ACTO

ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

ACTO NEWSLETTER №1

First Half of 2011

MOSCOW 2011

CONTENTS:

SUMMARY

In the first six months of 2011 the Ministry of Healthcare and Social Development issued 200 approvals for conducting of clinical trials. Compared to the same period of 2010 this indicator dropped by 35.9%. According to the number of issued approvals, in the first six months of 2011 international multicenter clinical trials (IMCTs) reached the level of 2010 – within that period the Ministry of Healthcare and Social Development approved 163 international trials. During the reporting period the number of local trials conducted by foreign sponsors dropped by 43.8% – for efficacy and safety trials, and by 33.3% – for bioequivalence trials.

But the most significant drop was observed in the sector of local trials conducted by Russian sponsors: in the first half of 2011 the number of approved efficacy and safety trials dropped by 78.4%, and the number of approved bioequivalence trials dropped by 84.4%. It is remarkable that the implementation of the law had a particularly tough impact specifically on the innovation activity of Russian companies, which is in direct contradiction with the governmental desire for import substitution in pharmaceutics.

The drop in the number of trials conducted by Russian companies is most likely, one way or another, tied to the changes in the registration system. In accordance with the new law "On Circulation of Medicines", local efficacy and safety trials have been incorporated in the registration process and there is no practical mechanism for conducting such trials other than within the registration framework. The drop in the number of bioequivalence trials has likely been caused by a couple of factors. First, there are no approved requirements for such trials. Second, manufacturers of generics are now forced to conduct their own preclinical trials before passing to the clinical stage.

Just as with all other types of trials, IMCTs, despite the reaching of the pre-crisis level after a drop by 30% in 2010, experienced rather difficult times in the first half of 2011. Very often it was not possible to commence an officially approved clinical trial due to regulatory challenges, particularly because of the ban on the import of registered products for clinical trials since the middle of October 2010 and the absence of new insurance rules, which should have been adopted by January 1, 2011. These problems were resolved only by the end of the first six months of 2011. Such long-lasting delay in the process affecting a great number of planned trials has certainly had an effect on patients' recruitment.

The new system also caused escalation of the issue with the constant problem of timeframes for the issuance of approvals. Though shorter timeframes have been legislatively established by the new law that did not bring the promised boost in the regulatory system's operating speed. The Ministry of Healthcare and Social Development failed to meet not only the time frames set forth by the new law, but also exceeded the historical maximum time frames statistically recorded at the time when the old system was in place. In the first six months of 2011 the total time needed to obtain an approval to conduct a clinical trial and import/export license permits amounted to 160 days. This is twice as long as the maximum period allowed by law and 30.5% longer than the all-time worst results shown by the Federal Service on Surveillance in Healthcare and Social Development (Roszdravnadzor).

However, by the middle of summer 2011 the most acute problem for the clinical trials market remains the problem of accreditation of medical institutions. Failure to meet the deadlines together with the cumbersome procedure of decision making has already turned the accreditation procedure into a hard-to-penetrate barrier. By the middle of July 2011 the Ministry of Healthcare and Social Development had managed to accredit only 152 medical institutions. According to expert estimates, at least 500-600 sites are needed to ensure normal functioning of the IMCT market. It is not clear what will happen to the current trials in the clinics which are unable to obtain re-accreditation by September 1, 2011. If no emergency measures are taken to rectify the situation, then in the fall of 2011 the clinical trials market may suffer another crisis.

STRUCTURE AND DYNAMICS OF THE CLINICAL TRIALS MARKET

While describing the dynamics of the clinical trials market in the first semester of 2011 we relied on official data from the register of approved clinical trials of the Ministry of Healthcare and Social Development. If there were doubts in the correctness of the data – most often with respect to the type of trials – they were checked the international registers (www.clinicaltrials.gov and www.clinicaltrialsregister.eu).

As the whole, the maintenance of the register so far is in need of improvement, which cannot but affect the quality of statistical data. For example, during the period of the Report's preparation the list of trials approved in the first and the second quarters of 2011 has been changed several times – the trials wandered from one quarter to the other, or even completely disappeared from the results of approved trials. In addition, as of July 2011 there were 20 approvals in the register marked as "reserved". These "reserved" permits nominally dated September 1, 2010 were not taken into account while summarizing the results of the first semester, since it is not possible to determine whether the approvals have been actually issued, and if yes, when have they been issued and what kind of trials they covered. As soon as information on these trials is entered into the register, the data on the first six months of 2011 will be corrected.

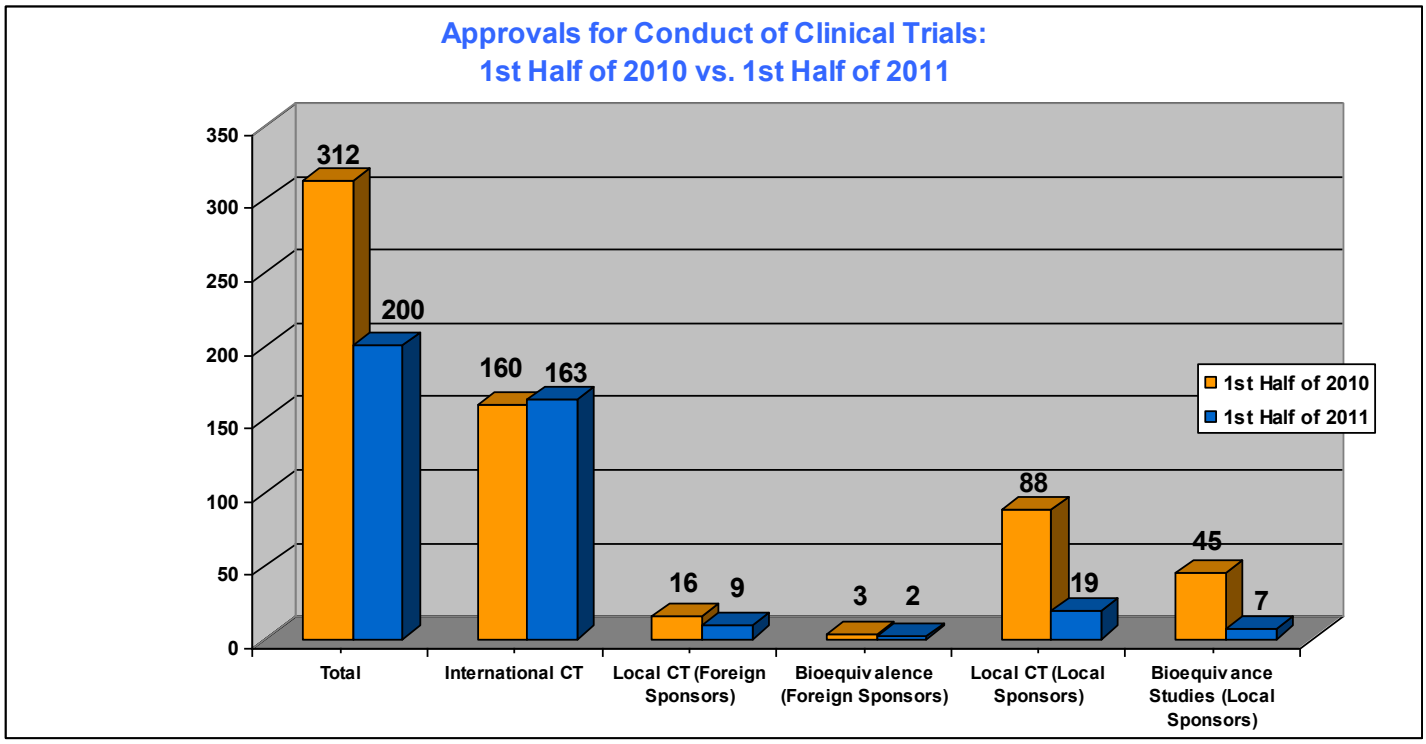
In the first six months of 2011 the Ministry of Healthcare and Social Development issued 200 approvals to conduct clinical trials. This is 35.9% fewer than the number of approvals issued by Roszdravnadzor in the first six months of 2010 (Table 1 and Diagram 1). At the same time, despite our pessimistic forecasts, the number of IMCTs approved in the first six months of 2011 did not decline and amounted to 163 trials. This was just 3 trials more than had been approved during the same period of 2010.

