ACTO

ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

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SUMMARY

The Ministry of Healthcare and Social Development issued 132 approvals for clinical trials in the third quarter of 2011, which is 1.5% and 13.7% fewer than in the third quarter of 2010 and 2009, respectively. Despite the continuing, in absolute terms, market decline in the third quarter of 2011, the rate of decline has slowed down (notably, the total number of studies was down 35.95% in the first half of 2011 as compared with the same period in 2010). General improvements are due to a certain increase in the number of approved trials performed by the Russian manufacturers we are seeing for the first time since the adoption of the new authorisation system.

At the same time, for the first time since the authorisation functions have been transferred to The Ministry of Healthcare and Social Development, we are seeing a decline in the number of approved international multicenter clinical trials (IMCTs). In the third quarter, the ministry approved only 84 such trials.

In order to reach at least the level of 2010 by the end of 2011, the Ministry of Healthcare and Social Development should issue at least 150 approvals in the fourth quarter. The ministry will be able to attain the level of 2009 if it issues not less than 245 approvals before the end of 2011, of which at least 100 for the IMCTs.

Problems with accreditation of medical institutions for the right to conduct clinical trials caused great concern of market participants in the summer, but were effectively addressed at the last moment largely thanks to strenuous efforts of the Department of State Regulation of Circulation of Medicines at the Ministry of Healthcare and Social Development. As you may know, only 190 medical institutions were accredited as of early August 2011. In August, the Ministry of Healthcare and Social Development issued 10 executive orders in a row to accredit 465 medical institutions, or 70% of the total number of medical institutions accredited in 2011. By September 1, 655 institutions had the right to conduct clinical trials, which helped to cover minimal needs of the market.

In addition to accreditation, we decided to use this newsletter to discuss the requirement to conduct local registration trials and activities of the Ethics Council at the Ministry of Healthcare and Social Development.

Arguably, the requirement to conduct local registration trials has become the most serious blow to the system governing the access of new medicines to the Russian pharmaceutical market over its entire recent history. By September 1, 2011, the Russian government was supposed to draft a proposal to cancel local registration trials initially proposed by President Dmitry Medvedev on June 2, 2011 following the 24th session of the Commission for Modernisation and Technical Advancement of the Economy. However, so far there is no hope that the situation will change any time soon. This newsletter describes the history of establishing rules for conducting local trials, the effects of their implementation, and the analysis of possible solutions.

The ethics review is very important for clinical trials. The Federal law On Circulation of Medicines drastically changed the Russian pharmaceutical market's regulatory system and also affected the ethics review which is now in its formative stage. We believe that key problems associated with the Ethics Council include unavailability of its standard operating procedures (SOPs) to the public, lack of transparency, unpredictability of the ethics review procedure, inability to track documents within the system, a large time lag between the decision and respective comments, as well as the inability of applicants to discuss these comments and defend their position.

STRUCTURE AND DYNAMICS OF THE CLINICAL TRIALS MARKET

The Ministry of Healthcare and Social Development issued 132 clinical trials approvals in the third quarter of 2011.

Summarizing the results of the third quarter of 2011, we were confronted with the choice of an appropriate reference period. As is known, the restructuring of the regulatory system led to the Ministry of Healthcare and Social Development issuing zero clinical trials approvals from September 1 to November 12, 2010. *De facto*, comparing the third quarter of 2011 and the third quarter of 2010 is about comparing *three* months of work of the Ministry of Healthcare and Social Development in 2011 with *two* months of work performed by the Federal Service for Supervision of Healthcare and Social Development in 2010. With this in mind, we believe that methodologically it is more correct to compare the results of the third quarter of 2011 with the results of the same period of not only 2010, but also 2009, which is the nearest pre-reform year.

Accordingly, 132 approvals have been issued during the third quarter of 2011, which is 1.5% and 13.7% fewer than in the third quarter of 2010 and 2009, respectively (Table 1, Diagram 1).

Table 1

Approvals for Conduct of Clinical Trials: Q3 of 2011 vs. Q3 of 2010 and 2009						
	Total	**International Multicenter CT**	**Local CT (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CT (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
Q3 of 2011	**132**	**84**	**4**	**1**	**30**	**13**
Q3 of 2010 (July- August)	**134**	**60**	**13**	**3**	**29**	**29**
Q3 of 2009	**153**	**93**	**7**	**2**	**32**	**19**
Q3 of 2011 vs. Q3 of 2010, %	**-1,5%**	**40,0%**	**-69,2%**	**-66,7%**	**3,4%**	**-55,2%**
Q3 of 2011vs. Q3 of 2009, %	**-13,7%**	**-9,7%**	**-42,9%**	**-50,0%**	**-6,3%**	**-31,6%**

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

Diagram 1

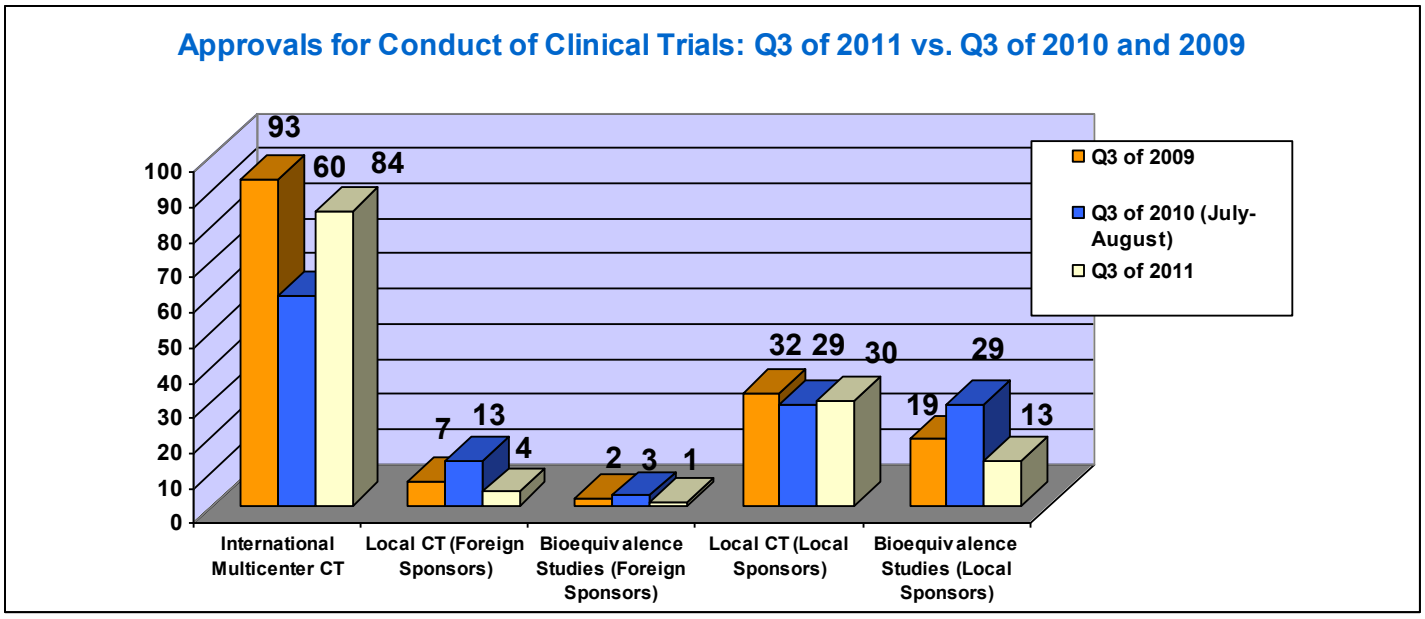
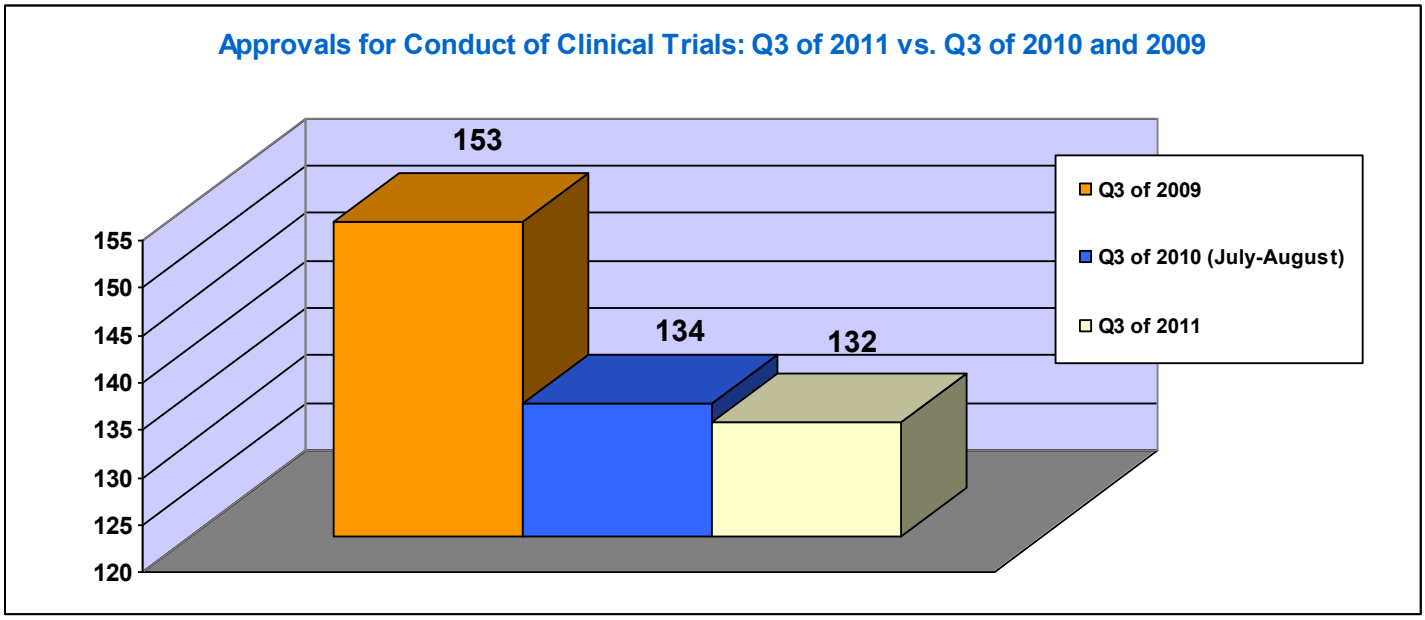


Diagram 2



As seen from Table 1, the drop in the total number of trials was in effect during the entire reporting period. However, its pace slowed down as compared with the first quarter of 2011. The market was down 35.9% by the end of the first six months of 2011. The situation improved in the third quarter of 2011 with more trial approvals issued to Russian companies (Table 1, Diagram 2). The number or clinical and bioequivalence trials conducted by Russian sponsors declined by 78.4% and 84.4% as of the end of the first six months of 2011 as compared with the same period in 2010, respectively; however, in the third quarter of 2010 the numbers were +3.4% and -55.2%, respectively.

