ACTO

ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

ACTO NEWSLETTER № 13

1st Half of 2016

MOSCOW 2016

CONTENTS

SUMMARY

The Newsletter starts with statistics for H1 2016. During this period the Russian Ministry of Healthcare issued 450 approvals to conduct clinical trials, which is 29.7% more than in the same period of the previous year. The number of approvals for international multicenter clinical trials (IMCTs) has remained practically unchanged at 135 compared with 131 in H1 2015, representing an increase of just 3.1% year-to-year. The growth in the total number of approvals was mainly due to an increase in the number of other types of trials. The largest increase (by 73.9% year-to-year) was in the number of approved bioequivalence studies initiated by foreign sponsors (80 versus 46). Bioequivalence studies of Russian generics also increased, by 55.6% (98 versus 63). The number of approved local efficacy and safety clinical trials of foreign medicinal products exceeded the H1 2015 volume by 50% (42 versus 28), and the growth for domestic products was 20.3% (95 versus 79).

The market share of IMCTs dropped to 30% of total approved trials, which is only half of their share in the pre-reform period. The reason for this is the steady increase in the share of other trial types, primarily of generics.

The Newsletter then analyzes current practice in expert examinations to approve clinical trials. The share of submitted trials, which received approval without comments from any expert body, was at a record low in H1 2016 at 38.3% (down from 42.6% in H1 2015). However, the share of the trials that were approved at first submission by the FGBU "Scientific Center for Expertise of Medical Products" (FGBU) increased slightly year-to-year from 58% to 59.8%. The share of submissions approved at the first examination by the Ethics Council declined from 66% to 62.2%.

The situation in expert examination of pediatric trials continues to worsen. Only 17.6% of "children's" protocols were approved by the Ethics Council on first submission in H1 2016 versus 40% a year earlier. Fortunately, most comments made by the Council are not of a very serious nature. The share of pediatric protocols approved at the first attempt by the FGBU fell to 33.3% from 34.6% and the share of refusals or critical comments on the part of the FGBU increased significantly to 66.7% from 57.7%.

As regards specific therapeutic areas, the Ethics Council remains ill-disposed toward trials in psychiatry, for which only 42.9% of protocols were approved at the first attempt. The percentage of trials in oncology approved without comments fell significantly from 53.8% to 44.4%, which gives a reason for concern. The FGBU has shown disfavor towards trials for infectious disease products approving only 16.7% of protocols at the first submission and issuing comments of a serious nature or refusals in 61.1% of cases.

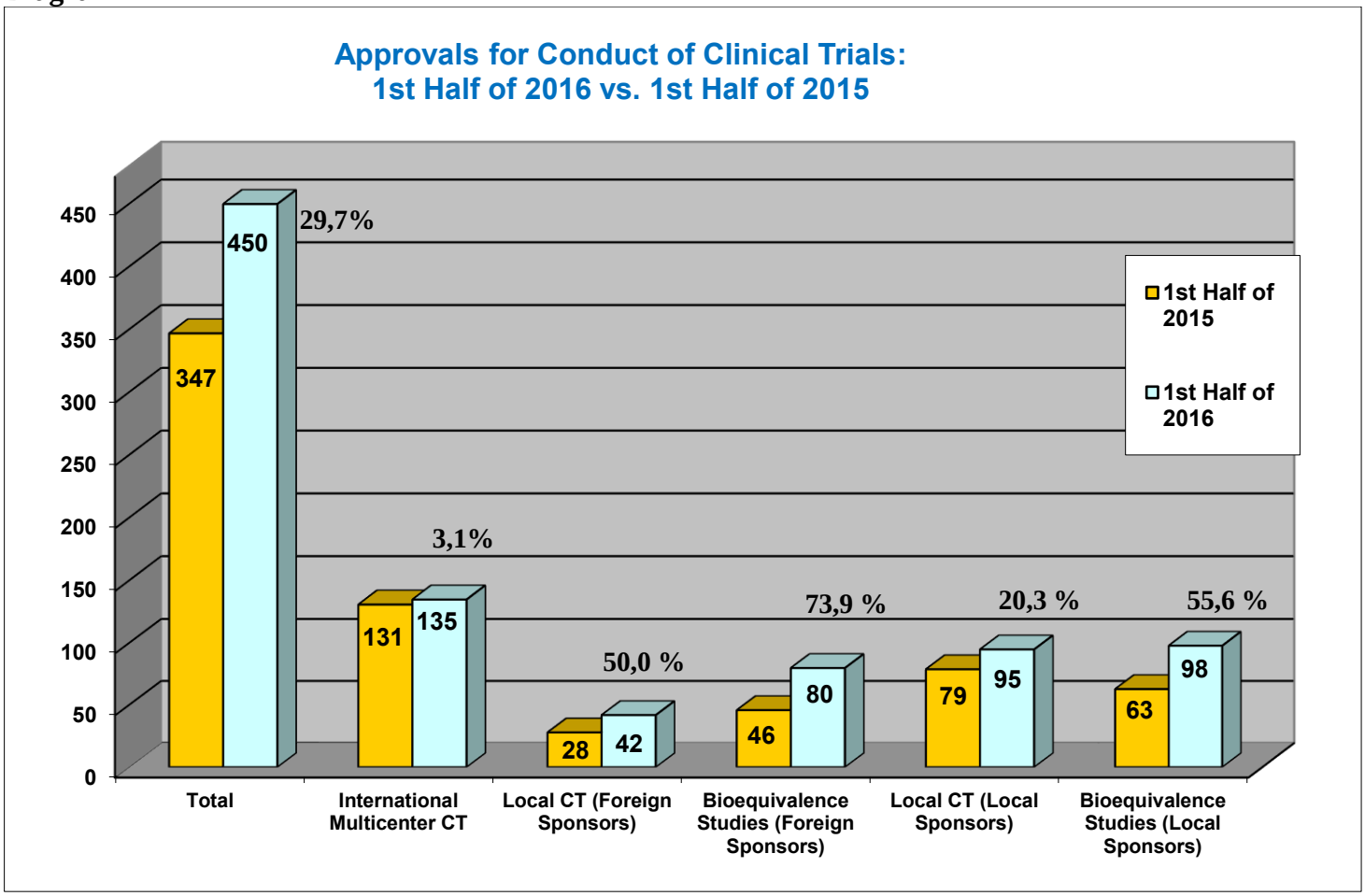
The Newsletter then reviews statistics for inspections by the Russian health sector watchdog, Roszdravnadzor. The share of IMCTs, which passed inspections without any identified violations was much higher than for local trials (84.9% versus 48.2%). Major violations in IMCTs were identified in 12.9% of all inspected trials, compared with 42.9% for local trials.

The Newsletter concludes with an account of a highly important dispute that arose from an inspection of a medical center by a regional Roszdravnadzor body. The case, concerning duties for the reporting of adverse events and adverse reactions during clinical trials, could have set a regrettable precedent for the entire clinical trials system. However, this was avoided thanks to a wise decision by the Rostov Appeal Court, which may help to prevent similar misunderstandings in the future.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

The Russian Ministry of Healthcare issued 450 approvals to conduct clinical trials in the half of 2016, which is 29.7% more than in the same period of last year (see Diagram 1). However, the number of approvals for international multicenter clinical trials (IMCTs) was almost unchanged (135 in H1 2016 versus 131 in H1 2015).

Diagram 1

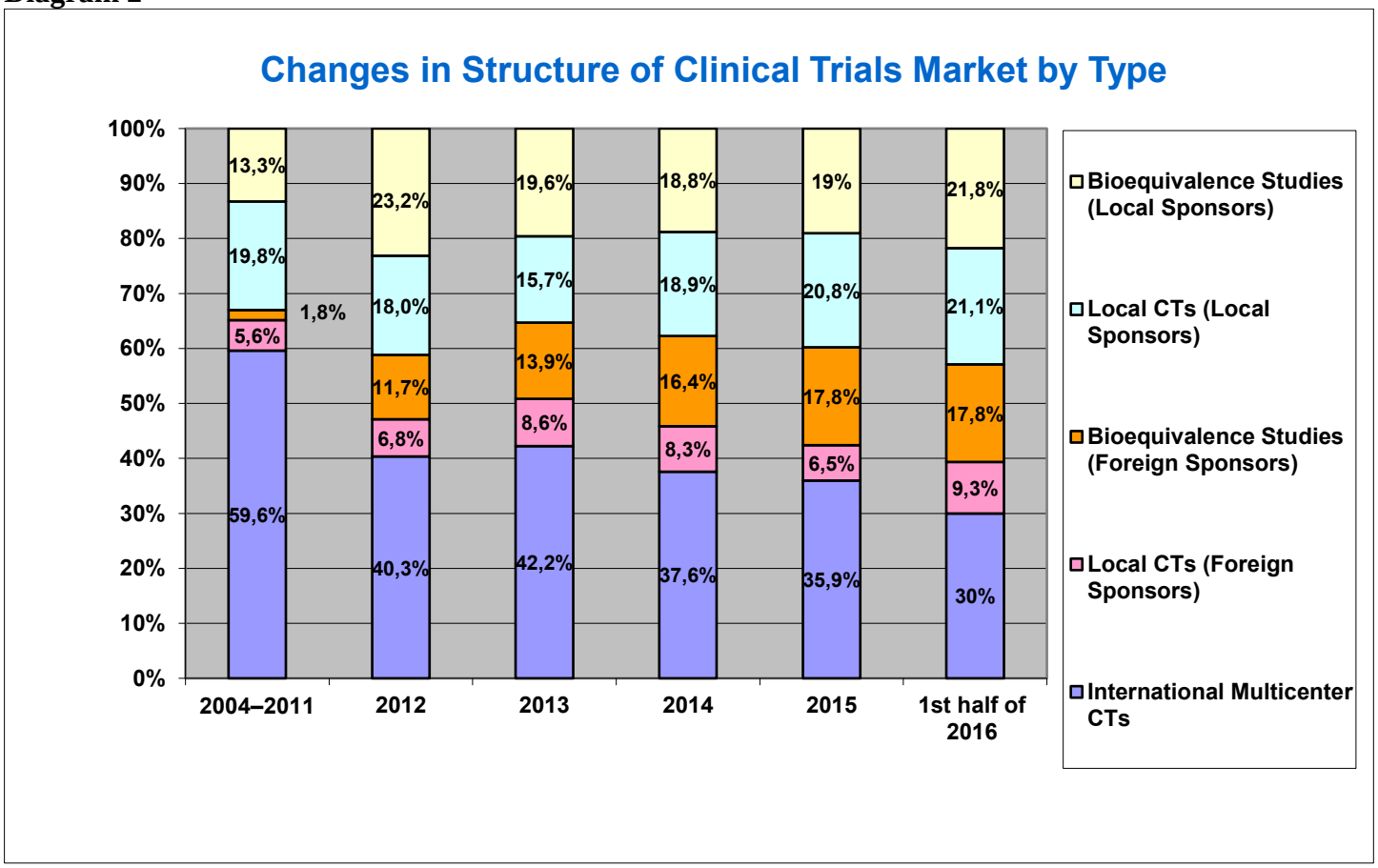


Data from www.grls.rosminzdrav.ru

The biggest increase was in approvals of bioequivalence studies of foreign products, which rose by 73.9% (80 versus 46). The number of approvals for bioequivalence studies initiated by Russian sponsors also increased significantly, by 55.6% (98 versus 63). Approvals for local efficacy and safety clinical trials by foreign sponsors increased by 50% (42 versus 28), despite our expectation that the abolishment of the requirement for therapeutic equivalence studies of certain pharmaceutical forms of generics would lead to a decline of this sub-group. The number of approvals for local efficacy and safety clinical trials by Russian sponsors also saw a modest increase, by 20.3% (95 versus 79).

Diagram 2 shows the change of market structure by types of trials over recent years. It can be seen that the trend towards reduction of the IMCT share and growth in the share of local trials and bioequivalence studies, which was observed after the adoption of the law “On Circulation of Medicines” is still continuing. The share of IMCTs in all trials approved in Russia had dropped to 30% by H1 2016, which is half of the level in the pre-reform period.

