ACTO

ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

ACTO NEWSLETTER №5

Q2 and 1st Half of 2012

MOSCOW 2012

CONTENTS

SUMMARY

The release of ACTO's latest newsletter coincided with the opening of a new chapter in the history of Russian pharmaceuticals. This spring saw personnel shifts and changes in the structure of the main authorities – the Ministry of Health and Social Development was reformed into two independent ministries – the Ministry of Health and the Ministry of Labour. Such changes necessitate subsequent changes in the regulatory system. Therefore we decided not to limit ourselves to covering the results of Q2 and the 1st Half of this year, but instead to devote this issue to looking at all of the results of the existing regulatory system.

The first section of the newsletter normally looks at statistical indicators – the volume and dynamics of the clinical trials market. In Q2 2012, the Ministry of Health and Social Development issued 228 approvals for clinical trials, which is nearly twice as much as in Q2 of the previous year (119 approvals). At the same time, the number of approvals for international multicentre clinical trials (IMCTs) remained the same as the previous year, at 94. And the number of local trials by foreign sponsors dropped by three (from eight to five). The number of local trials by Russian sponsors grew to 35, set against nine the previous year.

But the biggest growth can be seen in the bioequivalency trials sector. The number of such trials by Russian manufacturers grew by nearly 11 times compared to the previous year (65 approvals compared to six), while those by foreign manufacturers grew even faster, by 14.5 times (29 approvals compared to two).

The result was significant change in the previous-stable market structure. Based on the 1st Half of 2012 results, the share of IMCTs had dropped to 41% (compared to the previous eight-year average of 59.6%). At the same time the aggregate share of bioequivalency trials by foreign and Russian sponsors grew to 38%, compared to the previous 15.1%. Therefore, the share of bioequivalency trials was roughly equal to the share of IMCTs. It would be difficult to say that such a position on the clinical trials market is a reason for national pride. We can only add that these changes are the consequence of the law 'On Circulation of Medicines', principally on the standards laid out therein on the obligations of conducting local registration trials.

According to the results of monitoring of the period for issuing approval documents, we can say that the work of the Ministry of Health and Social Development in the 1st half of 2012 improved in comparison with indicators from the previous year. The average period to issue approvals to conduct clinical trials was 118 days, compared to 130 days in the previous year. The average period for issuing a permit for the import of medicines and for the import/export of biological samples was 21 days, which is nine days better than the indicator from the previous year for the import of medicines, and 13 days better on import/export of biological samples. The total period required for the applicant to obtain the necessary permits to start a trial improved on average by 25 days, and amounted to 139 days, compared to 164 days in 2011. In addition, the percentage of approvals issued within the period dictated by law also improved. However it still remains unacceptably low – 2% for approvals to conduct trials, 13.3% for permits to import studied medicines, and 43.6% for permits for import/export of biological samples.

The next subject for this issue was an analysis of the situation in the area of ethical reviews. Unfortunately, the conduct of the Ethics Council under the Ministry of Health and Social Development raises many questions connected with insufficient transparency of the ethical review process, and unpredictability on both deadlines and results. The requirements put forth by the Council are at times illogical and at other times even self-contradictory. This raises questions as well about how these requirements collate with existing legislation. We can only hope that the Ministry of Health in forming a new Ethics Council will devote the necessary attention to analysing the problems we have articulated.

Finally, in this issue we decided to take a closer look at those aspects of the legislation that are proving most problematic for the clinical trials sector – the qualification requirements for Principal investigators, the accreditation of medical organisations, and insurance.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

Before we get to describing the market situation in Q2 2012, we wanted to make two important comments.

First. Up to the beginning of July, the publication of this issue of the newsletter, or at least of its main, statistical section, was in doubt. The issue was that at the beginning of May, practically all important information – that enables us to evaluate the data on issued approvals – disappeared from the publically accessible part of the register of approved trials (located at www.grls.rosminzdrav.ru). For example, the numbers and names of reports disappeared, without which it is not possible to determine which studies were under discussion. Attempts to discuss this matter with representatives from the Ministry of Health and Social Development were unsuccessful right up until Marat Sakaev left his position as Director of the Department of the State Regulation of Medicines. After this it was possible to reach an understanding with the ministry on the importance of keeping a register in accordance with their own orders. Then more time was needed to solve the technical problems, and at the very beginning of July, the register was finally amended with the necessary information. It now reflects all the information required by law, including the centres where studies are conducted. This is especially important particularly for patients, who have at last gained the long-awaited chance to search for centres conducting the research in which they are interested.

Second. In processing the data for Q2 at the beginning of July, we discovered that the register was still being updated with approvals from June, namely June 27 and 29. The explanation turned out to be simple – the ministry was having problems with getting new approval forms, and the authorities – credit where it's due – tried everything within their power to avoid the approval-granting process from grinding to a halt. If we included the data from these approvals for Q2, we would as a result mess up the statistics for the next quarter, which would be inappropriate. In order not to misrepresent the real indicators of how the new ministry staff is working, we have excluded from the calculations those approvals granted on June 27 and 29 (a total of 28), and are planning in the future to include them in the Q3 statistics.

And so, in Q2 2012, the Ministry of Health and Social Development granted 228[1] approvals to conduct clinical trials, of which 94 were for international multicentre clinical trials (IMCTs). These data are virtually identical as those from Q1 (table 1). The total number of approvals issued increased by just eight (3.6%), and the number of approvals for IMCTs increased by three (3.3%). The more significant changes in comparison with Q1 were to be found in other types of trials. For example, the number of local efficacy and safety trials decreased, both by foreign and Russian sponsors (44.4% and 23.9% respectively), and bioequivalency trials increased (26.1% and 27.5% respectively).

But it is much more interesting to compare the results of Q2 of this year with the same period of the previous year. The total number of approvals issued was nearly double (228 this year, against 119). The number of approvals for IMCTs this year was the same as for the previous year – 94. And the number of local trials by foreign sponsors was down by three (five, against eight). Therefore, the nearly 100% growth in the number of approvals issued can be explained by the significant growth in other types of trials. The number of local trials by Russian manufacturers increased four-fold (35 against nine). But the biggest growth was seen in the bioequivalency sector. Compared to the same period of the previous year, the number of such trials by Russian manufacturers increased nearly 11 times (65 compared to six), while those by foreign manufacturers increased 14.5 times (29 compared to two).

[1] One additional approval did not figure in these calculations, because it was not in fact a clinical trial, but providing support for patients who had previously taken part in clinical trials for the drug before it was registered in Russia.

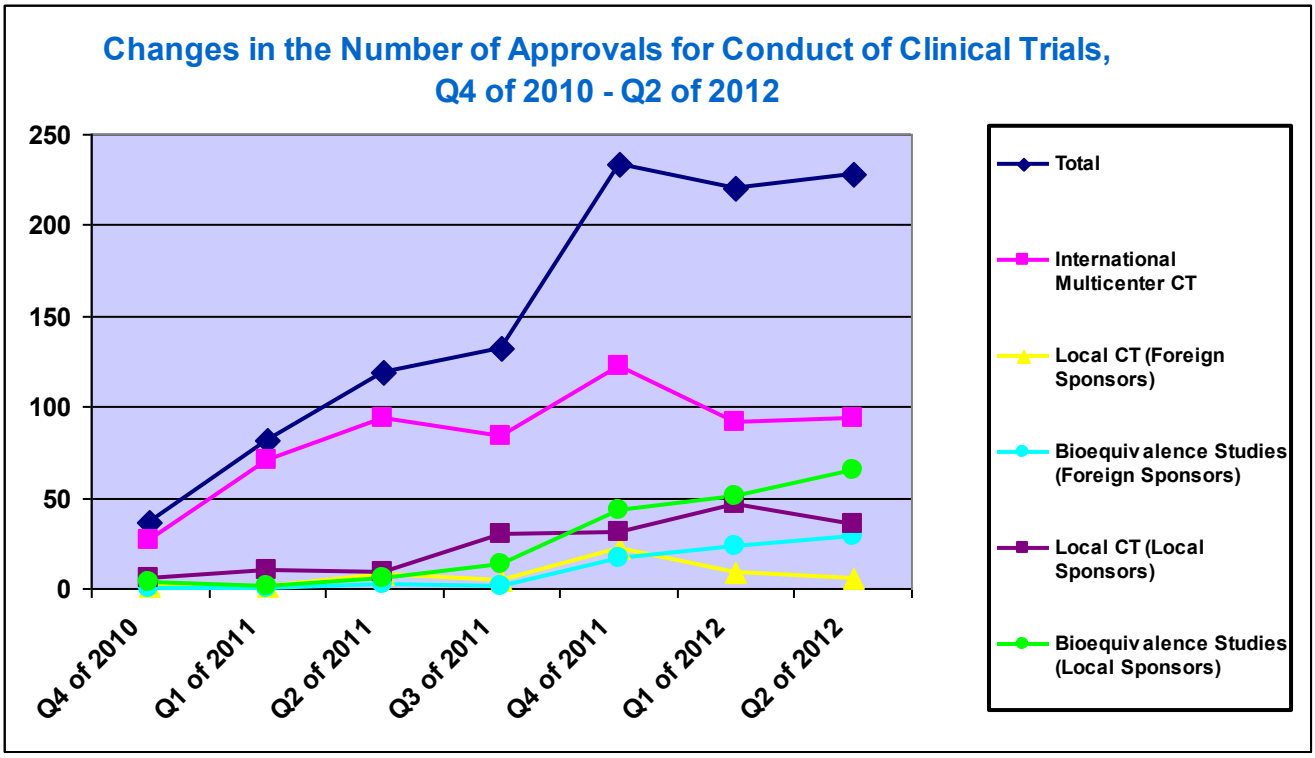
Table 1

Approvals for Conduct of Clinical Trials: Q4 of 2010 - Q2 of 2012						
	Total	International Multicenter CT	Local CT (Foreign Sponsors)	Bioequivalence Studies (Foreign Sponsors)	Local CT (Local Sponsors)	Bioequivalence Studies (Local Sponsors)
Q2 of 2012	228	94	5	29	35	65
Q1 of 2012	220	91	9	23	46	51
Q4 of 2011	234	122	22	16	31	43
Q3 of 2011	132	84	4	1	30	13
Q2 of 2011	119	94	8	2	9	6
Q1 of 2011	82	70	1	0	10	1
Q4 of 2010	36	26	1	0	6	3
Q2 of 2012 vs. Q1 of 2012, %	3,6%	3,3%	-44,4%	26,1%	-23,9%	27,5%
Q2 of 2012 vs. Q2 of 2011, %	91,6%	0,0%	-37,5%	1350,0%	288,9%	983,3%

Data from www.grls.rosminzdrav.ru

Diagram 1 vividly illustrates the quarterly change in approvals issued for various types of trials, beginning from the moment that the law 'On Circulation of Medicines' took effect.

