ACTO

ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

ACTO NEWSLETTER №7

MOSCOW 2013

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SUMMARY

By tradition we begin this edition of the newsletter with statistics. This time we highlight the results of the first half of 2013. During this period the Ministry of Health issued 404 approvals for conducting clinical trials, which is nearly 10% down on the same period of last year.

The number of approvals for international trials is down by 14.1% with 159 trials compared to 185 trials approved in the first half of 2012. The number of bioequivalence studies with Russian sponsors is also down by 20.7% (92 approvals compared to 116). Meanwhile, the number of bioequivalence studies with foreign sponsors remained steady – 53 approvals compared to 52 in 2012. The number of approvals for local trials of domestic medicines is down by 12.3% (71 compared to 81). However, the number of such trials with foreign sponsors increased – 29 approvals in the first half of 2013 compared to 14 in the same period of 2012.

In another section of this edition, we highlight the expert analysis practices conducted with the aim of issuing approvals for clinical trials. And so it became clear that just about half of trials pass the expert filter - FGBU and the Ethics Council after the first review. We also looked at how refusals and comments break down, by therapeutic area and by age categories of the potential trial participants. It turned out that nearly 40% of all refusals on ethics expertise come in psychiatry, where just 33.3% of clinical trials in this group get through the ethics barrier successfully on their first attempt. We can see another unimpressive number in oncology, with just 63% of clinical trials in this therapeutic area being approved at the first attempt. Regarding FGBU' expertise, a more worrying picture can be seen in paediatric protocols, where the number of refusals is approaching 50%.

We also attempted to analyse the primary reasons for disapprovals. While with the Ethics Council the majority of issues are concentrated, as we said, in psychiatry and therefore most likely due to personal factors, with FGBU expertise the matter is different. And so out analysis points to systematic problems in the expert institutions, caused by a whole range of factors. These include insufficient qualification of staff, and lack of responsibility for erroneous decisions and motivation to introduce any change in the existing environment. Meanwhile, the main reasons for the current state of FGBU' expertise lays, in our opinion, in the deficiencies of the current law *On the Circulation of Medicines*.

Another subject which we raise not for the first time, is the analysis of legislative initiatives. We continue to monitor progress in preparing amendments to the law *On the Circulation of Medicines*. Our efforts to objectively analyse the latest version of the document have led us to wonder whether the authors of the legislation have any overall concept at all in the field.

At the same time we will discuss one of the discoveries we came across among reports on the implementation of presidential orders. It turns out that the presidential order on the declaration in the Russian Federation of the results of clinical trials in the European Union and the United States has been successfully implemented. According to the publically accessible report, there is a draft amendment to Russian federal law, making changes to the law *On the Circulation of Medicines* based on the results of negotiations held between the Russian government and representatives from the European Commission. The chance to judge what the current bill under consideration has in common with the stated goal – the recognition of international clinical trials results – we leave to the reader.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET IN THE FIRST HALF OF 2013

In the first half of 2013, the Ministry of Health issued 404 approvals to conduct clinical trials. This is 10% lower than for the same period of the previous year (Table 1). The drop in the total number of approvals issued is based on a decrease of approvals in most of the specific types of trials.

And so, the number of approvals for international multicentre clinical trials (IMCTs) dropped by 14.1%, amounting to 159 compared to 185 trials approved in the first half of 2012. The number of bioequivalence studies by Russian sponsors dropped by 20.7% (92 compared to 116). The number of these sorts of studies, but with foreign sponsors, remained stable at 53 approvals compared to 52 last year. The number of approvals for local trials of domestic medicines also dropped, by 12.3% (71 compared to 81).

The only sector that demonstrated growth is local trials by foreign sponsors. The number of approvals for this type of trials more than doubled. However we must note that it wasn't high to begin with, so this level of growth can hardly be considered extraordinary: 29 approvals for the first half of 2013 compared to 14 for the same period of 2012.

Table 1

Approvals for Conduct of Clinical Trials: 2013 vs. 2012						
	Total	**International Multicenter CT**	**Local CT (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CT (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
1st Half of 2013	**404**	**159**	**29**	**53**	**71**	**92**
1st Half of 2012	**448**	**185**	**14**	**52**	**81**	**116**
1st Half of 2013 vs. 1st Half of 2012 г., %	**-9,8%**	**-14,1%**	**107,1%**	**1,9%**	**-12,3%**	**-20,7%**

Source: www.grls.rosminzdrav.ru

In evaluating the results of the first half of 2013, it is worth noting a variable figure of approvals in comparison with last year's figures. At this time it does not seem possible to talk about new trends. It is entirely possible that based on the full year's results we will see a similar picture to what we had in 2012. In any case, the relationship between the different types of trials that we see in the first half of 2013 is virtually identical to the structure of the market last year (Table 2). In turn we must remember that it was in 2012 that this structure changed dramatically for the first time since we commenced our statistical analysis in 2004 (see *ACTO Newsletters №5 and №6).* Specifically – there was a significant growth in the numbers of bioequivalence studies, as a result of which the total share of these studies by foreign and domestic producers grew from 15.1% (compared to the figures for the previous eight years) to 35%. And for the first time in the same period the share of IMCTs dropped from 60% to 40%.

Table 2

Structure of CT Market by Type					
	International Multicenter CT, % of Total	**Local CT (Foreign Sponsors), % of Total**	**Bioequivalence Studies (Foreign Sponsors), % of Total**	**Local CT (Local Sponsors), % of Total**	**Bioequivalence Studies (Local Sponsors), % of Total**
1st Half of 2013	**39%**	**7%**	**13%**	**18%**	**23%**
2012	**40%**	**7%**	**12%**	**18%**	**23%**
Average share for the years 2004-2011.	**60%**	**6%**	**2%**	**20%**	**13%**

It is perhaps worth bringing a little bit of clarity to our methodology in classifying and adding up the approvals for different types of trials. Sometimes ACTO's data differ slightly from the data presented by various analytical sources. The total numbers of approvals match (which is logical, since there is only one source for that figure – the Ministry of Health register), but the data on the breakdown between different groups (in particular IMCTs and local trials) may differ. This is due to the following.

The Ministry of Health register does not contain classifications of trials, we need to work this out ourselves, relying primarily on the name of the protocols. By the name and number of the protocol we can check if that trial exists on international registers, primarily on www.clinicaltrials.gov and www.clinicaltrialsregister.eu. If we don't find it, then we have a reason to question whether this trial is really international, as the sponsor stated in the name of the protocol. Particularly, if the 'international open randomised multi-centre comparative trial to study efficacy and safety' is studying an injectable form of a generic. In this case we understand that what we really have is an example of a sponsor, having come up against the demand to present data on 'therapeutic equivalency' of the generic to the original (when it is not possible to conduct a bioequivalence study), was forced to invent something to appease the Russian regulator. Sometimes the sponsor decides that it's easier and quicker to go through the procedure for obtaining approval for an international protocol rather than a local registration trial (we remind you that the law *On the Circulation of Medicines* splits these trials into two separate procedures). As a result, the sponsor announces centres in Russia and in one or several other countries, such as India, countries in Eastern Europe, or the former Soviet Union. But there is no mention of it in either American (most complete) or European registers. In these situations, we simply cannot attribute the protocol to IMCTs, and we include it instead in the local trials group.

Why have we decided to bring this to your attention at this time? Previously these problems came up relatively infrequently. Now the number of these kinds of 'debateable' protocols is on the rise – enough time has passed since the new law came into force and manufacturers have had a chance to think and find the best way to solve their registration trial problem. So we thought it is necessary to bring the readers' attention to this new trend.

