ACTO

ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

ACTO NEWSLETTER №9

1st Half of 2014

MOSCOW 2014

CONTENTS

SUMMARY

In the first half of 2014 the Russian Ministry of Health issued 363 approvals for conducting clinical trials. This was down by 10% compared to last year. The number of approvals for conducting international multicenter clinical trials (IMCTs) was down 14.5% (136 compared to 159). There was an even bigger drop, of 34.8%, in the number of bioequivalence studies by Russian sponsors (60 approvals compared to 92). The number of remaining types of trials increased marginally, however, this did not have a significant effect on the general decline.

In the overall structure of the market, in the first half of the year the share of IMCTs yet again reached a historic low, dropping below 40%. Main reason is not the decline in the number of international trials, but rather an increase in the number of generic trials.

In this issue of the newsletter we will again present a rating of the activity of medical organizations specializing in bioequivalence studies. The readers will see that the make-up of the main players in this sector of the market has undergone marked changes over the past two years.

The following section of the newsletter will highlight the analysis of the practice of expertise by the FGBU Research Centre for Expertise of Medicinal Products, and the Ethics Council. It turned out that just 43.7% of applications for conducting clinical trials have a chance of getting through expertise by both bodies on their first attempt (51.5% last year). We continue to see challenges with approvals for paediatric trials, as well as for the more complicated situation with psychiatry (where the Ethics Council grants just 33.3% of applications approval at first attempt) and neurology (in which just 33.3% of applications are approved, but this time by the FGBU). In contrast to the last year's analysis, this time we looked at several additional parameters. In particular, we were interested in the following issue: if the companies considered the comments from the experts fair, strategies they used to resolve issues, and outcomes for applications.

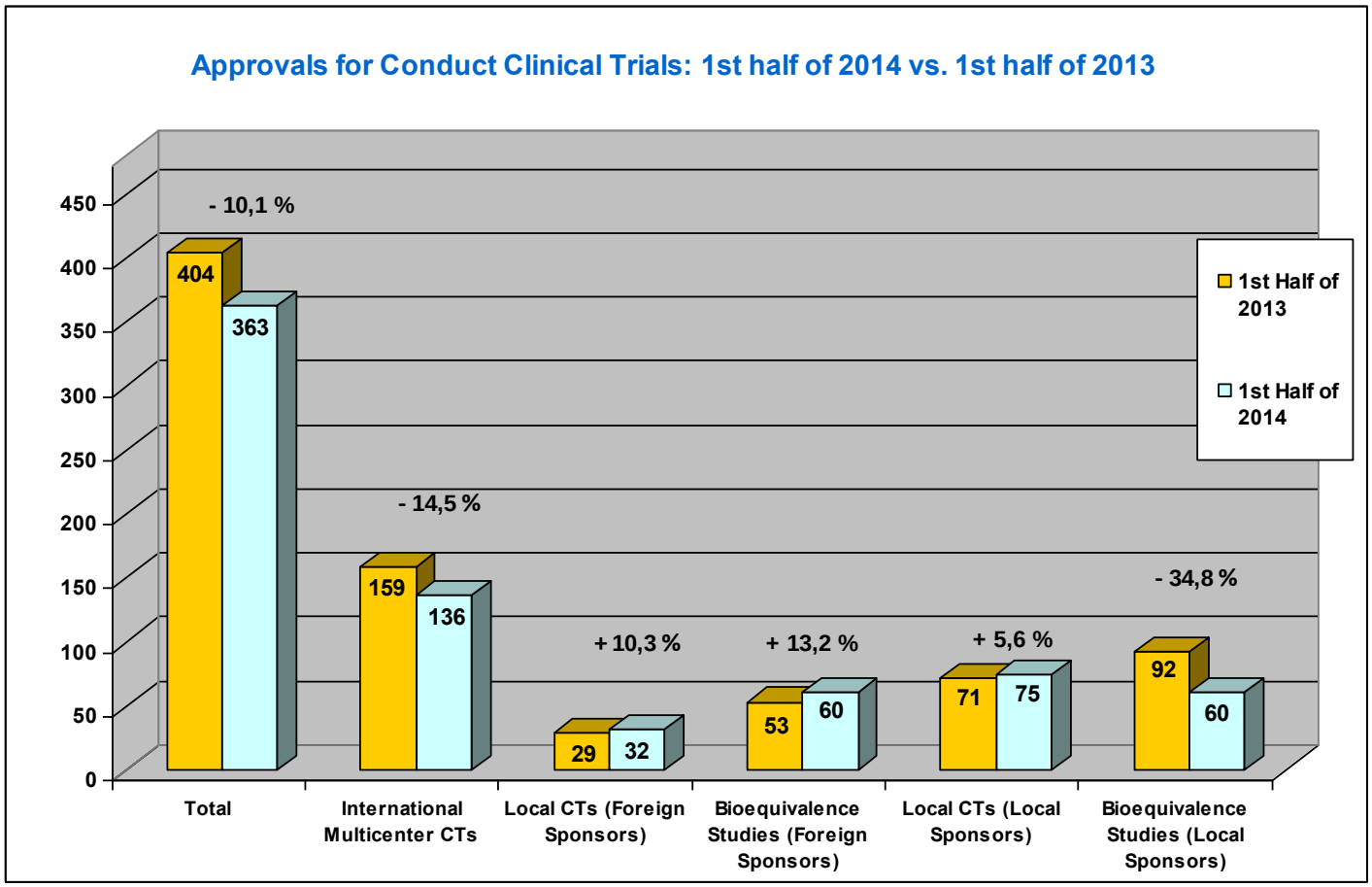
The next topic addressed in the newsletter is the quality of clinical trials. We again carried out a comparative analysis of the results of inspections by the FDA in Russia and in other countries. Additionally, we looked at the practice of Roszdravnadzor inspections. The results show that the number and, more importantly, the quality, of violations in international and local clinical trials differ significantly. Naturally, not in favor of the latter.

The final issue of this newsletter was Regulation (EU) № 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use, adopted this spring. This document replaces the Directive 2001/20/EU, which it significantly expands and adds to. The Regulation will come into force six months after the launch of the new EU database on clinical trials. This is expected no earlier than in the middle of 2016.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

In the first half of 2014 the Ministry of Health of the Russian Federation issued 363 approvals for conducting clinical trials, which is down by 10% compared to last year (Diagram 1). The number of approvals for conducting international multicenter clinical trials (IMCTs) is down by 14.5%, 136 compared to 159. But the most significant drop – by 34.8% - is in the sector of bioequivalence studies by Russian sponsors (60 compared to 92).

Diagram 1

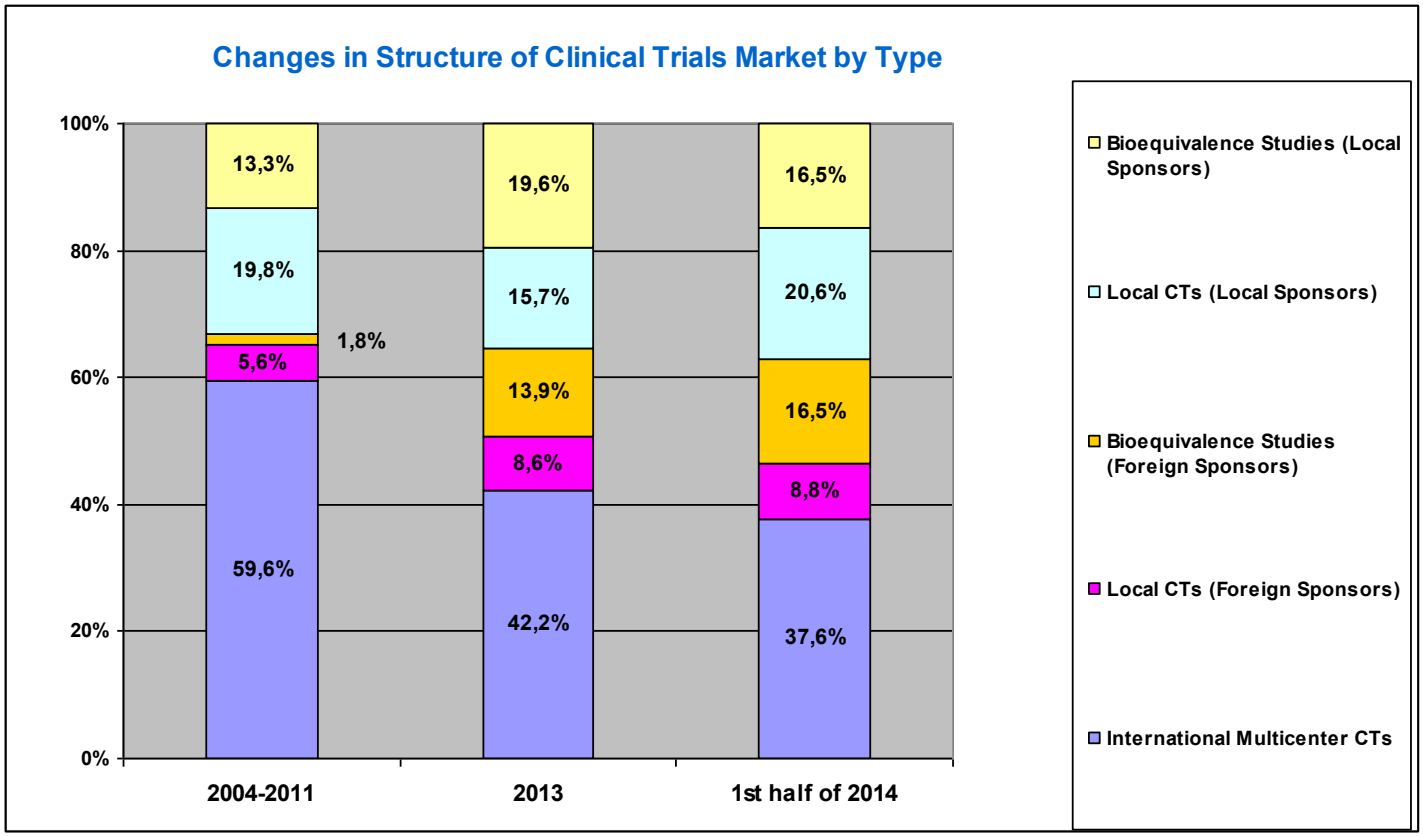


Data from www.grls.rosminzdrav.ru

The remaining three sectors: local efficacy and safety trials by domestic and foreign sponsors, as well as bioequivalence studies by foreign sponsors, grew by 5.6%, 10.3%, and 13.2% respectively. It should be noted that the market share of these types of trials is rather small, so the total growth in these three sectors compared to the same period of the previous year is just 14 applications. Such an insignificant addition could not change the downwards trajectory of the total number of approvals for trials in the first half of 2014.

Diagram 2 reflects changes in the market structure by types of trials. Attentive readers will be able to notice that we have been following these indicators since the introduction of the law “On Circulation of Medicines”. And they will see that the visible effects are a direct result of this law, particularly the implementation of mandatory production of the data on local registration trials and the need to conduct the so-called 'therapeutic equivalency trials' for those generic forms of medicines for which there are no bioequivalence studies underway.

Diagram 2



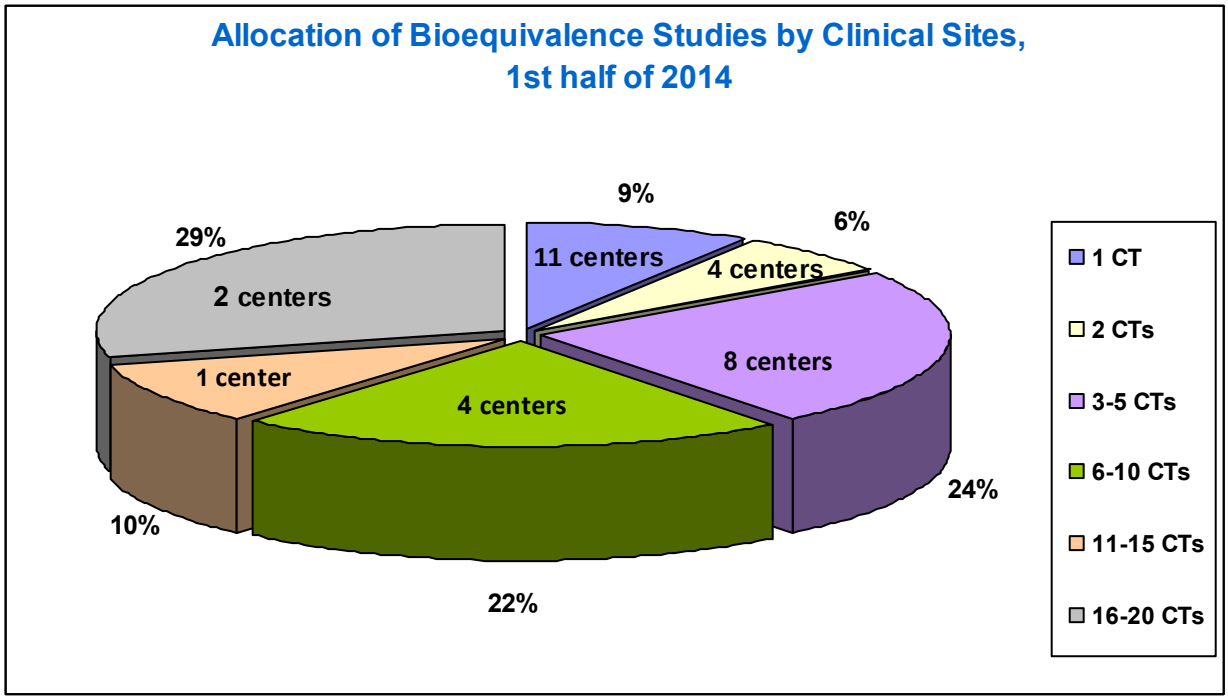
Data from www.grls.rosminzdrav.ru, www.roszdravnadzor.ru

Studying the data for the first half of 2014, first of all we should note that the share of IMCTs in the overall structure of the market continues to fall to historic lows, dipping below 40%. At the same time we see active growth in the sector of bioequivalence studies by foreign sponsors. The shares of the remaining types of trials have also grown compared to pre-reform levels, but are already not as significant.

We must note that at present the overwhelming share of the Russian market for clinical trials belongs to the generics sector. A third part of the market (33%) is bioequivalence studies. Let's see what this sector looks like today. As we can see in Diagram 1, overall in the first half of 2014 there were 120 approvals issued for this type of trial (60 for domestic and 60 for foreign medicines). These trials planned to recruit 3,837 volunteers. The average number of participants in a bioequivalence study for a domestic medicine was 27.2, and for a foreign medicine, 36.7. The last time we looked at this parameter, in the first half of 2012 (*ACTO Newsletter No. 5)*, the figures were 22.2 and 30.8 respectively.