In the third quarter of 2011, 84 IMCTs were approved, which is 24 more than in the third quarter of 2010. However, these numbers are still below the 2009 level.

Looking at the quarterly trend, which reflects the total number of approvals and the number of approvals for various research studies starting from the fourth quarter of 2010, when the new system actually became operative, it is clear that its productivity is on the rise (Table 2, Diagram 3).

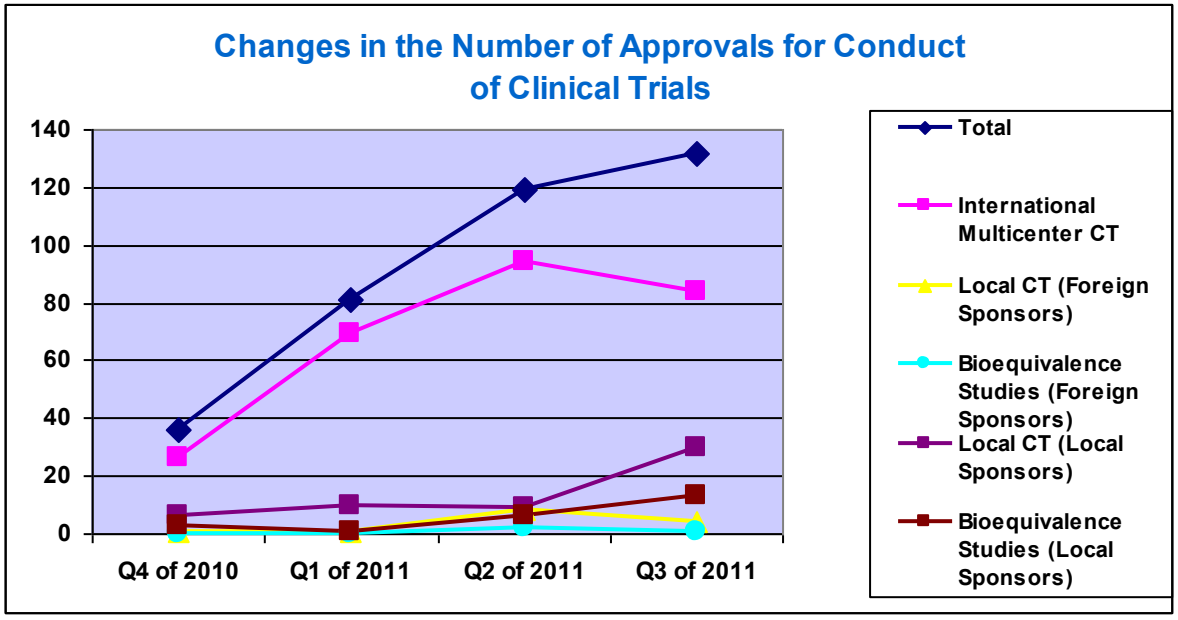
Table 2

Approvals for Conduct of Clinical Trials: Q4 of 2010 - Q3 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	81	69	1	0	10	1
Q2 of 2011	119	94	8	2	9	6
Q3 of 2011	132	84	4	1	30	13

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

As can be seen from Diagram 3, only the total number of issued approvals has been steadily on the rise starting from the fourth quarter of 2010. The number of IMCTs was up from the fourth quarter of 2010 through the second quarter of 2011; however, in the third quarter the number of approvals for this type of research declined again, this time by 10%. The total number of studies continued to grow, but this growth was attributable to an increased number of approved trials conducted by Russian companies, including bioequivalence studies and studies of effectiveness and safety.

Diagram 3

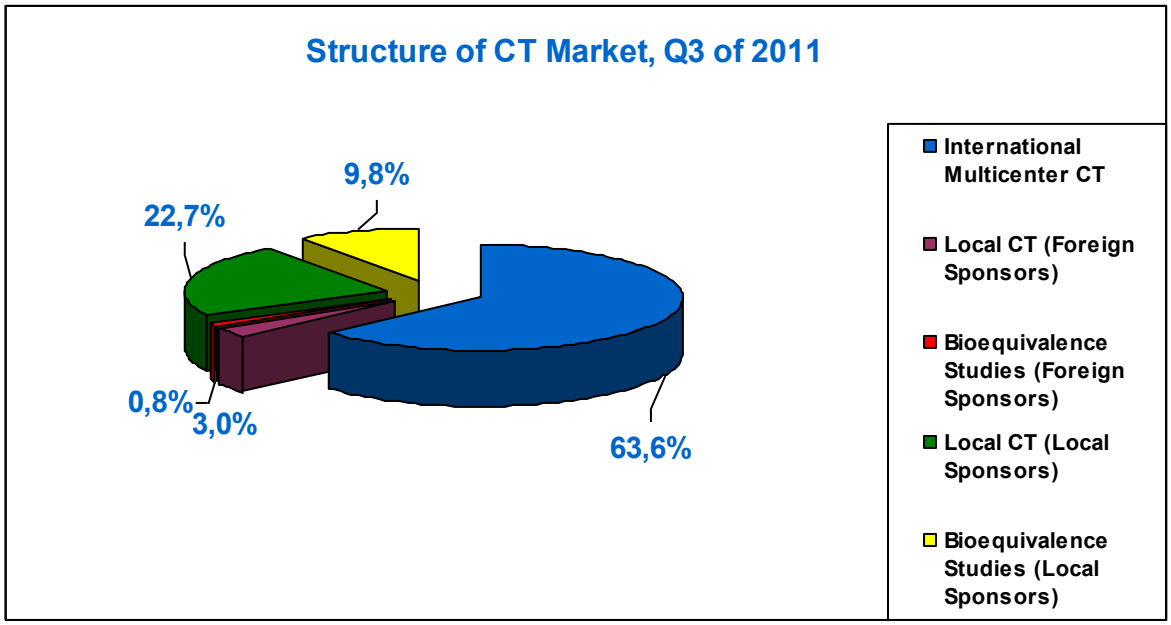


Despite the obviously positive general trend, it's too early to be optimistic. In order to reach at least the 2010 level, the Ministry of Healthcare and Social Development should be able to issue not less than 150 approvals in the fourth quarter of 2011. The Ministry will be able to attain the 2009 level, if it issues not less than 245 approvals before the end of 2011, of which 100 for IMCTs.

STRUCTURE AND DYNAMICS OF THE CLINICAL TRIALS MARKET BY TYPE

The outcome of the third quarter of 2011 suggests that the Russian market of clinical trials is gradually regaining its regular structure. As you may know, the share of IMCTs grew to an unprecedented high of 81.5% over the first six months of 2011 due to sharp decline in all types of clinical studies except IMCTs. In the third quarter of 2011, the share of IMCTs in the overall number of authorised studies amounted to 63.6% (Diagram 4). This number is within normal readings for the past seven years (50-65%). The respective shares of local clinical trials and bioequivalence studies conducted by Russian sponsors amounted to 22.7% and 9.8%, thereby also getting closer to average values of 20.6% and 13.6%, respectively.

Diagram 4



Data from www.grls.rosminzdrav.ru

STRUCTURE AND DYNAMICS

OF INTERNATIONAL MULTICENTER CLINICAL TRIALS BY PHASE

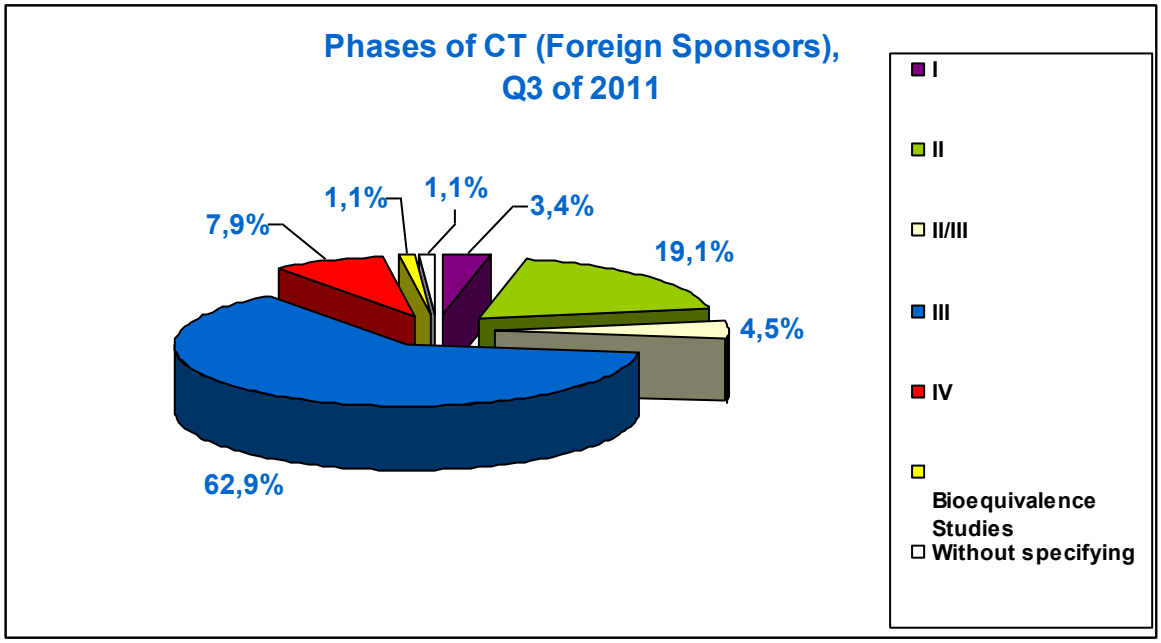
In the third quarter of 2011, the Ministry of Healthcare and Social Development issued 56 approvals for studies of the phase III (Table 3), which amounted to 62.9% of the total number of approvals for clinical trials supported by foreign sponsors (Diagram 5). Third-phase trials traditionally dominate international studies carried out in Russia. Fluctuations in the number of third-phase trials in 2004 – 2010 came to 50-60%. This number grew slightly to 63.2% during the first six months of 2011 and, according to the outcome of the third quarter, has so far remained unchanged.

