ACTO

Association of Clinical Trials Organizations

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CONTENTS

SUMMARY

In the 1st quarter of 2012 Ministry of Health and Social Development of the Russian Federation granted 220 approvals for conducting clinical trials, 91 of which — for international multicenter clinical trials (IMCTs). In comparison with the 4th quarter of 2011 the total number of issued approvals decreased by 6%, while the number of approvals for IMCTs decreased by 25.4%. And if since September 2010 the efficiency of the Ministry had been constantly growing from quarter to quarter, in the beginning of 2012 the growth gave way to recession for the first time.

Decrease of the total number of issued approvals took place primarily because of sharp decrease of the quantity of approvals for IMCTs. As a result, in the 1st quarter of 2012 for the first time after adoption of the law "On Circulation of Medicines" there were significant structural changes of the market. Thus, for the first time since the keeping of the statistics has been started the share of IMCTs dropped almost to 40%, deviating from the 8 year average for 18.2% at once. Primarily the lowest share of IMCTs (48.2%) occurred in 2004.

At the same time a significant growth of bioequivalence studies is observed. Share of such studies of local sponsors rolled over 23.2% (average is 13.3%). But the most significant growth was observed in the sphere of bioequivalence studies of foreign sponsors. Their share reached 10.5% (the average is 1.8%). The number of approvals granted for this kind of studies in the first quarter of 2012 has already exceeded the total number of such studies in the whole year of 2011.

There is no doubt that the observed growth of foreign sponsors' bioequivalence studies is a direct consequence of the requirement for local registration trials. Such structural changes of the market are bound to trigger concern. We remind that in case of local clinical trials we most often deal with repeated unjustified studies. Their quality is also a source of concern, which is, inter alia, confirmed by the results of inspections by Roszdravnadzor. One can state that negative consequences of adoption of the law "On Circulation of Medicines", namely the norm about compulsory registration clinical trials, started to show themselves fully in the 1st quarter of 2012.

In this issue of the Newsletter we are also representing results of the monitoring of the timeframes for issuance of approvals for clinical trials in 2011. The average time to obtain an approval for conducting a clinical trial amounted to 130 days (according to the law it should not exceed 57 days). Significant noncompliances with timelines of work of the regulatory system take place with other kinds of approvals. Establishment of clear timelines of work of the regulatory system was named as one of the main advantages of the new law. Nevertheless, the result so far is the opposite of the promised one. The terms of issuing of the clinical trial approval by the Ministry of Health and Social Development exceed the worst metrics of the work of Roszdravnadzor by one third.

Another topic of the issue is initiatives for revision of the current legislation. Thus, in the beginning of March 2012 Federal Antimonopoly Service (FAS) of Russia came up to the market players with a proposal to discuss amendments to the law "On Circulation of Medicines", which had been prepared by the Service. The most significant of them seem to be proposals of abolition of the local registration clinical trials. Amendments by FAS are the first step in this direction. But so far the Ministry of Health and Social Development has not showed any reaction to this draft.

Also in this issue the discussion of the draft of the administrative regulations of the Ministry of Health and Social Development on issuing approvals for clinical trial and hereto related topic of doubling of clinical trial application filing is continued.

Also in this issue we open a new column which will be devoted to analysis of the situation with clinical trials in Russia within various therapeutic indications/ diseases. The first article covers the situation with trials of medicines for treatment of HIV/AIDS, hepatitis C and tuberculosis.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

In the 1st quarter of 2012 Ministry of Health and Social Development of the Russian Federation granted 220 approvals for conducting clinical trials, and 91 of which — for international multicenter clinical trials (IMCTs).

It is rather senseless to compare these indices solely with the 1st quarter of 2011, because a year ago the system was only starting to work, and the number of issued approvals in the period was still very small.

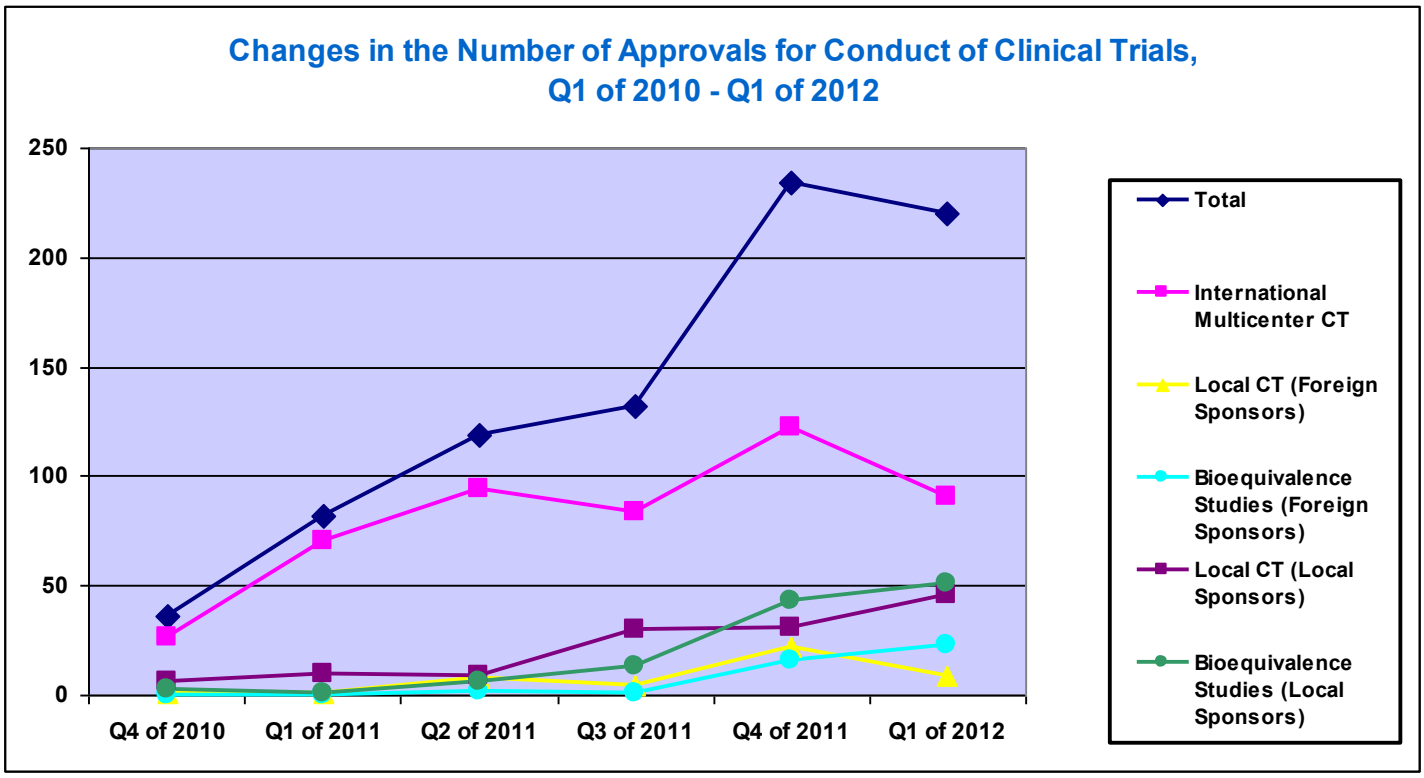
But we can compare the data of the 1st quarter of this year with all quarter indices of the preceding one, primarily with the past, 4th quarter of 2011 (table 1, diagram 1). Thus, in comparison with the period, the number of granted approvals decreased by 6%, and the number of approvals for IMCTs — by 25,4%. Moreover, as it can be seen from diagram 1, if before that the efficiency of work of the Ministry of Health and Social Development had been constantly growing from quarter to quarter, in the beginning of 2012 the growth gave way to recession for the first time.

