ACTO

Association of Clinical Trials Organizations

ACTO NEWSLETTER № 17

1st Half of 2018

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SUMMARY

In 2017 the Association of Clinical Trials Organizations (ACTO) reported on the reduction of approvals for conducting clinical trials and this trend continues. The number of approvals granted in H1 2018 fell by 15.1% year-on-year and by 32.4% as compared to H1 2016. Consistent reduction in the number of approvals issued throughout two recent years has affected all types of trials with the exception of international multicentre trials and bioequivalence studies by Russian sponsors, fluctuations in the number of which do not fit the named trend. The reduction is most evident in local trials sector by foreign sponsors. Last year their number sagged by 55.6% and the year before – by 35.7%. The number of approvals for bioequivalence studies by foreign sponsors has dropped as well: by 38.6%, as compared to H1 2017, and by 66.3% against H1 2016. The local trials sector by Russian sponsors has also shrunk. The fall stood at 11.9% as compared to January-June 2017, but in two years it was as deep as 37.9%. There are two main reasons behind the contraction of these market shares. The first one is the demand to provide results of the industrial site inspection by the Russian inspectorate, which was introduced two years ago. The second one is cancelling the requirement to study "therapeutic equivalence" for some forms of generics. The said changes in the market resulted in a growing share of international multicentre clinical trials. This sector accounts for 44% of all trials conducted in Russia, which is a maximum level since 2012.

An overview of the special market segment (domestic biosimilars) was prepared for ACTO by an invited author – Roman Drai, Director, Clinical Development, Gerorpharm Group. Drawing upon the data analysis for seven recent years, the expert states a consistent development of clinical trials of domestic biosimilars in Russia. During this time 65 drugs were examined in 102 studies, with 7 of these being granted approvals in the first half of 2018. The number of approvals for biosimilar trials has been steadily rising since 2013, whereas for now the number of investigational drugs is not rising consistently. But on the whole data testify to a potential increase in the number of copies of biological medicinal products developed domestically, along with a growing number of generic drugs.

A traditional survey of ACTO members regarding the expert evaluation in getting approvals for conducting clinical trials demonstrated that the share of trials passing the expert evaluation by the Federal State Budgetary Institution "Scientific Centre for Expert Evaluation of Medicinal Products" (SCEEMP[1]) without comments was best for the period monitored by ACTO (80.7% of submissions without comments). This contrasts with the indicator for the Ethics Council, which is the worst of all monitoring times (46.9%). For all that, the share of agreements with the Ethics Council's comments went down 1.5 times as compared to 2017 (from 63% to 40%), while the share of agreements with SCEEMP comments has grown three times (from 22% to 65%).

The bulletin is closed with an overview of clinical trials of drugs to treat autoimmune diseases for the period of 5.5 years (January 2013 – June 2018). It shows that Russia generally is in tune with major trends in studying medical drugs of "most popular" diseases (rheumatoid arthritis, multiple sclerosis and others); yet remedies for other diseases (e.g. Sjogren syndrome, vitiligo) are tested in one-two international multicentre studies at best, sometimes never entering this country, thus giving the Russian market great potential for quality growth.

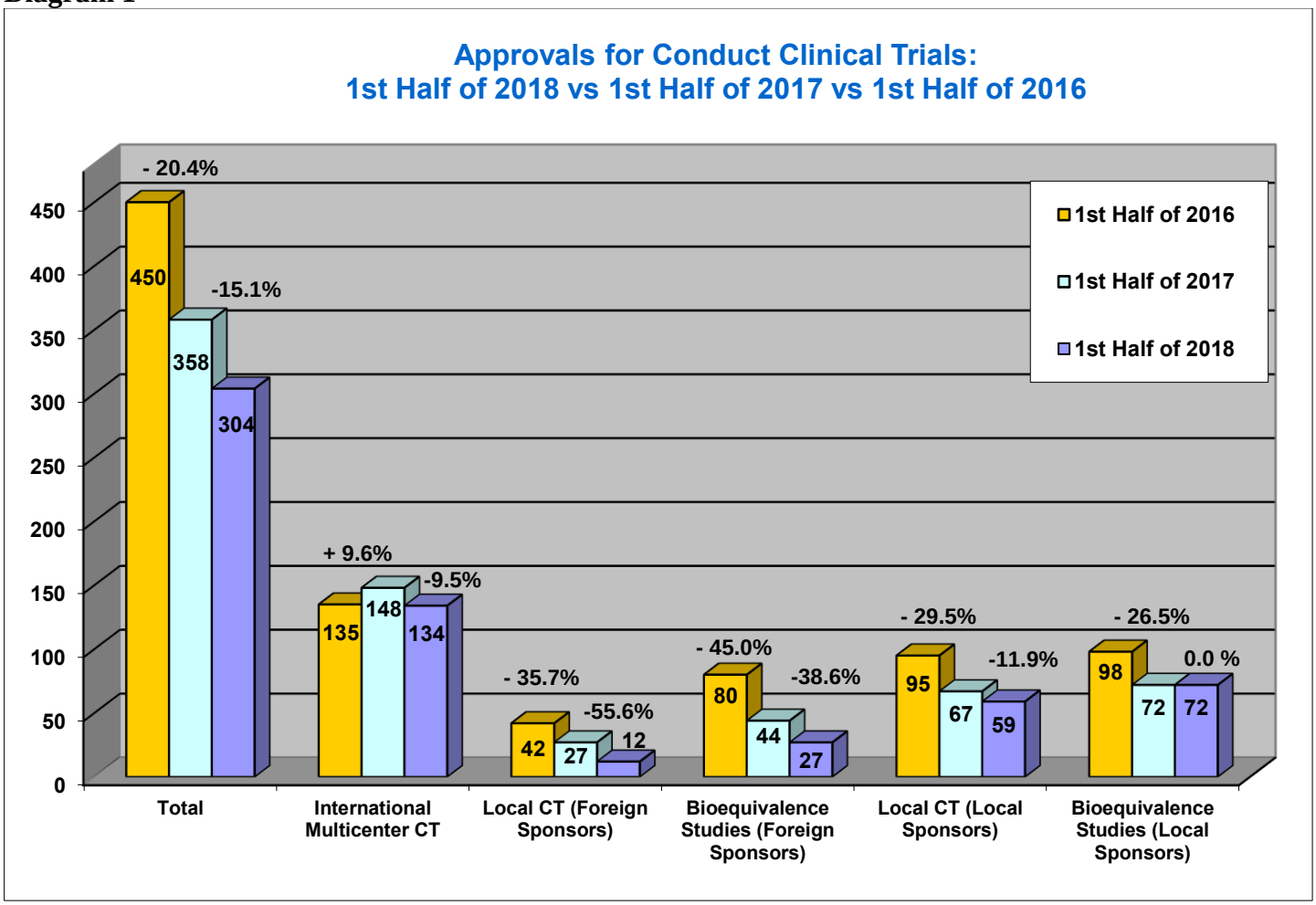
As an annex to this issue, we publish a selection of Diagrams showing statistical data on international multicentre trials in oncology and oncohaematology for 2017.

