ACTO

ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

ACTO NEWSLETTER №3

Q4 2011 and summary of 2011 results

MOSCOW 2012

CONTENTS

SUMMARY

As surprising as this may be, the overall results for the Russian clinical trials market in 2011can be considered acceptable and on a number of indicators even positive.

The main challenges that market participants faced in 2011 could be attributed to the implementation of the law "On Circulation of Medicines", either caused by oversights in the legislation itself, or in the practical application of said legislation. These challenges have been resolved over the course of the year. The process of importation of new medicinal products for clinical trials and establishment of necessary guidelines for patients' insurance have been put in place by the middle of the year, by means of issuing respective government orders. The accreditation of medical organizations had been brought to a breaking point by reason of inability of authorities to issue accreditation certificates within the specified timeframe, but the issue had been resolved just in time to avoid a crisis. Several unresolved issues have been put off to the 2012 agenda — administrative, which are related to the functioning of the regulatory approval system and fundamental – inherently created by the law "On Circulation of Medicines" itself.

The figures from the Ministry for Health and Social Development over the past year give some hope for the possibility of market growth in 2012. The Health Ministry granted approvals for 567 clinical trials, of which 370 were international multicentre clinical trials. Approvals for 370 of such trials make a record number: never in the entire history of international trials conducted in Russia have so many approvals been given in a particular year.

Based on 2011 results we have noticed significant growth in the number of local registration studies of generic drugs conducted by foreign companies in comparison with previous years — most likely this can be linked to the requirements of the new law. At the same time, the actual number of local registration trials of innovative drugs conducted by foreign companies stays relatively the same. This may be due to the fact that it is more difficult to commence such type of a trial and more expensive to conduct it. Nevertheless, the first trials are already underway. According to our figures, international companies are currently conducting 4 local registration trials of innovative drugs in Russia.

As for the trials of innovative drugs conducted by Russian manufacturers, in comparing 2011 results with those of 2009, the decline in this segment amounted to 35%. It is possible that this decline is the result of the new law's intent to build local trials into the registration system, as now it is only possible to commence such trials if you have already launched the registration process.

But we did not limit ourselves to the 2011 results in this newsletter. A separate topic for discussion is the inadequate maintenance of the registry of clinical trials. Pursuant to the order of the Ministry of Health itself, the registry entry must include the name of the protocol and information about the sites. The lack of this information does not allow patients in Russia to choose a trial in which they want to participate. Furthermore, it hinders the ability of the public to evaluate the trials on the basis of which a given medication has been registered. In addition, the Ministry's decision to use continuous numbering of approvals (previously, numeration was re-set annually), may in the future lead to complications in patients' trial insurance, as there are only three characters in the individual identification code allotted for the approval number.

Finally, in November, Russian media sources picked up inaccurate information about deaths in clinical trials, originally published in the British newspaper *The Independent*. ACTO's efforts to stop further dissemination of the misleading information by Russian media became the third subject for this Newsletter.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET IN 2011

Q4 results

In the fourth quarter of 2011, the Health Ministry granted approvals for 234 clinical trials, of which 122 were for international multicentre clinical trials (IMCTs) (Table 1).

As compared to the fourth quarter of 2009[1], we can see overall growth in the numbers of approvals granted for all types of clinical trials, except for the local trials of Russian sponsors.

Table 1

Approvals for Conduct of Clinical Trials: Q4 of 2011 vs. Q4 of 2010 and 2009						
	Total	**International Multicenter CT**	**Local CT (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CT (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
Q4 of 2011	**234**	**122**	**22**	**16**	**31**	**43**
Q4 of 2010	**36**	**26**	**1**	**0**	**6**	**3**
Q4 of 2009	**182**	**100**	**11**	**5**	**40**	**26**
Q4 of 2011 vs. Q4 of 2009, %	**28,6%**	**22,0%**	**100,0%**	**220,0%**	**-22,5%**	**65,4%**

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

As it is evident from Table 2 and Diagram 1, the Health Ministry is consistently increasing — from quarter to quarter — the efficiency of the regulatory approval system (measured in part by the number of approvals granted). The total number of clinical trials approved almost doubled from Q III to the Q IV of 2011. In comparison with the third quarter, we see that the number of approvals for each type of trials increased in the fourth quarter. As for other types of trials, such as local trials by foreign sponsors, and bioequivalence studies by foreign and Russian sponsors, the total numbers approved in the fourth quarter exceeded those of the previous three quarters combined.

Significant growth in the number of bioequivalence studies towards the end of the year — 23 approvals granted for the first three quarters, and 59 in the fourth quarter alone — may be explained by an assumption that the challenges that had lead to a dramatic contraction of this market segment in the first half of 2011 have been resolved (*for more details see ACTO Newsletter №1)*. Here we mainly refer to the requirements to present your own preclinical data to register generics; meeting such requirements held up manufacturers for a certain amount of time. It is also worth noting that on November 23, 2011 the Health Ministry issued Order No. 1413 regarding the format of the registration dossier. According to this Order, now generic manufacturers may present references to published data on the trials of the original products. This order is unlikely to have a significant impact on the statistics — it is more likely that by now some companies have already managed to

[1] It would be counterproductive to compare Q4 2011 with Q4 2010, because, as we know, the new regulatory approval system after the transfer of approval authority to Ministry of Health began working only in the middle of November 2010 and the number of approvals granted in the last quarter of 2010 was negligible as a result of such delay (see Table 1).

conduct preclinical trials, presented results and received approvals for further trials. But this is just our interpretation — the true reason behind such growth in bioequivalence studies remains unknown.

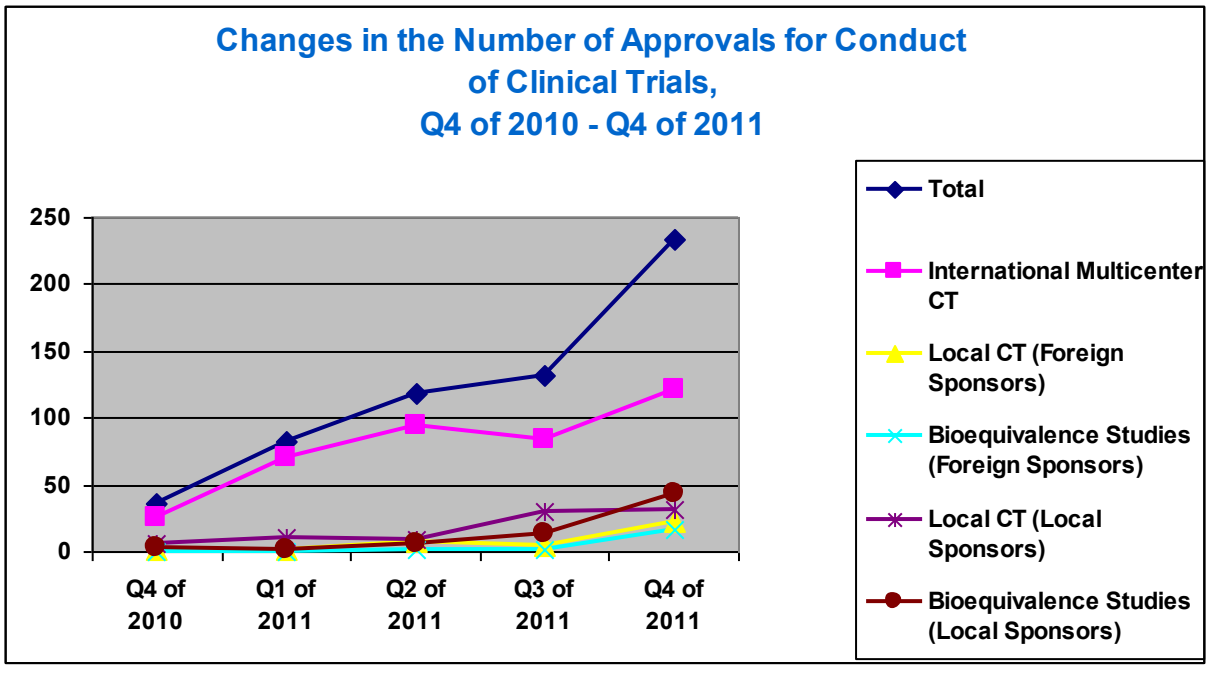
The dynamics of local trials and bioequivalence studies conducted by foreign sponsors will be considered and analysed in more depth at a later time, when we present annual results.