Diagram 1



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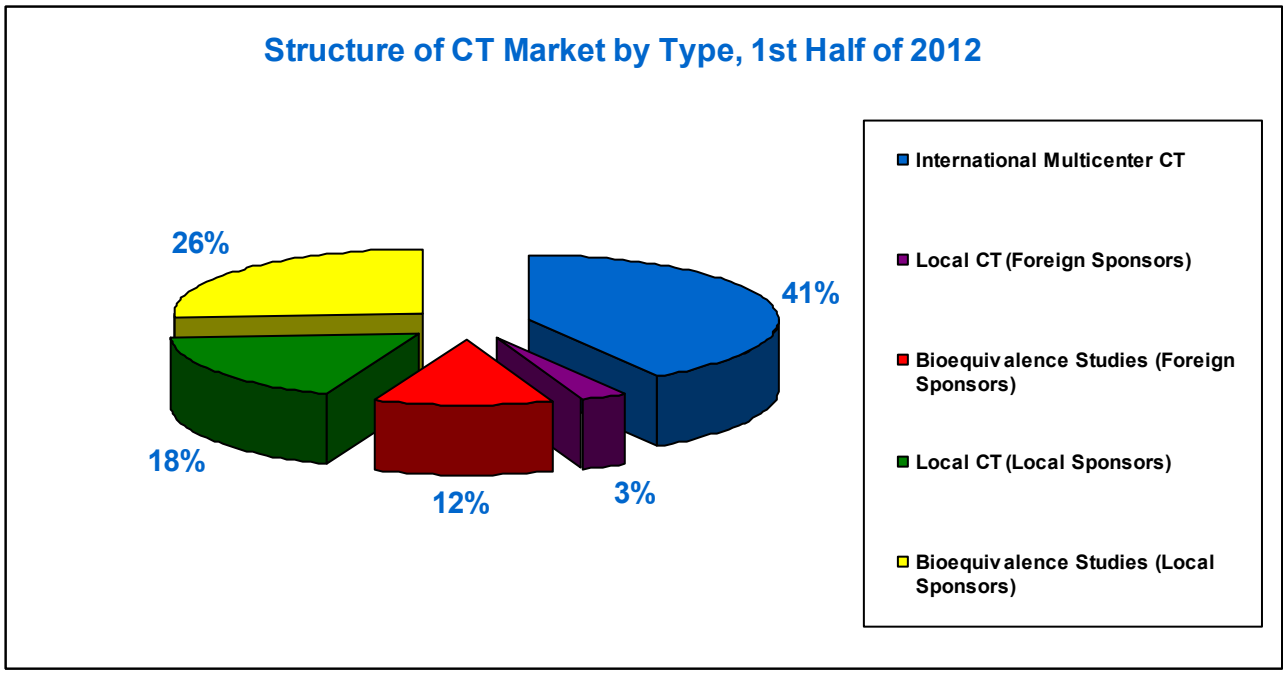
In the previous issue of the newsletter, we already noted that in early 2012, from the moment that the law 'On Circulation of Medicines' came into effect, there were significant structural changes on the market (*see ACTO Newsletter №4*). In Q1 2012 for the first time since records began, the share of IMCTs as a total share of the market dropped nearly to 40%. At the same time we saw significant growth in the bioequivalency sector. The share of bioequivalency research by Russian sponsors in Q1 2012 grew to 23.2% (compared to 13.3% - an average for the preceding eight years), and the share of such research by foreign sponsors grew from 1.8% to 10.5%. We should remember that previously and for a period of many years, the market structure was considered stable, and changes in the share size of various market segments were generally insignificant.

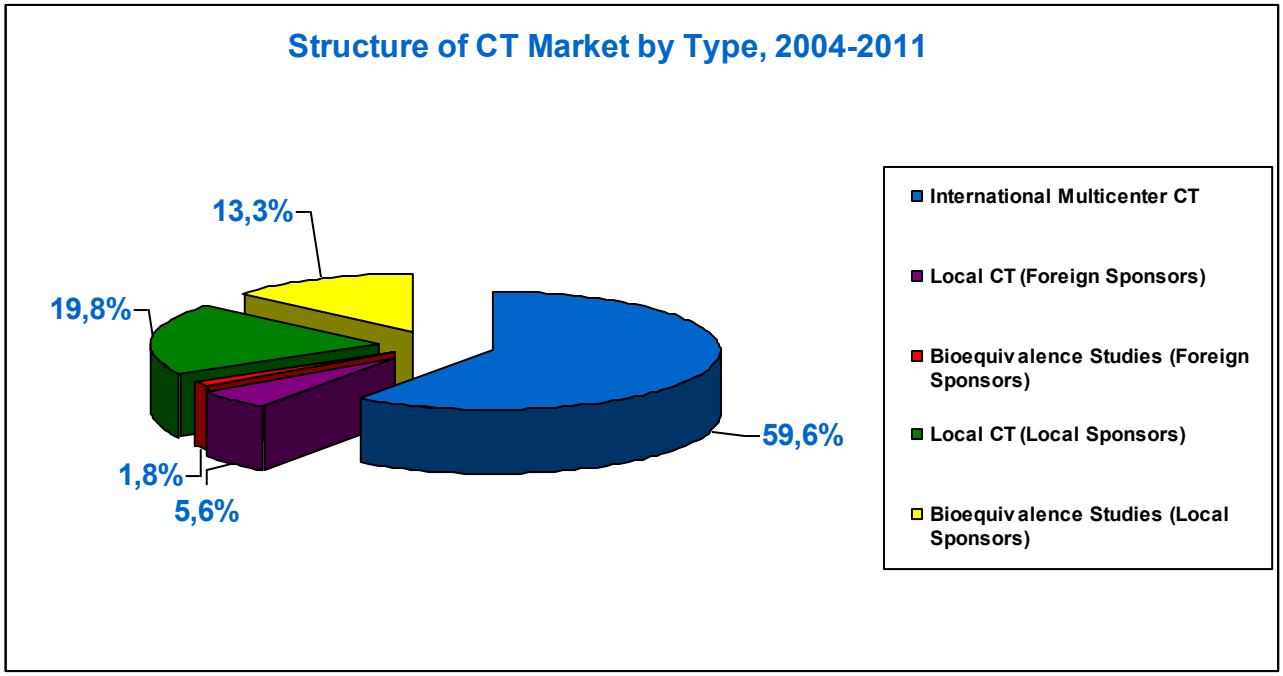
Based on Q2 results, we can confirm that the trend we saw from the beginning of the year has continued, and is reflected in the semiannual statistics. In Diagram 2 we see the structure of the clinical trials market by type for the first half of 2012. For comparison we look to Diagram 3, which reflects the average correlation between different types of trials over the eight-year period preceding the introduction of the law 'On Circulation of Medicines' , and characterized by stable dominance of IMCTs over all other types of trials.

Diagram 2



Data from www.grls.rosminzdrav.ru

Diagram 3



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

We can see that based on results from the first half of the year, there were practically no changes only in the share of local trials by Russian manufacturers.

The share of international trials dropped to 41% (compared to the previous eight-year average of 59.6%).

The share of local trials for efficacy and safety by foreign sponsors, strange as it may seem, also dropped in comparison with the 'pre-reform' level, and currently accounts for just 3%, set against its previous level of 5.6%.

We should remember that in Q1 just nine approvals were issued for trials of this type, and two of these were post-registration trials, four were for generics trials, and three were for original medicines (growth hormone, pancreatin, and a combination of two well-established use substances). In Q2 five approvals were issued for local trials by foreign sponsors, four of which represent trials for generics, and the fifth of which is a trial for a herbal medicine.

The small share of local trials by foreign sponsors means that companies – primarily representatives of the innovation sector – for whatever reason are still continuing to hold back on conducting local registration trials, taking these on only as a very last resort. This is no doubt good, taking into account the redundancy and superfluity of such trials. However this also indicates the possibility that there is a whole range of innovative medicines which could have already been registered but instead no one knows when they might become accessible for Russian patients.

However the brightest indicator to come out of adopting these standards on mandatory registration trials are the structural changes in the sector of bioequivalency trials by foreign sponsors. Based on results for the first half of the year, the share of such trials grew compared to the previous average, accounting for 12% as opposed to the previous 1.8%.

For Q1 and Q2 we can see growth in the sector for bioequivalency trials by Russian manufacturers as well. The share of these types of trials nearly double compared to the previous average, amounting to 26%.

Altogether in the first half of the year, 168 approvals for bioequivalency trials were issued, 116 to Russian manufacturers and 52 to foreign ones, which totalled 38% of the clinical trials market. A total of 4,175 volunteers are to take part. The average number of participants in the trials by foreign sponsors is 30.8, with Russian trials averaging 22.2.

It is clear that such sharp growth in the number of trials of this type could not help by increase their cost. And if before the law 'On Circulation of Medicines' took effect, the average cost of a bioequivalency trial was 500,000-600,000 rubles, we see that now market players are estimating the average cost at 1.5-2.2 million rubles and more, or an average of USD 2,000-3,000 per patient. We can say that today the cost of the simplest and shortest type of trial for a generic medicine in Russia is virtually the same as the cost of a full clinical trial for an original medication.

We decided to look at whether the bioequivalency trials were divided among clinical centres. All approvals from the first half of the year for this type of trials were divided among 57 centres. But the overwhelming majority of them (785) took place at just 11 centres. The division of trials among centres is set out in Table 2.

