ACTO

ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

ACTO NEWSLETTER № 15

1st Half of 2017

MOSCOW 2017

CONTENTS

SUMMARY

During the first half of 2017, the Ministry of Health of the Russian Federation issued 358 approvals to conduct clinical trials, which is 20.4% less than during the same period of the previous year. The reduction in number of approvals issued referred to all types of trials except international multi-center clinical trials (IMCT), which saw a 9.6% increase (148 approvals vs. 135 during the first six months of 2016). The biggest drop (45%) was observed in bio-equivalence studies by foreign sponsors (44 approved protocols vs 80 a year earlier). The number of approvals for local trials by foreign sponsors decreased by 35.7%; the number of local trials and bio-equivalence studies by Russian sponsors – by 29.5% and 26.5%, respectively. There is no reasonable explanation for such a drastic redistribution, besides the norm set for necessity to inspect foreign manufacturers against Russian GMP. The changes specified above influenced market structure: the ratio of IMCTs that had been successively decreasing since 2013, during the first six months of the current year increased by 7 points (41% vs. 34% following the results 2016).

The following section of the Newsletter contains the results of routine monitoring of expert examination practice upon receipt of approvals for conduct trials. During analysis both the FGBU "Scientific Center for Expert Examination of Medical Products" (FGBU) and the Ethics Council emphasized an apparent improvement of expert analysis. The most significant improvement was observed in the FGBU: an essential increase in the number of analyses by this expert organization without comments, that is 73.3% vs. 59.8% a year earlier. There was improvement in paediatric protocols expert examination results. The share of trials in children that the Ethics Council approved without comments increased from 17.6% up to 63.6%, the FGBU – from 33.3% up to 50%. Still, the data received as a result of polling embellish the real picture. What caused such results and how to apply to it are the subjects of discussion hereunder.

Analysis of dependence of expert examination results distribution from therapeutic area of trials reveals a long-awaited paradigm shift of the Ethics Council in regard to psychiatry. For the first time in five years this area made it out of the top slot in negative ratings due to an increase in the share of protocols approved without comments up to 66.7% (from 42.9% a year earlier and 33.3% for the last three years).

The issue of the Ethics Council modus operandi was raised again: the Ministry of Health continues to deny this expert organization the right to make requests to applicants. This technical issue has caused a serious practical one; there are examples of losses due to this restriction of international projects. In the view of the Association of Clinical Trials Organizations (ACTO), current legislation allows the Council to make requests along with the FGBU, and thus the Association asks the Management of the Core-Business Department of the Ministry of Health to reconsider its position regarding this issue.

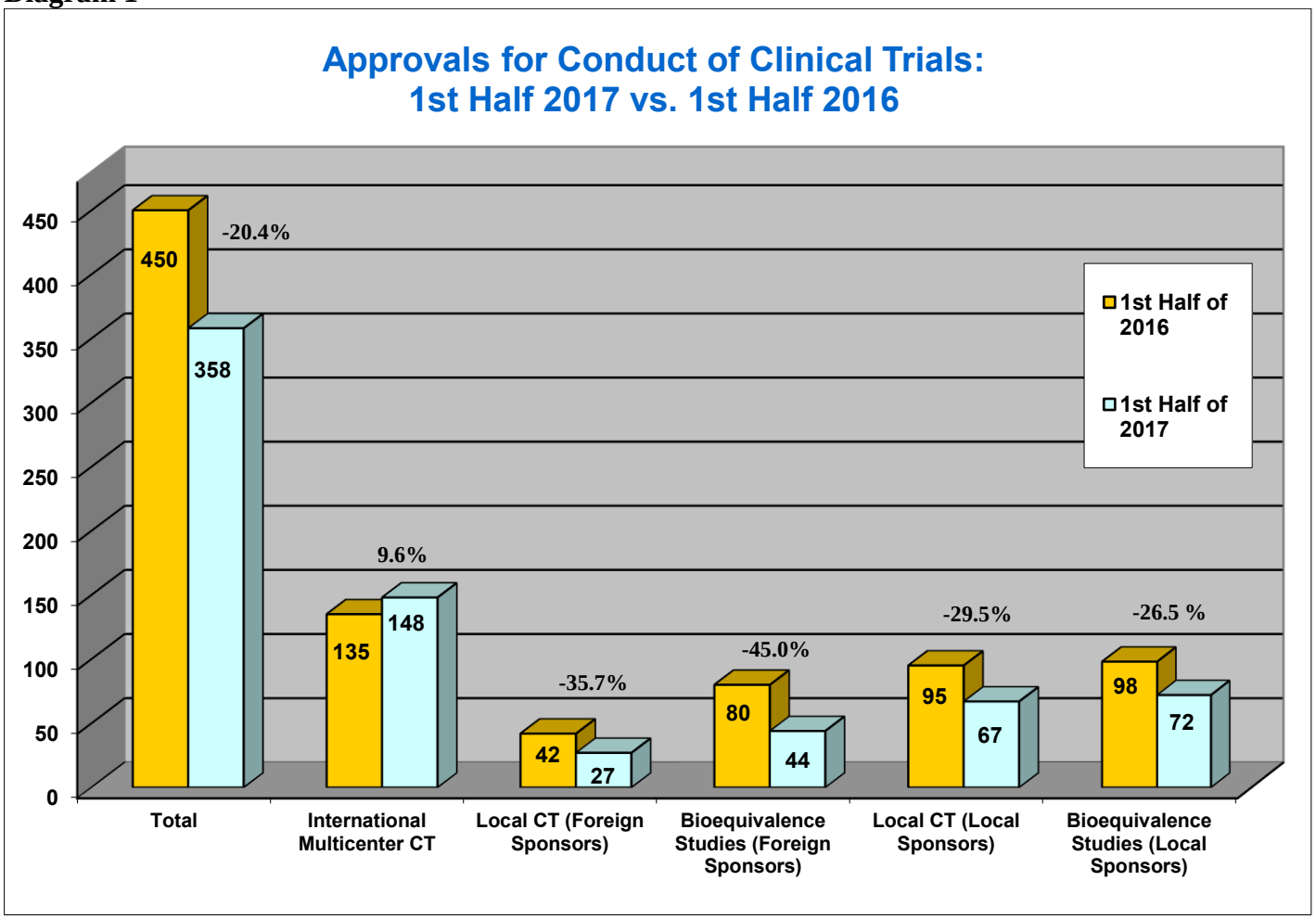
Section of analysis of inspections by Roszdravnadzor covers only the data for the second half of 2016. This period of time is explained by the fact that from the beginning of 2017 Roszdravnadzor changed the procedure for provision of information according to the results of the conducted inspections. Roszdravnadzor examined the totals of 76 clinical trials. There were 48 IMCTs (63.3%) and 28 (36.7%) local trials. The share of international trials inspections of those revealed no violation exceeds that of local trials (70.8% vs. 53.6%).

This conclusion raises the issue of importance of use of the proper terminology in reference to safety information. Wide-spread confusion over the use of the terms 'adverse event' and 'adverse reaction' had some unpleasant consequences (including legal). Thus, the ACTO reports about its campaign to raise awareness in this sphere.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

During the first half of 2017 the Ministry of Health of the Russian Federation issued 358 approvals to conduct clinical trials (Diagram 1), which is 20.4% less than during the same period of the previous year (450 approvals).

Diagram 1



Data from www.grls.rosminzdrav.ru

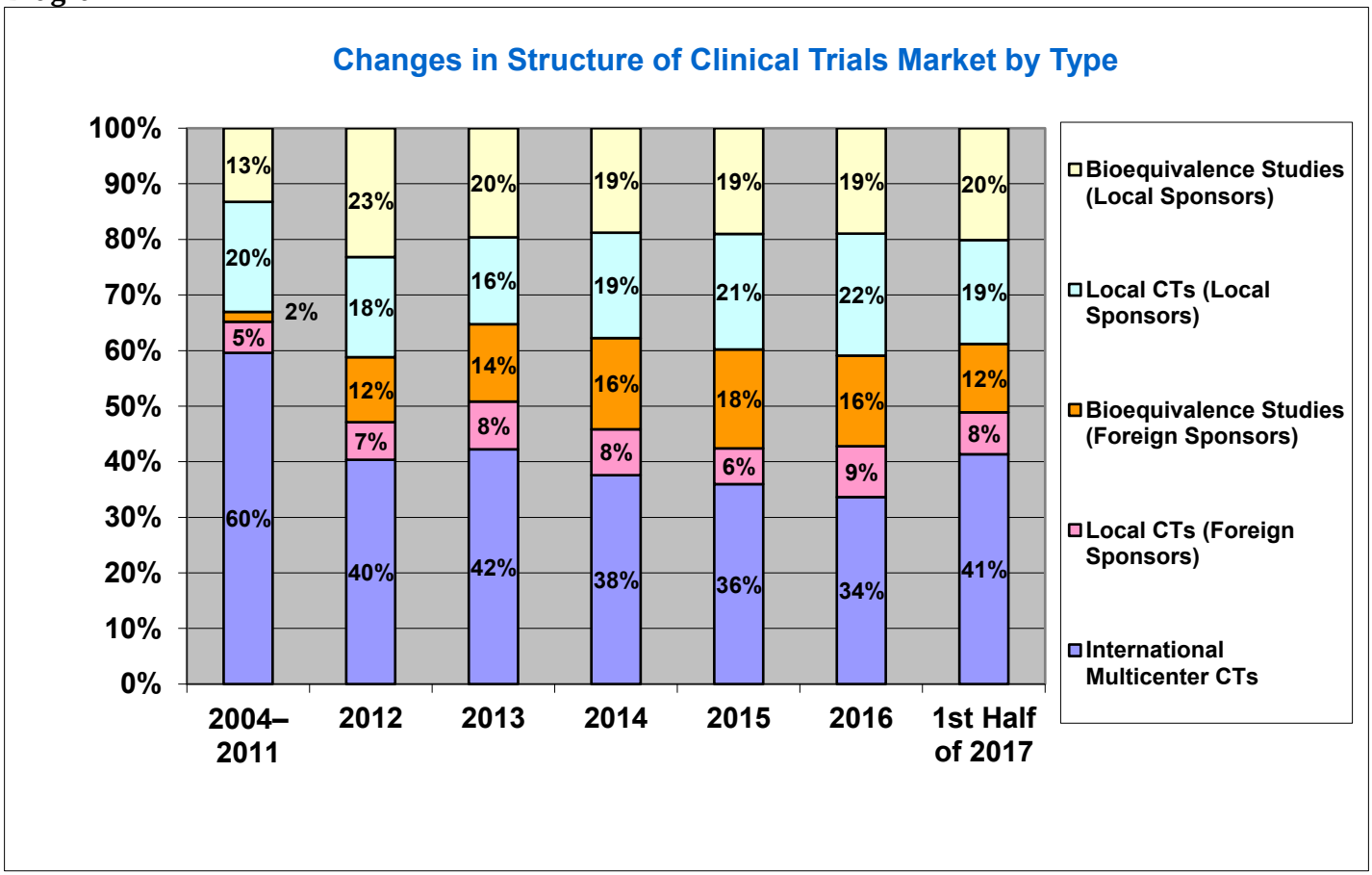
This reduction in the number of approvals issued referred to all types of trials except international multi-center clinical trials (IMCTs), for which a 9.6% increase was observed (148 approvals vs. 135 during H1 2016).

The greatest decrease, by 45%, was observed in the number of approvals for bio-equivalence studies by foreign sponsors (44 approved protocols vs. 80 approved a year earlier). A 35.7% reduction was observed in case of approvals for local efficiency and safety trials of foreign drugs (27 vs. 42 approvals). There was a slightly less, but still significant, reduction in the number of approved local trials of drugs of Russian manufacturers: a 29.5% reduction for section of efficiency and safety trials (67 vs. 95 approvals) and a 26.5% reduction for bio-equivalence studies (72 vs. 98).

But what caused such a drastic decrease in the number of approvals for all types of trials which, however, did not concern international projects? Surveyed experts agreed that it could be a consequence of the new requirement for obligatory inspection of foreign pharmaceutical manufacturers against Russian GMP as a condition for registration of a new medicine. This legislative change had already caused a suspension in registration of foreign drugs. And now, apparently, this trend has affected local registration trials, and primarily those sponsored by foreign companies. Trials sponsored by local manufacturers became affected too.

This was due to the fact that in several cases, foreign-made medicines (primarily from India) were used as the basis for development and release of Russian products. Of course, this is pure conjecture; still there is no other reasonable explanation for such a drastic reduction in local trials.

Diagram 2



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

Naturally, such changes influenced the whole structure of the market (Diagram 2). The share of IMCTs, which has been successively decreasing from 2013, increased rapidly in the first six months of the current year, exceeding other types of studies by 7 points (41% vs. 34% following the results of 2016). This increase was conditioned by a decrease in the share of bio-equivalence studies by foreign sponsors (the loss constituted 4 points vs. the results of 2016), and local efficacy and safety trials by local sponsors (a 3-point decrease). At the same time, the share of local trials of foreign medicines and bio-equivalence studies of Russian sponsors remained almost at the same level give or take 1 percentage point.

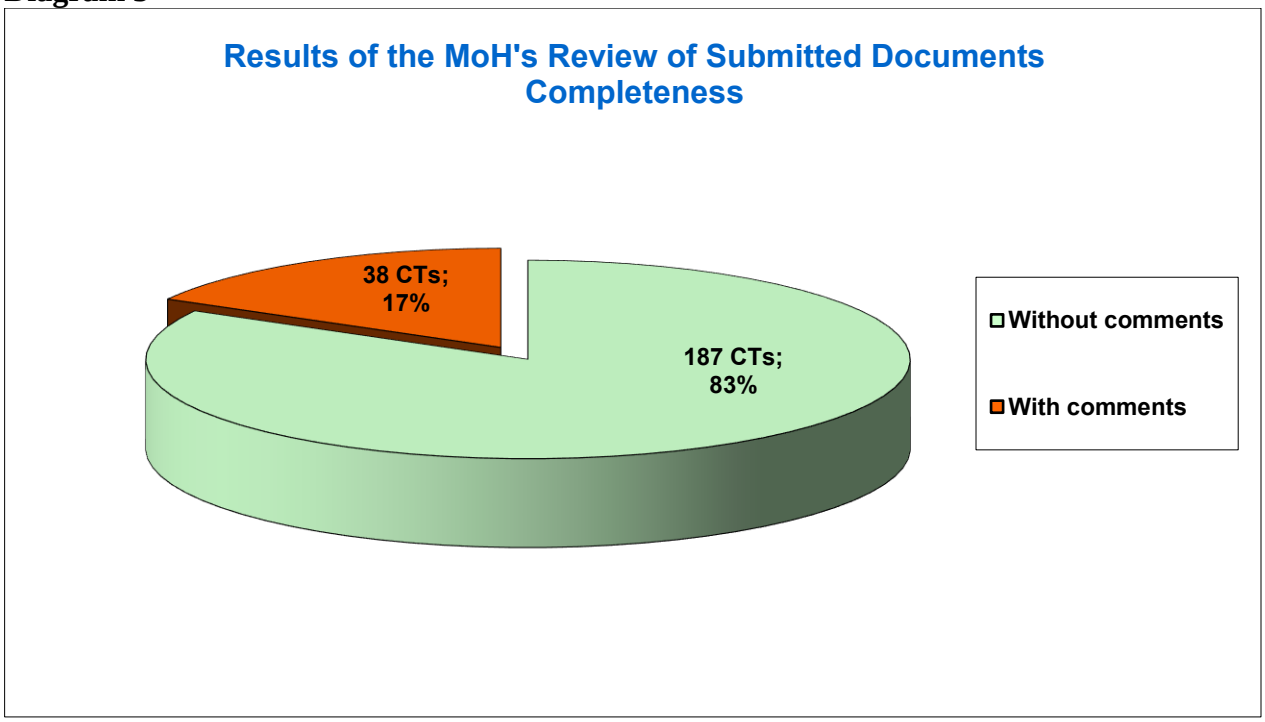
It will be quite interesting to see how long this trend continues into the second half of the year and whether it will influence whole-year results.