Diagram 2



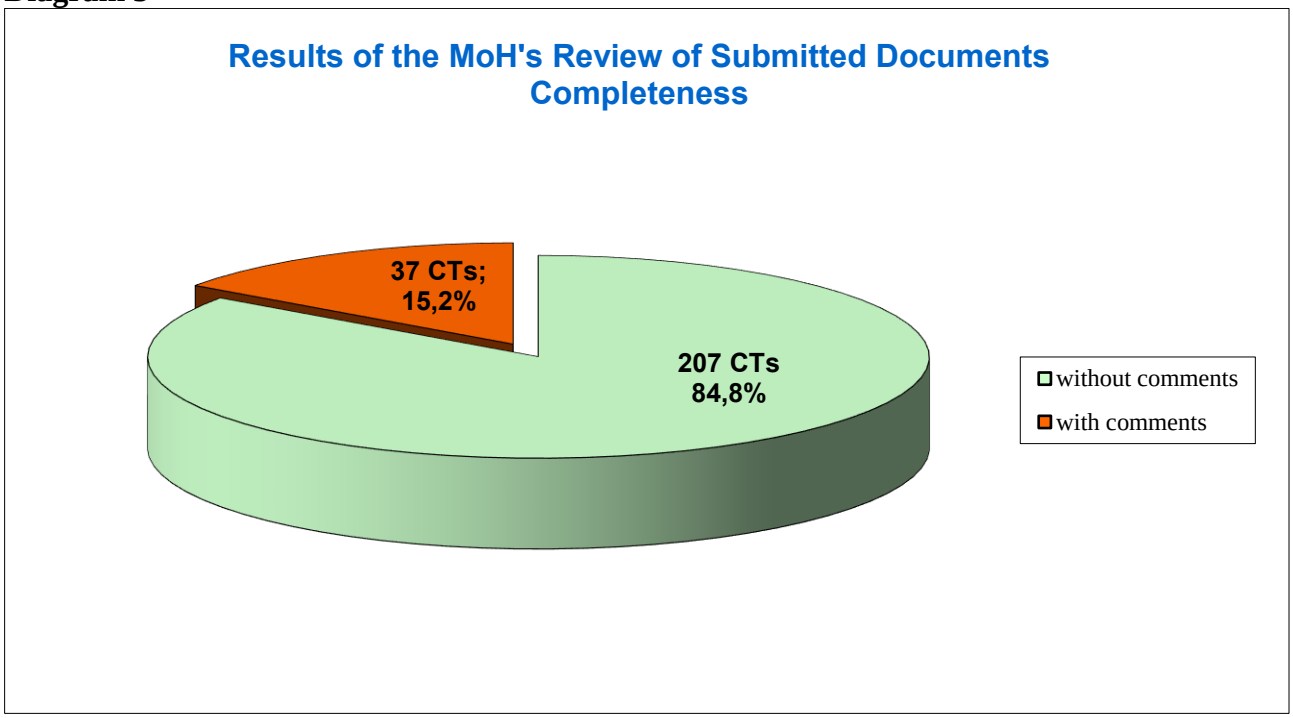
Data from www.grls.rosminzdrav.ru, www.roszdravnadzor.ru

EXPERT EXAMINATION OF PLANNED TRIALS: THE PRACTICE OF DISAPPROVALS

This year, as in the previous three years, ACTO analyzed developments in the conduct of expert review of planned clinical trials. As in previous years, the analysis is based on a survey of the experience of Association members relating to two types of expertise: that of the Ethics Council and that of the FGBU "Scientific Center for Expertise of Medical Products" (hereinafter "FGBU"). 26 companies took part in the survey. The analysis included responses by the expert authorities in the period from July 1, 2015 until June 30, 2016 to initial applications for the approval of international trials.

Diagram 3 shows the outcome of review by the Ministry of Healthcare of submitted documents (review by the Ministry is a necessary preliminary to the submission of documents for expertise). The Ministry had comments on 15.2% of applications with respect to their completeness, up from 7% in the same period last year. The increase was due to the adoption on July 1, 2015 of a new requirement to provide a copy of a statement, issued by the regulatory authorities of the medicinal product manufacturer, confirming that the manufacturer meets GMP requirements. Since such documents are only issued in certain countries (e.g., in the USA manufacturers are simply authorized and this information is published on the FDA website), applicants and Russian regulatory bodies took time to agree what supporting documents would be sufficient. It should be noted that the greatest number of comments on GMP certification were in H2 2015, when the new requirement had only just come into force. However, there are still cases now when applicants find it difficult to meet this requirement (e.g., if the manufacturer is based in Japan).

Diagram 3



Data from www.grls.rosminzdrav.ru

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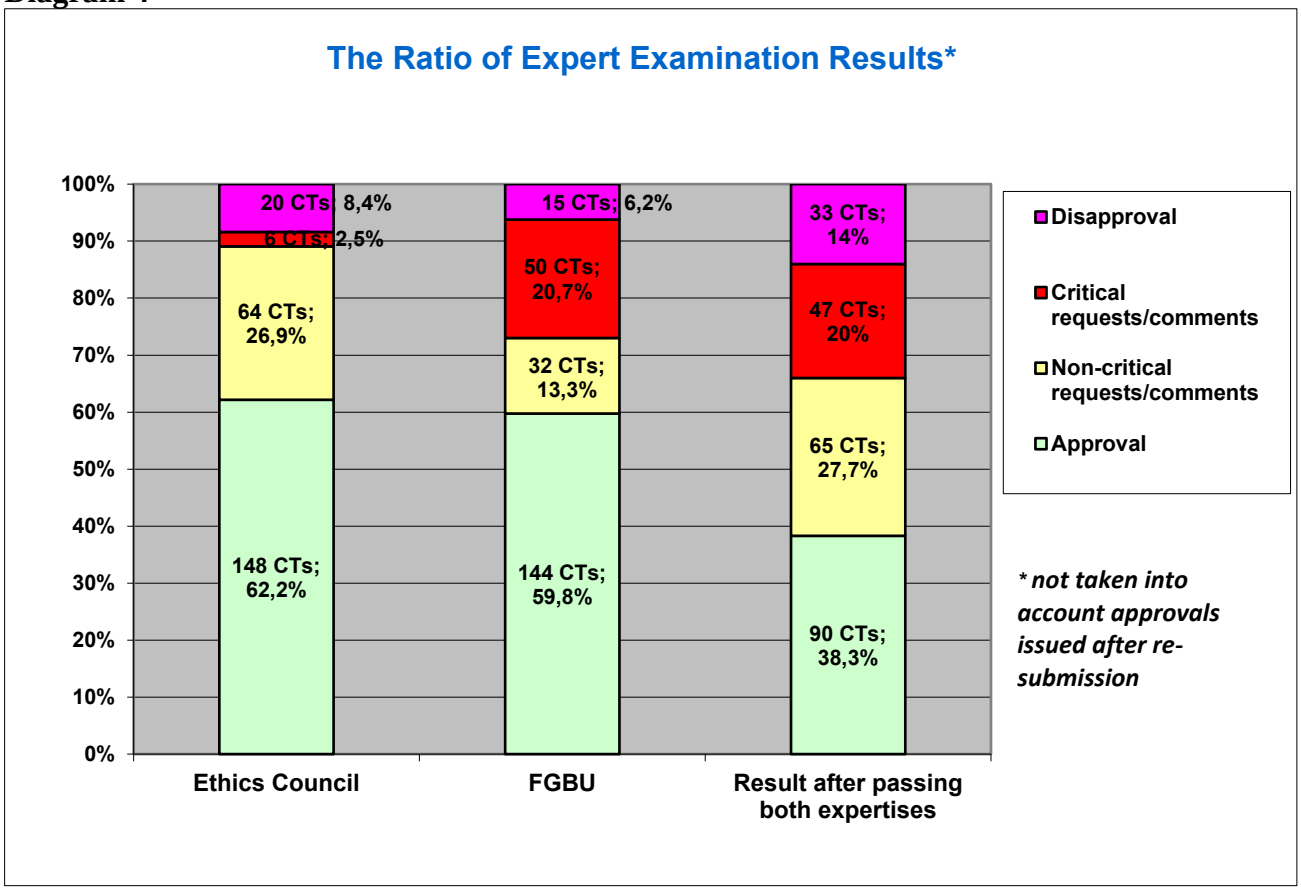
Diagram 4 shows the ratio of various outcomes of expert examination by the Ethics Council and FGBU of initial submissions for clinical trials, and the results of examinations by both expert bodies.

Requests by the FGBU and comments of the Ethics Council are separated into "critical" and "non-critical". Requests and comments are classified as critical if they require the conduct of further trials, changes to protocols, or if they concern design, etc. They are non-critical if they can be easily resolved by further

clarifications, minor amendments to wording, specifications and comments that do not relate to key documents and the trial program in general.

Diagram 4



Data from poll of ACTO members

The share of applications that passed expertise by both organizations this year without comments was lower than ever before at 38.3% (42.6% in the previous year). However, while the share of applications approved at the first attempt without comments by the FGBU increased slightly from 58% to 59.8%, the share of successes in a first expertise by the Ethics Council fell from 66% to 62.2%.

Official data of the Ministry of Healthcare should also be cited. At the end of June 2016 ACTO published an open letter to the Minister of Healthcare, Veronika Skvortsova[1], citing difficulties related to FGBU expertise, which, in the view of the Association, has worsened approvals of international trials. Immediately after the ACTO publication the Ministry issued a press release[2], apparently responding to the points made in the letter. We say "apparently", since the press release made no reference to ACTO's letter, nor did it give any other reason for the timing of the release, but was merely presented as a statement of the Ministry's position regarding clinical trials in Russia. The release included statistics on the conduct of expert examinations: Oleg Salagai, Director of the Public Health and Communications Department of the Ministry of Healthcare, stated that "the share of positive decisions for the conduct of international multicenter clinical trials has increased from 77.5% in 2012 to 96.4% in the first quarter of 2016".

It is not clear what the representative of the Ministry meant by "positive decisions", i.e. whether these are figures for both expert bodies review or for the FGBU only. In either case, the statistics do not correlate with those obtained from companies (Table 1). We do not make quarterly estimates, so we cannot provide data for

[1] http://www.pharmvestnik.ru/publs/lenta/v-rossii/otkrytoe-pisjmo-aoki-ministru-zdravooxranenija-rf-v-i-skvortsovoj.html#.V9kj2PmLTIU

[2] http://ria.ru/society/20160628/1453930197.html

the first quarter of 2016. But the difference between the results announced by the Ministry and those obtained by ACTO cannot be explained by merely non-matching measurement periods.

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
H1 2013	**71,4%**	**72,9%**	**51,5%**
H2 2013 and H1 2014	**71,8%**	**62,6%**	**43,7%**
H2 2014 and H1 2015	**58%**	**66%**	**42,6%**
H2 2015 and H1 2016	**59,8%**	**62,2%**	**38,3%**

Data from polls of ACTO members

Returning to the results of our last survey, it is pleasing to note that the share of applications that received critical requests/comments and disapprovals fell slightly for both expert bodies. The figure for the FGBU was 26.9% (20.7% for requests/comments + 6.2% for disapprovals) versus 30.2% a year earlier and the figure for the Ethics Council was 10.9% (2.5% + 8.4%) versus 14.2%. However, the overall share of critical requests/comments and disapprovals from both organizations was almost unchanged year-on-year at 34% versus 33.5%. This confirms once again that assessments by the two expert bodies of the same trials often differ and substantial comments of the FGBU and Ethics Council experts often refer to different protocols.

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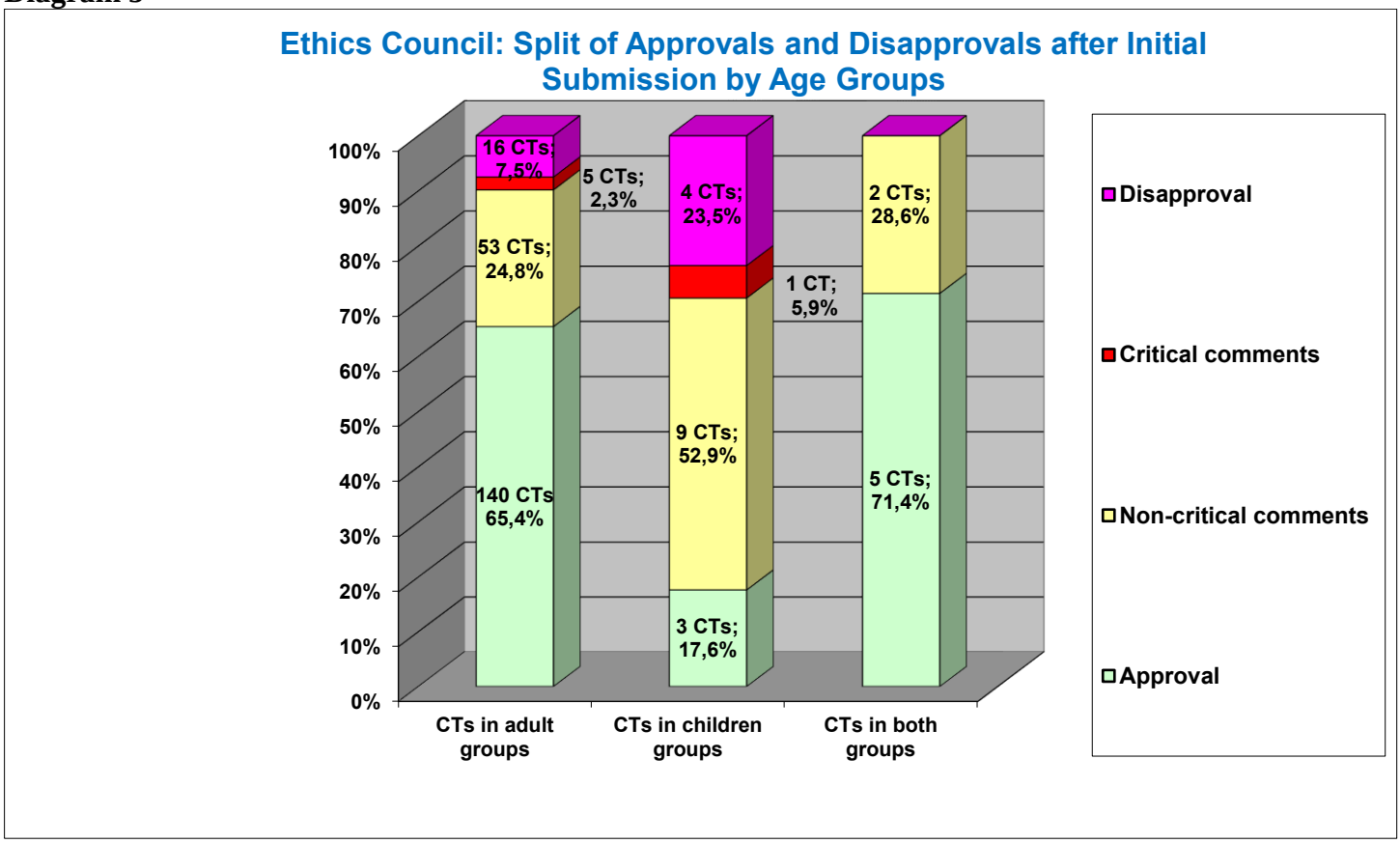
Diagram 5 shows the distribution of decisions by the Ethics Council relative to the age of the subjects of proposed trials. Only 17.6% of pediatric protocols (three trials) were approved by the Ethics Council on first submission. The share in 2014-2015 was much higher at 40%.