Table 2

Allocation of Bioequivalence Studies by Clinical Centers			
Clinical Center	Total number of bioequivalence studies in the center	Number of bioequivalence studies (foreign sponsors)	Number of bioequivalence studies (local sponsors)
Federal State Institution "State Scientific Research Centre for Preventative Medicine" of the Ministry of Health and Social Development, Moscow	22	17	5
The Municipal Health Institution Clinical Hospital №2, Yaroslavl	21	8	13
Federal State Institution of Science "Northwest Research Center of Hygiene and Public Health" of the Rospotrebnadzor, St. Petersburg	18	2	16
The Municipal Institution "Lyubertsy hospital № 2", Lyubertsy, Moscow Region	15	1	14
The State Educational Institution of Higher Professional Training I.M. Sechenov First Moscow State Medical University of thr Ministry of Health and Social Development, Moscow	11	1	10
The Municipal Institution "Central City Clinical Hospital of Reutov", Reutov, Moscow Region	10	5	5
The Research Centre of Biomedical Technology of the Russian Academy of Medical Science (RAMN), Moscow	9	3	6
The State Educational Institution of Higher Professional Education the St. Petersburg State Medical University named after I.P.Pavlov of the Roszdrav, St. Petersburg	7	0	7
The Scientific Research Institute of Pharmacology of Siberian Department of the Russian Academy of Medical Science (RAMN)", Tomsk	6	5	1
Federal State Institution "Scientific Research Institute of Influenza" of the Ministry of Health and Social Development, St. Petersburg	6	4	2
The State Health Institution of the Yaroslavl region "Yaroslavl regional Clinical Narcological Hospital", Yaroslavl	6	3	3

Data from www.grls.rosminzdrav.ru

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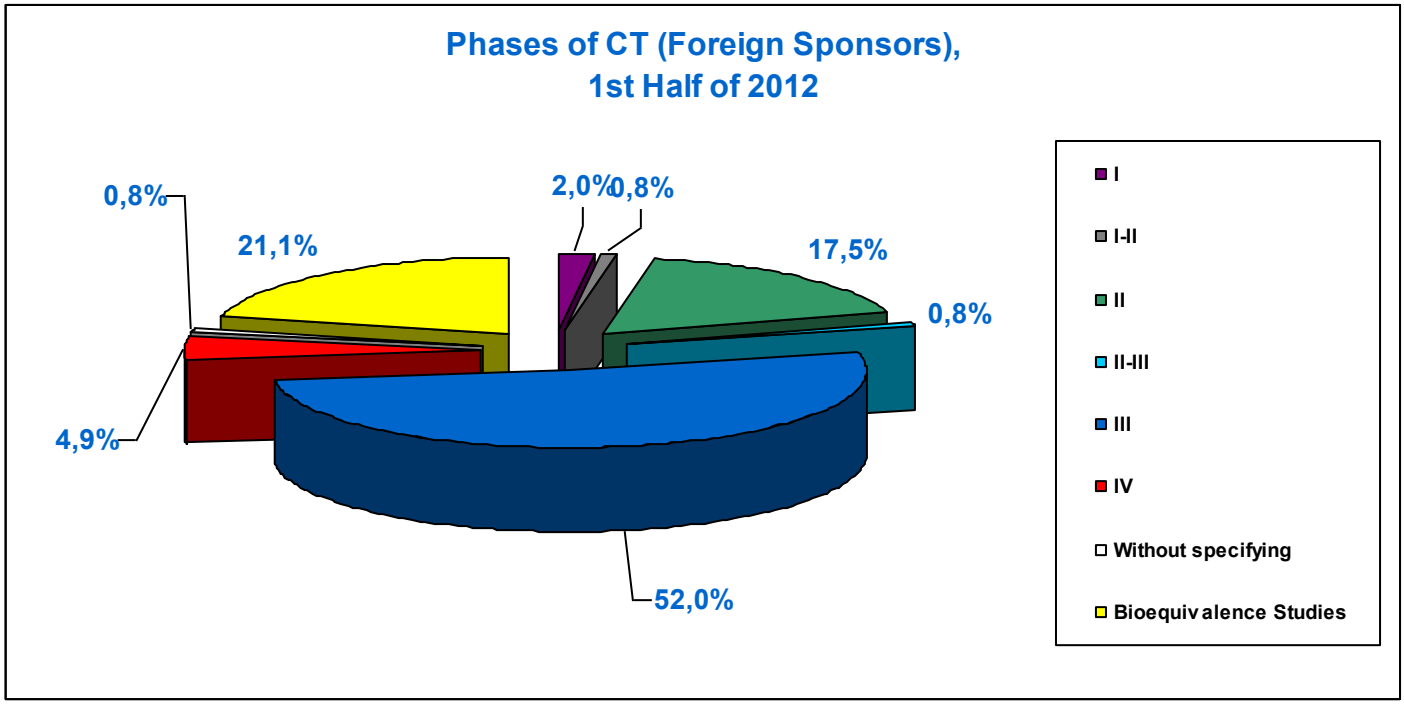
Data about the structure of trials by foreign sponsors by stages in the first half of 2012 are shown in Table 3 and Diargam 4.

Table 3

Phases of CT (Foreign Sponsors), 1st Half of 2012								
	I	I-II	II	II-III	III	IV	Without specifying	Bioequivalence Studies
Q1 of 2012	2	~	23	~	70	5	~	23
Q2 of 2012	3	2	20	2	58	7	2	29
Total for 1st Half of 2012	5	2	43	2	128	12	2	52

Data from www.grls.rosminzdrav.ru

Diagram 4



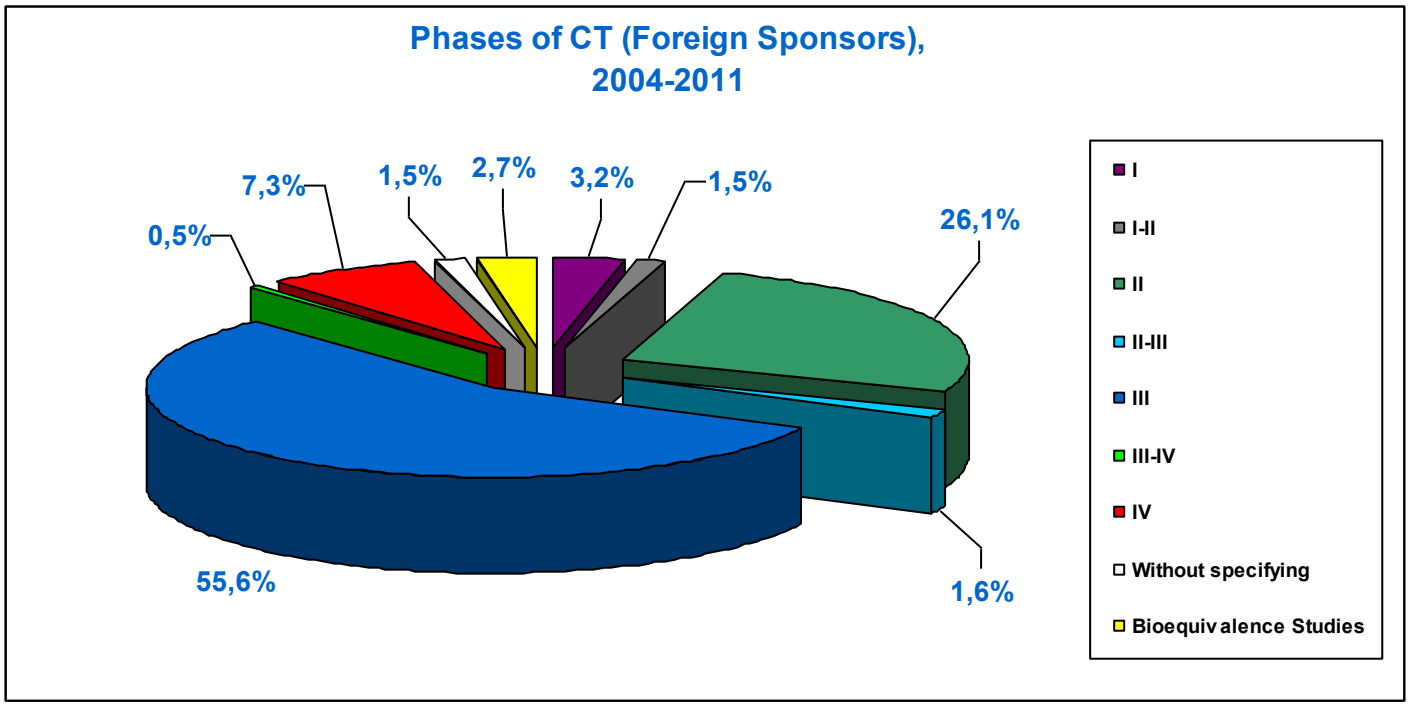
Data from www.grls.rosminzdrav.ru

In Diagram 5 we see the average data on the structure of the market for trials by foreign sponsors over the past eight years (from 2004 to 2011). In comparing the diagrams, it is clear that in the first half of 2012, there are several deviations from the average.

The most significant change, for reasons we have already described, can be seen in the share of bioequivalency trials (21.1% as compared to the average of 2.7%). Such significant growth in the share of a

given type of trial leads necessarily to reduced shares among all other sectors. However this decrease was not entirely proportional. We can see the smallest drop in the share of phase III trials (52% set against 55.6%). And the biggest drop in phase I trials (2% against 3.2%). This is understandable, since the second factor which undoubtedly influenced the decrease in share of trials in this sector, and about which we have already written several times in previous issues of this newsletter, is the legislative ban on conducting phase I trials for medicines made by foreign manufacturers using healthy volunteers.

Diagram 5



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

TIMEFRAMES FOR ISSUANCE OF APPROVALS

According to ACTO's monitoring of approval periods, the Ministry of Health and Social Development worked more efficiently in the first half of 2012 than in the previous year (*see ACTO Newsletter №4*). The average period to issue approval to conduct a clinical trial was 118 days (Table 4). This was 12 days better than the same indicator for 2011 (Table 5). But still 60 days longer than the period dictated by law.