Table 3

Phases of CT (Foreign Sponsors), Q3 of 2011						
I	II	II/III	III	IV	Bioequivalence Studies	Without specifying
3	17	4	56	7	1	1

Data from www.grls.rosminzdrav.ru

Diagram 5



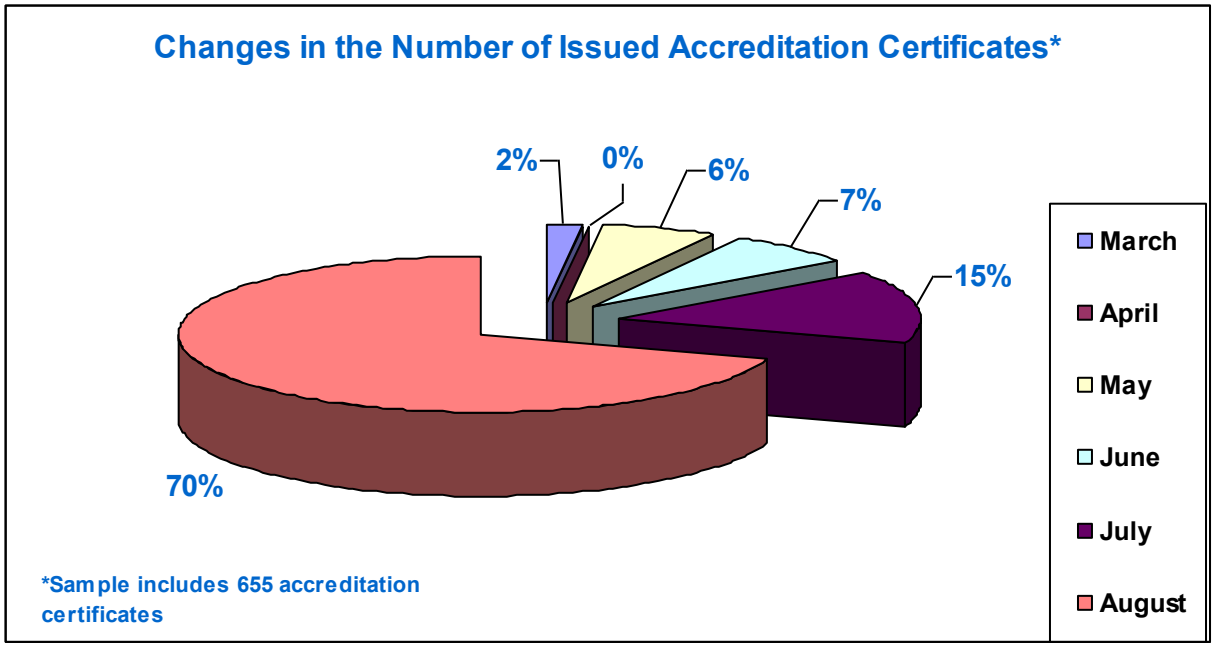
OVERVIEW OF PRACTICAL ISSUES

Results of accreditation of medical institutions for the right to conduct clinical trials

According to Resolution No.683 of the Russian government dated September 3, 2010, medical institutions participating in clinical trials should have had enough time to get accredited under new rules before September 1, 2011. This did not mean that after September 1 the accreditation process will stop, but it did mean that current studies could have continued only at the medical institutions that had obtained new certificates. Experts say that at least 600-700 institutions had to be re-accredited to secure normal functioning of the market. Clearly, the risk of failure to meet the deadline increased nervousness among market participants intensified as the deadline came closer.

By early August 2011, the Ministry of Healthcare and Social Development managed to accredit only 190 institutions, which is slightly over 30% of the required minimum. The situation was further aggravated by lack of accreditation of such flagships of the Russian medical science as the Blokhin Russian Cancer Research Centre at the Russian Academy of Sciences, the Mechnikov St. Petersburg State Medical Academy, the Petrov Cancer Research Institute, the Gerzen Moscow Cancer Research Centre, the Leningrad Regional Cancer Clinic, the Pulmonology Research Centre at the Federal Medico-Biological Agency, the Rheumatology Centre at the Russian Academy of Medical Sciences, Medical Academy for Postgraduate Studies, the Burdenko Main Military Clinical Hospital, and the Child Health Research Centre at the Russian Academy of Medical Sciences. This caused major concern among market participants, because these centers conduct dozens of clinical trials with the participation of thousands of patients at a time. The situation was remedied at the last moment and to a great extent due to strenuous efforts of the Department of State Regulation of Circulation of Medicines at the Ministry of Healthcare and Social Development. In August, the ministry issued ten executive orders in a row and accredited 465 institutions in a matter of one month. This is 70% of the total number of medical institutions accredited in 2011 (Diagram 6). Therefore, 655 medical institutions were authorized to conduct clinical studies by September 1, which helped cover minimal market needs.

Diagram 6



Data from www.grls.rosminzdrav.ru

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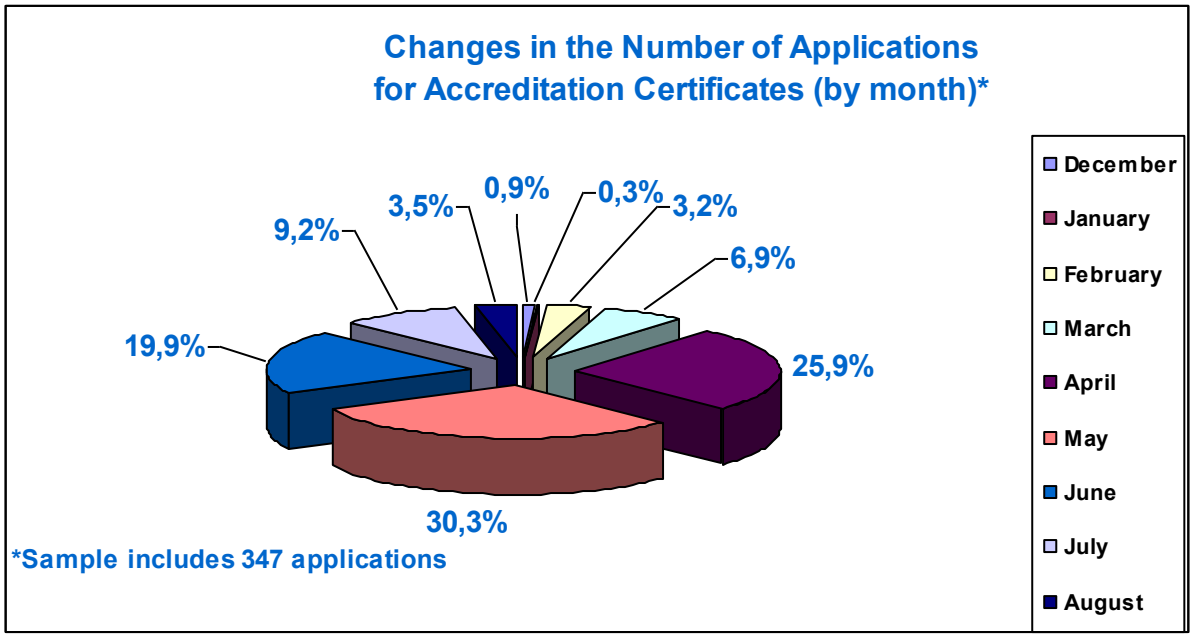
The information collected by ACTO with the assistance of member companies during the accreditation process, helped the association evaluate the activity of institutions in filing applications and average time going into issuance of accreditation certificates by months. The sample included 347 applications with known dates of filing to the Ministry of Healthcare and Social Development. As can be seen from Diagram 7, medical institutions were most active in April (almost 26%) and May (over 30%).