Table 2

Approvals for Conduct of Clinical Trials: Q4 of 2010 - Q4 of 2011						
	Total	**International Multicenter CT**	**Local CT (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CT (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
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**

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

Diagram 1



2011 results

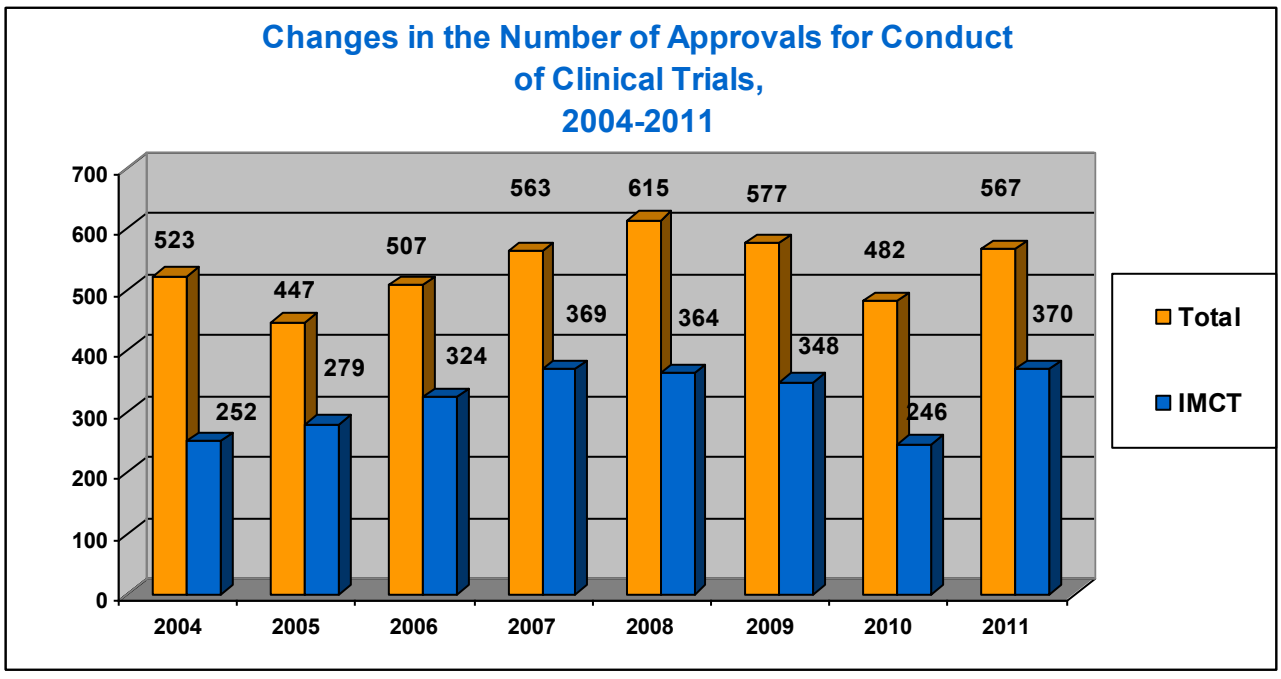
In analyzing the results of 2011 (Table 3), we can conclude that crisis of 2010, created by the reorganisation of the regulatory approval system and transfer of approval authority from Roszdravnadzor (the Federal Service for the Supervision of Public Health and Social Development) to the Health Ministry, has been overcome. In 2011 the Health Ministry issued 567 approvals for clinical trials, of which 370 were for IMCTs. The number of IMCTs approved in 2011 was a record for the entire period since statistics began, in 2004. Earlier, the best result has been achieved in 2007, when Roszdravnadzor approved 369 international trials. Regarding the total number of approvals, higher numbers (compared to 2011) were reached in 2008 and 2009 (615 and 577 trials approved respectively) only. Diagram 2 shows the relative data on the total numbers of approvals and IMCT approvals, from 2004 to 2011.

Table 3

Approvals for Conduct of Clinical Trials: 2011 vs. 2010 and 2009						
	Total	**International Multicenter CT**	**Local CT (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CT (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
2011	**567**	**370**	**35**	**19**	**80**	**63**
2010	**482**	**246**	**30**	**6**	**123**	**77**
2011 vs. 2010	**17,6%**	**50,4%**	**16,7%**	**216,7%**	**-35%**	**-18,2%**
2009	**577**	**348**	**32**	**8**	**112**	**77**
2011 vs. 2009	**-1,7%**	**6,3%**	**9,4%**	**137,5%**	**-28,6%**	**-18,2%**

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

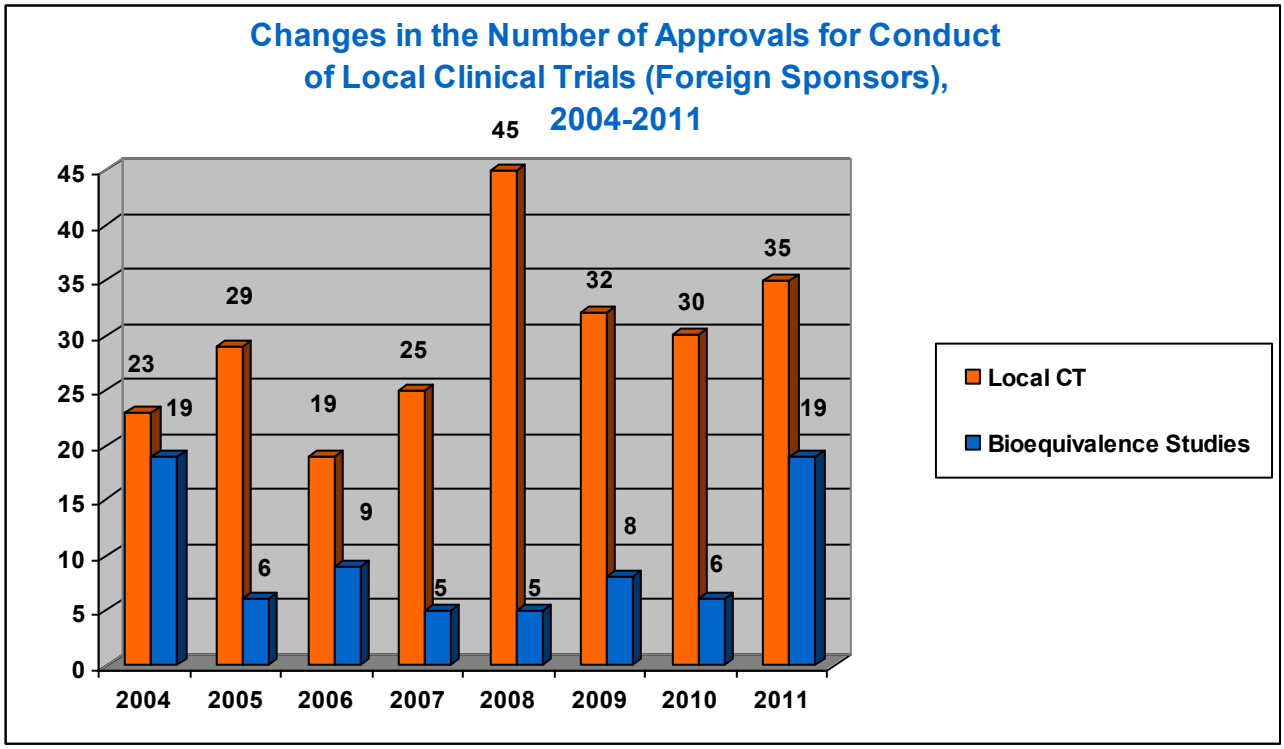
Diagram 2



We believe that the good results for IMCTs are a result of the hard work of the clinical trials department at the Health Ministry. The influence of other factors (such as, for example, the requirements for local clinical data to register medicinal products in Russia and, as a result, the need to include Russia in international programs) is unlikely to have been significant at that stage. However, despite the record results, there are numerous problems remaining with the functioning of the regulatory approval system. The most important problem is inability to issue approvals within the timeframe set out by law. In the next newsletter we plan to present the results of our year-long monitoring of approval timeline and an analysis thereof.