We are also seeing progress in other types of submissions. The average period to issue a permit for import of medicines and to import/export biological samples was 21 days, which is nine days better than the previous year's indicator for importation of medicines, and 13 days better for the import/export of biological samples. The total period required for the applicant to obtain the necessary approvals to start a study improved on average by 25 days, and amounted to 139 days, compared to 164 days in 2011.

Improvements by about three weeks (20 and 21 days respectively) were observed in approvals to make amendments to the protocol and for other approvals (approvals to prolong trials, approvals for additional centres, to enroll additional patients, and so on).

Table 4

Timeframes For Issuing Approvals, 1st Half of 2012[2]					
	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**	**118**	**16**	**410**	**101**
To Import Medicines	**8/12**	**21**	**8**	**54**	**143**
To Import/Export Biosamples	**13/19**	**21**	**7**	**47**	**337**
To Make Amendments to the Protocol	**34/48**	**71**	**15**	**246**	**176**
Other Approvals (to Prolong Clinical Trials, To Include New Sites, To Enroll Additional Patients, etc.)	**25/35**	**48**	**9**	**148**	**301**
Total Timeframes for Obtaining Approvals to Conduct Clinical Trials and To Import/Export	**54/76**	**139**	**~**	**~**	**~**

Data from timeframes' monitoring of ACTO

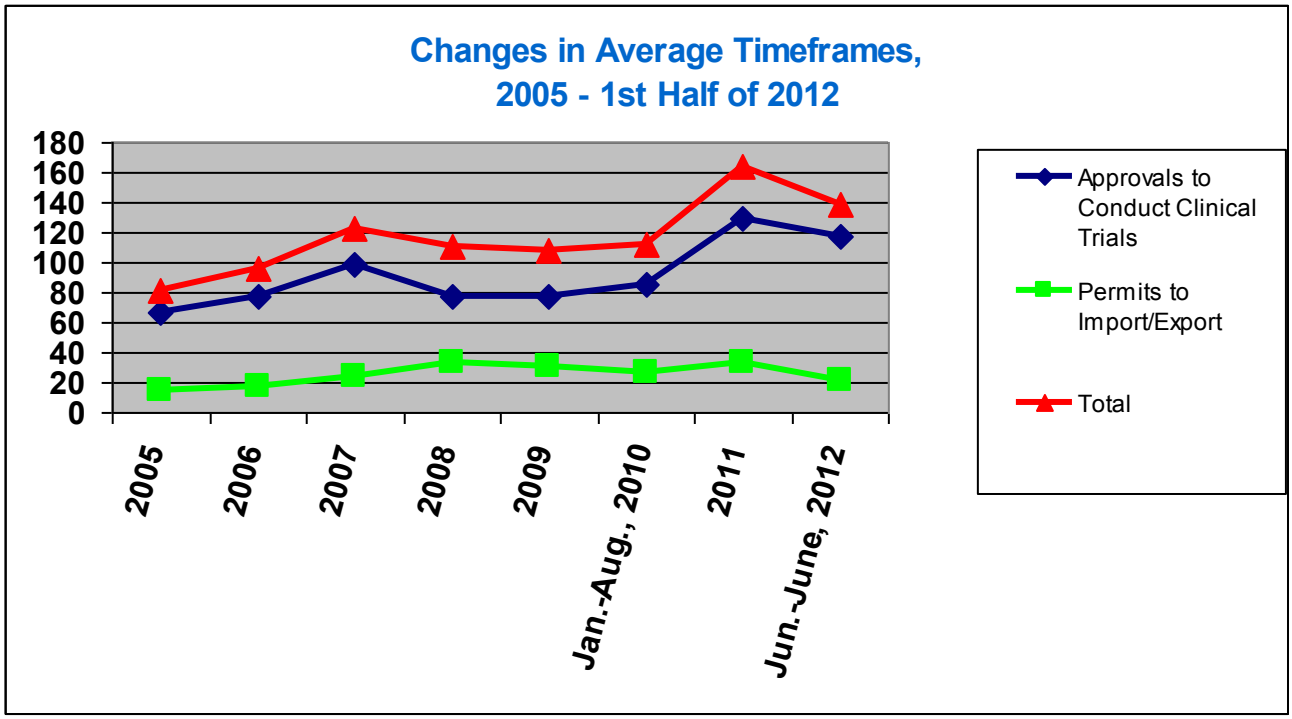
[2] During the calculation of legislative timeframes we were translating the workdays to calendar days and adding from 1 to 4 days (depending on the kind of submission) for registration of the application and awarding of a ready document to the applicant, despite the fact that in law these stages are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

Table 5

Changes in Average Timeframes, 2005 - 1st Half of2012								
	2005	2006	2007	2008	2009	Jan.-Aug., 2010[3]	2011	Jun.-June, 2012
Approvals to Conduct Clinical Trials	66,3	77,8	98,9	77,6	77	85,2	130	118
Permits to Import/Export	14,9	17,8	23,7	33,1	30,5	26,9	34	21
Total	81,2	95,6	122,6	110,7	107,5	112,1	164	139

Data from timeframes' monitoring of ACTO

Diagram 6



Unfortunately, the Ministry of Health and Social Development's hard work in the first half of the year was still not enough to achieve pre-reform indicators as demonstrated by Roszdravnadzor, with the exception of the period to obtain a permit for import/export of medicines and biological samples.

We can only hope that this next restructuring and the associated malfunctions with the Ministry of Health's new staff will not lead to further significant increases in waiting times.

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In Table 6 we see data on violations of timeframes to issue approval documents in the first half of 2012, as compared to the same indicators from the previous year.

[3] During 2010 monitoring data was examined only through August. A new law came in force in September, and till November the work of the regulatory system was almost fully paralyzed.

Table 6

Violations of Timeframes, 1st Half of 2012 vs. 2011								
		Approvals issued on time	Approvals Issued in Violation of Timeframes					
			Total	less than in 1,5 times	in 1,5-1,9 times	in 2-2,9 times	in 3-3,9 times	in 4 times and more
To Conduct Clinical Trials	Jan.-June 2012	2,0%	98,0%	12,9%	46,5%	23,7%	11,9%	3,0%
	2011	1,8%	98,2%	4,7%	30,6%	47,1%	12,3%	3,5%
To Import Medicines	Jan.-June 2012	13,3%	86,7%	29,4%	32,8%	18,2%	4,9%	1,4%
	2011	4,6%	95,4%	12,0%	15,9%	40,7%	17,1%	9,7%
To Import/Export Biosamples	Jan.-June 2012	43,6%	56,4%	40,9%	13,1%	2,4%	0,0%	0,0%
	2011	13,2%	86,8%	18,6%	36,0%	24,9%	5,7%	1,6%
To Make Amendments to the Protocol	Jan.-June 2012	21,0%	79,0%	36,9%	19,9%	19,9%	1,7%	0,6%
	2011	12,7%	87,3%	11,4%	30,0%	40,0%	4,5%	1,4%
Other Approvals (to Prolong Clinical Trials, To Include New Sites, To Enroll Additional Patients, etc.)	Jan.-June 2012	28,9%	71,1%	33,2%	24,3%	10,3%	3,0%	0,3%
	2011	15,7%	84,3%	20,8%	19,9%	27,9%	11,5%	4,2%

Data from timeframes' monitoring of ACTO

On the face of it, we have improvement across the board. This refers not only to the increasing numbers of documents issued within deadline, but also to the increasing share of documents issued post-deadline but closer to it, and accordingly, a decreasing share of approvals issued significantly after the deadline.

When speaking about non-compliance with established waiting times for approvals, we must make a clarification. The issue is that we have repeatedly been told by representatives from the authorities that the data used by ACTO do not correspond to the data held by the ministry itself. We have looked at possible explanations for this and come to the conclusion that the discrepancy is probably due to different methods of calculation. The Ministry of Health and Social Development used as the start date for the wait time, the date of registration of the application (which is logical from the point of view of the administrator who accepts the

document). However for the applicant, the wait starts the moment the document is lodged with the authorities' office. According to p. 16 of the Office Rules for Federal Authorities, the incoming document must be registered on the day it is received. But in practice this does not happen. The average period to register incoming correspondence in the first half of 2012 was 3 days (although among cases we examined we also found instances of two- and even three-week delays in registration[4]).

The same situation can be seen with the end of the period. As far as the administrator is concerned, the period ends on the official date that is stamped on the approval. But for the applicant, the wait is finally over on the actual date when he receives the document. The difference between these two dates averaged 10-13 days in the first half of 2012. Of course we can blame the company that did not receive the prepared approval on time. But is this always the case? Here is a real-life example. An application to include additional centres in a trial was lodged in the first half of May. At the end of June, it was discovered that the administrator had gone on holiday. The company was actively monitoring the situation by regularly telephoning the department and, finally, on July 19, was told that the document was ready. Imagine their surprise when, finally receiving the document, they discovered that it was dated June 21. Unfortunately, this situation is far from unique. And such practice was quite common in the Ministry of Health and Social Development, primarily in registering medicines. The guilty party in this case is clearly the regulatory manager. How can one explain to the boss that you've been holding on to a document all this time? There is only one solution to this situation – the authorities must put in place better oversight of incoming correspondence, which would allow them to avoid the practice of 'backdating' documents. But will the newly formed Ministry of Health be ready for such measures? Only time will tell.

[4] These data on deadline monitoring can be seen on ACTO's website www.acto-russia.org

ACTIVITIES OF THE ETHICS COUNCIL

OF THE MINISTRY OF HEALTH AND SOCIAL DEVELOPMENT

Since the subject of this issue of the newsletter is all connected with summarising the work of the Ministry of Health and Social Development, it would be difficult not to remark upon such an important factor as the ethical review of clinical trials. As we know, after the law 'On Circulation of Medicines' came into effect, responsibility for this review was placed on the Ethics Council under the Ministry of Health and Social Development.

Separate aspects of this body's work, as well as practical problems encountered, have already been described from our point of view (*see ACTO Newsletter №2*).

At that time, we defined the main problems with the ethical review:

- inaccessibility of the Ethics Council SOPs;

- lack of transparency of the ethical review and unpredictability of waiting times and results;

- impossibility of tracking documents through the system, and longtime lags between decisions being rendered and comments being received;

- lack of ability for the applicant to review comments and present his case.