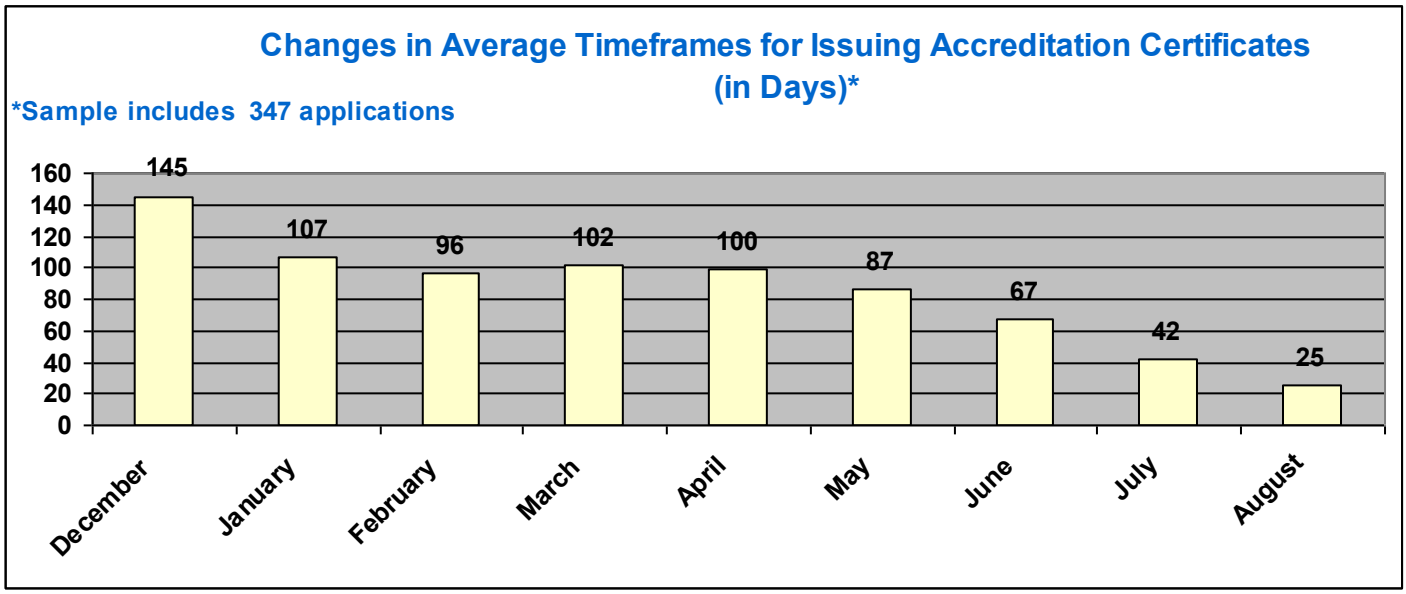
Diagram 7



Data from ACTO database of submitted applications for accreditation

The average time needed to obtain an accreditation certificate was 82 days (pursuant to the law, the certificates must be issued within 30 days). Notably, the time it took to obtain certificates gradually decreased as September 1 approached. Applications filed by medical institutions in late 2010 averaged about 145 days before the institutions could receive their accreditation certificates; medical institutions that filed documents in early August were able to obtain their certificates in under 25 days (Diagram 8). Clearly, the acceleration of the documents review process was primarily due to the approaching deadline.

Diagram 8



Data from www.grls.rosminzdrav.ru

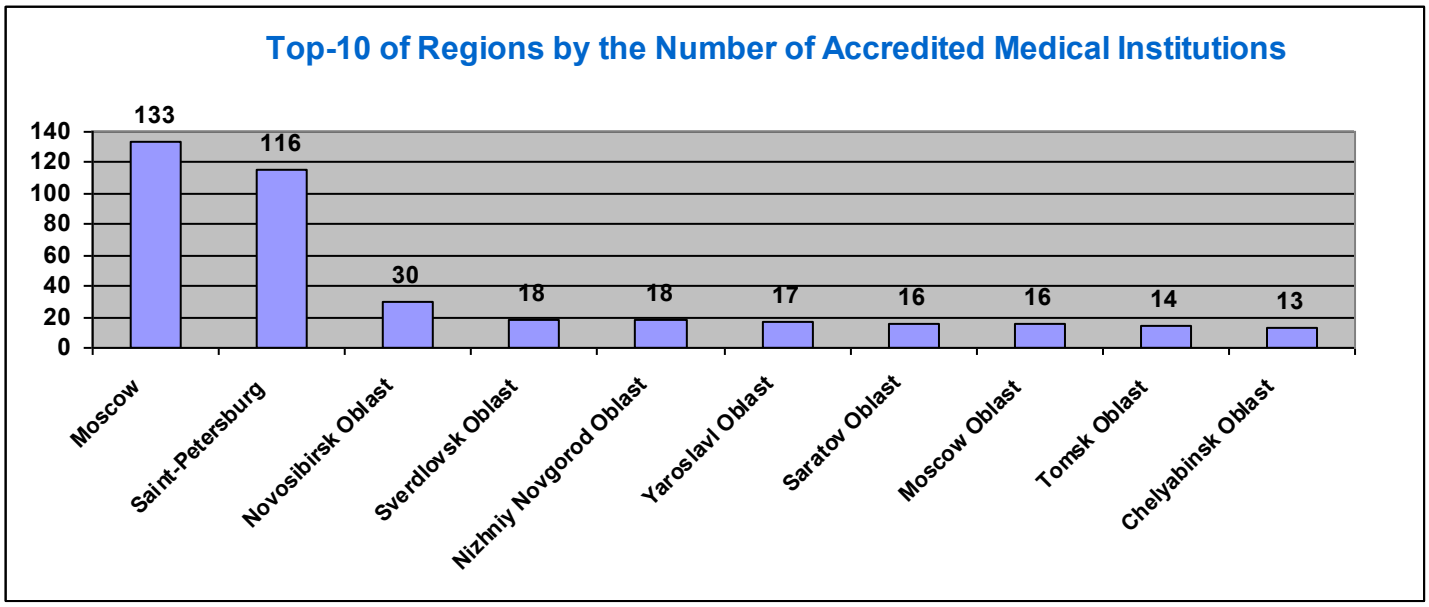
ACTO continually tracks progress of accreditation and monitors deadlines for issuance of certificates. We hope that new orders[1] will be issued soon, and timelines of accreditation that had gotten closer to the established standards by September will not increase dramatically.

* * *

It is interesting to see the distribution of accredited medical institutions by constituent entities and federal districts. The number of accredited medical institutions in constituent entities and federal districts is an indirect indicator of the level of involvement of the regions in international clinical programmes.

Moscow and St. Petersburg are incontestable leaders in the number of accredited medical institutions: 133 and 116 institutions, respectively. The Novosibirsk Oblast with 30 accredited institutions came in third (Diagram 9).

Diagram 9

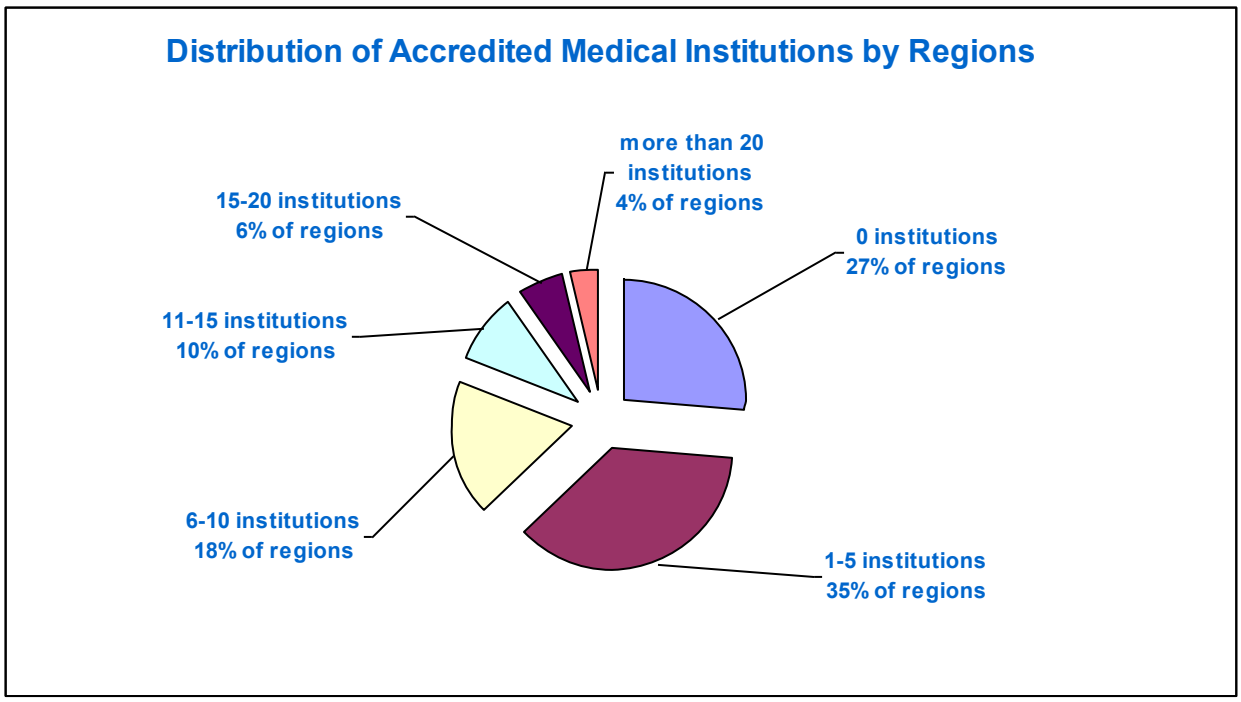


Data from www.grls.rosminzdrav.ru

[1] As of the date of issue of this newsletter, another executive order No.1317 about accreditation of 21 medical institutions was released on 2 November, 2011. Information about these organisations is not included in these calculations.

Diagram 10 shows the distribution of accredited medical institutions across Russian regions. In particular, it can be seen that 22 Russian regions (27%) have no medical institutions authorised to conduct clinical trials. One-third of the regions (35%) have one to five properly accredited medical institutions.