Table 1

Approvals for Conduct of Clinical Trials: Q1 of 2012 vs. Q4 of 2010 - Q1-Q4 of 2011						
	Total	**International Multicenter CT**	**Local CT (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CT (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
Q1 of 2012	**220**	**91**	**9**	**23**	**46**	**51**
Q4 of 2010	**36**	**26**	**1**	**0**	**6**	**3**
Q1 of 2011	**82**	**70**	**1**	**0**	**10**	**1**
Q2 of 2011	**119**	**94**	**8**	**2**	**9**	**6**
Q3 of 2011	**132**	**84**	**4**	**1**	**30**	**13**
Q4 of 2011	**234**	**122**	**22**	**16**	**31**	**43**
Q1 of 2012 vs. Q1 of 2011 г., %	**168,3%**	**30%**	**800%**	**~**	**360%**	**5000%**
Q1 of 2012 г. vs. Q4 of 2011 г., %	**-6,0%**	**-25,4%**	**-59,1%**	**43,8%**	**48,4%**	**18,6%**

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

Diagram 1



Looking at diagram 1, let us analyze, what has caused the decrease of the total number of granted approvals. Primarily it happened due to harsh (by a quarter at once) decrease of the quantity of IMCTs approvals. Taking into account, that IMCTs historically occupies the largest market share, it is decrease of the number of approvals for this kind of studies that became the main cause of lowering of the total rate. But besides IMCTs the number of issued approvals for local clinical trials by foreign sponsors sharply (almost by 60%) decreased. At the same time, the number of approvals for other kinds of trials showed growth in comparison with the 4th quarter of the past year. Thus, the bioequivalence studies by foreign sponsors increased by 43.8%, bioequivalence studies by Russian sponsors — by 18.6%, and local clinical trials of efficiency and safety by domestic companies increased by 48.4%. But aggregate growth of these kinds of studies was not enough to escape the decrease of the total number of issued approvals.

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To get a more detailed picture of the market we need also to look at correlation of shares of various kinds of trials. Thus, in the 1st quarter of the current year for the first time after adoption of the law “On Circulation of Medicines” significant structural changes of the market occurred. And for the first time in the period within which the statistics of clinical trials in Russia are observed (since 2004), the share of IMCTs dropped almost by 40%, deviating from the 8 year average by 18.2% at once (diagrams 2, 3). We can also add that previously the lowest share of IMCTs (48.2%) occurred in 2004 (table 2).

Diagram 2

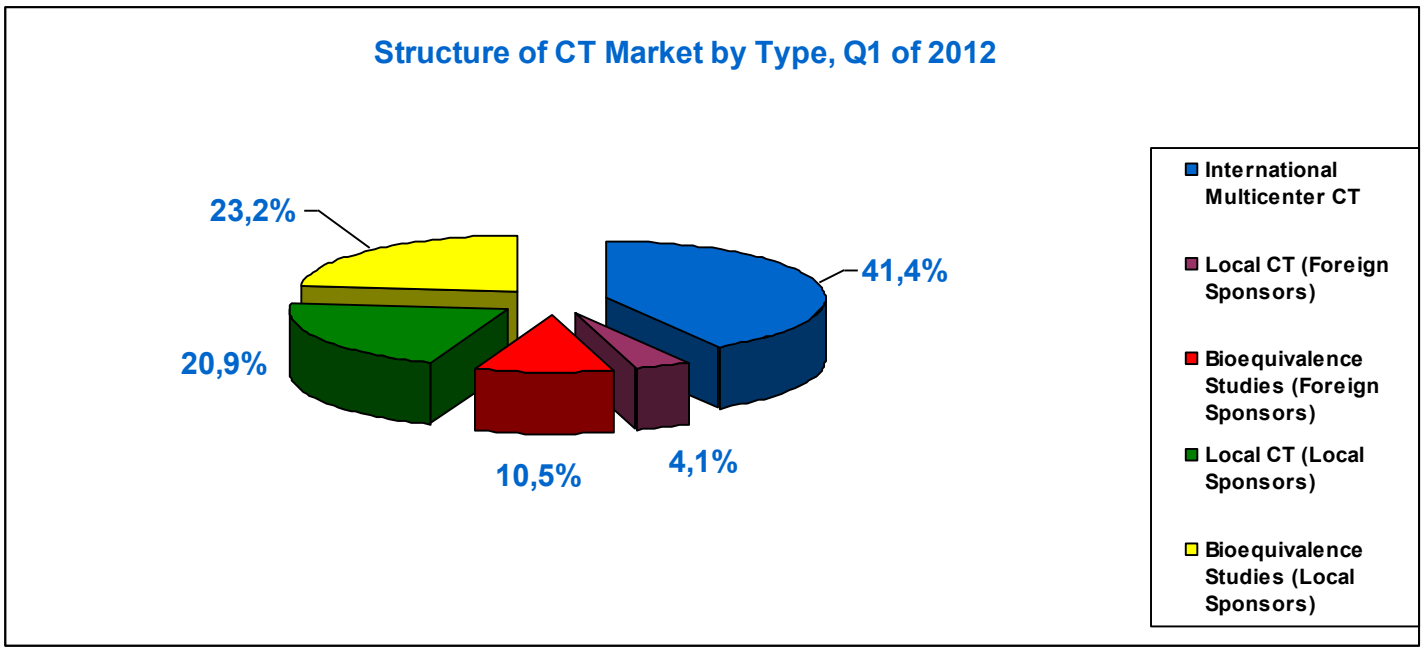
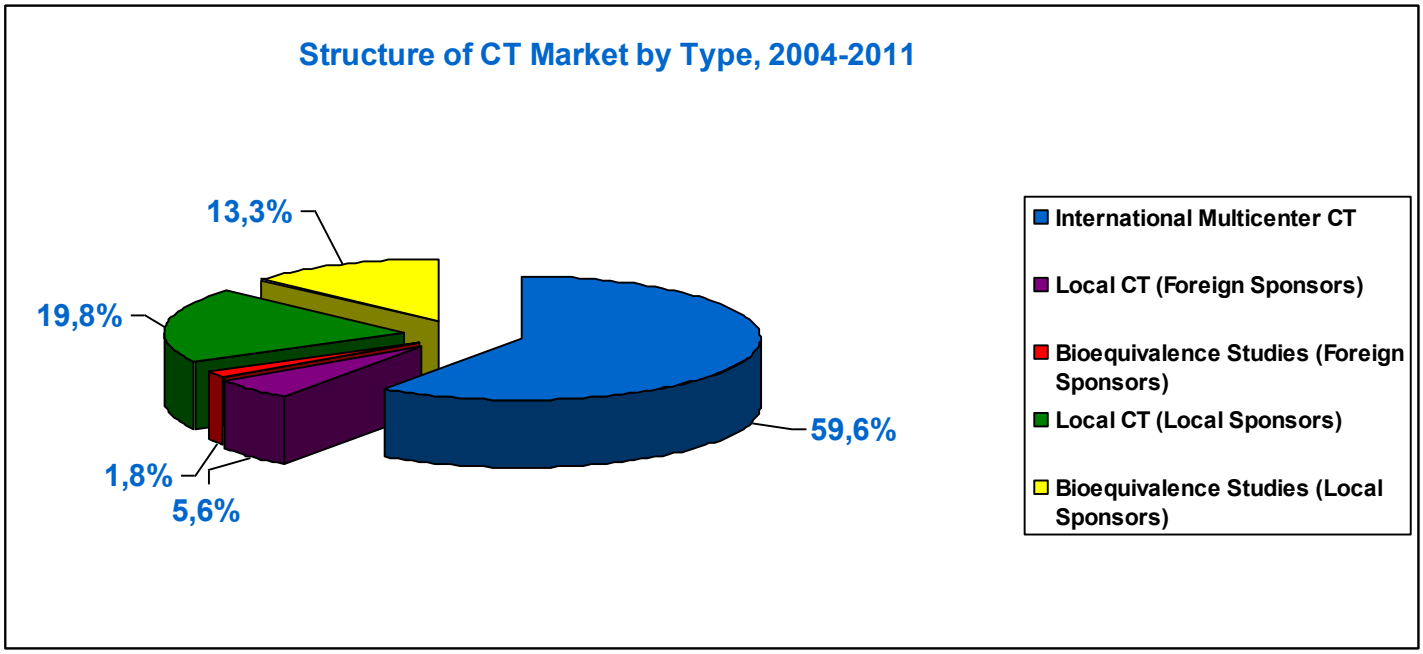


Diagram 3



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

At the same time in the 1st quarter of this year a significant growth of the share of bioequivalence studies took place. Thus, the share of these studies by domestic sponsors increased up to 23.2%, while the average is 13.3%. It should be noted that previously the highest share of this segment of the market had reached only 16.3%, which happened also in 2004.