Table 1

Approvals for Conduct of Clinical Trials: 1st Half of 2011 vs. 1st Half of 2010						
	Total	**International Multicenter CT**	**Local CT (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CT (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
1st Half of 2011	**200**	**163**	**9**	**2**	**19**	**7**
1st Half of 2010	**312**	**160**	**16**	**3**	**88**	**45**
1st Half of 2010 vs. 1st Half of 2011, %	**-35,9%**	**1,9%**	**-43,8%**	**-33,3%**	**-78,4%**	**-84,4%**

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

Diagram 1



As shown in Table 1, the general decline of the clinical trials market was caused, first of all, by a dramatic drop in the number of local trials conducted by Russian companies – both efficacy and safety trials and bioequivalence trials. Compared to the same period of 2010, their number in the first six months of 2011 dropped by 78.4% and 84.4%, respectively.

The decrease in the number of local efficacy and safety trials, and bioequivalence trials conducted by foreign sponsors was also quite significant – by 43.8% and 33.3%, respectively. However, in the longer term, if the requirement concerning local trials for the registration purposes of original medicines and generics remains in place, an increase in the number of such trials could be anticipated.

It is an encouraging sign that, judging by the number of issued approvals, in the first six months of 2011 IMCTs reached the level of the first six months of 2010. From our point of view, this is due to the fact that the new system, which was not in fact in operation during the first 2.5 months from September 1, 2010 (the first approval to conduct a trial was issued only on November 12, 2010), was more or less functioning by the beginning of 2011. We remind you that during September-December 2010, after the law "On Circulation of Medicines" came into effect and the licensing functions were transferred to the Ministry of Healthcare and Social Development, the IMCT market dropped almost by 30% of its annual volume.

However, despite the semblance of improvement by comparison with the end of 2010, in the first half of 2011 the IMCT market was still in crisis due to various regulatory problems. At that time, the issue of an approval to conduct a clinical trial by no means always made it possible to commence it. Many companies had to postpone the actual start of trials due to unresolved problems with the import of registered medicinal products and the absence of new insurance rules. Thus, there was no point in recruiting patients, since it was evident that soon it would be necessary to re-insure them in accordance with new rules. And due to the ban on importation of registered medicinal product for clinical trials it was impossible to provide participants of trials with necessary therapy if it included such registered products.

On the other side, the severe reduction in the number of clinical trials by local pharmaceutical companies can be explained by several factors. First, the new law limited the possibility of conducting local trials by the scope of registration. The law divided trials by those which could be conducted irrespective of

subsequent registration (IMCTs, post-registration trials and bioequivalence trials), and those clinical trials which would be conducted within the framework of the registration process. The possibility of conducting local trials outside the framework of the registration process was simply ignored. A local manufacturer in need to study its own original drug is now limited to these two options. Either it has to imitate an initiation of the registration process and for such purpose it will have to "make up" the registration dossier (to prepare a real dossier and provide it with efficacy data obtained at the stage of development, especially at an early stage of development, is inherently impossible) and receive an approval to conduct the trial within the registration framework. Or a local manufacturer will have to pass the local trial off as an IMCT and conduct it having paid an IMCT fee (200 thousand rubles instead of 75 thousand). The second factor contributing to the reduction in the number of local trials can simply be that the majority of manufacturers at this moment simply do not understand which local trials they have to conduct in order to register a medicinal product. The rules of the game in this sector have not yet been clearly established. Finally, the general instability in the registration system itself leads to the reduction in the number of local trials. Market players complain of numerous issues and constant failures in the work of the regulatory system. And, referring to the available data, a very small number of approvals to conduct clinical trials have been issued within the registration framework.

The new system also tightened the regulations concerning registration of generics. Sometimes for their registration it is not sufficient to provide references to the preclinical trials data on innovative medicines, instead it is necessary to provide one's own results. As a result, some manufacturers of generics have not yet commenced their clinical trials, being stuck at the preclinical stage. Besides, the regulations governing the conduct of bioequivalence trials are still lacking, resulting in a dramatic drop in the number of issued approvals to conduct bioequivalence trials.

Time will tell whether these assumptions concerning the principal reasons for the structural changes in the pharmaceutical market are true or not. However, so far the facts show that it is Russian manufacturers who turned out to be the most sensitive to the reorganization of the regulatory system. At the same time, the Ministry of Industry and Trade has just started implementation of a federal program for development of the Russian pharmaceutical industry (Pharma-2020) and tenders have already been announced for development of a multitude of both generic and innovative medicines. How exactly the development of the local pharmaceutical industry and the significant complication of the system of registration and issue of approvals for conduction of clinical trials will be made compatible remains to be seen.

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When analyzing structural changes on the clinical trials market, it is also interesting to study in detail its dynamics by quarter. In the first quarter of 2011 the Ministry of Healthcare and Social Development issued only 81 approval to conduct clinical trials, which is 39.6% fewer than in the first quarter of 2010 (Table 2). At the same time the number of approved IMCT was 69 – 16.9% less than in the first quarter of 2010.

In the second quarter of 2011 the Ministry of Healthcare and Social Development issued 119 approvals to conduct clinical trials, of which 94 were issued for IMCTs. And while the total clinical trials market in comparison with the second quarter of 2010, continued to decline (-33.1%), the IMCT figures, despite the general market trend, demonstrated growth (+22.1%). As a result, the increase in the number of approved IMCTs in the second quarter compensated for the decline observed in the first quarter, and according to the 1H results the IMCT segment managed to reach the level of the first half of 2010.