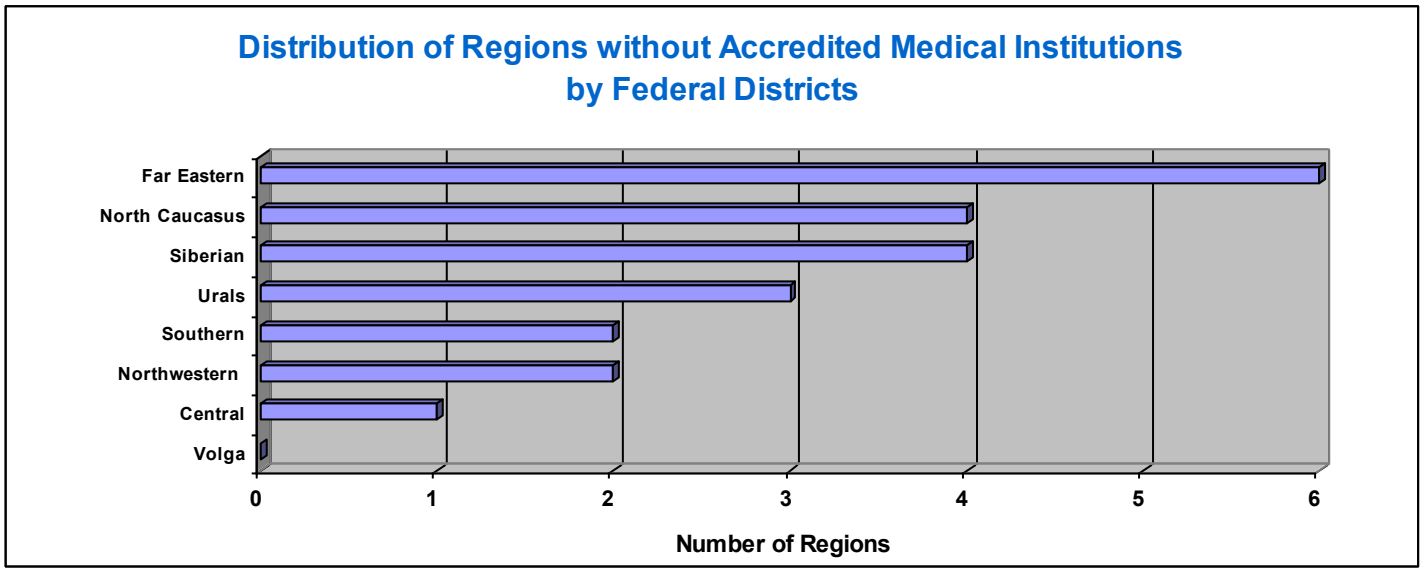
Diagram 10



Data from www.grls.rosminzdrav.ru

The distribution of Russian regions without accredited medical institutions by federal districts can be seen in Diagram 11. The greatest number of Russian regions (6) without a single accredited institution is located in the Far Eastern Federal District. Four regions in the Siberian and the North Caucasus federal districts, each (Altai, Buryatia, Tuva, Khakassia and Ingushetia, North Ossetia, Chechnya, Karachaevo-Cherkessia, respectively). In the Urals Federal District, there are no accredited medical institutions in the Khanty-Mansi and the Yamalo-Nenets Autonomous Districts and the Kurgan Oblast; in the South Federal District, Adygea and Kalmykia; in the Nortwestern Federal District, the Vologda Oblast and the Nenets Autonomous Area. In the Central Federal District the Kostroma Oblast is the only one without accredited institutions. All regions are involved in clinical trials only in the Volga Federal District.

Diagram 11

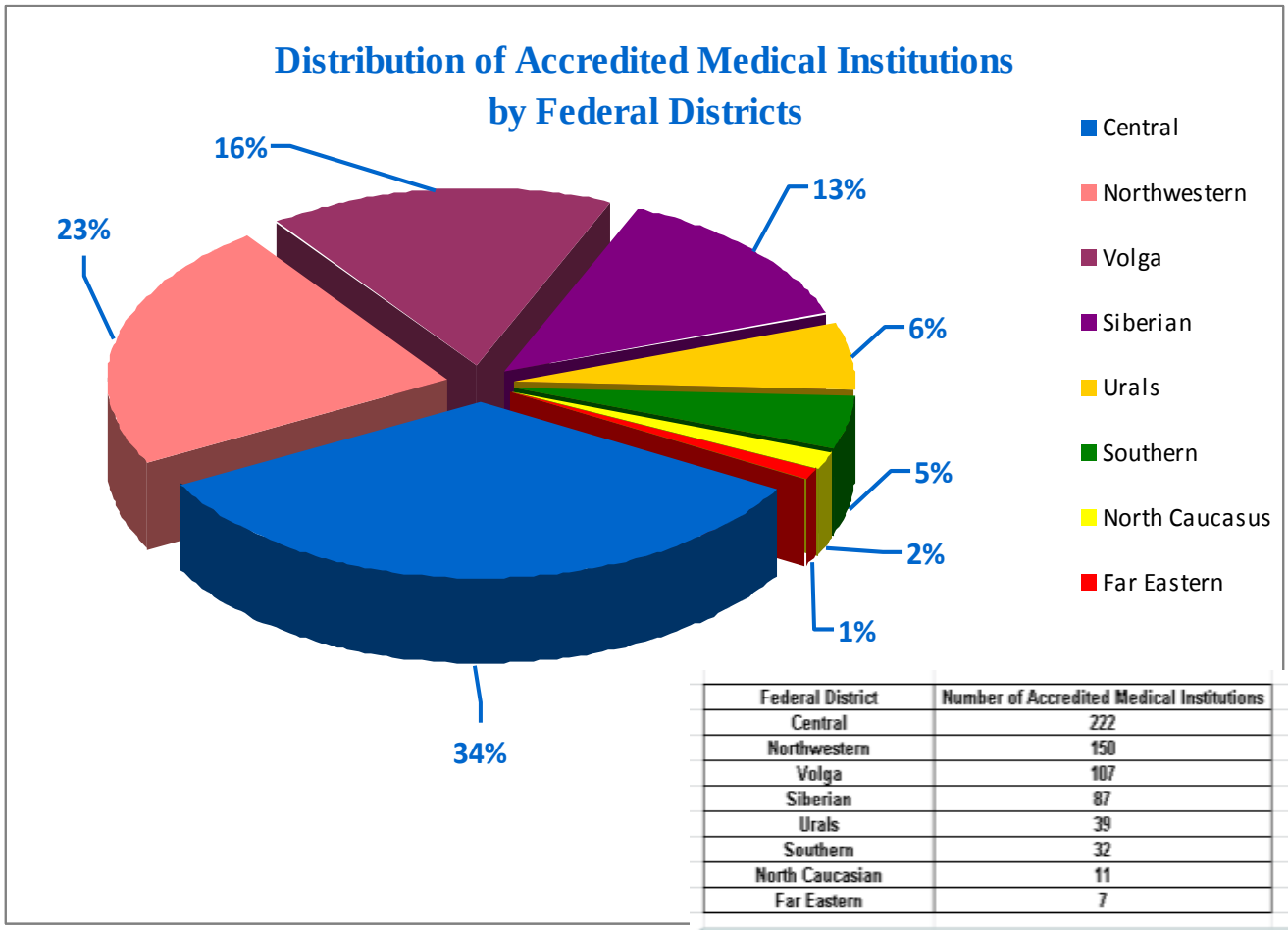


Data from www.grls.rosminzdrav.ru

The Central Federal District is the leader among federal districts in terms of the number of accredited medical institutions with 222 institutions located in this district entitled to conduct clinical trials (Diagram 12).

The Far Eastern Federal District has seven accredited medical institutions, which is the lowest number in Russia. All of them are located in three regions: Primorsky Krai and Khabarovsk Krai and the Amur Oblast. The North Caucasus Federal District has a slightly larger number of accredited medical institutions, 11. However, the district owes this achievement exclusively to the Stavropol Krai, which has 9 out of 11 accredited healthcare institutions. Of six North Caucasian republics, only Kabardino-Balkaria and Dagestan have accredited medical institutions.

Diagram 12



Federal District	Number of Accredited Medical Institutions
Central	222
Northwestern	150
Volga	107
Siberian	87
Urals	39
Southern	32
North Caucasian	11
Far Eastern	7

Data from www.grls.rosminzdrav.ru

Local clinical trials

In accordance with the instruction issued by President Dmitry Medvedev on June 2, 2011 following the 24th meeting of the Commission for Modernisation and Technical Advancement of the Economy, the Russian government was supposed to prepare a proposal to cancel local registration studies by September 1, 2011. Full text of the instruction runs as follows: "To prepare proposals seeking to amend regulations of the Russian Federation with the view to recognise in Russia the results of clinical trials of medicines conducted in the EU and the U.S., including those intended for use in paediatric practice." However, not a single amendment has been drafted yet that would give pharmaceutical market participants hope for a change in the foreseeable future.

Perhaps, one can assert that the requirement to conduct local registration studies has dealt an unprecedentedly serious blow to the system governing the admission of new medicines on the Russian market. Certainly, the issue of local studies has to do first and foremost with the registration system, not clinical trials per se. However, since this is so painful for most manufacturers, we decided to elaborate on it. In this newsletter, you will find an overview of background information about this rule and aftermath of its implementation, as well as an analysis of possible solutions.

I.

As is known, mandatory local registration studies were introduced in Russia by the Federal Law On Circulation of Medicines. This requirement was enshrined by establishing a two-stage registration process. According to the law, during the first stage, an applicant submits a registration file and documents for clinical trials approvals are examined. In case of a positive decision, the registration is suspended and the applicant conducts a study. During the second stage, the registration is resumed upon an applicant submitting an application; the results of a trial are evaluated and a decision is made on whether to register a medicine or not. The original draft law had this arrangement covering all products regardless of availability of results of full-fledged IMCTs, even if Russia was part of them. In fact, in order to register a medicine in Russia, manufacturers were to conduct mandatory repetitive studies.

Potential introduction of this requirement caused serious discussions of this draft law. Being against the introduction of local trials, market participants provided the following arguments. First, repetitive trials involving humans without acute need are considered unethical. In particular, the World Medical Association Helsinki Declaration says that "Medical research involving human subjects may only be conducted if the importance of the objective outweighs the inherent risks and burdens to the research subjects." The Directive 2001/83/EC runs as follows: "…there are reasons of public policy for not conducting repetitive tests on humans or animals without over-riding cause." The Directive 2001/20/EC says: "In order to achieve optimum protection of health, obsolete or repetitive tests will not be carried out, whether within the Community or in third countries. "

Second, it was obvious that the requirement for conducting local trials will postpone launching of new medicines by several years and that certain international manufacturers will refuse to register new medicines in Russia if they decide that costs involved in local trials will not pay off or are prohibitively high.

Finally, it is expected that local studies would not provide any new information about a product. Being a more limited sample in comparison with IMCTs, they lose to them by definition in the statistical significance of the results. It was predicted that the share of poor quality, if not artificially made-up local trials will grow. The goal of these trials is not about obtaining reliable data about the efficacy and safety of a medication, but drafting a "report" that will satisfy the regulator and help overcome administrative barriers.