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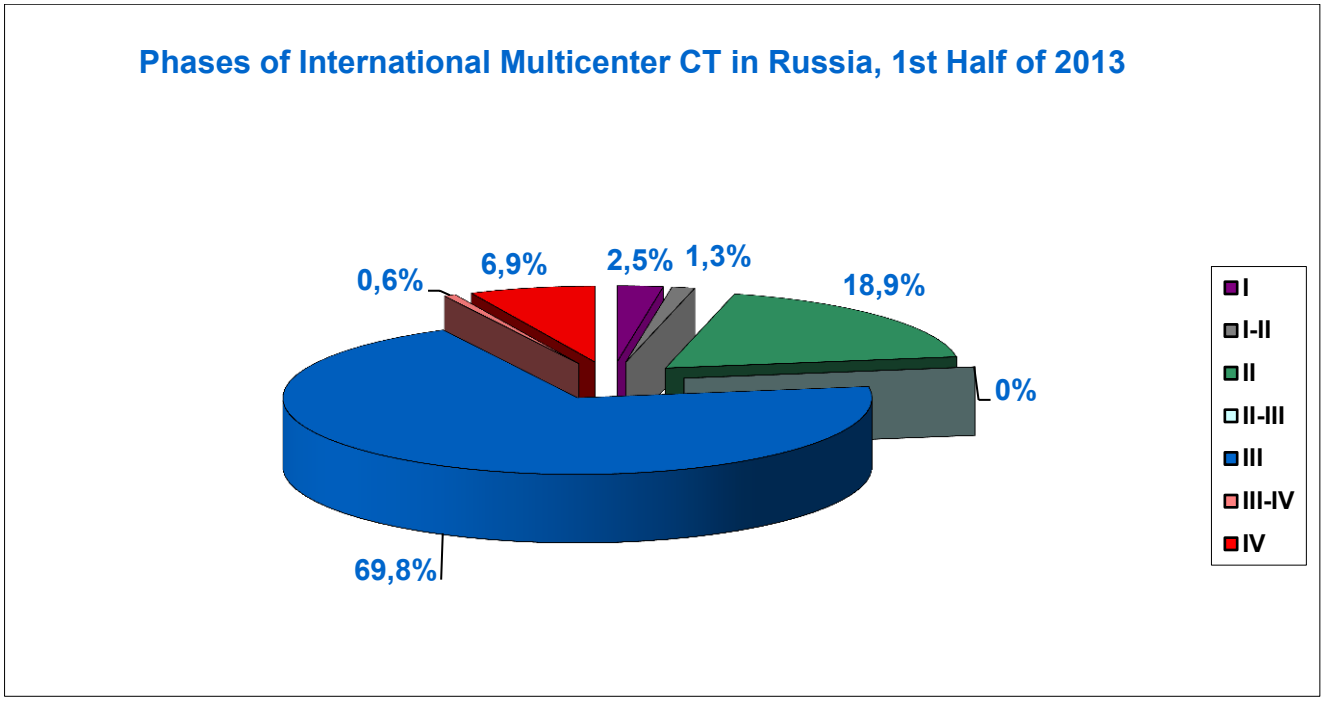
A breakdown of approvals in the first half of 2013 for IMCTs by stage is presented in Table 3 and in Diagram 1. We can note that this breakdown is quite typical and does not differ significantly from the usual pattern of the past years. So the majority of approvals (69.8%) were issued for phase III. Next comes phase II, which accounts for 18.9% of approvals in the first half of 2013. And the usual small number of approved trials (just four in the period) were for phase I trials.

Table 3

Phases of International Multicenter CT in Russia, 1st Half of 2013							
	I	I-II	II	II-III	III	III-IV	IV
QI of 2013	3	1	14	0	63	1	5
QII of 2013	1	1	16	0	48	0	6
Total of 1st Half of 2013	4	2	30	0	111	1	11

Diagram 1



Source: www.grls.rosminzdrav.ru

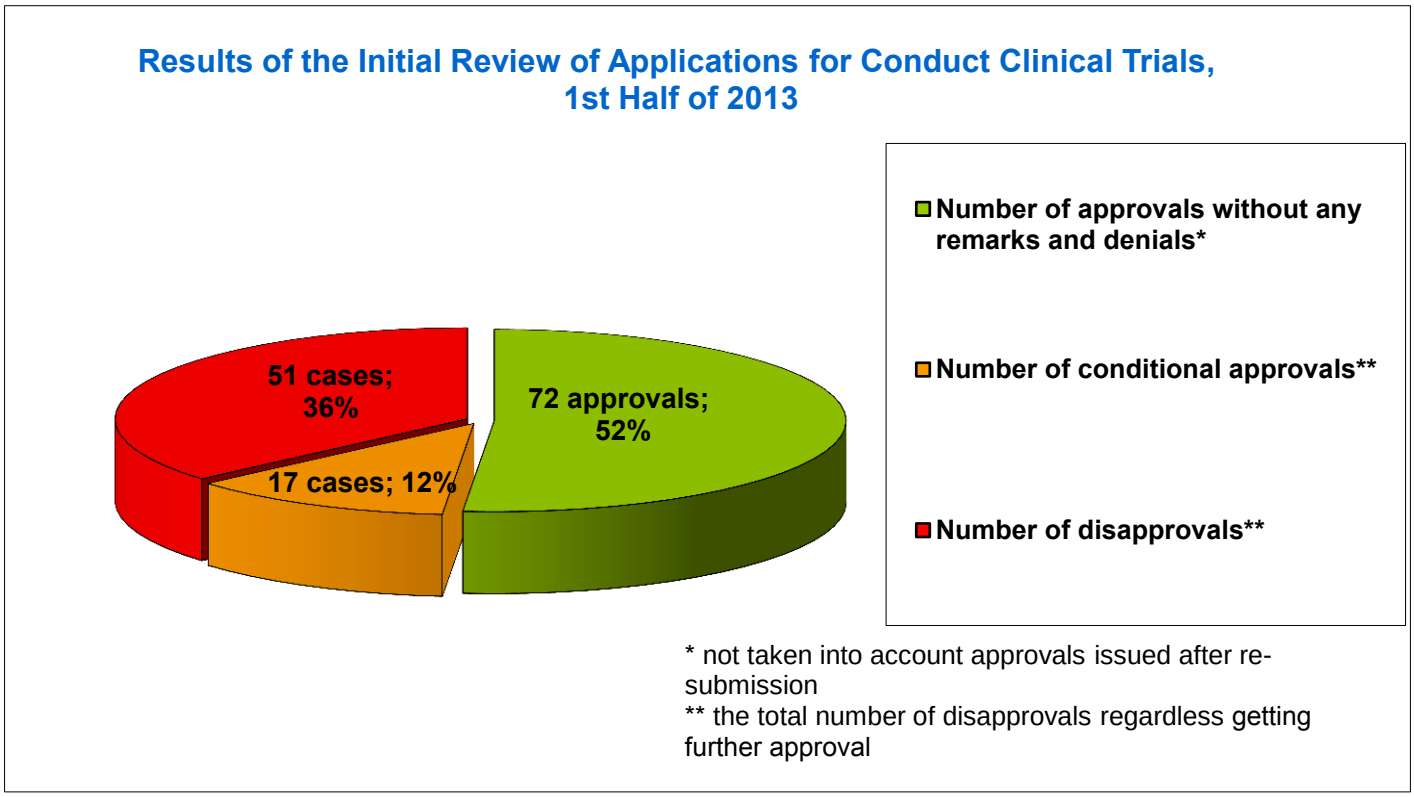
EXPERTISE OF PLANNED TRIALS: THE PRACTICE OF DISAPPROVALS

Let us remember that according to the law *On the Circulation of Medicines* in order to obtain an approval from the Ministry of Health, the materials for the planned trial must undergo review by FGBU and the Ethics Council experts and receive their positive conclusions.

We decided to analyse the practice of issuing negative conclusions by the expert bodies. With the aim of gathering statistics, ACTO conducted a poll of its members. Only 'first' submissions were considered – those including full materials on the trial, in contrast to amendments to the protocol and other changes to clinical trials that had already been approved and started. We defined disapprovals as decisions which led to the need to resubmit, regardless getting further approval. Under conditional approvals we meant comments from the experts which allowed for corrections or clarifications to be made to the trial materials without the need to resubmit.

The poll included applications the results of which were received within the first half of 2013. In total the poll of participants included 22 companies. We analysed data on 140 applications for approval to conduct clinical trials, a majority of which were for international protocols. The relationship between different results for initial review of applications is presented in Diagram 2. From this we can conclude that just 52% of applications successfully pass inspection and receive approval on their first attempt.