EXPERT EXAMINATION OF PLANNED TRIALS

This section of the Newsletter contains the results of routine monitoring by ACTO of the procedure for passing expert review during the process of obtaining approval to conduct clinical trials, which is an annual project covering the second six months of the previous year and the first half year of the current one. Data are acquired by polling 25 ACTO company-members and include the results of consideration of the initial applications to conduct IMCTs. Such applications are reviewed by expert organizations (the Ethics Council and the FGBU "Scientific Center for Expert Examination of Medical Products" (the FGBU). Data on local trials (including bio-equivalence studies) were not included in the monitoring.

The results of examination of completeness of documentation conducted by the Ministry of Health before documents were sent to expert organizations, are shown on Diagram 3. It is apparent that 17% of applications during this period have got comments of the Ministry of Health (15.2% a year earlier). As last time, the main reason for regulator's criticism was absence of GMP Certificate which states the conclusion about compliance of drug manufacturer with GMP requirements. This certificate must be issued by an authorized body in the country of origin. The complication is that not all countries are aware what this document is. Yet, clinical trials are in better conditions than registration affairs where one hands in results of inspection of foreign site conducted by Russian experts, but not a document from country of origin. Thanks are due to the legislator who listened to anguished cries and tempered justice with mercy, and replaced Russian certificates with documents from the country of origin exclusively for clinical trials two days prior to the second reading of draft legislation in the State Duma. Otherwise, we would have been left with nothing to do but celebrate a two-year anniversary of the decline of the IMCT industry in Russia.

Diagram 3



Data from www.grls.rosminzdrav.ru

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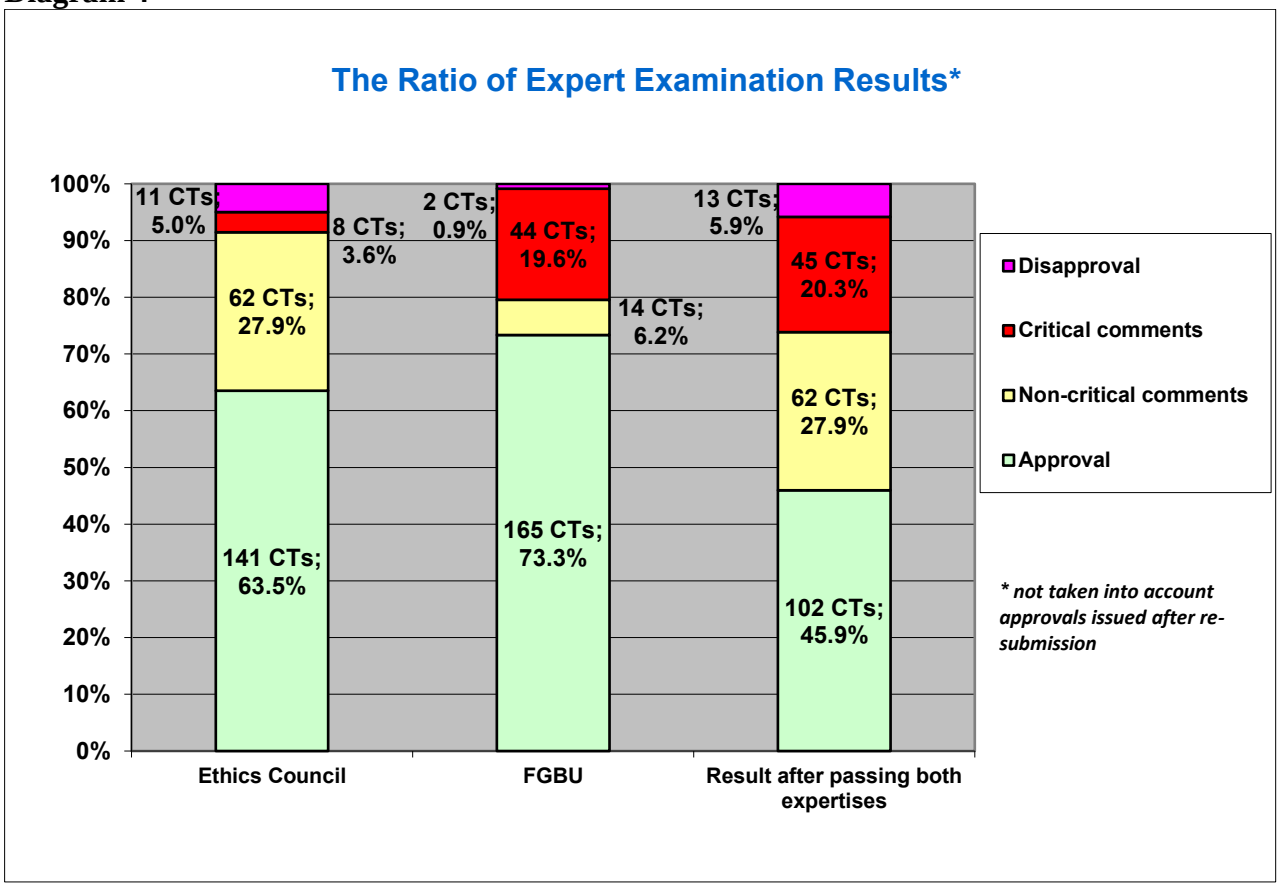
Diagram 4 shows the results of expert examination of documents for conducting clinical trials held by the Ethics Council and the FGBU, as well as result of these two kinds of expertise. Requests and comments were classified by the companies themselves depending on whether the study design was affected, whether additional studies were required (critical comments), or if there was any talk of insignificant corrections to informed consent form, clarification of information and other (uncritical comments).

Diagram 4



Data from poll of ACTO members

Comparing the results of the current and the previous years, a significant improvement in affairs with both types of expert examination is worth mentioning. Additionally, the most significant is improvement with the FGBU. This is confirmed by both the results of ACTO polling and companies' comments, this expert organization has become more prudent in its judgments, more careful in reading applicants' replies and more agreeable towards reasonable argumentation. Apparently, some staff changes in the FGBU in Spring 2016 affected such improvement.

Table 1

Analyzed period	Share of positive FGBU decisions on IMCTs	Share of positive Ethics Council decisions on IMCTs	Share of positive decisions by both bodies on IMCTs
1st Half of 2013	71.4%	72.9%	51.5%
2d Half of 2013 – 1st Half of 2014	71.8%	62.6%	43.7%
2d Half of 2014 – 1st Half of 2015	58.0%	66.0%	42.6%
2d Half of 2015 – 1st Half of 2016	59.8%	62.2%	38.3%
2d Half of 2016 – 1st Half of 2017	73.3%	63.3%	45.9%

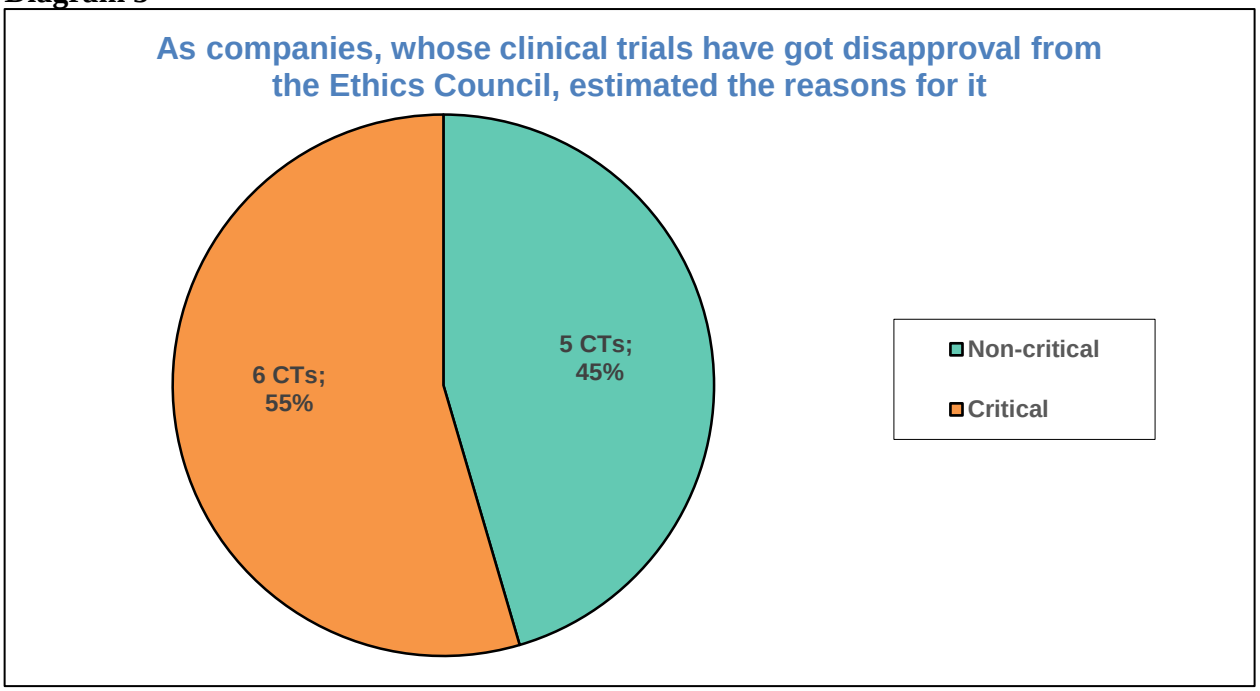
Data from polls of ACTO members

But let us return to the results. First of all, it is worth mentioning that the share of trials that underwent expert appraisal of the FGBU without comments increased by 13.5 percentage points (from 59.8% to 73.3%). Table 1 shows that this result is the best since 2013 when ACTO initiated monitoring of this parameter. The rate of the files approved without comments from the Ethics Council also increased, but this increase was not so significant – 63.3% vs. 62.2% a year earlier (the third result in rating from 2013). Still, it is worth mentioning that comments given by the Ethics Council are not critical for applicants so they are easier to be taken into consideration. As far as the results of both examinations, a significant increase in the rate of the trials that received no comments is observed (45.9% vs. 38.3%). This demonstrates more well-coordinated work between the two expert organizations.

The rate of disapprovals decreased from both expert organizations. But whereas for the Ethics Council this value was 5% (8.4% a year earlier), then for the FGBU it became almost minimum – 0.9% (6.2% according to the results of the last-year survey). What is the cause of such difference in values? An uninitiated reader might think that it is caused by strictness of the Ethics Council. Hardly. The issue is about the fact that the management of the Core-Business Department of the Ministry of Health believes that only the FGBU has a right to make requests to applicants. As a result, the FGBU's questions can be taken off the table during communication and exchange of opinions. The Ethics Council has no right to make requests. It can only approve or disapprove a trial, and issue its approval under condition that applicant shall make recommended amendments in working order. This way is not always acceptable, especially when there are a lot of points of comments. As a result, a company receives disapproval when in fact it could have resolved differences had it been made aware of the comments made by the Ethics Council earlier and had opportunity to reply.

This issue is quite significant for applicants. Such significance is demonstrated by the data in Diagram 5: in almost half of cases when companies received disapproval from the Ethics Council, they estimated causes as uncritical. This means that they could easily have made the necessary modifications. Running ahead of the story, we will say that the reason for such disapprovals was loss of one trial when sponsor refused to conduct it in Russia, especially recruitment in other countries went well.

Diagram 5



Data from polls of ACTO members

Taking into consideration the price to be paid for such an insignificant detail in regulation (failure of Russia to participate in IMCT can mean that a new drug would not be marketed in the country), we are eager to address the management of the Department for State Regulation of The Circulation of Medicines of the Ministry of Health of Russia with the request to solve this issue.