Unfortunately, the last problem listed cannot be resolved until such time as the law is amended to make the ethical review an independent function (and not just a part of the process to obtain approval from a state body) and allow the applicant to communicate directly with the Ethics Council. We should remember that at present, the Council conducts its review not based on an application by the company, but only on orders from the ministry. This model is unique among international practice, which however did not stop legislators from adopting it.

This problem is inextricably connected and indeed is one of the reasons of another issue listed above – the impossibility of tracking documents within the system and the long time lags between decisions being rendered and comments being received. Basically as far as the Ethics Council is concerned, the applicant, as a party in a legal relationship, simply does not exist. He does not have right to approach the Council directly with an application to conduct a review, further, he does not even have the opportunity to present direct answers to comments, to present his own point of view. All communication takes places strictly through the state authorities. The applicant quite often cannot even enquire as to the current state of his case – to find out whether it is on the agenda or if it has been removed from it for some reason, if it has been reviewed, what the results were. The Council simply ignores such enquiries, sending the information to the ministry. The time spent to get comments from the Council, sent around such a round-about way, at times plays a decisive role in placing an international trial. It's bad enough that the reviews take longer than the allotted time – 83 calendar days as opposed to the 30 working or 42 calendar days established by law[5]. And is just for cases whose review did not engender additional questions and comments. If further questions arise in the course of the review, they can take a month or more to reach the applicant: first an abstract from the minutes is prepared, and then it is sent to the ministry, the ministry prepares its own letter, and sends this to the applicant. And the same process must be followed in reverse with the answer. And then the applicant must wait until the answer gets on the next agenda for the Council. As a result, at least one and a half – two months are lost. For IMCTs, these timeframes are often unacceptable, and there are plenty of real-life examples of western sponsors – not managing to negotiate this bureaucratic labyrinth to its end – simply giving up and pulling the trial out of Russia.

[5] According to data from ACTO monitoring. For more information see www.acto-russia.org

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The next problem we raised, a year ago, was related to the inaccessibility of the Ethics Council SOPs (standard operating procedures) for public review. Simply put, in the year since the Council began functioning, such procedures simply did not exist, with the exception of SOP №1 "The legal basis for the activities of the Ethics Council", adopted November 24, 2010.

SOP №2 "The procedure for conducting ethical review of the informed consent form" appeared only on November 23, 2011. The next two, SOP №3 "Clinical trials with children. Requirements for information on the child as well as parents/carers" and SOP №4 "On the review of documents containing changes to the record of an approved clinical trial of a medicine for medicinal application", were adopted on February 29, 2012. And the last one at present, SOP №5 "Clinical trials with psychiatric patients. Requirements for patient information", took effect on March 28, 2012.

We could say that the industry's wishes regarding the existence and accessibility of the SOPs have been granted. However let's take a closer look at the contents of these documents. As is apparent from the name, a SOP should describe a procedure or the order of activities of the Ethics Council – how it functions. The relevant section of the ICH GCP on SOPs for ethical committees, states clearly that an ethical committee should develop, document, and follow its own procedures, determining, in particular, the order by which it calls and organizes its meetings, the order of first and subsequent review of the trial documentation, and the procedure for expedited review and approving insignificant changes, and so on.

A close inspection of the documents adopted by the Ethics Council reveals that these are certainly not standard operating procedures. Only SOP №1 actually applies to the Council itself. All the others, despite the fact that they may have phrases such as 'procedure for conducting expert review' or 'on the order for reviewing documents' in the titles, actually contain nothing like regulations for the review body, but rather requirements for the applicant – what they must present in their documentation, the order of obtaining informed consent, and so on. One would have thought that this is what the law is for. But the Ethics Council apparently thought differently. As a result we now have these documents, whose legal status is quite unclear, but whose requirements the applicant must nevertheless fulfill, or face the threat of not obtaining approval to conduct trials.

The provisions of several of the Ethics Council SOPs contradict not only one another, but also the existing relevant legislation. We shall look at several examples. According to SOP №2, the informed consent form must include the name of the trial (the full name of the report, and the number). At the same time, SOP №5 contains the requirement that in a clinical trial with participation of patients with a diagnosis of schizophrenia, the informed consent form should only indicate a diagnosis of 'psychotic disorder'. How can both of these requirements be fulfilled? Because as we well know, the name of the report on the trial includes the name of the illness on which the trial is being conducted. And the patient will see his diagnosis anyway. And in any case, how can one in principle make an ethical requirement to knowingly conceal the true diagnosis? Because the patient must be fully informed of all aspects of the planned trial. And this is not even to mention the fact that this aspect of SOP №5 directly contradicts the provisions in articles 19 and 22 in the federal law 'On Public Health Protection in the Russian Federation', according to which the patient has the right to receive information about his state of health, including information about any illness and subsequent diagnosis. Exceptions apply only to patients who are underage or to persons who are determined by a court to be legally incompetent. In this case, the information about the patient's health is presented to his legal representative, but it must be true and without misinformation

Another provision of SOP №5 raises just as many questions, stating 'when including in a trial a patient with psychiatric disorder, if there shall be doubts as to the patient's ability to express his own full consciousness (in other words, his ability to properly consider the risks) and voluntary participation in the trial, then the information sheet must include not only the signature of the patient himself, but also that of a close relative who looks after him.' At first this requirement may seem like a logical expression of care for the patient. But this is far from the truth, and, in ACTO's opinion, this provision has in fact lead to the violation of two human rights as enshrined in law.

The background to this provision is such. The Ethics Council received for review documents on an IMCT on schizophrenia. The trial proposed participation of only legally competent patients. In addition, these were patients who were not resident in a hospital facility, but would instead come to the doctor independently. However in comments on the results of the expert review, the Council said that in addition to the informed consent of the patient himself, the trial must obtain the signature of his legal representative. The company explained that the trial did not envisage including patients who were deemed legally incompetent. However for some reason the Council did not want to admit its mistake, and after a second examination of the case the company again received the comments, in which the requirement to obtain a signature from a legal representative had been replaced with a requirement to obtain a signature from a close relative. The attempt to explain that no one except a court of law has the right to limit an individual's legal competency, including his right to independently exercise his own rights, and that close relatives do not in any way constitute legal representation, fell on deaf ears. The Council insisted that the consent form must be signed by the patient and also by a close relative. The company could absolutely not do so, since in their opinion this would be a clear breach of human rights. They were forced to cancel the trial.

But the genie was already out of the bottle. Having come to its own understanding of the subject, the Council started including this requirement in comments for other companies. And not all sponsors were as scrupulous, and several of them went on to change the informed consent forms. It is worth noting that the specialist who started this whole debate was previously a member of the Federal Ethics Committee under Roszdravnadzor. However either because there were previously other psychiatrists on the committee with him, or for some other reason, these issues had never been previously arisen. Indeed they had never arisen in the more than fifty-year history of clinical trials in Russia.

Considering that we are discussing not only contradictions with the law 'On Psychiatric Care and Guaranteed Rights of Citizens Under Such Care', and the Civil Code of the RF, but also infringement on one of the most basic constitutional rights – the right of a competent adult to independently exercise his or her rights in full expression, ACTO got involved. The association sent an enquiry to the Ministry of Health and Social Development with the aim of figuring out its position on this issue. However the authorities, as is usual, brushed us off, avoiding the question about their own position and referring back to the Council's decision.

Soon after this, SOP №5 appeared. Apparently with the aim of legitimising their position, it included a clarification – the requirement to bolster the patient's signature with one from a relative is applicable in situations where 'doubts arise as to the patient's ability to fully express his own consciousness and voluntary consent'. And here we come upon the second violation. The issue is that if a patient as a result of his psychiatric condition is not able to fully express his own intentions and voluntary consent, but at the same time he has not been declared legally incompetent in the established manner, he simply cannot be included in a trial. The responsibility of the investigator lies in the fact that he must determine the patient's condition and his ability to make decisions about his participation. And in such a case he must not hide behind a signature 'from a close relative', who does not have the legally-granted authority to make decisions about including the patient in the trial.

But let's return to the SOPs. As we have already demonstrated, provisions from a number of the SOPs raise serious concerns. And the ambiguity of the legal standing of these documents engenders difficulty in contesting them. If this was an agency-level statutory regulation, one could simply petition the Ministry of Justice or the court. But since these are documents issued by a review panel which in principle cannot issue mandatory requirements for businesses, it by definition should not be applied. And any court will refuse to hear the case, referring to the non-mandatory nature of the SOP. In practice the applicant cannot but meet the requirements set out by the Ethics Council, or he will have no chance at all of getting his trial approved. This problem is particularly apt for IMCTs, where the sponsor simply does not have the time to wait around. Understanding that any argument will lead to delays, and therefore that holding the trial in Russia could become unfeasible, the company finds itself in an impossible situation.

We can only add that for its part, ACTO is not planning to accept the status quo on this situation. In the near future, we intend to continue discussing the matter of applying the debatable SOPs requirements with the new ministry and the newly-formed Ethics Council.

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The next problem that we identified a year ago with the ethical review was its lack of transparency. From the moment that the Ethics Council began its work, applicants have complained about a lack of clarity in its work. Out of 28 sittings held between September 2010 and October 2011, only 16 (57.1%) had published agendas available for review. And only seven (25%) had results published.

It must be said that on this matter there have been significant changes for the better. Our of 16 sittings held since our last publication on this topic, only two were not reflected on the Ministry of Health and Social Development website. The results of the others, though at times later than the allotted three-day period, were published. Data on the posting of information on the Ethics Council activities to the Ministry of Health and Social Development's website can be seen in Table 7.