Table 2

Structure of CT Market by Type, 2004-2011										
	International Multicenter CT		Local CT (Foreign Sponsors)		Bioequivalence Studies (Foreign Sponsors)		Local CT (Local Sponsors)		Bioequivalence Studies (Local Sponsors)	
	number	%	number	%	number	%	number	%	number	%
2004	252	48,2%	23	4,4%	19	3,6%	144	27,5%	85	16,3%
2005	279	62,4%	29	6,5%	6	1,3%	65	14,5%	68	15,2%
2006	324	63,9%	19	3,7%	9	1,8%	88	17,4%	67	13,2%
2007	369	65,5%	25	4,4%	5	0,9%	101	17,9%	63	11,2%
2008	364	59,2%	45	7,3%	5	0,8%	133	21,6%	68	11,1%
2009	348	60,3%	32	5,5%	8	1,4%	112	19,4%	77	13,3%
2010	246	51,0%	30	6,2%	6	1,2%	123	25,5%	77	16,0%
2011	370	65,3%	35	6,2%	19	3,4%	80	14,1%	63	11,1%
Q1 of 2012	91	41,4%	9	4,1%	23	10,5%	46	20,9%	51	23,2%

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

The most significant growth was observed in the sector of bioequivalence studies by foreign sponsors. Share of these studies in the 1st quarter of the current year is 10.5%, while the average for the period from 2004 to 2011 was 1.8%, and minimal (0.8%) and maximal (3.6%) values were observed in 2008 and 2004 respectively. It should be noted also that the number of issued approvals for this kind of studies in the 1st quarter of this year (23) has already exceeded the total number of them in the whole year of 2011 (19).

There is no doubt that the observed growth of the number of bioequivalence studies by foreign sponsors is a direct consequence of the requirement for local registration clinical trials. Altogether, according to the register of the Ministry of Health and Social Development, 725 people are going to take place in these studies.

The situation is much more settled in the segment of local studies on effectiveness and safety, initiated by foreign sponsors. Thus, in the 1st quarter of this year only 9 approvals for such trials were granted. 2 of them are post-registration phase II studies. The rest 7 are registration studies, 4 of which refer to generic medicines, and 3 — to innovative drugs. The first of them is intended for usage in cardiology and supposes the participation of 158 persons, the second one — in gastroenterology (60 persons — minors from 1 month to 4 years), and the third one — in endocrinology (39 persons). Altogether 607 persons shall participate in the registration clinical trials of efficiency and safety sponsored by foreign companies and approved in the 1st quarter of 2012.

The observed structural changes of the market are bound to trigger concern. We remind that in case of local registration clinical trials we most often deal with repeated and therefore absolutely unnecessary and unjustified trials, undertaking of which in developed countries is considered unethical (*for more details see ACTO Newsletter No. 2*).

Concern is triggered also by the second important factor — the quality of such trials. Historically Russia was proud of high quality of international trials, confirmed, primarily, by the results of FDA and EMA inspections. For international trials ICH GCP standard is compulsory. But this standard is not necessary for local clinical trials, and compliance with it left to the discretion of sponsor of such trial. Taking into account the

fact that results of such trial are assessed only by Russian authorities, and the control over their proceeding is limited, the sponsors may unintentionally be tempted to sacrifice the quality in favor of economy of time and funds.

Available information about results of inspections of local trial is bound to trigger concern. In the report of Roszdravnadzor at the "Pharma Circulation 2011" the following statement was made: "*Since 2010, along with the clinical sites conducting the international trials, medical institutions specializing in carrying out of local, including registration and post-registration, clinical trials of domestic and foreign manufacturers are included into inspections plans. During inspections of those clinical sites rather serious violations of the clinical practice rules have been brought to light.*" Thus, according to Roszdravnadzor, over the period from 2010 to the 3rd quarter of 2011 twenty eight centers were educed that had committed critical violations in the course of local clinical trials and 6 ones — in the course of international trials. I.e., the frequency of violations among local clinical trials is almost fivefold higher than among international ones. Among revealed violations there are significant protocol violations, incompliance regarding the procedures of investigational drug storage, lack of documents demonstrating that a clinical trial was conducted, enrollment of patients not meeting inclusion/exclusion criteria, conduct of a trial without approval (two centers) and absence of informed consent and inclusion of patients before they signed this consent (6 centers).

Summarizing the analysis of the market structure, one may state that negative consequences of adoption of the law "On Circulation of Medicines", namely the norm about compulsory registration clinical trials, started to show themselves fully in the 1st quarter of 2012. How far Russia will go this way, the future will show. On particular prospects of legislation revision we will settle a little later.

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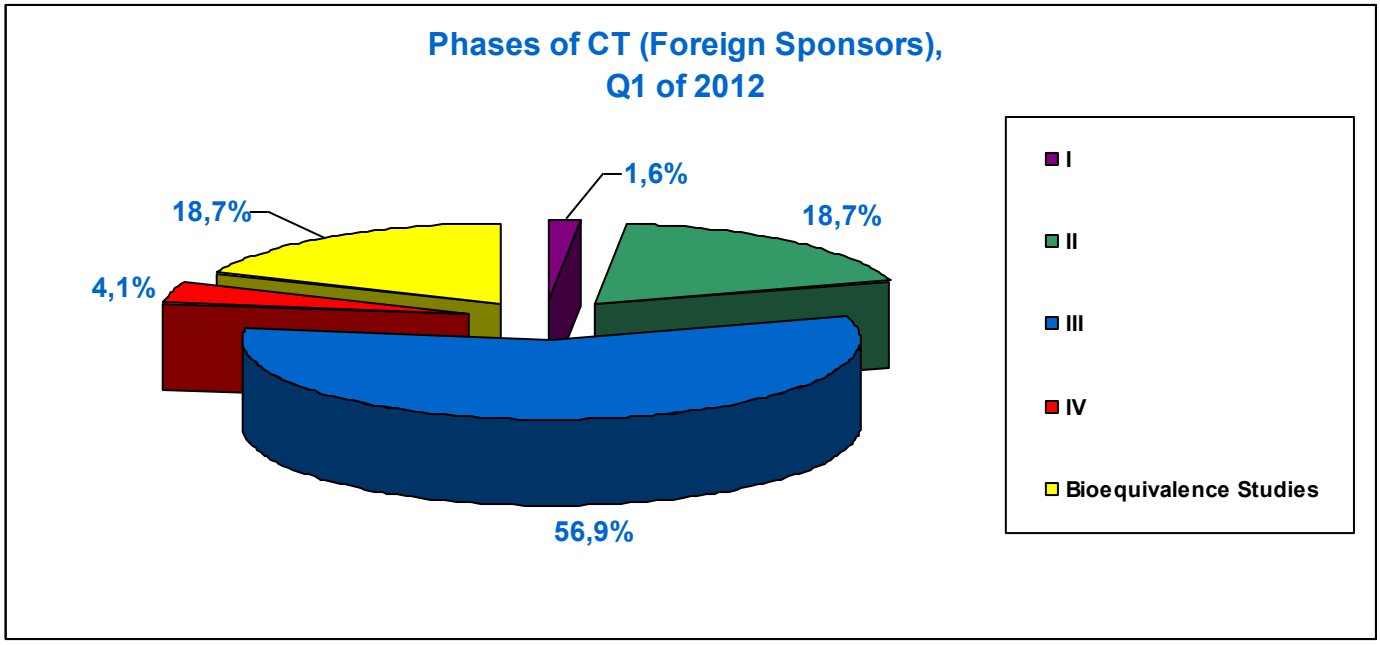
Data on the structure of clinical trials by foreign sponsors by phases in the 1st quarter of 2012 are represented in table 3 and diagram 4.