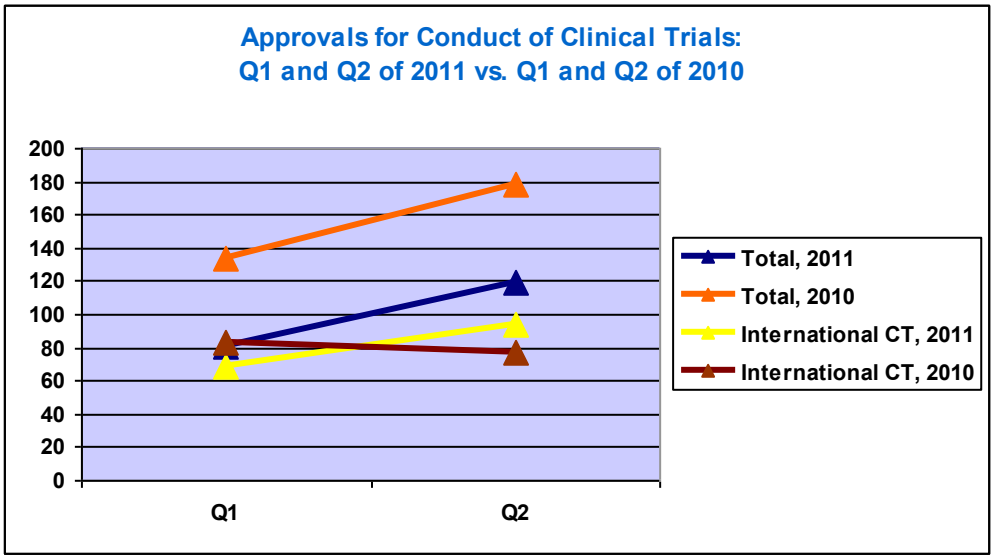
Table 2

Approvals for Conduct of Clinical Trials: Q1 and Q2 of 2011 vs. Q1 and Q2 of 2010						
	Total	**International Multicenter CT**	**Local CT (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CT (Local Sponsors)**	**Bioequivance Studies (Local Sponsors)**
Q1 of 2011	**81**	**69**	**1**	**0**	**10**	**1**
Q1 of 2010	**134**	**83**	**4**	**2**	**32**	**13**
Q1 of 2011 vs. Q1 of 2010, %	**-39,6%**	**-16,9%**	**-75,0%**	**~**	**-68,8%**	**-92,3%**
Q2 of 2011	**119**	**94**	**8**	**2**	**9**	**6**
Q2 of 2010	**178**	**77**	**12**	**1**	**56**	**32**
Q2 of 2011 vs. Q2 of 2010, %	**-33,1%**	**22,1%**	**-33,3%**	**100,0%**	**-83,9%**	**-81,3%**

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

Diagram 2 shows that the quarterly dynamics of the number of approvals issued for all the trials in 2011 basically repeated the dynamics observed in 2010 – the total number of approved trials demonstrated a growth in the second quarter by comparison with the first quarter. In 2010 the growth of the number of trials in the second quarter by comparison with the first quarter was 32.8%, while in 2011 - 46.9%. The situation with IMCT was absolutely different. In 2010 the number of trials approved in the second quarter fell slightly in comparison with the first quarter. While in 2011, on the contrary, a growth was observed in the second quarter by comparison with the first quarter.

Diagram 2



STRUCTURE AND DYNAMICS OF THE MARKET OF CLINICAL TRIALS

BY TYPE

The general market decline due to a dramatic reduction of all types of clinical trials, except for IMCT, led to a significant change in the market structure in the first six months of 2011. Thus the IMCT share reached 81.5% of the total number of trials (Diagram 3), while during the last 7 years it was steadily within 50-65% and on the average was 58.8% (Diagram 4).

Diagram 3

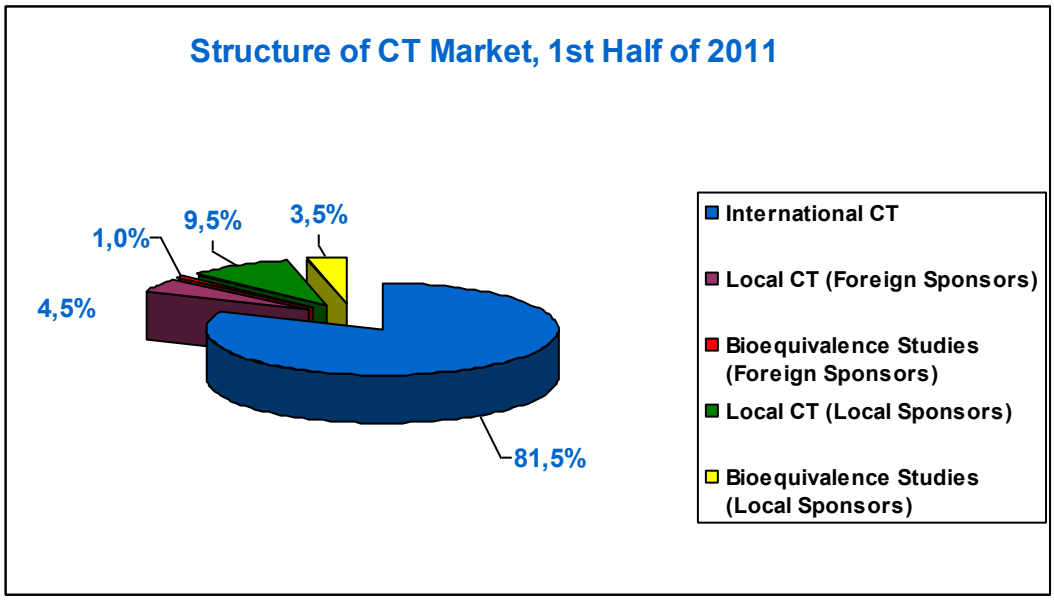
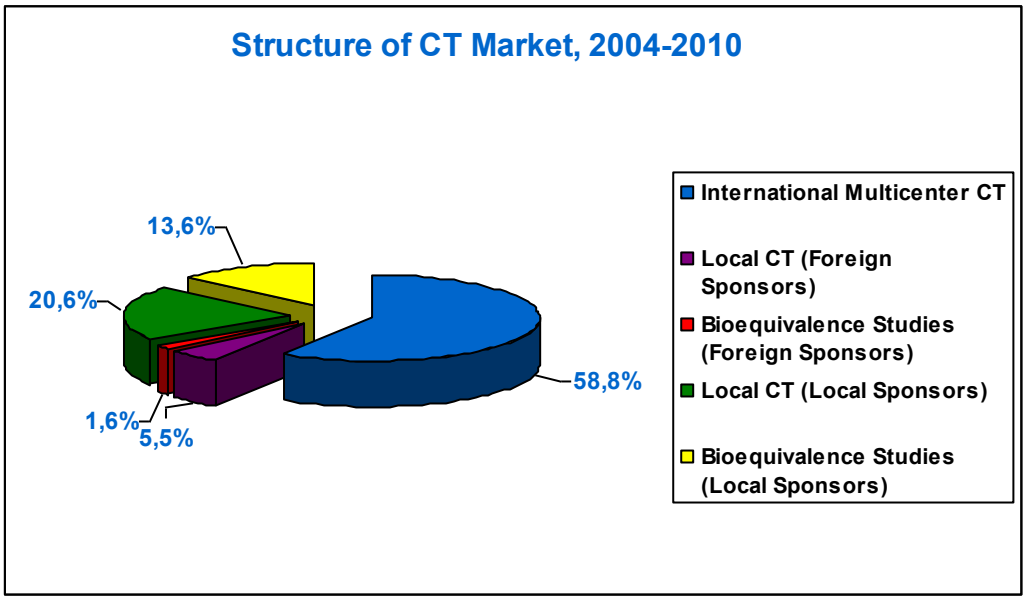


Diagram 4



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

One could reasonably suggest that such an increase in the IMCT share in the overall number of conducted trials was primarily due to the growth of the number of IMCTs in the second quarter of 2011 (by 22.1% compared to the second quarter of 2010, Table 2). However, quarterly analysis shows a different picture: the IMCT share, according to the results of the first six months, grew due to the increase of this figure in each quarter. Moreover, in the first quarter, despite the reduction in the number of approved IMCTs accompanied by a larger drop in the numbers of all other types of trials, the IMCT share reached its historical maximum of 85.2% (Diagram 5). In the second quarter the IMCT share decreased in comparison with the first quarter and amounted to 79% (Diagram 6).