Table 7

Publication of Information on the Ethics Council Activities							
№ of the Meeting	**Date of the Meeting**	**Publication of the List of Clinical Trials to be Reviewed**	**Publication of the Results of the Review**	**№ of the Meeting**	**Date of the Meeting**	**Publication of the List of Clinical Trials to be Reviewed**	**Publication of the Results of the Review**
1	n/a	-	-	**23**	10.08.2011	+	+
2	n/a	-	-	**24**	24.11.2011	-	-
3	06.10.2010	+	-	**25**	07.09.2011	+	-
4	20.10.2010	+	-	**26**	21.09.2011	+	-
5	10.11.2010	+	-	**27**	05.10.2011	+	+
6	24.11.2010	+	-	**28**	19.10.2011	+	+
7	08.12.2010	-	-	**29**	09.11.2011	+	+
8	22.12.2010	-	-	**30**	23.11.2011	-	-
9	19.01.2011	-	-	**31**	07.12.2011	+	+
10	26.01.2011	-	-	**32**	21.12.2011	+	+
11	09.02.2011	+	-	**33**	18.01.2012	-	-
12	02.03.2011	-	-	**34**	08.02.2012	+	+
13	16.03.2011	+	-	**35**	29.02.2012	+	+
14	30.03.2011	+	+	**36**	14.03.2012	+	+
15	20.04.2011	+	+	**37**	28.03.2012	+	+
16	27.04.2011	-	-	**38**	11.04.2012	+	+
17	11.05.2011	-	-	**39**	16.05.2012	+	+
18	25.05.2011	+	+	**40**	30.05.2012	+	+
19	08.06.2011	-	-	**41**	13.06.2012	+	+
20	22.06.2011	+	+	**42**	27.06.2012	+	+
21	06.07.2011	-	-	**43**	11.07.2012	+	+
22	20.07.2011	+	-	**44**	25.07.2012	+	+
Total Number of Meetings					**44**	**11**	**4**
% of Total Number of Meetings					**100,0%**	**26,2%**	**9,5%**

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

Why is information about the Council's work so important? The publication of results gives applicants the chance to find out if their case has been reviewed, and the result. And as we explained above, the Council refuses to release this information at the company's request.

But this information is just as important to the public. Publishing creates the chance to evaluate the statistical indicators of the Council's work and to follow any emerging trends. So in the past year we already evaluated statistics on approved and not approved cases by sittings that were published on the Ministry of Health and Social Development's website. And now we can compare this with the new data (Table 8). We should remember that for this report we looked only at initial submissions.

Table 8

Results of Initial Ethics Review*			
	% of Approvals	% of Conditional Approvals	% of Disapprovals
All Types of Clinical Trials	78,3%	2,2%	19,5%
International Multicenter Clinical Trials	81,0%	4,4%	14,6%

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

*** According to data from 21 meetings held from March 2011to July 2012, with results posted on the website run by the Ministry of Healthcare and Social Development**

The results for the period have clearly improved. The percentage of approved cases for all types of trials rose from 65.7% to 78.1%. In turn the percentage of denial of ethical approval dropped from 31.5% to 19.6%. For IMCTs, the approval percentage for first reviews of cases amounted to 81% compared to 63.7% in the previous year, while denials were 14.6% down from 31.8%. However despite this positive trend, the percentage of refusals on IMCTs remains high. We should remember that according to data from one of the most experienced and authoritative committees in Germany – the Freiburger Ethik-Komission International (FEKI), just 1% of cases are denied (though it's true that a larger percentage of their cases receive conditional approval, in other words approval with some comments, after which changes final approval can be granted within two weeks).

Having receiving the data on overall statistics of approval/refusal of cases, we decided to look at how they broke down across therapeutic areas. In the report we included only first reviews of cases on IMCTs. The results are presented in Table 9.

Table 9

Results of Ethics Review by Therapeutic Area*					
	Number of Initial Submissions	**Number of Approved CT**	**% of Approved CT**	**Number of Disapproved CT**	**% of Disapproved CT**
Psychiatry	**21**	**8**	**38,1%**	**13**	**61,9%**
Urology and Nephrology (incl. Pediatrics)	**14**	**9**	**64,3%**	**5**	**35,7%**
Dermatology and Immunology (incl. Pediatrics)	**16**	**13**	**81,3%**	**3**	**18,8%**
Oncology (incl. Pediatrics)	**98**	**80**	**81,6%**	**18**	**18,4%**
Pediatrics	**25**	**22**	**88,0%**	**3**	**12,0%**
Neurology (incl. Pediatrics)	**31**	**28**	**90,3%**	**3**	**9,7%**
Infectious diseases	**32**	**29**	**90,6%**	**3**	**9,4%**
Pulmonology	**32**	**29**	**90,6%**	**3**	**9,4%**
Cardiology and Cardiovascular diseases (incl. Pediatrics)	**34**	**31**	**91,2%**	**3**	**8,8%**
Endocrinology (incl. Pediatrics)	**37**	**34**	**91,9%**	**3**	**8,1%**
Hematology (incl. Pediatrics)	**13**	**12**	**92,3%**	**1**	**7,7%**
Gastroenterology (incl. Pediatrics)	**16**	**15**	**93,8%**	**1**	**6,3%**
Obstetrics and Gynecology	**6**	**6**	**100,0%**	**0**	**0,0%**
Rheumatology	**31**	**31**	**100,0%**	**0**	**0,0%**
Others (incl. Pediatrics)	**3**	**3**	**100,0%**	**0**	**0,0%**

*** According to data from 21 meetings held from March 2011to July 2012, with results posted on the website run by the Ministry of Healthcare and Social Development**

Let the reader determine for himself if there is evidence of a standard balance here.

Regarding psychiatry, the Council's comments were not limited to the problem discussed above of signatures from 'close relatives', but also had quite a creative and distinctive nature. Things which, apparently, never occurred to experts in the US, France, Austria, Italy, Switzerland, Germany, Denmark, the UK, and other countries where the trails we shut down are happily under way.

In fairness it must be noted that most of the trials which were refused at first review did go on to eventually pass ethical review. However, as we already described, in a number of cases the time spend on a second review is the nail in the coffin for the trial.

We can only hope that the Ministry of Health in forming its new Ethics Council will pay attention to the statistics we have gathered. And if they decide to leave in place the old specialists in the problem areas, that they will at least, with a view to improving the objectivity of case review, also include new Council experts for these fields.

REVIEW OF THE BASIC LEGISLATIVE PROBLEMS FOR THE CLINICAL TRIALS MARKET

The arrival of the new Minister for Health Veronika Skvortsova was met by the industry with optimism and hope that the long-awaited improvements in the sector of state regulation might finally be coming. And in fact, from the very first months of its work, the new body announced its plans for a full review of the provisions of the law 'On Circulation of Medicines'. They also promised that this would be done based on consultations with the industry and analysis of the corresponding proposals.

Taking into account the fact that in the near future the legislation may be subjected to another review, we decided in this issue to stick to the areas on legislative provision that have proven to be the most problematic for clinical trials. There are three:

- the unreasonably strict qualification requirements for the principal investigator;

- the redundancy of accreditation of medical organizations for the right to conduct clinical trials;

- the improperly selected type of insurance.

We would like to qualify straight away that we have not included the requirements for mandatory local registration trials in this list – not because we underestimate the negative consequences of this provision. Rather, it is simply because we assign this particular problem not to the sphere of clinical trials, but to registration and market access.

We have also not included in this list a large number of other problems with clinical trials. These include the artificially-implemented system of classifying trials by aims, and the unfounded (in our opinion) ban on conducting early-phase trials of foreign medicines on healthy volunteers, and the not-entirely reasonable limits on participation in trials by vulnerable groups of patients, and other provisions regarding various aspects of conducting trials. But all of these problems together do not limit the market and do not threaten its development to the same degree as the three listed above.

Qualification requirements for the principal investigator

According to the law 'On Circulation of Medicines' the principal investigator, responsible for conducting the clinical trial in the centre, must be a doctor with a therapeutic specialization that corresponds to the trial in question, with at least five years of experience working on the clinical trial programme.

The law 'On Medicines' had less strict requirements for investigator' experience – two years of participation in trials. What made legislators decide to make this requirement so much stricter? Unfortunately, the answer to this question like so many others remains a mystery. As, by the way, do the appearance in the law of a large number of other standards which have raised much discussion in the pharmaceutical community. As far as we can recall, the Ministry of Health and Social Development in preparing this law did not especially consult with any experts. The market was simply presented with a fait accompli and forced to accept to the conditions of the game.

At the same time, objective factors for tightening the requirements for researchers did not exist. The results of international trials conducted in Russia are accepted around the world, and their quality is satisfactory to strict international requirements.

According to the official website of the FDA, from 1995 and up to 2010, the year when the law 'On the Circulation of Medicines' was adopted, Russian centers were inspected by the FDA 51 times.

The result of 29 of these inspections was a NAI rating (No Action Indicated, meaning that there were no problems found);

The result of 21 of these inspections was a VAI rating (Voluntary Action Indicated, meaning separate, non-urgent comments that do not require the intervention of regulatory bodies and can be corrected by the researcher);

And just one inspection was rated OAI (Official Action Indicated, meaning a serious violation requiring intervention of regulatory bodies). This single case of a critical evaluation was recorded in February 2006, and concerned a principal investigator with more than 5 years of experience in clinical trials.

To compare the quality of trials conducted in Russia, in Table 10 we present the results of FDA inspections in a number of countries between 1995 and 2010.

Table 10

Results of FDA Inspections by Countries, 1995-2010							
Country	**Number of FDA Inspections, 1995 - 2010 г.**	**NAI**	**NAI, % of total number**	**VAI**	**VAI, % of total number**	**OAI**	**OAI, % of total number**
Denmark	**15**	**8**	**53,3%**	**7**	**46,7%**	**-**	**0,0%**
Sweden	**19**	**8**	**42,1%**	**11**	**57,9%**	**-**	**0,0%**
Germany	**56**	**22**	**39,3%**	**33**	**58,9%**	**1**	**1,8%**
Russia	**51**	**29**	**56,9%**	**21**	**41,1%**	**1**	**2,0%**
France	**44**	**8**	**18,2%**	**35**	**79,5%**	**1**	**2,3%**
United Kingdom	**77**	**26**	**33,8%**	**49**	**63,6%**	**2**	**2,6%**
Argentina	**28**	**15**	**53,6%**	**12**	**42,9%**	**1**	**3,5%**
Republic of South Africa	**28**	**14**	**50,0%**	**13**	**46,4%**	**1**	**3,6%**
USA	**3852**	**1580**	**41,0%**	**2128**	**55,3%**	**144**	**3,7%**
Spain	**16**	**8**	**50,0%**	**7**	**43,8%**	**1**	**6,2%**
Finland	**13**	**8**	**61,5%**	**4**	**30,8%**	**1**	**7,7%**
Italy	**32**	**17**	**53,1%**	**12**	**37,5%**	**3**	**9,4%**
Netherlands	**17**	**4**	**23,5%**	**11**	**64,7%**	**2**	**11,8%**
Belgium	**25**	**12**	**48,0%**	**10**	**40,0%**	**3**	**12,0%**

Data from http://www.fda.gov/

But is it possible that Roszdravnadzor, the body responsible during all those years for controlling the quality of trials in our country, could have had complaints about the work of Russian investigators? But no, there are no data at all to indicate a need to tighten qualification requirements for investigators, there was nothing at all.