However, there was a reduction in the number of pediatric applications that received denials and critical comments, from 48% (32% refusals + 16% receiving critical comments) to 29.6% (6.2% + 20.7%).

As suggested by these figures, the majority (52.9%) of comments by the Ethics Council to pediatric protocols in H1 2016 were judged by the survey participants to be non-critical, compared with 12% in the same period of last year.

Diagram 5

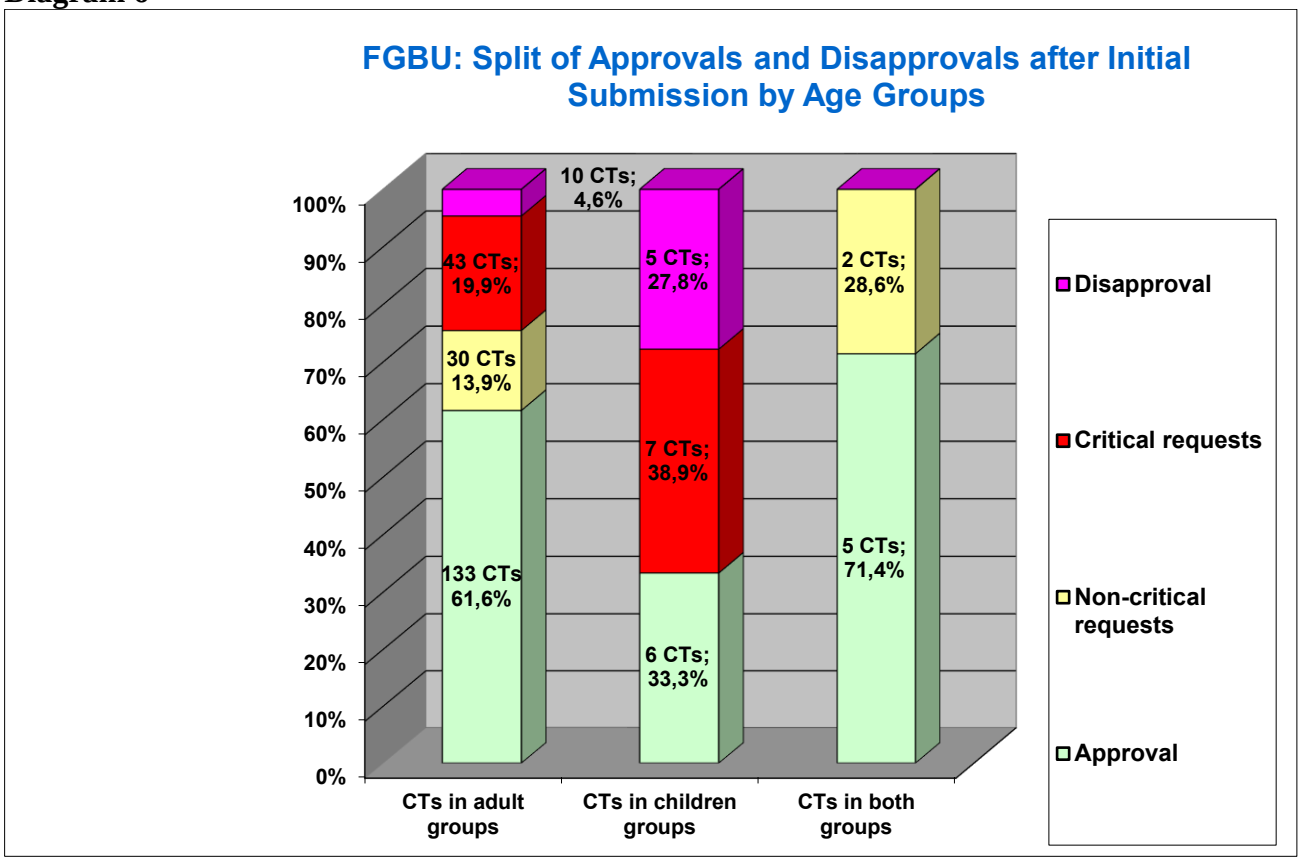


Data from poll of ACTO members

Diagram 6 shows the influence of the age of proposed trial participants on FGBU decisions. The share of pediatric protocols approved by the FGBU without comments decreased slightly on year-to-year basis from 34.6% to 33.3% and the share that were disapproved or received critical requests increased significantly from 57.7% (26.9% + 30.8%) to 66.7% (27.8% + 38.9%).

As in the past, most of the requests called for younger age groups to be excluded from the trials. So the biased attitude of the expert institution towards pediatric trials, which was already discussed in previous Newsletters (*see ACTO Newsletter No. 9 and 11*) is intensifying. Clearly, experts are unwilling to take responsibility for the approval of IMCTs involving younger patient populations, although this delays or prevents availability of modern treatment methods to young patients.

Diagram 6



Data from poll of ACTO members

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The next part of the analysis looks at the distribution of expert decisions relative to therapeutic areas of planned trials (Tables 2 and 3, Diagrams 7 and 8). Because the age factor has a substantial impact on decisions, the tables show two groups of data: the number of reviewed protocols and decisions regardless of the participants' age, and (in brackets) is the number excluding pediatric protocols. The data in the diagrams include pediatric trials.

As in previous years psychiatry fares worst in expert examinations by the Ethics Council (Table 2, Diagram 7) but there was some year-to-year improvement in 2015-2016, with 42.9% of protocols approved on first submission compared with 33.3% a year earlier. Psychiatry received the highest share of disapprovals in 2014-2015 (55.6%), but the share declined to 14.3% in 2015-2016, when three therapeutic areas (hematology, infectious diseases and ophthalmology) tied for the first place with 16.7% of applications being denied.

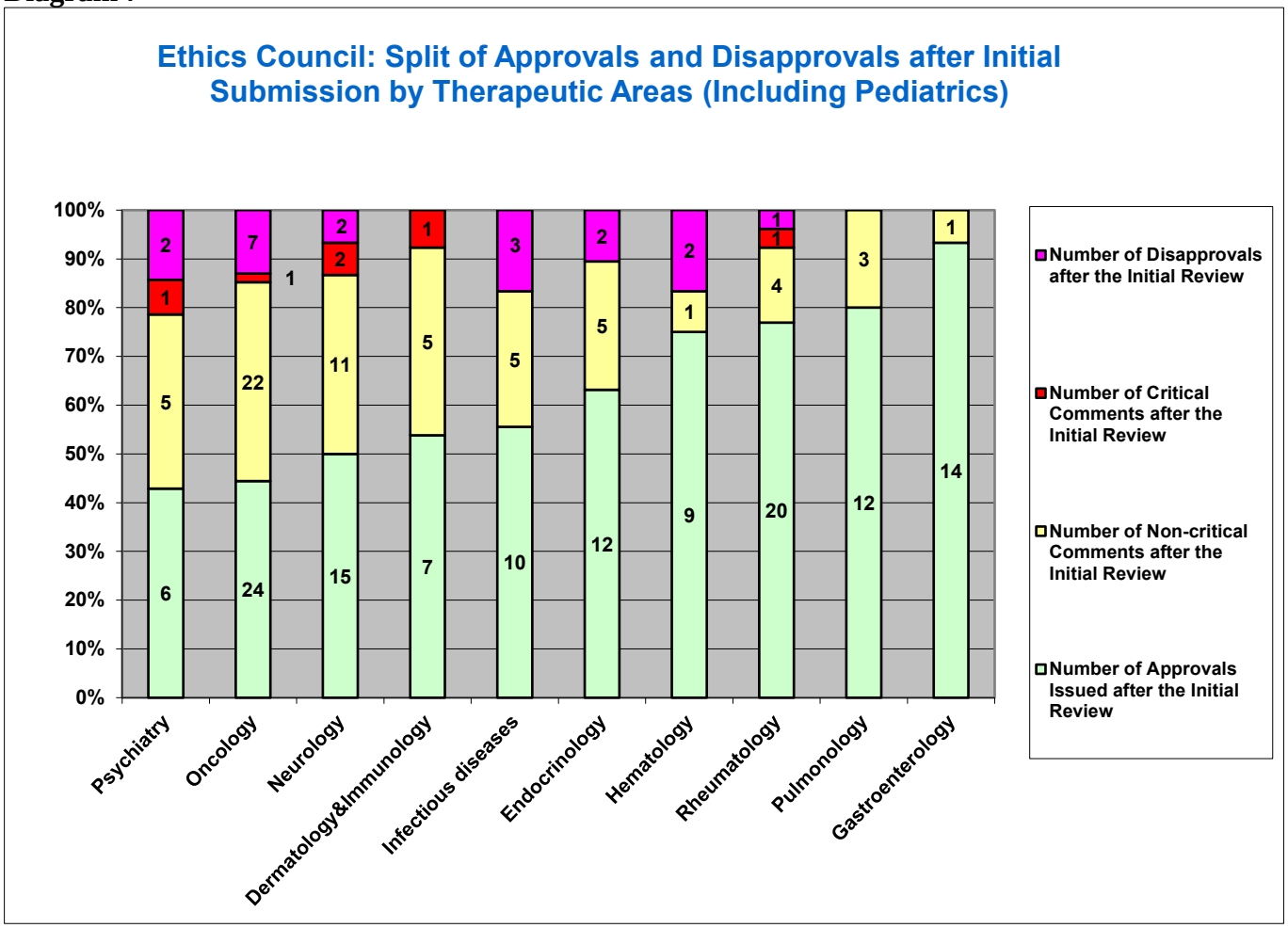
A major reduction in the share of oncology protocols approved at the initial submission (44.4% versus 53.8% a year earlier) gives cause for concern. There was also a major increase in oncology denials, from 5.1% to 13%.

Table 2

Ethics Council: Split of Approvals and Disapprovals by Therapeutic Areas (in Brackets Data Excluding Pediatric 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	54 (53)	24 (24)	44,4% (45,3%)	22 (21)	40,7% (39,6%)	1 (1)	1,9% (1,9%)	7 (7)	13% (13,2%)
Neurology	30 (25)	15 (13)	50% (52%)	11 (9)	36,7% (36%)	2 (2)	6,7% (8%)	2 (1)	6,7% (4%)
Rheumatology	26 (25)	20 (20)	76,9% (80%)	4 (3)	15,4% (12%)	1 (1)	3,8% (4%)	1 (1)	3,8% (4%)
Endocrinology	19 (18)	12 (12)	63,2% (66,7%)	5 (5)	26,3% (27,8%)	0 (0)	0% (0%)	2 (1)	10,5% (5,6%)
Infectious diseases	18 (16)	10 (10)	55,6% (62,5%)	5 (3)	27,8% (18,8%)	0 (0)	0% (0%)	3 (3)	16,7% (18,8%)
Pulmonology	15 (15)	12 (12)	80% (80%)	3 (3)	20% (20%)	0 (0)	0% (0%)	0 (0)	0% (0%)
Gastroenterology	15 (15)	14 (14)	93,3% (93,3%)	1 (1)	6,7% (6,7%)	0 (0)	0% (0%)	0 (0)	0% (0%)
Psychiatry	14 (9)	6 (6)	42,9% (66,7%)	5 (2)	35,7% (22,2%)	1 (0)	7,1% (0%)	2 (1)	14,3% (11,1%)
Dermatology and Immunology	13 (13)	7 (7)	53,8% (53,8%)	5 (5)	38,5% (38,5%)	1 (1)	7,7% (7,7%)	0 (0)	0% (0%)
Hematology	12 (12)	9 (9)	75% (75%)	1 (1)	8,3% (8,3%)	0 (0)	0% (0%)	2 (2)	16,7% (16,7%)
Cardiology and Cardiovascular diseases	7 (7)	7 (7)	100% (100%)	0 (0)	0% (0%)	0 (0)	0% (0%)	0 (0)	0% (0%)
Ophthalmology	6 (4)	5 (4)	83,3% (100%)	0 (0)	0% (0%)	0 (0)	0% (0%)	1 (0)	16,7% (0%)
Obstetrics & Gynecology	2 (2)	1 (1)	50% (50%)	1 (1)	50% (50%)	0 (0)	0% (0%)	0 (0)	0% (0%)
Urology	1 (1)	1 (1)	100% (100%)	0 (0)	0% (0%)	0 (0)	0% (0%)	0 (0)	0% (0%)
Other	6 (6)	5 (5)	83,3% (83,3%)	1 (1)	16,7% (16,7%)	0 (0)	0% (0%)	0 (0)	0% (0%)
Total	238 (221)	148 (145)	62,2% (65,6%)	64 (55)	26,9% (24,9%)	6 (5)	2,5% (2,3%)	20 (16)	8,4% (7,2%)

Data from poll of ACTO members

Diagram 7



Data from poll of ACTO members

The results of the FGBU expert examinations are shown in Table 3 and Diagram 8. The lowest success rate was for trials of infectious disease products[3], of which only 16.7% were approved on first submission (29.4% in 2014-2015). The share of critical requests and disapprovals for this therapeutic area was 61.1% (44.4% and 16.7%, respectively), up from 47% in 2014-2015.

The FGBU delivered critical requests and disapprovals for 71.4% of psychiatry protocols (50% and 21.4%, respectively) versus 55.6% in the previous year.

The situation in neurology was slightly improved on year-to-year basis with 36.7% of applications receiving critical requests and disapprovals versus 50% a year earlier and 46.7% of approvals at the first attempt versus 27.8% in 2014-2015. Could the favorable attitude of experts towards neurology be connected with the fact that the Health Minister is a neurologist by profession?