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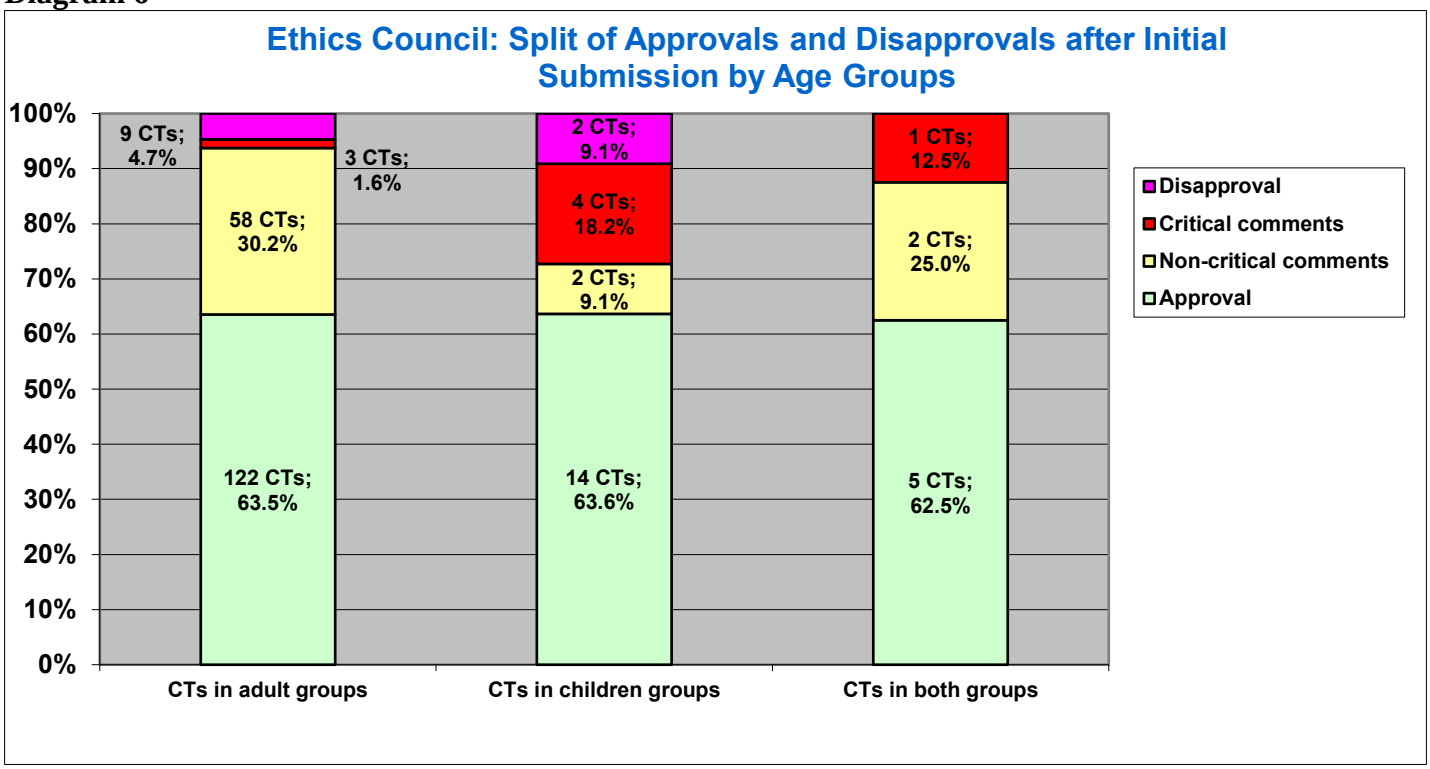
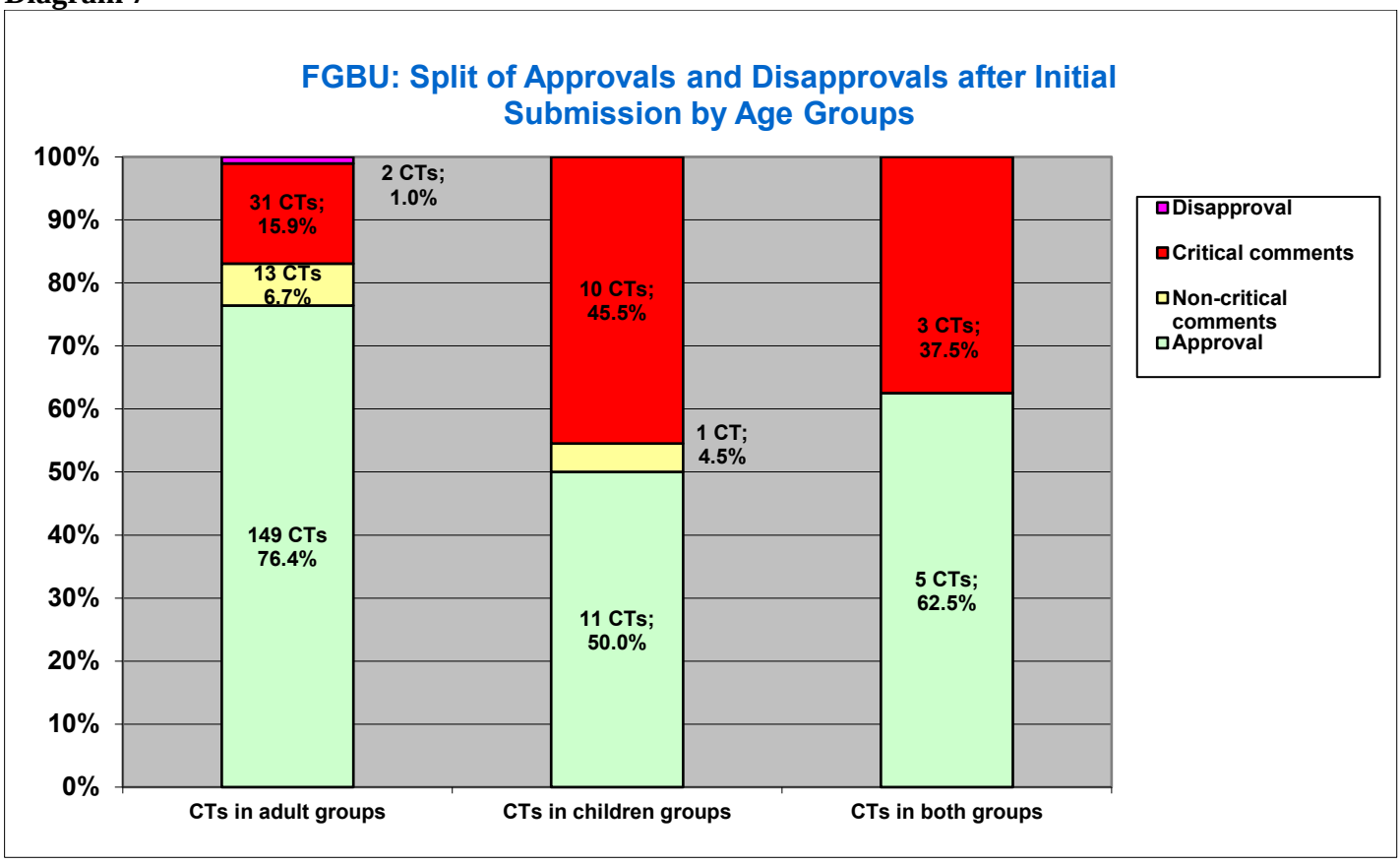
Diagrams 6 and 7 show the distribution of evaluations made by expert organizations depending on the age group of participants in the scheduled trial.

Diagram 6



Data from polls of ACTO members

Diagram 7

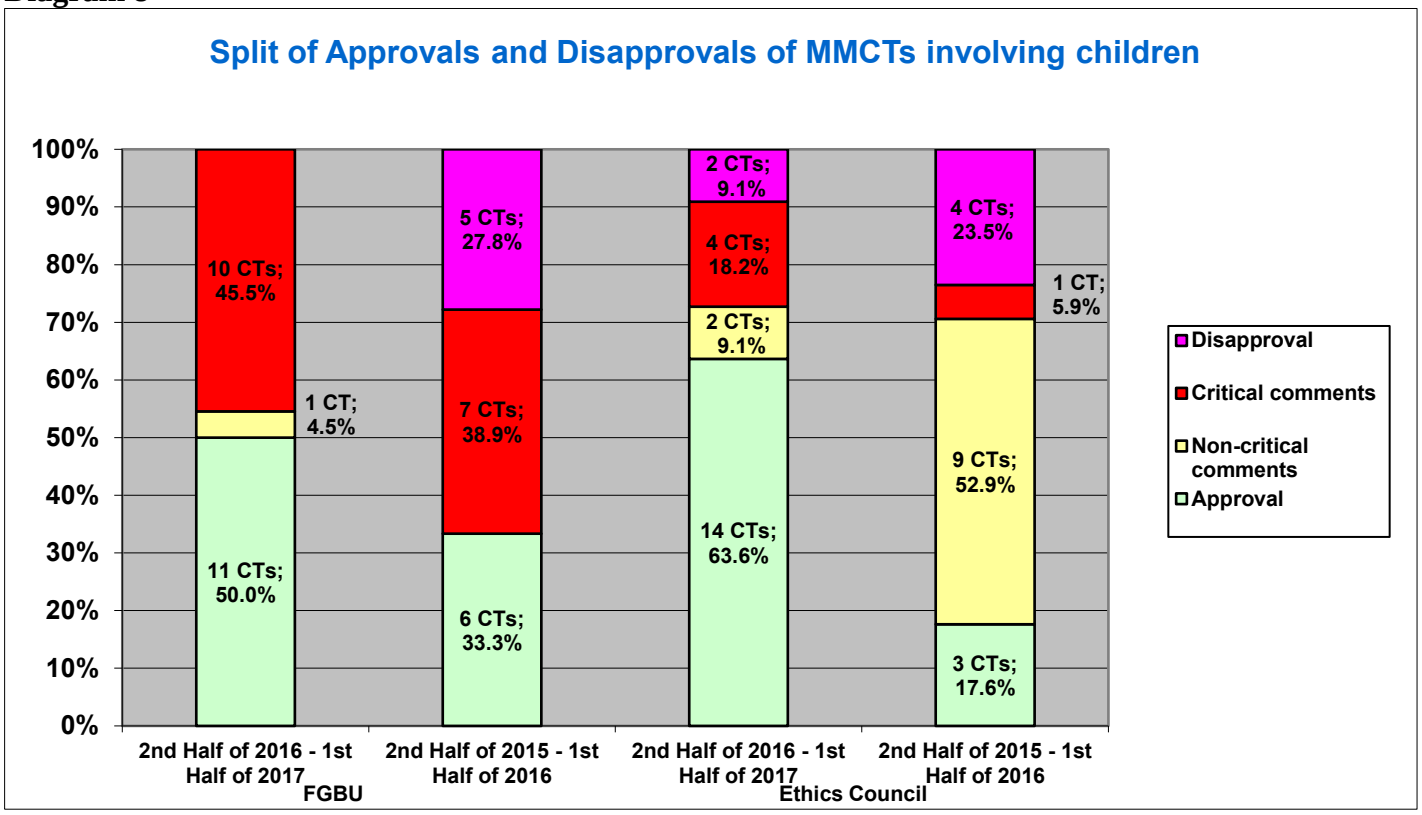


Data from polls of ACTO members

A comparison of the results obtained with that of the previous year (Diagram 8) demonstrates a significant improvement of the data on examination of paediatric protocols. The rate of files approved without comments by the Ethics Council increased by 46 points – from 17.6% up to 63.6%. The first cause was the reduction in the rate of trials that received uncritical comments (9.1% vs. 52.9% a year earlier). In addition, there was redistribution in the section of critical comments and disapprovals. The previous year's survey showed the rate of disapprovals made by the Ethics Council in relation to paediatric protocols equal to 23.5%; now this rate decreased down to 9.1%. On the contrary, the rate of files with critical comments increased from 5.9% to 18.2%.

A significant improvement in affairs with paediatric protocols can be observed subsequent to the results obtained by the FGBU. The rate of files approved from the first time increased up to 50% (33.3% a year earlier). There were no disapprovals in relation to such files (according to the results of the last-year survey the rate of such files was 27.8%). The rate of protocols with critical requests increased (45.5% vs. 38.9%). Still, with consideration of absence of disapprovals rate such an increase is reasonable.

Diagram 8



Data from polls of ACTO members

One would think that we saw the long-awaited fundamental change in the situation with examination of paediatric trials. Unfortunately, the true picture differs from that in schemes. The point is the following. The survey revealed that a minimum of three trials with paediatric population (probably, there were more of them but not all respondents mentioned it in comments) were really approved from the first time without any additional requests or comments from the side of the expert organizations. Applicants were surprised to receive an approval from the Ministry of Health and to see that minimum age of participants was more than the age initially specified by the sponsor. In consequence of application for clarification to department officers it turned out that this is a new procedure (that is not always applied as survey shows) – after receiving a comment from expert body the Ministry of Health does not send request to applicant, instead it eliminates the age of participants in authorization issued. And as it appeared, in two cases of three above-mentioned such decision was adopted based on position of the FGBU, and in one – according to conclusion of the Ethics Council.

Having encountered such an innovative approach, we could hardly develop a simple attitude to it. On the one hand, such a solution to the issue releases an applicant from sustained communications with experts and saves time. The sponsor can initiate the trial with a more mature group and at the same time try to get approval for the rejected group of a younger age. This is an apparent advantage. But there is a disadvantage – without experts' comments it is impossible to understand on what the regulatory authority based its decision; it is difficult to oppose. Also it is complicated to explain to the headquarters of foreign sponsors (who are used to more transparent relationships and open dialogue with regulatory authorities) that a decision can be adopted in such a way – without any respect to the applicant's position (as people say, 'be satisfied with what you received, you could have got nothing'). Well, in a country driven by bureaucracy, we can do nothing but be satisfied with such a situation. Taking into account the advantage of saving time and having opportunity to initiate trial earlier far outweighs the humiliation the applicant suffers when receiving approval that differs from what he expected, so we shall thank the Ministry of Health. Also we can ask the Ministry to somehow explain such decisions in the future or specify the expert body that rejected inclusion of younger age groups.

It is apparent that we could not take such cases into account when calculating statistics as we received no formal comments during examination. Still, estimating the data on Diagrams 6 and 7 one can see that the real picture for paediatric protocols is less encouraging than it might seem. In fairness it must be said that at least one trial with inclusion of new-born children was approved without comments and age limitations, which came as pleasant surprise for the applicants, who had already prepared for a prolonged battle.

There is one more reason for being optimistic in relation to trials with paediatric populations. On August 26, 2017, Russian President Vladimir Putin met with representatives of socially oriented non-commercial organizations, charitable organizations and voluntary associations. Following the results of this meeting the Russian leader approved a list of instructions. One instruction orders the Ministry of Health to take measures to reduce the terms for conducting expert examinations and provide infants with non-invasive painkillers until October 30, 2017. What could have happened to make the leader of such a big country tackle such specific questions? We cannot but hope that the experts of the Ministry of Health will remember that children need not only painkillers but other drugs as well. And that there are no drugs without clinical trials.

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Table 2 shows the distribution of the Ethics Council examination results based on therapeutic area of planned trials. To provide more clarity the same results are presented in Diagram 9.