[1] aka FGBU in common usage, presentations and in ACTO previous newsletters

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

In H1 2018 the Ministry of Health of the Russian Federation granted 304 approvals for conducting clinical trials. This means a 15.1% reduction year-on-year and a 32.4% reduction against 2016. As we can see from Diagram 1, a consistent reduction in the number of approvals throughout two recent years was a major trend for all types of trials with the exception of international multicentre clinical trials (IMCTs) and domestic generic bioequivalence studies.

Diagram 1



Data from www.grls.rosminzdrav.ru

In the IMCT sector a 9.5% reduction in the number of approvals granted in H1 2018 was recompensed by the fact that during the same period of last year 9.6% more approvals were granted, than in the year before last. Thus the number of approved IMCTs actually came back to the level of 2016.

The number of approved bioequivalence studies by domestic sponsors remained unchanged year-on-year: 72 approvals both in H1 2017 and H1 2018. Although, H1 2017 lost 26.5% of trials in this segment as compared to the same period of 2016.

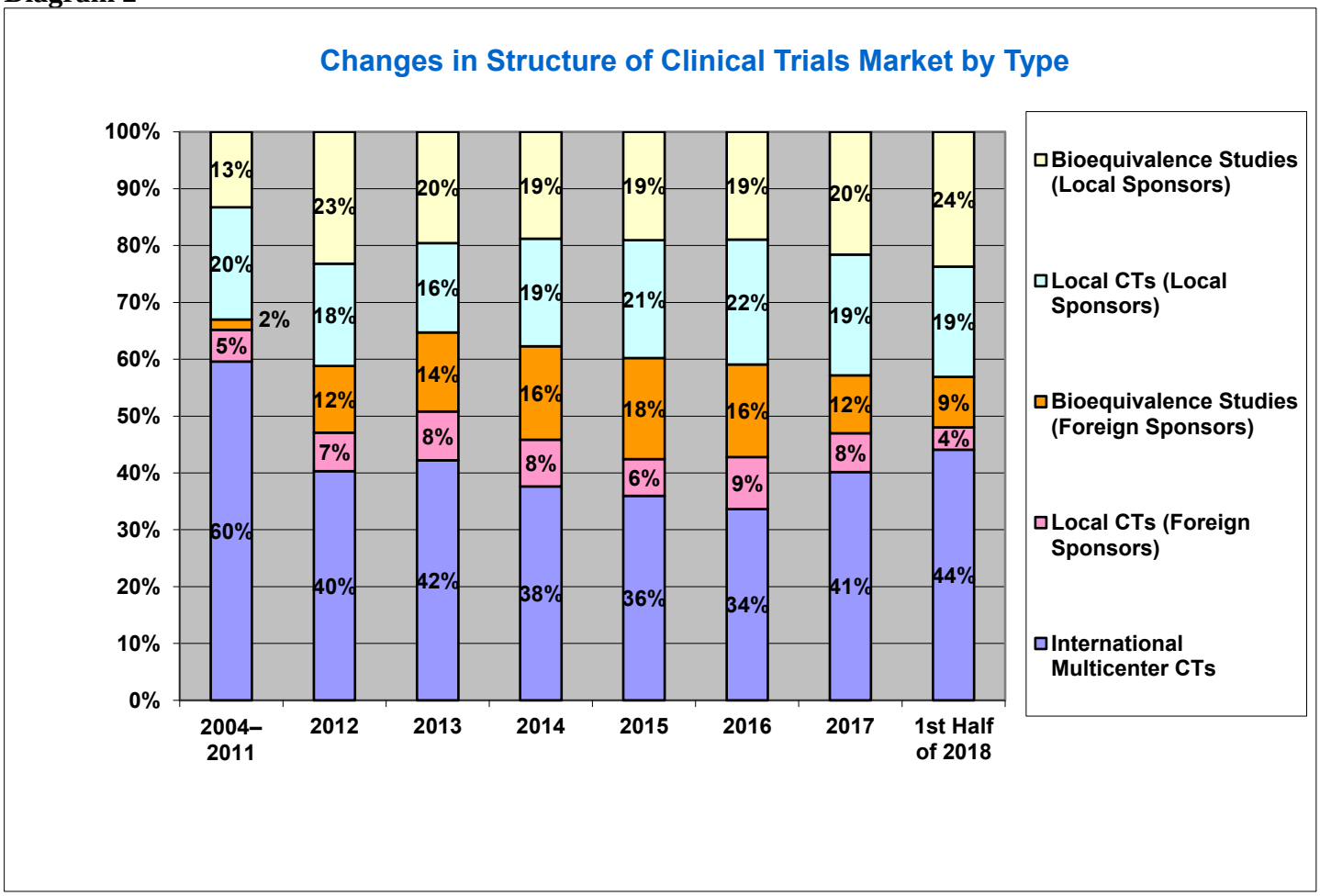
All other types of trials have tended to decline since 2017. This fall is most conspicuous in the sector of local projects supported by foreign sponsors. Last year the drop stood at 55.6%, and at 35.7% a year before. Total reduction for this type of trials during two years amounted to 71.4% (12 trials against 42 in H1 2016).

The number of approvals for bioequivalence studies conducted by foreign sponsors has also dropped significantly during two years. So, in H1 2018 it went down by 38.6% year-on-year and by 66.3% compared to 2016. (27 versus 80 approvals).

The reduction also tangibly affected the sector of local trials by Russian sponsors. It was less dramatic in the last period (11.9% fewer approvals in H1 2018 year-on-year); yet the drop was as deep as 37.9% in two recent years.

A nonuniform fall in the number of approvals in different sectors led to changes in the market structure (Diagram 2). It can be seen that the share of IMCTs has tended to grow since 2017, hitting the bottom in 2016 i.e. 34% of all trials conducted in Russia; during 18 months this sector bounced 10% back, hitting the maximum mark since 2012: 44%. The share of bioequivalence studies by Russian sponsors also reached the maximum level of 24% after the law "On Circulation of Medicines" has been passed. On the contrary, the shares of local trials and bioequivalence studies by foreign sponsors (4% and 9% respectively) have recently dropped to their lowest level in the past years. The share of local trials by Russian sponsors has also dwindled, albeit insignificantly – 19% versus the maximum 22% in 2016.

Diagram 2



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

We already mentioned some probable reasons for changes of the market structure in the previous issue of this bulletin, where we reviewed the results of 2017. Let's briefly reiterate two main ones.

The first is – the demand to produce the results of manufacturing site inspection by Russian inspectorate for registration of foreign drugs that has been in effect since early 2016. This naturally resulted in fewer registrations of medicines made abroad, also affecting the number of local trials (including bioequivalence studies). Naturally, it led to a reduction in the number of approvals of medicines of foreign sponsors. This is in turn affected the number initiated local trials of such drugs (including bioequivalence studies).

The second reason is cancelling the statutory requirement to submit the results of so called therapeutic equivalence for some pharmaceutical forms of generics.