We can also see in Table 3 that in 2011, as compared with previous years, there has been growth in the number of bioequivalence studies conducted by foreign sponsors (19 trials in 2011 compared to 8 in 2009 and 6 in 2010). Nevertheless, such number of bioequivalence studies is not unheard of: in 2004, Roszdravnadzor also issued 19 approvals for such trials (Diagram 3). It is clear that this growth in 2011 was due to the implementation of the law "On Circulation of Medicines" with its requirement for local trials to register foreign medicinal products in Russia. We have not yet seen proportional growth in the number of local trials for efficacy and safety as compared to previous years: in 2011 the Health Ministry approved 35 trials (32 in 2009 and 30 in 2010). This is not a significant deviation: over the previous years from 2004 to 2010, the number of approvals granted varied from 19 to 45 annually (Diagram 4). Such result seems logical — it is much more difficult to make a decision about conducting full-scale clinical trials (and actual conduct of the trials is much more expensive), than bioequivalence studies.

Diagram 3

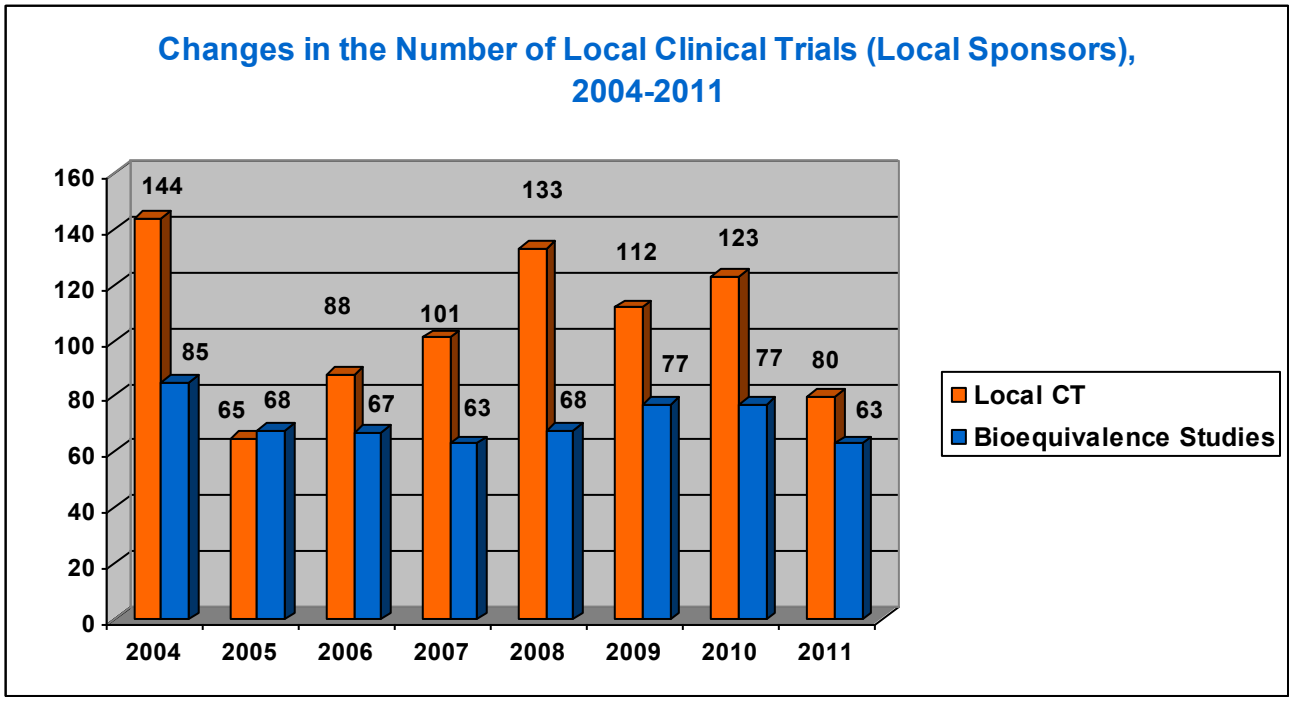


Data from www.grls.rosminzdrav.ru, www.roszdravnadzor.ru

However, we would like to note that positive dynamics in 2011 results, compared to 2009 and 2010, are only in the total number of trials and in the share of trials by foreign sponsors. Significant growth in the number of trials by Russian sponsors in the second half of the year could not entirely make up for a dramatic decline in same type of trials in the first half of the year. In comparing 2011 results with those of 2009, it is evident that the decline in the segment of local trials by Russian manufacturers amounted to (-28.6%), in bioequivalence studies, (-18.2%), and these figures were down 35% and 18.2% for 2010, respectively. Nevertheless, as we can see in Diagram 4, the results showing 63 Russian bioequivalence studies are much closer to the results of previous years than the recorded number of 80 local trials for efficacy and safety (a lower figure for these trials has been recorded only once, in 2005). It is possible that this decline is the result of the new law's requirement

that local trials should be built into the registration system as now it is only possible to commence such trials only if you have already launched the registration process (*for more details see ACTO Newsletter No. 1).*

Diagram 4



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

Let's take a closer look at the structure of a particular market segment, such as local trials by foreign manufacturers. As we can see in Diagram 3, such trials were conducted even before the law "On Circulation of Medicines" has been adopted and brought in a requirement for local clinical trials in order to register foreign medicinal products. In 2011 approvals were issued for 35 of such trials. Out of this number, 19 trials were post-registration Phase IV trials. The remaining 16 were local trials for efficacy and safety, conducted, as far as we can tell, to meet the requirements of the new law with the goal of registration in mind (so-called local registration trials). Among these local trials we found three trials for innovative foreign medicinal products which are already registered in the USA and the EU, conducted by international companies. Two medicinal products are intended to treat Hepatitis C and the third one is for treating post-herpetic neuralgia. Another registration trial of a cardiological medicinal product that is currently in the development stage and have not been registered anywhere is being conducted by an American company in Russia. The company's website says that the drug is undergoing clinical trial for registration purposes and such trial is conducted only in Russia. Eight trials are of generic medicinal products (not for bioequivalence) are also underway. Trials for efficacy and safety of generic medicinal products may be conducted either due to specific forms of medicinal product which does not allow to conduct bioequivalence studies (ointments, gels, solutions for intravenous injection, and so on) or for some other reason. Four more trials are aimed at researching vaccines, herbal medicines, etc.

* * *

Now we will look at the structure of the clinical trials market in 2011 (Diagram 5). Based on the year end results, share of international clinical trials in 2011 accounted for 65.3% of the total, slightly higher than the average for previous seven years (58.8%, Diagram 6). As we know, because of the sharp decline in all kinds of trials, share of international trials reached a record point of 81,5% in the first half of the year, gradually dropping to 63.6% in Q3 and finally to 52.1% in Q4. The share of trials by Russian companies is lower than average, compared to last seven years. According to the annual results, the share of local trials amounts to 14.1%, while the share of bioequivalence studies is 11.1% (the average numbers for the past seven years were 20.6% and 13.6%, respectively). There was almost no change in the referential share of local trials by foreign sponsors (5.5% to 6.2%) but the share of bioequivalence studies almost doubled from its average of 1.6% up to 3.4% in 2011.