Lawmakers have provided only one argument in favour of local trials. Allegedly, they account for "the population characteristics" of the Russian people. However, they did not specify any particular ethnic group while Russia, according to the census of 2002, is home to over 180 ethnicities.

By the time of the second reading and in an attempt to make a concession to the public opinion, the Ministry of Healthcare and Social Development introduced two exceptions into the law. The first one is about Russia's participation in IMCTs of a medicine. The second one is about the availability of an agreement on mutual recognition of the clinical trials' results between Russia and the country where they were conducted. However, only one exception is in effect, and the rule about mutual recognition has not yet become effective. Moreover, we believe that it cannot become effective altogether for reasons that will be discussed later. Notably, there is a specific presidential instruction with regard to agreements on mutual recognition, whose deadline also expired on September 1, 2011.

II.

The number of local trials has decreased. As of the end of the third quarter of 2011, the total number of approved local trials, including bioequivalence studies, was less than half of what was available during the pre-reform period. This is because companies need time to make a decision about conducting a clinical trial, prepare all necessary documents and obtain an approval. However, the situation is further compounded by the fact that applicants often do not understand what design can satisfy the regulator, how many patients should be included in the trial to make sure that the results are accepted for registration, etc.

According to market participants, the estimated cost of local trials of the efficacy and safety may start from 100,000 Euro and go as high as 1 million Euro and above. The upper limit depends on many factors. For example, local trials of cancer drugs cost companies much more. This amount will have to be paid to manufacturers of both original and generic medications, since bioequivalence studies cannot apply to all medication forms. Under the law, studies of therapeutic equivalence will have to be conducted for these forms. In essence, and hence in terms of cost, such trials of generic medications are not much different from local trials that should be carried out by originators. Experts say that registration of generic injectable cancer-fighting drugs has almost come to a halt.

In addition to expensive cancer medications, medications with narrow markets where sales may fail to cover expenses involved in conducting local trials also find themselves in the risk zone.

One Western company has kindly provided us with an opportunity to discuss in this Newsletter its attempt to register, based on new rules, an expanded list of indications for the use of a popular medication previously used to treat various conditions in women, including some pregnancy pathologies. The medication has already been registered for use during the first and second trimesters of pregnancy to prevent spontaneous abortion. The new indication scheduled for registration had to do with a prevention of preterm delivery in the third trimester. The potential population of pregnant women meeting the new indication is about 5%. According to calculations made by the sponsor, the lowest statistically justified number of randomised participants must be at least 200. Therefore, about 4,000 women must be screened in order to select 200 patients meeting the inclusion criteria. Screening procedures to detect this disease are very expensive. The trial was to last for nearly two years. Calculations showed that the cost of the study was close to 1 million Euro. To simplify the design, the company planned to conduct an open randomised study. It was assumed that patients in the control group would simply be observed by an investigator (there are no registered drugs for this indication in Russia). However, the drug is registered for this indication and is recommended for use by different physician guides in the developed countries; advanced Russian doctors know about it and often tell patients about its possible off label use. As a result, women included in the control group would have been at a distinct disadvantage as compared with regular female patients, since they would consciously agree to run a higher risk of premature delivery. In addition, it became clear during the planning period that proper screening of patients cannot be done by all medical institutions, primarily due to lack of accreditation for conducting trials (trials involving pregnant women are not very popular in Russia). Hence, an extremely high price of the research, serious difficulties involved in implementation, and ethical issues related to involvement of pregnant women in trials without an acute need for it. Most importantly, during the entire duration of the trial and registration, patients

needing medication will not have access to it and will be able to use it only on an off label basis. The requirement for conducting local trials in order to register new indications will inevitably encourage doctors to prescribe off label medications, the company believes.

In the case of medications needed for treatment of rare strains of certain diseases, research costs increase significantly due to the need to conduct large-scale screening for randomisation of a rather modest number of patients. If, for example, some kind of a definite pathology is found only in 10% of patients afflicted with such a disease, 500 patients will need to be screened when planned randomisation includes only 50 people. All 500 screened patients will need to be insured. If it is a phase III study, the mandatory insurance will cost the company 776,400 roubles with only 50 patients receiving the treatment. If the screening provides for expensive diagnostic procedures (e.g., MRI), the price will be several times higher.

In the case of orphan drugs, marketing problems are aggravated by the impossibility of collecting statistical data due to a negligibly small population of such patients.

After the law became effective, market participants learned that the requirement for local trials applies not only to the original, but also to generic drugs. Market participants say that increased demand for bioequivalence studies led to at least a threefold increase in their prices. Before the Federal Law On Circulation of Medicines became effective, a bioequivalence study cost 500,000-600,000 roubles, whereas now the price tag is 1.5-2 million roubles.

The issue of local trials is facing not only Western but also domestic manufacturers. Incorporation of clinical trials into the registration procedure led to problems associated with the development of new drugs by Russian companies. Under the law, only international and post-registration studies, as well as bioequivalence studies can be performed outside of the registration procedure. To conduct research of the effectiveness and safety of a new drug claiming to be an original medication, Russian manufacturers must either initiate a registration process or pass a local trial for an international one and pay a fee of 200,000 roubles instead of 75,000 roubles. Hence, a legit question for colleagues by a user of www.regprof.com – an independent forum of regulatory managers set up for mutual assistance and exchange of views after 1 September, 2010: “Well, that is kind of a new drug, therefore, it must go through a basic clinical trial so as to be able to at least include indications in the package leaflet. Am I right? Phase I and all that. How do I obtain an approval for such clinical trials? Or should I just prepare a registration dossier, get clinical trial papers ready and file all documents together? In this case, we are not sure yet whether we are going to register the medication at all. What if results of the Phase I make registration irrelevant?”

The requirement to conduct local registration trials has given rise to quite a few absurd situations. According to a user of www.regprof.com, the Ministry of Healthcare and Social Development came up with a requirement to conduct clinical trials for registration of an additional form in the form of pre-filled syringes with a ready-made solution. The drug has already been registered in Russia in the form of a lyophilisate combined with the solvent. “The argument that a patient receives the same pharmaceutical form – an injection (not pills and an injection solution as an additional pharmaceutical form) is not taken into account.” “Notably, employees of pharmaceutical companies sometimes seem to be willing to flog themselves.” “I need to register a sodium chloride solution. Do I need to conduct clinical trials or analysis of therapeutic effectiveness? Perhaps someone has already done so?” asks a fellow member of the www.regprof.com forum. “Sodium chloride (INN, not your specific sodium chloride) has been approved for medical use in Russia for over 20 years now. Trials are not required. In my opinion, everyone has gone crazy over this law and is prepared to conduct clinical trials of anything that turns up,” says another prudent user.

Prior to September 1, 2010, Russian-based offices of generic companies often had no medical units, because they did not need them. Now such units are being set up in a hurry. We can already see the results. For example, a generic company representative asked colleagues on www.regprof.com how to conduct a bioequivalence study of cytostatic agents and whether it can be done with healthy volunteers or necessarily with patients. Another forum member said that he had consulted an expert and had been told that Chinese and Indian

companies always investigate bioequivalence of cytostatic drugs using healthy volunteers. Good thing there was a specialist who knew that they don't conduct trials of these drugs using healthy volunteers, because these drugs are toxic. A healthy person cannot stay that way after using cytostatics," he wrote. Another participant asked colleagues: "Do I understand correctly that the consent [*meaning the patient's consent to participate*] is needed only for clinical trials and doesn't apply to bioequivalence studies?"

High demand for services related to conduct of clinical trials has brought to life a number of service companies that specialise in this type of trials, but unfortunately, are not encumbered with high moral standards and professionalism. Allow us to quote ourselves (*Overview of the Russian clinical trials market, 2010*, Remedium): "As long as developers and manufacturers of original and generic drugs are thrashing about the market trying to understand what they need to submit to the regulator in order to have their drug registered, new CRO's have already appeared that are prepared to do fishing in troubled waters. For example, one such newly available CRO has sales events every month offering free development of a protocol, an investigator's brochure, or a free trial approval from the Ministry of Healthcare and Social Development». Bona fide CRO's who value their reputation prefer to avoid local trials.

Here are a few examples of the above-mentioned "sales events": "When you sign a contract with us for 10 clinical trials (original and generic drugs) in December 2010, we will develop free primary set of documents for the registration dossier (clinical trial protocol, investigator's brochure, and a CRF), choose a site and a principal investigator for nine of them; in addition, we will perform free statistical data processing and centre monitoring for the tenth clinical trial.

Under another promotion entitled "Obtaining clinical trial/bioequivalence study approval," customers who signed an agreement for turnkey clinical trial in March 2011 were entitled to a bonus in the form of a free approval from the Ministry of Healthcare and Social Development. The issue was about filing an application on the ministry's web portal, as well as about work with the Ethics Council and the Federal Expert Institution and the Ministry of Healthcare and Social Development "until receipt of an approval for clinical trials." Meanwhile, communications between applicants and experts of the Federal Expert Institution and the Ethics Council are expressly prohibited by the Law On Circulation of Medicines..."

By the way, we have heard on many occasions that in conversations with prospective clients these firms unequivocally hint at the availability of "individual approaches" to the regulator's staff, which supposedly can guarantee the receipt of a study approval. As an association of major companies specialising in clinical trials, we can say with authority that you can throw lots of stones at the Ministry of Healthcare and Social Development, but this is not one of them. We will not pass judgment on the situation within the registration system, but "individual approaches" to obtaining clinical trials approvals are no longer practiced. Prospective customers of such firms should be aware that such statements are nothing but unfair marketing practice.

Websites run by the above companies can be used to find examples of not only ignorance about regulatory matters, but also lack of understanding of what clinical trials are all about. Answering customer's questions about what documents need to be filed for calculation of the cost and timing of a trial, a company rep said that in addition to other papers you will need to submit a "draft package leaflet indicating the dosage." A customer left a testimonial about one such company: "They do clinical trials. They do a sloppy job. A thorough analysis of their "reports" on clinical trials had my hair stand on end with horror. They are sassy and greedy operators."