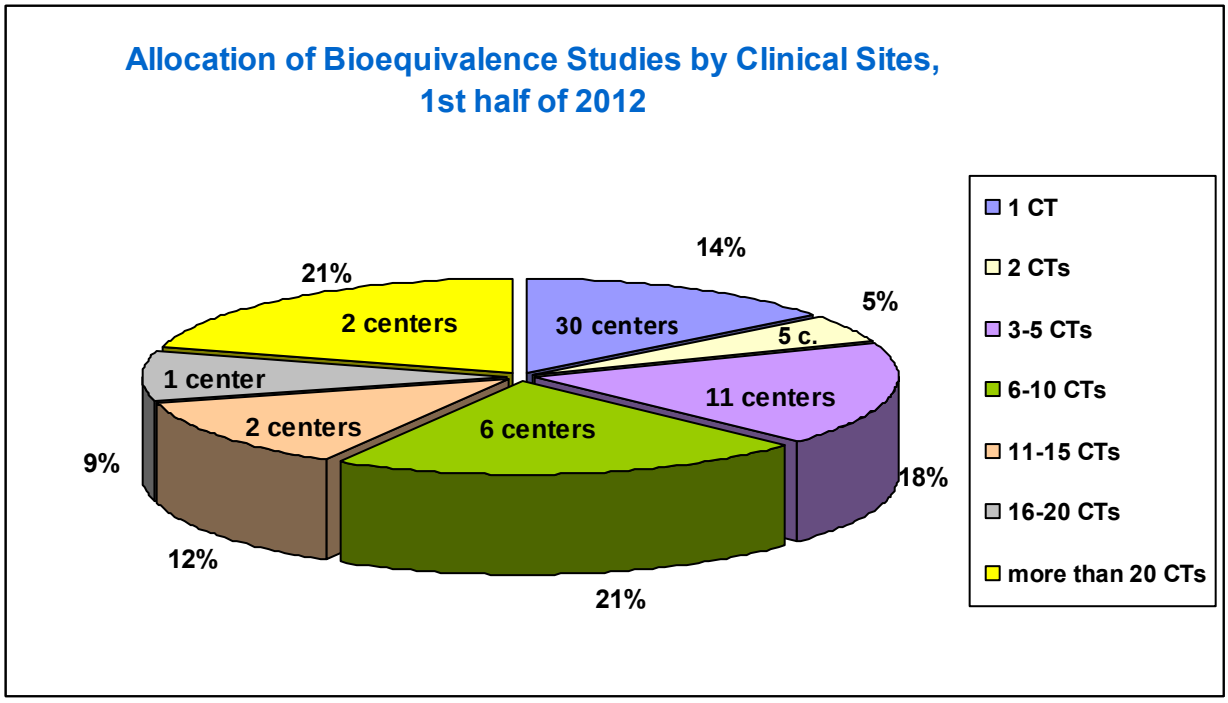
As in the previous case, we decided to look at the breakdown of bioequivalence studies by medical centers. And we discovered that over the past two years, this sector has seen specific changes. First, we can see an increasing concentration of trials in the medical centers. So, whereas in the first half of 2012 there were 57 centers taking part in bioequivalence studies, this year there were only 30. And as we can see in Diagrams 3 and 4, this contraction came primarily due to the elimination of the centers working on just one trial. Which, really, is quite logical. The majority of trials – 61% - were conducted at 7 centers. In 2012, 63% of trials were conducted at 11 medical organizations.

Diagram 3



Data from www.grls.rosminzdrav.ru

Diagram 4



Data from www.grls.rosminzdrav.ru

The pool of the most active centers, as we can see in Table 1, also underwent visible changes. The leader in 2012, the State Research Centre for Prophylactic Medicine, fell five places to the 6th position. This allowed Yaroslavl Clinical Hospital No. 2, previously in second place, to go to the top of the list. The St. Petersburg North-west Research Centre for Hygiene and Public Health moved up from the third to the second place. Moving up into the top three unexpectedly is the Family Doctor + Clinic from Nizhny Novgorod (in 2012 this center has been in a tie with 5 others for places 17-22). It is noteworthy that in contrast to the two different leaders, this center specializes exclusively in trials for domestic generics. The 4th place went to another Yaroslavl organization – Clinical Hospital Number 3 – which had been absent from the previous rating. City Clinical Hospital No. 15 named after Filatov in Moscow moved up from the 12th place to the 5th.

And finally, we should mention the First Moscow State Medical University named after I.M. Sechenov, which dropped from the 5th to the 9th place, which it shared with three other centers that had previously been insignificant players in the rating.

Table 1

TOP 12 Clinical Centers by Number of Bioequivalence Studies, 1st Half of 2014						
№	Clinical Centre	Total number of bioequivalence studies in the center	Number of bioequivalence studies (foreign sponsors)	Number of bioequivalence studies (local sponsors)	Place in the ranking, 1st half of 2014	Place in the ranking, 1st half of 2012
1	The State Health Institution of the Yaroslavl Region "Clinical Hospital № 2", Yaroslavl	19	10	9	1	2
2	The Federal State Institution of Science "The North-west Research Center of Hygiene and Public Health", St. Petersburg	17	10	7	2	3
3	LLC "The Family Doctor + Clinic", Nizhny Novgorod	12	0	12	3	17-22
4	The State Health Institution of the Yaroslavl Region "Clinical Hospital № 3", Yaroslavl	8	4	4	4	n/a
5	The State Health Institution of Moscow Department of Health «The City Clinical Hospital № 15 named after O.M. Filatov», Moscow	7	4	3	5	12-16
6	The Federal State Institution of The Ministry of Health "The State Research Centre for Prophylactic Medicine", Moscow	6	5	1	6-7	1
7	The State Health Institution of Moscow Department of Health "The City Clinical Hospital № 50", Moscow	6	5	1	6-7	n/a
8	LLC " The Medical Centre “Probiotech", Serpuhov, Moscow Region	5	0	5	8	n/a
9	The State Educational Institution of Higher Professional Training of the Ministry of Health “The First Moscow State Medical University named after I.M. Sechenov” , Moscow	4	1	3	9-12	5
10	The Regional Health Institution "Cardiological Dispensary", Ivanovo	4	1	3	9-12	17-22
11	The Federal State Institution of the Siberian Branch Russian Academy of Medical Science (RAMN) "The Scientific-Research Institute of Pharmacology name after E.D. Goldberg" , Tomsk	4	4	0	9-12	9-11
12	The Federal State Health Institution "Clinical Hospital № 123 of Federal Medical and Biological Agency", Odincovo, Moscow Region	4	4	0	9-12	n/a

EXPERTISE OF PLANNED TRIALS: THE PRACTICE OF DISAPPROVALS

Last year ACTO for the first time attempted to analyze the practice of review that forms the basis of approvals by the Ministry of Health to conduct clinical trials (*ACTO Newsletter No. 7)*. This experience has been quite useful and the results were in demand with the market players. Therefore this year we decided to repeat our analysis. This time we have improved our methodology, and also evaluated several additional parameters.

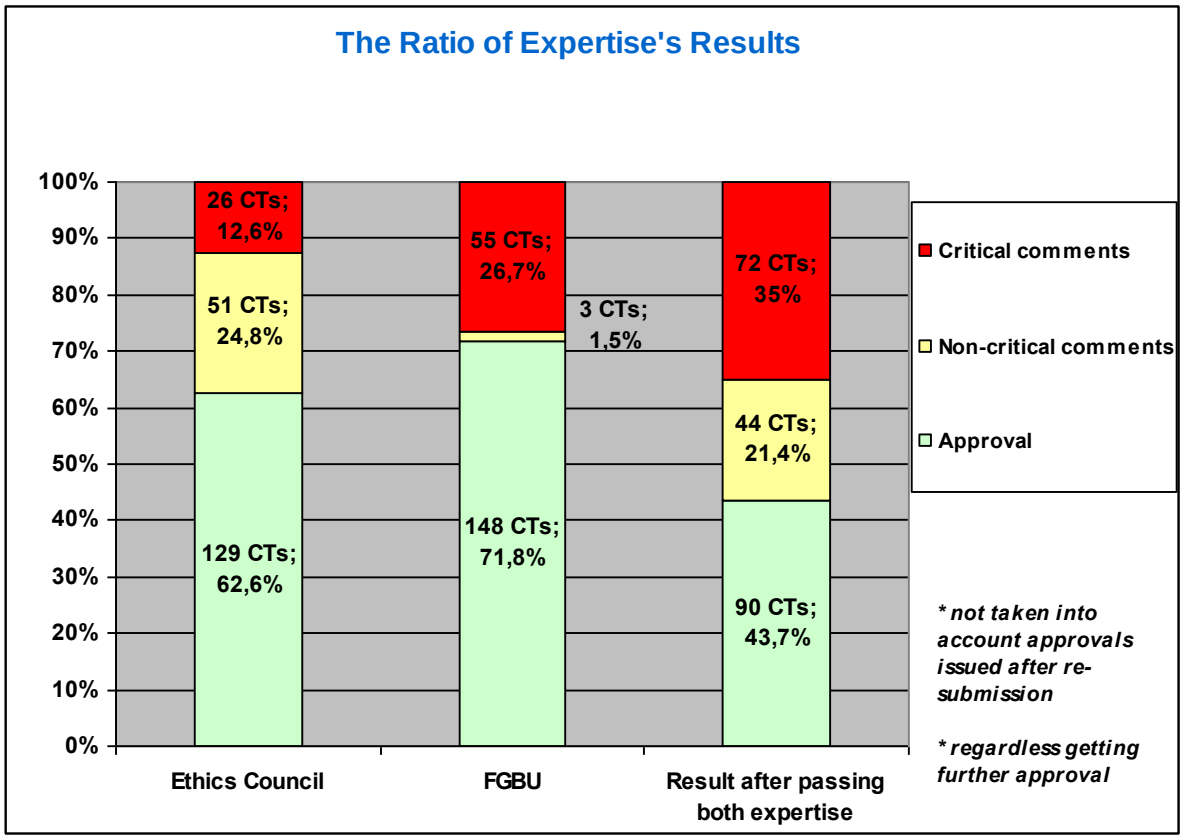
Let us remind you that the analysis is based on a poll of ACTO members on the results of two reviews – by the Ethics Council and by the Research Centre for Expertise of Medicinal Products (further – FGBU). This year the poll included applications for conducting clinical trials, for which the results of review have been received between July 01, 2013 and June 30, 2014, in other words a year from the last poll. Twenty one companies took part in the poll. The data on 206 applications were analyzed, the majority of them being for international clinical trials.

All comments received and reasons provided for refusals were classified as 'critical' and 'non- critical'. Critical ones included those which mentioned insufficient pre-clinical or clinical data, encompassed inclusion/exclusion criteria, suggested changes of the phase of the trial or making other changes in the protocol or Investigator's Brochure. Non-critical included the ones that raised comments on the translation of documents, suggesting corrections or submission of additional information for patients (not related to changes in the trial protocol), and other similar comments.

We had to use our own classification, since the practice has shown that the expert bodies do not always fully comprehend the consequences of a given comment. For example, there have been cases when they proposed that the applicant change the trial phase or increase the patient observation period in working order. It is possible that providing such comments the experts did not fully think of the steps that would be necessary to implement their suggestions. However, we are talking about making significant changes to the protocol, which in international trials you absolutely cannot make 'in working order'. They demand serious consideration at a relatively high level and sometimes lead the sponsor to decline inclusion of Russian centers in their trial. So we came to the conclusion that using the classification of the expert organizations would not provide an objective picture and we had to examine the comments according to our own classification.

Diagram 5 presents the relationship of various outcomes of initial expert review of applications to conduct clinical trials, by the Ethics Council, the FGBU, and also by the results of both expertise. Just 43.7% of applications have a chance of passing with no commentary from either side (last year this figure was 51.5%). And the share of cases approved after first review by FGBU was practically unchanged from last year (71.8% compared to 71.4%). But the same figure for the Ethics Council was down by 10% (62.6% compared to 72.9% last year). But on the whole, this was due to a growth in the number of not critical comments, which the Ethics Council made to nearly one in four of all cases. Regarding critical comments, it's clear that the FGBU makes them twice as often as the Council (26.7% compared to 12.6%). The overall total (based on the results of both expertise) percentage of critical comments (35%) shows that the two expert bodies often have questions coming up on different trials, and their opinion often differs. In other words, there is a relatively high chance that an application will successfully pass one expert body but will be turned back by another, or vice versa.

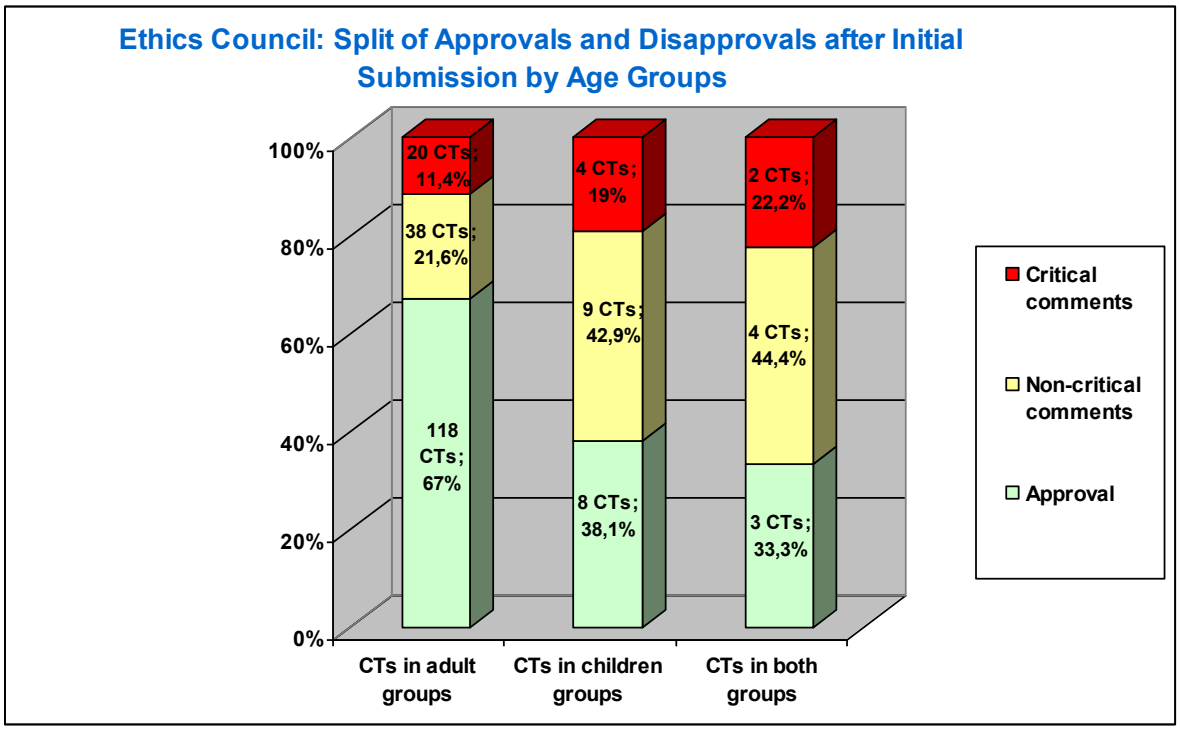
Diagram 5



Data from poll of ACTO members

The following criteria that we used, as we did last year to analyze this data, was to determine to what degree the age of the population influenced the decisions of the expert organizations. For this we divided all the applications into three groups – protocols with only adult patients, protocols with children, and protocols including both age groups. The results are presented in Diagrams 6 and 7.