Diagram 5

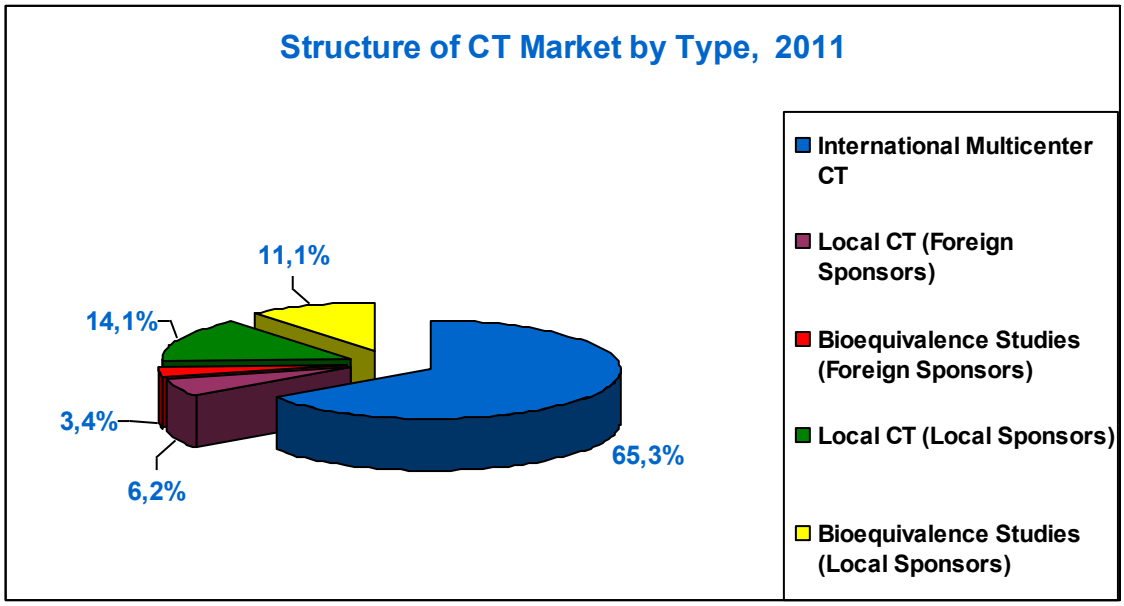
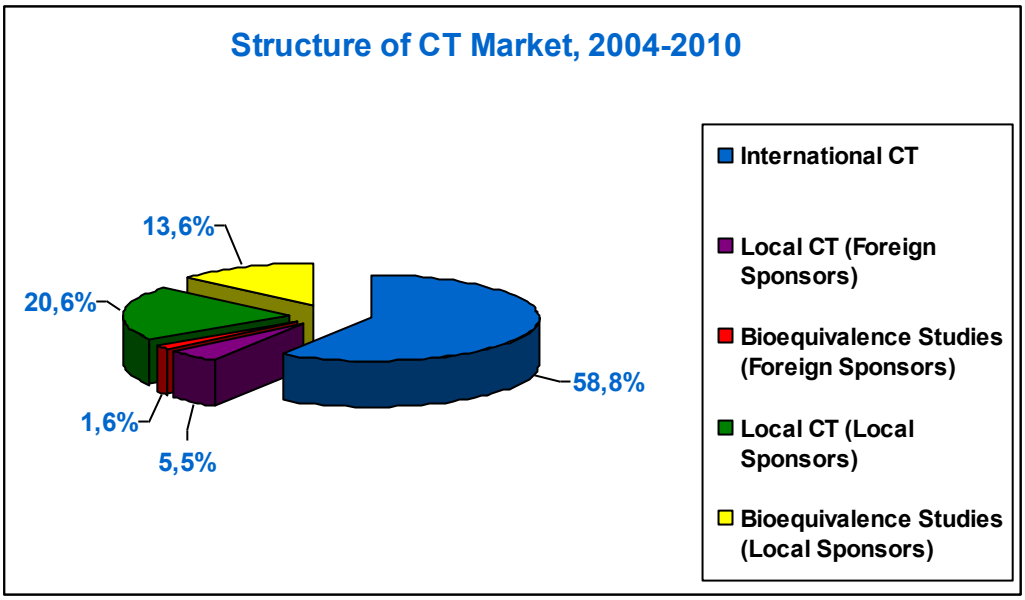


Diagram 6



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

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The data on the structure of trials by foreign sponsors for 2011 is presented in Table 4 based on a phase of a trial. This structure could be called a constant on the clinical trials market. Looking at last year results, there were no significant changes in this structure (Diagram 7). From the average market indicators (Diagram 8), only the share of bioequivalence studies stands out: it almost doubled, compared to seven-year average, reaching 4.5% against 2.4% average in previous years.

Table 4

Structure of CT Market (Foreign Sponsors) by Phase, 2011						
I	II	II/III	III	IV	Bioequivalence Studies	Without specifying
12	93	4	257	35	19	4

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

Diagram 7

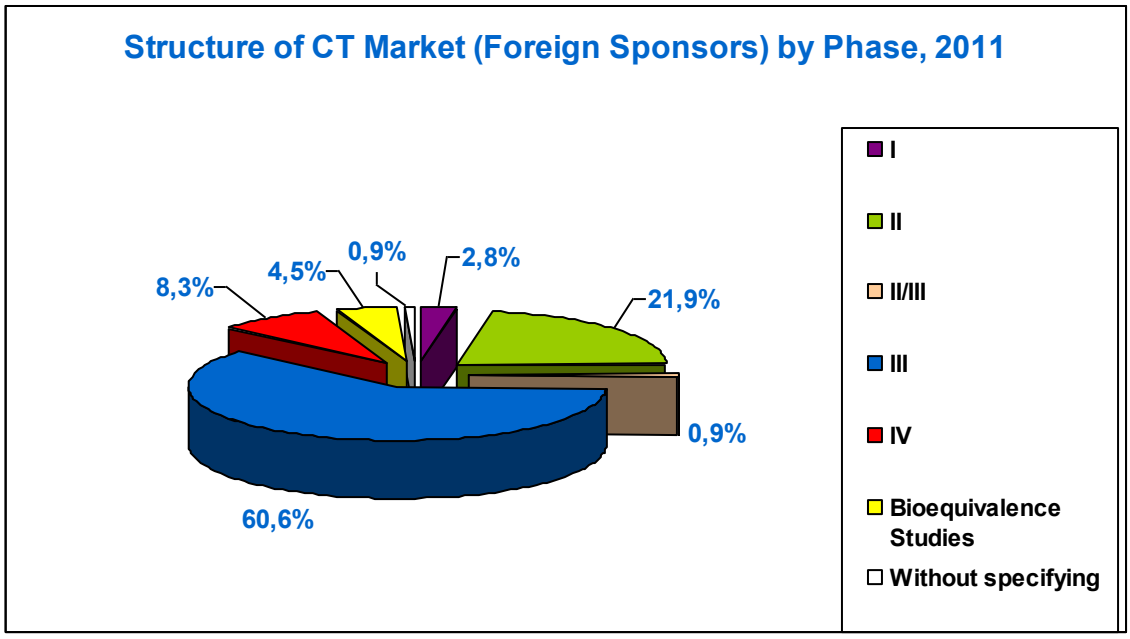
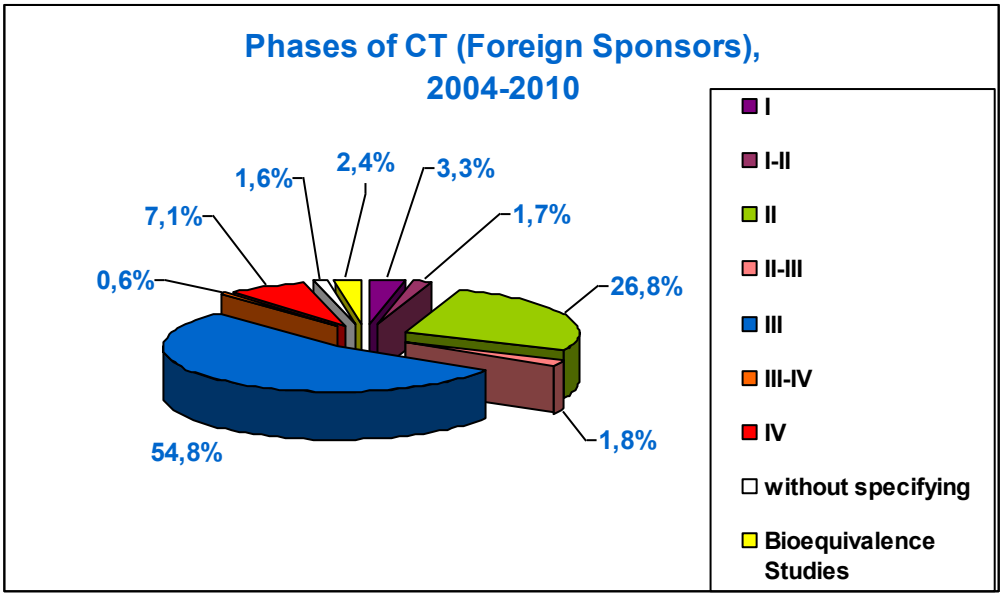