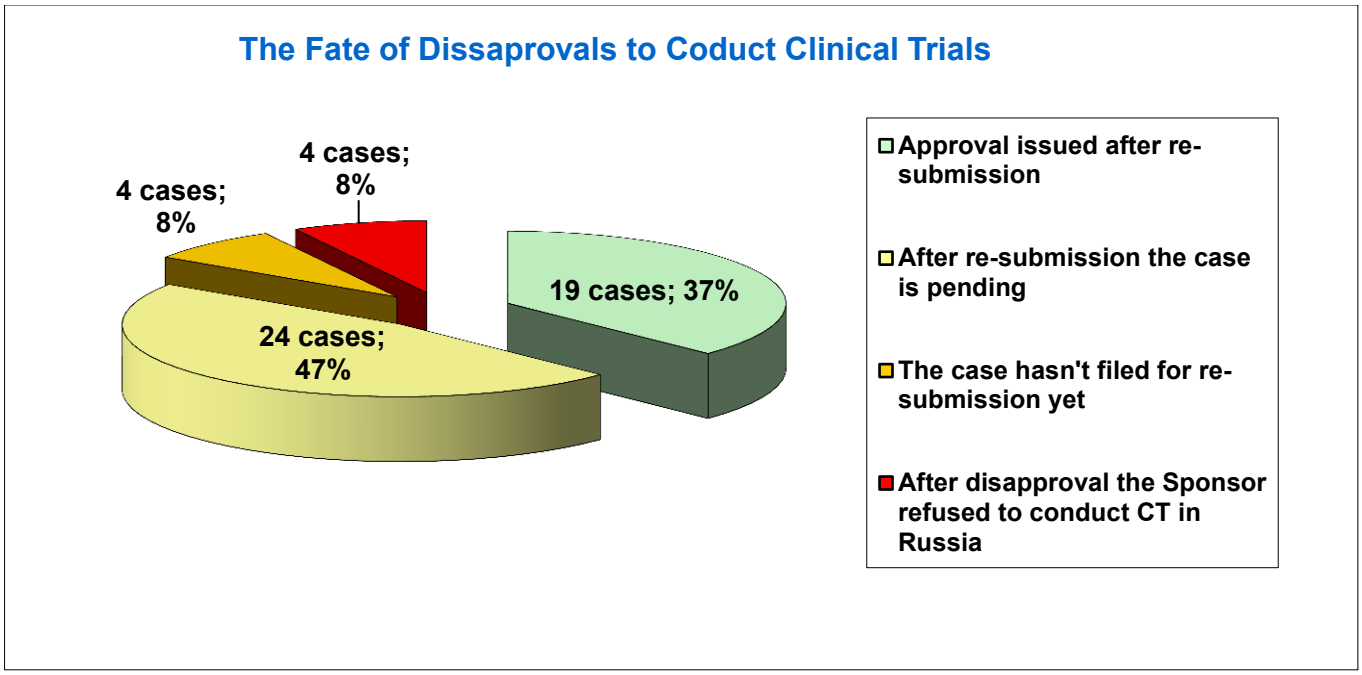
Diagram 2



Source: data from poll of ACTO members

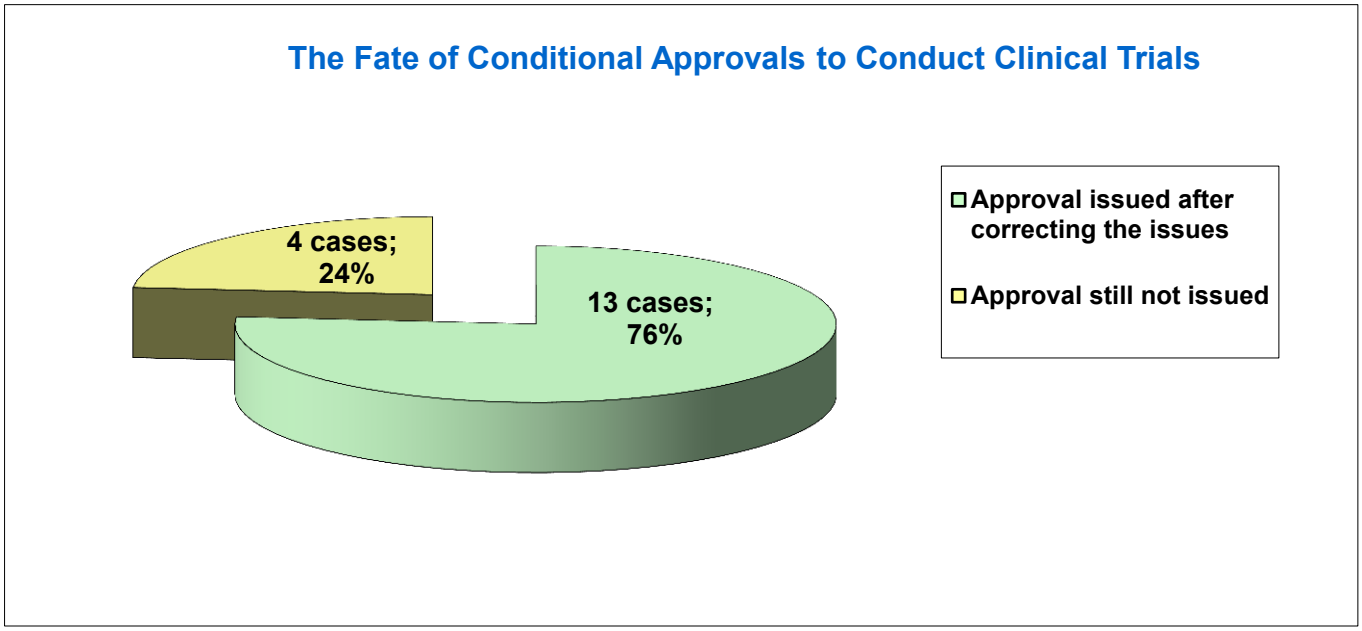
We also asked poll respondents about the further fate of cases in which they had disapprovals or conditional approvals. These results are presented in Diagrams 3 and 4. We can only add that in the number of four trials lost for Russia (Diagram 3) there were two trials on anti-psychotic medicines, one medicine used in pulmonology, and an antibiotic - also for a trial in pulmonology with children.

Diagram 3



Source: data from poll of ACTO members

Diagram 4



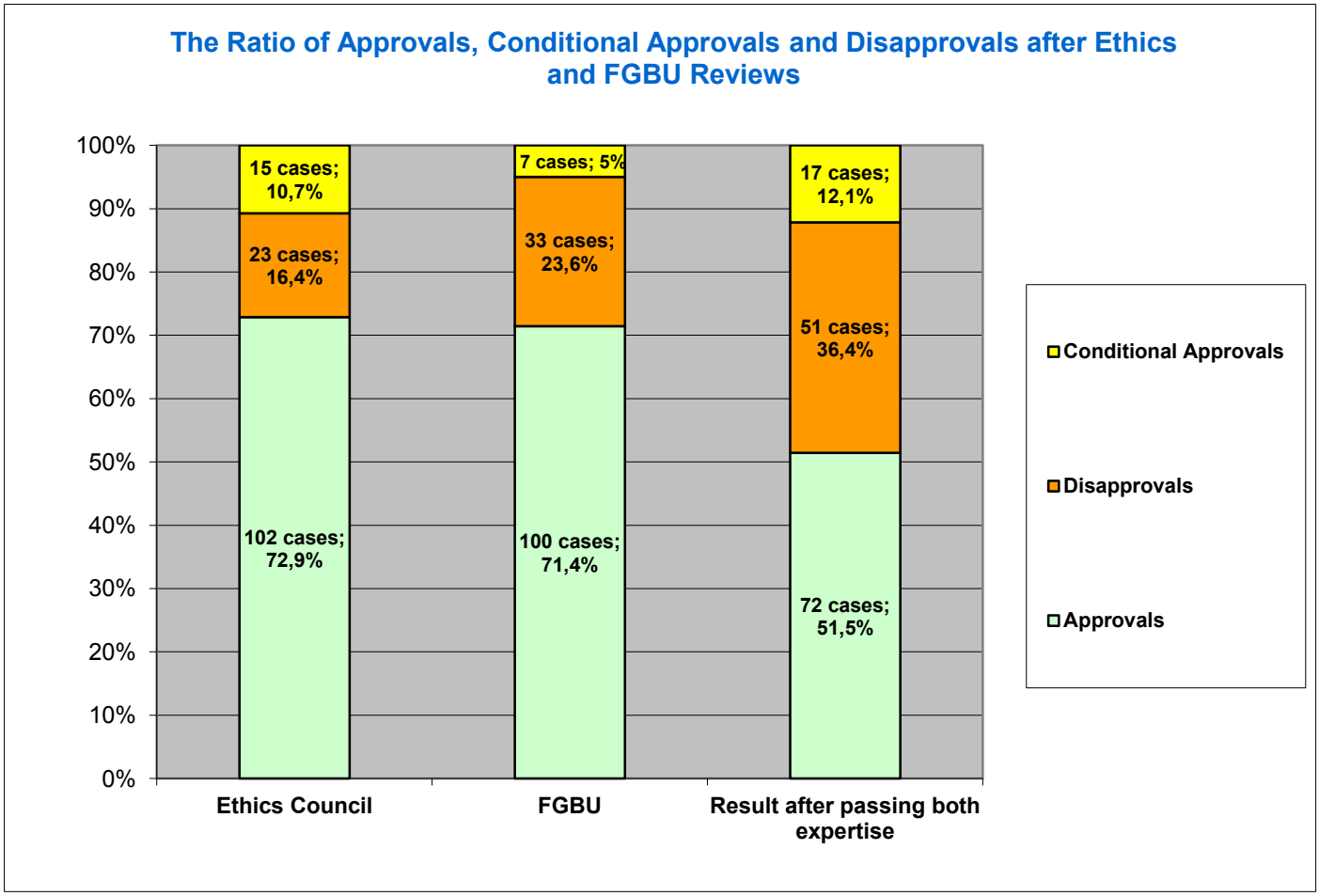
Source: data from poll of ACTO members

Diagram 5 reflects the relationship between cases in which there was an approval, disapproval, or conditional approval, based on the results of expert review by FGBU and the Ethics Council. It appears that the total number of cases approved on the first review by both bodies is practically the same. However FGBU almost always issues unfavourable decisions and this number exceeds the number of cases not approved by the Ethics Council by 7.2%. At the same time the Ethics Council issued conditional approvals 5.7% more often than FGBU, which is obviously preferable for the applicant from the point of view of time.

Despite the fact that the percentage of cases approved by each of the organisations looks not too bad (more than 70%), the results of going through both expertise are disappointing. Frequently, the evaluation by

FGBU and the Ethics Council do not match and the case which successfully passed one review risks being rejected by the other. As a result the share of trials approved on the first review by both organisations is just over half of those examined. We must not forget that here we are talking about IMCTs, where the level of document preparation for the planned trials meets the highest international standards. It is difficult for us to truly evaluate what is really going on with expertise in the local trials sector, since ACTO members rarely conduct such trials.

Diagram 5



Source: data from poll of ACTO members

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It is also interesting to look at the breakdown between approved and disapproved trials by therapeutic areas.

And so in Table 4 and in Diagram 6 we present the corresponding breakdown by results of the Ethics Council review. We can say that in the majority of therapeutic areas the picture looks quite acceptable. Concerns arise with cases in oncology – one of the most in-demand from the point of view of potential trial participants. The share of oncology protocols approved on the first review is 63%, set against an average across subjects of 72.9%. There are also several questions over hematology, although the overall number of trials for medicines in the area is relatively low, and it is still too early to draw conclusions from the statistics. But the picture in psychiatry is very worrying. Just 33.3% of trials for medicines in this group are approved on the first attempt. Another figure is also revealing – nearly 40% of disapprovals from the Ethics Council (not taking into account conditional approvals) are in psychiatry. And what is the reason for the council's special 'love' for this subject? We are convinced that this situation is entirely the result of the position taken by the expert.