Diagram 6

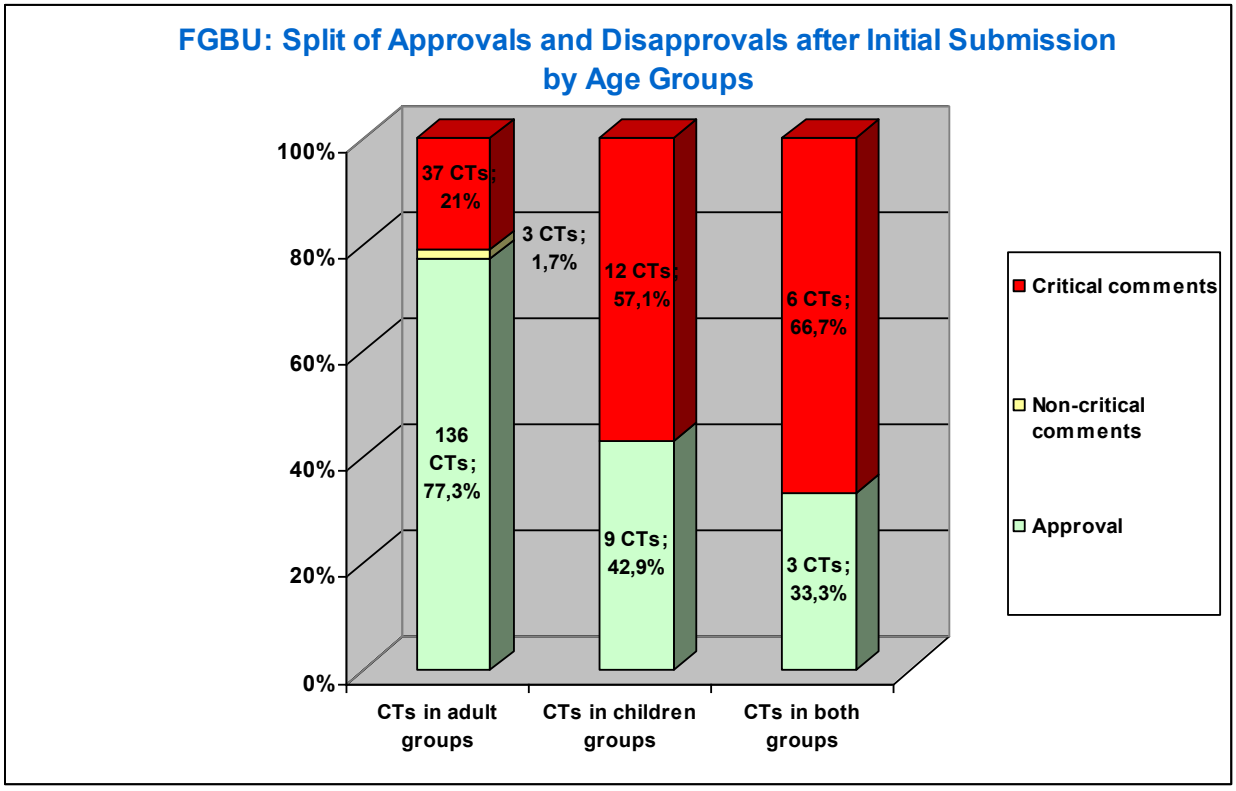


Data from poll of ACTO members

From Diagram 6 we can see that the Ethics Council's attention is clearly concentrated on the protocols using children. And the percentage of those approved at the first attempt compared to last year was significantly down – 38.1% compared to 69.2% for paediatric protocols, and 33.3% compared to 40% for protocols including both age groups. Although we can see that the overwhelming majority of the Ethics Council comments are not critical.

We see a different picture with the FGBU expertise (Diagram 7). The percentage of paediatric trials approved at the first attempt by the expert body also dropped compared to last year. Although not as evident as the Ethics Council's figures – here the numbers were 42.9% compared to 53.8% for trials with only children, and 33.3% compared to 40% for mixed groups. In contrast to the expertise by the Ethics Council, FGBU comments were always of a critical nature.

Diagram 7



Data from poll of ACTO members

The main problem with FGBU comments on paediatric protocols is as follows. There is usually a standard formula: "the results of previously-conducted clinical trials confirm the safety and efficacy of the medicine for adult patients and viability of further clinical study for children over the age of 12 and do not support the inclusion of children from the age of three in the trial" (*the ages indicated can vary, and are only provided as an example)*. Applicants have even noticed a tendency that in protocols with both adult and child participation, the FGBU has proposed eliminating the child participation. On trials with an exclusively child population, the experts are trying to 'clip off' the youngest of several proposed age groups. We are not talking about a complete denial of approval for the trial, but about attempts to prevent an inclusion of the youngest age groups.

Meanwhile, the current legislation contains requirements to conduct the trials with children only after the adult population trials. There is nothing in the law about further dividing the child population into separate age groups. Question comes - into what sort of groups? Who will determine them, and how? For we could take it to an absurd conclusion and demand that each trial with participation of a child of a given age must be preceded by a trial with participation of a child one year older, and so on.

Such a distinct trend suggests that at the heart of such comments from the FGBU lies not an expression of an expert thought, but rather more likely, a simple wish to avoid taking responsibility. It seems that refusal to include children in trials stems only from the expression of 'what if'. The consequences of such an approach are obvious – despite all the efforts by paediatricians to break through the administrative barriers, Russia still has an artificially complicated market for the medicines to help children. Without conducting clinical trials with the Russian patients it is not possible to register a medicine, or expand its use to another age group. And the most vulnerable in this situation, are the very youngest.

This has all led to the fact that several companies, trying to avoid drawn-out case reviews, have begun to exclude the paediatric group from the 'mixed' protocols. The only good thing is that this is not yet a common practice. As statistics show, over the past year the share of applications with the children participation has not decreased, and amounted to 11.9% for paediatric trials and 5.1% for mixed trials (10.6% and 4.1% in the first half of 2013).

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The next stage of the analysis highlights the breakdown of approved and disapproved trials by therapeutic area. Taking into account the obvious influence of the age aspect on the chance of passing review, we excluded paediatric protocols from this selection.

In table 2 and in Diagram 8 we present a breakdown of approved and disapproved at the first attempt protocols, by the results of their Ethics Council review. We see that psychiatry is in the worst position – just 33.3% of applications have been approved at the first attempt. Of course, this is hardly unexpected. We saw the same low proportion of approvals last year. What's more, the main issue in this area that we have already connected with the position of a leading member of the Council, has been addressed at length many times (*ACTO Newsletter No. 2, 5, and 7)*. We have warned that if the situation does not change, international trials of anti-psychotic medicines in Russia would soon be gone. This picture only confirms our fears. It seems that in the period under review (we recall that this includes data for a year), there were just six applications in psychiatry in the selection. In the first half of 2013 there were 18 applications. Of course this is still just a circumstantial indicator, more precise data will come at the end of the year after we analyze the statistics on approvals issued. Nevertheless, a six-fold decrease in the number of psychiatric protocols shows that the situation in this area is close to catastrophic. With this sort of volume, there will soon be no new anti-psychotics for the Russian market at all.

The second area with cause for concern is oncology. Last year the share of protocols approved at the first attempt by the Ethics Council was 63%. This year this was down to 53%, set against the average across all the therapeutic areas of 67%.

Also low, at just 50% approval rate, is the area of infectious diseases. But here the situation is not quite as urgent – since all the comments on these protocols were not critical.

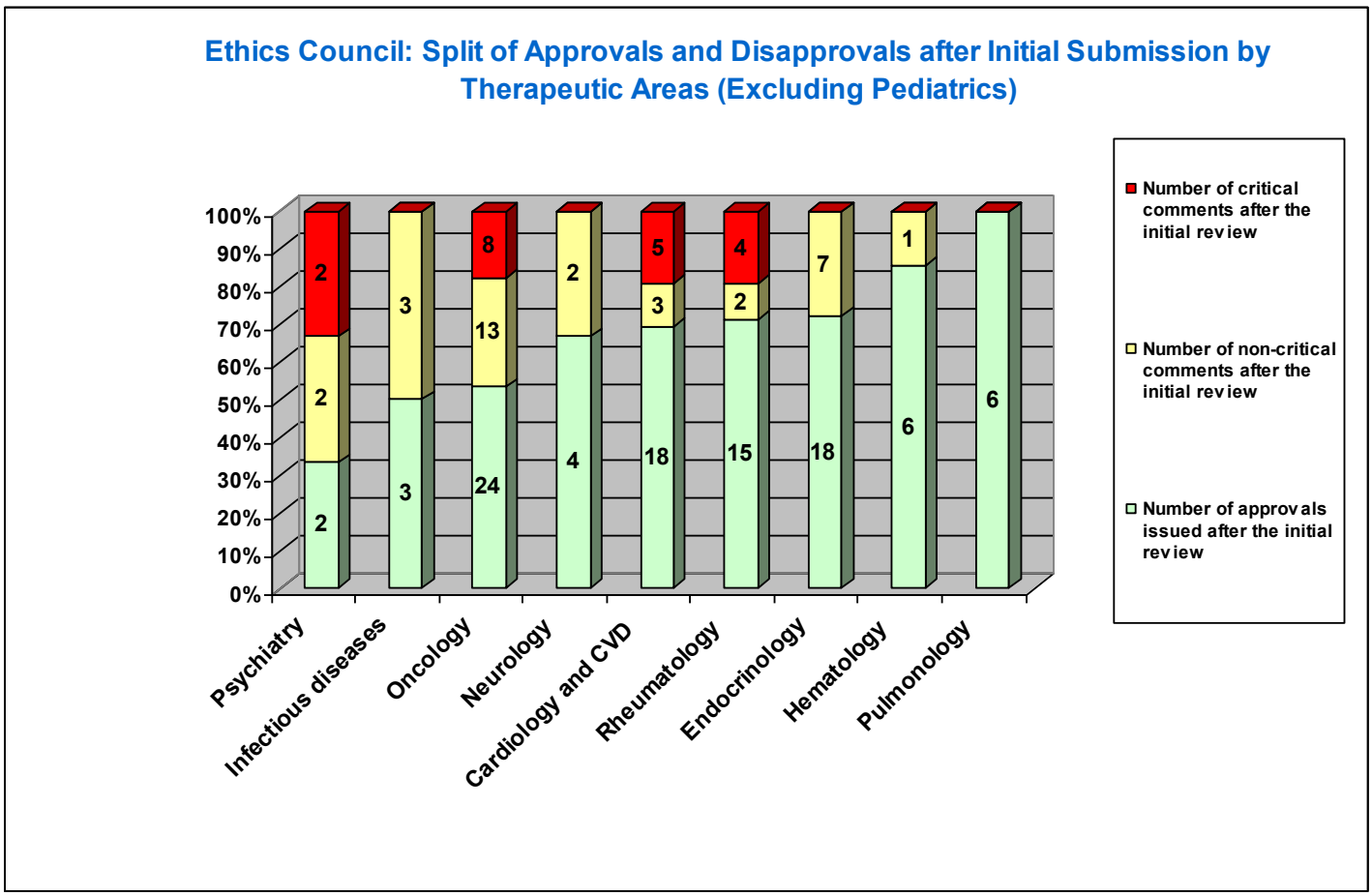
We can only add that the paediatric protocols which, as you will recall, we did not include in the overall account, break down by the therapeutic area in the following way (data are only for those trials that received critical comments from the Ethics Council): two trials in neurology (only children), two in infectious diseases (only children), two in ophthalmology (mixed population).

Table 2

Ethics Council: Split of Approvals and Disapprovals by Therapeutic Areas (Excluding Pediatrics)							
Therapeutic Areas	Total Number of Initial Submissions	Number of Approvals Issued after the Initial Review	Approvals Issued after the Initial Review, % of Total	Number of Non-critical Remarks after the Initial Review	Non-critical Remarks after the Initial Review, % of Total	Number of Critical Remarks after the Initial Review	Critical Remarks after the Initial Review, % of Total
Oncology	45	24	53,3%	13	28,9%	8	17,8%
Cardiology and Cardiovascular diseases	26	18	69,2%	3	11,5%	5	19,2%
Endocrinology	25	18	72,0%	7	28,0%	0	0%
Rheumatology	21	15	71,4%	2	9,5%	4	19%
Hematology	7	6	85,7%	1	14,3%	0	0,0%
Psychiatry	6	2	33,3%	2	33,3%	2	33,3%
Infectious diseases	6	3	50,0%	3	50,0%	0	0,0%
Neurology	6	4	66,7%	2	33,3%	0	0,0%
Pulmonology	6	6	100,0%	0	0,0%	0	0%
Gastroenterology	5	3	60,0%	1	20,0%	1	20,0%
Ophthalmology	5	4	80,0%	1	20,0%	0	0,0%
Dermatology and Immunology	5	4	80,0%	1	20,0%	0	0%
Others	5	5	100,0%	0	0,0%	0	0%
Urology and Nephrology	4	3	75,0%	1	25,0%	0	0%
Obstetrics and Gynaecology	4	3	75,0%	1	25,0%	0	0%
Total	176	118	67,0%	38	21,6%	20	11,4%

Data from poll of ACTO members

Diagram 8



Data from poll of ACTO members

Table 3 and in Diagram 9 demonstrate the data on the breakdown of approvals and disapprovals by therapeutic area according to the results of FGBU expertise. There are a few peculiarities. The lowest percentage of protocols approved at the first attempt is in neurology (33.3%). We note that last year the same analysis also showed neurology in the worst place at 35.3%.

The second therapeutic area where the share of protocols approved at first attempt is also quite low (50%) –infectious diseases. True, here the situation is more optimistic, since the drop is primarily attributed to non-critical comments.

In the area of cardiology and cardio-vascular diseases, which was a real cause for concern last year (when the percentage of trials approved at first attempt was 46.7%) the picture is much better, with 88.5%.

Finally, the data on paediatric protocols not included in the overall account. As with the Ethics Council, we used only the data on trials that received critical comments.

In trials with both age groups, the experts at the first attempt refused two protocols in ophthalmology, and one in each area of oncology, cardiology, hematology, and smoking cessation treatment.

Regarding trials with proposed participation of children only, critical comments broke down into the following groups: one protocol each in oncology, cardiology and CVD, dermatology and immunology, as well as hematology. Critical comments received also two trials in infectious diseases. The most disturbing picture is seen in neurology. All six paediatric trials failed to pass the FGBU review at their first attempt. It's hard to say if this has been a coincidence or not, although taking into account the fact that trials which also had adults,

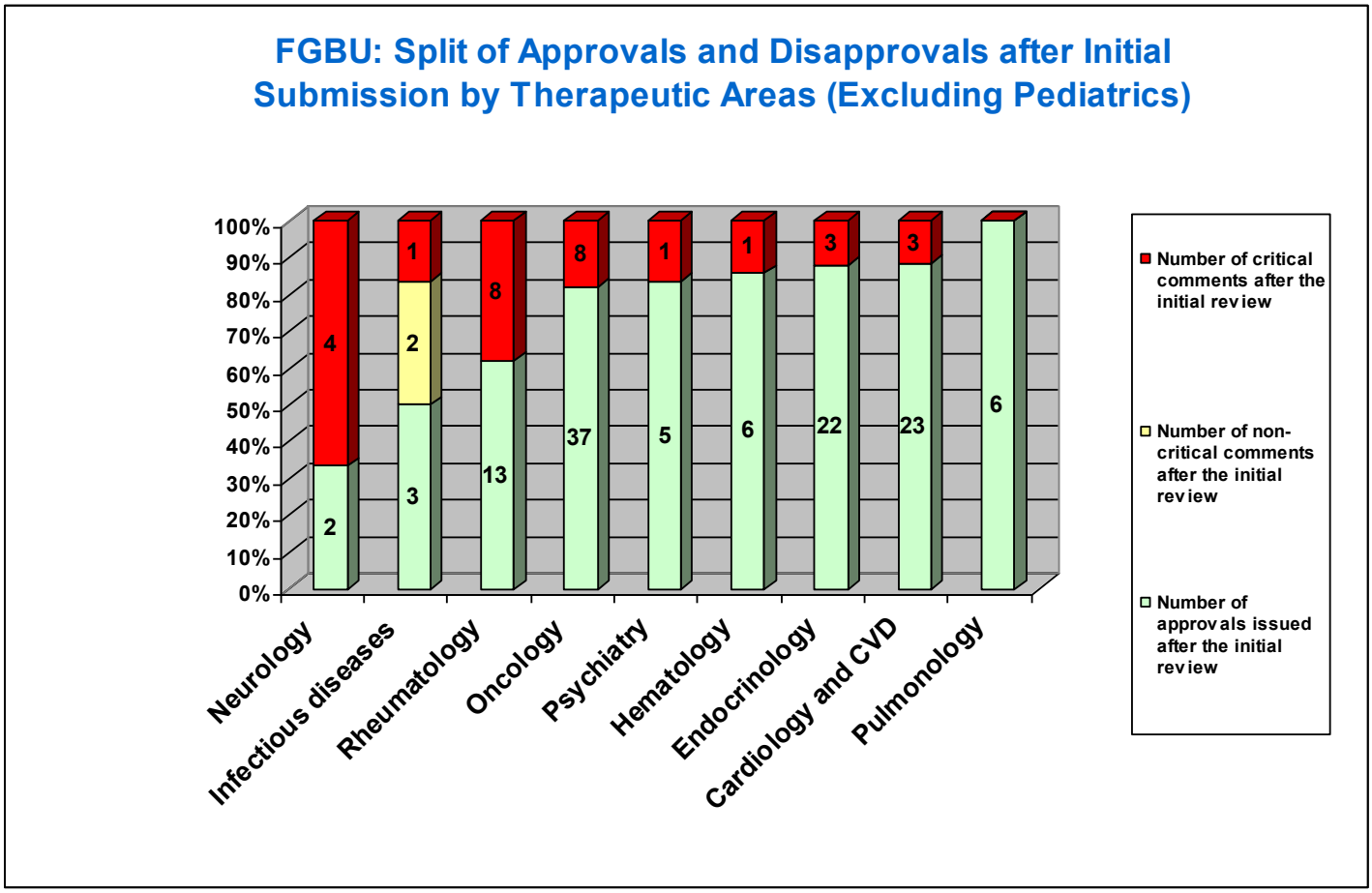
neurology was in the worst position (four out of six trials, or 66.7%, received critical comments from FGBU), the situation in this area is a serious cause for concern.