Diagram 8

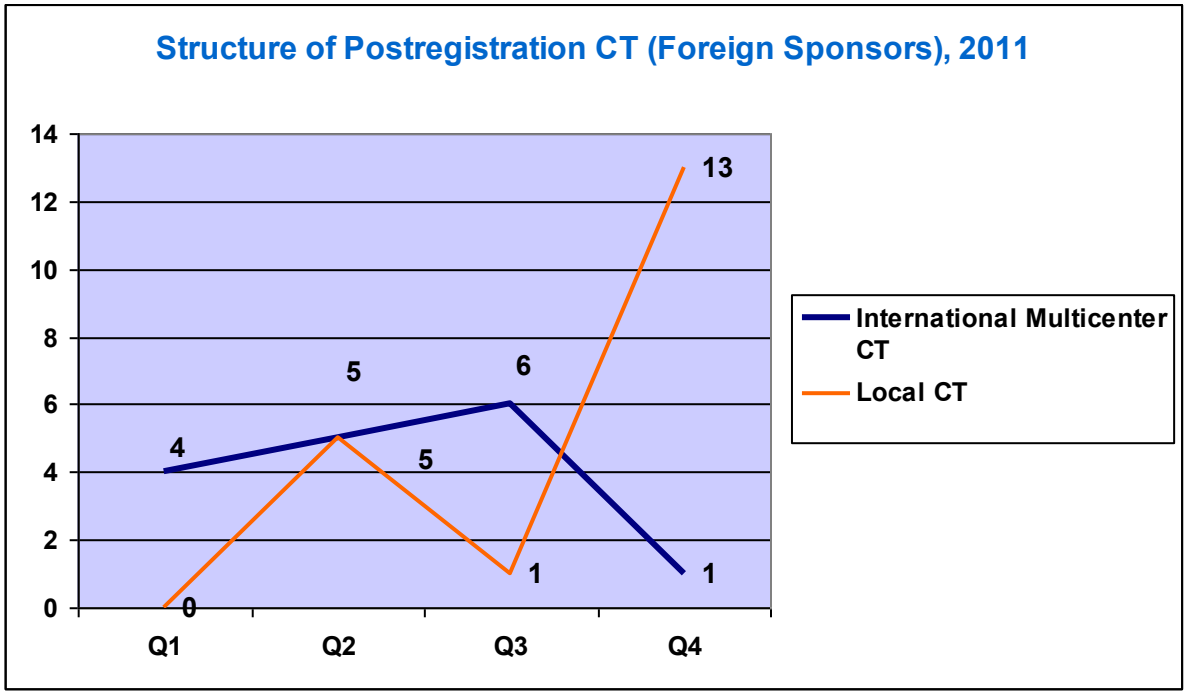


Data from www.grls.rosminzdrav.ru, www.roszdravnadzor.ru

As we know, the law "On Circulation of Medicines" prohibits Phase I trials of foreign medicinal products in healthy volunteers in Russia. In the first half of 2011 we saw a decline in the share of Phase I trials to 1.7% (down from 5.7% in 2010) and it should be noted that previously this indicator had been growing steadily since 2004. Based on 2011 results, the share of Phase I trials grew to 2.8%, getting closer to the 3.3% average for 2004—2010. It is worth explaining that we are referring to Phase I trials in patients, and not in healthy volunteers. Approved Phase I trials include studies of medicinal products for treatment of various types of cancer, rheumatoid arthritis, multiple sclerosis, cystic fibrosis, and hepatitis C.

It is also interesting to look at the structure of Phase IV trials by foreign companies. Diagram 9 shows the quarterly breakdown in local trials and IMCTs in the structure of post-registration trial. While in the first three quarters the overwhelming majority of post-registration trials were international multicentre ones and the number of local post-registration trials was insignificant, in the fourth quarter the distribution has changed and out of 14 approved Phase IV trials only one was an international multicentre one. The miniscule sample size does not allow us to draw any conclusions or make prediction about the presence of certain trends. However, we did find this indicator interesting and we plan to monitor its dynamics in the future.

Diagram 9



Data from www.grls.rosminzdrav.ru

MAJOR ISSUES FACED BY THE CLINICAL TRIALS INDUSTRY IN 2011

As expected, almost of the challenges faced by the Russian clinical trials industries in 2011 were in some way or another related to the implementation of the new law "On Circulation of Medicines".

In 2010 (or more accurately, in just five months of 2010), four government orders and twelve Health Ministry orders were issued for the purposes of regulating various aspects of the clinical trials market. Many of these orders were adopted in a hurry, without the necessary involvement and input from market participants. As a result, these orders not only created excessive administrative barriers and difficult working conditions, but sometimes, as in the case of the initial version of the insurance regulations, they were completely impossible to implement.

Three government orders created main challenges for market participants in 2011 — regulating the import of medicinal products, regulating compulsory insurance for clinical trial participants, and governing accreditation of medical institutions for the right to conduct clinical trials.

The reason for the eight-month halt on import of registered medicinal products was a technical mistake in the respective governmental order and the lengthy process of inter-departmental work to correct it. The original version of the document did not take into account that in clinical trials not only unregistered medicinal products (the ones being studied) but also registered ones (substances used as comparators, for accompanying therapy, and so on). As a result, the Health Ministry denied permissions to companies to import batches containing registered medicinal products. This continued until June 2011, when the corrections to the defective governmental order were finally adopted.

It is impossible to calculate the exact damage caused to the market by this eight-month ban on import of unregistered medicinal products. However, market participants have indicated that the consequences of the suspension of imports of registered medicinal products had been grave. Russia has missed out on a number of new international trials because once sponsors learned of the problems with importation of registered products they removed Russia from the list of participating countries. In addition, for many trials which did come to Russia anyway and were approved by the Health Ministry in the first half of 2011, the companies were unable to start patient enrollment on time, partly because of the suspension of importation *(for more details on the problem of registered medicinal products import, see ACTO Newsletter No. 1).*

At the same time market participants have been waiting for almost six months till a new version of the insurance rules has been harmonized with the amended law "On Circulation of Medicines". ACTO was forced to expend tremendous effort to get the corrections implemented in the new insurance guidelines. The changes affected the definition of insurance event, which can now be connected not only with the administration of a medicinal product to a patient, but with any involvement of a patient in a clinical trial. These changes can only be welcomed, as the rules are now more in conformance with international standards. In addition, the new rules solved the most important ethical problem of protecting confidentiality of personal information of participating patients.

The insurance mechanism formed after the new version of the insurance rules has been adopted can be considered satisfactory and sufficient, however, it is not easy to use and it adds extra workload to all parties. In particular, to protect patient data there is a 33-digits individual identification code (in international practice companies usually use a code with 6-8 digits). In addition, there is now a requirement to issue individual insurance policy to every patient, within the framework of the general policy for the trial. This requirement adds nothing extra from the viewpoint of insurance coverage, it only serves to complicate the amount of necessary paperwork and as a result leads to the risk of mistakes, loss of documents and data. The system in its adopted version has a whole slew of insufficiencies, some not yet discovered, but expected to come out in practical application of the system. We are of the opinion that the insurance system is in need of a serious overhaul in the near future *(for more details on the problem with changes to standard insurance rules, see ACTO Newsletter No. 1).*

As to the order governing accreditation, here the problem lays not in the legislative intent, but in the application of the regulations. This issue kept market participants in a state of high alert because after September 1, 2011, each medical institution without re-accreditation according to the new rules would not be able conduct clinical trials. In practice, the process of re-accreditation was extremely slow. By the beginning of August 2011, the Health Ministry had managed to re-accredit only 190 medical institutions, which slightly exceeded 30% of the minimum number of clinics needed for basic functioning of the market. Then in August 2011 the authorities issued 10 consecutive orders, thus accrediting another 465 institutions in one month. And by the end of the year, another 78 clinics received accreditation. As a result, 733 medical institutions currently have the right to conduct clinical trials *(for more details on the accreditation problem, see ACTO Newsletter No. 1, 2).*

To summarize, as of today all above-listed challenges have been resolved. Some of them, such as the problem with import of registered medicinal products, we hope have been resolved once and for all. Others, such as the accreditation issue, have possibly been solved only for the next five years (according to the governing order, clinics need to be re-accredited every five years). As to the insurance aspect, all that has been accomplished here is a temporary resolution of the issue as a response to the most pressing concerns, allowing market participants to insure patients in accordance with the law.

