the working process, the Ministry of Health is creating more work for itself and the expert organisations. The application must again be registered, sent for expert examination, analysed, and so on.

The second reason we have to suspect a worsening in wait times are the changes to the law "On Circulation of Medicines" prepared by the Ministry of Health (*for more details see the section on Legislative Initiatives*). The project envisages extending times for both expert examination and the technical stages of document review. The total time to issue approval to conduct trials would increase to 70 business days from 45 days under the current law. We have no doubt that adopting these changes would give officials a great deal of freedom, but they are not likely to get them working any faster. As a result we could see further increases in the time it takes before a trial can begin.

QUALITY OF CLINICAL TRIALS: RESULTS OF US FDA INSPECTIONS

It is well-known that the quality of clinical trials is ensured by rigorous GCP compliance. And in turn GCP envisages a three-pronged system of control – monitoring (routine control in the course of the trial, by the sponsor), auditing (comprehensive checks conducted either by the sponsor or by a third party), and inspection (official reviewing conducted by the regulatory authorities).

When we speak of the launch of a new medicine on the international market and, consequently, of international trials, the quality of them is controlled not only by the regulators in the country in which the trial is conducted, but also by leading organisations in the countries with a highly-developed regulatory system, principally the USA and the European Union[4].

The US FDA is undoubtedly the superior force in conducting inspections in third countries. Taking into account the activity of this body with regards to control over clinical trials, as well as the transparency of information on inspection results, it is good to use US FDA data for a comparative evaluation of the quality of international trials conducted in various countries.

According to the data from the official FDA website, between 1995 and April 2013, there were more than 92 FDA inspections of Russian trial sites, aimed at checking the quality of the clinical trials being conducted there.

In 61 of the cases, the result of the inspection was NAI (No Action Indicated. No objectionable conditions or practices were found during the inspection.)

In 30 of the cases, the result of the inspection was VAI (Voluntary Action Indicated. Objectionable conditions were found but the problems do not justify further regulatory action. Any corrective action is left to the investigator to take voluntarily.)

One inspection resulted in an OAI (Official Action Indicated. Objectionable conditions were found and regulatory and/or administrative sanctions by FDA are indicated.). This single critical evaluation took place in February 2006 at Moscow City Hospital Number 23, investigator Olga Ostroumova.

To compare the quality of trials conducted in Russia we present a Table of results of FDA inspections in a number of other countries for the same period between 1995 and the first quarter of 2013 (Table 7). A full comparison of the data would not be entirely correct, because the share of inspections ending in one or another result will be affected by the total number of inspections carried out in the country. And the greater the range is, the more accurate the total evaluation of quality is. We can see that the number of US FDA inspections in Russia is significant, and the figures for our country show high quality of IMCTs.

[4] Unfortunately, this system is not extended to cases of conducting local trials, the results of which are not planned for presentation for registration in a country with a developed regulatory system. Therefore an objective evaluation of the quality of such trials is significantly more difficult.

Table 7

Comparative Table of the Results of US FDA Inspections							
Country	**Total number of FDA Inspections with results 1995-Q1 of 2013**	**NAI**	**NAI, % of Total**	**VAI**	**VAI, % of Total**	**OAI**	**OAI, % of Total**
North America							
USA	**4757**	**2031**	**42,7%**	**2509**	**52,7%**	**217**	**4,6%**
Canada	**141**	**57**	**40,4%**	**84**	**59,6%**	**0**	**0,0%**
Mexico	**21**	**6**	**28,6%**	**15**	**71,4%**	**0**	**0,0%**
South America							
Argentina	**48**	**29**	**60,4%**	**18**	**37,5%**	**1**	**2,1%**
Brazil	**33**	**18**	**54,5%**	**15**	**45,5%**	**0**	**0,0%**
Peru	**9**	**4**	**44,4%**	**3**	**33,3%**	**2**	**22,2%**
Chile	**10**	**6**	**60,0%**	**4**	**40,0%**	**0**	**0,0%**
Australia	**12**	**6**	**50,0%**	**6**	**50,0%**	**0**	**0,0%**
Africa							
South Africa	**42**	**20**	**47,6%**	**21**	**50,0%**	**1**	**2,4%**
Asia							
Japan	**7**	**5**	**71,4%**	**2**	**28,6%**	**0**	**0,0%**
Thailand	**12**	**5**	**41,7%**	**7**	**58,3%**	**0**	**0,0%**
China	**17**	**6**	**35,3%**	**11**	**64,7%**	**0**	**0,0%**
India	**41**	**23**	**56,1%**	**18**	**43,9%**	**0**	**0,0%**
Turkey	**7**	**1**	**14,3%**	**5**	**71,4%**	**1**	**14,3%**
Israel	**6**	**4**	**66,7%**	**2**	**33,3%**	**0**	**0,0%**
South Korea	**8**	**3**	**37,5%**	**5**	**62,5%**	**0**	**0,0%**
Taiwan	**6**	**4**	**66,7%**	**2**	**33,3%**	**0**	**0,0%**
Europe							
Austria	**13**	**2**	**15,4%**	**11**	**84,6%**	**0**	**0,0%**