And while we consider the first amendment to the law to negatively affect the pharmaceutical market as a whole, the second one can only be saluted. The fewer unnecessary, artificially imposed trials we have in Russia, the more robust the industry is. This is unlikely to happen quickly, but maybe someday our officials will mature enough to abolish the requirement of local trials for medicines to get registered in Russia. So, now the talk about it has resumed: the idea is to simplify access to the market for drugs that have undergone clinical trials in EU, USA of Japan. In particular, this idea is reflected in the government-approved road map "On Competition in Health Industry". For now we'd not take the given initiative seriously, but it's the first step that counts. Hopefully one day Russia will scrap local registration trials, following the example of China.

So the trend we talked about in our previous newsletter continued in the first half of 2018. It will be interesting to see how the shares of different trial types will change at the end of this year.

CLINICAL TRIALS OF DOMESTIC BIOSIMILARS

R.V. Drai
PHD, Director, Clinical Trials Department, GEROPHARM Group

During the last several years the Russian Federation has traditionally been perceived as a country of generic medicinal products. This is corroborated both by the number of approvals for clinical trials granted to pharmaceutical firms and by the number of registered medicinal products. Generics – low-molecular medicinal products produced via chemical synthesis – accounted for most of domestic developments in several recent years. There were very few originator medicines made in Russia.

Rapid global advances of pharmaceuticals in the last decade brought a large number of biotechnological products to the market. The programme of their preclinical and clinical development differs substantially from that for products of chemical synthesis. The replication development programme for such medicines is also stark different. Copies of biotechnological molecules are ranked among biosimilars, not among generics. Compared to generics, biosimilars have more extensive programmes of preclinical tests and clinical studies.

We are interested in the involvement of domestic pharmaceutical companies in trials and launch of not only generics, but also biosimilars. Thus, we conducted our analysis of clinical trials of domestic biosimilars over the last seven years. Statistical data were obtained by analysing the downloaded register of approved clinical trials[2]. These may contain minor inaccuracies due to specifics of keeping the register and objective difficulties of working therewith. Yet we supposed this did not distort the general picture reflecting the trends in the development of clinical trials of biosimilars in the Russian Federation during 2011–2018.

Why did we analyse data for the recent 7 years and not for 10–15 years, for example? There are several reasons.

First, for now biosimilars have a limited background: the first one was authorized in Europe in 2006 and there were only 11 of these by 2010. Prior to 2011 biosimilars had not been studied in Russia in keeping with modern requirements of evidence-based medicine and the concept of biosimilars.

Secondly, keeping the register of approved clinical trials that serves as a source for the present analysis became mandatory just at that time – since late 2010.

Thirdly, it is starting with the adoption of the new law “On Circulation of Medicines” in 2010 that a more or less modern law on clinical trials emerged, whereas those that had been approved and conducted prior to 2010 are not always analysable.

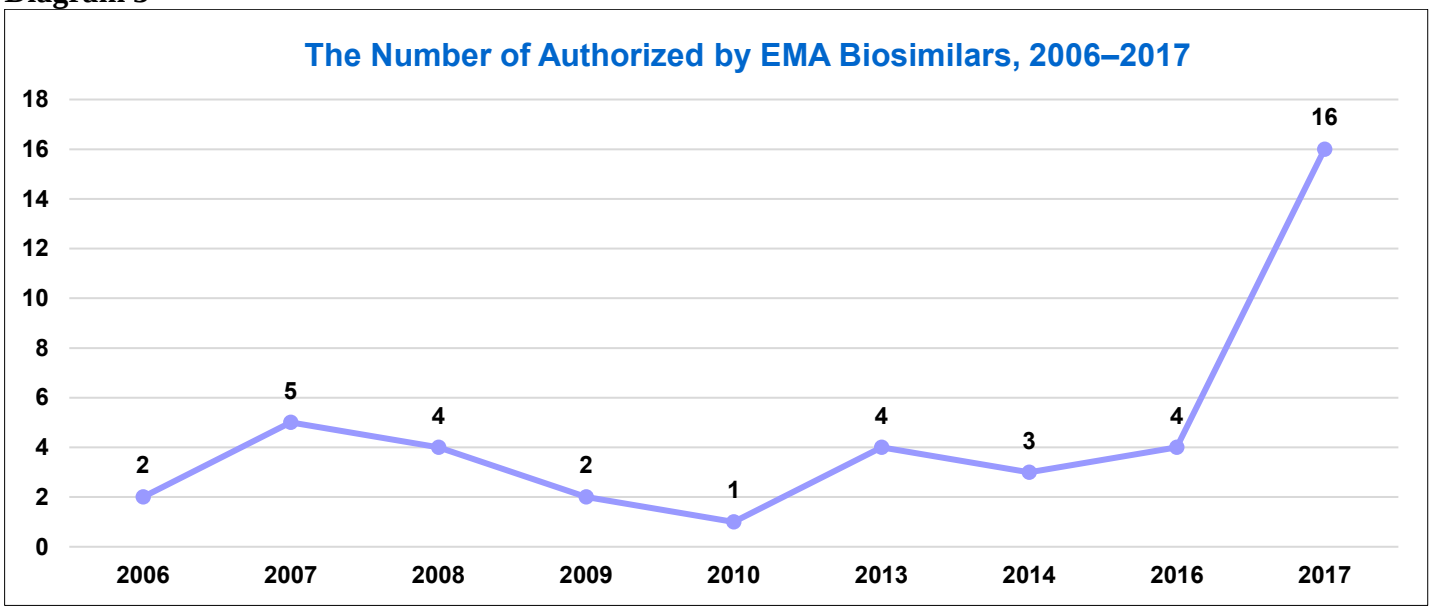
For comparison, marketing authorization for biosimilars in Europe from 2006 to 2018 was analyzed on the basis of European public assessment reports from the EMA website[3].

[2] http://grls.rosminzdrav.ru/CIPermitionReg.aspx
[3] European public assessment reports (access date: 09.07.2018).

Biosimilars in Europe

As of the end of 2017 EMA authorized 41 biosimilars. It is the year 2017 (Diagram 3) that accounted for most authorizations. In other words, clinical trials of those medicines were conducted in 2010–2015. Three more products were approved in H1 2018.