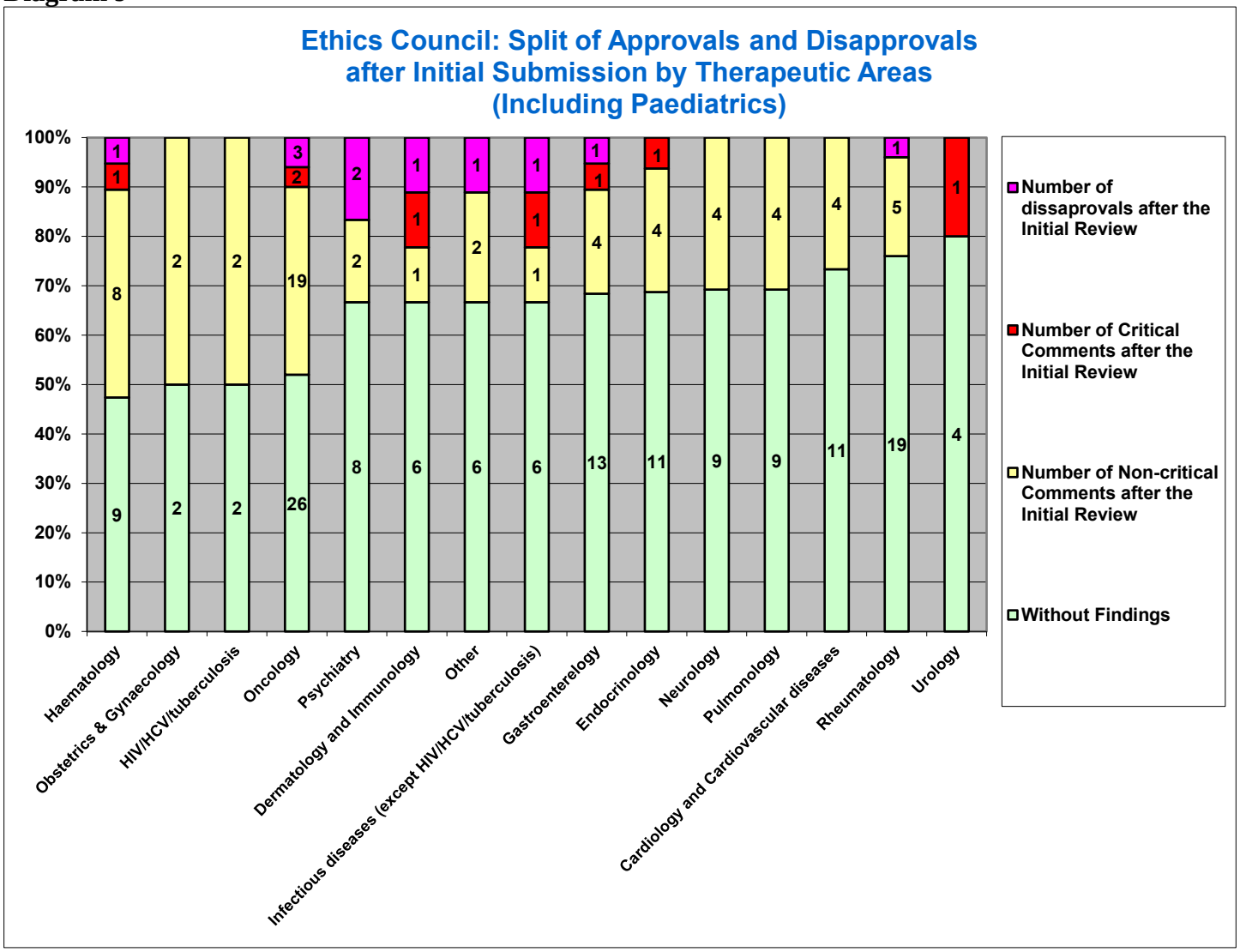
The first that we would like to note when analyzing the data provided is psychiatry. For the first time in five years this area lost its doubtful claim of victory to the lowest rate of trials approved without comments and got 5^{th}-8^{th} positions in the negative rating with result of 66.7%, sharing this place with other three therapeutic areas. To make it clearer how remarkable this event is, we shall recall that a year earlier in psychiatry the rate of trials approved without comments was 42.9%. And prior to that for three years it was 33.3%. Such circumstances seriously influenced the attitude of sponsors. The number of innovative developments in psychiatry throughout the world has reduced significantly over the last few years. An apparent prejudice from the side of the Russian expert body became a considerable negative factor in solution of the issue of choosing Russia as a country for conducting trials in this area. We can do nothing but hope that this drastic trend change will help to recover trust from the side of developers and return their attention to Russian centers.

Table 2

Ethics Council: Split of Approvals and Disapprovals by Therapeutic Areas (in Brackets Data Excluding Paediatric Protocols)									
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 Comments after the Initial Review**	**Non-critical Comments after the Initial Review, % of Total**	**Number of Critical Comments after the Initial Review**	**Critical Comments after the Initial Review, % of Total**	**Number of Disapprovals after the Initial Review**	**Number of Disapprovals after the Initial Review, % of Total**
Oncology	**50 (49)**	**26 (25)**	**52.0% (51.0%)**	**19 (19)**	**38.0% (38.8%)**	**2 (2)**	**4.0% (4.1%)**	**3 (3)**	**6.0% (6.1%)**
Rheumatology	**25 (22)**	**19 (16)**	**76.0% (72.7%)**	**5 (5)**	**20.0% (22.7%)**	**0 (0)**	**0.0% (0.0%)**	**1 (1)**	**4.0% (4.6%)**
Haematology	**19 (16)**	**9 (8)**	**47.4% (50.0%)**	**8 (7)**	**42.1% (43.8%)**	**1 (0)**	**5.3% (0.0%)**	**1**	**5.3% (6.3%)**
Gastroenterelogy	**19 (18)**	**13 (13)**	**68.4% (72.2%)**	**4 (3)**	**21.1% (16.7%)**	**1 (1)**	**5.3% (5.6%)**	**1 (1)**	**5.3% (5.6%)**
Endocrinology	**16 (13)**	**11 (9)**	**68.8% (69.2%)**	**4 (4)**	**25.0% (30.8%)**	**1 (0)**	**6.3% (0.0%)**	**0 (0)**	**0.0% (0.0%)**
Cardiology and Cardiovascular diseases	**15 (14)**	**11 (10)**	**73.3% (71.4%)**	**4 (4)**	**26.7% (28.6%)**	**0 (0)**	**0.0% (0.0%)**	**0 (0)**	**0.0% (0.0%)**
Neurology	**13 (13)**	**9 (9)**	**69.2% (69.2%)**	**4 (4)**	**30.8% (30.8%)**	**0 (0)**	**0.0% (0.0%)**	**0 (0)**	**0.0% (0.0%)**
Pulmonology	**13 (11)**	**9 (7)**	**69.2% (63.6%)**	**4 (4)**	**30.8% (36.4%)**	**0 (0)**	**0.0% (0.0%)**	**0 (0)**	**0.0% (0.0%)**
Psychiatry	**12 (10)**	**8 (6)**	**66.7% (60.0%)**	**2 (2)**	**16.7% (20.0%)**	**0 (0)**	**0.0% (0.0%)**	**2 (2)**	**16.7% (20.0%)**
Dermatology and Immunology	**9 (8)**	**6 (6)**	**66.7% (75.0%)**	**1 (1)**	**11.1% (12.5%)**	**1 (1)**	**11.1% (12.5%)**	**1 (0)**	**11.1% (0.0%)**
Infectious diseases (except HIV/HCV/tuberculosis)	**9 (6)**	**6 (5)**	**66.7% (83.3%)**	**1 (1)**	**11.1% (16.7%)**	**1 (0)**	**11.1% (0.0%)**	**1 (0)**	**11.1% (0.0%)**
Urology	**5 (4)**	**4 (4)**	**80.0% (100.0%)**	**0 (0)**	**0.0% (0.0%)**	**1 (0)**	**20.0% (0.0%)**	**0 (0)**	**0.0% (0.0%)**
Obstetrics & Gynaecology	**4 (4)**	**2 (2)**	**50.0% (50.0%)**	**2 (2)**	**50.0% (50.0%)**	**0 (0)**	**0.0% (0.0%)**	**0 (0)**	**0.0% (0.0%)**
HIV/HCV/tuberculosis	**4 (4)**	**2 (2)**	**50.0% (50.0%)**	**2 (2)**	**50.0% (50.0%)**	**0 (0)**	**0.0% (0.0%)**	**0 (0)**	**0.0% (0.0%)**
Other	**9 (8)**	**6 (5)**	**66.7% (62.5%)**	**2 (2)**	**22.2% (25.0%)**	**0 (0)**	**0.0% (0.0%)**	**1 (1)**	**11.1% (12.5%)**
Total	**222 (200)**	**141 (127)**	**63.5% (63.5%)**	**62 (60)**	**27.9% (30.0%)**	**8 (4)**	**3.6% (2.0%)**	**11 (9)**	**5.0% (4.5%)**

Data from poll of ACTO members

Diagram 9



Data from poll of ACTO members

Subsequent to the results of the current survey, haematology is the therapeutic area with the lowest rate of trials approved without comments, at 47.4%. This was unexpected, as a year earlier its value was 75%. A higher rate (50% of protocols approved at the first attempt) belongs to obstetrics and gynaecology, as well as to anti-HIV, anti-hepatitis C and anti-tuberculosis drugs. In fairness it must be said that comments to the trials belonging to the above-mentioned areas were uncritical. Against this background, oncology is in the worst position. Even though the rate of trials approved without comments in this area a little higher (52%), a rather high cumulative rate of protocols with comments and disapprovals causes disturbance (10% in total: 4 % of comments and 6% of disapprovals). This situation is a little better than a year earlier, when there was 1.9% of critical comments for trials in oncology and 13% of disapprovals.

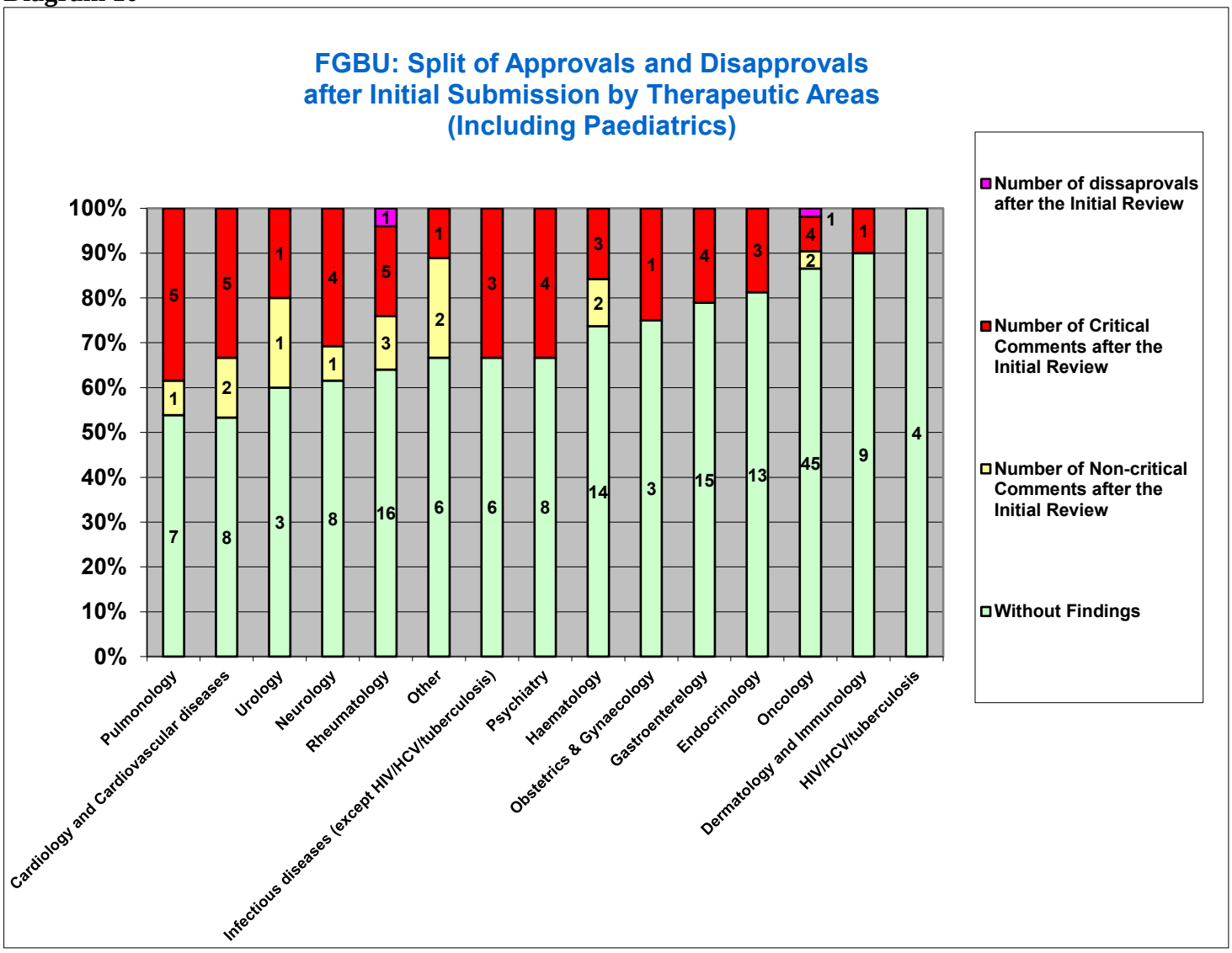
Table 3 and Diagram 10 reflect the distribution among therapeutic areas depending on decisions of the FGBU examination. The FGBU's requests more frequently have a critical character, as distinct from the Ethics Council comments. According to this value, trials in pulmonology (38.5%), cardiology and cardio-vascular diseases (CVDs), psychiatry and infectious diseases (these three areas demonstrated 33.3% each) turned out to be in the worst position. Position of trials in cardiology CVDs as well as in pulmonology were exacerbated due to uncritical requests; as a result these areas demonstrated the lowest rate of protocols approved without comments (53.3% and 53.8%, accordingly).

Table 3

FGBU: Split of Approvals and Disapprovals by Therapeutic Areas (in Brackets Data Excluding Paediatric Protocols)									
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 Requests after the Initial Review	Non-critical Requests after the Initial Review, % of Total	Number of Critical Requests after the Initial Review	Critical Requests after the Initial Review, % of Total	Number of Disapprovals after the Initial Review	Number of Disapprovals after the Initial Review, % of Total
Oncology	52 (51)	45 (45)	86.5% (88.2%)	2 (1)	3.8% (2.0%)	4 (4)	7.7% (7.8%)	1 (1)	1.9% (2.0%)
Rheumatology	25 (22)	16 (14)	64.0% (63.6%)	3 (3)	12.0% (13.6%)	5 (4)	20.0% (18.2%)	1 (1)	4.0% (4.6%)
Gastroenterelogy	19 (18)	15 (15)	78.9% (83.3%)	0 (0)	0.0% (0.0%)	4 (3)	21.1% (16.7%)	0 (0)	0.0% (0.0%)
Haematology	19 (16)	14 (12)	73.7% (75.0%)	2 (2)	10.5% (12.5%)	3 (2)	15.8% (12.5%)	0 (0)	0.0% (0.0%)
Endocrinology	16 (13)	13 (11)	81.3% (84.6%)	0 (0)	0.0% (0.0%)	3 (2)	18.8% (15.4%)	0 (0)	0.0% (0.0%)
Cardiology and Cardiovascular diseases	15 (14)	8 (8)	53.3% (57.1%)	2 (2)	13.3% (14.3%)	5 (4)	33.3% (28.7%)	0 (0)	0.0% (0.0%)
Neurology	13 (13)	8 (8)	61.5% (61.5%)	1 (1)	7.7% (7.7%)	4 (4)	30.8% (30.8%)	0 (0)	0.0% (0.0%)
Pulmonology	13 (11)	7 (7)	53.8% (63.6%)	1 (1)	7.7% (9.1%)	5 (3)	38.5% (27.3%)	0 (0)	0.0% (0.0%)
Psychiatry	12 (10)	8 (7)	66.7% (70.0%)	0 (0)	0.0% (0.0%)	4 (3)	33.3% (30.0%)	0 (0)	0.0% (0.0%)
Dermatology and Immunology	10 (9)	9 (8)	90.0% (88.9%)	0 (0)	0.0% (0.0%)	1 (1)	10.0% (11.1%)	0 (0)	0.0% (0.0%)
Infectious diseases (except HIV/HCV/tuberculosis)	9 (6)	6 (4)	66.7% (66.7%)	0 (0)	0.0% (0.0%)	3 (2)	33.3% (33.3%)	0 (0)	0.0% (0.0%)
Urology	5 (4)	3 (3)	60.0% (75.0%)	1 (1)	20.0% (25.0%)	1 (0)	20.0% (0.0%)	0 (0)	0.0% (0.0%)
Obstetrics & Gynaecology	4 (4)	3	75.0%	0 (0)	0.0% (0.0%)	1 (1)	25.0%	0 (0)	0.0% (0.0%)
HIV/HCV/tuberculosis	4 (4)	4 (4)	100.0%	0 (0)	0.0% (0.0%)	0 (0)	0.0% (0.0%)	0 (0)	0.0% (0.0%)
Other	9 (8)	6 (5)	66.7% (62.5%)	2 (2)	22.2% (25.0%)	1 (1)	11.1% (12.5%)	0 (0)	0.0% (0.0%)
Total	225 (203)	165 (154)	73.3% (75.9%)	14 (13)	6.2% (6.4%)	44 (34)	19.6% (16.7%)	2 (2)	0.9% (1.0%)