After the last hot topic (the issue with accreditation of medical institutions) has been resolved by September 1, 2011, the remaining items on the agenda are administrative questions related to the functioning of the regulatory approval system, and fundamental problems with the law "On Circulation of Medicines".

* * *

Timeframe for issuing approvals is a traditionally difficult issue in Russia. Waiting times were unsatisfactory under Roszdravnadzor, but according to results of six months of monitoring by ACTO, the Health Ministry has managed to perform even worse, bringing down the waiting time by 30.5%. The waiting time for regulatory approvals are actually two and sometimes as much as four times longer than the term set forth by the applicable law *(for the results of the waiting times monitoring of the first half of 2011, see ACTO Newsletter No. 1).*

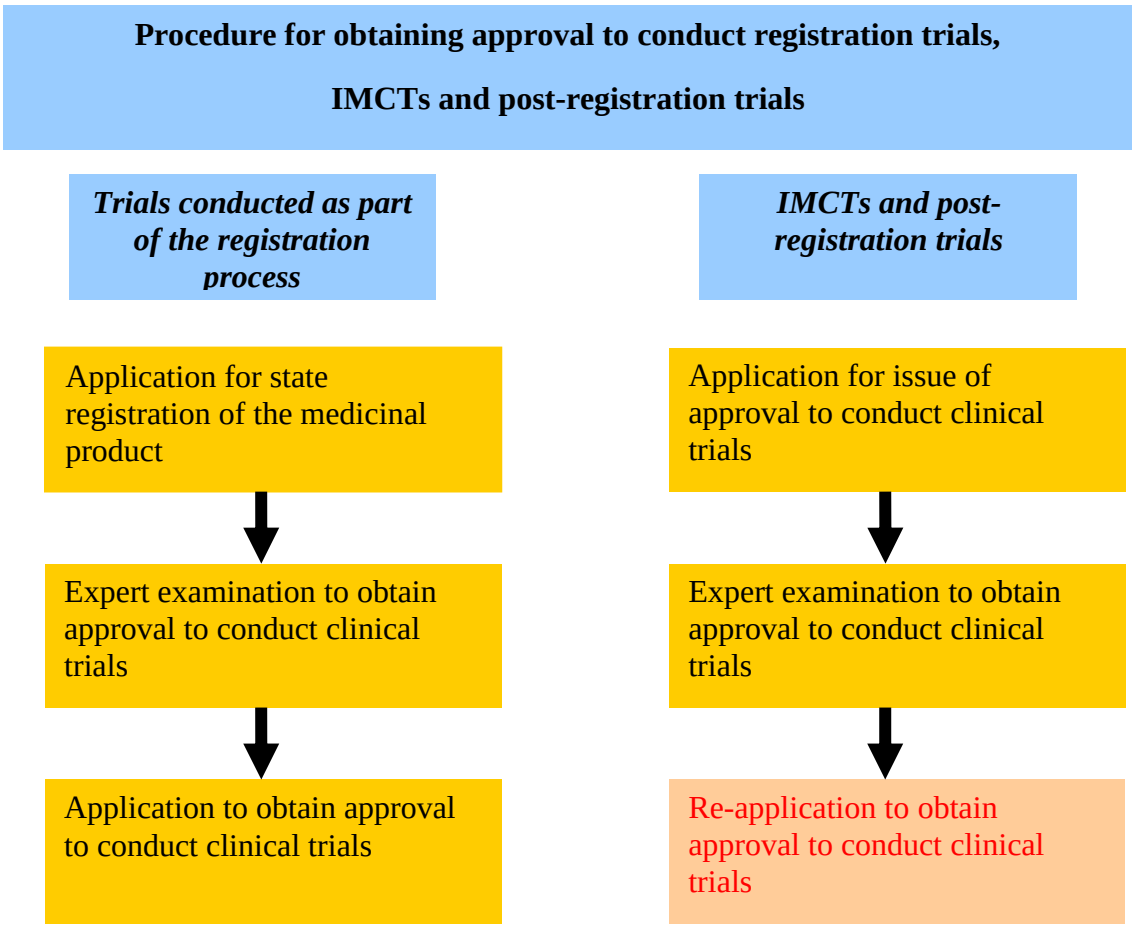
It would be possible to improve the statistics by using the following two approaches. First approach is to adopt adequate administrative regulations, clearly specifying timelines for carrying out all internal procedures and ensuring strict compliance to those regulations. Second approach is to remove the requirement to re-file documents to carry out clinical trials.

This requirement may seem absurd. But as experience shows, problems of this sort are often the most difficult to solve. How did this practice come about?

The law "On Circulation of Medicines" sets out various procedures for obtaining approvals for various types of clinical trials. Thus, the procedure of issuing approvals to conduct clinical trials within the framework of registration process is detailed in article 22. And the procedure for obtaining approval for IMCTs and post-registration clinical trials is governed by article 39.

The distinction between these two procedures for issuing approvals is in the sequence of the ethical expert examination and professional expert examination and submission of the application to conduct trials (figure 1).

Figure 1



If clinical trials are conducted as part of the registration process, then the expert examination is conducted on the basis of the registration application and before the application for clinical trial is submitted. When conducting IMCTs and post-registration trials, the expert examination is conducted after the application to obtain approval to conduct such trials has been submitted.

At the same time, the law says nothing about the need to submit an additional application after expert examination for IMCTs and post-registration trials has been conducted. However, the Health Ministry has come up with its own interpretation, applying to these types of trials a procedure that was intended to be used for registration trials[2]. As a result, in practice after announcing the results of the expert examination, the applicant is forced to re-file the application to conduct clinical trial. This increases the already quite significant waiting times for approval by another 3—4 weeks.

The situation is further exacerbated by the fact that at the end of 2011, the Health Ministry developed and sent out for consultation draft administrative regulations on issuing approvals for clinical trials. This document, which, apparently, will cover all sorts of trials, still refers to just one isolated case — namely, issuing approval to conduct clinical trial as part of the registration process. Regarding IMCTs and post-registration trials, the draft does not specify the stages of assigning or conducting expert examinations as clearly intended by article 39 of the law. In our opinion, adopting the proposed draft regulations would lead to certain consequences. First, it would create additional legal ground for the bad practice of re-filing applications for international and post-registration trials. Second, it would cause the most important procedure to evaluate planned trials — the expert examination of documentation —to fall outside of the administrative procedures.

[2] According to the annual statistics, the share of IMCTs and post-registration trials amounted to 75.3% of the market, while registration trials made up just 24.7%.

We will have to concentrate our efforts in 2012 to correct these draft regulations as well as remove the requirement for re-filing of application for clinical trial.

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In 2011, the efficiency of the approval system has also been affected by regular technical problems and hold-ups, in addition to the artificially created ones.

For example, over the course of the year, market participants complained many times on the amount of time it took the Health Ministry to register incoming correspondence. According to the legislation, the Ministry must register all incoming documents within one day of receipt. In practice this takes much longer. According to monitoring of the timeframes in the first half of 2011, the average time to register documents was 3.9 days. In September-October 2011 the situation worsened. According to the data from a poll of association members, the average time to register incoming correspondence in these months was up to 6 days, and in some cases as long as 10 days. It is remarkable that ACTO's letter to the ministry requesting timely registration of all correspondence has been registered 6 days after its receipt. Alas, it has not been answered.

There are periodic problems with distribution of documents. At the end of March 2011, just one employee was working at MoH on issuing documents and only for two hours per day. This lead to huge queues and it was only possible to collect the documents from MoH by appointment made at least two weeks in advance. The situation improved somewhat towards summer, when an additional person has been assigned to the station and the working hours were expanded. However, towards fall 2011, the situation again became strained. It was back to just one employee at MoH, responsible for distribution of documents. In addition, free access to the files with letters for civil transactions has been restricted and one general queue was formed to obtain approval documents for registration and clinical trials. As a result, the number of pharmaceutical company specialists queuing for documents became several dozen on a daily basis. Towards the end of the year the situation was made yet more difficult by renovations in the ministry building. At the beginning of 2012, the situation remains unsatisfactory.