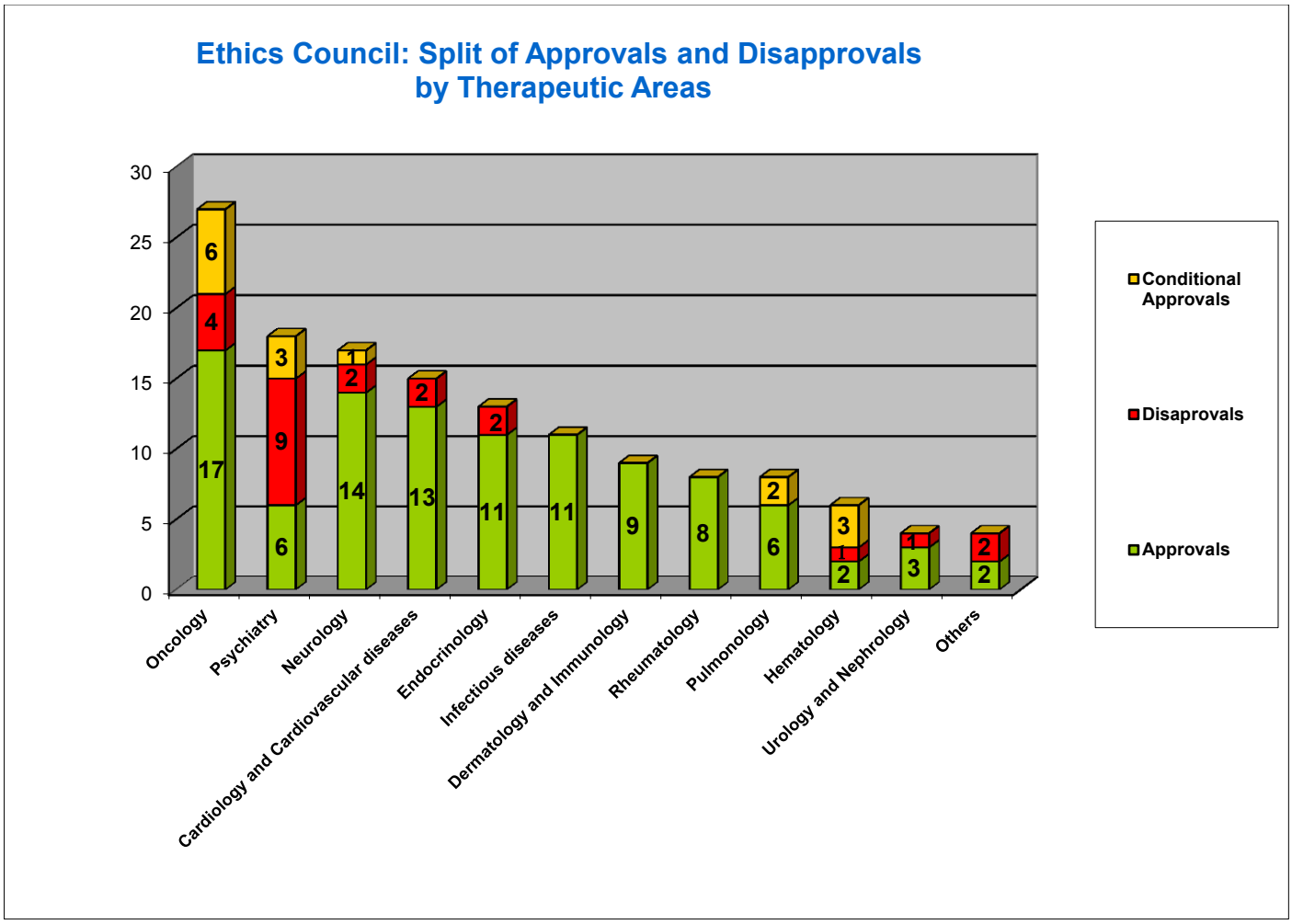
Let us keep in mind that we already brought this subject to your attention more than once (*see ACTO Newsletters №2 and №5)*. Since that time the composition of the Ethics Council has changed, but the expert in this subject has remained the same. The results are pretty clear. And although the number of applications for approval in psychiatry remain fairly high for the time being, several companies have already said that they refuse to place international trials for anti-psychotic medicines in Russia, until such time as the climate in this subject changes for the better.

Table 4

Ethics Council: Split of Approvals and Disapprovals by Therapeutic Areas							
Therapeutic Area	Total Number of Initial Submissions	Number of Approvals Issued after the Initial Review	Approvals Issued after the Initial Review, % of Total	Number of Disapproval Issued after the Initial Review	Disapprovals Issued after the Initial Review, % of Total	Number of Conditional Approvals	Conditional Approvals, % of Total
Oncology	27	17	63,0%	4	14,8%	6	22,2%
Psychiatry	18	6	33,3%	9	50,0%	3	16,7%
Neurology	17	14	82,4%	2	11,8%	1	5,9%
Cardiology and Cardiovascular diseases	15	13	86,7%	2	13,3%	0	0,0%
Endocrinology	13	11	84,6%	2	15,4%	0	0,0%
Infectious diseases	11	11	100,0%	0	0,0%	0	0,0%
Dermatology and Immunology	9	9	100,0%	0	0,0%	0	0,0%
Rheumatology	8	8	100,0%	0	0,0%	0	0,0%
Pulmonology	8	6	75,0%	0	0,0%	2	25,0%
Hematology	6	2	33,3%	1	16,7%	3	50,0%
Urology and Nephrology	4	3	75,0%	1	25,0%	0	0,0%
Others*	4	2	50,0%	2	50,0%	0	0,0%
Total	140	102	72,9%	23	16,4%	15	10,7%

***in the 'other' section, we included one trial in surgery and three in midwifery and gynaecology**

Diagram 6



Source: data from poll of ACTO members

In Table 5 and Diagram 7 we present data on the breakdown of approved and disapproved cases by therapeutic areas based on the results of expertise by FGBU. Here we encountered problems with entirely different illnesses, than we did with the Ethics Council. The lowest percentage of cases approved on the first attempt went to neurology (35.3%) and also to cardiology and cardiovascular disease (46.7%).

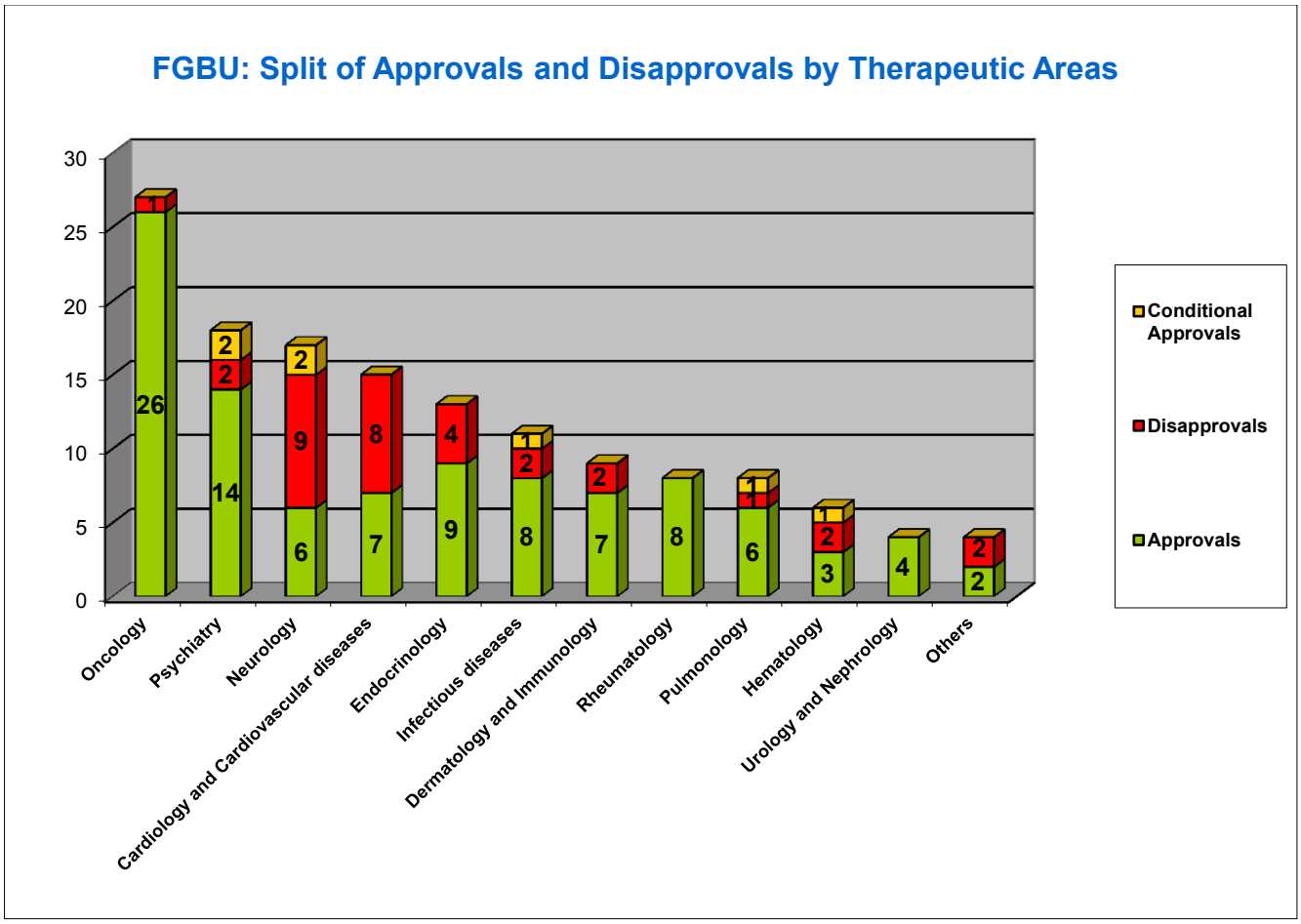
However, we cannot confirm that the two stated therapeutic areas are the subject of a special attitude on the part of the experts, as is the case, in our opinion, with psychiatry and the Ethics Council. Conducting this analysis for the first time, we did not appreciate all the nuances beforehand. And only having gathered additional comments from poll respondents, we were able to understand that the majority of comments from FGBU were connected with toxicology. However the initial question of what formed the major basis for refusals was not put to the respondents. And at present time we can only guess at what might be behind the high rate of refusals by FGBU in different therapeutic areas.