Data from poll of ACTO members

Diagram 10



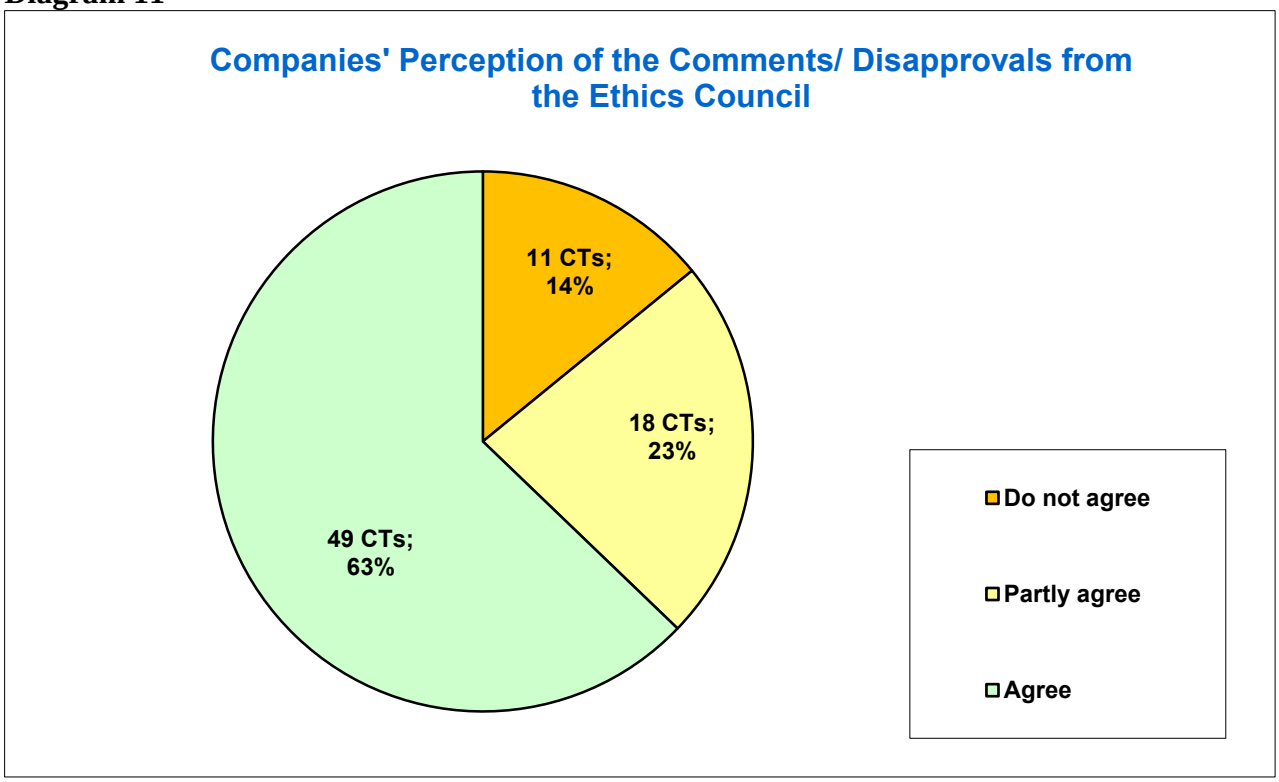
Data from poll of ACTO members

Still, in any case these data are much better than those we discussed a year earlier. It is to be recalled that at that time, the lowest rate of the protocols approved at the first attempt belonged to trials of drugs for infectious diseases, which was 16.7%, and the cumulative rate of critical requests and disapprovals in this area was 61.1%. In psychiatry, just 21.4% of protocols were approved without requests and 71.4% got critical requests and disapprovals.

***

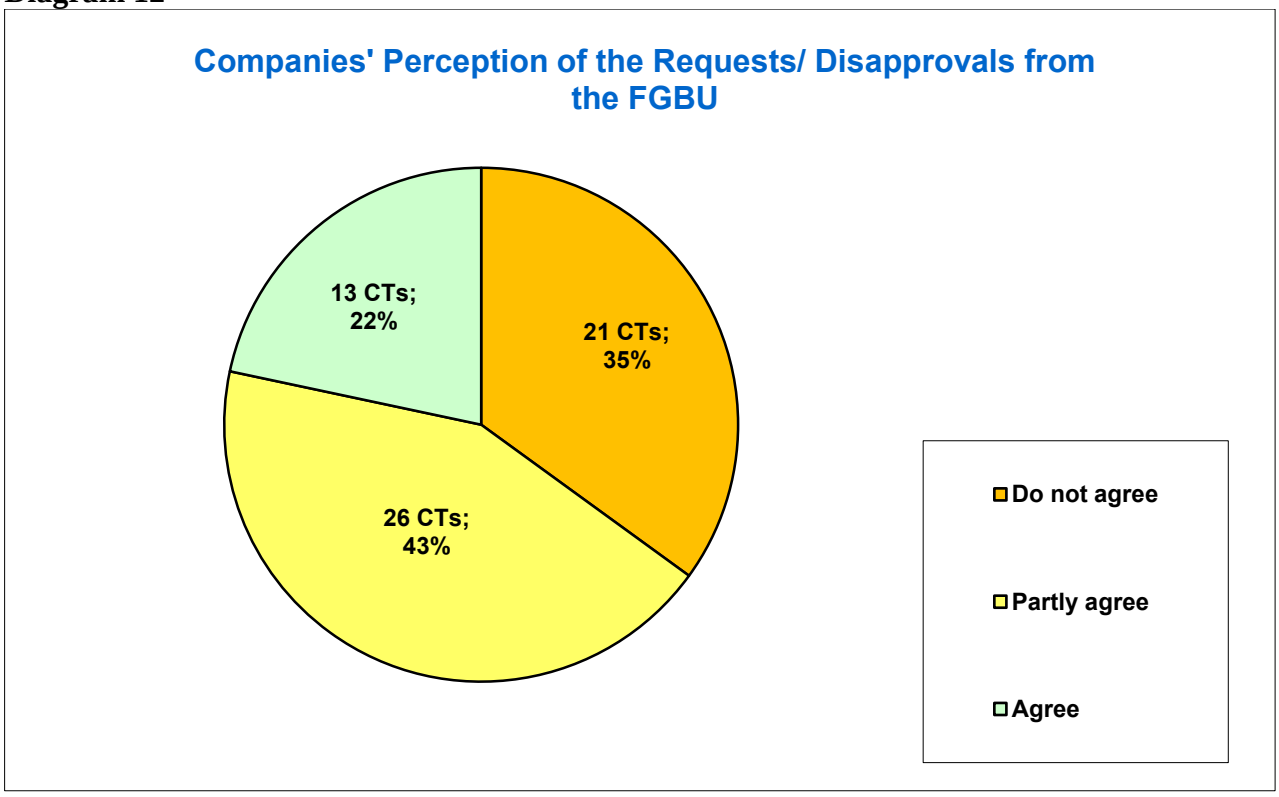
The following section of monitoring is devoted to an assessment by companies of the fairness of requests and comments issued by the expert organizations (Diagrams 11 and 12). The picture here is almost the same as a year earlier but with a certain trend towards growth of trust of applicants in the experts' positions. The share of agreements with the conclusions of the Ethics Council increased by 11 points in a year and reached 63%. On the contrary, the share of disagreements decreased from 18% to 14%, the rate of partial disagreement – from 30% to 23%. The situation with assessment of the FGBU's position given by companies is quite similar; apart from the fact that applicants' attitude to the FGBU examination is more critical that is conditioned by some objective background forming over the years. The share of cases when companies disagreed with position of the experts decreased from 37% to 35%. In 2014 it was almost 75%. On the contrary, the share of agreements increased from 9% to 22% since 2014. One can argue about the cause of growth in trust of applicant – objective improvement of examination quality or such situation is a sort of Stockholm syndrome when companies get used to typical remarks and consider them quite reasonable. But the fact remains – subjective assessment of fairness of expert comments given by applicants increases from year to year.

Diagram 11



Data from poll of ACTO members

Diagram 12



Data from poll of ACTO members

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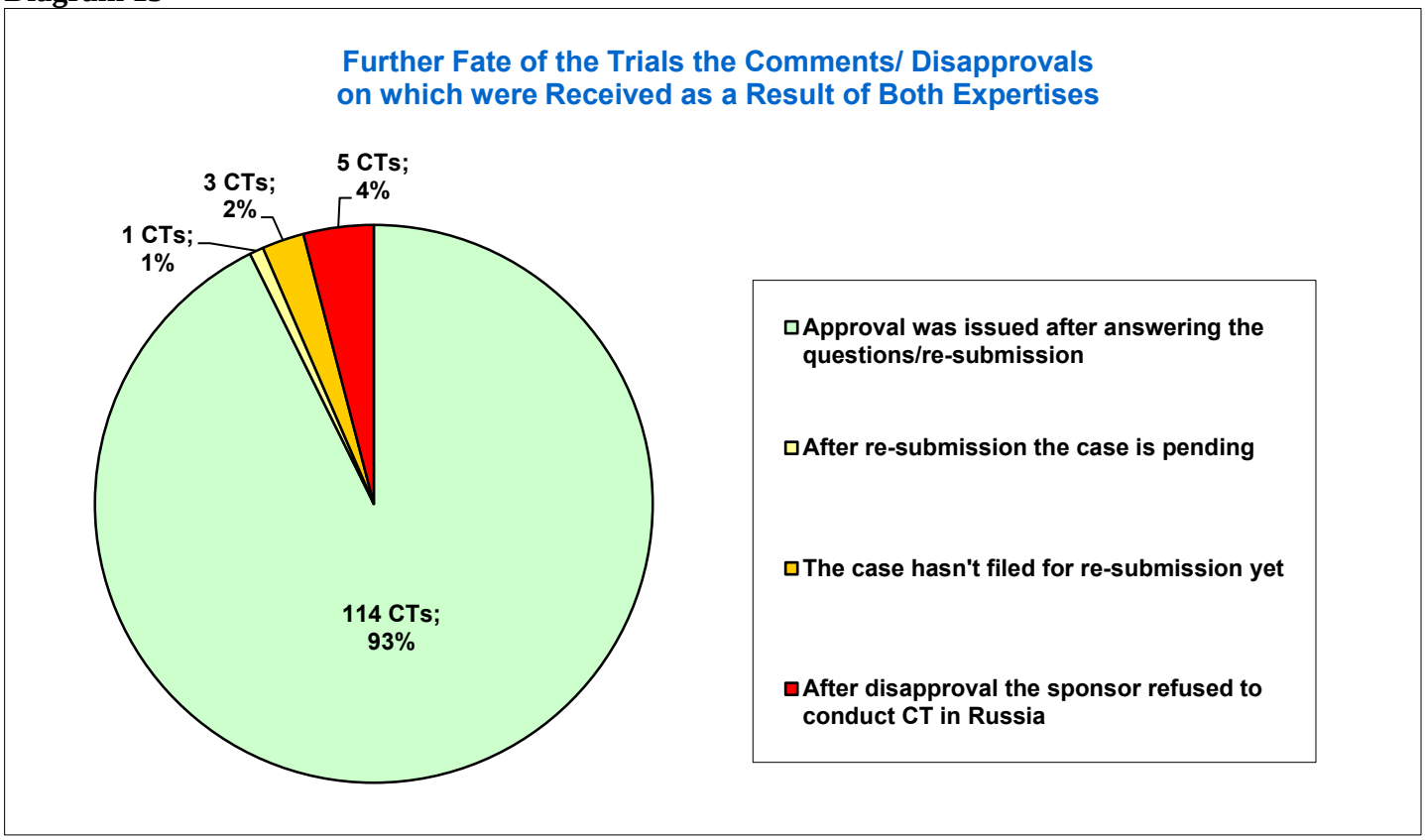
The last section of analysis is devoted to the future of trials that received requests or disapprovals. Diagram 13 shows that the overwhelming number of such trials finally got approval (93%). It is gratifying to see a decrease in the share of cases when sponsor refused from conducting the trial in Russia. According to the results of the current survey this share was 4% (5 trials), as compared to 5.4% (8 IMCTs) a year earlier, and more than 10% in the past.

Diagram 13



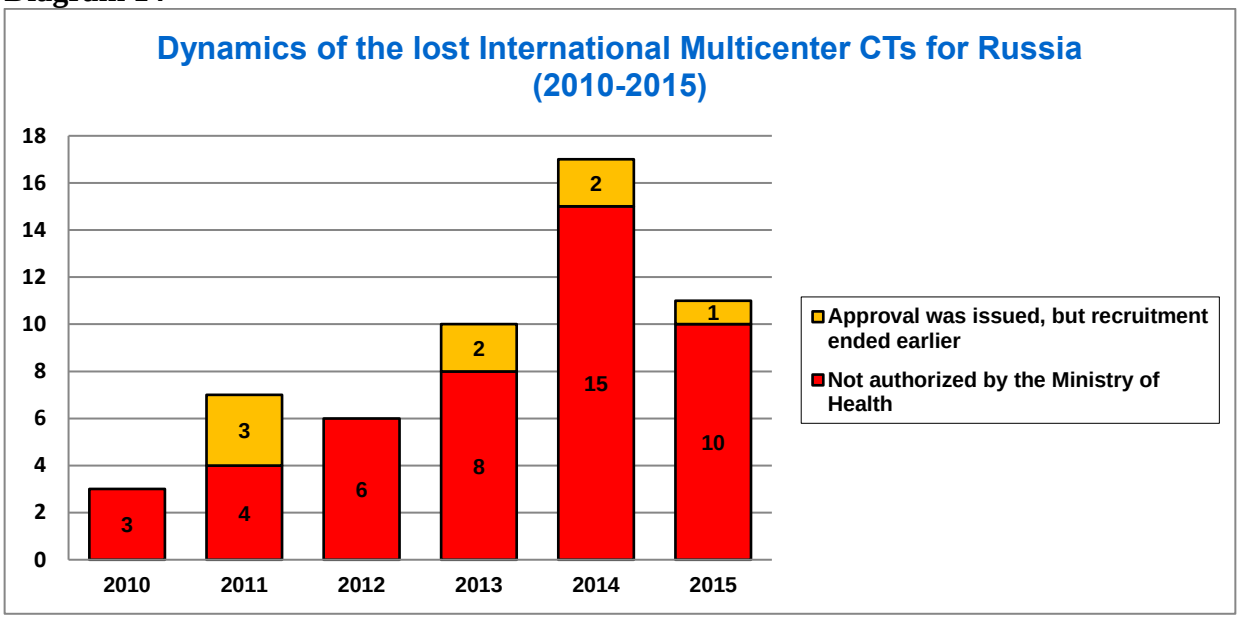
Data from poll of ACTO members

We would like to remind readers that statistics on loss obtained during this monitoring are not precise. First of all, they reflect the data on initial consideration of cases (this means it does not include cases when companies were forced to submit applications for several times). Additionally, it does not include cases when authorization was obtained but recruitment had been already completed. Besides, some of the outcomes of current cases are still unknown.