Diagram 5

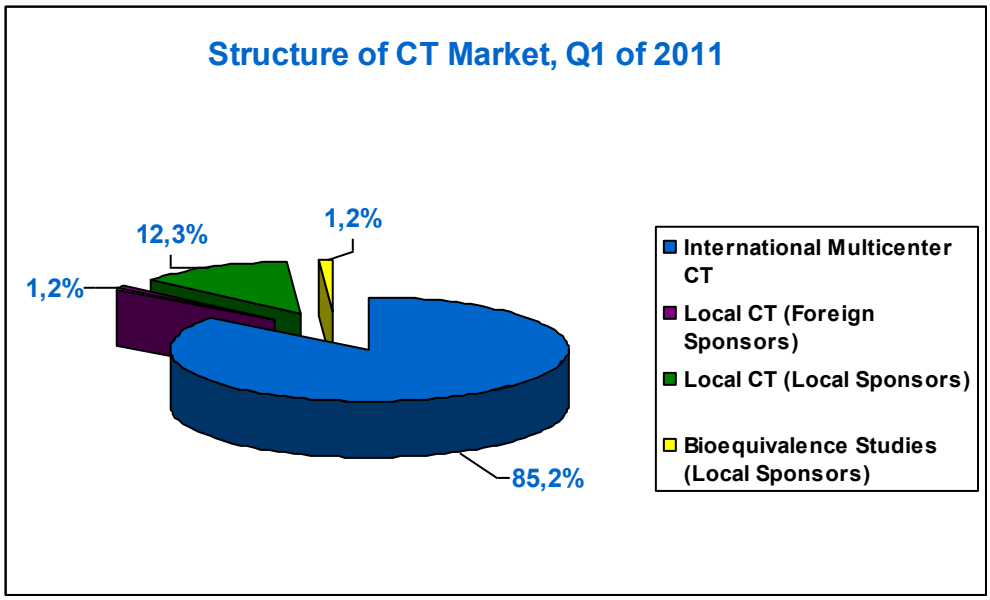
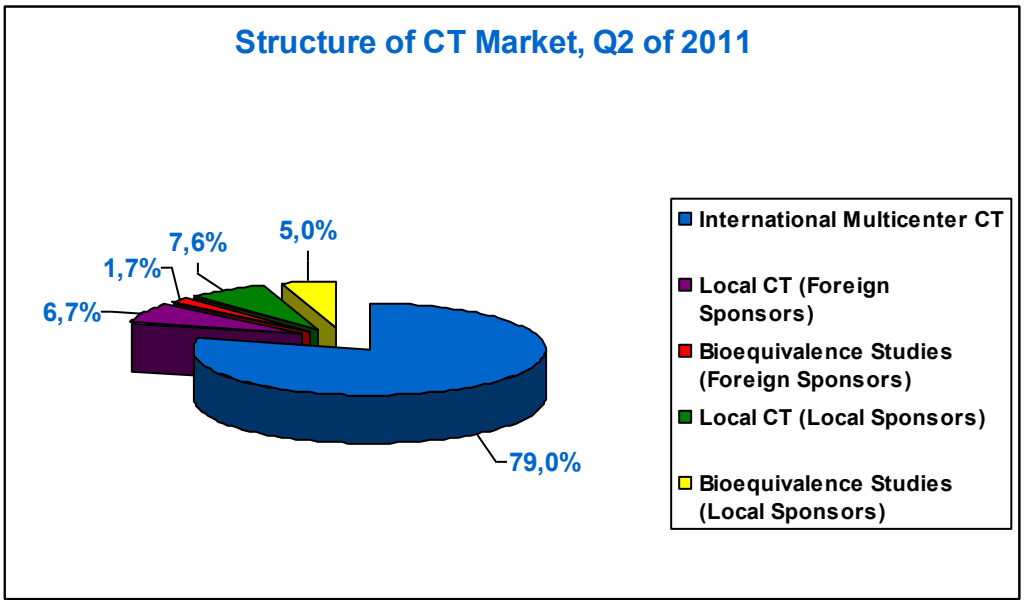


Diagram 6



Perhaps the market will gradually stabilize and the IMCT share will come back to the level of past performance. Subject to probable growth of the number of local registration trials, it might even decrease.

STRUCTURE AND DYNAMICS OF THE MARKET

OF INTERNATIONAL MULTICENTER CLINICAL TRIALS BY PHASE

Traditionally, Phase III trials dominate in the structure of IMCT conducted in Russia. The average share of Phase III trials during the last 7 years was 54.8% (Diagram 8). In the first six months this indicator slightly grew – 110 approvals were issued for Phase III trials (Table 3), which was 63.2% of the total number of approved IMCT (Diagram 7).

Table 3

Phases of CT (Foreign Sponsors), 1st Half of 2011					
I	II	III	IV	without specifying	Bioequivalence Studies
3	42	110	14	3	2

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

Diagram 7

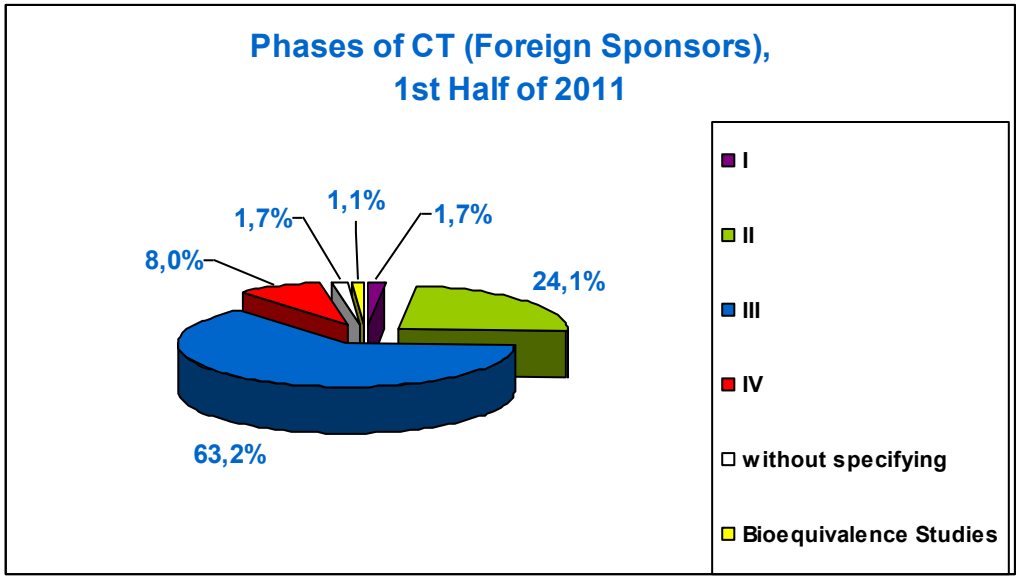
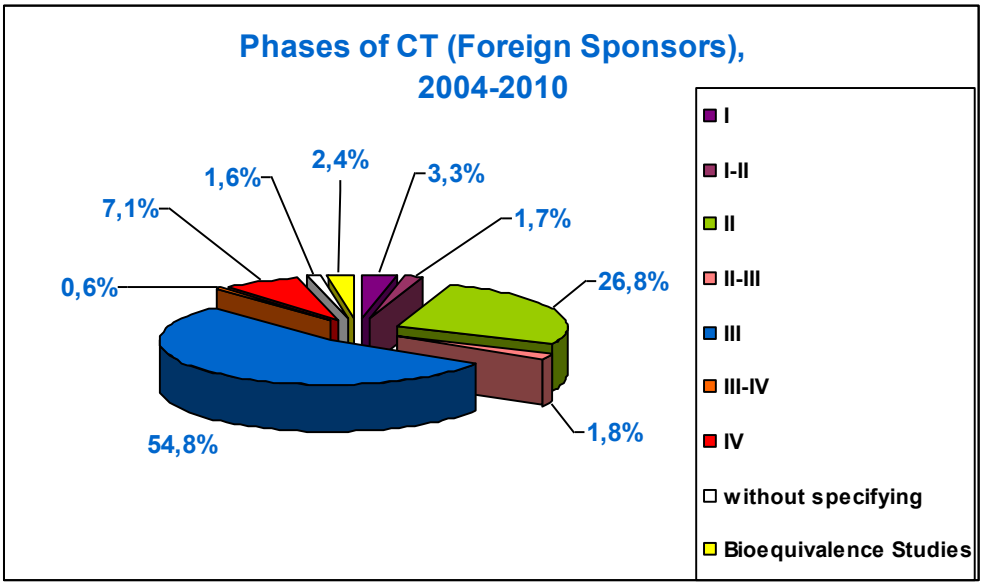