The demand dictates the supply. "Colleagues, after I've read the forum postings I understood that most companies don't bother with conducting clinical trials. Of course they get approvals, but they make reports up. I hope I'm wrong. Otherwise, I am seriously concerned about the consumers" a visitor to www.regprof.com says. "Please don't look so surprised as if you've just discovered America. Everybody is trying to survive. Our people don't get sick because of that. Isn't running clinical studies over and over again dumb? Isn't it dumb to run clinical studies on healthy people only because we allegedly don't trust "those damned imperialists" with their results? And still use exclusively imported medications (I'm talking about lawmakers)," another user

retorts. In all appearances, just like a forum visitor said, “no animals were harmed during bioequivalence studies in Russia or the CIS countries[2], since all of them are nothing but dry runs.”

III.

So, what's the solution? Many market participants expect an early signing of long-promised international agreements on mutual recognition of results of clinical trials. We do not share such optimism.

Just to reiterate, para. 5, Art.3 of the Federal Law On Circulation of Medicines setting forth that "In the Russian Federation in accordance with the international treaties of the Russian Federation and (or) based on the principle of reciprocity, results of clinical trials of medicinal products for medical use conducted outside the Russian Federation shall be acknowledged.” is, in our opinion, a legal nonsense.

The concept of treaties between countries about mutual recognition of clinical trials does not exist in the international practice [3]. Such a treaty is impossible by definition, since the results of the trials do not result from decisions (activity) of state bodies. Trials are carried out not by a country, but by companies, so the results of clinical trials cannot be the subject of an international treaty on mutual recognition. All developed countries recognise results of clinical trials conducted in accordance with the international ICH GCP standard. Russia has a similar national standard GOST R 52379-2005 called “Good Clinical Practice.” For over 10 years, Russia has been effectively participating in IMCTs, and the results of these trials with the participation of Russian patients are recognised by other countries without any international treaties. In addition, it is not clear how the availability of an international treaty may address the need to account for the population factors.

Even if we assume that Russia were to sign such a treaty, then it should automatically have to recognise not only the results of all trials conducted in other countries, but also the results of its “own” studies. According to this logic, it then should register all Russian medications regardless of their quality or results of clinical trials.

Despite the absurdity of these rules, they have tried to implement them on several occasions. Following the meeting with the EU Commissioner John Dalli in September 2010, the Ministry of Healthcare and Social Developmentissued a press release stating that “this point was approved by Mr Dalli.” Meanwhile, John Dalli wrote in his blog on the website of the European Commission that he "discussed with the Minister concerns related with the Russian law on pharmaceuticals, in particular as regards … requirements on clinical trials». After the second meeting in Brussels in February, the Ministry of Healthcare and Social Development stated that “the parties are very close to solving the issues ... regarding mutual recognition of the results of clinical trials.” “Russia and the EU are prepared to promptly address all issues related to preparation of the treaty that will establish rules for mutual recognition of the results of clinical trials.” Unable to find any comment by representatives of the European Commission this time, we sent a request for clarification. The official response came on April 6: “There are no mutual recognition agreements on clinical trials. The EU accepts the clinical trials performed in accordance with Good Clinical Practices.” The European Commission has thus confirmed what experts have repeatedly stated. However, the talks continued. For the third time this issue was raised at the meeting with John Dalli in Moscow on October 10, 2011 “During the meeting they have also discussed preparation of a future agreement that is supposed to settle the issue of mutual recognition of clinical trials,” said Minister Golikova at a briefing following the meeting.

The proposal to sign a treaty on mutual recognition of clinical trials was made not only to the EU, but to India as well, the Indian Minister of Healthcare Ghulam Nabi Azad told Russian reporters. The minister came to Moscow in late April 2011 to attend the First Global Ministerial Conference on Healthy Lifestyles. This statement was not commented on the website of the Russian Ministry of Healthcare and Social Development.

[2] Most likely, this popular phrase was used in jest. Clearly, bioequivalence studies involve humans rather than animals.

[3] However, there is a one such treaty. It’s a treaty about promotion of cooperation in the area of manufacturing and mutual supplies of medications between Russia and Belarus signed in 2007. Art. 6 of this treaty says that Russia and Belarus undertake to mutually recognise results of pre-clinical and clinical trials. The Ministry of Healthcare and Social Development refuses to recognise this treaty referring to lack of shared standards for conducting such trials.

Mr. Azad told reporters that he had conveyed complaints of Indian companies about delays in registration of medications to the Russian minister. The proposal by the Ministry of Healthcare and Social Development came as a response to these complaints: allegedly, signing an agreement on mutual recognition of trials will save time and money for Russian and Indian companies.

There is plenty of evidence that The Ministry of Healthcare and Social Development actively raises the mutual recognition issue during meetings with healthcare authorities of other countries. But what are the real prospects of these negotiations? Unfortunately, our view remains unchanged: treaties on mutual recognition are not feasible, and talking about them is nothing more than a political game. In our opinion, the only solution is for Russia to recognise results of trials carried out in accordance with recognised international standards. Of course, Russia can sign an external agreement setting forth the opinion of the parties that GCP is a good thing. But there's no real need to do so. The only thing that needs to be done is to clearly indicate in the registration section of the Federal Law On Circulation of Medicines that during registration Russia shall accept the results of trials carried out in accordance with ICH GCP regardless of the country of origin. And finally drop the requirement for mandatory local trials.

Activities of the Ethics Council at the Ministry of Healthcare and Social Development

Ethics review significantly affects the conduct of clinical trials in Russia. The Ethics Council work affects both the quantity of trials allowed in Russia and the choice of trials that will get the final approval by the Ministry of Healthcare and Social Development (The Ethics Council has been established pursuant to the Federal Law On Circulation of Medicines under the Ministry of Healthcare and Social Development).

The Ethics Council was established by the executive order No.774н of the Russian Ministry of Healthcare and Social Development on August 31, 2010. According to approved Regulations, its activities are based on independence, transparency, fairness, respect for human rights and freedoms and civil rights of legal entities, objectivity, competence, responsibility for experts' accountability for the conduct and quality of ethics review.

Historically, the vast majority of ethics committees that existed in Russia at different times were part of the state authorisation system. Their findings were used to issue trials approvals. It is hard to imagine anything different, because both under the repealed Law On Medicines and the new Law On Circulation of Medicines the ethics committee/board is set up under the aegis of the main regulator. This makes the Russian system different from many other systems recognising ICH rules of the countries where ethics review is conducted independently and operates in parallel to the authorisation system. However, earlier when they were part of the authorisation system, Russian ethics committees did their best to adhere to accepted international standards of ICH GCP ethics review and WHO guidelines. The adoption of the Law On Circulation of Medicines had ethics review fully integrated with the authorisation system, which gave rise to a lot of complications of both philosophical and practical nature.

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First and foremost, these practical difficulties are related to the rule under which the Ethics Council cannot conduct expert review at direct request of organisations or individuals. An expert review has to be commissioned by the Ministry of Healthcare and Social Development, and formal findings must be submitted to it as well. Perhaps, in an attempt to limit the communication between the Council and the applicants, the lawmaker thought that this was the only way to secure independent nature of ethics review. As a result, Russia became sainter than the Pope, since in other countries ethics review involves direct contact and communication between ethics committees and applicants. The adoption of the new Law On Circulation of Medicines resulted in excessively cumbersome and unwieldy arrangements which further complicate the process and increase the time it takes to consider submitted cases.

Ethics review is invariably a living process. In some cases, experts may have questions that can be answered only by applicants. Therefore, it's normal practice to invite them over to a meeting if the committee needs to get clarifications or explanations under the protocol. In other cases, experts may have minor comments that can be addressed fairly quickly by making necessary changes out of session. In case of the Ethics Council, it is not an option since all papers go a full circle. An applicant submits them to The Ministry of Healthcare and Social Development located on Rakhmanovsky Lane in Moscow, from where they are taken to another ministry's building located on Ilyinka Street. There, they pass through the Administration Department, then go to the Department of State Regulation of Medicines Circulation and, following the completion of a ticket for review, are sent to the Ethics Council. Papers, CD-ROMs and other documents tend to get lost along the way... The return path retraces the original one. Applicants would be happy to quickly correct mistakes and re-submit papers. But they cannot get a statement with comments within a reasonable time following the Council meeting. First, the statement is sent to The Ministry of Healthcare and Social Development (again via Rakhmanovsky to Ilyinka and then from one department to another), after which the ministry prepares a cover letter and only then sends the statement to the applicant. As a result, the earliest the company can read comments issued by the Council is one month after the meeting. Having complied with the comments, the applicant has to send the response using the same circuitous route. As a result, correspondence about a trivial issue may take several months. However, the issue is also about including international trials, where deadlines, given the competition between countries, have a special meaning. The time it takes for a company in Russia to get an approval, other

countries may already finish the enrolment, and all efforts will be in vain, since Russia won't be able to participate in a trial.

The companies are particularly upset over the lost time, when comments are mixed or don't have much to do with ethics. For example, early in its work, the Ethics Council required applicants to rename Patient Information and Informed Consent Forms to the Patient Information Sheet. Yes, indeed, our legislators decided to call this fifteen- and sometimes twenty-page long document actually comprised of two documents (the information and the form signed by the entity), a "sheet" ignoring its universally accepted name. Perhaps, realising that content is more important than the form, the Ministry of Healthcare and Social Development, whose functions under the law include checking completeness of submitted documents, accepted Forms of Informed Consent without any problem. The Ethics Council refused to approve such studies, although the name of the document seemingly has nothing to do with the level of the patients' protection. The requirement to substitute form with "sheet" has never been made known before, so a lot of applications that piled up during September when the system was not yet operative came under the blow. Refusal to accept papers and time involved in re-submission took another 45-60 days. A little later the Ethics Council decided that a Patient Information Sheet must necessarily have a disclosure that a patient will receive an insurance policy (this explanatory note was supposed to supplement an existing section featuring terms of insurance and compensation). Some companies who have just changed Patient Information into the Patient Information Sheet were turned down and had to re-submit documents.