Table 3

FGBU: Split of Approvals and Disapprovals by Therapeutic Areas (Excluding Pediatrics)							
Therapeutic Areas	Total Number of Initial Submissions	Number of Approvals Issued after the Initial Review	Approvals Issued after the Initial Review, % of Total	Number of Non-critical Remarks after the Initial Review	Non-critical Remarks after the Initial Review, % of Total	Number of Critical Remarks after the Initial Review	Critical Remarks after the Initial Review, % of Total
Oncology	45	37	82,2%	0	0,0%	8	17,8%
Cardiology and Cardiovascular diseases	26	23	88,5%	0	0,0%	3	11,5%
Endocrinology	25	22	88,0%	0	0,0%	3	12,0%
Rheumatology	21	13	61,9%	0	0,0%	8	38,1%
Hematology	7	6	85,7%	0	0,0%	1	14,3%
Neurology	6	2	33,3%	0	0,0%	4	66,7%
Infectious diseases	6	3	50,0%	2	33,3%	1	16,7%
Psychiatry	6	5	83,3%	0	0,0%	1	16,7%
Pulmonology	6	6	100,0%	0	0,0%	0	0,0%
Ophthalmology	5	3	60,0%	0	0,0%	2	40,0%
Dermatology and Immunology	5	4	80,0%	0	0,0%	1	20,0%
Gastroenterology	5	3	60,0%	0	0,0%	2	40,0%
Other	5	3	60,0%	1	20,0%	1	20,0%
Obstetrics and Gynaecology	4	3	75,0%	0	0,0%	1	25,0%
Urology and Nephrology	4	3	75,0%	0	0,0%	1	25,0%
Total	176	136	77,3%	3	1,7%	37	21,0%

Data from poll of ACTO members

Diagram 9



Data from poll of ACTO members

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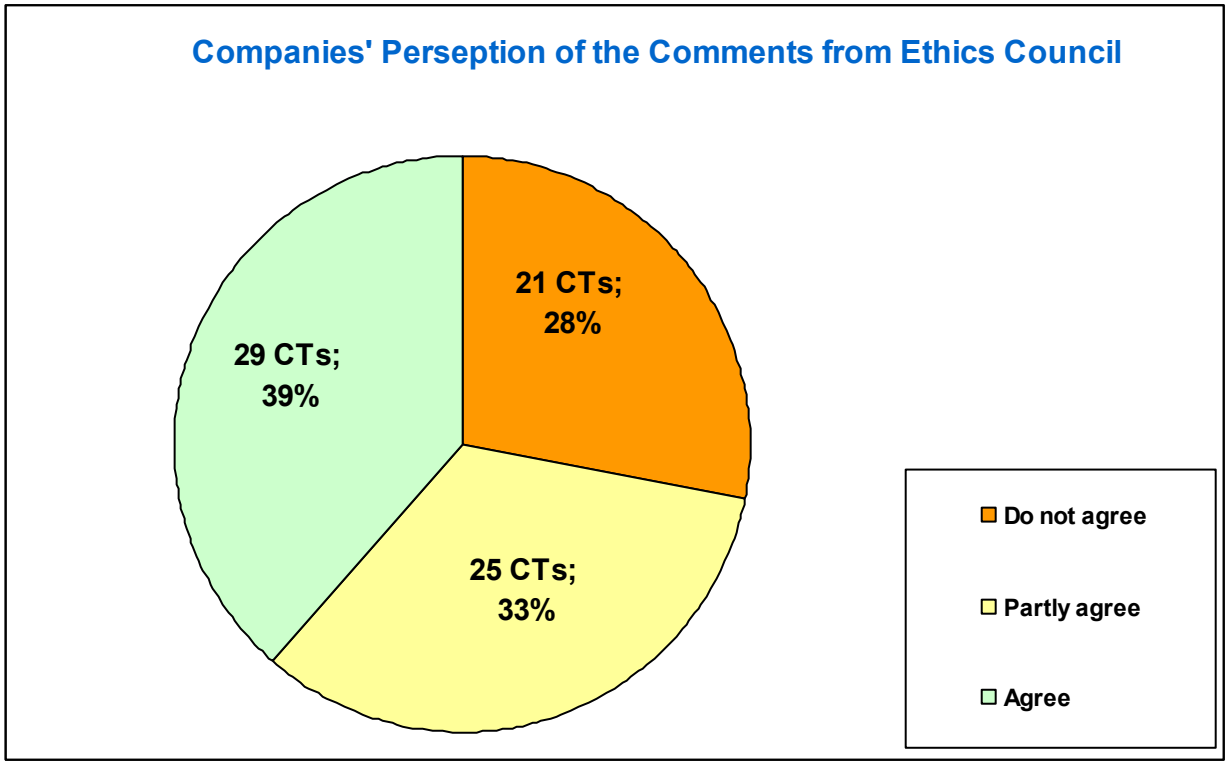
Another parameter that we decided to look at under this analysis was how justified the companies considered the comments they received from the expert bodies to be. We used three evaluation criteria: 'agree', 'partly agree', and 'do not agree'. If the same protocol received several comments, some of which the company agreed were justified and some of which they felt were unjustified, the case was included under 'partly agree'. However if the company absolutely disagreed with the main comment, and the others were rather insignificant and not of fundamental importance, then the case was included under 'do not agree'.

The results are presented in Diagram 10 (Ethics Council) and 11 (FGBU).

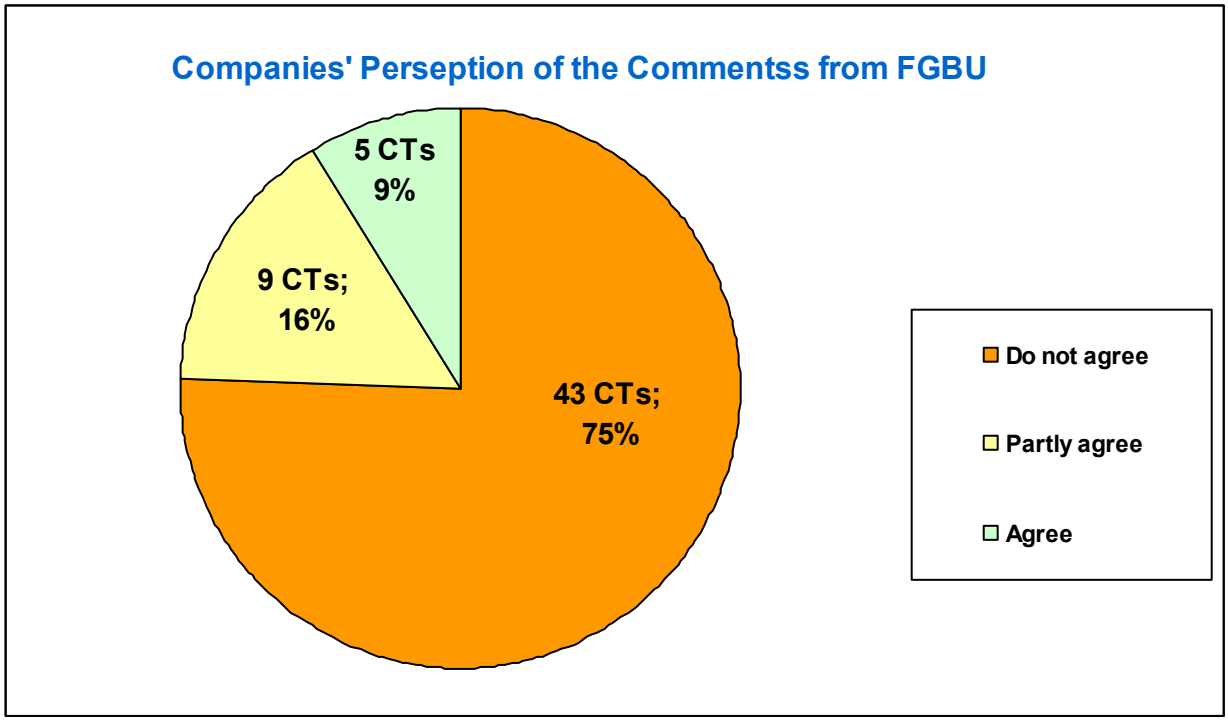
From this data we can see that in general the review by the Ethics Council is seen by the companies as much more fair than that conducted by the FGBU. So, the applicants fully agreed with 39% of Ethics Council comments, while just 9% fully agreed with FGBU comments. Companies partially agreed with Ethics Council comments in 33% of cases, but with FGBU comments in just 16% of cases. And companies did not agree with the Ethics Council comments in 28% of cases, but with regard to the review by FGBU, a huge proportion, in 75% of the cases, has been deemed unjust by the companies. Of course, everyone can interpret these results differently, you may look for our bias, or for lack of objectivity in the poll participants. But the fact that three quarters of applications to the FGBU ended up with comments unacceptable to the applicants (we remember that in our poll, in 99.9% of cases they include only international trials which are already running successfully in many countries), clearly demonstrates that the situation with expert review in this institution is quite negative.

Diagram 10



Data from poll of ACTO members

Diagram 11



Data from poll of ACTO members

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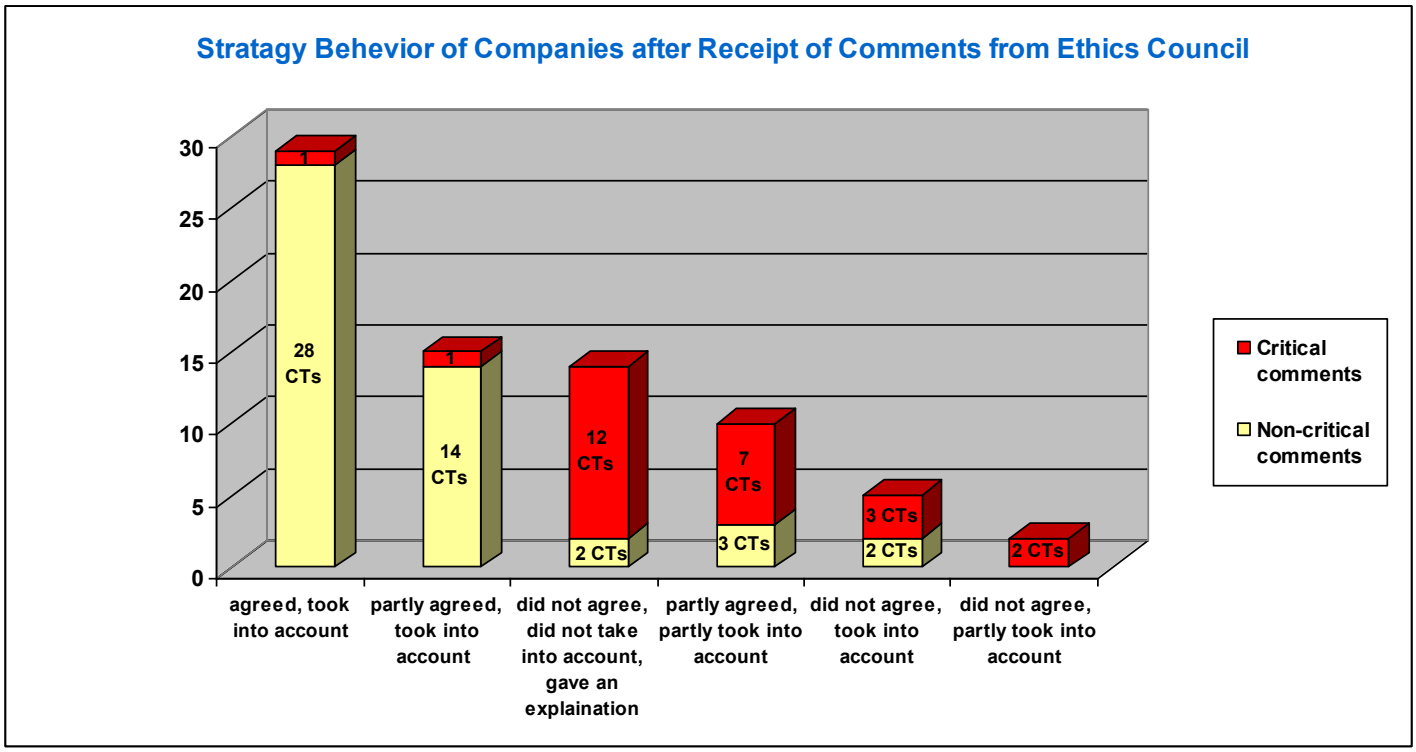
The way a company feels about the comments received is, at the end of the day, its own business. It is much more interesting from a practical point of view to look at what strategy they choose to address problems arising in reapplying to the expert review. The following are the strategies elected by the participants with regard to addressing the fairness of the comments:

- agreed with the comments and fully took them into account;
- partly agreed with the comments, but fully took them into account;
- did not agree with the comments, did not take them into account, but tried to explain their position;
- partly agreed with the comments, partly took them into account;
- did not agree with the comments, but were forced to take them into account;
- did not agree with the comments, but partly took them into account.