Table 3

Phases of CT (Foreign Sponsors), Q1 of 2012				
I	**II**	**III**	**IV**	**Bioequivalence Studies**
2	**23**	**70**	**5**	**23**

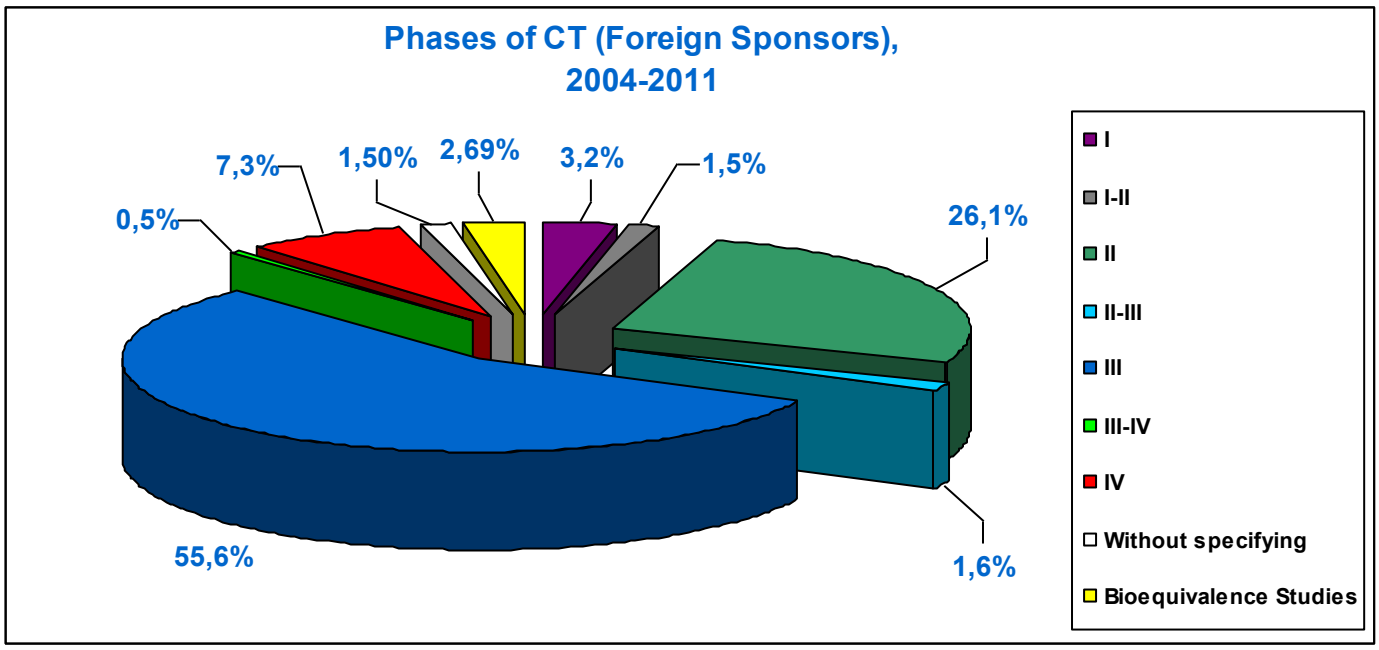
Data from www.grls.rosminzdrav.ru

Diagram 4



Comparing current quarterly data with averages for the last eight years (diagram 5) we can see that the main share is still occupied by phase III trials. But the trends that we observed following the results of the past year *(for more details see ACTO Newsletter No. 1, 3)* redoubled in the beginning of the current year. Thus, if in 2011 the share of bioequivalence studies in the whole volume of trials by foreign sponsors amounted to 4.5%, exceeding the average for preceding years almost by twofold, in the 1st quarter of 2012 it already reached 18.7%.

Diagram 5



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

At the same time the share of phase I studies decreased even more and reached 1.6% against 3.2% — the average for the last eight years (we remind that following the results of the past year it amounted to 2.8%). The cause of the sharp decrease of the share of early phase studies was repeatedly sounded by us in preceding

issues of the Newsletter. These are also consequences of adoption of the law “On Circulation of Medicines”, videlicet the prohibition of phase I studies by foreign sponsors with the participation of healthy volunteers. It only remains for us to add that both phase I international trials approved in the 1st quarter of 2012 are trials of medicines for treatment of oncological diseases, at that one of them supposes participation of oncological patients, and the other one — a peculiar group of patients with liver function abnormality of varying severity.

TIMEFRAMES FOR ISSUANCE OF APPROVALS

As it was promised in the preceding issue of the Newsletter, ACTO represents the results of monitoring of the timeframes for issuance of approvals for clinical trials for the whole year of 2011.

Thus, according to the data from the annual monitoring, in 2011 the average time to obtain an approval for conducting a clinical trial amounted to 130 days (table 4), while in law it must not exceed 57 days[1]. Permit for import of medicinal product is granted on the average within 30 days, while the legislative term is 12 days. Permit for import/export of biological samples can be received averagely within 34 days, while the legislative term in 19 days. Granting of approvals for protocol amendments takes 92 days, while the law gives 48 days for it. Granting of all other approvals (for trial prolongation, inclusion of new sites and enrollment of additional patients, etc.) takes averagely 69 days (necessary term is 35 days). The total time required for obtaining an approval for conducting clinical trial and an import/export permits reached 164 days.

Table 4

Timeframes For Issuing Approvals, 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**	**130**	**25**	**338**	**257**
To Import Medicines	**8/12**	**30**	**10**	**85**	**281**
To Import/Export Biosamples	**13/19**	**34**	**5**	**103**	**584**
To Make Amendments to the Protocol	**34/48**	**92**	**13**	**237**	**344**
Other Approvals (to Prolong Clinical Trials, To Include New Sites, To Enroll Additional Patients, etc.)	**25/35**	**69**	**12**	**284**	**513**
Total Timeframes for Obtaining Approvals to Conduct Clinical Trials and To Import/Export	**54/76**	**164**	**~**	**~**	**~**

Data from timeframes' monitoring of ACTO

Despite our expectations, average timelines for issuance of approvals at year-end decayed in comparison with data from monitoring for the 1st half year of 2011 *(see ACTO Newsletter No. 1)*. Thus, the time to obtain an approval for conducting a clinical trial and the total time required for obtaining an approval for clinical trial and an import/export permits increased by 4 days. Terms for issuance of permits for import of medicinal

[1] 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

products increased by 2 days, for approvals of protocol amendments — by 1 day. Terms of granting of permits for import and export of biological samples remained unchanged. The only index showing a little improvement is additional submissions (trial prolongation, inclusion of new sites and enrollment of additional patients, etc.), average term of which decreased by 2 days.