Table 5

FGBU: Split of Approvals and Disapprovals by Therapeutic Areas							
Therapeutic Area	Total Number of Initial Submissions	Number of Approvals Issued after the Initial Review	Approvals Issued after the Initial Review, % of Total	Number of Disapprovals Issued after the Initial Review	Disapprovals Issued after the Initial Review, % of Total	Number of Conditional Approvals	Conditional Approvals, % of Total
Oncology	27	26	96,3%	1	3,7%	0	0,0%
Psychiatry	18	14	77,8%	2	11,1%	2	11,1%
Neurology	17	6	35,3%	9	52,9%	2	11,8%
Cardiology and Cardiovascular diseases	15	7	46,7%	8	53,3%	0	0,0%
Endocrinology	13	9	69,2%	4	30,8%	0	0,0%
Infectious diseases	11	8	72,7%	2	18,2%	1	9,1%
Dermatology and Immunology	9	7	77,8%	2	22,2%	0	0,0%
Rheumatology	8	8	100,0%	0	0,0%	0	0,0%
Pulmonology	8	6	75,0%	1	12,5%	1	12,5%
Hematology	6	3	50,0%	2	33,3%	1	16,7%
Urology and Nephrology	4	4	100,0%	0	0,0%	0	0,0%
Others*	4	2	50,0%	2	50,0%	0	0,0%
Total	140	100	71,4%	33	23,6%	7	5,0%

*** in the 'other' section, we included on trial in surgery and three in midwifery and gynaecology**

Diagram 7



Source: data from poll of ACTO members

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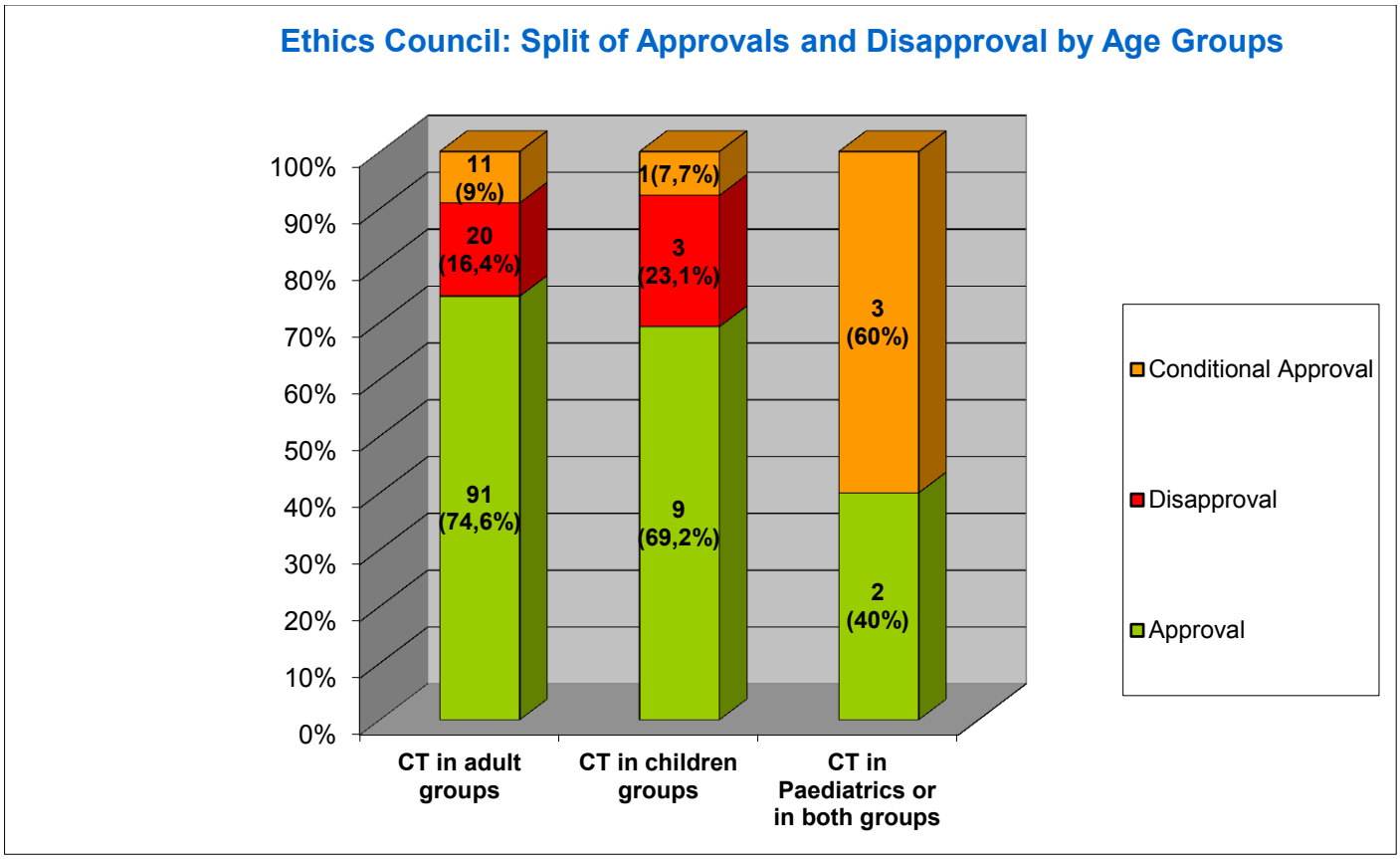
Another parameter that we decided to look at with this poll was whether or not the age of the population in the trial had an effect on approval by the expert bodies. We split all the trials into three groups – protocols with an adult population, protocols only with children, and protocols which intended to study both groups. The results are shown in Diagrams 8 and 9.

As we can see in Diagram 8, in Ethics Council decisions there is no detectable bias with regards to paediatric protocols. The percentage of disapprovals for such trials was just a little higher than for trials with adults. However in the 'mixed' group there were no disapprovals at all. And if you calculate the total share of disapprovals in the paediatric and 'mixed' groups, it is practically even with the same in trials with adult populations (16.7% compared to 16.4%). To be sure, the third group had more cases to receive conditional approvals. However, this does not appear to tell us anything determinative. All we could conclude is that the Ethics Council maintains a positive attitude towards trials with children. It might be that the positive outlook continues to be influenced by the position of the ex-Chair of the Council. Previously a neonatologist, now holding the position of the Director of the Department of children's medicine and obstetrics of the Ministry of Health, this is a specialist who appears to truly understand the importance of new research in paediatric pharmacology and the practical consequences of adequate medication for the child population.