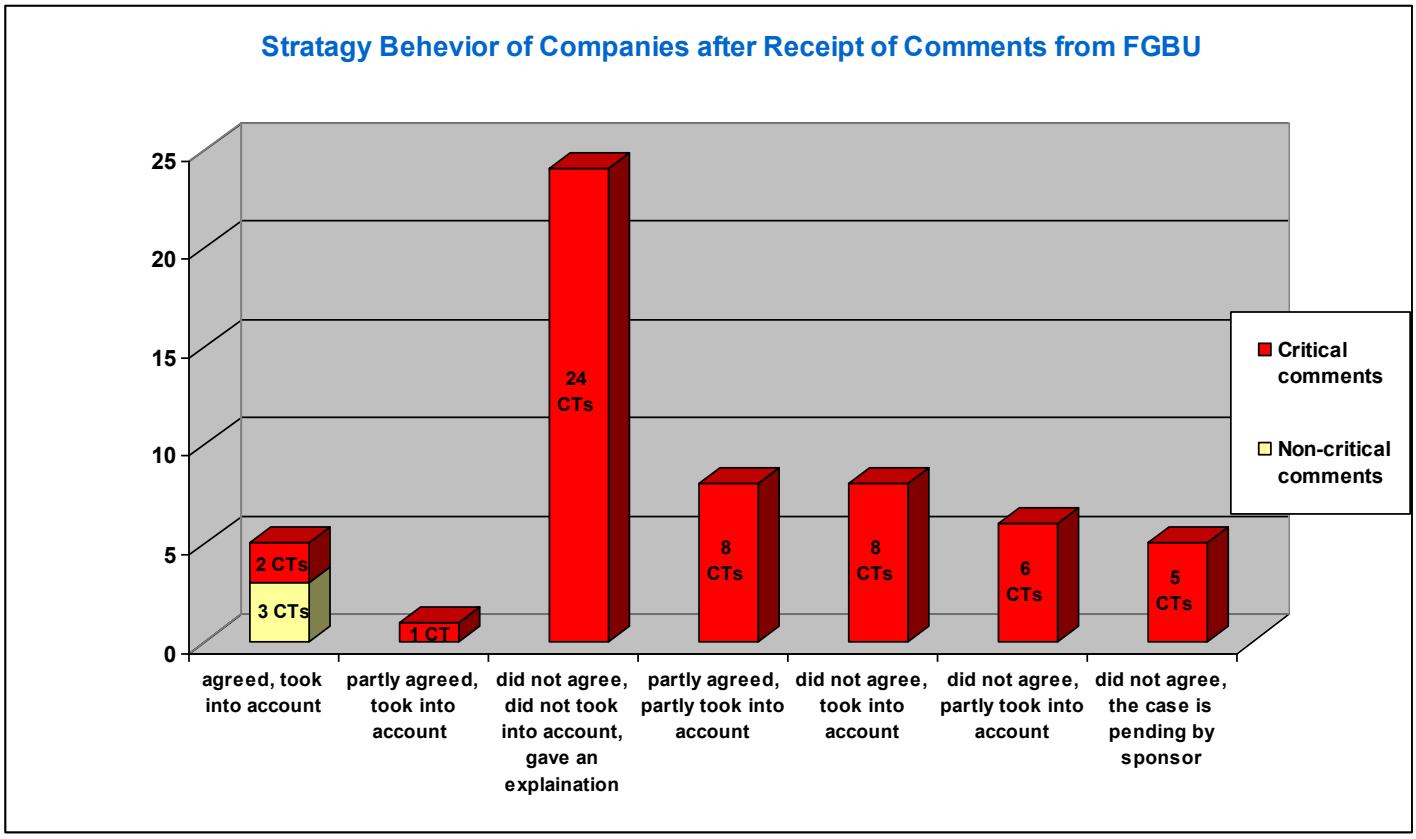
We show how these strategies worked in practice, in Diagrams 12 (Ethics Council) and 13 (FGBU) respectively.

Diagram 12



Data from poll of ACTO members

Diagram 13



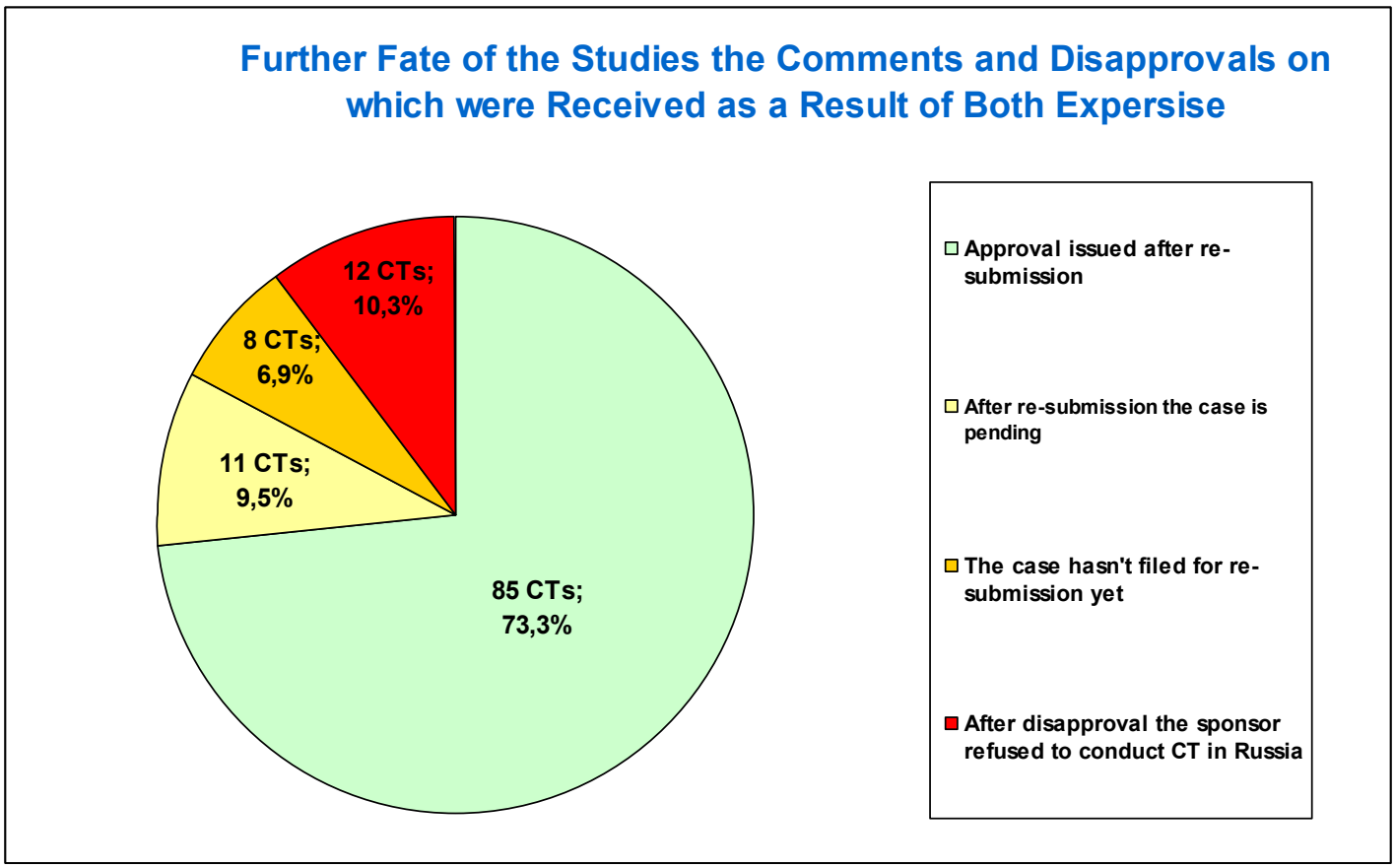
Data from poll of ACTO members

It's immediately obvious that the most frequent approach in relation to the Ethics Council has been to agree with the comments and, consequently, implement them (nearly 40% of cases). By the way, the majority of such comments were of a non-critical nature. A completely different picture can be seen in relation to the FGBU. Here the most common strategy (in 42% of cases) was 'did not agree, did not take into account, gave an explanation'. We need to clarify that companies choose this strategy not based on their own whims, but by virtue of practical impossibility to implement comments. It's understandable that when an applicant on an international protocol suddenly gets an open-ended comment such as 'the data from pre-clinical and clinical trials do not allow the evaluation of the efficacy and safety of the medicine', the opportunities to do something are objectively limited. If there are several countries participating in the trial, and everyone else is satisfied but FGBU in Russia is not, then no one is going to give up on the whole trial plan and try to find some additional evidence, just for the sake of one country. The sponsor is left either to try to show that the data they have is sufficient to address the issue of continuing with a trial, and if that is not enough, they will just refuse to run the trial in Russia. Admittedly, not all such attempts to get through to the experts have failed. In a number of cases, as we will see below, the companies did manage to succeed in making their point.

One more thing to say about the strategy of 'did not agree but took into account', selected by applicants only with regards to the FGBU (14% of cases). The majority of these cases referred to paediatric protocols, when the experts wanted to carve out the youngest age group. Often the companies had to go to a local issue (limited to our country) of amendments to the protocol, according to which the trial was limited to the older age group.

And the last indicator that we evaluated within the framework of the poll was the long-term fate of the cases that received comments in the course of the first review. The generalized data on the results of both reviews is presented in Diagram 14.

Diagram 14



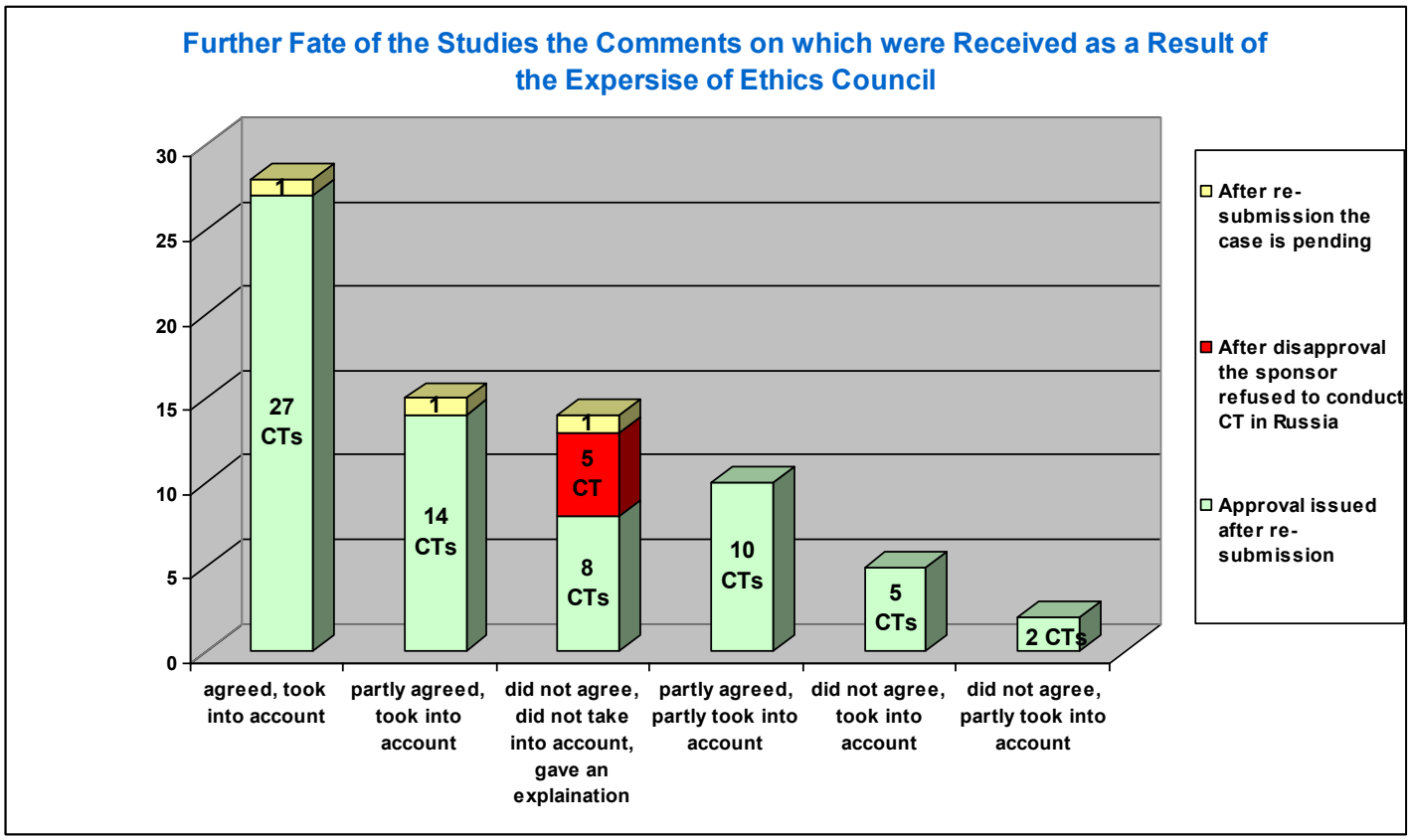
Data from poll of ACTO members

It is clear that the majority of trials (73.3%) were approved after a repeated (sometimes more than one) application for review. Unfortunately, in 12 cases (10.3%), the sponsors eventually declined to conduct the trials in Russia. We cannot directly confirm that the cause of such a decision was the review process. In some cases the sponsor realized that there was no more time to wait, in others they had already finished patient enrolment by the time the approval came through, and in still others, the decision was dictated by the utterly absurd (in the opinion of the company) demands by the experts, as a result of which the company considered it pointless to continue a dialogue. Unfortunately, the outcome is the way it is.

Out of these trials lost for Russia, there was one each in dermatology/immunology, cardiology, and psychiatry, and another in vaccine research. There were two trials each for medicines in neurology and endocrinology. Also, there were four trials on cancer treatments. We can also add that nearly all the trials indicated were planned on adult patients, with the exception of two paediatric medicines in the area of neurology.

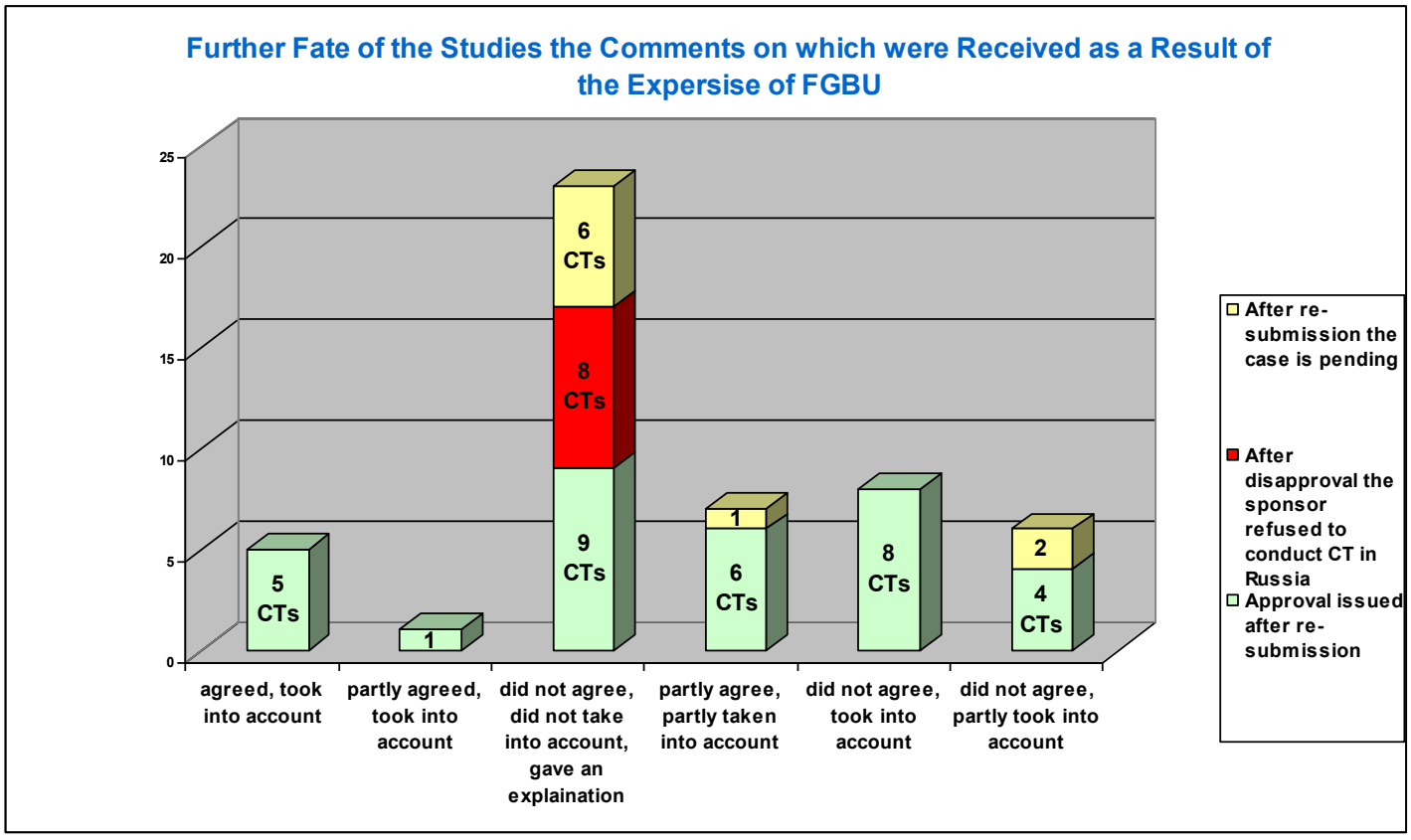
In Diagrams 15 and 16 we also present the data on the further fate of those trials which in the beginning received comments, but for a different type of expertise. We connected the following outcome of the case to the strategy that the company chose in responding to the commentary.