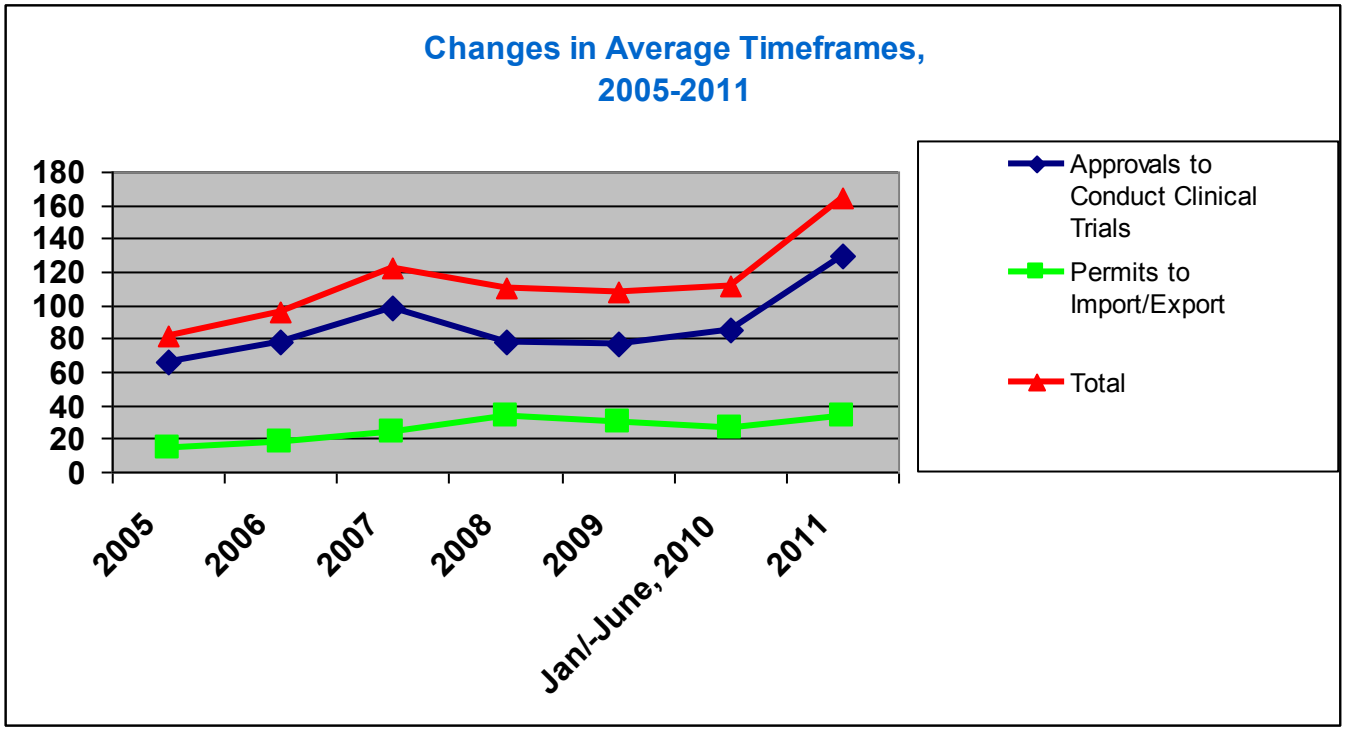
For comparison of the timeframes for issuance of approvals for clinical trials summarizing the results of 2011 with the terms documented in the preceding years see table 5 and diagram 6.

Table 5

Changes in Average Timeframes, 2005-2011							
	2005	2006	2007	2008	2009	Jan/-June, 2010[2]	2011
Approvals to Conduct Clinical Trials	66,3	77,8	98,9	77,6	77,0	85,2	130,0
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	164,0

Data from timeframes' monitoring of ACTO

Diagram 6



[2] 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.

Statistics of violation of established deadlines for issuance of approvals is represented in table 6.

Table 6

Violations of Timeframes, 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	1,8%	98,2%	4,7%	30,6%	47,1%	12,3%	3,5%
To Import Medicines	4,6%	95,4%	12,0%	15,9%	40,7%	17,1%	9,7%
To Import/Export Biosamples	13,2%	86,8%	18,6%	36,0%	24,9%	5,7%	1,6%
To Make Amendments to the Protocol	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.)	15,7%	84,3%	20,8%	19,9%	27,9%	11,5%	4,2%

Data from timeframes' monitoring of ACTO

For some kinds of approvals the share of timely issued documents increased. For example, if in the 1st semester of 2011 no approvals for conducting clinical trials had been granted at term, at year-end the share of timely granted approvals amounted to 1.8%. Almost by twofold the share of timely issued permits for biological samples import/export increased — from 7.2% to 13.2%. By fractions of percent the number of timely issued permits referring to other submissions (from 15.5% to 15.7%). At the same time, the share of timely issued approvals for protocol amendments slightly decreased — from 13.3% to 12.7%.

Despite the fact that the share of timely issued approvals increased, simultaneously the other index decayed. Thus, for the majority of positions the share of approvals issued with a delay in 4 times and more increased in comparison with the 1st semester of 2011. For example, if in the 1st quarter of 2011 with fourfold and more violation 1.4% of clinical trial approvals had been issued, at year-end this index rolled over 3.5%. The share of permits for import of medicinal products granted with big delay increased from 7.1% to 9.7%. In the 1st semester no permits for import/export of biological samples and approvals for protocol amendments issued with fourfold and more term violation, while at the year-end these indices amounted to 1.6% and 1.4%, respectively.

Remarkably, the establishment of clear timeframes of work of the regulatory system was named by the Ministry of Health and Social Development as one of the main advantages of the new legislation. But, as practice shows, the result so far is the opposite of the promised one. Thus, the terms of issuing of the clinical trials approvals by the Ministry of Health and Social Development exceed the worst metrics of the work of Roszdravnadzor by one third.

Analyzing main causes of violation of the timeframes for issuance of approvals summarizing the results of the first semester *(see ACTO Newsletter No. 1)* we talked about three factors. Firstly, it was rebuilding of the

regulatory system. Secondly, it was sending of some documents (primarily, various annexes to approvals) via mail, despite repeated requests of companies to start hand-delivering them. Thirdly, it was the requirement of repeated filing of application for trial after the expert examination.

As for sending documents via mail, some positive changes took place there. In the second half of 2011 at the non-public authority of Department for State Regulation of The Circulation of Medicines of the Ministry of Health and Social Development an opportunity of receiving right in hands the documents previously sent via mail aroused. But to use this way companies need to ask the Ministry of Health and Social Development department employees about it proactively. Additionally, there still remain a significant number of companies that wish to elude sending documents via mail, but have not received the opportunity yet. But the companies that have got the opportunity of receiving the documents right in hands also are by no means in ideal conditions. Hand-delivering of the ready approvals leaves a lot to be desired, primarily because of shortfall of the human resources allocated by the Ministry of Health and Social Development for this purpose.

Besides the described issues with receipt of issued approvals there is another unresolved problem also influencing the total timeframes. It is requirement for repeated filing of an application for the clinical trial after expert examinations *(see ACTO Newsletter No. 3)*. In more detail we will look at this question in the section devoted to legislative initiative analysis.

SITUATION WITH CLINICAL TRIALS OF MEDICINES FOR TREATMENT OF HIV/AIDS, HEPATITIS C & TUBERCULOSIS

In this issue ACTO opens a new column which will be devoted to analysis of the situation with various therapeutic indications/diseases clinical trial in Russia.

For the first issue the object of the analysis are clinical trials of medicines for treatment or prevention of HIV/AIDS, and also hepatitis C and tuberculosis, that often are being present in HIV positive patients. Statistical sampling of clinical trials was formed based on studied therapeutic indications (treatment or prevention of HIV/AIDS, hepatitis C and tuberculosis), but not patient enrollment criteria (presence of the above diseases in the patients).

It is a well-known fact that in general the engagement of Russia into the global process of clinical trials is still very low. For example, such index as number of active trials per 1 million of population, in our country is several tenfold lower than in leading countries. If in the USA per 1 million people there are 46.9 clinical trials, in Canada — 72.4, and in Belgium — 82.5, in Russia there are only 3.4 ones. Assuming the capacity of the USA clinical trials market as a basis, one can say that the Russian potential is used only for 7%.