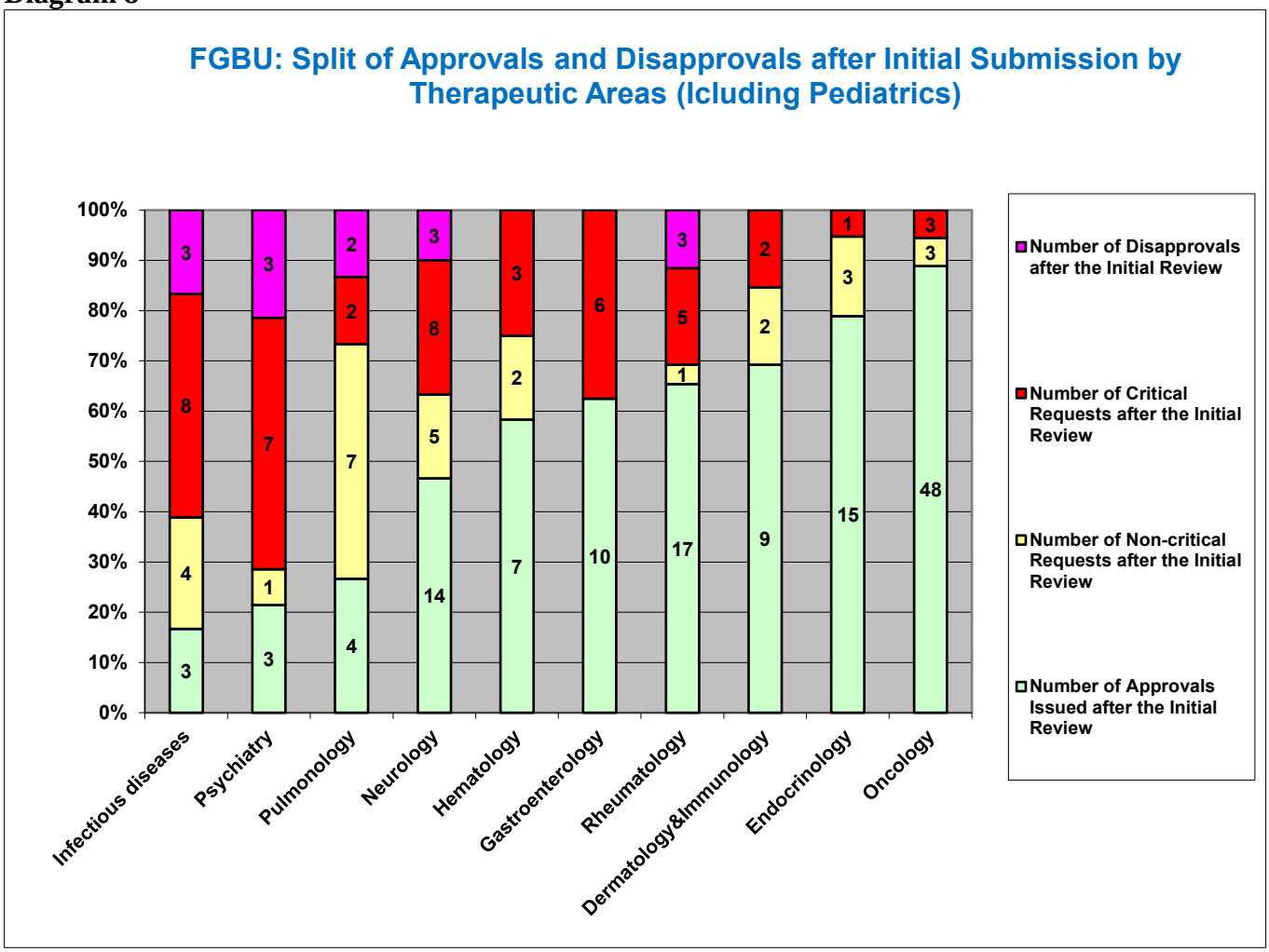
[3] Excluding urology, for which no trials were approved at the first attempt, but statistics for urology are not indicative, since only two protocols were examined.

Table 3

FGBU: Split of Approvals and Disapprovals by Therapeutic Areas (in Brackets Data Excluding Pediatric 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	54 (53)	48 (47)	88,9% (88,7%)	3 (3)	5,6% (5,7%)	3 (3)	5,6% (5,7%)	0 (0)	0% (0%)
Neurology	30 (25)	14 (12)	46,7% (48%)	5 (5)	16,7% (20%)	8 (6)	26,7% (24%)	3 (2)	10% (8%)
Rheumatology	26 (25)	17 (17)	65,4% (68%)	1 (1)	3,9% (4%)	5 (5)	19,2% (20%)	3 (2)	11,5% (8%)
Endocrinology	19 (18)	15 (14)	78,9% (77,8%)	3 (3)	15,8% (16,7%)	1 (1)	5,3% (5,6%)	0 (0)	0% (0%)
Infectious diseases	18 (16)	3 (3)	16,7% (18,8%)	4 (4)	22,2% (25%)	8 (6)	44,4% (37,5%)	3 (3)	16,7% (18,8%)
Gastroenterology	16 (16)	10 (10)	62,5% (62,5%)	0 (0)	0% (0%)	6 (6)	37,5% (37,5%)	0 (0)	0% (0%)
Pulmonology	15 (15)	4 (4)	26,7% (26,7%)	7 (7)	46,7% (46,7%)	2 (2)	13,3% (13,3%)	2 (2)	13,3% (13,3%)
Psychiatry	14 (9)	3 (2)	21,4% (22,2%)	1 (1)	7,1% (11,1%)	7 (6)	50% (66,7%)	3 (0)	21,4% (0%)
Dermatology and Immunology	13 (13)	9 (9)	69,2% (69,2%)	2 (2)	15,4% (15,4%)	2 (2)	15,4% (15,4%)	0 (0)	0% (0%)
Hematology	12 (12)	7 (7)	58,3% (58,3%)	2 (2)	16,7% (16,7%)	3 (3)	25% (25%)	0 (0)	0% (0%)
Cardiology and Cardiovascular diseases	8 (8)	7 (7)	87,5% (87,5%)	1 (1)	12,5% (12,5%)	0 (0)	0% (0%)	0 (0)	0% (0%)
Ophthalmology	6 (4)	3 (2)	50% (50%)	0 (0)	0% (0%)	2 (1)	33,3% (25%)	1 (1)	16,7% (25%)
Obstetrics & Gynecology	2 (2)	1 (1)	50% (50%)	0 (0)	0% (0%)	1 (1)	50% (50%)	0 (0)	0% (0%)
Urology	2 (1)	0 (0)	0% (0%)	0 (0)	0% (0%)	2 (1)	100% (100%)	0 (0)	0% (0%)
Other	6 (6)	3 (3)	50% (50%)	3 (3)	50% (50%)	0 (0)	0% (0%)	0 (0)	0% (0%)
Total	241 (223)	144 (138)	59,8% (61,9%)	32 (32)	13,3% (14,4%)	50 (43)	20,7% (19,3%)	15 (10)	6,2% (4,5%)

Data from poll of ACTO members

Diagram 8



Data from poll of ACTO members

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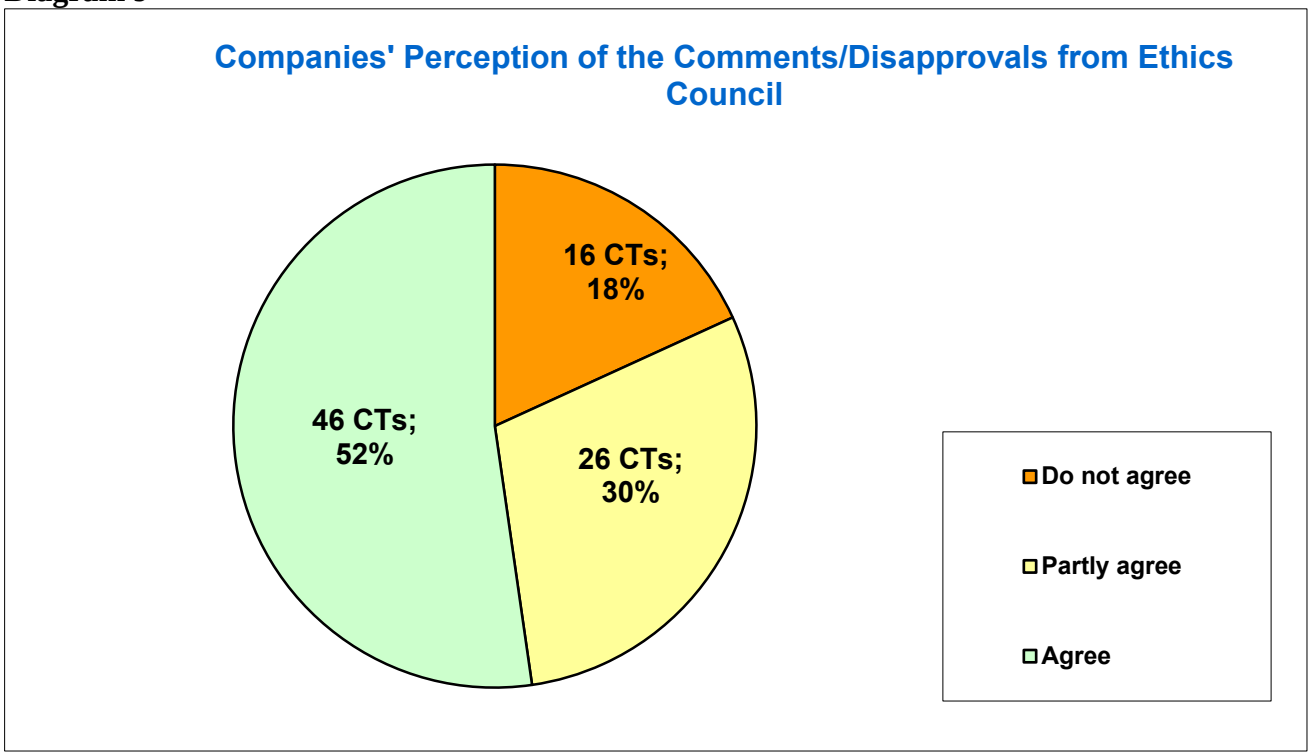
Diagrams 9 and 10 show to what extent companies judged the comments made by the Ethics Council and FGBU to be fair. Historically (*see Newsletters Nos. 9 and 11*) applicants show more agreement with the comments of the Ethics Council. However, the share of instances when companies disagreed strongly with the Council's assessments increased from 14% to 18% year-to-year in 2015-2016. At the same time, companies agreed with the Ethics Council experts in 52% of cases compared with 49% a year ago and instances of partial agreement fell from 37% to 30%.

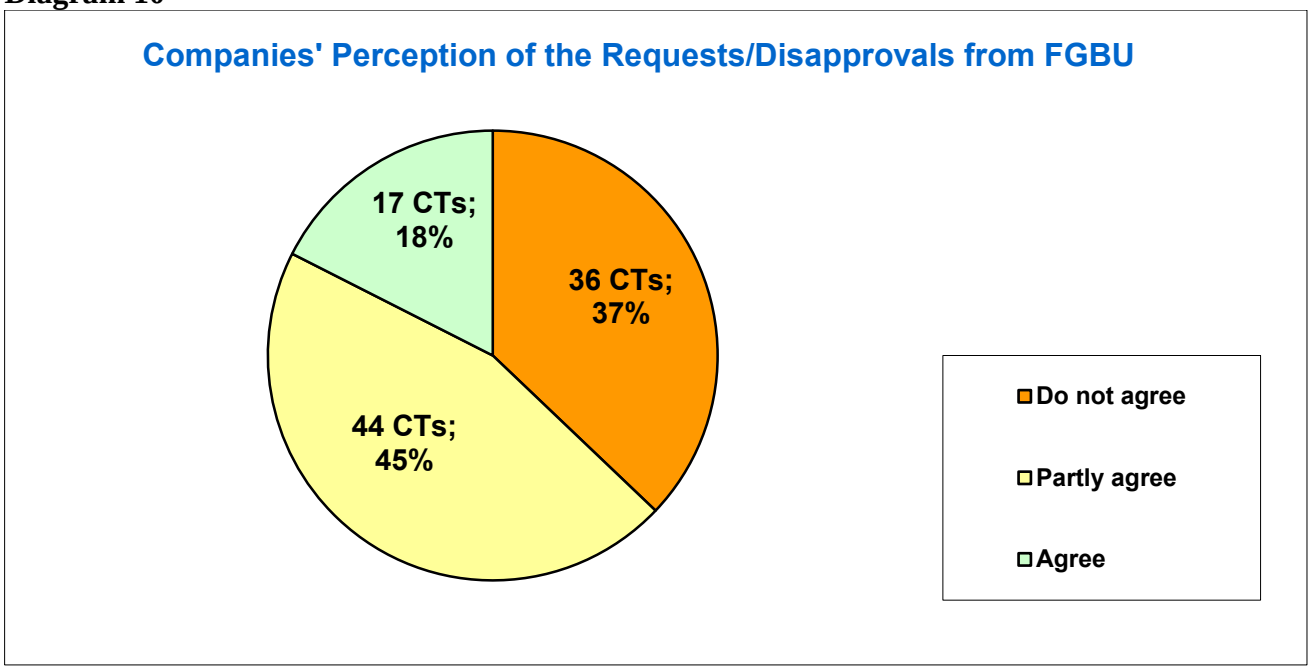
Companies' perception of FGBU decisions changed to a lesser extent. The share of strong disagreements with its experts decreased to 37% from 39%, The share of consent has declined by 1% (18% vs. 19%). Finally, the share of expert comments to which the companies were ready to partially agree has increased from 42% to 45%.