Diagram 15



Data from poll of ACTO members

Diagram 16



Data from poll of ACTO members

The most interesting thing was the outcome of the more risky, but often necessary strategy – 'did not agree, did not take into account, tried to explain our position'. If one does not take into account those cases where the result is not yet known, then for the FGBU this strategy was successful 9 out of 17 times (53%), which, we think, is not too bad. With the Ethics Council, this was even better – it worked in 8 out of 13 cases (61.5%), which were approved after the company tried to convince the expert panel of their position.

In addition, in four out of eight cases mentioned, the successful result was related to the unexpected position of the Ethics Council with regards to trials on monoclonal antibodies. The situation has developed in Spring 2014 and is as follows. Several companies received the proposal to increase the patient observation time after giving the dose of investigation medicinal product, up to 24 hours in an in-patient facility. The trials were approved, and the companies were advised to make the proposed changes 'in working order'. Simultaneously, a rumour spread around the market that henceforth all trials on monoclonal antibodies would have such conditions as obligations. The applicants quelled the panic. There were no objective pre-conditions for increasing patient observation time only because the medicines are classified as monoclonal antibodies. The companies which cases were first made known to us had already conducted trials with these medicines (in Russia, and with the approval of the Ethics Council), and now the point was about large, phase III trials. The data available at the time did not say anything about an increased risk of developing an allergic reaction to the medicines being studied. More significant was that the demand for 24 hour observation in an in-patient facility seriously affected plans and threatened successful completion of trials. These changes were impossible to implement in a working order, they needed to be developed as protocol amendments. But the most serious problem was that the illnesses which were being treated with the investigational medicines in and of themselves do not merit in-patient treatment, but rather in real clinical practice are treated on an out-patient basis. And so consequentially, the overwhelming majority of the medical organizations that had planned to participate were out-patient facilities. And the proposal to make changes in working order would have seriously changed the trial plans, as it would have placed potential patient enrolment under direct threat. The companies appealed to the Ethics Council, explaining their positions. And they were heard – the trials were approved in their initially proposed format. This way, the Ethics Council has set a very good example of their readiness to listen to the arguments put forth by the industry. Which, unfortunately, is not such a common occurrence now.

QUALITY OF CLINICAL TRIALS: RESULTS OF INSPECTIONS BY REGULATORY BODIES

Results of FDA Inspections

In 2012 ACTO had already raised the subject of quality of clinical trials and had analyzed the data of the results of FDA inspections of Russian centers participating in international clinical trials (*ACTO Newsletter No. 6).*

A year and a half has passed and we decided to look at whether the situation has changed. According to the official FDA website, since our previous survey period in Russia there were 7 FDA inspections, 4 without any findings and 3 with non-critical findings. In total, beginning in 1995 when the FDA carried out its first inspection in Russia, up to July 2014, there have been a total of 99 inspections of Russian trial centers.

The results of 65 inspections was **NAI** (No Action Indicated. No objectionable conditions or practices were found during the inspection.)

The results of 33 inspections was **VAI** (Voluntary Action Indication. Objectionable conditions were found but the problems do not justify further regulatory action. Any corrective action is left to the investigator to take voluntary.)

One inspection resulted in **OAI** (Official Action Indicated. Objectionable conditions were found and regulatory and/or administrative sanctions by FDA are indicated.). This result has occurred in February 2006 in a trial being conducted by the Principal Investigator Professor O.D. Ostroumova.

As in the previous time, for comparison of the quality of trials conducted in Russia we present a table of the results of FDA inspections in a number of countries in the same period, from 1995 to the first half of 2014, inclusive (Table 4). We must note that FDA activity varies from country to country, therefore in comparing the results we also need to take into account the total number of inspections conducted in any given country. The greater the number, then of course the more accurate the overall evaluation of the quality of international trials being conducted in the country.

Table 4

Comparative Table of the Results of US FDA Inspections, 1995 - 1st Half of 2014							
Country	**Total number of FDA Inspections with results 1995 - 1st half of 2014**	**NAI**	**NAI, % of Total**	**VAI**	**VAI, % of Total**	**OAI**	**OAI, % of Total**
North America							
USA	**6476**	**2863**	**44,2%**	**3353**	**51,8%**	**260**	**4,0%**
Canada	**149**	**63**	**42,3%**	**85**	**57,0%**	**1**	**0,7%**
Mexico	**23**	**6**	**26,1%**	**17**	**73,9%**	**0**	**0,0%**
South America							
Argentina	**49**	**30**	**61,2%**	**18**	**36,7%**	**1**	**2,0%**

Brazil	**41**	**20**	**48,8%**	**21**	**51,2%**	**0**	**0,0%**
Peru	**9**	**4**	**44,4%**	**3**	**33,3%**	**2**	**22,2%**
Chile	**10**	**6**	**60,0%**	**4**	**40,0%**	**0**	**0,0%**
Australia	**16**	**9**	**56,3%**	**7**	**43,8%**	**0**	**0,0%**
Africa							
South Africa	**48**	**23**	**47,9%**	**24**	**50,0%**	**1**	**2,1%**
Asia							
Japan	**7**	**5**	**71,4%**	**2**	**28,6%**	**0**	**0,0%**
Thailand	**12**	**5**	**41,7%**	**7**	**58,3%**	**0**	**0,0%**
China	**23**	**8**	**34,8%**	**14**	**60,9%**	**1**	**4,3%**
India	**49**	**30**	**61,2%**	**19**	**38,8%**	**0**	**0,0%**
Turkey	**7**	**1**	**14,3%**	**5**	**71,4%**	**1**	**14,3%**
Israel	**6**	**5**	**83,3%**	**1**	**16,7%**	**0**	**0,0%**
South Korea	**15**	**8**	**53,3%**	**7**	**46,7%**	**0**	**0,0%**
Taiwan	**8**	**6**	**75,0%**	**2**	**25,0%**	**0**	**0,0%**
Europe							
Austria	**14**	**3**	**21,4%**	**11**	**78,6%**	**0**	**0,0%**
Denmark	**17**	**9**	**52,9%**	**8**	**47,1%**	**0**	**0,0%**
Sweden	**22**	**9**	**40,9%**	**13**	**59,1%**	**0**	**0,0%**
Germany	**97**	**41**	**42,3%**	**55**	**56,7%**	**1**	**1,0%**
France	**73**	**22**	**30,1%**	**50**	**68,5%**	**1**	**1,4%**
United Kingdom	**95**	**30**	**31,6%**	**63**	**66,3%**	**2**	**2,1%**
Spain	**33**	**19**	**57,6%**	**12**	**36,4%**	**2**	**6,1%**
Italy	**53**	**30**	**56,6%**	**20**	**37,7%**	**3**	**5,7%**
Finland	**15**	**10**	**66,7%**	**4**	**26,7%**	**1**	**6,7%**
Netherlands	**26**	**8**	**30,8%**	**16**	**61,5%**	**2**	**7,7%**
Belgium	**30**	**15**	**50,0%**	**12**	**40,0%**	**3**	**10,0%**
Polang	**88**	**53**	**60,2%**	**35**	**39,8%**	**0**	**0,0%**
Hungry	**25**	**10**	**40,0%**	**15**	**60,0%**	**0**	**0,0%**
Czech Republic	**28**	**15**	**53,6%**	**13**	**46,4%**	**0**	**0,0%**
Ukrain	**26**	**16**	**61,5%**	**10**	**38,5%**	**0**	**0,0%**
Russia	**99**	**65**	**65,7%**	**33**	**33,3%**	**1**	**1,0%**

Data from www.fda.gov

In addition to the FDA, international clinical trials being conducted in Russia are also subject to control by the regulatory body of the EU - the EMA. Unfortunately, in contrast to the American agency, this body does not maintain an open register of inspections, so it has not yet been possible to obtain and analyze those results. However, taking into account the fact that the EU is presently implementing a policy of more openness on the data of clinical trials to the public, in the foreseeable future this question will be resolved in the form of an accessible inspections register.

Results of Roszdravnadzor Inspections

In evaluating the activity of the regulatory bodies in other countries it would have been unjust to keep silent on the activity of the Federal Service on Surveillance in Healthcare of the Russian Federation (Roszdravnadzor). In our country this is the body with the responsibility of an oversight over the conduct of clinical trials. While Roszdravnadzor may not have as much experience as the FDA, and their methodology for conducting inspections might have a few little peculiarities, we have found it interesting to analyze this experience and to present the results to the judgment of our readers.

We were able to do this based on the information that Roszdravnadzor posts quarterly on its website, containing precise information about the results of inspections of organizations conducting pre-clinical and clinical trials of medicines. Unfortunately, the format in which the information is presented is not convenient for analysis, because the inspection tables are published as PDFs, and it means the data have to be entered manually. For a more or less objective picture we have analyzed the results of inspections for a year and a half – for all of the 2013 and the first half of 2014.

First of all, we begin with the method of analysis and also with the peculiarities of Roszdravnadzor inspections. First, the results published by Roszdravnadzor contain data on control over two different areas at once – pre-clinical and clinical trials. Obviously, for our purposes we excluded the first. Second, the subjects of the inspections are primarily clinical sites. We will say right away that there are significant differences from FDA inspections. For the latter, the subjects of inspections are not the clinical sites themselves, but the principal investigators. They are the ones, according to the GCP, who carry the responsibility for conducting the trial at the site. It is the actions of the principal investigator that are evaluated in the course of the inspection. In the event of uncovering any breaches or inconsistencies, they can be given reprimands or warnings, up to being prohibited form involvement in any future trials. Our bureaucrats cannot understand this approach, as the role of the principal investigator under Russian legislation is undeservedly belittled and it seems that the main responsibility for conducting the trial is held by the organization of the location where it is being carried out. Also, there is no acknowledgement of the fact that responsible, and irresponsible, doctors can be employed in the same establishment. In the event that an investigator, for example, has falsified trial data, formally the breach will be recorded against the organization, while the investigator is free to simply move to another clinic and do the same thing again, until he gets caught again. But must give credit to Roszdravnadzor, as they understand this perfectly. Therefore the documentation on their inspections also contains the surnames of the principal investigators. Although they may not be included in the official lists, the market participants have an opportunity to study the data themselves and get information about the potential reliability of those investigators that they may be planning to invite on to their project. We also need to add that in addition to clinical sites, over the analyzed period of a year and a half, Roszdravnadzor carried out inspections of two sponsors and one contract research organization (CRO).

Third, and here we see the difference between Roszdravnadzor and the FDA – is in the object of inspections. For the FDA these are always specific clinical trials. For our regulator these can be any subject's activity in the area of clinical trials as a whole. In other words, within the framework of one inspection, they check the entire organization carrying out the trials, regardless of how many active protocols there currently are. A simple example: the maximum number of trials that was included in a single Roszdravnadzor inspection during the period under review was 27 protocols, which had input from three main principal investigators. This is all considered to be one inspection. This is the way it appears in the official Roszdravnadzor reports.

However, here the authority demonstrates an understanding and the documentation lists separate protocols and shows which findings apply to which protocol. This is important for an objective evaluation. This information is also valuable in that it provides an opportunity to see specific trials and also to classify them by type. We remember that the FDA data gives us a picture only of international trials. Local trials, the results of which are not planned to be presented to the FDA, are not within its remit. At the same time, taking into account the nature of such trials, we had serious doubts about their quality. Simply saying, the results, as the reader will shortly see, have only confirmed our fears.

The next thing we need to reexamine is the type of inspections. Our legislation splits them into planned and unplanned. The latter in turn can be divided into two types – as a measure of control over notices issued as the result of a previous inspection, and also as a response to complaints received by regulatory authority (officially this is called 'in connection with the receipt of information from a citizen about the existence of a threat to life or health'). In addition, all the listed inspections can be of two types – documentary or field visit.

The last aspect that we would like to address before moving on to the results are the requirements on the basis of which the inspections are conducted and, consequently, the classification of any findings. Here we can see objective problems in in the work of Roszdravnadzor. It is clear that the regulator in any country shall act in strict accordance to the law. The legislation in developed countries, regardless of whether it is the American Code of Federal Regulations, the European Directive on Clinical Trials, or the laws of individual countries, is based first and foremost on GCP. As we know very well, compliance with GCP provides public assurance that the rights, safety and well-being of trial subjects are protected and that the clinical trial data is credible. Russian legislation does not ignore GCP, but often concentrates on matters which bear no relationship to patient protection or to the quality of data obtained. Take a look at the requirement for mandatory information from the medical organization to the Ministry of Health about the beginning of a clinical trial within a three-day period from the beginning of the trial at the site. What does this give the patient, if all trials have *a priori* already undergone all necessary procedures for approval and have been approved by the Ministry of Health? Or the requirement about appointing as the principal investigators the head doctor of this clinic? In the order of appointment there cannot be any name other than that which has been selected by the sponsor and also approved by the Ministry of Health in issuing approvals to conduct the trial. But these requirements exist and Roszdravnadzor checks the execution. In Russian legislation there is no classification of findings by severity and the lack of a mentioned clinic’s order of appointment for principal investigator and in case of a patient not signing the informed consent form (ICF), or discrepancies between data in source documents and patient’s individual registration cards from a formal point of view are all deemed breaches of equal severity. In addition, Roszdravnadzor when conducting inspections must 'pile up' all the inadequacies uncovered, whether they affect the work of the local ethics committee, the medical organization as a whole, or a specific principal investigator. In our analysis we tried to take all these nuances into account as much as possible.

Table 5 demonstrates the data on the total number of inspections and also on the subjects whose activity has been inspected.

Table 5

Statistics on inspections by Roszdravnadzor of the activities of conducting clinical trials, 2013 – 1st half of 2014					
	Number of medical organizations inspected	**The number of principal investigators whose work was inspected**	**The number of inspected clinical trials**	**The number of sponsors inspected**	**The number of contract research organizations inspected**
Planned on-site inspections	**92**	**101**	**157**	**1**	**1**
Unplanned on-site inspections to ensure compliance with previously issued orders	**8**	**8**	**8**	**1**	**-**
Unplanned documentary inspections to ensure compliance with previously issued orders	**13**	**13**	**13**	**-**	**-**
Unplanned on-site inspections (complaint-based inspection)	**4***	**4**	**6**	**1**	**-**
Unplanned documentary inspections (complaint-based inspection)	**-**	**-**	**-**	**1**	**-**

Source: www.roszdravnadzor.ru
***data from one further inspection are not reflected in the total, since information about it in the Roszdravnadzor report says: "The inspection was stopped due to the lack of the inspected organization"**

It appears that the most common form of Roszdravnadzor inspection is the planned on-site inspection. So, for the year and a half period under review, there were 92 planned on-site inspections of medical organizations. They checked 157 trials being conducted under the supervision of 103 principal investigators. We will look at the results of these inspections a little bit later. But first a few comments about unplanned inspections.