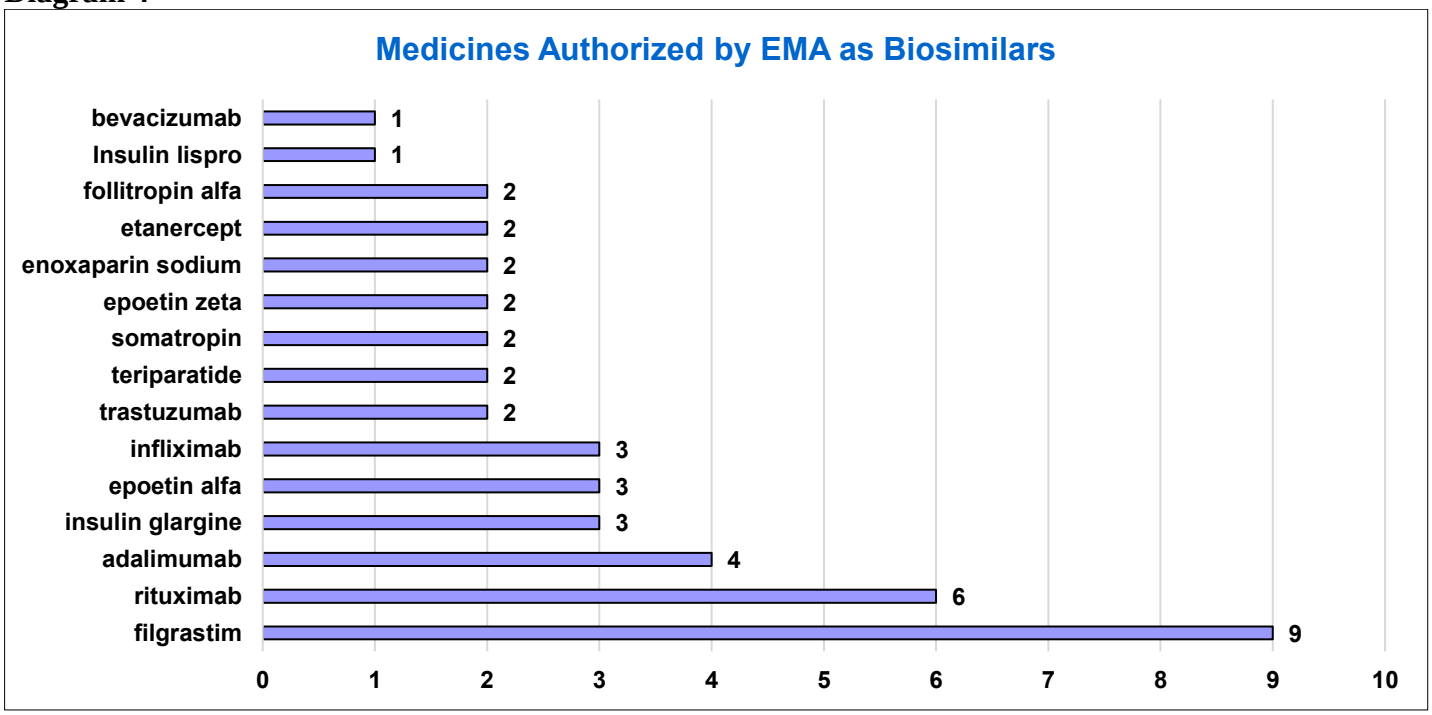
Diagram 3



Data from http://www.ema.europa.eu

You may see from Diagram 4 that the majority of biosimilars authorized in Europe is filgrastim (nine medicinal products), rituximab (six) and adalimumab (four).

Diagram 4



Data from http://www.ema.europa.eu

Sandoz and Celltrion were most active or successful among pharmaceutical companies, each responsible for six medicines, as well as Samsung with four products (Diagram 5).

Diagram 5

Data from http://www.ema.europa.eu

Yet we should pay heed to one peculiarity in the given statistics that is not visible to the naked eye.

For some reason several companies launched medicinal products having one INN under different trade names. Thus Sandoz ended up having two rituximab drugs (Riximyo and Rixathon), Celltrion – four rituximab drugs (Blitzima, Ritemvia, Rituzena (former Tuxella) and Truxima), Amgen – two adalimumab drugs (Solymbic, Amgevita), Ratiopharm – two filgrastim drugs (Ratiograstim, Filgrastim ratiopharm). Indications normally concur: fully in some cases and partially in other cases. It remains unclear why one company markets different medicinal products under different trade names in the same region. But in this way 38 products have been authorized in Europe, not 44 as they usually state in their presentations. Which means their number falls short of 40. Nevertheless, we are confident that this threshold will soon be surpassed, because Europe is not going to reduce the number of biosimilar authorizations. The contrary is true: we are witnessing a simultaneous liberalization of biosimilar trials guidelines and a growing number of large and medium-sized businesses entering the race of biosimilars. Europe is followed by the United States.

Clinical trials of biosimilars in the Russian Federation

At present, about 65 domestic biosimilars are being tried in Russia. If we add to this IMCTs and local trials of foreign sponsors, then there will certainly be more of them, but it is domestic products that were the subject of our research.

Insulins account for 25% of all trials: Glargine (five medicinal products), genetically engineered human insulin (solution, suspension NPH and a mix, two each, six in total), Aspart (two), Lispro R (two) and Lispro mix (one) – the total of 16 new insulins.

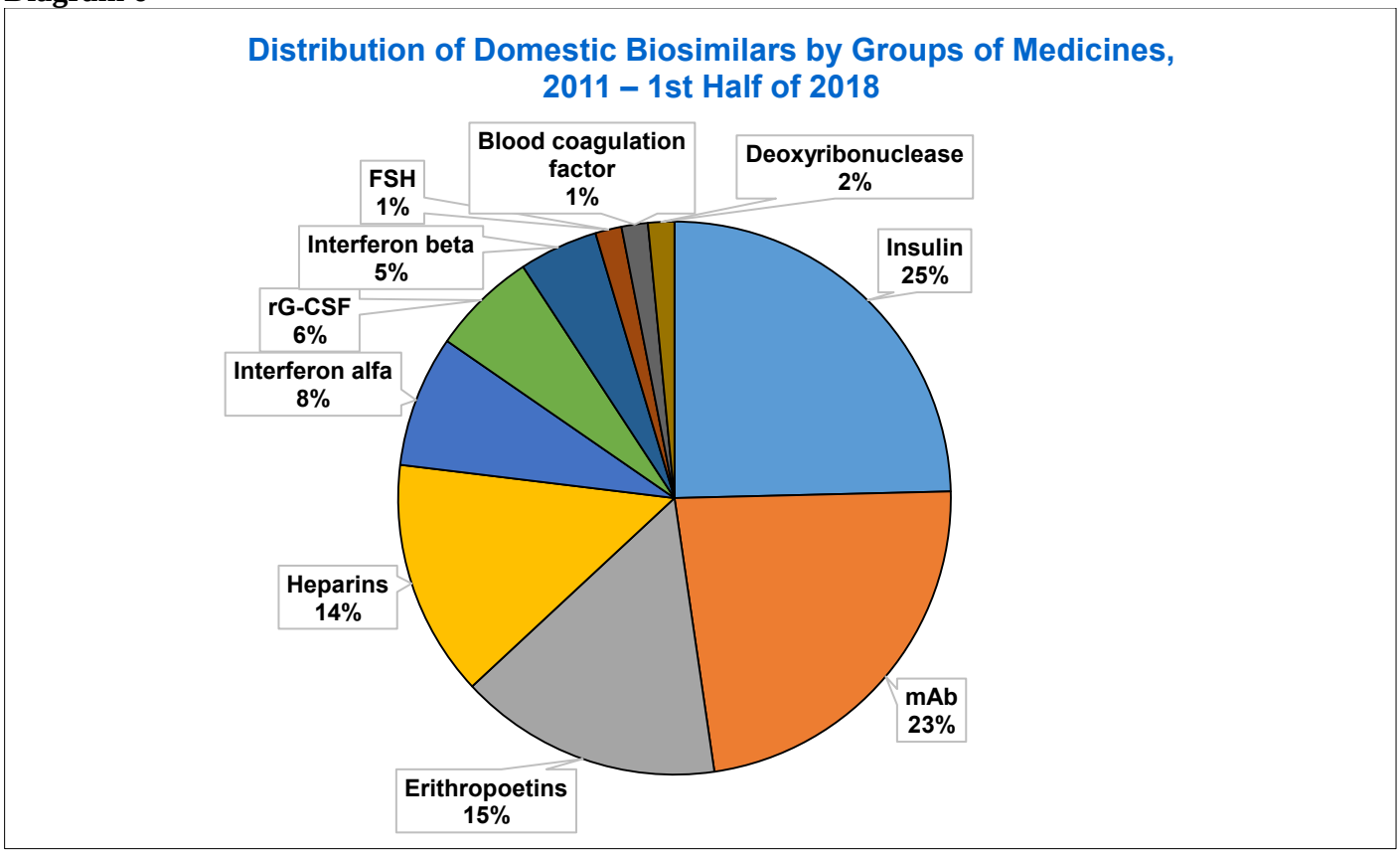
Monoclonal antibodies account for 23% of all biosimilar studies. Lying in store for us in the future to come are: rituximab (three medicinal products), infliximab (three), trastuzumab (two), bevacizumab (two), osteoprotegerin-IgG1(Fc) (one), eculizumab (one), adalimumab (one), omalizumab (one).