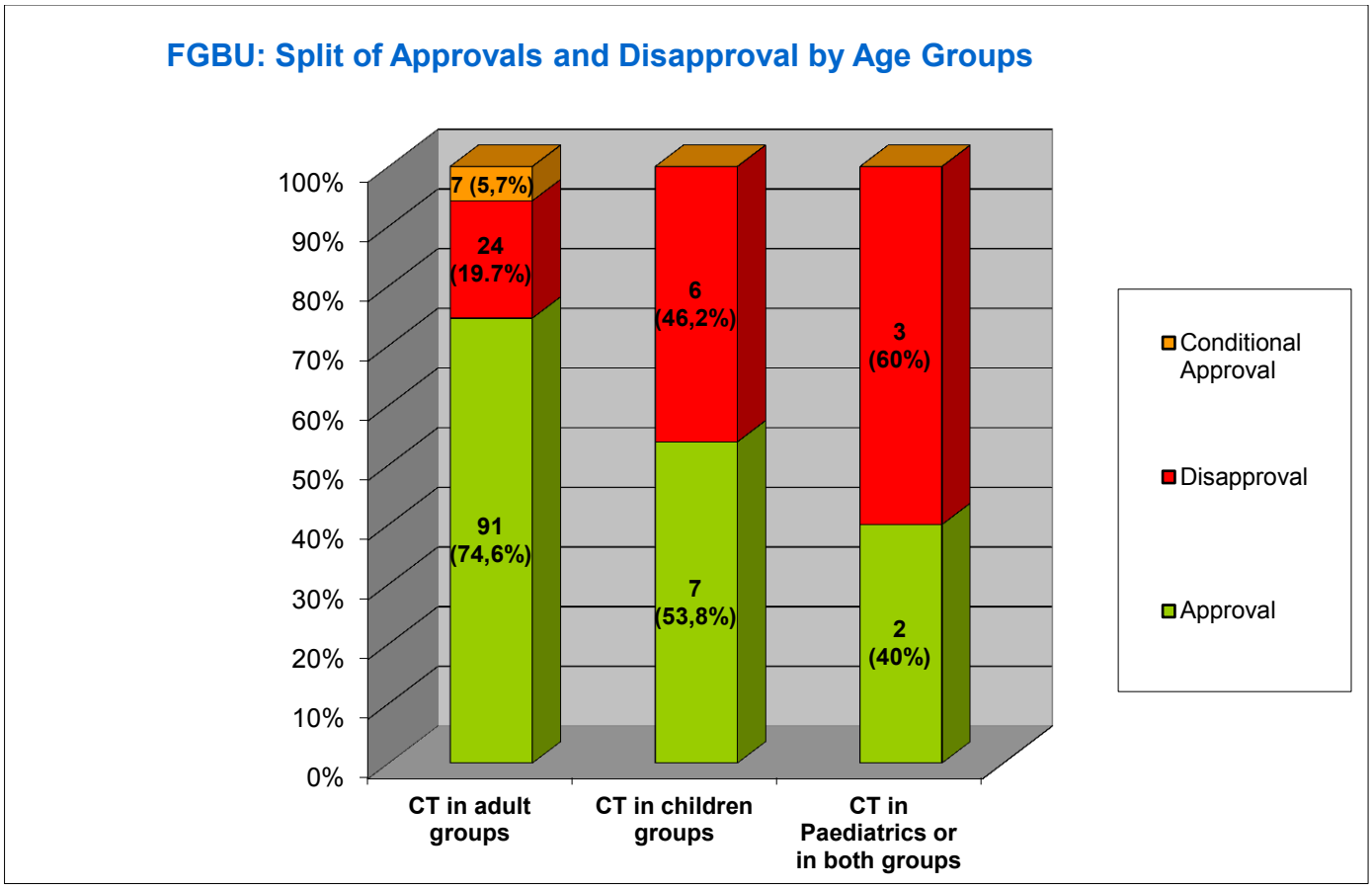
Diagram 8



Source: data from a poll of ACTO members

We see a different picture in the decisions by FGBU. In Diagram 9 we clearly see that the percentage of refusals on protocols with children, and also protocols combining both age categories, significantly exceeds that of trials with only adults (46.2% and 60%, compared to 19.7%). These results support the theory already expressed by market participants – that the experts from FGBU are extremely biased against trials in Paediatrics.

Diagram 9



Source: data from poll of ACTO members

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In addition to collecting statistical data, we also asked poll respondents to comment on their perceived reasons for refusals. As expected, these reasons were completely different between experts from FGBU and the Ethics Council.

The Ethics Council expertise

We must admit that in general the applicants were agree with the majority of comments received from the Ethics Council. This was with regard to inaccuracies in translations, inconsistencies with the form of informed consent, and sometimes corrections to terminology.

It's true that in a number of cases the demands to clarify terminology were rather amusing. For example, historically the Ethics Council has quivered over the word 'diarrhoea'. Historically, because it inherited this 'love' from its predecessor, the Ethics Committee of Roszdravnadzor. The experts believe that the term is not understandable to potential trial participants and ask for it to be changed. The permissible alternative – 'loose stools' – was also invented by the predecessors of the current experts (presumably due to the fact that the word 'stool', at least in one of its meanings, would be better understood by patients). Is this demand for a change justified? Perhaps, if you imagine a person who has never before had cause to understand its meaning, not even from widely-broadcast television commercials. And it's difficult to argue with the experts – they can always say that if they find just one patient who doesn't know what the term means, it needs to be changed to something else which, in their view, is easier to understand. But then another problem arises – the understanding of the expression 'loose stools' does not reflect the intensity of process. This in turn could lead the patient to confused expectations of the effect. True, there is hope that in

the near future the experts will be able to suggest that applicants use something else, probably easier to understand and more accurately reflecting the accepted pathological status of the term.

It is clear that applicants are never going to argue with the experts over a matter such as that described above. It would most likely be pointless, and it would definitely be a waste of time discussing such matters and delaying the start of the trial. We can only call upon the respected experts in evaluating the issue of accessibility of information for the patient to not forget the other side of the coin – the issue of reasonable balance. The average volume of written information for the patient in an international clinical trial today averages 12-14 pages (and sometimes 20 or more). And over time this figure can only increase. Sponsors must describe everything as fully as possible which affects conditions of participation in the trial. Question is where is the limit, where does the level of detail begin to conflict with the common sense and the volume of information start to exceed potential patients' ability to adequately evaluate it?

Standalone cases are the conditional approvals and disapprovals on psychiatric protocols, which we have already mentioned above. The Ethics Council as represented by its lead expert continues to go against the existing legislation, legal opinion, and other psychiatrists by demanding to sign informed consent form by 'close relative responsible for caring for the patient' in addition to signed consent by a legally-capable patient. And at the same time insisting that clinical trials can and should include patients in a condition 'where there are doubts as to the capacity of the patient to express full understanding and voluntary consent', which directly contradicts the fundamental ethical postulates. It seems that the only thing capable of dislodging this expert from this position and bringing the long-running legal violations into line would be the Commissioner for Human Rights or the Prosecutor. And there is some reasons to believe that until that happens there will not be any international trials in psychiatry left in Russia.

Further, the disapproval by the Ethics Council of an international trial for a medicine to treat medulloblastoma (a rare cancer of the brain, found primarily in children), is quite impossible to understand. The reason for the disapproval was phrased as follows: "The main problem is that it is a rare illness, an orphan drug." Just that, short and incomprehensible, what were they trying to say with this phrase. That medicines for rare diseases don't need trials? Or that Russian children can just as well, without participating in trials, wait for them to finish and go through the registration procedure first in the world at large and then in Russia, and then after all of that, they can begin treatment? And that is only assuming that by that time the law will have been changed and the registration procedure will no longer require participation of Russian sites. Or did the comment mean that medicines for these kinds of diseases are as a rule very expensive, and there's no point in studying them, with subsequent registration in Russia, because the state won't be able to pay for them anyway? Or did they mean something completely different? Unfortunately, the sponsor did not receive an answer to this question. Though to be fair, the story has a happy ending. Just before this newsletter went to press, we found out that the trial did in fact receive ethical approval.

But we must repeat that in quite a large number of cases, comments from the experts of the Ethics Council have been well understood by the applicants. The picture is quite different with expertise by FGBU.

FGBU expertise

As we already said above, a large number of comments by FGBU are regarding matters of toxicology. Frequently these issues are linked to the fact that in the opinion of the experts, the applicants have not presented necessary pre-clinical data. In addition, in a number of cases they feel there is simply insufficient pre-trial evidence.

The first under the hammer are the generics. Frankly speaking, nowhere but in Russia have they dreamt of requiring generics to have their own results of pre-clinical studies. Western colleagues simply cannot understand – why would you subject lab animals to unnecessary testing, when there are already numerous studies on the very same active substance. But FGBU experts insist that there must be own data. As it turned out later, not just any trials, but comparative ones with the original (reference) medicine (animal rights supporters are weeping in the arms of the biostatisticians). At the same time the existing Order from

the Ministry of Health and Social Development of November 23, 2011 No. 1413N clearly says that the report on pre-clinical studies for generics may contain evidence and data published in specialised publications. Later the analogous standard was implemented in the Order of the Ministry of Health and Social Development of August 26, 2010, regulating the matter of conducting expertise. But for some reason this argument has no effect on the experts, nor do explanations by companies appealing to the widely-accepted approach, to the international guidance and information on websites of the EMA and FDA. Even the Ministry of Health, acknowledging the problem and coming down on the side of the applicants in this case was ineffective to restrain FGBU. With a perseverance worthy of the toughest test, the experts reply that data on the mutagenity or carcinogenetic aspects of a certain substance, which has been on the market already for many years, is missing.

In the 'risk group', in addition to generics, also fall new combinations of well-established substances, whose combined use is standard, as well as several biological products in particular substitutes for natural hormones and enzymatic drugs. They also require data on pre-clinical studies. Frequently without regard for the fact that in Russia it is already in a phase III trial, which means the medicine has already successfully undergone a trial with human subjects at earlier phases of development. What do the experts have against Russian mice?

Another frequent comment from the experts at FGBU was the requirement to remove the youngest and oldest age groups from the study (which, in particular, confirms our statistical analysis of the relationship to paediatric trials). The basis for this verdict is the experts' conclusion that 'the results of previous trials do not allow us to judge the safety of the medicine for use with the young (old) age group'. Perhaps this is a new concept for the specialists of the institutions, but clinical trials are conducted precisely in order to obtain data on efficacy and safety, which will subsequently, in the case of positive results, increase indications for using the medicine in children or the elderly. In what other way would it be possible to develop medicines, other than evaluating their actions, including on specific groups of patients? Mankind has not yet found an answer.