Denmark	**16**	**9**	**56,3%**	**7**	**43,7%**	**0**	**0,0%**
Sweden	**21**	**9**	**42,9%**	**12**	**57,1%**	**0**	**0,0%**
Germany	**81**	**34**	**42,0%**	**46**	**56,8%**	**1**	**1,2%**
France	**71**	**22**	**31,0%**	**48**	**67,6%**	**1**	**1,4%**
United Kingdom	**92**	**30**	**32,6%**	**60**	**65,2%**	**2**	**2,2%**
Spain	**25**	**14**	**56,0%**	**9**	**36,0%**	**2**	**8,0%**
Italy	**48**	**27**	**56,3%**	**18**	**37,5%**	**3**	**6,2%**
Finland	**15**	**10**	**66,7%**	**4**	**26,7%**	**1**	**6,6%**
Netherlands	**24**	**6**	**25,0%**	**16**	**66,7%**	**2**	**8,3%**
Belgium	**28**	**14**	**50,0%**	**11**	**39,3%**	**3**	**10,7%**
Poland	**75**	**42**	**56,0%**	**33**	**44,0%**	**0**	**0,0%**
Hungary	**23**	**9**	**39,1%**	**14**	**60,9%**	**0**	**0,0%**
Czech Republic	**23**	**14**	**60,9%**	**9**	**39,1%**	**0**	**0,0%**
Ukraine	**18**	**11**	**61,1%**	**7**	**38,9%**	**0**	**0,0%**
Russia	**92**	**61**	**66,3%**	**30**	**32,6%**	**1**	**1,1%**

Data from www.fda.gov **(as of April 5, 2013)**

LEGISLATIVE INITIATIVES

We wouldn't be too far wrong if we described 2012 as a year of waiting and of unrealised hopes for the clinical trials market and for the entire Russian pharmaceutical industry.

In May 2012 after the new Russian president took office, he formed a new government. The changes affected the main regulator in healthcare: the Ministry of Health and Social Development was reorganised into two independent ministries – the Ministry of Health and the Ministry of Labour. The former minister, Tatyana Golikova, stepped down and Veronika Skvortsova was named the new head of the Ministry of Health. Shortly afterwards came radical staffing changes throughout the Ministry, including in the Department of State Regulation of Circulation of Medicines.

The representatives of the new Ministry almost immediately announced the need to introduce changes to the law "On Circulation of Medicines" including fixing mistakes, and their intention to work on this project. At the same time in the pharmaceutical community discussions continued on the consequences of the law for Russian pharmaceutical market.

The project appeared only by the end of the year, eliciting all-around disappointment. Contrary to expectations, the Ministry of Health's proposals on amendments did not take into account anything that had been suggested by the industry associations and experts. And so the 'gnarled' registration system that had artificially included clinical trials remained unchanged. The only exception was the proposal for orphan medicines. Other problems with the regulations were also left unchanged in the law "On Circulation of Medicines". In speaking of their readiness to change the situation and bring about harmony with international standards as one of the priorities for the Strategy for medicine provision for the Russian population to 2025, the Ministry of Health nevertheless stood fast to protect the brainchild of its predecessor.

However in addition to keeping practically all of the problems with the current law, the Ministry of Health also proposed implementing a whole range of new administrative barriers and hurdles. So the legislative project introduced three new problems for the clinical trials market.