Erithropoetins account for 15%. The trials of 10 products from this group have been conducted.

14% fall to the share of heparins.

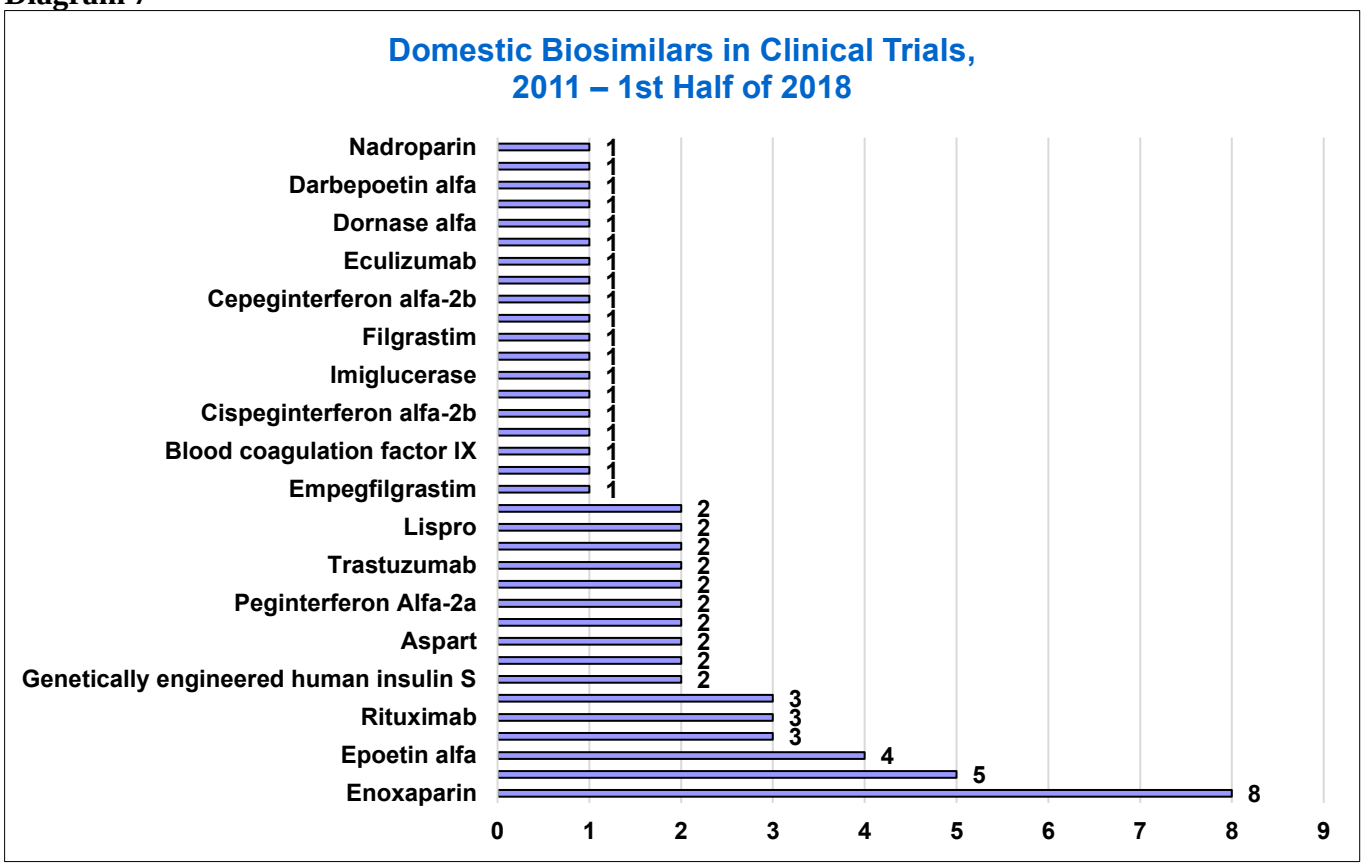
The rest account for less than 10%. For more detail see Diagrams 6 and 7.

Diagram 6



Data from www.grls.rosminzdrav.ru

Diagram 7



Data from www.grls.rosminzdrav.ru

An undisputed national leader in clinical trials of biosimilars has been Biocad (Diagram 8).