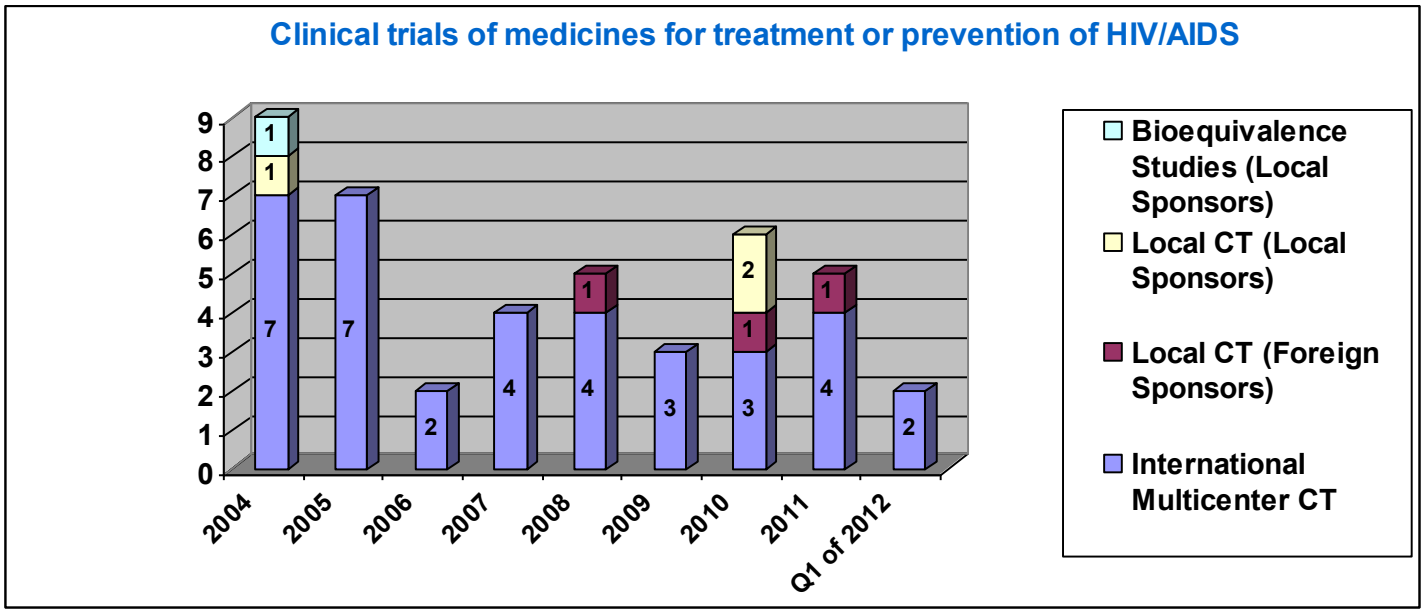
The question of placement in Russia of international multicenter clinical trials of medicines for treatment of hepatitis C and tuberculosis becomes particularly sharp because of two circumstances. Firstly, in recent 20 years for the first time in the history of treatment of hepatitis C a real breakthrough has been outlined. In 2011 FDA and EMA approved two innovative medications for treatment of hepatitis C — Incivo/Incivek (telaprevir) manufactured by Janssen and Victrelis (boceprevir) manufactured by MSD, which significantly improve the efficiency of standard therapy with ribavirin and pegylated interferon, and also give a chance for cure to those who had no response to standard therapy. According to the companies, in the pipeline there are some more promising molecules. Among them, first of all, we can highlight daclatasvir by Bristol-Myers Squibb and GS-7977 by Gilead Sciences.

As for tuberculosis, where all the medicines are several tens of years old and the main issue is coping with multidrug resistance, two new molecules have entered the final phase of development. These are bedaquiline (TMC207) and delamanid (OPC6783) of Tibotec and Otsuka, respectively. The second circumstance is the requirement of the law “On Circulation of Medicines” to submit for registration in Russia data acquired with the participation of the Russian patients. Not having timely engaged Russia into international program, a company will then have to carry out a local clinical trial,, that can put into question the registration of the medicine at all. Thus, Victrelis and Incivo are forced to undergo such registration clinical trials as soon as research programs for the products had been performed without the participation of Russia.

Let us see in more detail, what clinical trials referring to HIV/AIDS, hepatitis C and tuberculosis took place in Russia since 2004.

From 2004 to the 1st quarter of 2012 in Russia 43 clinical trials of medicines for treatment and prevention of HIV/AIDS were initiated by Russian companies and placed by foreign sponsors (diagram 7). Overwhelming majority of them are international multicenter clinical trials. During these trials 17 molecules have been studied within 8 years. 3 studies were undertaken by foreign sponsors, but only in the territory of Russia. These are trials of Wobenzym (manufacturer — Mucos Emulsions), Isentress (manufacturer — MSD) and Maraviroc (manufacturer — Pfizer). Russian companies in those 8 years initiated only 3 trials: Research Institute of Extremely Pure Drugs of Federal Medical and Biological Agency studied in the phase I reactogenicity, safety and immunological potency of CombiVICHvac and DNK-4 vaccines, and the Immunology Institute undertook limited phase I trials of Vichrepol. One more domestic manufacturer initiated a bioequivalence studies of Ribavirin-Verte and Rebetol. There were no phase I studies among trials of foreign sponsors. Overwhelming majority of IMCTs were phase III studies.

Diagram 7



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

Annual number of patients planned to be enrolled into trials of medicines for treatment of HIV in those years was extremely small and amounted, according to the information from the registry, from 101 persons in 2007 to 388 persons in 2005. For comparison, annually about 40—45 thousand people are enrolled in international multicenter clinical trials in Russia.

From methodological point of view it is rather difficult to assess correctly the situation with clinical trials in Russia in reference to global situation using quantity indices — for example, the number of patients enrolled or trials undertaken. As for the first figure, the number of patients stated both in Russian and international registers never reflects the real number of enrolled patients. It may be either surpassed or underrun. Moreover, it is very difficult to separate from trials referred to in the international register those ones that match our criterion (treatment or prevention of HIV/AIDS) because of great information volume and lack of option of automated search by this criterion.

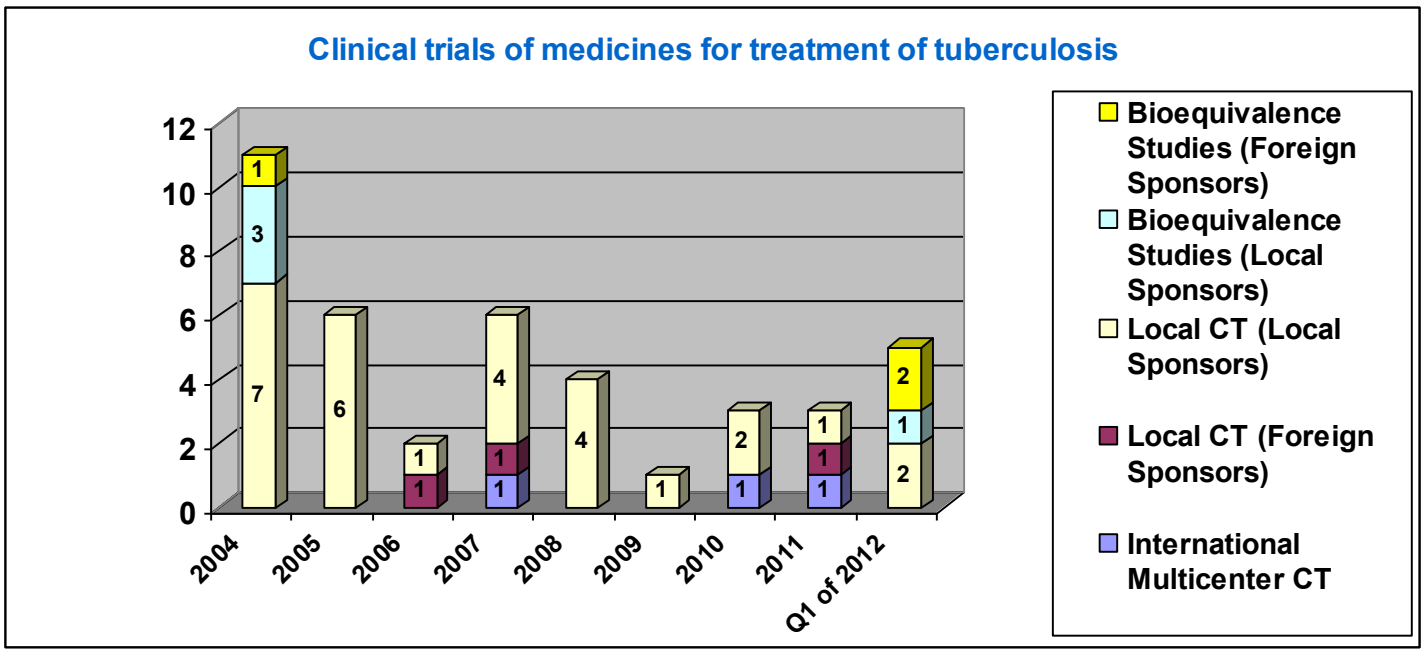
It seems that in some measure two criteria can help to estimate to what extent Russian patients can acquire early access to new medications. We should analyze, firstly, how many medicinal products approved by FDA since 2004 have been studied in Russia, and, secondly, what percent of molecules currently in the pipeline is studied in Russia inter alia. Since 2004 FDA has approved 6 HIV treatment drugs. These are Aptivus (tipranavir), Prezista (darunavir), Isentress (raltegravir), Selzentry (maraviroc), Intelence (etravirine), and Edurant (rilpivirine). All the medicines, apart from Edurant, marketing authorization of which is scheduled for 2012, are already present in Russia. And all these medicines have been in due course studied in Russia, so our patients had acquired the access to the therapy that consequently has been recognized as efficient. At the same time, according to the Pharmaceutical Research and Manufacturers of America (PhRMA) report «Medicines in Development for HIV/AIDS»[3] from December 1, 2011, at that moment 88 molecules and vaccines for HIV treatment and prevention were in the pipeline. While in Russia, as it was mentioned above, in 8 years fivefold less (17) molecules were studied.