Diagram 8



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

There were no significant changes in the shares of Phase II (24.1% versus the average 26.8%) and Phase IV trials (8% versus the average 7.1%).

On the whole, all the described changes in the shares of trials of particular phases are within the standard, for the last seven years, annual fluctuations (Table 4).

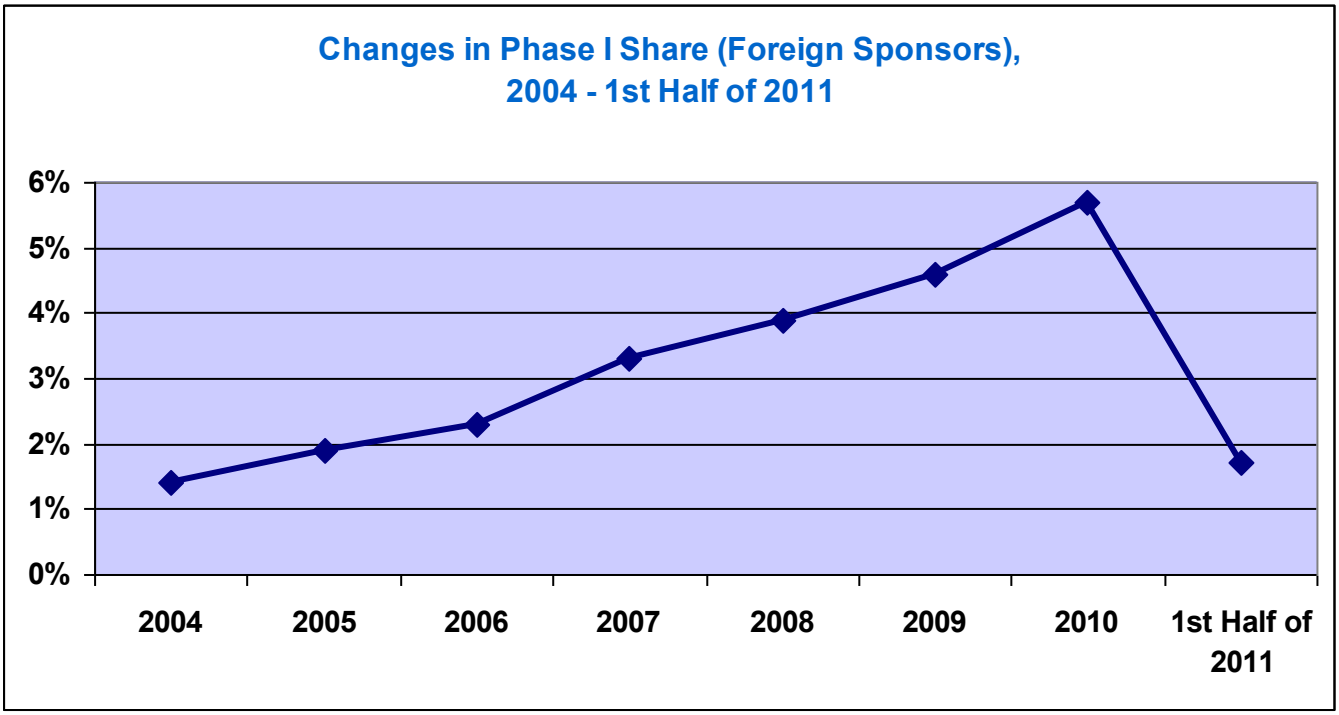
Table 4

Changes in Phase I-IV Shares (Foreign Sponsors), 2004-2011								
	2004	2005	2006	2007	2008	2009	2010	1st Half of 2011
Phase I, %	1,4%	1,9%	2,3%	3,3%	3,9%	4,6%	5,7%	1,7%
Phase II, %	18,0%	26,8%	26,4%	31,6%	28,3%	28,9%	24,5%	24,1%
Phase III, %	60,0%	54,8%	56,8%	50,1%	55,8%	53,4%	52,8%	63,2%
Phase IV, %	10,0%	6,4%	7,4%	6,3%	6,3%	6,7%	8,2%	8,0%

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

The situation is much different with Phase I trials in the first six months of 2011. If we compare the share of such trials in the first half of 2011 with the average share during the last seven years, the reduction will also seem to be insignificant (from 3.3% down to 1.7%, Diagram 7). However, it is important to look at the dynamics of this type of trials from year to year. Until now, from 2004 to 2010, the share of Phase I trials has been steadily growing – from 1.4% in 2004 to 5.8% in 2010 while in the first half of 2011 it dropped down nearly to the level of 2004 (Diagram 9).

Diagram 9



There may be several reasons for that. First, the law "On Circulation of Medicines" prohibited conduct of Phase I trials of medicinal products produced by foreign companies with the participation of healthy volunteers (Phase I trials with the participation of patients are still allowed). Second, it is possible that in the conditions of this transition period, when the regulatory system is constantly failing, sponsors chose not to make any attempts to conduct Phase I trials in Russia even with the participation of patients – it is often much easier and faster to conduct such trials in stable and well-developed markets.

REVIEW OF LEGISLATIVE INITIATIVES AND AMENDMENTS

1) The problem of registered medicinal products importation for clinical trials is resolved

It should be noted that the import of registered medicinal products has been placed on hold in the middle of October 2010 because Government Order No. 771 of September 29, 2010 did not give consideration to the specificity of clinical trials. The Ministry of Healthcare and Social Development had the authority to issue permits for import of only unregistered medicinal products for clinical trials. Import of registered medicines was handled by the Ministry of Industry and Trade. Registered medicinal products intended for clinical trials just "fell out" of the regulation. The Ministry of Healthcare and Social Development refused to issue permits for the import of registered medicines. Companies could not assign commercial status to "clinical" batches and were unable to obtain a license from the Ministry of Industry and Trade for the reason that most of them do not hold a pharmaceutical license, since they are not engaged in wholesale or retail trade in medicines.

The problem of licensing could easily be solved if the Ministry of Healthcare and Social Development took account of the relevant provision of the Customs Union, which properly addresses this problem. However, the Ministry of Healthcare and Social Development chose to ignore this despite the fact that international treaties take priority over the domestic Russian legislation.