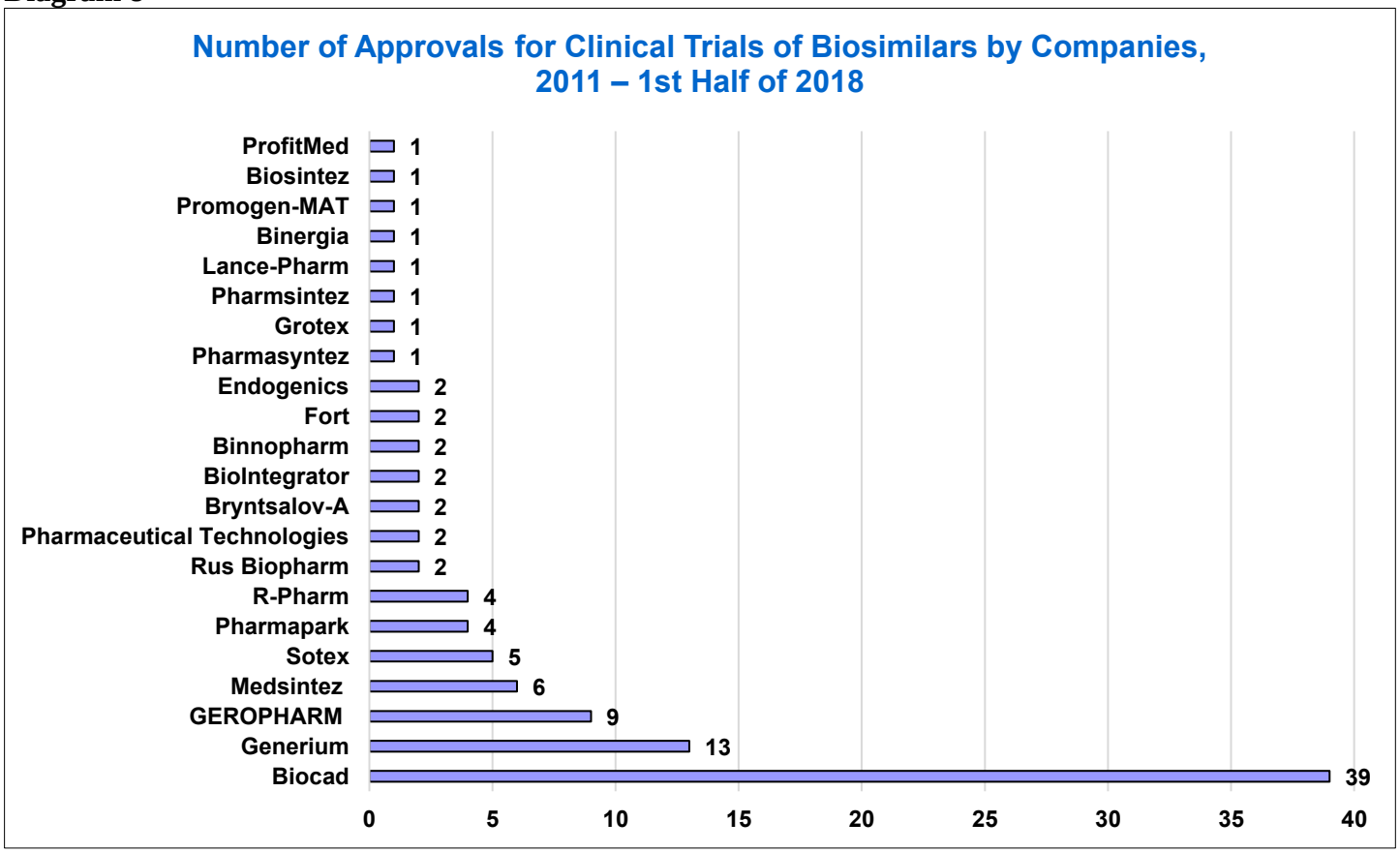
Biocad topped the list of national companies by the number of clinical trial approvals back in 2011 and since then it has stood its ground. Overall from 2011 to 2018 the company was granted 39 approvals for the trials of 19 products. This year (as of the early July 2018) Biocad has not been granted a single new approval for biosimilar studies. This might be attributed to its orientation towards innovative medicinal products.

Generium ranks second: during the period under study it got 13 approvals for the trial of eight products.

GEROPHARM ranks third: nine clinical trials of six products.

Overall in more than seven recent years 22 national pharmaceutical companies were granted 102 approvals for conducting clinical trials of 65 products. Seven approvals have been provided in 2018: for Generium (three), GEROPHARM (one), Medsintez (one), R-Pharm (one) and Pharmaceutical Technologies (one).