It should be mentioned that unfortunately Gilead Science Company — one of the key players of the HIV treatment market (Tenofivir and its new prodrug, Emtriva, Truvada, Atripla, Elvitegravir, new booster cobicistat, QUAD) and, until quite recently, hepatitis C treatment market (polymerase inhibitor HCV GS7977), doesn't still have a representative office in Russia. Absence of this company in the country has a significant negative influence to the number of clinical trials in the analyzed segment. Probably, in the nearest future the company will open its representative office in Russia, and this gap will be filled.

[3] http://www.innovation.org/index.cfm/FutureofInnovation/NewMedicinesinDevelopment/HIV-AIDS

As for tuberculosis, from 2004 to the 1st quarter of 2012 forty-one clinical trials of medications for treatment of this disease were approved in Russia (diagram 8). As distinct from trials of HIV treatment drugs, where IMCTs dominate, in this segment, on the contrary, we observe the overweight of efficiency and safety or bioequivalence studies of generics or "endemic" for Russia medicines undertaken by Russian manufacturers. In those years only three international trials came to Russia. They were dedicated to above mentioned bedaquiline of Tibotec Company. Enrollment of 100 patients was planned for these three clinical trials. The other promising drug — delamanid of Otsuka Company — has not been studied in Russia so far.

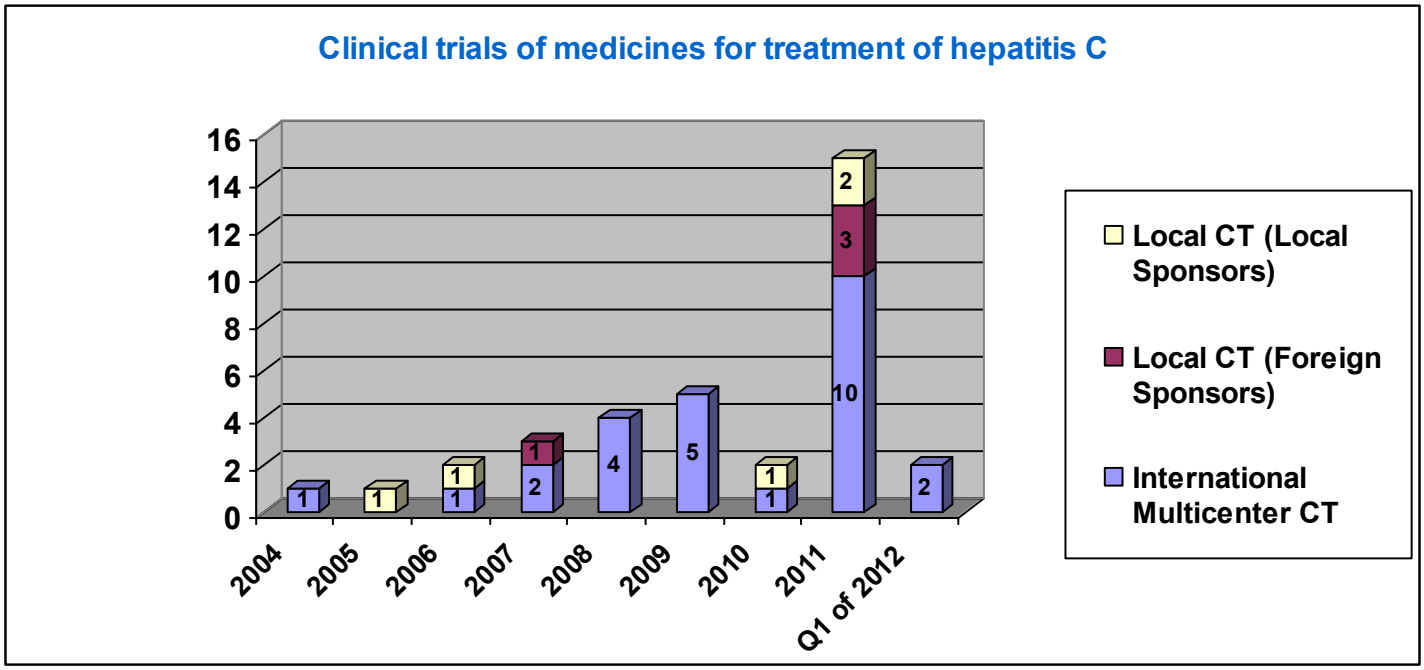
Diagram 8



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

As for clinical trials for the third nosology — hepatitis C — since 2004 in Russia 35 clinical trials were approved, overwhelming majority (74.3%) of which relates to international multicenter ones (diagram 9).

Diagram 9



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

In these years western companies placed in Russia four local clinical trials. Two post-registration trials of Pegasis drug were conducted by Roche Company in 2007 and 2011, the trial approved in 2011 was very large — for 1,000 patients. Two more local trials were also initiated in 2011 with the purpose of registration of Victrelis and Incivo, as it was already mentioned above. In all, according to the register, over 3.5 thousand people could have taken part in these trials. Russian companies in these years initiated five clinical trials, in two of which biosimilars of peginterferon-alfa2b (manufacturers — Pharmaktivy and Biokad Companies) are studied.

In international and local clinical trials from 2004 to 2011 western companies studies 18 new molecules. At the same time, according to PhRMA report «New Medicines in Development for Infectious Diseases 2010»[4], threefold more drugs were in the pipeline at that time — 52 ones.

[4] http://www.phrma.org/sites/default/files/422/infectiousdiseases2010.pdf

LEGISLATION INITIATIVE REVIEW

Proposal of Federal Antimonopoly Service for revision of the law "On Circulation of Medicines"

In the beginning of March 2012 the Federal Antimonopoly Service (FAS) came up to the market participants with the proposal to discuss amendments to the law "On Circulation of Medicines", which had been prepared by the FAS. A trigger for its work in this direction was a commission from Vice Chairman of the Government of the Russian Federation I. I. Sechin from September 19, 2011. According to this commission FAS and the Ministry of Health and Social Development should have undertaken an analysis of the current drug registration and clinical trials approval system, and also prepare proposals for improvement of transparency of decision-making.

Executing this commission in the end of the past year FAS undertook an inspection of the Ministry of Health and Social Development practice of drug registration and clinical trial approval. Total results of the inspection and proposals for improvement of the system were manifested by the antimonopoly service in the beginning of the current year. The conclusions were rather serious: during undertaken measures FAS educed significant number of violations of the timeframes for issuance of approvals and also identified a range of issues of legal nature. A result of the work of the Service became one more governmental commission, under which the Ministry of Health and Social Development and FAS had to prepare their proposals for the revision of the current legislation.