Diagram 9



Data from poll of ACTO members

Diagram 10



Data from poll of ACTO members

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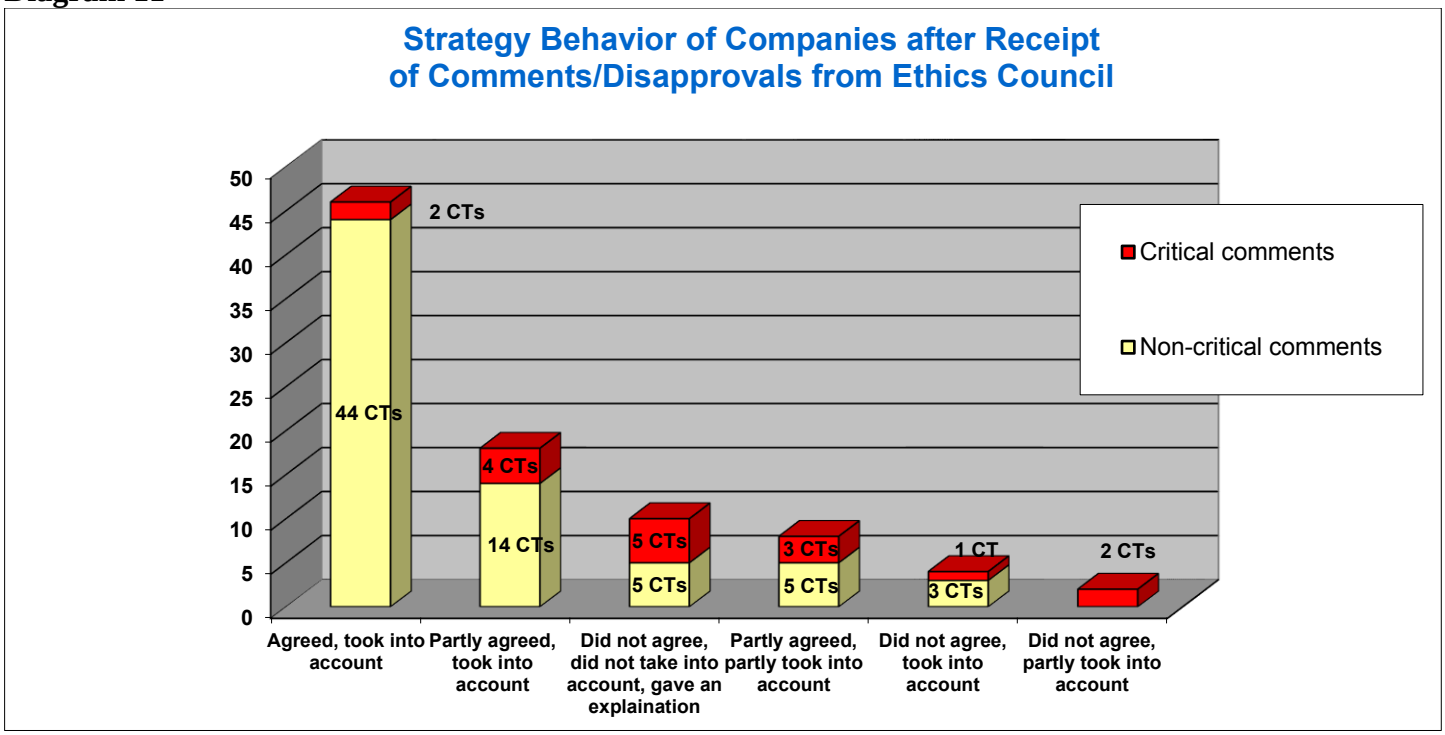
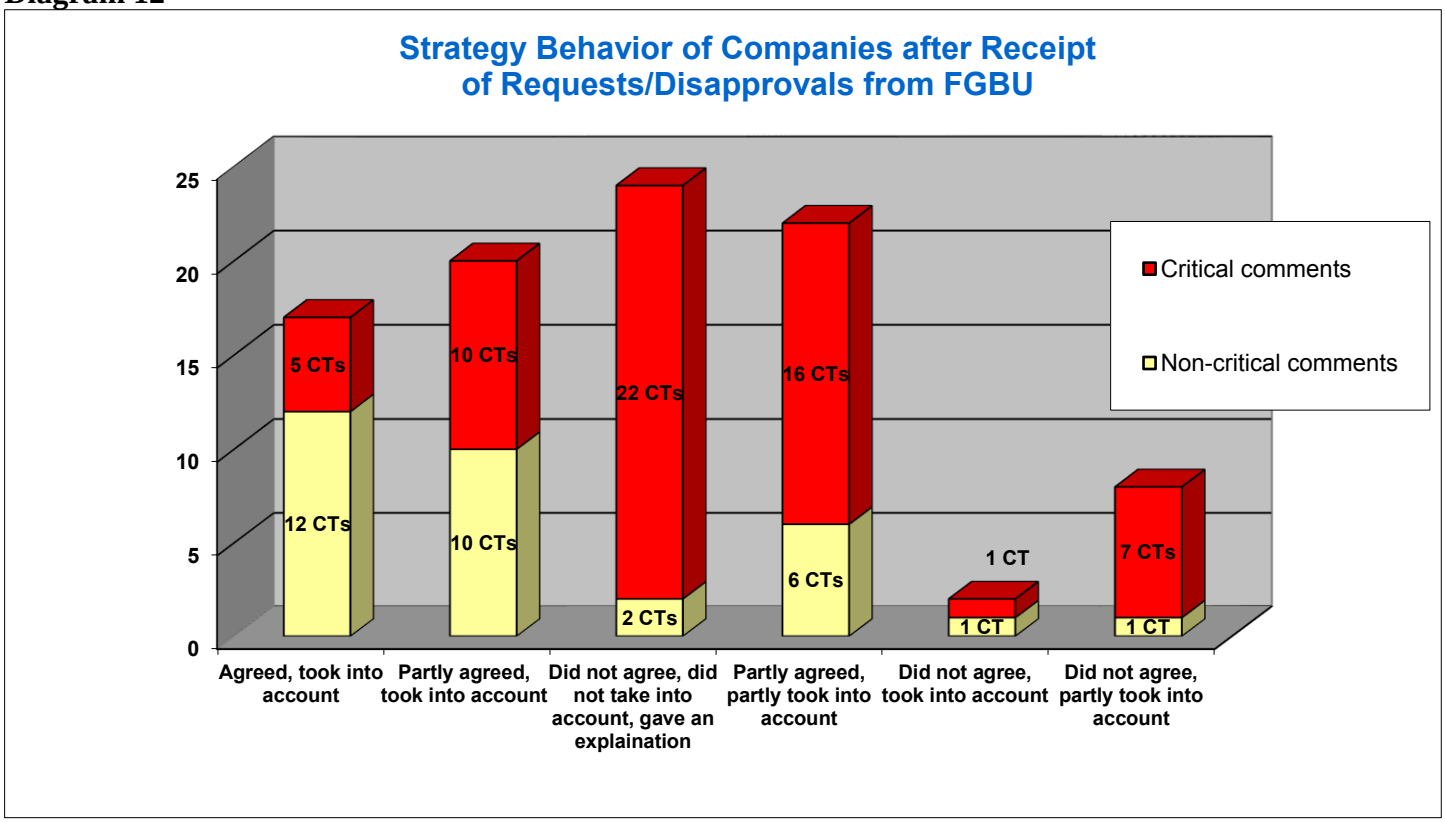
Next we consider the strategies adopted by companies in response to comments or denials by the expert bodies (Diagrams 11 and 12).

Diagram 11



Data from poll of ACTO members

Diagram 12



Data from poll of ACTO members

As in previous years, companies more frequently agreed with comments by the Ethics Council and therefore made the relevant adjustments (in 52.3% of cases). By contrast, the most common reaction to the

FGBU's comments was "not agreed, not taken into account, explanations provided" (25.8% of cases). In nearly all cases this reaction was due to the fact that the adjustments proposed by the FGBU would require the conduct of further preclinical trials that are not required elsewhere in the world or requiring changes to the protocol, which are impossible for the sponsor in view of the international status of the proposed trial. The sponsor therefore had no choice but to ask the FGBU to reconsider its decision or to leave Russia out of the trial.

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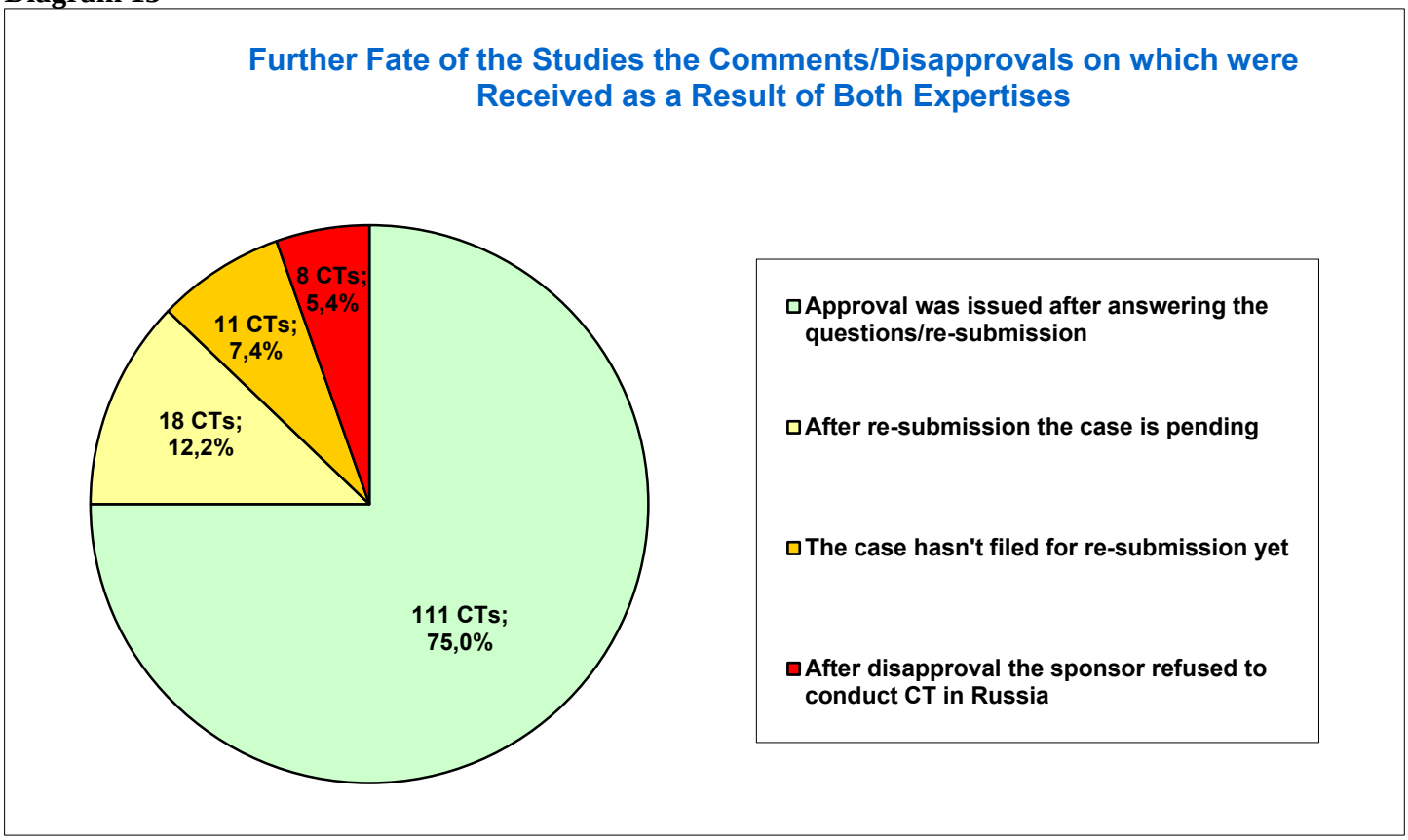
Diagram 13 shows what happened to applications, which received requests for information, comments or denials from either or both expert bodies when they were first submitted.