More precise statistics for international trials that never got round to conducting in Russia are reflected in a separate ACTO project, which is a database of IMCTs lost for Russia. This database contains information on trials name, the disease for which the investigational drug is used, and countries where the trial was initiated, instead of Russia. In summer 2017, these statistics were completed with data on applications submitted in 2015[1] The overall picture of the lost trials from 2010 till 2015 is shown on Diagram 14.

[1] More subsequent data are not included in the open part of database as statistics on such data is not completed - for some trials the outcome remains unknown, and some of them are still under examination.

Diagram 14



Data from poll of ACTO members

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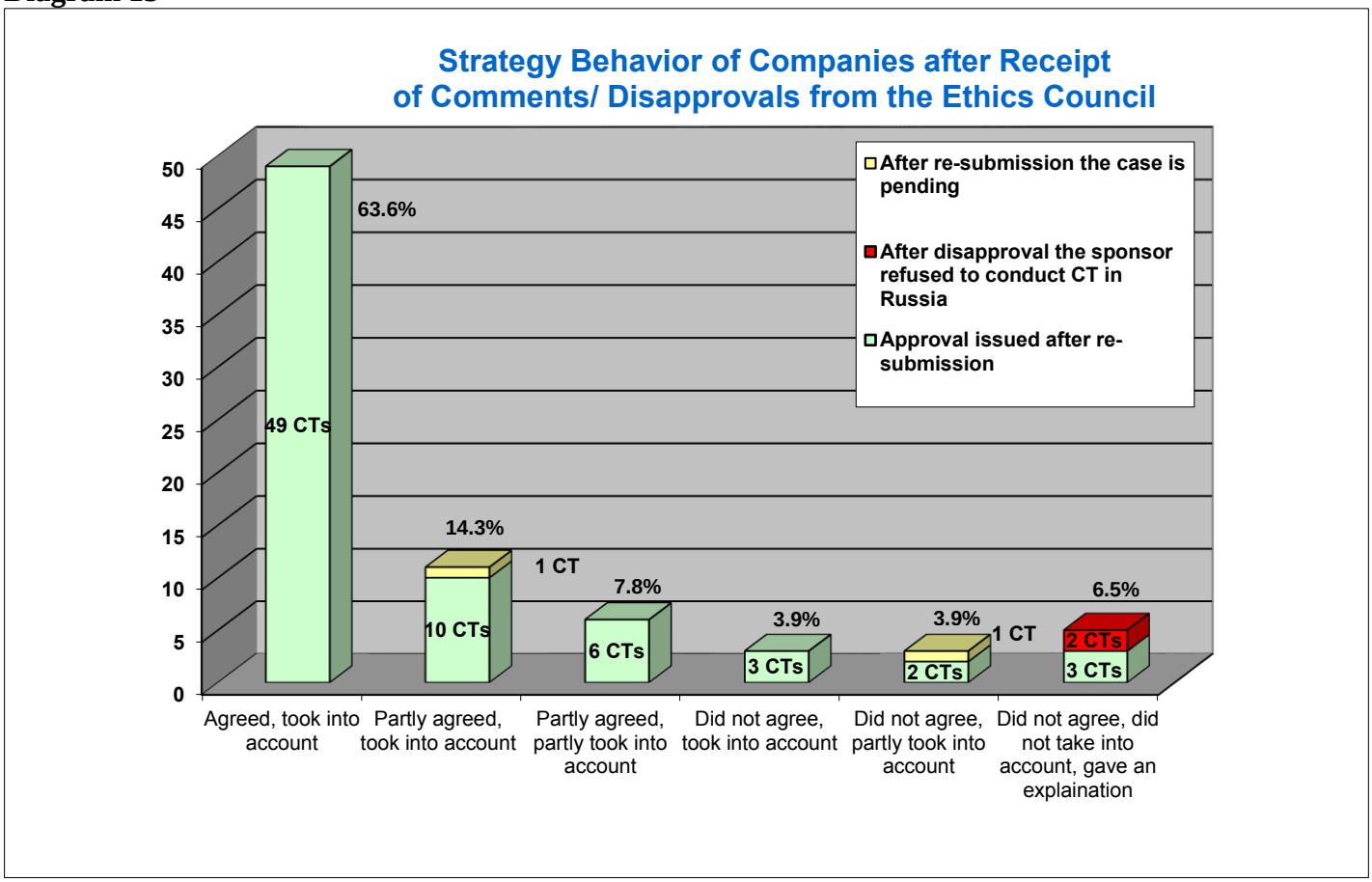
Diagrams 15 and 16 show the relationship between company's strategy for further actions in the event of obtaining request or disapproval and the final outcome of file examination for some types of expertise. It is apparent which line is usually chosen by companies in case of obtaining requests/disapprovals from expert organizations.

A variant 'agreed, taken into account' is the leading one for the Ethics Council – 63.6%. Tactics in the FGBU have changed a little bit. Whereas in recent years, companies were forced to choose the variant 'not agreed, not taken into account', the current survey shows that the most common tactics is now 'partially agreed' (25.4%). The strategy of disagreement and non-admission of the FGBU decision takes second place, 20.3% vs. 25.5% a year earlier. Possibly, this difference is not so significant, but it shows a shift to the better that happened in the FGBU during the last year.

The given diagrams show as well, in what expert organization was arisen the problem which led to the loss of the trial. Two trials were lost due to disapprovals obtained from the Ethics Council. One of them, in psychiatry, has already been mentioned: the Ministry of Health restricted the Ethic Council in its right to make requests. The reason why the Ethics Council did not approve conduction of the trial was not so critical and the company could have solved the issue by responding to comments. But due to the necessity put in a new application, the sponsor decided not to include Russian centers in the trial, especially recruitment in other countries went well. The second trial rejected by the Ethics Council concerned a drug for treatment of paediatric infectious diseases. This trial received the critical request from the FGBU as well. After receiving disapproval from the Ethics Council the sponsor did not answer the request of the FGBU, and the trial was lost.

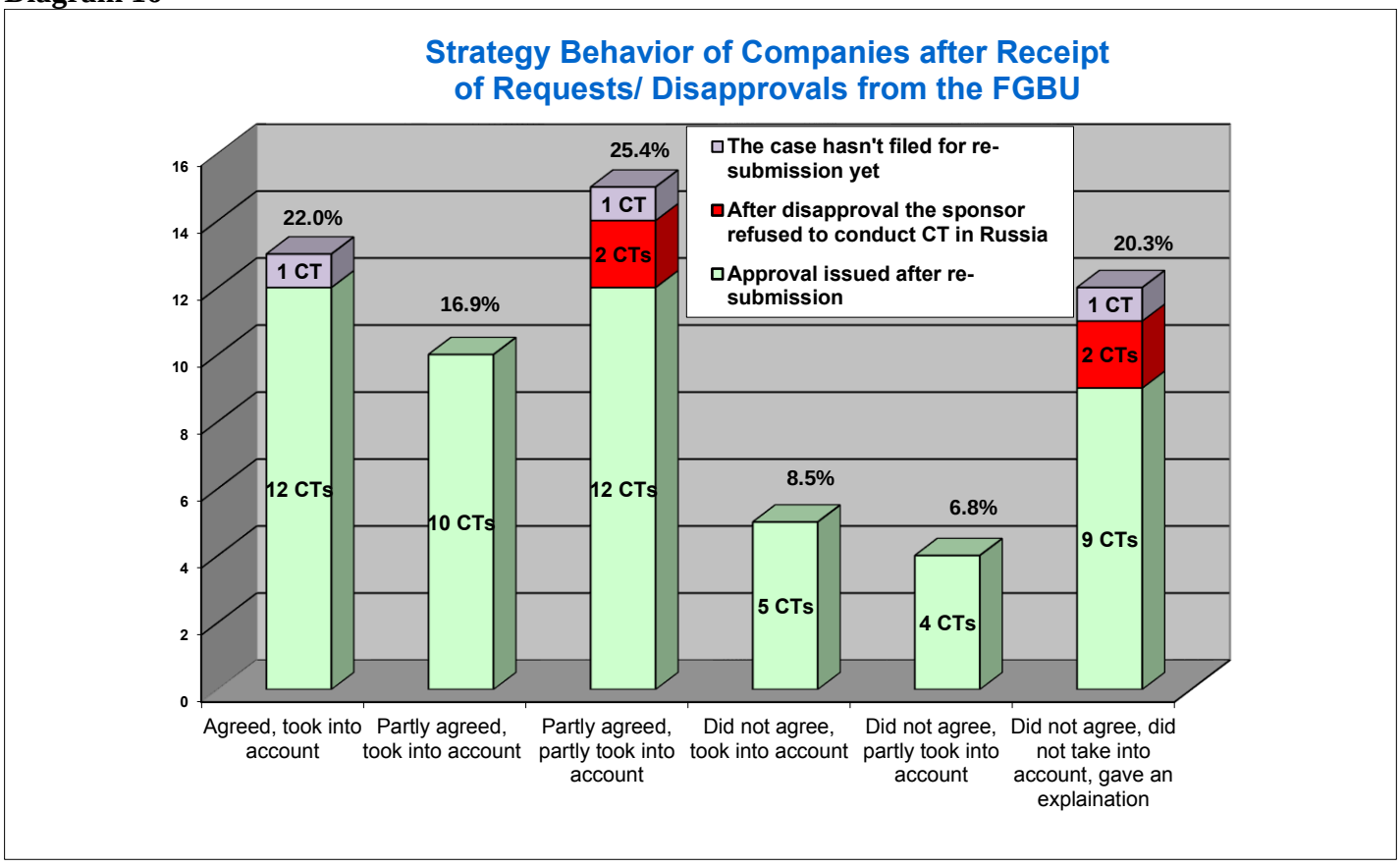
Three trials that met failure subsequent to the results of the FGBU examination were in oncology, rheumatology and dermatology.

Diagram 15



Data from poll of ACTO members

Diagram 16



Data from poll of ACTO members

QUALITY OF CLINICAL TRIALS: RESULTS OF INSPECTIONS BY REGULATORY BODIES

Results of FDA inspections

Two years ago we covered the results of FDA inspections in different countries (*see Newsletter № 11*). Since then data in Russia were replenished with four new inspections, and the number of examinations changed in other countries as well.

In order to better understand the data given (Table 4) let us recall the FDA's classification:

NAI (No Action Indicated) – no objectionable conditions or practices were found during the inspection;
VAI (Voluntary Action Indicated) – objectionable conditions were found but the problems do not justify further regulatory action. Any corrective action is left to the investigator to take voluntary;
OAI (Official Action Indicated) – objectionable conditions were found and regulatory and/or administrative sanctions by FDA are indicated.

It is worth recalling as well that for a more correct assessment of data in the table it is necessary to consider the total amount of inspections in a particular country. The more inspections that are included, the more precise the picture of trials quality is.

Periodically, western publications show distrust and doubt towards the quality of data from Russian centers. This is complicated to oppose – it requires consideration of particular cases and a check of violations, if there were any, and their reasons. Results obtained from FDA is considered to be quite objective (hardly can inspectors of American regulatory body be suspected of excessive loyalty towards Russian investigators). The statistics are such that among other European countries Russia turned out in first place in the share of inspections resulted in NAI (67.3%). Undoubtedly, this picture is spoiled by one case with an OAI result that took place in 2006. Though, it can be mentioned that this case served as a lesson for the whole IMCT industry in Russia.

Table 4

Comparative Table of the Results of US FDA Inspections, 1995 – 1st Half of 2017							
Country	**Total number of FDA Inspections with results 1995 – 1st Half of 2017**	**NAI**	**NAI, % of Total**	**VAI**	**VAI, % of Total**	**OAI**	**OAI, % of Total**
North America							
Canada	**187**	**92**	**49.2%**	**94**	**50.3%**	**1**	**0.5%**
USA	**6070**	**2783**	**45.8%**	**3014**	**49.7%**	**273**	**4.5%**
Mexico	**26**	**9**	**34.6%**	**17**	**65.4%**	**0**	**0.0%**
South America							
Chile	**14**	**9**	**64.3%**	**5**	**35.7%**	**0**	**0.0%**
Argentina	**58**	**37**	**63.8%**	**20**	**34.5%**	**1**	**1.7%**
Brazil	**54**	**30**	**55.6%**	**24**	**44.4%**	**0**	**0.0%**
Peru	**11**	**5**	**45.5%**	**4**	**36.4%**	**2**	**18.2%**
Australia	**23**	**14**	**60.9%**	**9**	**39.1%**	**0**	**0.0%**
Africa							
South Africa	**57**	**30**	**52.6%**	**26**	**45.6%**	**1**	**1.8%**
Asia							
Taiwan	**14**	**12**	**85.7%**	**2**	**14.3%**	**0**	**0.0%**

Japan	**19**	**15**	**78.9%**	**4**	**21.1%**	**0**	**0.0%**
Israel	**11**	**8**	**72.7%**	**3**	**27.3%**	**0**	**0.0%**
India	**61**	**38**	**62.3%**	**21**	**34.4%**	**2**	**3.3%**
South Korea	**23**	**12**	**52.2%**	**11**	**47.8%**	**0**	**0.0%**
Thailand	**15**	**7**	**46.7%**	**8**	**53.3%**	**0**	**0.0%**
China	**29**	**12**	**41.4%**	**16**	**55.2%**	**1**	**3.4%**
Turkey	**8**	**2**	**25.0%**	**5**	**62.5%**	**1**	**12.5%**
Europe							
Russia	**104**	**70**	**67.3%**	**33**	**31.7%**	**1**	**1.0%**
Poland	**126**	**82**	**65.1%**	**44**	**34.9%**	**0**	**0.0%**
Ukraine	**27**	**17**	**63.0%**	**10**	**37.0%**	**0**	**0.0%**
Finland	**16**	**10**	**62.5%**	**5**	**31.3%**	**1**	**6.3%**
Czech Republic	**40**	**23**	**57.5%**	**17**	**42.5%**	**0**	**0.0%**
Hungary	**42**	**24**	**57.1%**	**18**	**42.9%**	**0**	**0.0%**
Italy	**78**	**44**	**56.4%**	**31**	**39.7%**	**3**	**3.8%**
Spain	**47**	**26**	**55.3%**	**19**	**40.4%**	**2**	**4.3%**
Belgium	**41**	**22**	**53.7%**	**16**	**39.0%**	**3**	**7.3%**
Denmark	**21**	**11**	**52.4%**	**10**	**47.6%**	**0**	**0.0%**
Germany	**121**	**59**	**48.8%**	**61**	**50.4%**	**1**	**0.8%**
Sweden	**23**	**10**	**43.5%**	**13**	**56.5%**	**0**	**0.0%**
France	**96**	**38**	**39.6%**	**57**	**59.4%**	**1**	**1.0%**
Netherlands	**38**	**15**	**39.5%**	**21**	**55.3%**	**2**	**5.3%**
United Kingdom	**104**	**35**	**33.7%**	**67**	**64.4%**	**2**	**1.9%**
Austria	**17**	**5**	**29.4%**	**12**	**70.6%**	**0**	**0.0%**

Data from https://www.accessdata.fda.gov/scripts/cder/cliil/index.cfm

Results of Roszdravnadzor inspections

In term of analysis of inspections by Roszdravnadzor, the following should be mentioned. In contrast to the previous years when annual data were summarized (the second half of the previous year and the first half of the analyzed one), this time we are confined by information received in the second half of 2016.