At the same time the implementation by this law of the requirement for work experience does not correspond to international practice. According to ICH GCP, the qualification requirements for investigators extend to having relevant education, training and experience to enable the investigators to take on the responsibility of conducting the clinical trials. In the US, for example, it is not even necessary for the principal investigator to be a doctor. Although in this case, there must be a doctor as a co-investigator. On the whole in international practice, regulation proposes to evaluate an investigator's qualifications on the basis of his CV at the stage of deciding whether to allow him to participate in the specific trial in question.

Evaluating the CVs of potential investigators with a view to issuing approvals to conduct trials is also enshrined in Russian law. A person whose experience or qualifications raise any doubts can be denied approval as an investigator at approval stage, and there is no need for such strict requirements.

Here for the reader who may not have a full in-depth understanding of the subject matter, it is necessary to clarify what exactly is the role of the investigator in the context of a clinical trial. It does not include any independent 'research' activities, in fact it does not differ markedly from routine patient management practice. The task of the doctor-investigator is to select patients who meet the inclusion criteria for the study, to administer the therapy in strict accordance with the protocol, to collect the necessary samples and data to send them to the sponsor. The main requirement for an investigator is the need to strictly follow protocol and precisely maintain all documentation. Regarding the activities of the principal investigator, his or her function is more organizational and administrative. Based on the fact that there are no special, complex skills required from the doctor to do this job, the implementation of a legal requirement that he/she possess five years of experience working on clinical trials is entirely superfluous.

The adoption of these standards has lead to a significant drop in accessibility of clinical trials for Russian investigators, primarily in regions far from the capital. Based on the most conservative estimates, as a result of implementing these new standards, the market for active investigators has contracted by 25-35%. It is not possible to open new centers in regions lacking doctors who already have experience in working on trials.

The requirements to have a relevant therapeutic specialization corresponding to the clinical trial has further limited the number of available qualified investigators. And so generalist and primary care doctors are robbed of the chance to take part in most trials. In routine medical practice, the generalists treat a wide range of diseases, which is most topical in the regions of Russia located far from Moscow and St. Petersburg, where the number of doctors possessing narrow specializations is much lower. Despite the lack of further postgraduate qualifications, these doctors nevertheless have the full right to treat the sick, but are denied the right to take part in trials. Patients, in turn, particularly those in the most remote Russian regions, are denied the right to take part in trials, because they do not always have access to a doctor with the required levels of specialization.

In addition, this requirement leads to denials for trials in narrow specializations, where developing new medicines is practically non-existent or is limited. Such as example is tuberculosis. In Russia there are very few specialist phthsiologists (TB doctors) who have five years of experience in working on trials. Therefore, despite the unacceptably high rates of tuberculosis infection in our country, the opportunity to conduct trials into new treatments is severely limited.

It is possible that in implementing these new standards, someone decided that this would improve the quality of the data and create better protection for patients. But we propose that this is an extremely short-sighted point of view. In reality such an approach will lead directly to the opposite result – the limitation of competition among doctors, with a high concentration of clinical trials in the hands of a limited number of investigators, and correspondingly, to reduced quality in conducted trials and simultaneously inflation of costs.

In addition, this approach leads to contradictions with the strategy for innovative development in the pharmaceutical sphere, because it creates a significant brake on the development of an important innovation sector – the clinical trials market. The standards that hinder trials in Russia inexorably lead to slower development of the domestic pharmaceuticals industry.

Accreditation of medical organizations for the right to conduct clinical trials

According to the law, to participate in a clinical trial a medical organization must have special accreditation. This requirement was also enshrined in the previous law 'On Medicines'. But in the pre-reform era the process was more of a notification and did represent the serious administrative barrier that it has now become.

What are the basic problems with the accreditation system? First of all, this is an additional and completely unnecessary bureaucratic process. The fact that in Russia we have a system wherein to obtain various forms of approvals, one must periodically make changes, change the approval document in a timely fashion before it expires, and so on, we do not need to explain to anyone. But accreditation has brought in a whole chain of additional problems. For example, in Russia historically many professorial chairs of medical educational institutions are based at various medical establishments, and by no means all of them are related to the educational institutional structure. The frequently-seen relationship between the chair and the hospital is based on a business contract or an agreement of cooperation. This is logical, for educational institutions do not always have their own hospitals where they can meet the needs of medical practice as set out by the institution. The practice of conducting trials in Russia was also based on this structure of cooperation. Often, the investigators are professors from the educational institutions, whose appointments are based at city or regional hospitals. Previously, before the law 'On Circulation of Medicines' came into force, the approval to conduct a trial would stipulate that it was to be conducted by chair of educational institution A, based at hospital B. With the implementation of accreditation, this practice has been called into question. The Ministry of Health and Social Development has begun refusing applications to conduct trials at hospitals being used as a base for the educational institution to conduct the trial. Why?

The issue is that accreditation has brought a new interpretation of 'location of the trial'. In the information on the accreditation certificate, only the address listed on the medical license of the medical institution was indicated. And further on, functionaries at the Ministry of Health and Social Development raised the logical question – if accreditation is based at one address, why is the approval to conduct the trial including another address, which is the actual location of the chair? And they began to demand proof that the trial would be conducted at the actual hospital. It would seem that there is a simple solution to this problem – in order to avoid confusion, applicants should get accreditation at both the educational institution and at the hospital. But this does not in fact solve the problem. To obtain approval for the trial you must also present documentation on the principal investigator. And in this case we're back to square one – the professor officially works at the educational institution but in reality is based at the hospital. To get approvals for both institutions with the same principal investigator is not possible. And we should not forget that the principal investigator must also have five years of experience in clinical trials. We have a vicious circle. The educational institutions have the staff, but not the facilities. The facilities want to take part in trials, but often cannot be named as independent centers because they do not have the necessary specialists who meet all the criteria. And the accreditation systems does not allow to officially record their cooperation, which clearly refers the trial to 'the place of employment' of the principal investigator.

The resulting situation has caused a great deal of anxiety with market players who work on the 'educational institution based at a hospital' model. On the one hand the system is legal, it has existed for many, many years, and no one is trying to hide anything. On the other hand – what if someone suddenly decided it is in violation of regulations?

At the same time, international practice does not require any kind of special license or accreditation for medical organizations to participate in clinical trials, since conducting these trials does not require any kind of additional procedures that would fall outside the scope of licensing of normal medical activities.

Such special requirements do not exist in Russia either. According to the Rules of Accreditation, set out by Government Decree N 683 of September 3, 2010, the main requirement to obtain accreditation is the possession of a valid license to practice medicine. And the only special requirement is the presence of a separate department (ward) for ICU and resuscitation for those organizations applying to conduct Phase I trials. But it is not worth implementing such a complicated mechanism just because of this one extra requirement. It would be perfectly sufficient to have an amendment to the law and check for compliance during the approval process for Phase I trials.

In any case the decision about participation by a given healthcare institution is made after examining the application to conduct clinical trials. As a result, the implementation of the accreditation system is duplicating work: first the clinic must obtain a special right in the form of an accreditation certificate, and then subsequently must undergo additional approval for participation in the specific trial in question and obtain approval to conduct clinical trials.

Insurance in clinical trials

The law 'On Circulation of Medicines' brought in a mandatory type of insurance – personal insurance for patients participating in clinical trials. At the same time, a more appropriate way to regulate the relationship would be liability insurance for the entities organizing and conducting the trials. In international practice it is the liability of sponsors and investigators in the conduct of the clinical trial, that is the object of insurance.

The incorrect choice of insurance has lead to the creation of a number of conceptual problems which are creating a threat to the normal functioning of the insurance mechanisms in this area, and potentially for the clinical trials market as a whole.

What is the fundamental difference between the two types? For answers to this question we need to look deeper at several legal points.

1. The legal nature of the relationship

The legal nature of the relationship between the parties in terms of clinical trials does not fit the substance of personal insurance. The idea of personal insurance is that the specified insurance sum will definitely be paid out in the event that the insured person experiences harm to life or health, reaches a pre-determined age, or another contractually pre-determined phase of life (article 934 of the Civil Code of the RF). There is no condition that the harm must come from any person's specific actions. It might be the result of physical actions, a natural disaster, terrorist acts, or a simple accident. Simply put, we are speaking about any unfortunate event which lead to harm to life or health, regardless of the cause or even person responsible.

At the same time, an agreement of liability insurance can offer insurance against the risks incurred by a person of responsibility whose job may inflict harm. In other words, an insurance payout is made if harm to life or health occurs specifically as a result of the actions of the insured individual, or another person who is liable for the responsibility.

Since within clinical trials we are talking about the actions of a specific individual who develops the medicines, and it is precisely this which may potentially bring harm to a patient, it would appear that at the core of these relationships we must look at precisely the liable individual conducting the trial for the harm which could be a result of some heretofore unknown adverse effect of the medicine being studied, or a medical mistake.

We must also take into account that the payment under personal insurance does not release the insured from recompense under civil legislation. In other words the present model of insurance allows the patient to receive a payout based on a personal insurance policy, and alongside this makes a claim against the sponsor or investigator to get out of them an additional sum taking into account the harm done. This 'double' indemnification has become possible because from a legal point of view, these are distinct reasons for payouts – the requirement on the personal insurance policy (article 934 of the Civil Code of the RF) and the requirement on the wrongdoing (article 1964, 931 of the Civil Code of the RF).