Diagram 13



Data from poll of ACTO members

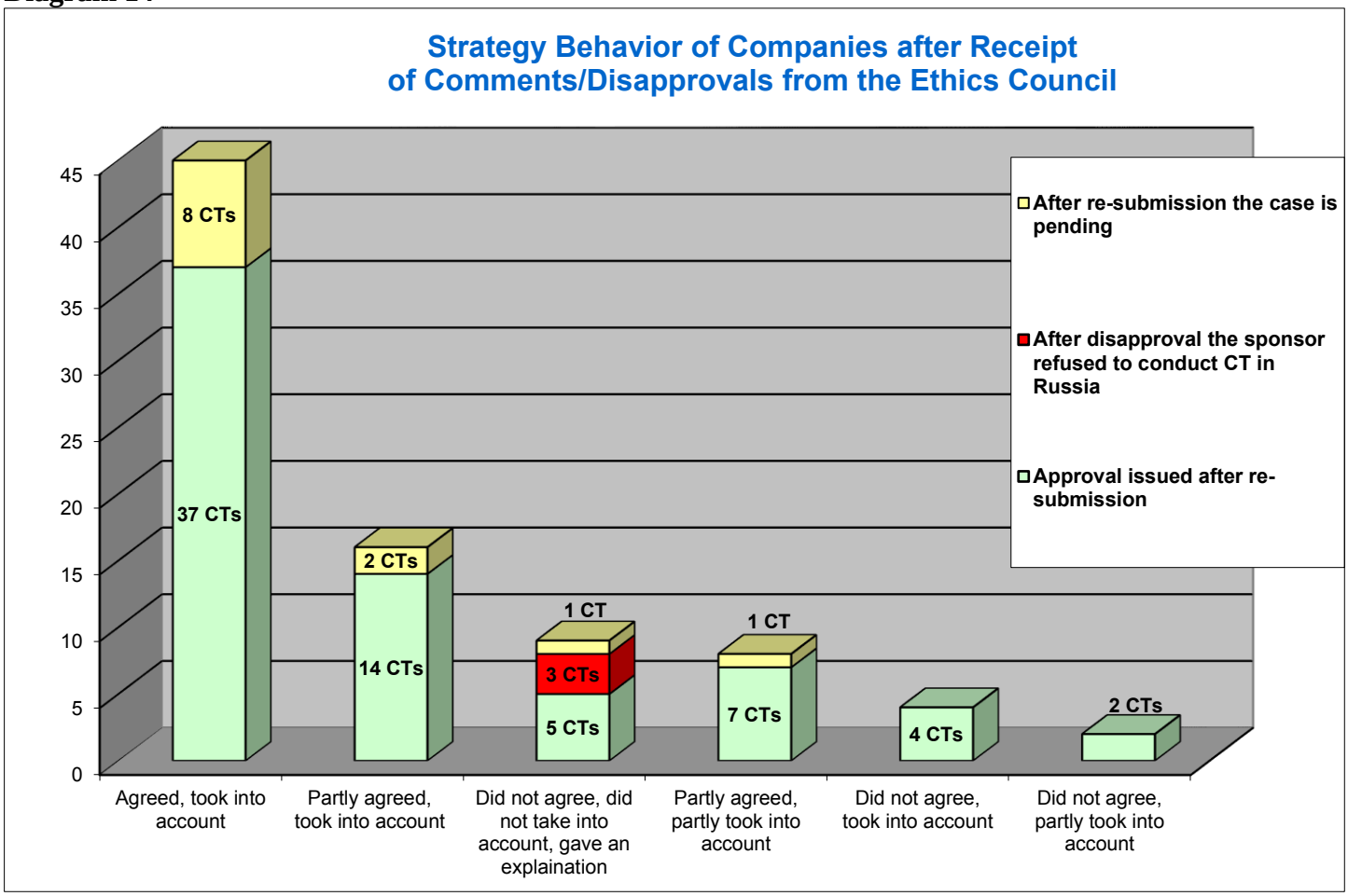
Most trials (75%) were finally approved after addressing the requests or after repeat submission in case of a denial. This represents an improvement from a figure of 65.8% in H1 2015. At the time of the ACTO survey 12.2% of cases were still undergoing secondary reviews and 7.4% were preparing for repeat applications for such reviews. In eight cases (5.4%) the sponsor had abandoned plans to hold a clinical trial in Russia. That also represents an improvement from 2014-2015, when the share of abandoned applications was 10.8%.

Diagrams 14 and 15 also show data on applications, which received requests for more information or denials with respect to particular types of expertise. For greater clarity, this information is shown in relation to the strategy used by companies in response to the decision of the expert body.

As can be seen from Diagram 14, the vast majority of cases (95.8%)[4] that were reviewed again by the Ethics Council were successfully approved.

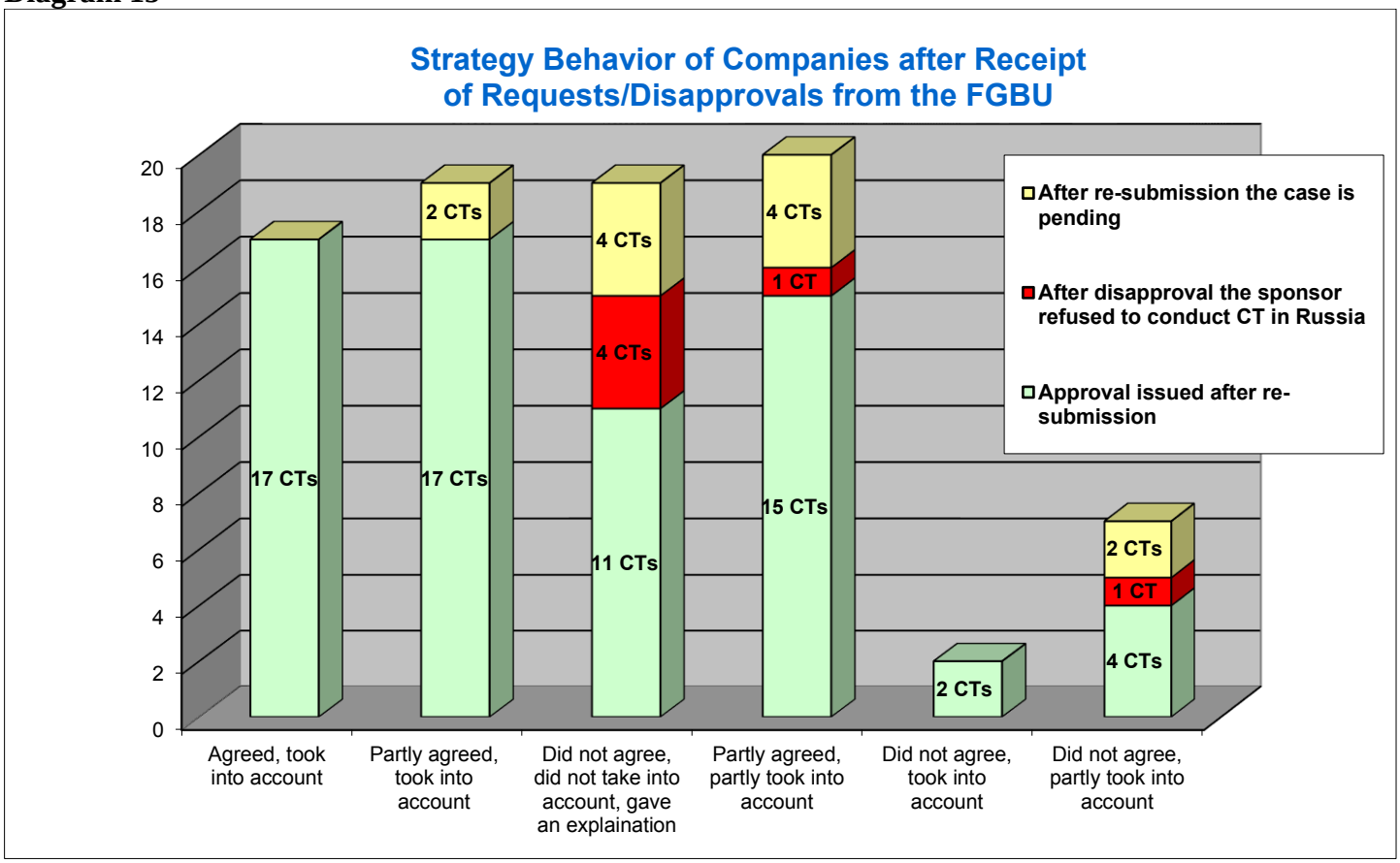
[4] Not including cases, for which the final outcome was not known at the time of the survey

Diagram 14



Data from poll of ACTO members

Diagram 15



Data from poll of ACTO members

The percentage of cases that were finally approved by the FGBU was also high. Naturally, the chances of success are lower when companies are unable to make adjustments in response to the experts' comments, and can only offer clarifications to substantiate their case. However, the share of successful outcomes was quite high even in these instances: 11 out of 15 trials (73.3%), which were initially disapproved or returned with comments, and for which companies made the response "not agreed, not taken into account, clarifications provided" were finally approved, sometimes after several repeat submissions. Four trials were still under consideration at the time of the survey.

While in last year survey all abandonments of trials were due to refusal of the FGBU to grant approvals, at that point there were two instances when such abandonment was due to the position of the Ethics Council (one was an endocrinology trial and the other was for a product to treat infectious diseases). One other trial of a product for the treatment of infectious diseases was not initiated in Russia due to negative decisions by both expert bodies (it is therefore shown in both figures). The attitude of FGBU experts forced the abandonment of six trials: two in neurology, one in rheumatology, one in pulmonology and two in the treatment of infectious diseases (one of these two was also rejected by the Ethics Council). The sponsors had different reasons for giving up their plans to conduct trials in Russia. In most cases, they were simply unable to meet the experts' requirements. However, in two instances the applicants were able to substantiate their case, but agreement was reached too late: the enrollment stage in other countries had already been completed by that time.

The abandonment of international projects in Russia due to inability to pass through the expert filter is very harmful to the industry. The main question, which applicants have in these cases, is why a trial that is acceptable in other countries (notably, in developed countries) should be rejected by Russian experts. ACTO has initiated a new database from the start of 2016, recording IMCTs that were abandoned in Russia[5]. To date the database only refers to clinical trial applications submitted in 2010-2014. The outcome of several applications for trials submitted in 2015 was still unknown at the time of the latest survey, due to bureaucratic obstacles. We fully intend to maintain and regularly update the database.

[5] http://acto-russia.org/index.php?option=com_content&task=view&id=331

OUTCOMES OF ROSZDRAVNADZOR INSPECTIONS

We now consider the outcomes of inspections by Roszdravnadzor (the Russian healthcare watchdog) in H2 2015 and H1 2016 based on data for inspection results published quarterly by Roszdravnadzor on its website[6]. Information on the number of inspections and the entities inspected is provided in Table 4.

Roszdravnadzor carried out scheduled on-site inspections at 77 medical institutions during the period (14 of the institutions were not carrying out clinical trials). A total of 149 clinical trials conducted by 83 principal investigators were inspected. The number of scheduled on-site inspections of medical institutions has slightly changed from the previous period when 147 trials with 89 principal investigators were inspected. However, we note that the number of scheduled inspections of sponsors increased: there were six inspections in the most recent period against one in the previous period, although the previous period included inspections of two contract research organizations (*see Newsletter No. 11*).

Table 4

Statistics on inspections by Roszdravnadzor of the activities of conducting clinical trials, 2nd half of 2015 – 1st 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/The number of clinical trials inspected**	**The number of contract research organisations inspected/The number of clinical trials inspected**
Planned on-site inspections	**77 (14 of them do not conduct CTs)**	**83**	**149**		**6/13**	**-**
Unplanned on-site inspections to ensure compliance with previously issued orders	**6**	**6**	**5**		**-**	**-**
Unplanned documentary inspection to ensure compliance with previously issued orders	**2**	**2**	**2**		**3/3**	**-**
Unplanned on-site (complaint-based) inspection	**2 (one of them does not conduct CTs)**	**1**	**1**		**-**	**-**
Unplanned documentary (complaint-based) inspection	**2**	**2**	**3**		**5/5**	**-**

Data from www.roszdravnadzor.ru

[6] See the ACTO Newsletter No. 9 for a description of the analysis procedure and the classification used.

The six pharmaceutical companies that were inspected in the recent period were as follows: ZAO Bryntsalov-A; AO I.I. Mechnikov Biomed, OOO NPO Petrovax Pharm (one trial was inspected at each company); OOO KRKA-RUS (two trials), ZAO Sandoz (three trials), and ZAO R-PHARM (five trials). Roszdravnadzor made comments to all of the sponsors, which were inspected. The most serious comments concerned the trial by ZAO Bryntsalov-A. They included: failure to provide valid and correct information in the report on the trial, failure to conduct the trial according to the protocol, lack of documentation on the product batch used in the trial, lack of proper accounting of the investigational product, etc.

In the past, inspections by Roszdravnadzor to monitor the implementation of recommendations, which it had made following earlier inspections, were mainly carried out by means of reports submitted by the inspected entities to Roszdravnadzor, without on-site visits. However, in the most recent period six repeat visits were carried out by on-site inspections and only two were limited to the submission of documents. The on-site inspections covered all clinical centers, while pharmaceutical companies, which had been criticized in previous inspections, were only required to submit reports. All of the follow-up inspections determined that previous violations had been resolved.

We now describe Roszdravnadzor inspections, which were carried out on the basis of complaints received. During the most recent period Roszdravnadzor carried out two such inspections on-site (one of the medical organizations, which was inspected, has not been carrying out clinical trials) and two inspections by means of documents. Violations were discovered as a result of one of the on-site inspections and one of the documentary inspections. This violations in the on-site inspections were insignificant, mainly concerning administrative issues. The documentary inspection was of the V.I. Razumovsky Saratov State Medical University with respect to the following trial: “Prospective, multicenter, randomized, comparative, open-label trial to evaluate the efficacy and safety of Ertapenem J., a lyophilisate for preparation of a solution for intravenous and intramuscular administration, 1g (produced by Jodas Expoim Pvt Ltd., India) and Invanz®, a lyophilisate for the preparation of a solution for intravenous and intramuscular injection, 1g (produced by Merck Sharp & Dohme, France) in patients with skin and soft tissue infections.” The trial was conducted under the supervision of the principal investigator A.A. Shuldiakov. According to the Roszdravnadzor report, there were a number of failures, in particular: deviations from the protocol, the source documents did not contain complete information about the trial, specifying all events and their time periods; Invanz was administered intravenously instead of intramuscular administration; the CRF data are inconsistent with data in the source medical documentation.