The first was implementation of pharmaceutical analysis of samples of medicines at the stage of obtaining approvals to conduct clinical trials. The first version of the new project proposed applying this requirement to all types of medicines, later this standard was boiled down to just a requirement for such analysis for biological products which did not in fact change the fundamentals of the issue. And the pharmaceutical community continued to insist that such an approach would not comply with generally accepted international practice in regulation. In the event of implementing pharmaceutical analysis of samples, this would become an almost insurmountable barrier for innovative medicines (when there are not yet officially confirmed methods of quality control) and would seriously slow down the approval process for conducting clinical trials for the other groups of medicines. It is worth noting that practically all market players came out against the new standards – both foreign and Russian manufactures, of innovative and generic medicines. New initiatives from other state bodies such as the Federal Anti-Monopoly Service and the Ministry of Economic Development were also placed in doubt. The Ministry of Health continued to insist on pharmaceutical analysis of samples for biologicals, but without offering any statistical data that would have demonstrated any problems with quality of medicines used in clinical trials. And only just before the release of this newsletter it became known that the Ministry, meeting such united resistance on this issue, had finally agreed to remove the rule on conducting pharmaceutical analysis of samples from the text of the amendment. So there is hope that this problem may now be resolved.

The second problem for the clinical trials market was the proposal to increase times for administrative procedures on issuing approvals to conduct clinical trials. In particular, the period for checking documentation and for assigning expert examination could be increased from five to ten business days. The period for informing the applicant about the results of the examination was also increased from five to ten business days, another ten days the amendment adds to the review of a repeated submission for approval. The period for the expert examination itself they propose to increase from 30 to 50 business days (in a later draft of the amendment this suggestion was changed to 40 business days). As a result the total period to manage all administrative actions would increase to 70 business days from 45 business days under the current law.

Let us remind that one of the main factors affecting the issue of placing IMCTs in the country is the time it takes to get started on a trial. In Europe, as it is known, the period to review an application may not exceed 60 days – calendar days, not business days. And they are now looking at the possibility of reducing this period further. The Russian Ministry of Health at the legislative level is introducing standards potentially weakening our country's position on the international clinical trials market. This is not acceptable, first of all from the point of view of the goals of the Ministry of Health's own Strategy for medicine provision for the Russian population to 2025, in particular increasing global competition in the fight to attract strategic investment into the healthcare system and the creation of conditions in which healthcare development will be attractive for both Russian and foreign investors. Let us also remind that clear, competitive timescales were one of the arguments in adopting the current version of the law "On Circulation of Medicines". In proposing to increase times, officials are practically announcing their intention not to fulfil the responsibilities they took on just 2.5 years ago.

The third problem in the draft legislation is the new version of article 333.32.1 of the Russian Tax Code. While in the current version, state duties for IMCTs and post-marketing trials are paid for issuance of approval to conduct trials, the new amendment proposes that it should be paid for conducting the expert examinations. This contradicts the general approach, under which state duties are collected from entities when they apply to state bodies to take legally significant actions with regard to these entities. The current standards in the Tax Code also say that state duties are collected for federal authorities' actions.

However the expert examination is carried out not by the state bodies, but by the subordinate (not state) organizations. In addition, the examination itself is not a legally significant action, it does not lead to the establishment (changes or elimination) of a legal relationship. The applicant is not applying for this examination at all, he is applying for approval to conduct clinical trials. The ordering party of the expert examination is the Russian Ministry of Health.

Changing the situation with the Tax Code will have negative consequences for the applicant. At present when the applicant gets comments from the expert organisation, the applicant can address them, and in this case he does not need to pay the state duty a second time. Under the changes to the formula, the applicant would need to pay the fee again for resubmission of documents. There is also a high probability that the changes in the process could lead to abuses and an increase in the number of unfounded comments and refusals with the aim of sending the applicant through a second expert examination to extract additional payment of state duties.

There is also the following practical issue. As it is known, when reviewing an application to conduct clinical trials there are two types of expert examination – FGBU examination and an ethical review by the Ethical Council. The draft legislation proposes a single state duty for both types of examinations, with the cost of each one not being detailed. In the event that one of the examinations returns a positive result and the other a negative one, repeated payment and carrying out the same examination again once it has already been passed is completely baseless.

To be objective it should be noted that the last (or in any case the last at the time of this newsletter) version of the draft included an undoubtedly positive proposal. Changing the type of compulsory insurance in clinical trials from personal insurance to sponsors' and investigators' liability insurance as is standard in international practice, and as was the case in Russia before the new law "On Circulation of Medicines". If this amendment is adopted it will solve a great many problems with the current insurance system (*for details see Informational-Analytical Newsletter No. 5*).

Only time will tell what the prospects are for the Ministry of Health's new proposals. For our part, we suggest working to make corrections to the law as publically and multilaterally as possible.