What is the sponsor left with as a result of receiving such a verdict? Depending on the aims of the trial he can either remove the 'displeasing' age group from the patient enrolment in Russian sites, or can just decide not to run a trial in our country at all. Set against the global trend of increasing the number of paediatric trials, we are off in another direction – that of further limiting them. And this is all in conflict with the published policy – one only needs to remember the presidential order to expand clinical trials of medicines in paediatric practice, issued as a result of the session of the Committee on the Modernisation and Technological Development of Russia's Economy of May 24, 2011. However, as practice shows, the president says one thing, and the experts of the FGBU say something else. Perhaps the common man might say – well that's good, let them run experiments on their own children and we'll get the medicines once they are ready. But the problem is that Russia's refusal to participate in international paediatric trials may mean not only delays in bringing the medicine to the international market (which as we recall does not concern our experts overly much), but also delays in registering it in Russia, and that means further inaccessibility of new treatments for Russian children. This problem is also very pertinent in the context of mandatory local trials, when the officials believe that the results of international trials are insufficient to register a medicine in our country.

The following fashionable trend in our time is the evaluation of the announced phase of the trial. There have been cases when an international protocol receives a comment on the need to change the phase because in the opinion of the experts it does not match the true stage of development. Then it is really difficult to say anything. Trials which are approved by the FDA and EMA and are conducted in all countries in a given phase, and in Russia for some reason must be called by a different one. And only because that seems better to our experts. But in Russian legislation (just as, by the way, in the legislation of other countries), there is no clear classification on phases. The guideline E8 ICH speaks directly of the inapplicability of strict classification. In particular, in point 3.1.3., it states, *"It is important to recognise that* ***the phase of development provides an inadequate basis for classification of clinical trials because one type of trial may***

occur in several phases... It is important to appreciate that the phase concept is a description, not a set of requirements. *It is also important to realise that the temporal phases do not imply a fixed order of studies since for some drugs in a development plan the typical sequence will not be appropriate or necessary."*

It seems that our experts do not even understand what a confused position they put themselves in by taking it upon themselves to comment on that about which they frequently have only the faintest understanding. And it is not clear if they even realise that in issuing what seems to them to be fairly innocuous comments about changing the phase, they are deciding the fate of a trial in Russia. An international sponsor cannot change the phase of development for the whole world based on the opinion of experts in one country, just as neither can he make it different for just one country.

And finally, two more real-life examples, both on international clinical trials. Comments given on the results of expertise by FGBU 'along the way to change the inclusion criteria' (we will clarify for the reader that inclusion criteria are one of the fundamental parameters of a trial protocol, which it is absolutely impossible to change 'along the way'). The second comment for a clinical trial that received the negative conclusion was 'further development of the medicine would be not reasonable'. We can only sympathise with Russian employees of the companies that were forced to send translations of such priceless decisions from the Russian expert body to their western colleagues.

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We will try to summarize the information we have received on the state of expertise by FGBU and to analyse the reasons for the current problems.

The most common characteristic we hear with regards to the activities of the expert body is the very low qualifications of many of the experts. That could of course be a biased judgement. Moreover, we often hear counter-accusations – of the low quality of preparation of documents by applicants, which also is undoubtedly the case sometimes. Indeed, mutual pretentions between the expert bodies and applicants have always existed. Is there anything significantly different about today's situation from the typical picture of the past years? We believe that there is. And there is a reason for that.

Let us remember first of all what the expert body is most frequently accused of – and that is a high level of corruption. The fight against corruption has become one of the slogans used by the 'healthcare reformers' to change the foundations of the expert activity. There was a full ban implemented on the contact between experts and applicants (only via the Ministry of Health) and the expertise itself could only be conducted at the request of the ministry. The experts have no opportunity to ask direct questions on the subject of the expertise and the applicants cannot provide straight answers. FGBU has transformed into a black hole and it is extremely difficult to get any information about the process within. Specialists are still judging whether these changes have helped at all in the fight against corruption. What we definitely do have is the predicted side effect – the emergence of an aggressive illiteracy protected by full impunity and certainty in their own righteousness. And here we have a number of factors at play.

One of them is the appearance of new leadership at the body and a new policy of full secrecy. Against this backdrop, there is the current influx of young staff. That, probably, in and of itself, is not a bad thing. But we must also take into account the conditions in which this influx is happening. So, the ranks of experts are being filled in by former students that have just been graduated. We will not discuss the problems with current level of education, but facts are facts – there are currently plenty of poorly-qualified and quite ignorant graduates in all fields. What should these new experts do, but improve their knowledge in practice? And that brings us to the next problem. The "old guard" of experts, of those still in the system, prefer either not to get involved so as to avoid being accused of 'acting in the interests of the applicants', or they just don't care what happens to the quality of the expertise. It is difficult for the young specialists to get information from the outside – they are forbidden not only to have contacts with applicants, but also it is practically impossible for an ordinary expert to take part in external events, such as academic congresses and conferences. And where else can they get information about the latest methods and approaches to evaluating

medicines as practiced in the modern world? There's only one solution – to work off a boilerplate. Especially since there is one ready for use.

Working based on a boilerplate is the surest way. There is an existing legislation where a huge number of nuances and specific groups of medicines remained left out of attention. There is also a great document – the order by the Ministry of Health and Social Development No. 750n of August 26, 2010, which sets the rules for expert review and final form of expert examination for the FGBU experts. The form contains specific subsections, which must be filled out by the experts. So if the form has a separate graphs for 'mutagenity', 'carcinogenicity', and 'irritants', then that means that the expert must evaluate those parameters. And if they are in the section on pre-clinical trials, then they should be obtained in the pre-clinical stage. The fact that the nature of medicines is more varied than the tables offered on the form – this is not a problem for the expert. That is the only way to explain the logic of FGBU employees, who demand pre-clinical studies on water for injection…

Another point we would like to touch on here is the total lack of motivation on the part of FGBU to change anything about the current situation. The experts do not have contact with the applicants and they have no risk of being publically humiliated. Orders for expertise are guaranteed for the institution, regardless of what the quality of that expertise may be. In these conditions, it is undoubtedly simpler and safer to issue a refusal. Especially since you can always defend your actions by saying that they are only with the goal of patient safety. For who can say what medical tragedy has been prevented thanks to the higher vigilance by experts, acting as guardians of public health?

It is interesting that in these conditions, the Ministry of Health (at least, its current composition) is demonstrating a high degree of good sense. Perhaps they have grown tired of struggling with endless questions from applicants, or maybe they are embarrassed to look their western colleagues in the eye, who knows? But the position taken by the authorities at least in part acknowledges the redundancy of requirements to conduct pre-clinical studies for generics, which can only be welcomed. The position is already backed by supplementary acts and there is a planned additional strengthening with amendments to the law. But the absurdity of this situation is in the fact that FGBU does not share this position, and steadfastly refuses to listen to the head authority on the matter and to carry out their orders! And here is another conceptual problem with the new legislation. The Ministry of Health (or more accurately, its predecessor the Ministry of Health and Social Development) itself washed its hands from taking part in the decision, writing itself only a technical role in the law – issuing tasks to the experts and issuing on the basis of the expert decision a refusal or an approval. As a result there is no responsibility for the decision by any civil servant. But without responsibilities – there are no rights. In transferring all powers on decision-making to the expert institution, the civil servants have themselves created a decision where the tail has begun to wag the dog.

LEGISLATIVE INITIATIVES

It will soon be a year since the Ministry of Health began work on preparing amendments to the current law *On the Circulation of Medicines*. In that time there has been a lot of discussions, many arguments, first provisions came and went, replaced by others. Adopted by the Russian Government at the beginning of May, the draft was subsequently returned for further development and new inter-agency agreement. At the end of the summer it went back to the White House. Market players, after many requests, got a chance to see the new version.

The text has undergone significant changes. Up to and including that the sense of some provisions has been replaced for the exact opposite. That is what happened, for example, with the understanding of interchangeability, the subject of the main arguments over the bill, with the main players being representatives of the commercial sector of the pharmaceutical industry – manufacturers of original and generic medicines, as well as the Federal Anti-Monopoly Service and patients' groups.

Regulating the issues of clinical trials has also gone through certain changes. We recall that the extremely concerning proposal by the Ministry of Health to implement pharmaceutical analysis of samples of medicines at the stage of obtaining approval for clinical trials, which threatened to exclude Russian participation in international trials, was removed by the authors back before the bill was sent to the Government. At that point on the suggestion of the Federal Anti-Monopoly Service a new article was included on insurance, changing the type of insurance from personal to liability insurance. This approach gave us hope of resolving serious problems in this area and of harmonising the Russian system of insurance in clinical trials with the generally-accepted international practice. The fact that the Ministry of Health supported this unquestionably progressive proposal allowed us to accept the bill, although it had other problems which were rather difficult for the clinical trials market – increasing waiting period for approvals and changes the basis for state fees for trial approvals (*for more details see ACTO Newsletter №6).*

What has changed regarding the regulation of clinical trials in the new version of the bill? Unexpectedly, a proposal on insurance has been excluded from the text. According to representatives from the Ministry of Health, the new system was not approved by the Ministry of Finance. Now we have an interesting breakdown. Problems were long evident and explained by representatives of companies conducting trials and insurers. The new system of insurance accommodated everyone – market players, the Federal Anti-Monopoly Service, and the Ministry of Health. In the process of discussion there were also taken into account comments from representatives of the patients' groups. Finally, a rare example of consensus was achieved. But then the Ministry of Finance spoke up (it is not clear whose interests they are representing in this instance), and the Ministry of Health suddenly backed down, agreeing to leave the current, flawed insurance system unchanged.