As for the inspections carried out with the aim of ensuring compliance with a previously issued notice, we can see that they are usually carried out in a documentary form. This sort of inspection consists of having the organization that had previous violations and had an order issued to instructing to address such violations, prove to the authority what steps exactly have been taken to rectify the violations. Although in a number of cases Roszdravnadzor has not stopped at a documentary inspection and has actually conducted a repeat on-site visit. We can say immediately that in all unplanned inspections in the period under review, the result has been positive, in other words no repeated violations have been uncovered.

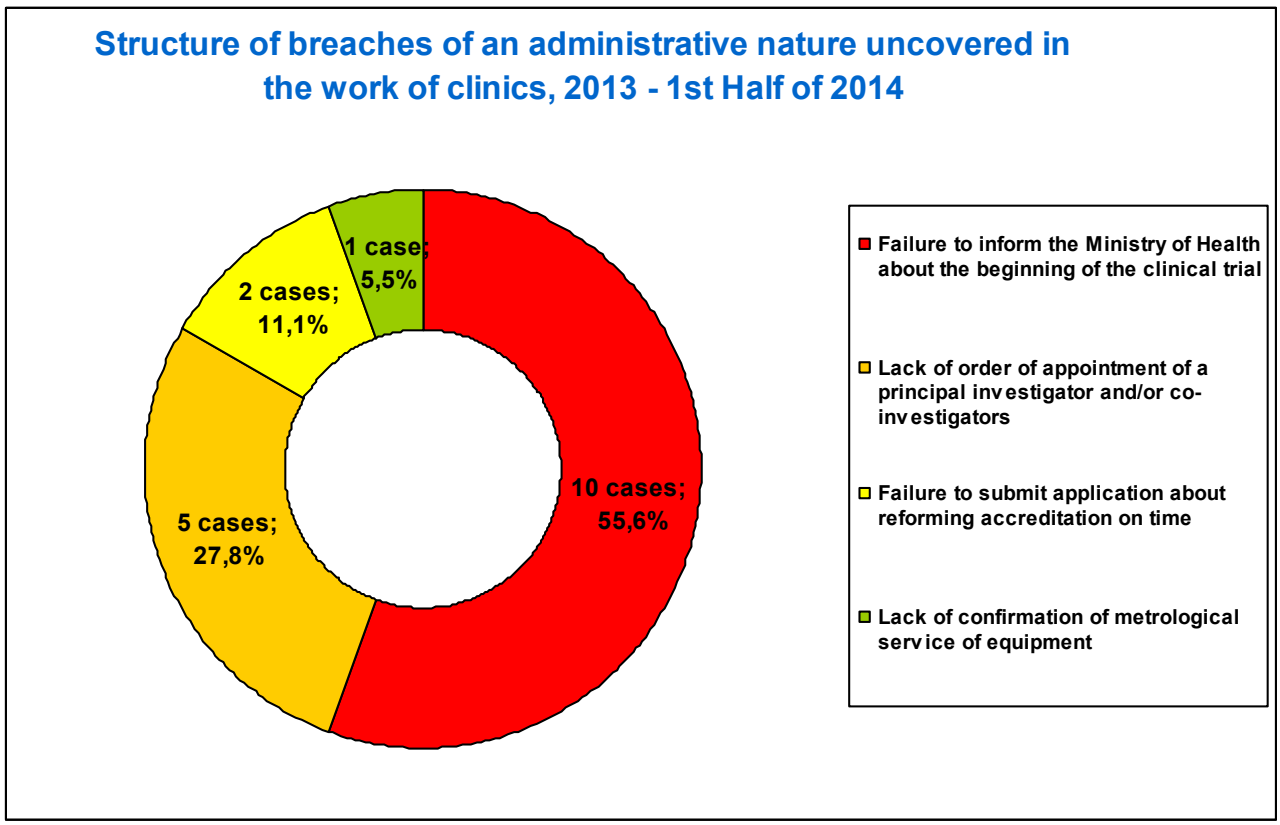
Now, regarding the unplanned inspections based on complaints. Altogether in the period under review there were five inspections of medical organizations initiated by Roszdravnadzor "in relation to the information received from a citizen complaining about a threat to life or health". One of them was stopped due to the absence of the organization under inspection. Four sites were inspected, and in just one of them a breach has been uncovered, although this affected not the activity of the site itself, but of the local ethics committee, since the latter has not been following standard operating procedures (SOPs). We can only guess what the complaints were related to that brought on the unplanned inspections, but as we can see from the Roszdravnadzor reports, they are unlikely to have had any real basis.

A completely different development of events happened with the complaint against a sponsor – the company Pharmasyntez. Although the report lists two unplanned inspections of this company, they were probably both initiated based on the same complaint. One of them was documentary and resulted in nothing, as we see in the notes in the Roszdravnadzor report, the requested documents were not presented within the given timeframe. A month and a half later there was an on-site inspection, the report on which includes a note that the regulatory body has not been presented with the documentation on the investigational medicinal product and they were also not given access to the data acquired in the course of the trial. As a result, a protocol of administrative violation has been rendered by Roszdravnadzor to the judicial system and the prosecutor's office. But this, it seems, was not the end of the saga with Pharmasyntez. Nearly a year later, Roszdravnadzor made another on-site visit to this company, this time a planned one. The results are again concerning. There are some formal problems which we would not be overly concerned by, such as 'failure to communicate a message about the end of the clinical trial to the Ministry of Health within five days'. And there are others which are a serious cause for alarm. Such as, according to the report, the organization lacks both procedures to regulate the work of company employees in organizing the trial and also associated instructions for the investigators. But that is not even the most grave violation. The report states: 'no documentation for the import of the unregistered substance Ritonavir, used in manufacturing the Kalidavir medicine'. If we have correctly understood the bureaucratic language, the regulator could not work out where the medicine that they were inspecting had come from. Of course, the information we have is not sufficient to draw a conclusion. But it certainly raises a lot of questions.

Another unplanned on-site inspection looking at compliance with previously issued orders has been made in relation to another domestic manufacturer – the company Valenta Pharmaceutica. We do not know what violations have been discovered previously at the company. But the outcome of the repeat inspection was positive. Just like the result of the only planned on-site inspection conducted by Roszdravnadzor of a CRO – Cromos.

Let’s return to the planned inspections of clinics, since here the volume allows us to draw a more objective picture of the trends on the market. As we have already said, all findings in such inspections were listed against the medical organizations, regardless of whether they were related to the work of the clinic, the local ethics committee, or the trial investigator team. We decided to break it down. We will start with the breaches that we attributed to the area of the clinics themselves (since this is what the law specifically tells us), and which have more of an administrative nature. In the period under review four such types of breaches were uncovered: failure to send a message to the Ministry of Health about the beginning of a clinical trial, lack of an order from the head doctor on the appointment of a principal investigator and/or co-investigators, application to restructure the accreditation of the medical organization not submitted in time, and lack of confirmation of metrological service of the equipment. Altogether, as we see from table 5, in the course of planned control inspections, 92 medical organizations were inspected. Breaches that we attributed to the named group were uncovered in 14 clinics (15.2% of the total number of those inspected). Since there were several types of breaches recorded simultaneously in several clinics, the total number was 18 cases. The distribution of various types of breaches is presented in Diagram 17.

Diagram 17

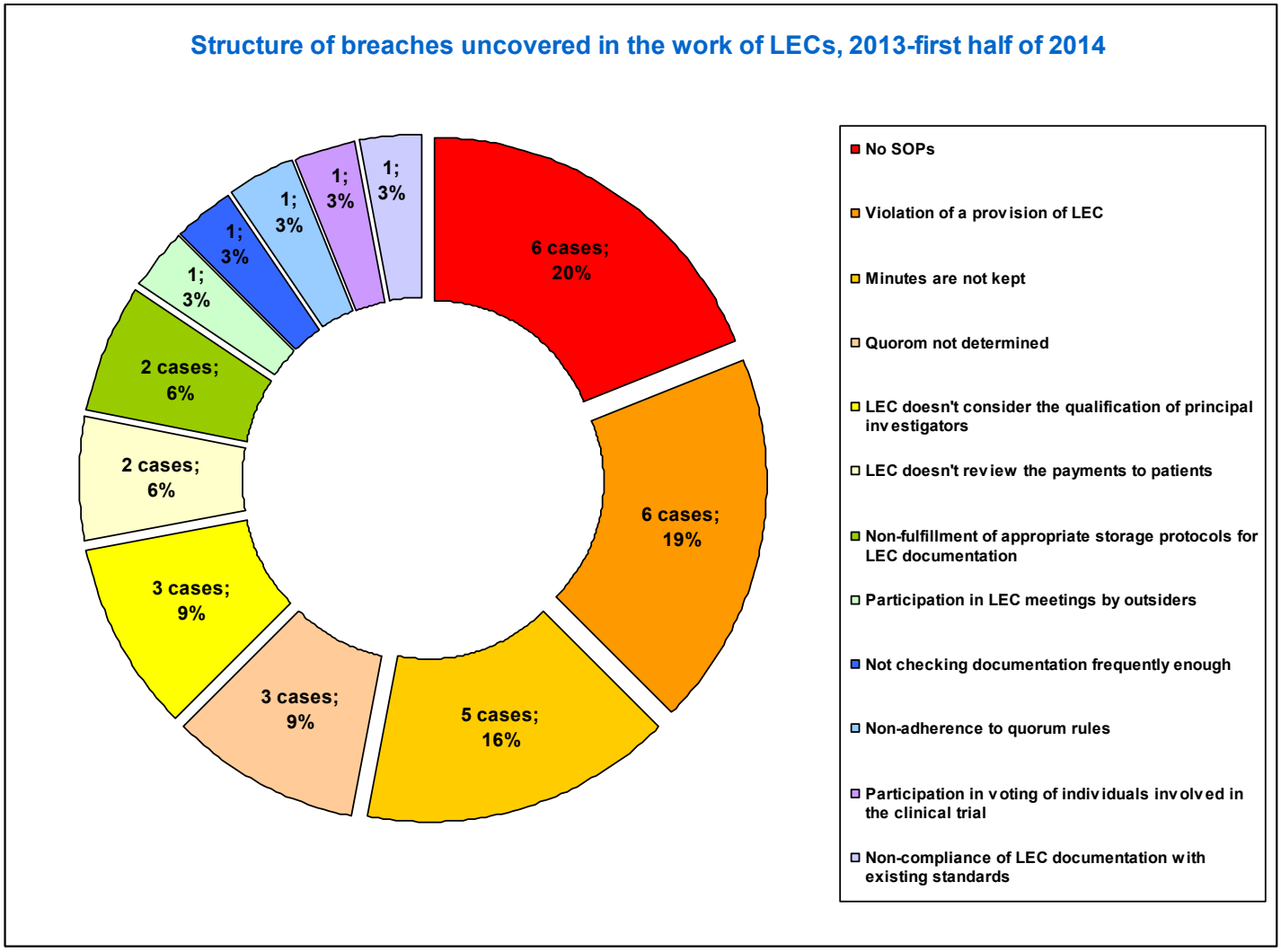


Data from: www.roszdravnadzor.ru

It is clear that the most common breaches found at clinics is the lack of notification to the Ministry of Health about the beginning of the clinical trial (55.6%). The second most common is a lack of order of appointment from the head doctor for the post of principal investigator and/or co-investigators (27.8%). We remind you that in our opinion, these breaches are of a purely formal nature and have no impact on the trial itself or on the health of those participating in it. Out of these, only the lack of confirmation of metrological service of equipment could conceivably have any impact on the results of the trial – in the event that the equipment in use was unacceptably erroneous.

The next subject for analysis was breaches in the work of local ethics committees (LECs). Russian legislation does not require obligatory LECs in each medical organization. According to the law "On the Circulation of Medicines", the planned clinical trial must be reviewed by the Ethics Council under the Ministry of Health. But not all sponsors consider the Council to be an independent body in the sense of meaning contemplated by GCP, some treat it as part of the official approval process and for an ethical review rely on LECs within medical organizations, or so-called 'umbrella' ethics committees, whose decisions are applied simultaneously to several clinical sites. Precisely because of this double system of ethical review, Roszdravnadzor does not treat LECs as an obligatory attribute of any inspected clinic. The presence or absence of an LEC is not reflected in its report on inspections. Therefore we cannot evaluate the total number of ethics committees whose work has been inspected. Accordingly, we cannot calculate how many of them meet all GCP guidelines. Regarding breaches, they were uncovered in a total of 18 LECs. The spectrum of breaches is a much broader here – from breaches in the frequency of reviewing documentation, to a lack of SOPs and minutes of LECs meeting. Altogether we distinguished 12 types of breaches, with a varying degree of frequency in the inspected committees. The results are represented in Diagram 18.

Diagram 18



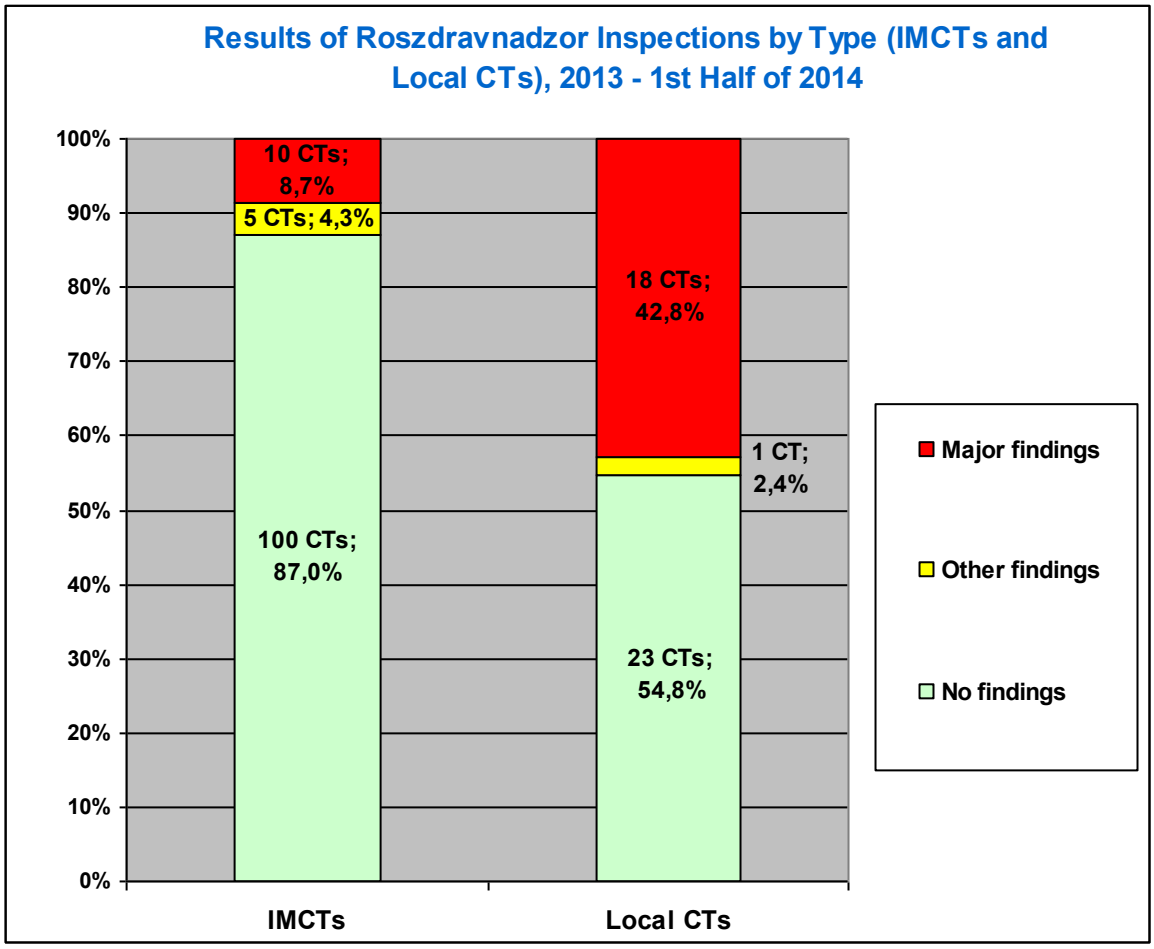
Data from www.roszdravnadzor.ru

Finally, we set about analyzing the biggest set of data – direct inspections of clinical trials. From table 5 we can see that in the year and a half under review, Roszdravnadzor inspected 157 trials as part of planned, on-site inspections. First of all, we looked at what kinds of trials these were. 115 trials were international multicenter clinical trials (IMCTs), 42 were local clinical trials (7 for local safety and efficacy trials by Russian sponsors, 28 for local safety and efficacy trials by foreign sponsors, 2 for bioequivalence studies by foreign sponsors, and 5 for bioequivalence studies by Russian sponsors).