REPORT ON THE EUROPEAN COMMISSION PROJECT "COOPERATION IN THE FIELD OF CLINICAL TRIALS"

In 2012 the European Commission together with the Russian Ministry of Health worked on a project entitled "Cooperation in the Field of Clinical Trials". A report on this project was prepared in September 2012, although it was only made accessible to the public in early 2013 after the document appeared on the European Commission website[5].

The report contains a detailed comparative analysis of EU and Russian legislation on clinical trials. The general conclusion was that "In general, it can be stated that for the conduct and supervision of clinical trials in the EU and the Russian Federation equivalence of the respective regulatory/legislative framework provisions is given" (which allows the European Union, and in particular the EMA, to accept the results of clinical trials conducted in Russian centers in accordance with the Russian legislation).

However they also noted legislative differences, classified by the report's authors into four categories. There were a total of 17 differences.

One of the most important from the point of view of Russian interests is the requirements to conduct local registration clinical trials. Regarding these, the report said: "In particular, the requirement to repeat safety and efficacy clinical trials (so-called local registration studies) whose results have already been assessed in the "original" registration process, which put study participants on unnecessary risk(s), generate additional costs for the applicant, and postpone access of the population to modern medicines, should be re-assessed".

They also criticised the standard under which clinical trials are included into the process of registration: "Except of so-called international multicenter clinical trials (IMCTs) and post-registration studies, applications for conducting a clinical trial in RF can only be submitted in the course of a registration process". The report recommends, "The link between registration process and authorisation to conduct of a clinical trial should be removed". This approach seems to be correct, since the law "On Circulation of Medicines" in Russia created a unique mechanism otherwise unknown in the international practice. Around the world, the process of launching a medicine onto the market works differently – first the manufacturer studies the characteristics of the medicine, obtains proof of its safety and efficacy, and then on that basis creates registration documentation and applies for registration.

The report also commented on the standards in the law "On Circulation of Medicines" on the possibilities of signing international agreements to share the results of trials. The report gives a clear answer: "Such provision is not in place in EU: clinical trials conducted outside EU are recognized on the basis of principles, "which are equivalent to the provisions of Directive 2001/20/EC[6]." Mutual recognition Agreements exist only in the GMP area." This yet again confirms the argument that the main recognition of clinical trials no matter where they are conducted must lie exclusively under the international standard ICH GCP, and that an international agreement on mutual recognition of the results of clinical trials as an agreement between countries is simply legal nonsense.

Among other elements in our country's legislation, characterised as "more strict" and "exceeding those in EU", but not relating to differences that could affect "the rights, safety, and welfare of trial participants, credibility of study data and thus acceptance of the clinical study results in the EU", they named problems that clearly slow down development in the sphere of clinical trials in Russia and raise criticism from the experts:

- Clinical trials can be conducted only for pre-defined purposes. Such restrictions (concerning the purpose of a trial) are not reflected in the applicable EU regulations: clinical studies need to involve "research" and must be "scientifically sound".

[5] The full text of the report can be found at http://ec.europa.eu/health/files/international/report_clinical-trials__sept2012.pdf A Russian translation can be found at http://acto-russia.org/files/EPRD_Analytical%20Report_RU.pdf

[6] In turn Directive 2001/20/EU is based on the principles of the ICH GCP and on the Helsinki Declaration of WMA.

- Direct contacts of an applicant with the Ethics Council or the Expert Organisation are not allowed. This is different in EU where a dialogue between applicant and drug regulatory authorities and Ethics Committees is considered to be beneficial.
- Clinical sites for conducting clinical trials need to be accredited by the Ministry of Health and Social Development. Such an accreditation requirement is not reflected in the applicable EU regulations, as there is no such accreditation process for clinical sites in place.
- (Principal) investigators must have a 5-year experience in the conduct of clinical trials in order to be eligible as investigator in a clinical trial.
- The law provides very strict rules concerning the conduct clinical trials on defined vulnerable persons, exceeding those in EU.
- Clinical trials involving healthy volunteers, i.e. in phase 1 studies, with "medicinal products manufactured outside the Russian Federation", are prohibited, but for local sponsors are permitted. Also phase 1 studies with foreign drugs involving patients are possible.

It is suggested that removing these and other differences named in the report would allow not only the harmonisation of Russian legislation with European equivalents, but would also limit the excessive administrative barriers, which would increase the investment attractiveness of our country for international trial programmes. In the meantime, as we see in practice, the Ministry of Health continues to ignore the results, preferring its own path of development and from time to time offering the Russian pharmaceutical market new administrative barriers.