For a long time, and despite repeated requests from companies, there was a recurring problem of Health Ministry's refusal to issue approvals to company representative and instead the ministry sent the documents by regular mail. This added an average of two weeks to the already long approval waiting periods. By the end of the year this issue had been partially resolved for those companies who proactively notified the ministry of their desire to collect documents in person.

Regarding the situation with approval waiting times, we will very soon be able to evaluate whether or not the system has seen a change for the better in the second half of 2011. ACTO is currently monitoring the approval waiting times for 2011, the results of which we plan to include in the next issue of this newsletter. It is possible that the negative statistics from Q4 2010 and the first half of 2011 were due to the problems of setting up the new system and that there will be gradual improvement.

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Nevertheless, despite the very difficult period of adjustment, the clinical trials market made it through 2011. And as a whole, the year end results may be characterised as adequate, and in some parts even positive. For example, the number of approved IMCTs managed not only to exceed the figures for 2010 — when there was a precipitous drop — but in fact have set a record for the entire period statistics is maintained. We do hope for a period of stability and growth in the future.

In addition to administrative issues, the long-term goals will concentrate on a resolution of strategic problems arising out of the reform. Some of these problems already existed in one form or other, but have been exacerbated after September 1, 2010. Among these are the artificial limitations on doctors' access to participation in clinical trials by instituting a mandatory level of experience in clinical trials (five years compared to two years in the early version), the mandatory accreditation procedure for medical institutions

(previously achieved by notification), and the failure to meet established timelines for issuance of approvals. Some of these problems have been caused by of the implementation of the new law "On Circulation of Medicines". For example, requirement for individual insurance policies for patients instead of general liability insurance from the sponsor and requirement for local registration trials. Majority of these issues can be resolved by changes in legislation. We hope that they will be resolved sooner rather than later.

MAINTENANCE OF THE REGISTRY OF APPROVED CLINICAL TRIALS

The law "On Circulation of Medicines" required the Health Ministry to create a publicly accessible registry of approved clinical trials. From 2004 to September 1, 2010, Roszdravnadzor maintained such registry at its own initiative.

However, although it has already been a year and a half since the law came into force, the maintenance of the registry still leaves much room for improvement. In the beginning there were discrepancies with dates and numbers of issued approvals - this implies that there may have been some errors in document workflow processes. In addition, the Health Ministry's own Order No. 754n of August 26, 2010, regulating the order of entries and the publication of the registry, is not being followed by the Health Ministry, especially concerning the contents of the registry entries.

If you look at the registry, you can see that in 2010 and early 2011, approvals are not always numbered in strict sequence according to date of issuance, as required by document workflow processes and common sense. For example, immediately after approval No. 21 comes approval No. 25, and No. 65 is followed by No. 69. When Health Ministry announced in December—February 2011 the number of issued approvals, it actually referred to the last numbers in the record rather than the total number of approvals issued. So, on February 3rd a ministry representative announced that as of that date, 69 approvals had been issued. In reality, approval No. 69 has been issued on February 3rd , but the total number of approvals actually issued as of that date was just 45. The skipped numbers were held 'in reserve', and then meted out to approvals granted later. Approval No. 23 turned up between No. 35 and No. 36, and approval No. 67 finally appeared between No. 90 and No 91. However, as of this moment twenty one numbers are still unaccounted for — these approvals are intended as 'reserves' and are notionally dated September 1, 2010.

There is another problem connected to the maintenance of the registry and the procedure of issuing approvals, namely a technical problem that seems of an insignificant nature. We are talking about the numbering procedure that the Health Ministry applies to the approvals it issues. In contrast to Roszdravnadzor, which used an annually-resetting system for documents (starting with No. 1 each year), the Health Ministry in 2011 continued the numeration that had begun in 2010. Thus, the first approval issued in 2011 was No. 55, and the last was No. 622. What does this mean? According to typical insurance rules, the number of characters in the approval number, which shall be used to create the individual patient identification code, is limited to three digits and thereby can only be between 001 and 999. Because of this, at one of the meetings in 2011, ACTO asked ministry representatives to address this problem and consider re-setting the numeration in 2012. However, this request went unheeded and the first approval issued in the new year was No. 623. What will be done when the last three-digit number is used and how will it be possible to meet the requirements of insurance rules — the regulator does not currently seem to care about this issue.

According to Health Ministry Order No. 754n of August 26, 2010, in addition to other data the Health Ministry must enter into the registry information about the form and dosages of the medicinal product being studied, the name of the study and its goal, and the name and address of the medical institutions where the trials are conducted. However, the Health Ministry is not following its own order — this information is not in the registry.

Is anyone harmed by the lack of this information? In order to answer this question we need to understand whether this Russian registry of clinical trials is needed at all, and if it is, who needs it and for what purpose. Unfortunately, in the law "On Circulation of Medicines" and in Health Ministry Order No. 754n of August 26, 2010, there is no mention of the purpose of this registry.

World Health Organization (WHO), which maintains a global registry of clinical trials, including information from many national registries, names such goals of a clinical trials registry as eliminating

unnecessary conduct of duplicate clinical trials, helping to reveal gaps in scientific research, and improving its quality, ensuring that resolutions in the healthcare sphere are based on comprehensive information and helping to develop cooperation between investigators, etc.

It goes without saying that the Russian registry is unlikely to be able to make a significant contribution to achieving these global targets. Most of the clinical trials of scientific value are initiated by American and European pharmaceutical companies, and therefore are registered in the European (www.clinicaltrialsregister.eu) and American (www.clinicaltrials.gov) registries. But does this mean that all other local country registries are completely unnecessary?

Although the largest reference registries — the American and European ones —to a great extent help meet the goals set out by the WHO, they themselves do not state them as their own goals. For example, according to US legislation, the goals of www.clinicaltrials.gov are "To enhance patient enrollment and provide a mechanism to track subsequent progress of clinical trials…". The goal of opening public access to the EMA registry, which happened on March 22, 2011, was, according to the press release to "increase transparency of medical research and make it much easier for patients to find information about clinical trials taking place in Europe". These are likely to be the two primary functions for any local registry.

In fact, the Health Ministry's registry, even with the minimal amount of data in the registry entries as required by ministry's order, would be able to fulfill these functions. However, non-compliance with the order and the absence of the protocol name and information about the clinics list robs Russian patients of the opportunity to choose appropriate clinical trials for participation. Many patients cannot use international registries because they do not know English. In addition, such registries frequently do not list clinics conducting trials. Without this information, a patient cannot choose to see a research physician and be included in a trial.

In addition, having information about the protocol in the registry would allow the whole process of registering medicinal products in Russia to be much more transparent. Medical specialists and the public would have an opportunity to evaluate the trials that served as the basis for approving a given medicinal product. Information about the trials used as the basis for registering foreign-made medicinal products can be found in international registries, but information about local trials for Russian-made medicinal products cannot be obtained from anywhere, but the Health Ministry's registry.

In conclusion, we want to underline that maintaining a registry of approved trials is undoubtedly an important and necessary task. However, there are quite a few issues that have to yet to be resolved. We can only hope that the problems we discussed in this newsletter, as well as so many other regulatory challenges that the market has faced, are attributed to the 'growing pains' of the new system and will be corrected in the future.