Next we looked at how many trials were found in the inspection to have breaches of rules. The findings themselves we split into two groups – "Major" and "Other" findings. Major ones included those that could potentially impact on the rights and interests of the trial subjects, or could influence the credibility of the trial results. These included various deviations from procedures to obtain informed consent, breaches in the necessary documentation on the trial procedures on accounting for and storing medicines, deviating from the protocol, and so on. Other findings included ones that, accordingly, did not have such influence. For example, questions of the distribution of functional responsibility among employees taking part in the trial, confirming their qualifications, and so on. However, if according to the results of the inspection of the trial both major and other breaches were discovered, then the trial itself was marked as having major findings.

The results are presented in Diagram 19. From this we can see the significant difference in the quality of conducting local trials versus IMCTs. Whereas in international trials, 87% of trials sailed through Roszdravnadzor inspections without any comments, in local trials only 54.8% made it through without commentaries. The share of trials which had major breaches of rules uncovered in the course of the inspections was nearly five times higher in the local sector (42.5%, against 8.7% of IMCTs). And as we remember, the absolute number of inspected IMCTs is nearly three times greater than that of local trials.

Diagram 19



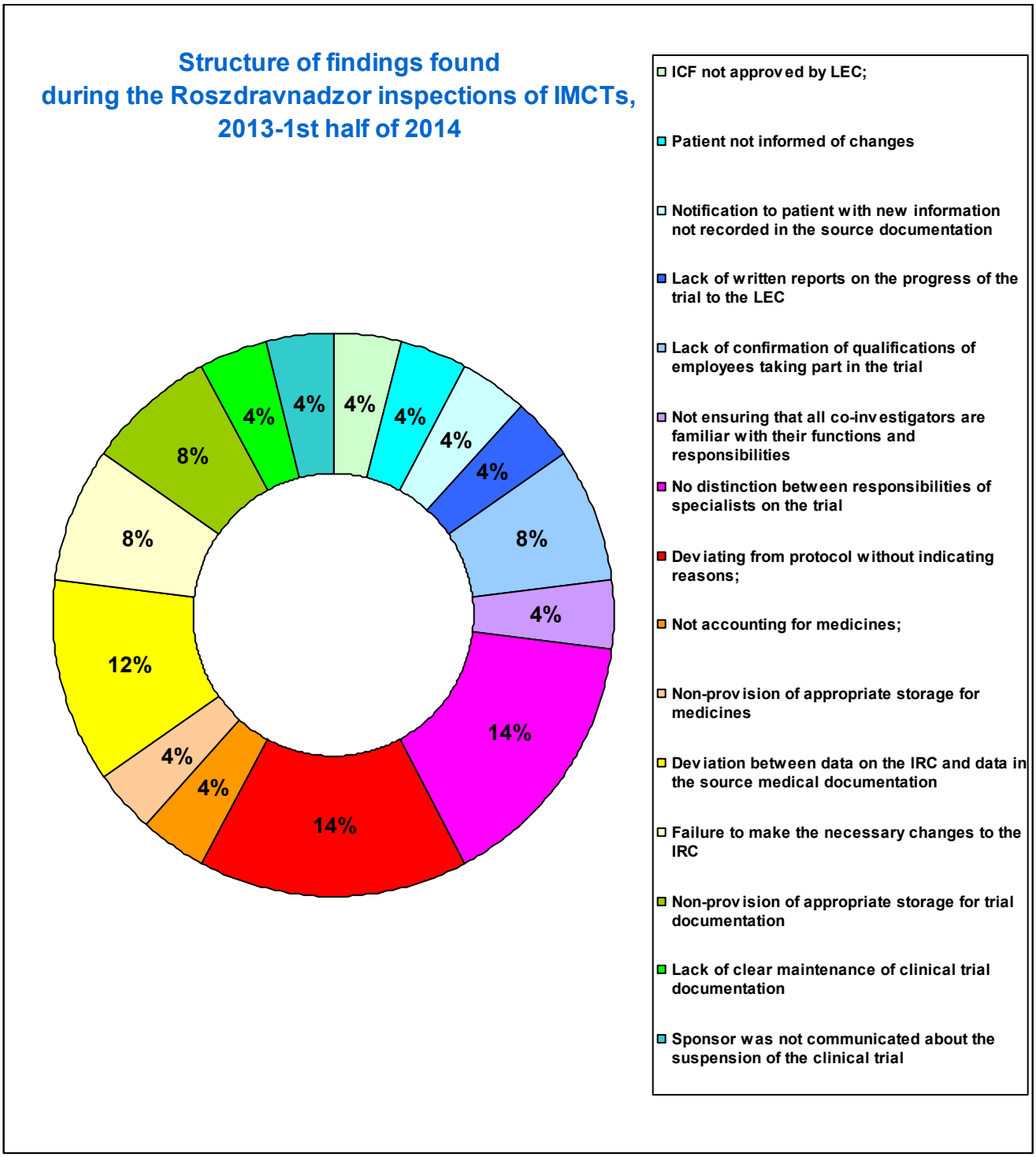
Data from: www.roszdravnadzor.ru

In addition to the distribution of the share of inspections in which Roszdravnadzor found or did not find any findings, it was also interesting to look at precisely what kind of violations they found, and how often these occurred, in IMCTs versus in local trials. The full list of discovered findings is presented in table 6. A more graphic structure of the findings discovered in inspections of IMCTs and local trials is represented in Diagrams 20 and 21 respectively.

Table 6

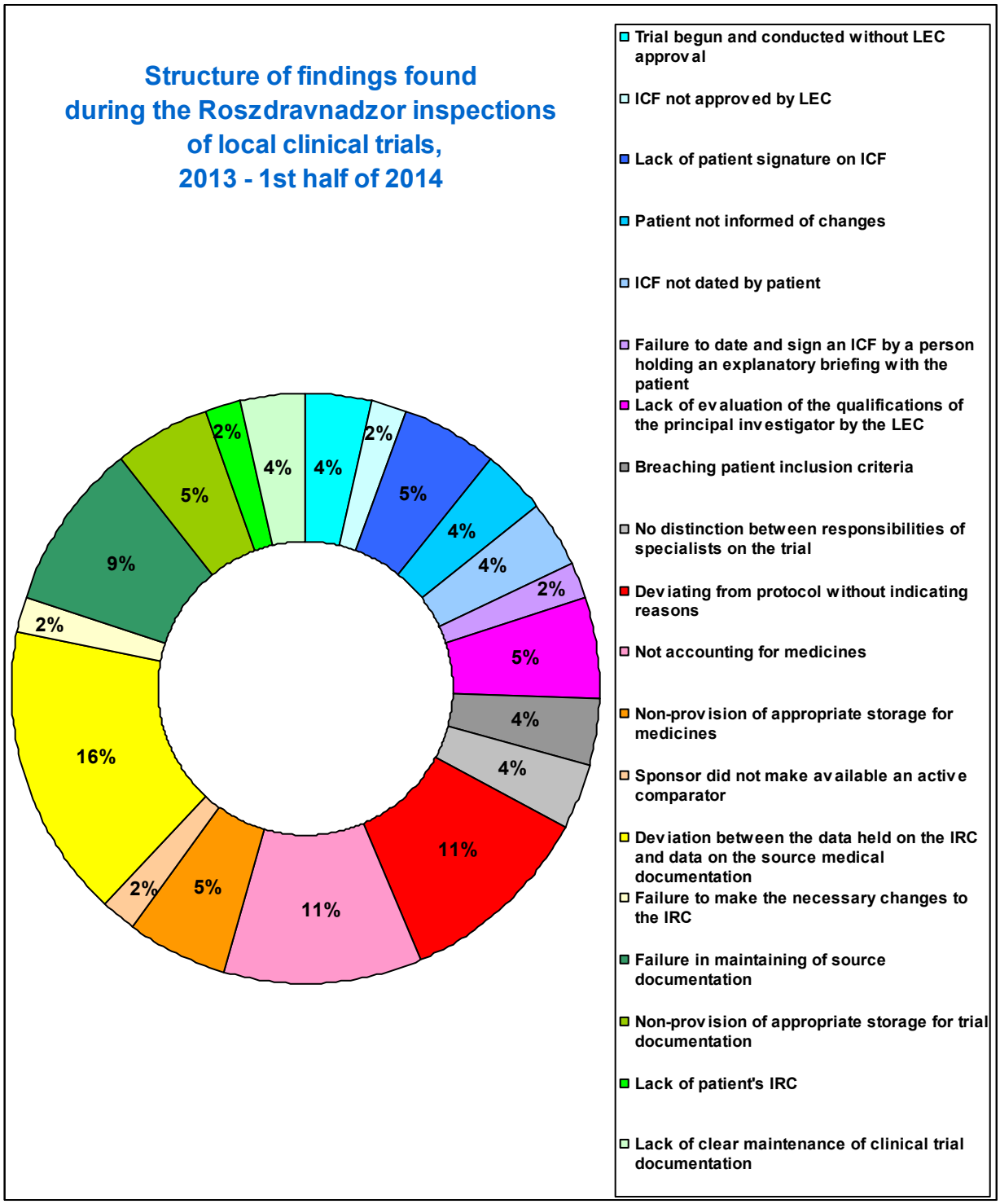
Findings uncovered in the course of inspections of clinical trials, 2013 – first half of 2014		
	IMCT	**Local Clinical Trial**
Obtaining informed consent		
Lack of patient signature on Informed Consent Form (ICF)	**-**	**3**
Patient not informed of changes (*a new ICF was either missing or was not signed)*	**1**	**2**
ICF not dated by patient	**-**	**2**
Notification of patient with new information not recorded in the source documentation	**1**	**-**
Failure to date and sign an ICF by a person holding an explanatory briefing with the patient	**-**	**1**
Maintenance of clinical trial documentation		
Deviation between the data held on the individual registration card (IRC) and the data on the source medical documentation	**3**	**9**
Failure to make the necessary changes to the patient's IRC	**2**	**1**
Failure in maintaining of source documentation	**-**	**5**
Non-provision of appropriate storage for trial documentation	**2**	**3**
Lack of patient's IRC	**-**	**1**
Lack of clear maintenance of clinical trial documentation	**1**	**2**
Deviation from the protocol		
Breaching patient inclusion criteria	**-**	**3**
Deviating from protocol without indicating reasons	**4**	**6**
Accounting, storage, and use of medicines		
Not accounting for medicines	**1**	**6**
Non-provision of appropriate storage for medicines	**1**	**3**
Sponsor did not make available an active comparator	**-**	**1**
Approval by local ethics committee (LEC)		
Trial begun and conducted without LEC approval	**-**	**2**
ICF not approved by LEC	**1**	**1**
Lack of written reports on the progress of the trial to the LEC	**1**	**-**
Lack of evaluation of the qualifications of the trial principal investigator by the LEC	**-**	**3**
Administrative matters		
No distinction between responsibilities of specialists on the trial	**4**	**2**
No confirmation of the qualifications of employees taking part in the trial	**2**	**-**
Not ensuring that all co-investigators are familiar with their functions and responsibilities	**1**	**-**
Sponsor was not communicated about the suspension of the clinical trial	**1**	
Total	**26**	**56**

Diagram 20



Data from: www.roszdravnadzor.ru

Diagram 21



Data from: www.roszdravnadzor.ru

It is clear that not only the share of trials with and without findings, but also the type of findings, vary significantly between IMCTs and local trials. The character of findings found in local trials is much more serious. We can see that in three local trials the patients did not sign informed consent forms. Therefore we do not know if the subjects were informed about their participation in a clinical trial. During inspections, five local trials were found by Roszdravnadzor to lack record-keeping of source documentation. Yet in another local trial there was a total lack of patient's individual registration cards. In three others, patients were enrolled with violations of the inclusion criteria. Reading about these findings of the inspectors, one cannot stop wondering how we can trust the results of such trials. Not one of those findings mentioned above has been found in an IMCT.

Other findings which were discovered in both groups of trials were much more common in local trials than they were in IMCTs. So in nine local trials, compared to three IMCTs, inspectors found discrepancies between the data on the individual registration cards and the data in the source medical documentation. In six local trials as compared to one international trial, they found problems in drug inventory, and in three local trials compared to one IMCT, they found problems in drug storage arrangements.

The resulting picture does not surprise us. ACTO began raising concerns about the quality of local trials back on the eve of the adoption of the law “On the Circulation of Medicines”. Even at that time it was clear that our market would soon be flooded with an influx of low-quality trials which no one wanted or needed, which had one goal – to get the checkmark of 'tested on a Russian patient'. This analysis of the Roszdravnadzor inspections has only confirmed the logical result of such a law. What next? It's not yet clear. Arguments around planned amendments to the law have not led to changes in the bureaucrats' positions in relation to local trials. In this situation it is important to make a clear distinction between real trials and trials just to get the 'checkmark'. We wanted to appeal to the officials of Roszdravnadzor on this – when presenting the results of your work in official reports on international and local clinical trials, do not mix them all up in one bag. Otherwise you end up with that old joke – the hospital's average patient temperature is 36.6 degrees, including the fever ward and the morgue.

NEWS FROM ABROAD

At the end of May, 2014, Regulation (EU) No 536/2014 of the European Parliament and of the Council of 16 April 2014 on clinical trials on medicinal products for human use, and repealing Directive 2001/20/EC, has been published in the Official Journal of the European Union. The document had been under development since 2011.

This Regulation came into force 20 days after it was published and will be effective half a year from the time that a new EU database on clinical trials starts functioning. The document, as it is clear from the name, will replace the previous Directive 2001/20/EC. Experts believe that the new Regulation will properly be in force from the second half of 2016. Clinical trials which will begin in the transitional period between the publication of the Regulation and the launch of all of its requirements, will have to be conducted in accordance with Directive 2000/20/EC up to 2018.

The Regulation directly regulates all clinical trials for medicinal products for human use, both in single and multiple centers, in all 28 EU member states (national rules will be superseded as will the Directive 2001/20/EC). The document does not apply to non-intervention trials, or to clinical trials of medical devices. The requirements of the Regulation do apply to clinical trials conducted outside of the EU if their results will be used within the EU.

The procedure to obtain approvals for conducting clinical trials will change. EU member states will take part in decision making on approving clinical trials, but there will be strict timeframes, a system of coordination with distributed functions in the process of approving multicenter clinical trials between the countries in which the trial is planned.

The main source of information on matters of clinical trials for EU member states will be a special database. This will be accessible as an online resource. Each clinical trial will have to register in this database and get a unique code before it can begin. Communication between sponsors and regulators, as well as between national regulatory bodies, will be maintained via a website, where sponsors can register applications for approval for conducting clinical trials, get information about decisions and so on.

The Regulation includes new definitions for basic terms in the area of clinical trials, and also additions to previously existing terms. The contents of the Regulation are quite extensive compared to Directive 2001/20/EC (24 articles in the Directive and 99 in the Regulation), and separate sections are detailed. But the Regulation will not change the fundamentals of conducting clinical trials, based on ICH GCP.