Complaints about clinical trials were not limited to the activity of medical organizations, but also concerned sponsors and contract research organizations. Roszdravnadzor reviewed five such complaints during the period and all of the reviews were in a documentary form (i.e., without an on-site visit, on the basis of the organization’s written response to the complaint). Only one of five complaints, that regarding ZAO F-Sintez, led to the discovery of violations. In the other four cases Roszdravnadzor judged that: “No violations of good clinical practice have been found”. It is interesting that Roszdravnadzor has begun to identify the complainants in its reports, though not in all cases. Three complaints were brought by the Celgene company (concerning OAO Pharmasintez, ZAO Biokad and OOO RegEkspert representing the interests of the company Laboratory Tuteur S.A.C.I.F.I.A., Argentina). In turn ZAO Biokad made a complaint in respect of OOO Dr. Reddy's Laboratories.

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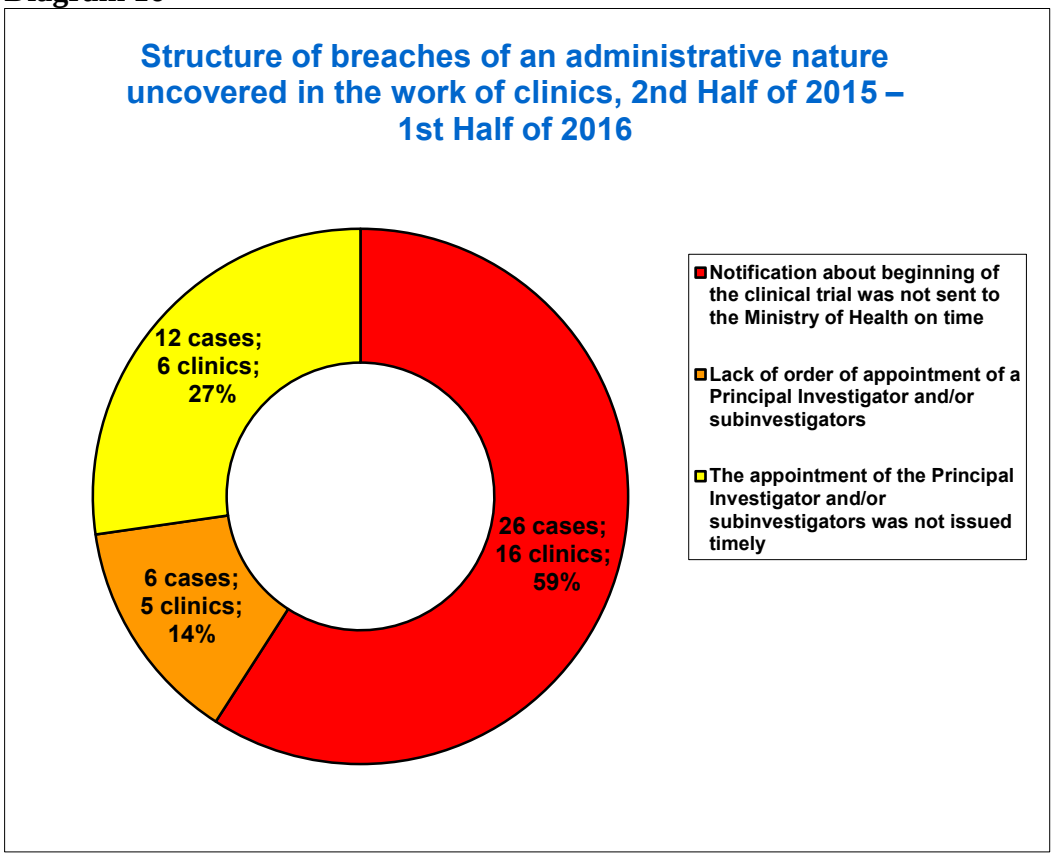
As in previous Newsletters, we traditionally divide violations found during scheduled inspections of clinics into three groups: those in the area of responsibility of medical organizations themselves; those concerning Local Ethics Committees (LECs); and those in the area of responsibility of principal investigators (according to GCP).

Let us first address the violations in the area of responsibility of medical organizations, as specified by the law "On Circulation of Medicines" (Diagram16). Such violations generally concern compliance with the formal requirements of the law and are mainly administrative, not affecting the credibility of clinical trial data and the safety of trial subjects.

Diagram 16



Data from www.roszdravnadzor.ru

The most frequently reported violation in this group was a failure to notify the Ministry of Healthcare of the start of a clinical trial (26 cases or 59% of the total). In second place was a failure to appoint a principal investigator or subinvestigator at the required time (12 cases or 27% of the total), and the third most common violation was a lack of the order of the chief physician of the clinic appointing the principal investigator and subinvestigator (6 cases or 14% of the total).

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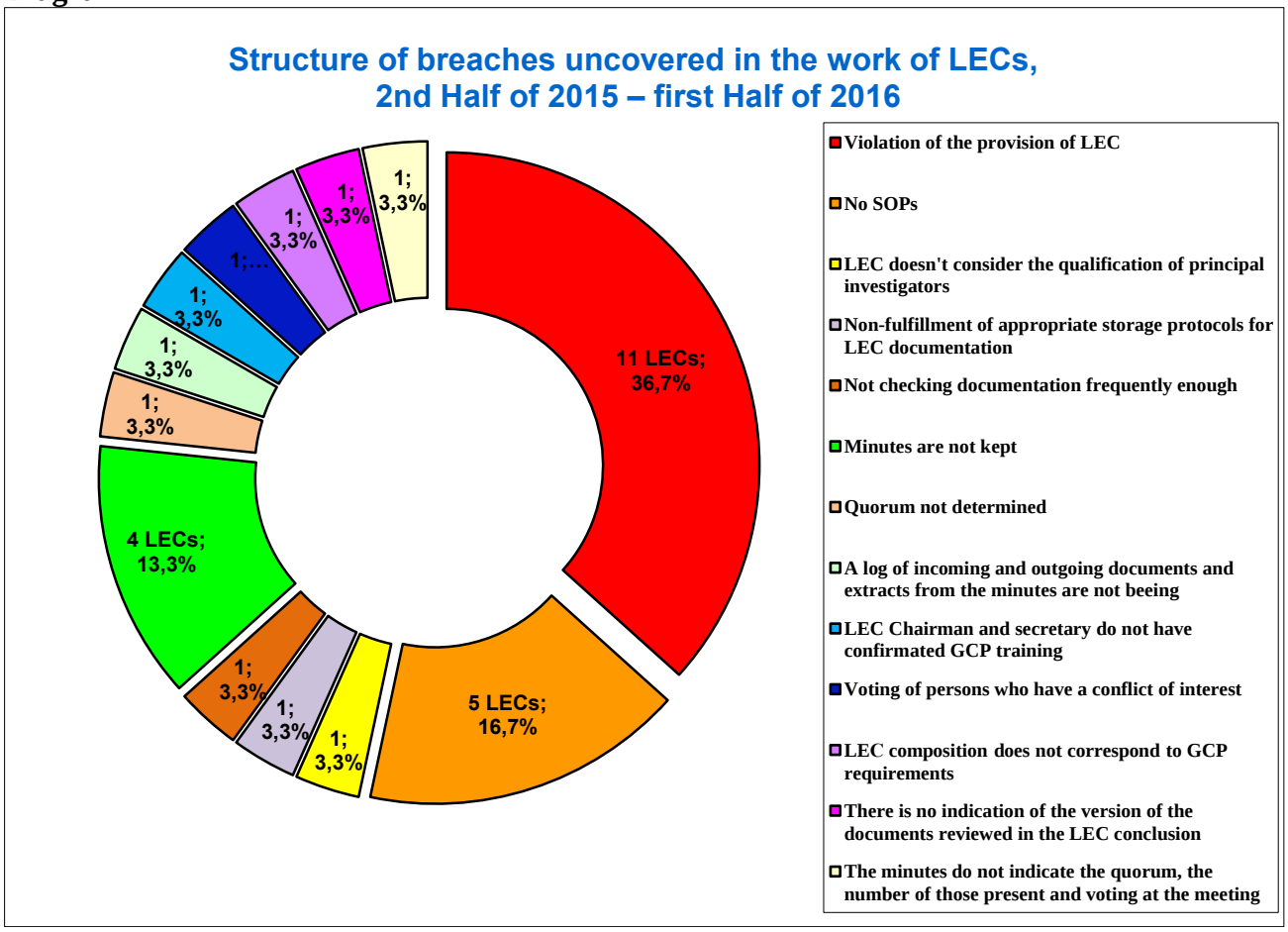
We do not have data on the total number of inspected LECs, since Russian law does not require that every medical organization should have its own LEC. However, violations were found in the work of 16 LECs at 63 clinics that were inspected. The structure of the violations is shown in Diagram 17.

Diagram 17



Data from www.roszdravnadzor.ru

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Finally, with regards to violations by principal investigators and their teams, Diagram 18 shows the inspection results by types of clinical trials. As shown above in Table 3, Roszdravnadzor inspected a total of 149 clinical trials during the period, of which 93 (62.4%) were IMCTs and 56 (37.6%) were local trials (13 and 39 local trials initiated by foreign and Russian sponsors, respectively, and 1 and 3 bioequivalence studies initiated by foreign and Russian sponsors, respectively).

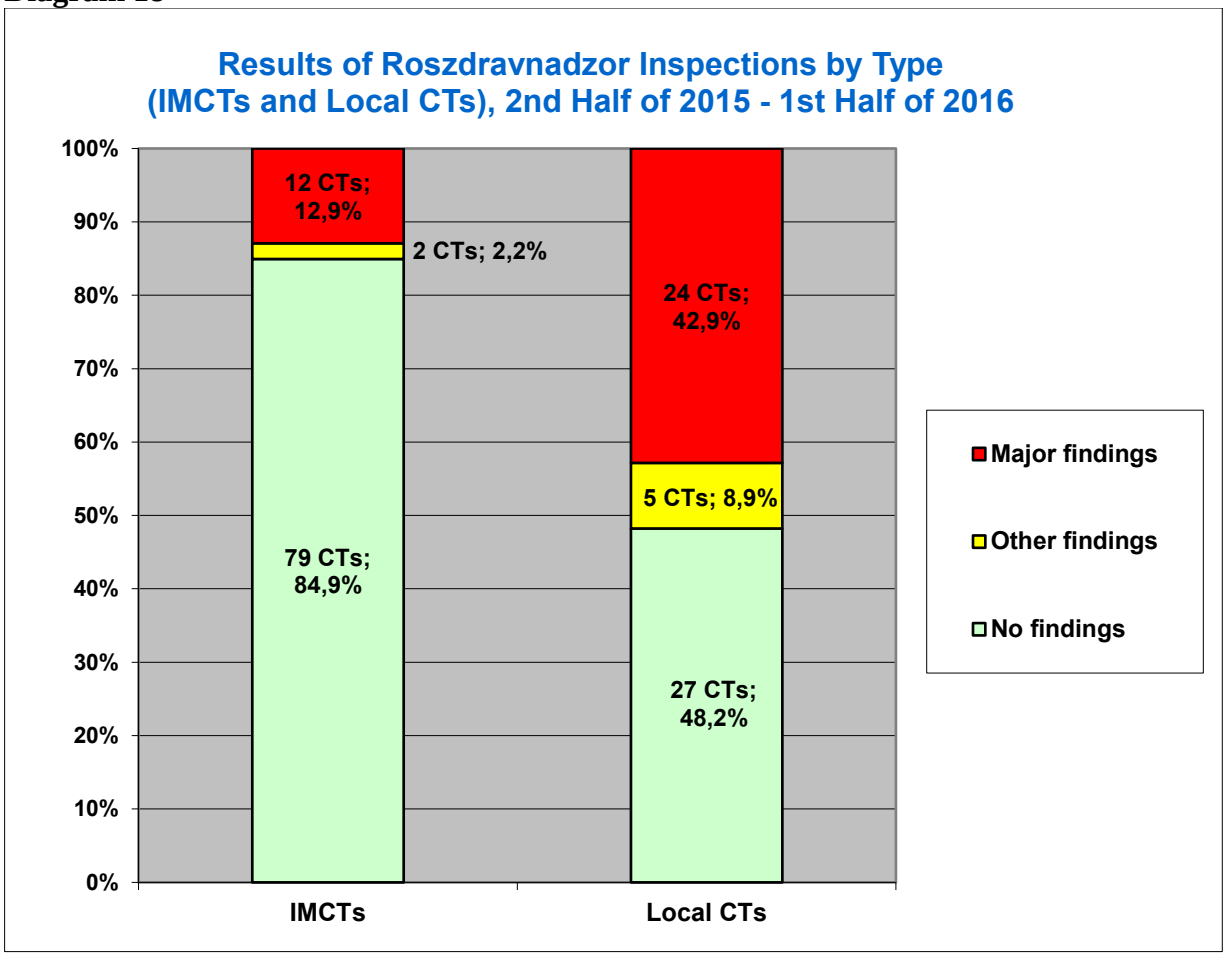
Findings are assigned to one of two groups depending how serious they are. Major findings are those, which potentially affect the rights and interests of the clinical trial subjects and/or credibility of clinical trial data.

It can be seen that the share of international trials without violations found during inspections is much higher than the analogous share for local trials (84.9% versus 48.2%). Serious violations were found in 12.9% of all IMCT trials, while the figure for local trials was 3.3 times greater at 42.9%.

It should be remembered that IMCTs currently represent only 30% of all clinical trials authorized in Russia. It is not clear why Roszdravnadzor shows such a preference for IMCT inspections. But, judging by the

figures in the last paragraph, there is every reason to believe that, had the agency distributed its attention more evenly, many more violations would be discovered. (In this case, the 93 IMCT inspections should have been matched by 217 instead of 56 local trial inspections).

Diagram 18



Data from www.roszdravnadzor.ru

All of the identified violations are shown in Table 4. For convenience, we group them by type and we separate IMCTs and local trials.