Is the Council entitled to make such recommendations? Perhaps, it is. Although, there's not much sense in this addition, since failure to issue a policy is an explicit violation of the law. Why would a sponsor do so if it has already fully paid for the insurance? In fact, the process of adding patient information has no end to it. General requirements for patient information are set forth by the law; everything beyond it is a matter of taste. For example, we know that one of the Council curators enjoys making comments about the need to include contact information of a contract research organisation (CRO) in the Patient Information Sheet, which is unheard of in the rest of the world. Conversely, information for patients has to include contact information of persons whom they may contact for more information about the research study or their rights. Typically, this includes a phone number of a physician researcher who can answer medical questions and of a local ethics committee or any other person who may provide a competent answer with regard to research subjects' rights. Normally, sponsors of research studies and CRO's never directly contact patients and prefer to work exclusively via the investigator. Moreover, they tend to refrain from receiving any personal information about participants. The company which received the above comment had four other contacts listed already. Now, it has to indicate its own contact number. But there is no guarantee that next time the Council will not ask to include the number of the reception room of the Ombudsman or the Strasbourg Court. One more thing about the additional information: one of the applicants was asked to provide a list of countries that have already registered the drug under study. The company had no objection to this, but it wonders how the other two protocols, essentially identical to the one in question, managed to pass expert review without causing any objections. There are many such instances. Many companies are complaining about the differentiated approach to the same text. Two or three research studies may be approved without any problem, while the fourth may fail to get the approval because of some trifling matter. Things that were fine yesterday aren't good enough today. We believe we know the reason: different experts have different opinions. Explaining these fickle judgments by the same committee to the headquarters is a tall order, indeed.

We are in no way questioning the right of ethics committees to make such comments. But we believe that comments should be of categorical nature only when the situation is clear. Comments by the Ethics Council are always categorical, even if the issue is about an editorial correction or minor additions. They would not be a problem to applicants, if they didn't cause unjustified waste of time. In the international practice, they often use a "conditional approval" approach in such cases when the final approval is made in due course subject to further consideration of the comments by the applicant. This means that the corrected documents are not subjected to another review and are not considered by all members of the committee at a meeting, but can instead be checked even by the secretariat committee, which will issue the final approval. By the way, the Ethics Council also occasionally uses a form of "approval in due course," although very rarely. In the published

materials of the Ethics Council, we have found only 12 such cases out of 462 primary applications (i.e., less than 3%). All other comments are accompanied by a verdict "rejected" and require re-submission according to the general rules.

In general, it appears that the Ethics Council takes pride in high percentage of rejected studies. Perhaps, the Council thinks that it is indicative of high standards of ethics review in Russia. According to information provided by a representative of the Council at a press conference on May 20, 2011, they have reviewed 636 files from October 2010 to March 2011, with 21.7% of rejected cases, including 34.7% during the initial filing and 12% during re-submission.

We decided to compare these statistics with the data that can be obtained from the few Council materials available on the website run by the Ministry of Healthcare and Social Development (the results of case considerations are available only for 7 out of 28 meetings). At these seven meetings, they have considered 462 primary cases, of which 280 (65.7%) were approved, 12 (2.8%), as mentioned above – "approved in due course," and 134 (31.5%) rejected. Could such high rejection rates be associated with approval of a large number of local protocols? After all, it is a known fact that much more money is spent on the development of documents for IMCTs, and leading scientists and specialists from many countries participate in the effort. However, the ratio of positive and negative decisions on IMCTs was the same if not worse: of 179 protocols related to IMCTs only 114 (63.7%) were approved during the initial review, 8 (4.5%) were "approved in due course," and 57 (31.8%) were rejected (Table 4).

How are things handled internationally? We were able to get information from one of the most experienced and authoritative German committees, Freiburg Independent Ethics Committee (FEKI). Over the last three years, out of every 100 cases submitted for review, the committee rejected only one (i.e. 1%). Approximately 30% of studies end with requests to make changes, i.e. get a conditional approval. After the requisite changes are made, the final decision is issued within two weeks. Maybe that is why Germany, whose population is almost half that of Russia, carries out twice as many clinical trials.

Table 4

Results of Ethics review			
	% of Approvals	**% of Conditional Approvals**	**% of Disapprovals**
The Ethics Council, Initial Review, All Types of Clinical Trials*	**65,7%**	**2,8%**	**31,5%**
The Ethics Council, Initial Review, International Multicenter Clinical Trials*	**63,7%**	**4,5%**	**31,8%**
The Freiburg Ethics Commission International (FEKI)**	**69,0%**	**30,0%**	**1,0%**

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

**** At the rate of 100 studies reviewed during the last three years**

Another complaint that we often hear from applicants is about unavailability of SOPs (standard operating procedures) of the Ethics Council for the public. The only SOP published at a time of issue of this newsletter is SOP No. 1. It was posted on the website of the Ministry of Healthcare and Social Development only on November 7, 2011, whereas November 24, 2010 is indicated as the date of its approval. Availability of SOPs is part of the ICH GCP requirements and recommendations of the WHO ethics committees. Without them, the applicant cannot understand requirements and conditions of case consideration. For example, one of the most recent protocols of the Council features a mysterious record in the "decision" field to the effect that "an issue about an independent expert is being contemplated." All attempts to find out the meaning of this phrase or the duration of postponement at the Secretariat of the Council resulted in failure. There were also cases where the discussion of cases was deferred to later dates, because "a field-specific expert wasn't present at the meeting." But the issue is about an ethical, not a professional expert review! And even if the Council needs specialist advice for clarification of some professional aspects, we believe it should be obtained without violation of deadlines. By the way, we found out that for one of the two trials where the Council wanted independent experts to be involved, Russia has been excluded from the list of participants exactly because it violated deadlines for obtaining an approval (the documents were submitted 7 months before).

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A few words shall be said about transparency, which is one of the main principles underlying Ethics Council activities. According to paragraph 24 of the Regulations governing the Council activities, the information "about working plans of the Ethics Council is posted in the form of a message in a corresponding section of the website of the Ministry and kept updated," and "information about current activities of the Ethics Council is posted in the form of a message in the corresponding section on the website of the Ministry within three business days from the date of the meeting of the Ethics Council."

However, we managed to find only the schedule of meetings for the first half of 2011 on the website of the Ministry of Healthcare and Social Development. Out of 28 Council meetings held at the time of writing this newsletter, there was no information about agendas or results of 12 of them. Agendas of nine meetings were posted, but voting results were not disclosed. Results were posted for only seven meetings, but, for some reason, they were designated as "tentative decisions".

Voting results are often released late in violation of the three-day deadline established by the executive order of the Ministry of Healthcare and Social Development. The results of the meeting of March 30 were published only on April 25; the results of the meeting of August 10 on September 14. Information about posting information about the Board's activities on the website of The Ministry of Healthcare and Social Development can be found in Table 5.

Table 5

Publication of Information on the Ethics Council Activities			
№ of the Meeting	**Date of the Meeting**	**List of Clinical Trials to be Reviewed is Published**	**The Results of the Review are Published**
1	n/a	-	-
2	n/a	-	-
3	06.10.2010	+	-
4	20.10.2010	+	-
5	10.11.2010	+	-
6	24.11.2010	+	-
7	08.12.2010	-	-
8	22.12.2010	-	-
9	19.01.2011	-	-
10	26.01.2011	-	-
11	09.02.2011	+	-
12	02.03.2011	-	-
13	16.03.2011	+	-
14	30.03.2011	+	+
15	20.04.2011	+	+
16	27.04.2011	-	-
17	11.05.2011	-	-
18	25.05.2011	+	+
19	08.06.2011	-	-
20	22.06.2011	+	+
21	06.07.2011	-	-
22	20.07.2011	+	-
23	10.08.2011	+	+
24	24.11.2011	-	-
25	07.09.2011	+	-
26	21.09.2011	+	-
27	05.10.2011	+	+
28	19.10.2011	+	+
Total Number of Meetings	**28**	**16**	**7**
% of Total Number of Meetings	**100,0%**	**57,1%**	**25,0%**

*** * ***

To summarise, the following key interrelated problems of ethics review exist in Russia:

- Unavailability of the Ethics Council's SOPs for the public;

- Lack of transparency of ethics review and its unpredictability in terms of timeframes and results;

- Inability of applicants to track the movement of documents within the system and a large time lag between the decision and the receipt of comments;

- Inability of applicants to discuss comments and defend their positions.

Many of the above problems could have been solved in due course. Then there would be no need for this Newsletter. However, the industry cannot do so today, because there's no public dialogue with the Ethics Council. The publicly available information about the Council's activities is scarce. As a result, market participants see the Council as an unpredictable "black box." Since the business flow is very large, some hope to be able to "slip through." However, if you accidentally get hit by the system, this may put an end to your research study. You can't help get the impression that the Ethics Council believes that companies conducting "experiments on humans," cannot be right by definition. Hiding behind the Ministry of Healthcare and Social Development, the Council is unwilling to learn anything about problems facing clinical trials. The Council's experts armed with such strong bargaining chips as ethics and patient care and fully aware of their unique monopoly status are running the risk of completely losing the sight of reality. Do we need to remind anyone that the idea of own uniqueness often leads to permissiveness? How else can one explain the fact that the percentage of protocols rejected by the Russian Ethics Council is thirty (!) times greater than that of their Western counterparts, and that research studies approved in the U.S. and Europe get rejected in Russia? Let us keep in mind that the purpose of ethics review across the world is to protect rights and interests of subjects, rather than protect patients from the research. As is known, the best way to deal with a problem is to eliminate its cause. What about the requirement for local trials? If the drug does not go through a trial in Russia, it will not be registered. And if it is not registered, what will our patients be left with tomorrow?