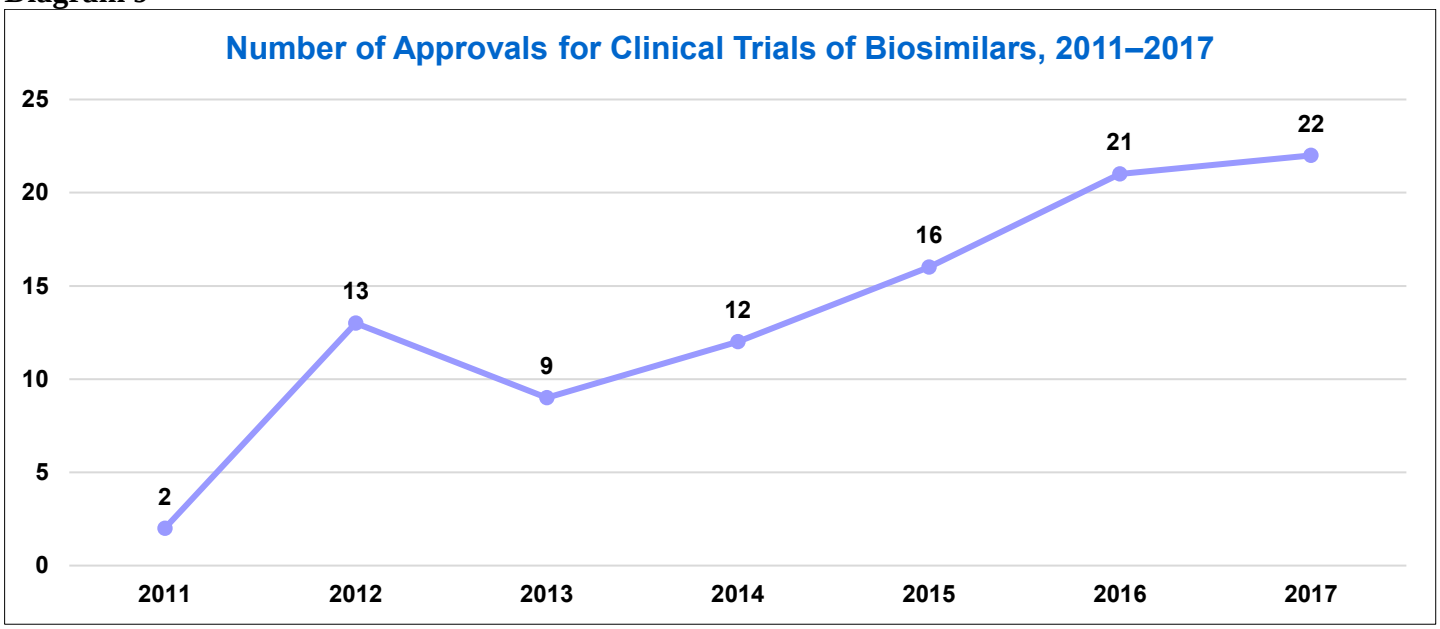
Diagram 8



Data from www.grls.rosminzdrav.ru

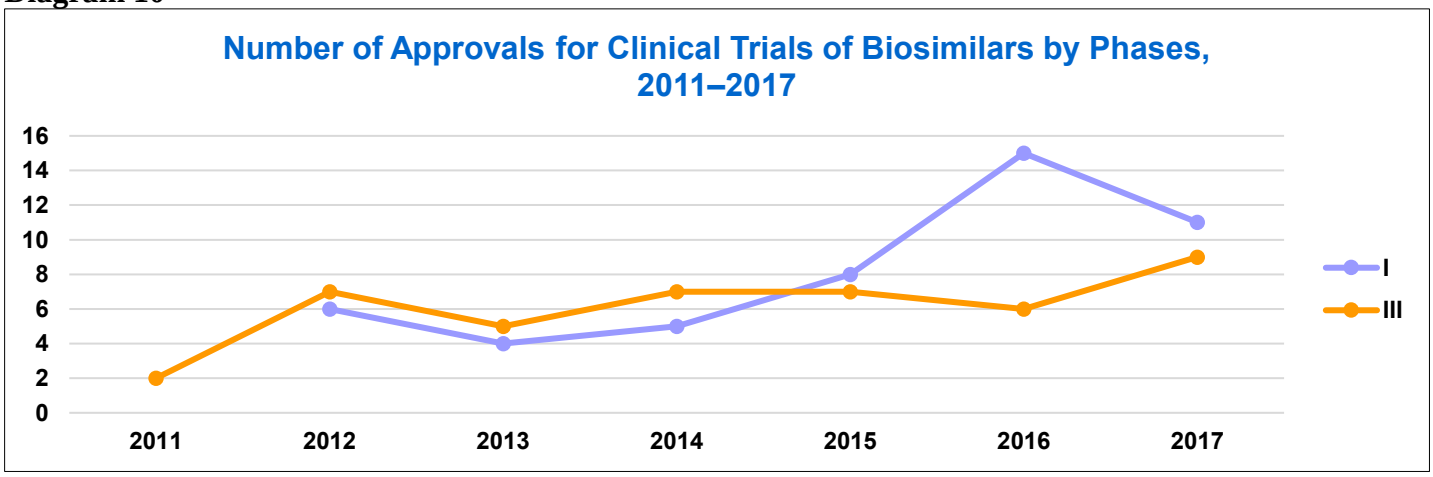
The number of approvals provided since 2011 has been steadily rising, with a minor sag in 2013 and 2014, which is most likely caused by a large number of approvals issued in 2012 (Diagrams 9 and 10).

Diagram 9



Data from www.grls.rosminzdrav.ru

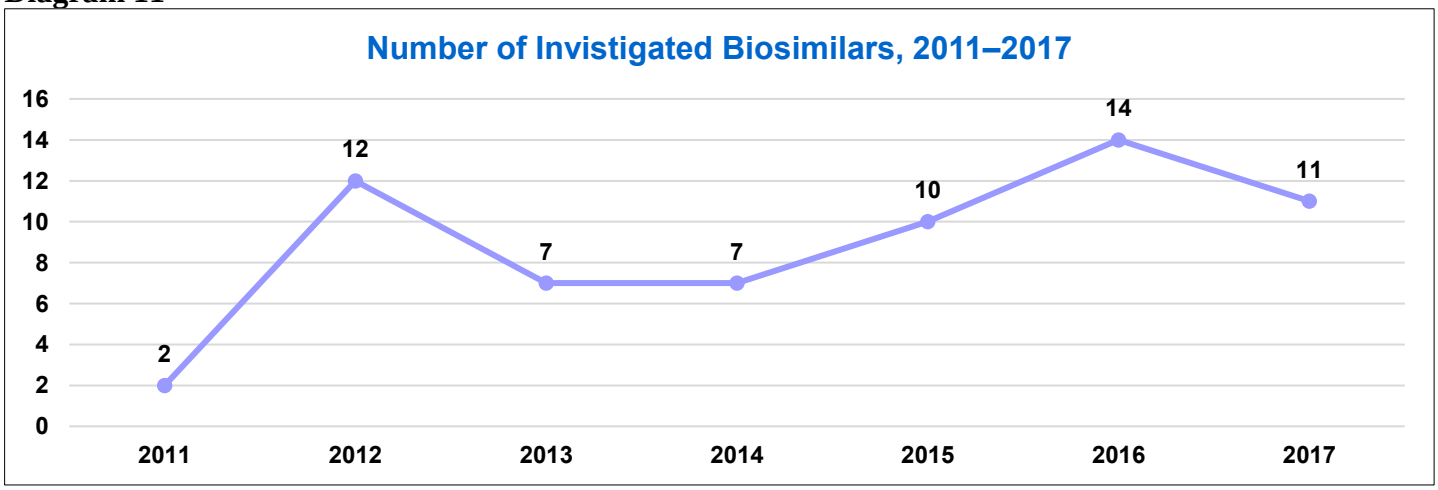
Diagram 10



Data from www.grls.rosminzdrav.ru

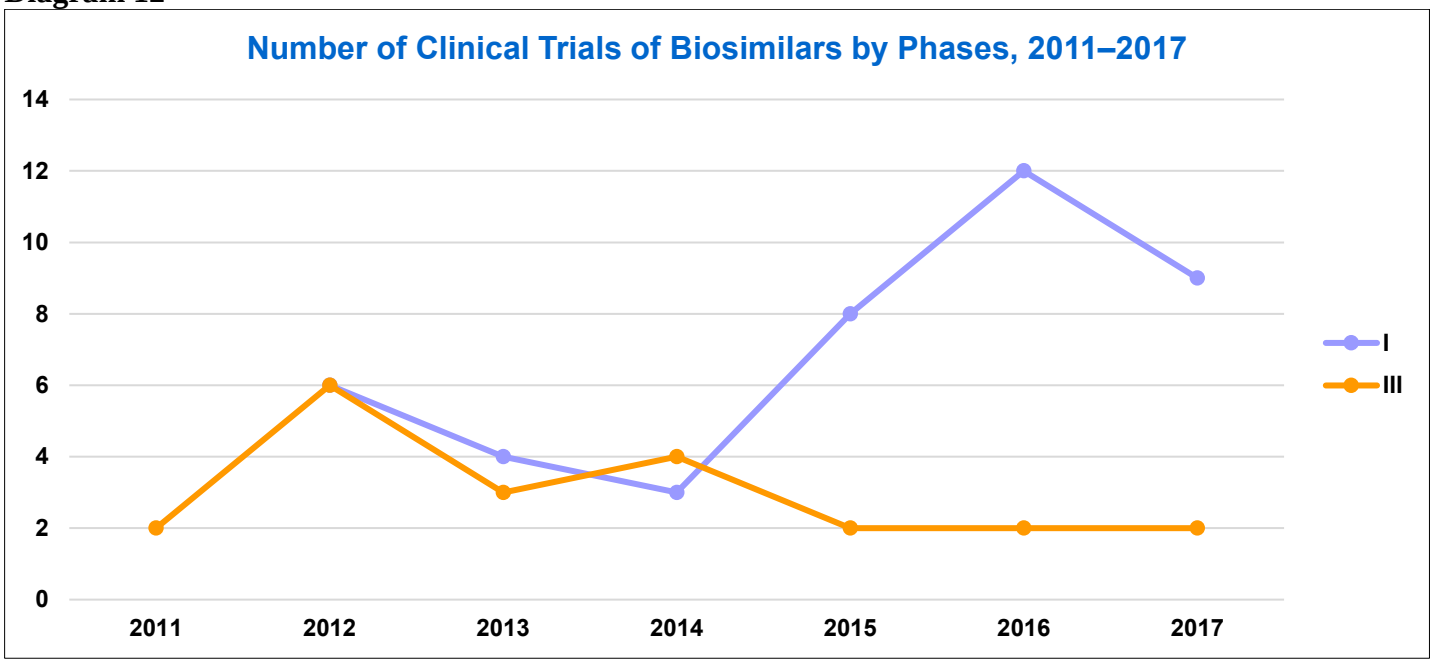
Yet the number of medications studied did not grow; on the contrary: there was a minor setback in 2017 – 11 new biolsimilars as compared to 14 in 2016 (Diagrams 11 and 12).