2. Insurable event

According to the law 'On Circulation of Medicines', an insurable event is held to be the death of a patient or the worsening of his health with a clear casual relationship between the onset of the event and the patient's participation in the clinical trial.

In other words, based on the understanding of personal insurance, the patient has the right to make an insurance claim on the basis of any adverse drug reaction upon taking the medicine in the study, regardless of whether the reaction was expected, in other words even if the patient was warned about it in advance, or whether it was unexpected.

The peculiarities of medicine are such that their application characteristics as a product present a balance of usefulness from application and risk of the origin of adverse reactions to the medicine. This is why the instructions for any medicine contain a list of possible adverse drug reactions, warning the consumer of these in advance. And as a rule, the more effective a medicine is, the longer is the list of potential adverse drug reactions. But the manufacturer does not bear the liability for any harm caused to the consumer's health as a result of these 'expected' or foreseen adverse drug reactions.

However liability arises in the event of unexpected adverse drug reactions not included in the instruction sheet for the medicine. This provision is conditional in provisions of civil legislation, in accordance with which the harm to life or health of a citizen as the result of structural, chemical, or other faults of the products, as well as a consequence of misleading information about the product, is laid on the seller or manufacturer of the product, regardless of their fault, and also of whether their level of scientific and technical knowledge allowed them to have any understanding of the nature of the product or not.

It appears that a similar procedure must be applied to the relationship in the area of clinical trials. The potential participant in such trials is warned in writing about all the known or foreseen adverse drug reactions to the medicine being studied and takes this information into account when making a decision about whether or not to participate in the trial.

There is the point of view that when personal insurance is used instead of liability insurance, this gives the patient the right to seek compensation for harm to health due to any adverse drug reactions to the medicine, including those about he clearly knew, and the risk of which was nearly 100%. It would seem that this does not entirely correspond with generally accepted principles of logic and justice.

In preserving this condition there is a great risk of misuse by patients, which could lead to insurers refusing to participate in this form of insurance. In turn this could put the entire process of clinical trials under threat.

3. The circle of insured persons (beneficiaries)

Personal insurance has clearly indicated insurance of specific insured persons set out in the insurance agreement. In our case these are the specific patients included on clinical trials.

At the same time the circle of people who could potentially suffer as a result of the clinical trial is broader, and may be undetermined. The potential harm caused by a previously unknown effect of a medication could

cause harm to a fetus or to a child from a possible pregnancy both for a woman participating in the clinical trial herself, or for a woman whose sexual partner was a trial participant. This risk is real, and pharmaceutical companies always warn participants to avoid pregnancy both for themselves and for their sexual partners. But in the event that a pregnancy does occur, the company will be liable for any harm that comes to the fetus or the child.

The current system only insures an unreasonably narrow circle of people facing potential harm as a result of participation in clinical trials. This problem could be solved by replacing personal insurance with liability insurance. Then, in the case of an insurable event, the beneficiaries would be all individuals who could be harmed by the person whose liability is insured, and therefore the circle of people is not limited only to those directly participating in the trial.

4. Other problems of using personal insurance

Introduction of this type of insurance that does not conform to the legal requirements of the situation has led to significant difficulties for the whole insurance scheme utilized in clinical trials.

As was described above, personal insurance supposes that the agreement is signed to benefit a specific person. This has triggered the requirement to keep a list of all patients included in clinical trials. However at the moment that the insurance agreement is signed, this requirement cannot be fulfilled. Before the start of the trial, it is not known who will visit a doctor, who will agree to participate in a trial, who will meet all the criteria and be included on it. And even after the trial starts, the patient list may be added to for quite some time. Selection for trials is not a momentary procedure, it is a lengthy process. It can take months, and for longer studies even years.

As a result, both the sponsor and the insurer are put in a difficult situation of needing to constantly update the register of insured people. This problem is exacerbated by the fact that the first edition of the Model Rules for Insurance envisaged recording patient personal data, which was not permissible from an ethical point of view. Later this led to changing the requirement for personal data to the extremely inconvenient and cumbersome 33-figure subject identification code. Using this code in practice, including the need to write it by hand on the patient information sheet, has led to significantly more difficult work and an increased risk of errors.

In addition, according to the established Model Rules, the document establishing the agreement on behalf of the insured person is a mandatory insurance policy issued to every insured person. This document must be produced when making an insurance claim.

The need to issue personal policies for all patients has led to additional technical problems. If before the implementation of this mechanism, the insurance agreement covered all participants in a given study, and the patient had only to confirm the fact that he participated in the trial (by presenting a copy of the informed consent form or by proving his participation in some other way), now he/she must have a copy of his/her personal policy. This significant increase in the number and complexity of necessary documents has made work significantly more difficult for insurers, the insured parties, and investigators. It is also necessary to consider the risk of loss of the patient's copy of the insurance policy, which could lead to a formal refusal to pay out any claim.

5. The risk of an insurable event occurring

The statistics we have for insurable events allow us to assign clinical trials to the category of activities with a relatively low level of risk.

According to European statistics[6]:

– The 'German KKS Netzwerk — Koordinierungszentren für klinische Studien' has reported three liability cases with minor damages in trials over a period of 10 years (1997-2007) involving more than 20 000 trial subjects.

– In Finland, the Finnish Patient Insurance Centre and the Finnish Pharmaceutical Insurance Pool, between 2005 and 2010, received 19 requests for compensation, of which 4 led to compensation payment. According to EudraCT, since the entry into force of the Clinical Trials Directive there have been 299 059 trial subjects planned for enrolment in Finland.

– In Denmark, according to the Danish Patient Insurance System (DPIS), over a period of 10 years 27 claims for compensation have been accepted from patients taking part in clinical research projects. This amounted to a sum of approx. €550 000. According to EudraCT, since the entry into force of the Clinical Trials Directive there have been 117 450 trial subjects planned for enrolment in Denmark.

The access to Russian statistics allows us conclude that before the law came into force, the number of insurable events was also very small. According to ACTO's data, the result of a poll of members, in the period 2007 to 2009, the number of patients insured by ACTO members was more than 71,000. There was not a single recorded insurable event.

After implementing the new insurance system, there was a sharp increase in the number of patients lodging unfounded insurance claims. And so according to data from the largest operator on the market for insurance in the clinical trials sector – Ingosstrakh – the number of first contacts (telephone calls, letters) increased 8-10 times after the new legislation was adopted. And there is cause to believe that patients and relatives do not fully understand the point of insurance and immediately insist on being paid for their claims, without regard for the need to establish a causal relationship between participating in the trial and the onset of symptoms – the harm to health or death. It seems that many of them are attracted simply by the sums of money that may be offered in payouts.

This is confirmed by the fact that 75% of all first contacts are in reference to deaths (payout on death is worth 2 million rubles, and is a maximum possible payout). Taking into account that the vast majority of patients who are suffering from serious illness and take part in clinical trials could die as a direct result of the progression of their disease, according to the protocol (especially in oncology), mortality rates can be up to 100%. There is no doubt that the relatives of such patients are attracted by the opportunity to get such a large sum of money. But in fact once the patients or relatives discover that the claim is only paid if a direct causal relationship can be established, about 80% of potential claimants disappear. Nevertheless, according to Ingosstrakh's figures, the number of official written claims has quadrupled since the new system was put in place.

Investigators also confirm this negative trend towards 'patient extremism'. There have been cases where patients have, for no apparent reason (and even sometimes as doctors observe overall improvements in their condition), suddenly begun clearly faking signs of deteriorating health, revoking their agreement to participate in the study and making an insurance claim. The situation is quite understandable. The potential to make between 300,000 and 1.5 million rubles (or up to 2 million upon the death of a patient) is, particularly in the far-flung corners of our country, extremely enticing. But does this benefit the clinical trials market? Not very likely.

In summation, we can state that adopting this system of insuring patients in clinical trials has given rise to a whole host of problems both for the insured parties and the insurers. In many ways it fails to protect the interests of those taking part in clinical trials. And from a different perspective, it leads to an increase in 'patient

6 *SANCO/C/8/PB/SF D(2011) 143488 Revision of the 'Clinical Trials Directive' 2001/20/EC, Concept Paper Submitted for Public Consultation, Brussels, 09/02/2011*

extremism'. This matter could be resolved by changing the type of insurance from personal insurance to sponsors' and investigators' liability insurance.

FOREIGN NEWS

While we struggle with administrative hurdles in our country, in Europe not only have they put paid to the negative influence of superfluous bureaucratic pressure on the market, but they have even worked out a treatment plan.

The Commission's proposal to review and simplify the rules governing clinical trials is aimed at increasing the EU's attractiveness for development in this sector – according to a press release from the European Commission7 published July 17, 2012.

The reason for this announcement was the Commission's serious concern over the decreasing numbers of clinical trials in Europe. According to the press release, an unfavourable regulatory framework for clinical trials lead to a decrease of 25% of clinical trials conduced in the period between 2007 and 2011. In 2007 the number of applications to conduct trials in the EU was 5,000, but by 2011 it had dropped to 3,800.

According to the European Commission's, the new measures would on the one hand make approval and accounting procedures faster and simpler, and on the other hand, preserve a high level of protection for participants and high reliability in the data.

The European Commissioner for Health and Consumer Policy John Dalli said, 'Patients in Europe should have access to the most innovative clinical research. Clinical trials are crucial for developing new medicines and improving existing treatments.' He claims that, 'the new proposal will significantly improve the management of clinical trials, while maintaining the highest standards of patient safety and the robustness and reliability of trial data. 800 million euros per year could be saved in regulatory costs and boost research and development in the EU, thus contributing to economic growth.'

If the new rules are adopted they will replace the Clinical Trials Directive of 2001. The legislative proposal will now be discussed in the European Parliament and in the Council. It is expected to come into effect in 2016.

We should remember that at present the European market is significantly larger than the Russian market in terms of the number of trials conducted. Whereas European countries see about 30% of the global totals of clinical trials, Russia's share amounts to just 1.5%. We can assume that against the background of the planned reforms in Europe, the continuing existence of unwarranted administrative hurdles in Russia will only increase this difference.

[7] http://europa.eu/rapid/pressReleasesAction.do?reference=IP/12/795&format=HTML&aged=0&language=EN&guiLanguage=en