At the same time in the latest version of the bill there are still comments regarding increasing waiting periods for trial approvals, as well as changes to the basis for paying state fees. We remind readers what the latter entails. According to the current provision in the Tax Code, the applicant pays for the approval issued to conduct a trial. The bill proposed changing the rules to require payment for the expertise. The consequences are obvious – an applicant who does not get through the expertise will have to pay again for a resubmission. Mind you, applicant will have to pay the full fee, regardless of whether both expert bodies gave a negative decision, or one was positive. But that is not even the root of the problem. The very proposal to pay for the expertise is absurd in and of itself from a legal point of view. This approach contradicts, first of all, the essence of the Tax Code. It is true that there is already a precedent in particular with registration of medicines, thanks to the previous Minister of Health, who did not experience difficulties in conducting, including via the Ministry of Finance, the most insolent and unexpected decisions.

What is wrong with the approach proposed by authorities? First of all, the expertise itself does not constitute a legally significant event, and the expert organisation is not a state body (and those are the basis for state fees as set out in point 1 section 333.16 of the Tax Code). The very understanding of the fees is that it is a tariff but not a payment for work or services rendered. But in our opinion that is not even the major

legal issue. That is the fact that the applicant is no longer the party who orders the expertise. The expertise can only be conducted at the request of the Ministry of Health. The applicant cannot communicate directly with the expert organisation, and moreover any contact between experts and the applicant is forbidden by law. In other words, the system under the current legislation is as follows: the company wants to conduct trials and applies for permission to the state authority, then the state authority, apparently, acknowledges that it is not an expert in regards to evaluating the application, and turns for expertise to a third party – FGBU or the Ethics Council. We also remember that there is no responsibility for the final decision on the part of the Ministry of Health – it is formed exclusively on the basis of the expert decision. And now, apparently, the applicant is required to pay not for the issued approval (what he has actually applied for) but for the expertise that the Ministry ordered. And therefore the question arises – why is the Ministry of Health needed in this system at all?

And then in general, why bother with all the reforms that took the authority to issue approvals away from Roszdravnadzor and gave it to the Ministry of Health, if it then turns out that it is not necessary at all? But let us return to the bill.

We must say that in the process of discussing the bill, ACTO repeatedly made clear its position on the problem of state fees, communicating directly with the Ministry of Health. This issue also arose in the quality of commentary on evaluating the regulatory actions of the Ministry of Economic Development of the Russian Federation. In addition, it was supported in the process of expert discussion in the Analytical Centre under the Russian Government and was included in the official summary table of results of discussions. Nevertheless, the Ministry of Health has completely ignored these comments when preparing the bill, proposing that the provision remains unchanged. And there are no reasonable arguments to support the basis of the authorities' position to be heard at all.

Taking this into account, we must say that the current edition of the bill offers absolutely no improvements for clinical trials whatsoever. They have added new documents, increased waiting periods, and there is a risk that financial expenses for the applicant will be increased for repeat expertise. But perhaps the bill in its current form will fix the situation in other sectors? But this is also impossible to confirm, judging by the reaction of other market players. In proposing a solution for one problem, the bill creates a new one someplace else. In supporting one idea, the Ministry of Health will tomorrow reject it and propose something else. Overall it creates the impression that at present the authors have completely lost sight of what was the point of all of this.

And now it's time to come back to the history of the issue. What area has been affected the most by the reforms of the pharmaceutical sector embodied in the law *On the Circulation of Medicines*? Based on our assessments, it is an area of access of new medicines to the market, and not just originals, but generics as well. The registration system, already far from perfect, has now become so convoluted that it now doesn't even vaguely resemble that of developed countries. Primarily due to clinical trials being included into the registration process. There were also requirements added about the need to present results of clinical trials conducted within the Russian Federation. Previously acceptable results of international trials are now deemed insufficient and new ones must be conducted with participation of Russian sites. This comes on top of the requirement to present the results of pre-clinical studies for generics and the need to conduct trials of 'therapeutic equivalency' in the event that the pharmaceutical form of the medicine cannot be avoided with bioequivalence studies. By the way, we won't even bother to repeat everything we've already said numerous times in previous issues. All this has led to a collapse in registration system from which manufacturers are only just beginning to emerge, and only in the cases where solutions have been found to the multitude of problems. And this is far from always being the case.

Clearly, such a situation on the pharmaceutical market could not remain unnoticed at the government level. And so the Government (in an order dated December 14, 2012), introduced into the bill a point on developing amendments to the law *On the Circulation of Medicines* "partly taking measures aimed at timely clearance of procedures connected with state registration of medicines".

What do we have in the text of this bill? Waiting periods for separate administrative procedures have been increased. The waiting time for an approval for clinical trials (which, let us remind you, are also part of registration), has also been increased. Despite all of that, the civil servants proudly proclaim that the overall period for registration has not changed. That is so if you believe that the registration process slows down over the time to conduct trials. The time to bring a medicine to market is still growing, and it is already so long that another month and half will hardly spoil the already depressing picture. The fact that for international clinical trials this month and a half might be quite critical – might in fact lead them to avoid conducting trials in our country – does not seem to trouble the civil servants at all. Another explanation for the strange way of implementing the Government decision is the peculiar method of interpretation. For who said that 'measures aimed at timely clearance of procedures', would not include increasing the stated periods? As a result, the law is merely coming closer to current practice and that means it is easier for the civil servants to do their job.

The situation with the Presidential Orders issued on the basis of the meeting of the Committee on the Modernisation and Technological Development of the Russian Economy held on May 24, 2011 in Moscow is even more interesting. There were two orders of interest to us. The first required that by September 01, 2011, 'to organise negotiations with countries of the European Union and the USA with the aim of including the Russian Federation in international agreements on mutual recognition of the results of clinical trials of medicines'. History is silent on the implementation of this Order. At a minimum, as far as we know, negotiations were organised with the EU, which we know about via the expert report[1] published as part of the European Commission's project 'Cooperation in the field of clinical trials' (*see ACTO Newsletter №6)*. It seems that the results of these negotiations were disappointing for the Russian side. Most likely, the western officials explained to them that the concept of 'an international agreement on mutual recognition of the results of clinical trials' was not familiar to them.

More attention should be paid to the fate of the second Order. It instructed 'to prepare a proposal on implementing changes to the normative legal acts of the Russian Federation, envisaging possible recognition in the Russian Federation of the results of clinical trials conducted in the European Union and the USA on medicines, including those intended for use in paediatric practice'. This is an entirely different breakdown. Here we are dependent not on the will of other countries, who for some reason persistently do not wish to support the idea of a unique kind of international agreement. Here Russia itself can propose changes to its own legislation. This Order was to have been implemented by September 1, 2011. Since thus far nothing at all has happened, we forgot about it. But as it turns out, there were civil servants who had not forgotten and tirelessly slaved away at it. Imagine our surprise when, two years after the deadline had passed, we suddenly saw on the website of the President of the Russian Federation[2] information about the implementation of this Order! It is dated May 2013. We present the whole text:

*"**On the implementation of the Presidential Order for the Russian Federation to recognise the results of clinical trials conducted in the European Union and the USA"***

May 8, 2013, 14:30

On the results of the meeting, the Russian Government was ordered to prepare a proposal on implementing changes to the normative legal acts of the Russian Federation envisaging the potential to recognise in the Russian Federation the results of clinical trials conducted in the European Union and the USA on medicines, including those intended for application in paediatric practice.

With the aim of legislative regulation in the areas of concluding an agreement on mutual recognition of the results of clinical trials on medicines for medical applications between the Russian Federation and countries of the European Union on the results of negotiations held between Russia and representatives of

[1] The full text of the report can be seen at : http://ec.europa.eu/health/files/international/report_clinical-trials__sept2012.pdf The Russian translation can be seen at http://acto-russia.org/files/EPRD_Analytical%20Report_RU.pdf

[2] http://www.kremlin.ru/assignments/18647

the European Commission, a federal bill was prepared to implement the changes to the federal law "On the Circulation of Medicines".

It seems that the bill we discussed (for there is unlikely to be another one that no one has ever heard of) takes into account the results of negotiations with representatives of the European Commission and in some way solves the problem of recognition of results of international trials. Re-reading the European Commission report and comparing the conclusions therein with the proposals in the bill, we were not able to find anything linking these two documents. The only exception was the provisions on recognising the results of international trials for orphan drugs – that tiny concession made by the Russian Ministry of Health in its inexplicable fight to keep the current regulatory system unchanged. What of the patients who are suffering not from such rare diseases, well apparently they can wait a few extra years while each new medicine slowly clears all the bureaucratic hurdles in the Russian system and can finally enter the domestic market. Although in all honesty there is not a single word about all of this in the report on the implementation of the order.