The wordings that describe particular violations are given as in the summary data published by Roszdravnadzor. Unfortunately, it is not always possible to tell from them exactly what the violation consisted of and what was behind it. For example, the formula “proper management of clinical trial documentation is not ensured” could refer to any number of faults with a variety of consequences for the clinical trial results. It also seems that Roszdravnadzor’s classifications for the period H2 2015 and H1 2016 were much reduced in comparison with previous periods: we found only 17 types of named violations in work by the investigators and their teams, compared with 31 in the previous period.

In view of this fact and also in view of the plans of regulatory authorities to introduce specific administrative responsibility for violation of regulations of Good Clinical Practice, ACTO intends, if possible, to analyze Roszdravnadzor data in more detail in the future, in consultation with companies, which were subject to criticism of their trials as a result of inspections.

Table 4

Violations found during clinical trial inspections, H2 2015 and H1 2016			
	Type of violation	**IMCTs**	**Local CTs**
Obtaining informed consent, patient rights			
	Patients were included in the CT without signing the ICF	**–**	**1**
	Sufficient time to make a decision on CT participation was not provided when the informed consent was obtained	**–**	**1**
	The ICF was not dated by the patient	**2**	**2**
CT documentation management			
	Data in the Case Report Forms was not consistent with data in the source medical documentation	**1**	**2**
	Accurate corrections were not made to patients' CRFs	**1**	**1**
	Management of the source medical documentation does not comply with current regulations	**1**	**2**
	Safe storage of the CT documentation/prevention of accidental destruction is not ensured	**–**	**5**
	Proper management of clinical trial documentation is not ensured	**10**	**21**
Deviations from the protocol			
	Deviations from the protocol without specifying the reason	**–**	**3**
Accounting, storage and use of the medicinal products			
	Proper accounting of the product is not ensured	**1**	**5**
	Proper storage of the product is not ensured	**1**	**–**
Local Ethics Committee (LEC) approval			
	The company's LEC has not assessed proper qualification of the investigator	**1**	**2**
	The LEC has not provided an opinion	**1***	**–**
Administrative issues			
	The qualifications of personnel involved in the CT have not been confirmed	**1**	**1**
	Proper acquaintance of personnel with their functions and responsibilities as part of the CT is not documented	**–**	**3**
	A doctor, not the investigator, is responsible for medical care issues as part of the CT	**1**	**–**
	The CT procedures involve persons who are not listed in the responsibility log.	**2**	**–**
Total		**23**	**49**

Source: **www.roszdravnadzor.ru**

* In fact, the trial was approved, but by the Interdisciplinary Ethics Committee and not by an LEC. Unfortunately, the principal investigator did not officially inform the inspectors of this fact.

THE KRASNODAR CASE

We conclude this Newsletter with the description of a judicial dispute, which arose from an inspection by Roszdravnadzor.

In autumn 2015 the regional body of Roszdravnadzor for Krasnodar Territory in southern Russia carried out a scheduled on-site inspection of OOO Medical Center Nefros, in the course of which the inspectors took note of two reports by the principal investigator on serious adverse events, which the investigator had forwarded to the Local Ethics Committee. Both reports concerned the same female patient who was taking part in the international clinical trial, "Phase 3, multicenter, randomized, open-label, active-controlled study of the efficacy and safety of FG-4592 in the treatment of anemia in incident-dialysis patients". The female patient has been receiving the comparator product, erythropoietin alpha. In March 2015 she was hospitalized for six days with the diagnosis, "community-acquired bilateral multisegmental pneumonia of mixed origin". During the hospitalization the patient continued the long-term hemodialysis treatment at OOO Medical Center Nefros, and the dosage and method of administration of the product remained the same. In late April, the patient was admitted to the hospital again for about a month with the diagnosis "ARMS, autosomal dominant polycystic kidney disease". Erythropoietin administration was suspended during the hospitalization, but resumed at the same dose after discharge.

Why the LEC required the adverse event reports was not clarified. But, the inspectors of the regional Roszdravnadzor body did not see any difference between an event and a reaction, and apparently were not well acquainted with the specifics of the procedure for reporting of safety data during a clinical trial. They therefore accused the clinic of failing to report serious adverse reactions to Roszdravnadzor.

A protocol on an administrative violation has been issued, stating the following:

"OOO MC Nefros was required to forward information on a serious adverse reaction in patient No. 15013 during administration of Erythropoietin Alpha to the regional body of Roszdravnadzor for Krasnodar Territory or via the Roszdravnadzor automated system "Pharmacovigilance" on the website http://npr.roszdravnadzor.ru/ no later than 15 days after the relevant information became known. The notification about a serious adverse reaction in patient No. 15013 during Erythropoietin Alpha administration has not been submitted by OOO MC Nefros in this time period.

"The above facts indicate the failure of OOO MC Nefros to submit a notification to the federal body carrying out the functions of control and supervision in the sphere of healthcare or its regional body, whereas such notification is required to be submitted under the legislation in the sphere of health, thereby committing a wrongful action (inaction), which entails administrative liability under part 1 of Article 19.7.8 of the Code of Administrative Offences."

The administrative sanction has followed immediately: the clinic has been ordered to pay a fine of 30,000 rubles. However, the clinic did not accept the decision and appealed it.

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Before describing further developments in this story it will be helpful to consider the mistakes committed by the regional body of Roszdravnadzor in justification of the fine.

Firstly, there was a wrong interpretation of the requirements of current legislation as to which safety information must be submitted by subjects of the circulation of medicines during a conduct of clinical trials. The safety control system in clinical trials is fundamentally different from that, which is applicable for authorized medicinal products. During trials, when knowledge of the medicinal product is being accumulated, any information potentially related to product safety should be collected. That is why clinical trials use the term "adverse event", which is not applicable to the circulation of authorized medicines, and which refers to any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. The basic principle here is "to collect everything, whether or not related to the product".

Investigators collect this information and submit it to the sponsor. The study doctor expresses his own opinion as to causality between the product administration and an adverse event, but this opinion is provisional. The sponsor carries out final assessment of the event by classifying the information as probably product-related or not product-related and classifies it either as an "adverse reaction" or as "an adverse event not related to the product".

The event only has to be reported to the authorized body after it has been determined to be a reaction (serious reactions should be reported urgently). This reveals another mistake by the regional body: the duty to report adverse reactions to the authorized body lies with the trial sponsor and not with the investigator. Moreover, the duty is not that of reporting to the regional Roszdravnadzor body, as the Krasnodar inspectors suggest.

This approach has a very clear logical justification: only the sponsor has the complete information on all adverse events that occur during an international clinical trial in all participating countries. No regulatory authority of a single country (not to mention a particular regional body) has the same ability. And the sponsor is responsible for the classification of product-related events and timely notification of the competent authorities. To take a simple example: a patient may be hit by a car during the clinical trial. This is a serious adverse event and the investigator must report it to the sponsor. If this event is the only one per 1000 study subjects, it is likely to remain in the "adverse events" category. However, if, during data collection from all study centers the sponsor finds that six people in various countries have fallen from windows, one has jumped from a bridge and two have fallen under trains, there will be serious grounds for suspecting that the administered product causes suicidal behavior. Considering the complex design of modern clinical trials, and also the fact that the randomization list (a system making it possible in blind trials to decode whether a study participant was in the product group or the control group) is held by the sponsor, the competent authority of any country cannot draw any conclusions based on data about serious adverse events received individually from study doctors.

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Returning to the Krasnodar case: considering that the charges against it to be unjustifiable, the medical center appealed to a court the decision by the regional Roszdravnadzor body. The center applied for clarifications from the central office of Roszdravnadzor to help its case. Unlike the regional inspectors, the central office of Roszdravnadzor showed excellent understanding of the specifics of safety data collection during clinical trials, stating in its reply to the medical center that "under legal requirements for pharmaceutical industry supervision, subjects of the circulation of medicines are not required to report adverse events to Roszdravnadzor without established causal relationship with the administered medicinal products". However, the central office cautiously added a postscript stating that "this letter is not a clarification of current legislation, since Roszdravnadzor is not appropriately authorized" and recommended the medical center to refer to the Ministry of Healthcare. The regional body cited this postscript in its response to the court application, made by the medical center.

The medical center sent a very clearly worded application to the Ministry of Healthcare, as follows: "Is there a requirement to send notification to Roszdravnadzor of the occurrence of an adverse event, which does not have a causal link to the administration of the investigational product?" However, the Ministry in its reply avoided giving a clear answer to this question. The reply cited various regulatory acts, with more or less relevance to the specific instance, and concluded with the strange statement that "the term 'adverse event' is not used in Law No. 61-FZ" (this is, of course, true, but the term is defined in the by-law, Order No. 266 of the Ministry of Healthcare, dated June 19, 2003, which was still effective at the time).

A court hearing took place on April 25, 2016 in the Arbitration Court of Krasnodar Territory (Krasnodar), at which Judge I.A. Pogorelov rejected the application by OOO Medical Center Nefros to declare illegal and cancel the decision by the Roszdravnadzor body for Krasnodar Territory on administrative liability In his verdict the judge effectively repeated the arguments of the regional body. Stating the reasons for his verdict the judge noted that replies of the Ministry of Healthcare, Roszdravnadzor and the Association of Clinical Trial Organizations (ACTO also submitted its opinion on the issue), "are not accepted by the court as evidence demonstrating the absence of an obligation to provide information, because they are not regulatory acts".

Disappointed by the decision of the court of first instance, the clinic brought an appeal, which was heard by the 15th Arbitration Appeal Court in Rostov-on-Don on August 8, 2016. The panel of judges carefully studied the case materials and the appellant's arguments and also heard the expert opinion of a nephrologist working at Rostov State Medical University, who stated that community-acquired pneumonia cannot be caused by the administration of any medicinal product, as the disease is always (regardless of its form) caused by malicious viruses and bacteria. The specialist further clarified that polycystic kidney disease, also known as autosomal dominant polycystic disease of adults, is a hereditary disease. So the female patient was born with a pathological gene, and a medicinal product used in the clinical trial could not have caused the disease and, consequently, hospitalization. The doctor concluded that the "serious adverse events" consisting of hospitalizations due to an infectious disease and a genetic disease cannot be classified as "serious adverse reactions".

Having studied the case materials, considered the arguments of the appeal and heard representatives of the medical center and the nephrologist, the panel decided that the court of first instance had confused the terms "adverse/serious adverse reaction" and "adverse event" and therefore delivered an incorrect verdict. So the verdict of the Arbitration Court of Krasnodar Territory was reversed and the decision of the regional Roszdravnadzor body in Krasnodar Territory to impose administrative liability on OOO Medical Center Nefros was recognized as improper and was canceled.

This decision came as a great relief both to the medical center and also to ACTO members, who knew of the dispute and had followed it with great interest. The case was highly important for all those involved in the clinical trial market because if an investigator was obliged to inform Roszdravnadzor (or its regional body) of adverse events observed in clinical trials, a precedent would be set with unpredictable consequences. The outcome would have been regrettable, though not catastrophic, if the practice of the regional body was confined to a single Russian region. In this case, the sponsors and CROs, understanding that such a precedent could seriously threaten the integrity of the international trials system, might have decided to stop working in Krasnodar Territory. As it happens, Krasnodar is far from being the leading Russian region in terms of clinical trials. In 2015, it was ranked 17th by the number of IMCTs among Russian regions and 36th by the number of IMCTs per million population (*ACTO Newsletter No. 12*). Matters would have been more serious, with unpredictable consequences, if the bad practice had spread to other regions.

Finally, another bizarre episode should be mentioned, which is connected with the Krasnodar case. After the successful resolution of the dispute, a study doctor contacted an ACTO member company to seek clarifications relating to the following letter, which the doctor had received from another company (the author is unknown):

"Allow us to remind you once more of the importance of timely reporting of serious adverse events by investigators.

According to the Federal Law No. 61 "On Circulation of Medicines", the Investigators and the Sponsor are obliged to report side effects, adverse reactions, serious adverse reactions and unexpected adverse reactions to the competent federal authority.

The reporting by the Investigator should be immediate and not later than within 24 hours from the receipt of the notice.

In the event of reporting failure or non-disclosure of this information, liabilities under the laws of the Russian Federation shall be imposed.

An inspection by Roszdravnadzor at the center in XXXXXX found violations of time limits for the transfer of information to the Federal Service for Surveillance in Healthcare and Social Development [Roszdravnadzor] *following the detection of a serious adverse reaction to a study product. The institution was subjected to administrative liability and fines were imposed. The clinic applied to court and lost in the first instance.*

The outcome of an appeal against this verdict has now became known, according to which both the decision of the court of first instance and the decision of the regional RZN body to make the clinic liable under administrative law have been revoked (the clinic was able to prove that the SAE was not related to the study product).

Please keep in mind that a clinic may be held liable for not reporting SAEs in a timely manner, with very unpleasant consequences".

Since the author of the letter could not be established, nor the number of clinics to which the letter had been sent, ACTO judged it necessary to urgently inform its members of what had happened and to remind them of the provisions of current Russian legislation and of the ICH GCP, which do not state that data on adverse events must be reported to regulatory authorities.

Bearing this curious case in mind, we would repeat once again the fundamental principles governing urgent reporting of safety data during clinical trials:

1) Serious unexpected adverse reactions, and not serious adverse events, are subject to expedited reporting (i.e. reporting within the established time limits) to the competent authority (in Russia, to Roszdravnadzor);

2) The duty to report serious unexpected adverse reactions observed in clinical trials to Roszdravnadzor lies with sponsors or their authorized CRO, and not with investigators or the medical organizations where the trials are conducted;

3) Reports concerning safety in clinical trials should be forwarded to the central office of Roszdravnadzor, and not to its regional bodies. Otherwise the consequences may be unpredictable.