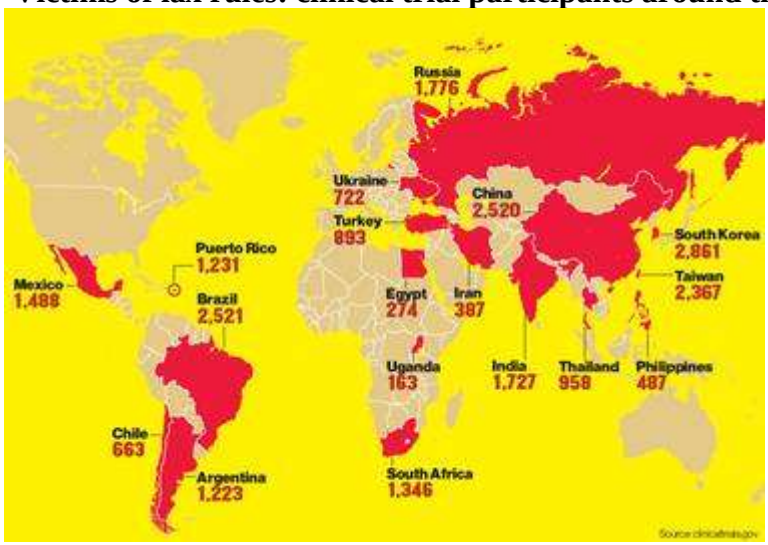
THE HISTORY OF ONE PUBLICATION

In November, *The Independent* – a British newspaper which is considered to be a serious publication and not a tabloid — published two articles about how Big Pharma uses poor, uneducated, and unprotected citizens of developing countries as guinea pigs for clinical trials. The first article about numerous violations of ethical standards in conducting trials in India (in particular, about the lack of informed consent) appeared on November 14, 2011 ('Without Consent — how drugs companies exploit Indian 'guinea pigs'). The second part has been published the next day as 'From Tragedy to travesty: Drugs tested on survivors of Bhopal' and talked about clinical trials conducted on victims of the Bhopal disaster[3] — as the authors noted, often without their knowledge and with risks to their health. As this article was primarily concerned with the Indian situation, with which ACTO is not familiar, it was difficult for us to respond to the accusations leveled in the article — that was a task for the global association of CROs and pharmaceutical companies. For example, the day the first article was published, on November 14, 2011, the Association of the British Pharmaceutical Industry responded to it. But we can not avoid making a few comments — in particular about the information on death rates for participants in clinical trials, as reported by *The Independent*. First, because the data was also shown for Russia, and second, because this statistics has been picked up by Russian press.

The Independent had said that in India, from 2007 to 2010, a total of 1,730 clinical trial participants died. The journalists did not draw a cause-and-effect relationship between death and participation in clinical trials — on the contrary, the statistics were qualified as appropriate to the situation. In the article 'Without consent…", it was noted that all deaths occurred 'during or after participation in such trials'. However, no mention has been made of what timeframe has been used when mentioning 'after participation' — a year, five years, ten years. The article also said that 'Many of those people, often only eligible for the studies because they were ill, might have died anyway' and that in these cases 'Many may have died from natural causes…'. For example it is well known that the highest death rates are recorded in cancer research — most patients die during the course of the trials or within a short time after the trial has ended. All of these qualifications were noted quite casually and in no way influenced the overall impression for the reader that the death rates in Indian clinical trials are extremely high.

The article 'Without consent…' was accompanied by a map with the caption 'Victims of lax rules: clinical trial participants around the world'.

'Victims of lax rules: clinical trial participants around the world'



The map published in The Independent

[3] The disaster at the Union Carbide plant in Bhopal, the capital of Madha-Pradesh, on December 3, 1984

According to the map, in Russia 1,766 people became ‘victims of lax regulation’. In addition to Russia, data about the number of fatalities was included for 17 other countries — mostly developing ones. This is probably what ignited the media in those countries to pick up this ‘sensational news’. Turkey has been the most active, as a whole range of local publications picked up *The Independent’s* story and ran it with screaming headlines of ‘893 Turks die in major drug companies’ experiments’. The topic even made it onto Turkish television. From Turkish media, the news were picked up in Armenian and Ukrainian publications.

However, in reality, the map published in *The Independent* bore absolutely no relationship to death rates in clinical trials. The map was taken from the international registry for clinical trials www.clinicaltrials.gov and in fact shows the number of trials underway in various countries, and has nothing at all to do with numbers of ‘victims’.

The Turkish Health Ministry and the Turkish Medical Drug Companies Association together issued a rebuttal on November 15, 2011 and refuted the claims. They clearly noted that the figure quoted in *The Independent* refers not to the number of deaths during clinical trials, but to the number of trials being conducted in Turkey according to the international register www.clinicaltrials.gov. “As of November 2011 around the world there were 116,223 clinical trials, 87% of which were in the USA, Canada, and Australia. Only 893 trials are being conducted in Turkey, which is less than 1% of the total,” they said.

But the information had already made it to the Russian press — on November 15, 2011 the headline ‘*The Independent*: 893 Turkish citizens are victims of clinical trials’ ran on the website of an industry newspaper. Similar pieces turned up on Ukrainian and Armenian news services, on several sites covering medical and pharmaceutical subjects and on sites highlighting events in Turkey.

On November 18, 2011, the story took another turn in Russia, when the news about victims of clinical trials were published on the website of one of the national papers. This time, however, the details were not about Turkish citizens, but about the total number of victims around the world — the news went out with the headline ‘120,000 people around the world have died from testing new medicines’. The source of the information was listed as another Turkish newspaper, this time an English-language one, *The Hive Daily*. *The Hive Daily* in turn credited *The Independent* as its source, although it had completely misinterpreted the data presented in that paper. *The Independent* had not discussed the number of deaths around the world, but rather the number of clinical trials (‘'Globally, it is estimated that around 120,000 trials are taking place in 178 countries').

After the news appeared on the website of a national publication with a huge audience and whose RSS feed is picked up by many other news outlets, we realised that we needed to take urgent action.

That same day, we contacted both publications which were the primary sources of information in Russia, explained the situation, and requested that they remove the incorrect information which was confusing their readers. The editors of both papers were willing to work with us and a few hours later the articles had been removed. Because the news on the website of the national newspaper had only been up for a few hours, the number of reprints was not very significant. All together, as of November 18, 2011 in the Russian-language electronic media, we noted 19 references to victims of clinical trials, based on the information from *The Independent*. We decided to send a request to remove the incorrect information to all publications which had published it. An official ACTO announcement has been prepared for this purpose.

In analyzing the data presented by *The Independent*, we turned our attention to another interesting aspect- in their desire to frighten readers with a huge number of deaths, the publication had not even made an effort to check the facts. As a result, the theories about the ‘fatality’ of clinical trials and the ‘colonial exploitation’ were easy to rebut using the statistics from *The Independent* itself. If you believe *The Independent’s* data about the numbers of fatalities in India over four years (1,730) and the total number of participants in clinical trials in that country (150,000), then at an average of 432.5 fatalities per year, the death

rate for Indian trial participants comes out at 2.9 per 1,000 patients. At the same time, the overall death rate in India according to a variety of sources[4] varies from 6 to 8 per 1,000 of population. Consequently, if you believe the statistics published by the newspaper, you would conclude that participating in clinical trials not only does not increase the likelihood of death, but in fact cuts it by more than half.

ACTO's statement, including a version in English, was published on the association's website. We even provided it upon request to those media outlets which had reprinted news about the scandal. We asked them to either remove the information as incorrect or to offer us the opportunity to respond. For the most part, our requests were accommodated — after double-checking, the information was either removed or our rebuttal has been added.

The editors of one of the Ukrainian sites which published ACTO's statement laid the blame at the feet of Turkish and Russian journalists. The rebuttal was published under the headline 'Owing to a lack of English, Turkish journalists 'killed' 120,000 people / Turkish journalists, and then Russian ones, fail to understand the material and 'kill' 120,000 people'. A Russian publication then followed the Ukrainian example. In the rebuttal it noted that 'the Turkish journalists released incorrect information, having incorrectly translated the article from the British *Independent* and presenting data about participants in clinical trials as a death toll', in connection with which the editors asked readers to forgive their Turkish colleagues.

On November 17, ACTO sent a query to *The Independent*, in which we asked the authors of the original articles to name their sources for the data of numbers of victims of participants of clinical trial participants Russia, to provide the criteria on which they judged the relevant Russian legislation to be weak, and to provide the criteria on which they selected countries for the map, and finally, for the reason they chose not to show data for the USA and the EU on that map. In addition, we asked the authors to clarify whether they actually believe that a patient, who dies during or after the conclusion of a clinical trial because of the progression of his disease, is still a victim of clinical trials. To date ACTO has not received any response.

[4] CIA World Fact Book, United Nation, World Bank