The cessation of import of registered medicinal products for clinical trials appeared to be very painful for the IMCT market. The problem affected not only new studies but active studies as well, where the stock of medicinal products was running short. Some new studies which were supposed to use registered medicinal products in Russia have been cancelled and transferred to other countries. As for active studies, the organizers desperately sought various ways of handling the problem, so that the studies could continue - for example, to redistribute remaining medicinal products among participating clinical sites.

After 8 months of delay, a Government Order No. 441 of June 03, 2011 "On making amendments in some acts of the Russian Federation Government on the Import of Medicines for Medical Use into the Russian Federation" has been published. Pursuant to this Government Order, the import of both registered and unregistered medicines for clinical trials falls within the competence of the Ministry of Healthcare and Social Development. After that the import of medicinal products for clinical trials has finally been resumed.

2) A new version of standard rules for insurance of patients involved in clinical trials has been adopted

The amendments made in the standard rules for compulsory insurance of patients were approved by Government Decree No.393 of May 18, 2011. These amendments were adopted with over four months of delay. They should have been approved by January 01, 2011 based on the requirements set forth in the respective amendment to the Federal law "On Circulation of Medicines" that changed the concept of the insurance event and adjusted the insurance procedure.

The new version of the standard rules is undoubtedly better than the previous one and serves the interests of patients as it now protects confidentiality of their personal data, which is of primary importance for patients suffering from some diseases such as HIV, hepatitis C, and mental diseases.

Nevertheless, the new version of these rules brings a number of other problems.

For starters, it is the issuance of individual policies to all patients. It would seem to be more sensible to stop using individual policies after the personal data requirement is cancelled. The availability of an agreement between the Insured and the Insurer is confirmed by the Insurance Contract which applies to all patients participating in a specific clinical trial (as it is done throughout the world). The patient shall just confirm the fact of his participation in a clinical trial by delivering his/her informed consent to the Insurer.

Individual policies are fairly often avoided in Russian practice even in personal types of insurance. For example, no individual insurance policy is issued to a passenger to be covered irrespective of nearly any type of passenger transportation. To make a claim, such a passenger shall present his/her ticket to confirm the availability of the passenger transportation contract.

Issuance of individual policies implies a multiple increase in documents and complication of document management. This results in a higher risk of mistakes, loss of documents or data.

Moreover, the structure of the individual identification code to encipher personal data is too bloated and complicated. We know some examples of making use of a 33-bit code in international practice. The subject identification code (according to the ICH GCP requirements) to be used for clinical trials is assigned to the patient by the investigator based on the sponsor's requirements. Most commonly, this is a six-digit code (as far as we know, such a code consists of 11 digits as maximum). Dealing with 33-digit codes to be entered into the patient information sheet by the investigators will inevitably cause mistakes.

All these problems could have been avoided if the Government renounced the idea of using individual policies and vested patients with the right to claim benefits upon their participation in a trial. In our opinion, a patient acquires such a right as soon as he/she is included into a trial, i.e. upon signing his/her informed consent, whatever the insurance policy is in place. This practice is used worldwide.

The new insurance instruments have other weaknesses, which are not so noticeable at first but may show up as material challenges once the insurance practice has some time to develop. It is, however, obvious now that legislative amendments will have to be made sooner or later to harmonize Russian requirements with generally accepted international practice.

REVIEW OF PRACTICAL ISSUES

1) Timeframes for issuance of approvals

The law "On Circulation of Medicines" established maximum allowable timeframes to issue clinical trial approvals, which are comparable with European terms. However, in practice these timeframes are not observed.

According to the monitoring data, in the period from January 2011 to June 2011, average time to obtain an approval for conducting a clinical trial reached 126 calendar days, while according to the new law it should not exceed 57 calendar days (Table 5). A permit to export biological samples shall be issued within 19 days, but it is actually takes 34 days. The law prescribes issuance of a permit to import medicinal products within 12 days; however, it currently takes 28 days. It takes an average of 91 days instead of statutory 48 days to issue a permit to make changes in a report. Finally, instead of 35 days prescribed to issue other permits (for prolongation of trials, involving more patients and so on), it takes 71 days now.

Table 5

Timeframes For Issuing Approvals, 1st Half of 2011					
	Timeframes According to Legislation (Business Days/ Calendar Days)	Average Timeframes (Calendar Days)	Minimum Timeframes (Calendar Days)	Maximum Timeframes (Calendar Days)	Sampling
To Conduct Clinical Trials	41/57	126	70	236	74
To Import Medicines	8/12	28	10	60	99
To Import/Export Biosamples	13/19	34	9	68	222
To Make Amendments to the Protocol	34/48	91	13	177	135
Other Approvals (to Prolong Clinical Trials, To Include New Sites, To Enroll Additional Patients, etc.)	25/35	71	16	273	194
Total Timeframes for Obtaining Approvals to Conduct Clinical Trials and To Import/Export	54/76	160	~	~	~

Data from timeframes' monitoring of ACTO (January-June 2011)

The Ministry of Healthcare and Social Development declared that fixed time established for all the procedures will make the performance of the regulatory system more efficient. Indeed, the performance of Roszdravnadzor left much to be desired. From 2005 till 2010 the total time for obtaining an approval for a trial and an import/export permit varied from 81.2 to 122.6 days, which is far from standard 60 days in Europe. However, as we can see from Table 6 and Diagram 12, the Ministry of Healthcare and Social Development is working even slower than Roszdravnadzor. In the first half of 2011 total time required for obtaining an approval for conducting a trial and an import/export permits reached its maximum in the whole history of the regulatory system monitoring, i.e. 160 days. This is 30.5% more than the maximum time registered with Roszdravnadzor in 2007 (122.6 days) and 42.8% more than in the period from January 2010 through August 2010.

Poor performance of the regulatory system is caused not only by objective factors related to its reconstruction, but also by artificially created complexity of the process. In particular, the applicant has to submit an additional request for approval of the trial after expert evaluation has been completed. This way a single and logical process is needlessly split into 2 phases. Another problem is sending approval documents (for prolongation of trials, involvement of additional sites and patients) by mail. The applicant receives documents by regular mail with an average delay of 2 weeks. Requests by companies to allow in-person collection of approval documents still remain unanswered because the Ministry of Healthcare and Social Development refers to the "lack of technical capability".