This is explained in the following way: from the beginning of 2017 Roszdravnadzor significantly changed the procedure for provision of information subsequent to the results of the inspections conducted. Prior to that, all necessary data were published quarterly on Roszdravnadzor's website. The summary table showed quite complete information about monitoring and controlling measures conducted, including the name of inspected subjects, the name of the clinical trial protocol, the names of investigators and most important – violations revealed. From the beginning of the year the situation changed significantly: now the data published are poor (name of inspected subject, type of inspection, date and number of inspection order). In addition to this, whereas previously the main website of Roszdravnadzor showed summarized data on activity of the Central Office and Territorial Bodies, now it reflects only inspections conducted by the Central Office. The results of inspections by territorial bodies have to be looked for on their websites. There is no comprehensive information except the fact that a particular hospital was inspected within a specified period and some violations were revealed (they remain unknown); such data cannot be obtained from the Roszdravnadzor's website now.

The rest of the information necessary for analysis can be found on website of the General Prosecutor Office of the Russian Federation via the search option. Still, it takes a great deal of time. One must find the organization that have been inspected, then the inspection he is interested in, and only then can one obtain information about inspection in a separate window. But an unprepared person could hardly find what he needs – there can be no information about the trial's protocol or name of the investigator, the violation might be described in an incorrect way, only with specification of number of violated paragraph of regulatory act. Taking into account that paragraphs can include several norms at a time, it is not always easy to understand what a concise violation was. It is not clear yet how one can obtain and process information about inspections by Roszdravnadzor efficiently. The monitoring method needs a substantial change. But now we are confined to the results for the second half of 2016.

During this period Roszdravnadzor carried out scheduled on-site inspections at 52 medical organizations (Table 5), in 8 of them no clinical trials were conducted. A total of 76 clinical trials were inspected under the supervision of 66 principal investigators.

Along with medical centers a planned inspection was conducted in one contract research organization, RCT–Global. Two trials have been inspected in this organization: sponsored by Marinus Pharmaceuticals and Octapharma. During inspection by Roszdravnadzor the following violations were revealed: '*in agreements between RCT–Global and the clinical sites that conducted clinical trials the following information is missing: form for provision of trial results to an authorized body; documents for laboratory equipment used during the trial, as well as CV of the laboratory head. Absence of such information means than the monitor exercised insufficient control over the laboratory that participated in clinical trial conduction*'. There were no planned inspections of clinical trials sponsors during this period of time.

Table 5

Statistics on inspections by Roszdravnadzor of the activities of conducting clinical trials, 2nd half of 2016						
Type of inspection	**The number of medical centers inspected**	**The number of principal investigators whose work was inspected**	**The number of clinical trials inspected**		**The number of sponsors inspected/ clinical trials inspected**	**The number of CROs inspected/ clinical trials inspected**
Planned on-site inspections	**52 (in eight is not conducted)**	**66**	**76**		**–**	**1/2**
Unplanned on-site inspections to ensure compliance with previously issued orders	**2**	**3**	**4**		**–**	**–**
Unplanned documentary inspection to ensure compliance with previously issued orders	**32**	**50**	**58**		**1/1**	**–**
Unplanned on-site (complaint-based) inspection	**4 (in one is not conducted)**	**2**	**2**		**–**	**–**
Unplanned documentary (complaint-based) inspection	**–**	**–**	**–**		**1/1**	**–**

Data from www.roszdravnadzor.ru

Documentary inspection prevails over other types when it comes to control over previously-issued instructions. During the analyzed period the number of such inspections was far more than the number of on-site ones that were conducted to control instructions issued earlier (32 vs. 2 clinical centers and one for sponsoring company Petrovax Pharm). Subsequent to the results of one repeat inspection (inspected organization – the State Budgetary Institution of Healthcare City Clinical Hospital named after A.Eramishantsev of the Department of Healthcare of Moscow) it was established that the previously revealed violations were corrected just partially. As far as other inspections are concerned, all violations were acknowledged corrected.

During the period specified Roszdravnadzor conducted four on-site inspections of medical organizations; in one case a medical organization did not conduct clinical trials. Sanofi Aventis Group was a complainant in relation to two centers (State Budgetary Institution of Healthcare No. 40 of the Department of Healthcare of Moscow and Moscow State University of Medicine and Dentistry named after A.I. Evdokimov). Inspection of the first organization revealed no violations; during inspection of the second one some administrative violations were documented, violations of procedure for provision of new informed consent form to study participants, as well as comments in relation to documentation of clinical trial. The fourth organization that was subject to inspection was the Federal Budgetary Institution of Healthcare St. Petersburg Clinical Research and Practical Center of special types of medical assistance (oncology). The following violation was revealed: a patient signed an earlier version of an informed consent form as compared to the form approved at that moment.

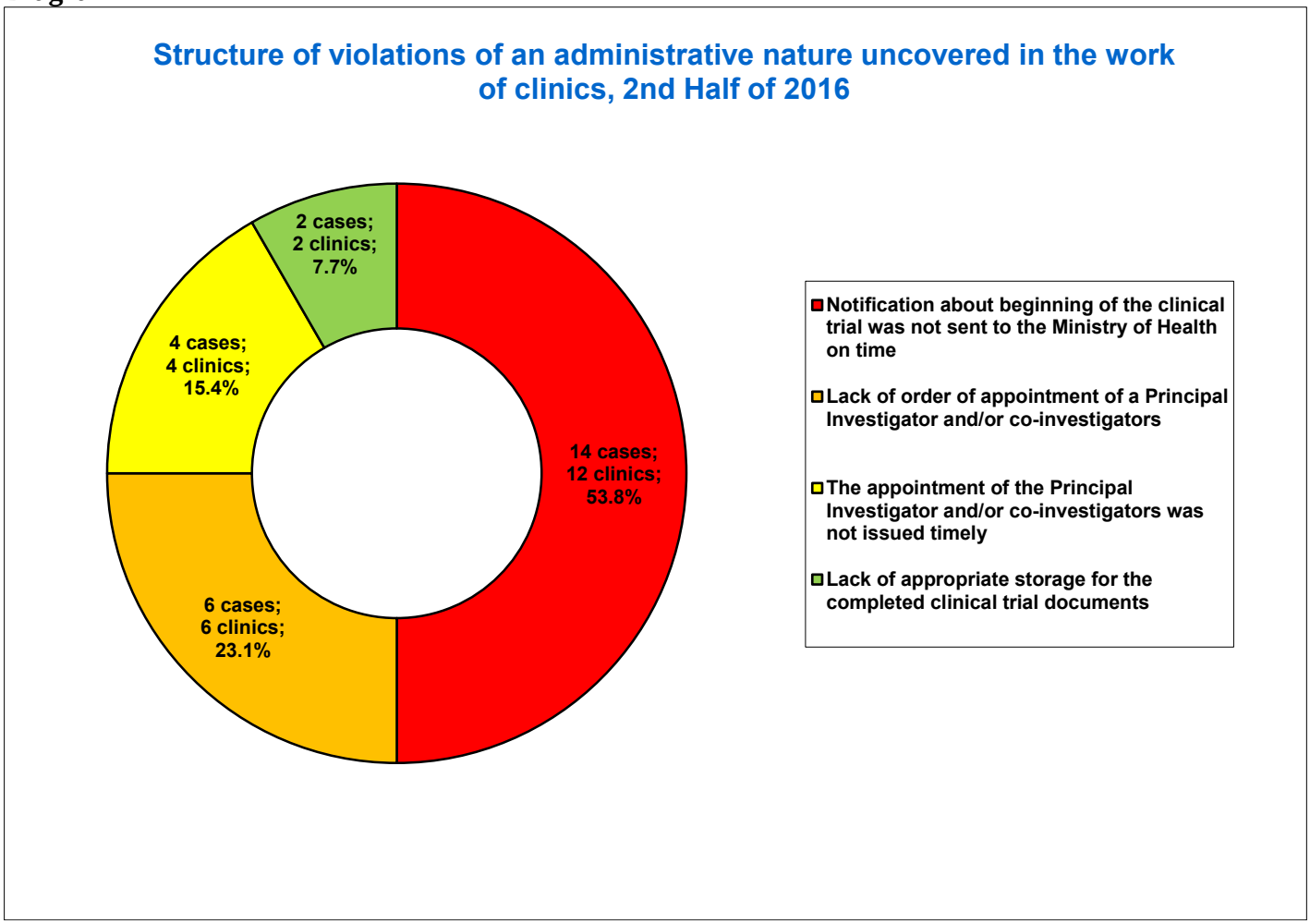
Documentary inspections in regards to complaints among other medical organizations were not conducted; such inspection was conducted in respect of Genfa LLC, a clinical trial sponsor; the inspection was initiated after inquiry of Selgen Company and after receipt of documents from RegExpert LLC. No violations were revealed subsequent to the results of inspection.

***

The following is a classification of violations revealed by Roszdravnadzor during scheduled inspections. Taking into consideration the experience we possess, we traditionally divide violations into three groups: violations that are in the responsibility of medical organizations (more of an administrative character), violations in activity of the local Ethic Committees (LEC), and violations connected with activities of Principal Investigators.

Violations that are in responsibility of clinics are provided in Diagram 17. In 24 inspected organizations out of 44 administrative violations were revealed (in 54.5% of total number of institutions). It is worth recalling that these violations mainly concern formal legal requirements and have no influence on quality of data and safety of study participants.

Diagram 17



Data from www.roszdravnadzor.ru

As in the previous period, the most common documented violation in this group was absence of notification about beginning of the clinical trial sent to the Ministry of Health of Russia – 14 cases (53.8%). The second common group of violations is lack of order from Chief Physician about appointment of Principal Investigator or co-investigators – 6 cases (23.1%). The third group of violations is untimely appointment of Principal Investigator and co-investigators – 4 cases (15.4%). The last in incidence was violations that we have never documented: when medical organization fails to provide proper storage of completed clinical trials documents – 2 cases (7.7%). Previously Russian legislation did not clearly specify storage conditions for documents of completed and uncompleted clinical trials. Today rules of the Good Clinical Practice approved by the Order of the Ministry of Health of Russia under No. 200n, have a separate paragraph devoted to storage of documents on completed trials. We considered it reasonable to classify this violation as connected to medical organization as Roszdravnadzor gives no information about certain trials and investigators to whom violations in storage conditions of documentation completed trials concerns.

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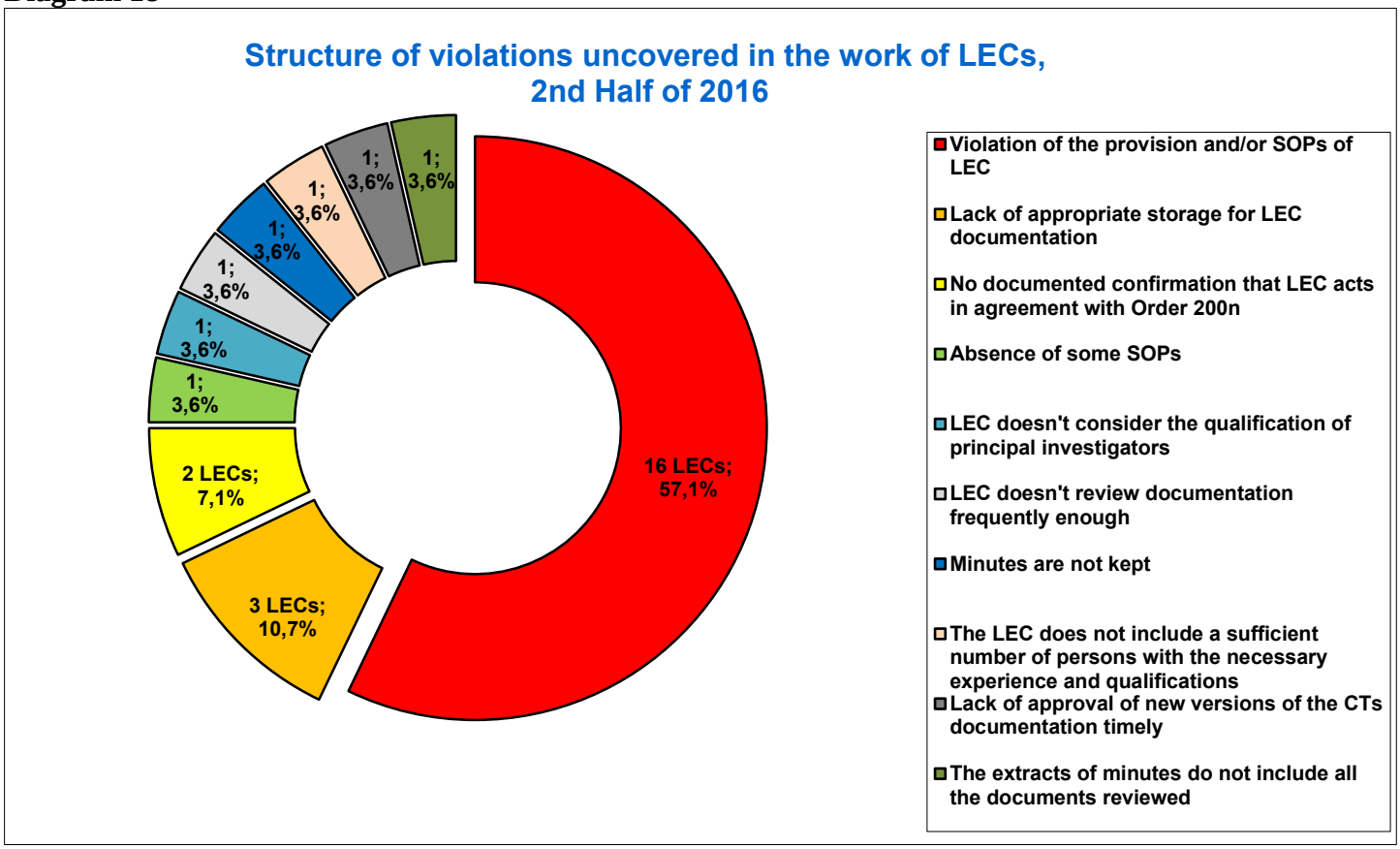
Further, violations by LECs are given consideration. Among 44 inspected medical organizations such violations were documented in the activity of 25 committees (it remains unknown whether all organizations had a LEC). We will not dwell upon the structure of violations as they are clearly described in Diagram 18. It is worth mentioning that the greatest rate belongs to violations of LEC provisions or SOPs – 57.1% vs. 36.7% in previous analyzed period.