But the market participants are still waiting for any proposals from the Ministry. Instead, the Antimonopoly Service prepared and offered for airing its own variant of amendments. On March 5, 2011 a meeting of the Expert Council of the FAS for developing competition in the social sphere and healthcare took place. During the meeting the market participants had the opportunity not only to discuss the proposed amendments, but to come up with their own suggestions. On March 11, summarizing the results of the discussion, FAS published a text of the offered draft law on its website[5].

We would like to expand on the backbone of the offered amendments. The most significant of them seem to be proposals for abolition of local trials. The statement about obligation of such trials during the registration of medicines is, probably, the most criticized norm of the current law. This question, inter alia, was discussed during the session of the Commission for Modernization and Technical Advancement of the Economy on June 2, 2011, following the results of which an instruction of President of Russia Dmitri Medvedev was issued. According to it the Government of the Russian Federation should have prepared proposals for abolition of local registration clinical trials by September 1, 2011. But no proposals were made within the indicated period.

So, the amendments by FAS were the first real step in this direction. Thus, FAS offered to acknowledge the results of international trials, abandoning their division on a territory basis. After consultation with the market participants the idea was broadened — it was offered to divide the processes of clinical trial and registration/marketing authorization, as it is made in the international practice, and as it had been made in Russia prior to adoption of the law "On Circulation of Medicines". It means that an applicant must first undergo all trials and tests (both preclinical and clinical), then form a dossier on the ground of collected data about efficiency and safety of the drug and only after that apply for registration. At that the results of the trials can be accepted only if appropriate trials were conducted in compliance with GLP and GCP.

Amendments are also offered to clarify the order of generics registration and registration dossier amending, institute an accelerated registration procedure for orphan drugs and forgo the necessity endorsement of registration.

[5] http://www.fas.gov.ru/legislative-acts/legislative-acts_50891.html

But besides the registration process the FAS's amendments also bring advanced ideas to the sphere of clinical trials. Thus, one is bound to welcome the proposal to abandon the accreditation of the medical institutions — a clearly excessive administration barrier which is not used in the international practice and significantly limits the access to participate in the trials for medical institutions. Also FAS has heard the proposals of the market participants for solution of other issues complicating the process of trials undertaking in Russia. Therefore it included into the text of amendments the renunciation of the requirement for five year experience of study participation for principal investigators (it is offered to return a two-year experience that had been in force before the adoption of the new law) and the expunction of the artificial classification of the clinical trials by their purposes.

Summarizing all above mentioned, one can say that the adoption of the offered amendments could have allowed solving many existing problems and doubtlessly would have brought the Russian legislation more in line with the international practice of regulation of the sphere.

As it was already mentioned, the draft law was prepared and submitted for general public judgment in the beginning of March. In the meantime it was referred to the Ministry of Health and Social Development. But the specialized Ministry gave no reply to the proposals. To inquiries made by journalists a stock answer was given: "The Ministry of Health and Social Development is studying the law revision proposals of FAS like other offers sent to the Ministry". Apparently, the Ministry decided, as it had happened earlier, to ignore the topic that is unpleasant for it. All the more so, as the situation is appropriate — the closer are anticipated changes in the Government, the quitter the agency activities become. In all appearances, we will have to return to the theme already after the assignment of the new Government.

Draft of administrative regulations of Ministry of Health and Social Development of the Russian Federation on issuing approvals for clinical trials

We already mentioned one of the practical problems influencing the timeframes for issuance of approvals for clinical trials — requirement for repeated filing of the application for clinical trial. This requirement is absurd on its own, and the more so in the contest of announces of the Ministry of Health and Social Development that the new legislation allowed to build an efficient and transparent regulatory system. But despite the undoubted superfluity of filing of two successive applications in order to get one approval document, the Ministry, it seems, tries to retain the practice at all means.

As it was already told in Newsletter No. 3, in the end of 2011 the Ministry of Health and Social Development developed and sent on approval a draft of administrative regulations on issuing approvals for clinical trial. In this draft one of the most important stages was omitted — sending of documents by order of the Ministry of Health and Social Development for expert examinations and decision making following their results. As ACTO mentioned in its comments to the draft, it was raising a threat of, firstly, the further continuation of the repeated application filing practice, and, secondly, falling out of the statutory regulation field of the most important part of issuing approvals - the expert examination. These concerns were heard by the Ministry of Economic Development that was investigating the draft as part of its function of governing response assessment.

As a result the Ministry of Health and Social Development prepared a new version of the regulations with which the market participants were able to get familiar in the middle of February. It includes the description of stages of assignment and undertaking of the expert examination, that were absent in the original version, but the problem of repeated application filing was not solved. Its actions carrying out after the expert examination the Ministry of Health and Social Development shaped as reference rule to the order of clinical trial approvals granting for registration clinical trials. Thus, it is assumed that on the final stage the applicant still will have to file the application for clinical trial and the document suite repeatedly, and the Ministry of Health and Social Development — to check their completeness.

ACTO concerns referring to regularizing of the malpractice of repeated filing of the application in a normative legal act were shared by Ministry of Economic Development. Thus, in its report on the draft of the regulations from March 14 the Ministry pointed out: "*At the same time the point 41 of the draft regulations already stipulates the provision by an applicant of application and documents named in the point 17 of the draft regulations. We bring to notice that a part of provided documents listed in point 16 coincides with the documents called in point 17. For another thing, point 44 of the draft regulations already stipulates the check of completeness and authenticity of the information and coherence of the provided data. Thus, the above mentioned reference to the points 33—36 of the draft regulations leads to excessive doubling of actions either of an applicant (filing of application and part of documents) or the Ministry of Health and Social Development (check of application and documents that arrive for the second time*)".

As a result the draft with this and other remarks was again sent for follow-up revision. The market participants only have to wait for yet another version.

And at the same time in the beginning of March the Ministry of Health and Social Development published on its website information about availability of a new form of electronic application for getting an approval for clinical trials "in case of presence of conclusions of expert organizations about the possibility of conducting international multicenter clinical trials and post-registration clinical trials". This is how it is called in an instruction — Application #2. And now applicants will be unable to say that the second application is quite the same as the first one, because the form is different, although insignificantly. It once again confirms our assumption that the Ministry of Health and Social Development does not hurry to get rid of the clearly excessive requirement.

FOREIGN NEWS

On March 7, 2012 the Commissioner of the European Commission responsible for Health and Consumer Policy John Dalli addressed a meeting with representatives of pharmaceutical industry with his speech "Clinical Trials Directive — Meeting Patients' Needs". The session was devoted to revision of the European Clinical Trials Directive that is planned for the nearest future. There is no need to cite the whole speech of the Commissioner here. But we'd like to quote some of its statements to show what consideration is given to the sphere of clinical trials at the level of European countries.

Thus, here is a quotation from Commissioner John Dalli's speech:

"There has been a decline in clinical trials in the EU in recent years of about 15%[6]. At the same time, costs for bureaucracy and resource requirements to handle paperwork have doubled, and delays have increased by 90%.

These trends worry me, as I am sure they worry you.

They worry me as Commissioner responsible for health. And they worry me as member of a Commission which is committed to building a Europe fit for the future, to stimulate growth and to contribute to job creation.

Clinical trials are crucial for the development of new medicines, and equally to improve and refine treatments with existing medicines.

Clinical trials are also a key contributor to growth and jobs in the area of public health. Clinical trials mean research and investment, including inward investment from outside the Union. Today, clinical trials account for investments of over €20 billion per year in the EU."

All that is left to do — to hope that this level of understanding of importance of the clinical trials sphere will come to Russia sooner or later.

[6] As reference: according to the website www.clinicaltrials.gov as on April 18 in European countries 9448 clinical trials are in progress, of which 2374 in France, 2116 in Germany, 1715 in Great Britain, 889 in Belgium. We remind that, according to the Ministry of Health and Social Development, in 2011 in Russia 567 approvals for clinical trials were granted, of which 370 for IMCT