Table 6

Changes in Average Timeframes, 2005-2011							
	2005	2006	2007	2008	2009	Jan/-June, 2010	Jan.-July, 2011
Approvals to Conduct Clinical Trials	66,3	77,8	98,9	77,6	77,0	85,2	126,0
Permits to Import/Export	14,9	17,8	23,7	33,1	30,5	26,9	34,0
Total	81,2	95,6	122,6	110,7	107,5	112,1	160,0

Data from timeframes' monitoring of ACTO (January-June 2011)

Diagram 10

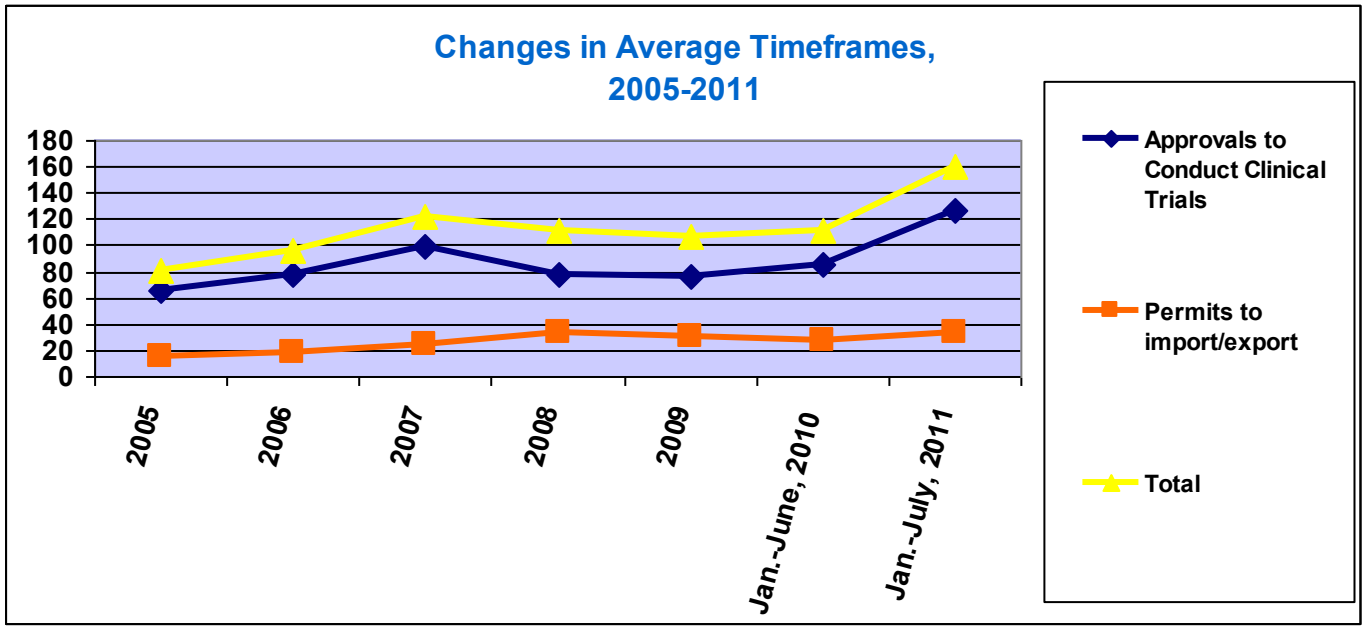


Table 7 provides information on violation of established deadlines for issuance of approvals in the first six months of 2011. According to ACTO, no approval for clinical trials has been issued at a stated time in the first half a year, and most approvals are still being issued with a delay from 1.5 to 3 times over the established timeframes.

Table 7

Violations of Timeframes, 1st Half of 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	0%	100%	2,7%	39,2%	44,6%	12,2%	1,4%
To Import Medicines	5,1%	94,9%	10,1%	22,2%	42,4%	13,1%	7,1%
To Import/Export Biosamples	7,2%	92,8%	24,8%	36,9%	26,6%	4,5%	0%
To Make Amendments to the Protocol	13,3%	86,7%	6,7%	34,1%	40,7%	5,2%	0%
Other Approvals (to Prolong Clinical Trials, to Include New Sites, To Enroll Additional Patients, etc.)	15,5%	84,5%	18,6%	21,1%	28,3%	10,8%	5,7%

Data from timeframes' monitoring of ACTO (January-June 2011)

2) Accreditation of medical institutions for clinical trials

New rules for accreditation of medical institutions for clinical trials were approved by Government Decree No. 683 of September 03, 2010. Clinics that have not completed accreditation under the new system are entitled to conduct clinical trials till September 01, 2011.

Ministry of Healthcare and Social Development has managed to accredit only 152 medical institutions by middle of July 2011.

It is worth noting that the format of an application for accreditation was approved by the Ministry of Healthcare and Social Development only on December 03, 2010. Moreover, suffocating under the press of "the reconstruction", representatives of the Ministry of Healthcare and Social Development informally addressed market participants with a request to wait a little and hold over their applications for accreditation at least until the beginning of 2011. Thus, a one-year re-accreditation period the Decree prescribes has been reduced to 8 months.

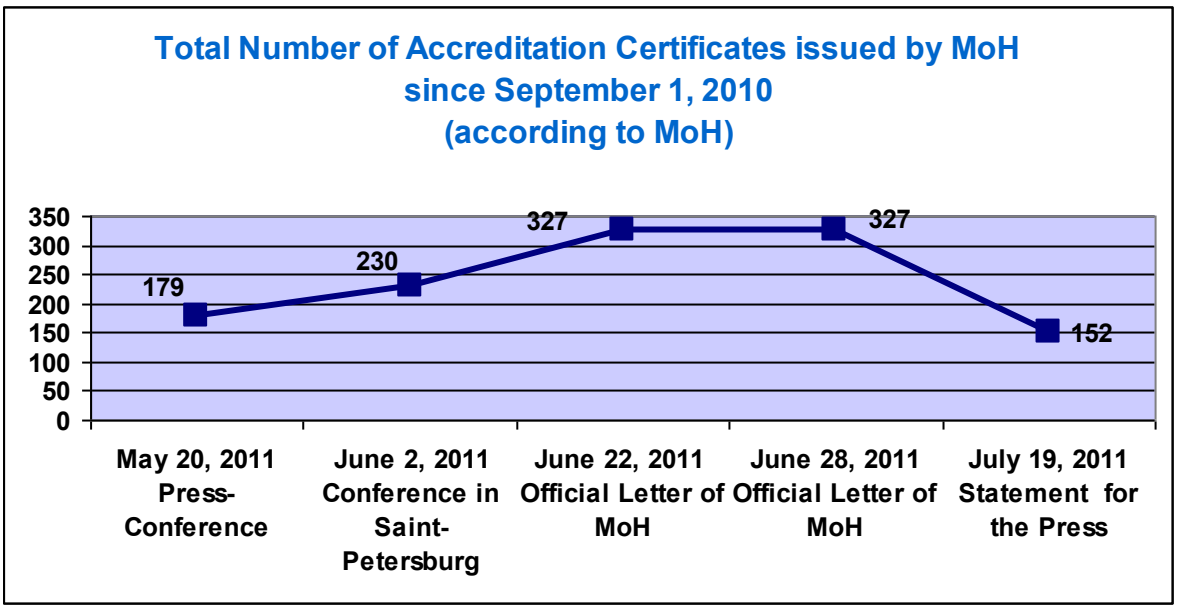
It should also be noted that the number of clinics authorized to conduct clinical trials was more than 1,100 by the time the new accreditation rules were adopted. It is clear that not all of these clinics really actively participated in clinical trials. According to expert evaluation, the minimum number of medical institutions required to meet the needs of the market is 500 to 600. Thus, a month before the new accreditation regulation came into force, not more than 30% of the number of clinics sufficient for normal functioning of the market could actually be accredited.

Initially, the Ministry of Healthcare and Social Development seemed to be planning to meet the challenge in the established period and tried to calm down the market participants (asked them "not to diabolize the process" and not to stir up the "apocalyptic spirit"). In public addresses and official letters representatives of the Ministry of Healthcare and Social Development always overstated the real number of accredited clinics. Thus, at a press-conference on May 20, 2011, Marat Sakaev, Director of the Department of State Regulation of Circulation of Medicines at, the Ministry of Healthcare and Social Development declared that 179 medical institutions had received certificates of accreditation (Diagram 11). However, on June 02, 2011, at a clinical trials conference, he announced that 230 clinics had been accredited. The Ministry of Healthcare and Social Development in its official letters of June 22 and 28, 2011 forwarded to ACTO indicated that the number of accredited clinics was 327, and 481 medical institutions in total had applied to the Ministry with respective applications. However, the information posted on the official website of the Ministry www.grls.rosminzdrav.ru does not support these figures. From the beginning of the year until the middle of July, only three orders dated March 23 (11 clinics), May 4 (40 clinics) and June 17 (43 clinics) were published on the website.