Diagram 18



Data from www.roszdravnadzor.ru

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Finally, we would like to give consideration to the last group of violations that directly concern conduction of clinical trials and responsibility of Principal Investigators. All violations revealed are given in Table 6.

Table 6

Violations discovered in the course of inspections of clinical trials, 2d half of 2016			
Type of finding		**IMCTs**	**Local clinical trials**
Obtaining informed consent, patient rights			
	No documented confirmation of providing the patient with new ICF	**1**	**–**
	Non-compliance with the procedure of obtaining informed consent	**–**	**1**
CT documentation management			
	Data in the Case Report Forms was not consistent with data in the source medical documentation	**–**	**1**
	Accurate corrections to patients' CRFs were not made	**–**	**1**
	Lack of appropriate storage of clinical trial's documents/guard against accidental destruction	**1**	**3**
	There is no clear management, accuracy, completeness and reliability of the clinical trial documentation	**1**	**2**
Deviations from protocol			
	Deviations from the protocol	**2***	**1**
	Violations of patient inclusion criteria	**–**	**1**
Approval/accompaning by local ethics committee (LEC)			
	Lack of provision of an immediate written report to LEC on all changes that have a significant impact on the conduct of the study and/or increases the risk to the subjects	**–**	**1**
	Non-compliance with existing regulatory requirements on safety expedited reports to LEC	**2***	**–**
	New versions of the CTs documentation were incorporated without the previous approval from the Ethics Council of the Ministry of Health of Russia	**1**	**–**
Administrative matters			
	The participation of PI with the appropriate qualifications was not provided	**–**	**1**
	Persons who are not employees of a medical institution attracted to perform procedures within the clinical trial	**–**	**1**
Total		**9**	**13**

Source: www.roszdravnadzor.ru

*Violation is documented but comments have no legal basis.

As one can see from the table, several violations are marked with an asterisk with corresponding comments about the fact that the criticism given by the inspection body has no legal basis. This entails one and the same inspection when two IMCTs were examined and were given the above-mentioned remarks.

It happened so that we encountered instruction on this inspection (inspection of Gatchina Clinical Inter-regional Hospital by territorial body of Roszdravnadzor in St. Petersburg and Leningrad region). ACTO previously came across peculiarities in collaboration with this regional body. However, this case can be called indignant in terms of ignorance of inspectors. The inspection made three distortions of current legislation in one statement. So, the clinic was blamed on the following violation: '*failure to provide notification about adverse events to the Ministry of Health of the Russian Federation and to the Ethics Committee within 24 hours (p. 9.6 of the Order No. 266 dd June 19, 2003*[2]*)'*. We would like to dwell upon the confusion between the notions 'event' and 'reaction' in more detail in the following section hereof where the above-mentioned case is also described. Besides the fact that inspectors of territorial body confuse terminology, it turned out that they do not know that pharmacovigilance responsibilities belong to Roszdravnadzor, but not to the Ministry of Health of Russia. It is Roszdravnadzor that should be notified about safety issues. But not within 24 hours. It remains

[2] Paragraph 9.6 to the out-of-date Order of the Ministry of Health of Russia dd June 19, 2003 No. 266 had the following content: 'Investigator must follow the current regulatory requirements on provision of reports on serious unexpected side-effects to the authorities and the Ethics Committee'.

unknown what regulatory act served as the basis for inspectors to set such reporting terms. Still, we are eager to understand this strange inspection. With this aim we made inquiry to Roszdravnadzor.

Taken as a whole it is worth underlining that the examples similar to the above-mentioned give us a view on statistics of activity of regulatory and supervisory authority from another angle. Taking into consideration the difficulty in obtaining official information that occurred from the beginning of 2017, we cannot exclude that one would need to gather such information directly in inspection subjects. Possibly it will allow opening new sides of this topic.

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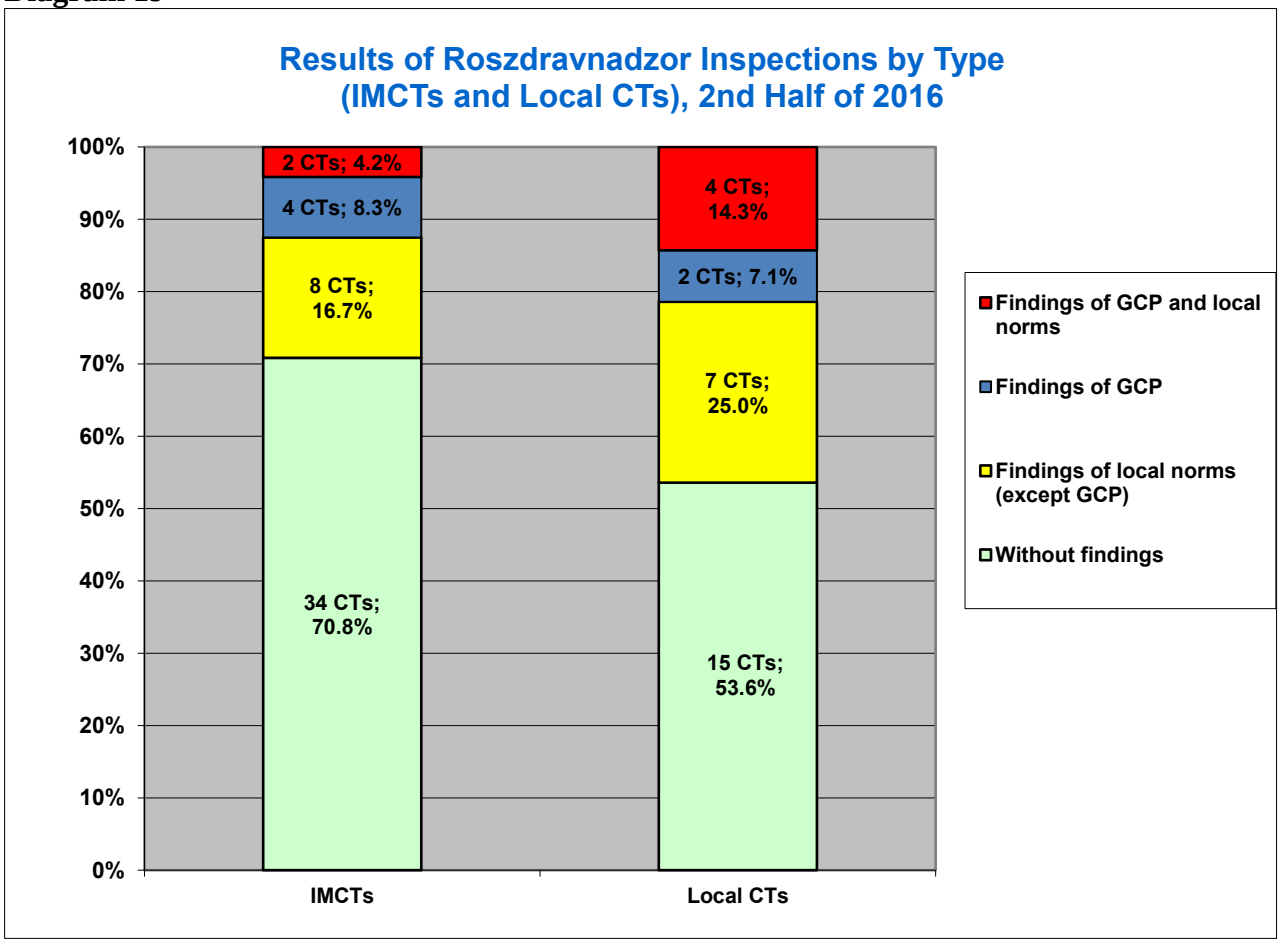
Diagram 19 provides inspection results depending from types of clinical trials: international and local ones (including bio-equivalence studies). The total of 76 clinical trials were examined by Roszdravnadzor. There were 48 (63.3%) IMCTs and 28 (36.7%) local trials.

These figures include two of the three above-mentioned groups – administrative violations and violations that concern trial procedure (violations from LEC's side are excluded) that are divided into three categories: violations concerning GCP, violations of local requirements and violations of both.

The share of international trials examination of those revealed no violations exceeds that of local trials (70.8% vs. 53.6%). Also we would like to mention that as in previous periods, we can trace an apparent domination of IMCTs inspections over that of local trials.

Diagram 19



Source: www.roszdravnadzor.ru

ADVERSE EVENTS VS. ADVERSE REACTIONS: DANGEROUSLY SIMILAR TERMS

ACTO became aware that in autumn 2016, Gatchina Inter-district Hospital received instruction from Territorial Body of Roszdravnadzor[3] to inform the regulatory body and the Ethics Committee about serious adverse events documented in the course of a clinical trial within a 24-hour period. The watchdog considered the absence of such notifications a violation[4], and quarterly reports about adverse events to be insufficient.

This routine incident in communication between a medical organization and the regulatory authority would not have far-reaching repercussions and would not deserve discussion if it was not a marker of a bigger issue. The Territorial Body of Roszdravnadzor's instruction to the Gatchina hospital is based on terminological confusion that has already lead to legal proceeding (in 2016) and even to suspension of international clinical trial (in 2009).

The case connected with legal proceeding was discussed by ACTO in detail in Newsletter № 13 for the first half of 2016. Let us recall the chronology of that case. In Autumn 2015 a scheduled inspection conducted by Roszdravnadzor at the Nefros medical center resulted in a protocol about administrative violations. Inspectors paid attention to two reports about serious adverse events presented by the investigator to the Ethics Committee. However, the medical center was blamed for the failure to provide timely data about serious adverse reactions but not event to the territorial body of Roszdravnadzor. Nefros was obliged to pay 30 000 rubles as penalty, but it preferred to initiate a proceeding. On April 25, 2016, the Court of Arbitration of Krasnodar region agreed with opinion of Roszdravnadzor and confirmed the fact of administrative violation. The medical center appealed the judgment. On August 8, 2016 the Fifteenth Arbitration Court of Appeal in Rostov-on-Don rejected the decision of the court of the first instance. The judicial board came to the conclusion that during the first session, notions of adverse events and adverse reactions were confused. Therefore, Nefros did not violate the requirements of Russian legislation.

The key difference between the two notions is that they refer to different stages of processing information gathered during a clinical trial. The standard procedure is the following: the investigator provides the sponsor with reports about all adverse events connected to the health status of study participants (complaints about weakness, hospitalization cases, safety incidents and other), and suggests whether medicinal product administration could have been the cause. It is only a suggestion as modern clinical trial design uses double-blinded method when neither investigator, nor trial subject, nor those who monitor trial process (and sometimes even those process data) know whether a particular participant receives investigational product or comparator drug (for example, placebo). The investigator can make suggestions about causal relationships between an event and drug administration, but he/she does not possess the complete information to make a final conclusion about such relationship.

The sponsor accumulates and analyzes information from different clinical trials protocols and different research centers, and then estimates the case from his/her perspective. Those with confirmed possible relationship with investigational product administration get the status of adverse reaction. The following does not refer to adverse reactions: adverse events with proved casualty (correlation with drug administration is absent). This criterion means the possibility of causal relationships between drug administration and events that are adverse from medical perspective and can be used for differentiation adverse reactions and adverse events in ICH GCP.

[3] Instruction of Territorial Body of Roszdravnadzor in St. Petersburg and Leningrad region No. 78-738/16 dd. September 28, 2016

[4] Namely, by violation of Paragraph 9.6 of the Order of the Ministry of Health of Russia No 266, dd June 19, 2003: 'Investigator must follow the current regulatory requirements on provision of reports on serious unexpected side-effects to the authorities and the Ethics Committee'.

Adverse drug reactions (in case of pre-approval clinical use) are all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase responses to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. <…> any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

The difference between the notions based on this criterion means that prior to a sponsor's assessment of a serious adverse event, medical institutions have no information about whether a particular case should be reported to regulatory authorities. That is why responsibility for timely provision of information about adverse reactions can lie (and lies[5]) with sponsor. Neither Russian, nor International, legislative acts contain requirements for investigators to provide regulatory bodies and Local Ethics Committees with expedited reports on adverse events. Only sponsors receive them. This does not mean that information about adverse events remains closed. Such information is provided in the aggregate form of periodical safety reports but without expedition. Information exchange itself poses no problem until confusion of notions appears. And it appears.

In the case that took place in Krasnodar, adverse events in Nefros reports that caused anxiety in inspectors referred to a patient who took comparator drug. The trial participant was hospitalized twice due to various causes; the patient did not take the investigational product so it could not be the reason for hospitalization[6]. If the procedure of information exchange and processing worked without fail (including those caused by misunderstanding), the case would have never made it to court.

Such communicative failure can be called traditional; in 2009 international trial of influenza vaccine had the same confusion. The sponsor considered it reasonable to provide data on adverse events to regulatory authorities, though the law has no such requirements. Officers decided to terminate the trial without trying to see the difference in terminology. Then the clinical trial was successfully accomplished after dialogue between interested parties. But today such scenario cannot be excluded minimum on the local level.

When the Nefros medical center was accused of failure to provide data on adverse reactions, ACTO specified that such incident bears risk for the whole system of conducting international trials. If a requirement to inform a Territorial Body of Roszdravnadzor about adverse events was acknowledged as legal in Krasnodar, it could have lead sponsors and CROs to unexpected actions up to leaving the region. ACTO carefully monitored Nefros's file and noted in it the following poll: if similar practice spreads over other regions, the consequences for the market of clinical trials will be unforeseen. The appellate decision in the Nefros case in August 2016 gave grounds for optimism, still as regulation in Gatchina hospital in September 2016 shows – such optimism was too early. Confusion of such notions as adverse events and adverse reactions are common not only in the Krasnodar region. This means that the legal environment for clinical trials remains unstable.

As far as the case in Gatchina hospital in September 2017 is concerned, ACTO sent a letter to Roszdravnadzor in St. Petersburg and Leningrad region to ask them to clarify to inspectors the difference between adverse events and adverse reactions, as well as the procedure of providing safety information.

Here we would like to mention one more initiative from the Association. In May 2017, ACTO published an open letter, addressed to local Ethics Committees (LEC) and Principal Investigators. In this letter

[5] Order of Roszdravnadzor dd February 15, 2017 No. 1071 'On Approval of Procedure for Pharmacovigilance'.

[6] During the second session the court heard medical expert that showed that hospitalization in the first case was caused by viruses and bacteria, and in the second - hereditary disease. Hospitalization was caused neither by administration of the investigational product nor by administration of any other drug.

the Association asked LEC to assess if the requirements to provide expedited reporting about adverse events introduced by the Committees in SOPs were reasonable. The association asked Clinical Investigators to provide LEC only with those safety data that are required by the Russian legislation. Three LECs responded to the letter: the Independent Multidisciplinary Committee on Ethical Review of Clinical Trials, the Inter-university Committee on Ethics and LEC of Bekhterev St. Petersburg Scientific and Research Institute of Psychoneurology. These institutions have already introduced changes into their SOPs.

ACTO plans to continue discussion of the issue and involve those Ethics Committees that preserve the requirement of expedited reporting about adverse events in their SOPs. Herewith, the organization remains open to discussion with other interested parties.