Having foreseen the crisis and the possibility that the Ministry of Healthcare and Social Development will shift the blame on the applicants, from April 2011 ACTO compiled its own database of submitted applications for accreditation. The information came from ACTO members who, in turn, received it from clinics. At the end of July 2011 ACTO opened free access to the database and also made a public announcement about the crisis situation in the sphere of accreditation.

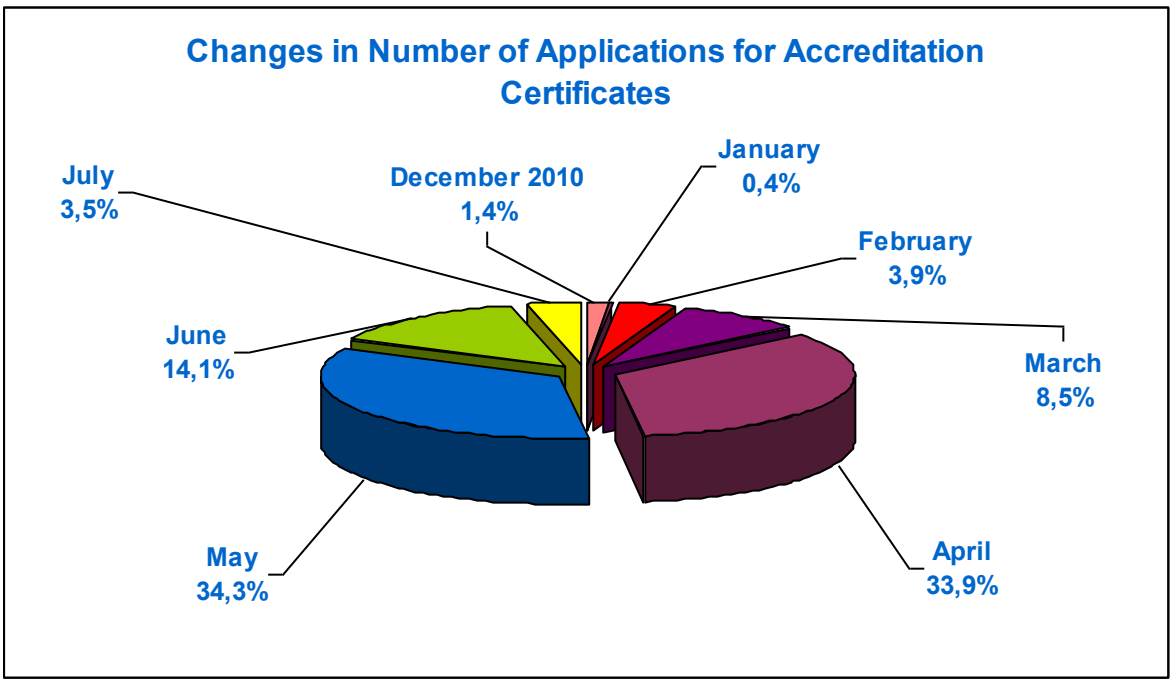
Understanding that this problem cannot be concealed any more, the Ministry of Healthcare and Social Development had to announce the real figures to mass media: only 152 clinics have been accredited throughout the whole time. On July 21, 2011 two more Orders dated July 14, 2011 – No.728 (14 clinics) and No.729 (29 clinics) – were published on the Ministry's web site. Hence, the number of clinics accredited by the middle of July turned out to be even less than the number mentioned in May 2011 (Diagram 11).

Diagram 11



At the same time the Ministry of Healthcare and Social Development announced that some clinics allegedly did not rush to submit applications for accreditation, while those who wanted to be accredited, had submitted them in time and had already received accreditation certificates. However, according to the available data, as of the end of June 2011 there are at least 250 applications under consideration. And it is clear that the number of applicants is in fact much greater, since the database represents the information received only from ACTO member companies. Many clinics have been waiting for a decision since April-May 2011 (Diagram 12). The greatest amount of applications has been submitted during this exact period.

Diagram 12



Data from ACTO database of submitted applications for accreditation

Evidently, the real reason for the low pace of re-accreditation is not the absence of interest on the part of medical institutions, but the failure to meet the deadlines for the issuance of licenses on the part of the Ministry.

In practice, the process takes an average of 70 days, while according to the law it should take no more than 30 days.

But it is unlikely that the Ministry would voluntarily acknowledge its mistakes. As expected, the Ministry soon resorted to the ever strongest argument: the applicants were accused of improper preparation of documents. The package of documents for accreditation is quite limited, and all the necessary papers are easy to prepare (license copies, extracts from the Unified State Register of Legal Entities (USRLE), etc.), except for the "document setting out the procedure for handling confidential information". And since the requirements for this document were not established in advance (the Ministry's comments on the contents of the document appeared only on July 21, 2011), it will most probably become the target of all the principal claims. And its improper preparation will be the main excuse for the disruption of accreditation process after September 1, 2011, if the Ministry of Healthcare and Social Development does nothing to prevent it.

We have to acknowledge the fact that the Ministry of Healthcare and Social Development once again created a problem out of nothing. Accreditation of medical institutions for conducting trials is in itself an excessive administrative barrier and is not used in the international practice. At the same time, the procedure for accreditation as described in the Governmental Order did not appear to be a formidable barrier. However, it turned into one during the last year due to untimely preparation of necessary regulations, complicated and intricate procedure for making decisions on issuance of licenses, absence of clear and pre-established requirements to the documents which the applicants must present, and failures to meet the timeframes. It will be clear very soon how this situation is going to be resolved – whether a great number of current trials will actually be stopped or the Ministry of Healthcare and Social Development will find a way out.

ABOUT ACTO

ACTO was duly established at the end of November 2007 as non-commercial organization of the companies/ legal entities and clinical research community engaged in clinical trials in Russia. The situation involving the export of biological samples, which occurred in May 2007, was the stimulus that led companies to create the Association. At that time there was a lack of uniting power, to appeal on behalf of business.

The primary objectives of the Association are to further develop Russia as clinical research country/market, to ensure a proper and effective balance between the interests of parties involved in clinical trials including the patients, the medical community, and the governmental agencies, to harmonize local legislative basis for the clinical trials with the respective worldwide standards, and to promote an ethical business model.

To date, ACTO members are 26 pharmaceutical companies and contract research organizations: Almedis, Amgen, Bayer Schering Pharma, Boehringer Ingelheim, Bristol-Myers Squibb, ClinStar, Covance, Cromos Pharma, Eli Lilly Vostok S. A., i3, ICON, Janssen Pharmaceutica, Kendle, MB Quest, Medpace, Novartis, Novo Nordisk, Parexel, Pfizer, PharmaNet, PPD, PRA International, PSI, Quintiles, Servier, Worldwide Clinical Trials (WCT).

Each ACTO member conducts clinical trials in accordance with international standard of Good Clinical Practice (ICH GCP). In accordance with the Statutes of Association ACTO members should follow the principles of integrity, respect for other market participants, and not admit cases of unfair competition.

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