Diagram 11



Data from www.grls.rosminzdrav.ru

Diagram 12



Data from www.grls.rosminzdrav.ru

How can we explain an increase in the number of approvals for trials and simultaneous reduction in the number of medicinal products studied? Several factors are at play.

First of all, more than one clinical trial is needed for the marketing of biosimilars: pharmacological properties of a product are studied first (so-called phase I – PK/PD) as well as the efficacy and safety of a future medicine with an eye on immunogenicity (phase III) As long as extrapolation of indications based on one trial of phase III is impossible, several trials of phase III are conducted. In rare cases, PK and PD are studied separately.

Secondly, as we can see from the diagrams, clinical trials of biosimilars in Russia began with phase III (two approvals in 2011). In general, this is not forbidden by valid requirements; nevertheless, pharmacological properties need to be studied later, which has been the case. Starting in 2015, the number of trials Phase I of biosimilars keeps rising both due to new products and due to the fact that companies have started completing the studies of early phases for those medicinal products, for which they were never done before.

The number of third-phase trials has been falling since 2015, keeping at a stably low level for three years in a row. Yet we see a considerable growth of both the number of first-phase trials and the number of medical drugs studied. This gives reasons to surmise that in the future we may see a growing number of third-phase trials of biosimilars in Russia. This is partly corroborated by 2018 statistics showing that as of the early July 2018 seven approvals had been granted, including one approval of the trial Phase I and six approvals of trials at later stages. The year 2018 is not over yet and it will be interesting to watch future dynamics.

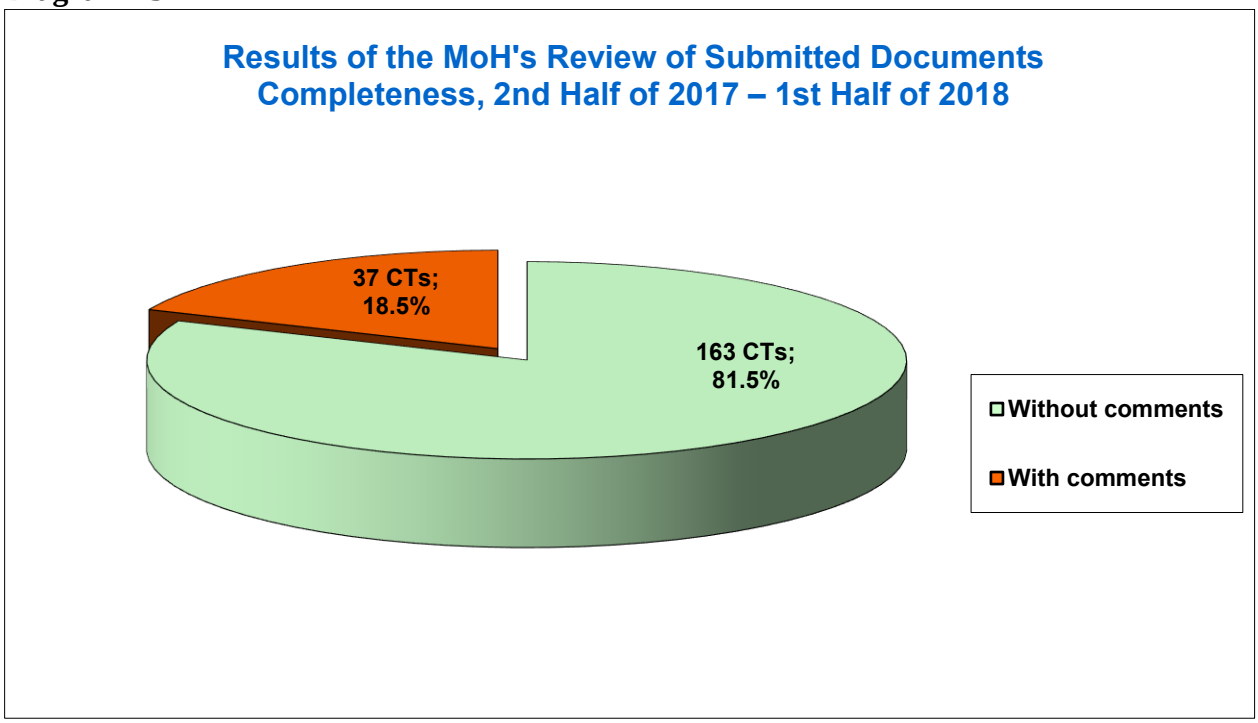
Thus we can witness a consistent development of clinical trials of biosimilars in the Russian Federation. On the one hand, this is some evidence of their potential numerical growth along with the number of generics. On the other hand, we can witness national pharmaceutical companies and CROs accumulating experience in conducting sophisticated PK/PD trials as well as efficacy studies. This inspires hope that the Russian market of clinical trials may develop not only due to the effort of foreign companies, but also due to the activity of national business.

EXPERT EXAMINATION OF PLANNED TRIALS

Every year we analyse the practice of passing expert evaluations, to get approvals for conducting trials. As usual, the analysis was based on a survey of ACTO members from the second half of 2017 to the first half of 2018, with 24 companies involved.

The results of the Russian Ministry of Health's document completeness review are shown in Diagram 13. Problems arose in the submission of 18.5% of all applications (37 trials) versus 17% a year before.

Diagram 13



Data from www.grls.rosminzdrav.ru

While indicators remained almost unchanged, applicants complain about a more complicated document submission procedure. The main difficulties faced by companies at the present stage are related to the need to include in the regulatory submission package a conclusion of the authorized body in a manufacturing nation about compliance of the manufacturing site with GMP requirements. The problem is that for some reason they do not read the Russian law "On Circulation of Medicines" in all countries and, accordingly, do not authorize their national agencies to provide such certificates.

Normally, we have less problems with production of European countries. With the USA the situation is more difficult, since GMP certificates are not issued there. Yet the Russian Ministry of Health favorably accepts a translation of a relevant page from the FDA Drug Establishments Current Registration Site. Yet missteps are possible in cases of experimental manufacture which does not imply an output of commercial batches. In such cases manufacturing sites are not licensed in the USA. The situation is even worse in Japan which simply lacks manufacture inspection systems like ours. Surely, inspection can be organised, when it is requested by a company. But this will take a lot more time and entail plenty of headache to boot. But if a sponsor wants to include Russian centres in IMCT no matter what, they may certainly undertake all those procedures. Although in such cases it's easier to forego a country with such bizarre requirements. The situation with other eastern nations like China and Korea is in no way easier. Every time the licensing systems meeting the requirements of the Russian law does not exist in the country where a medicine under study is manufactured, applicants have to invent increasingly more complicated systems of evidences that they are not four-legged. The good news is there are not so many losses on this front: according to another survey[4], so far ACTO members have lost only two international trials

[4]Regarding IMCTs that never kicked off in Russia, despite applications submitted to the Ministry of Health.

because of problems with the GMP certificate (in 2016 and 2017). Yet applicants keep on complaining at an increasingly more complicated situation regarding this matter.

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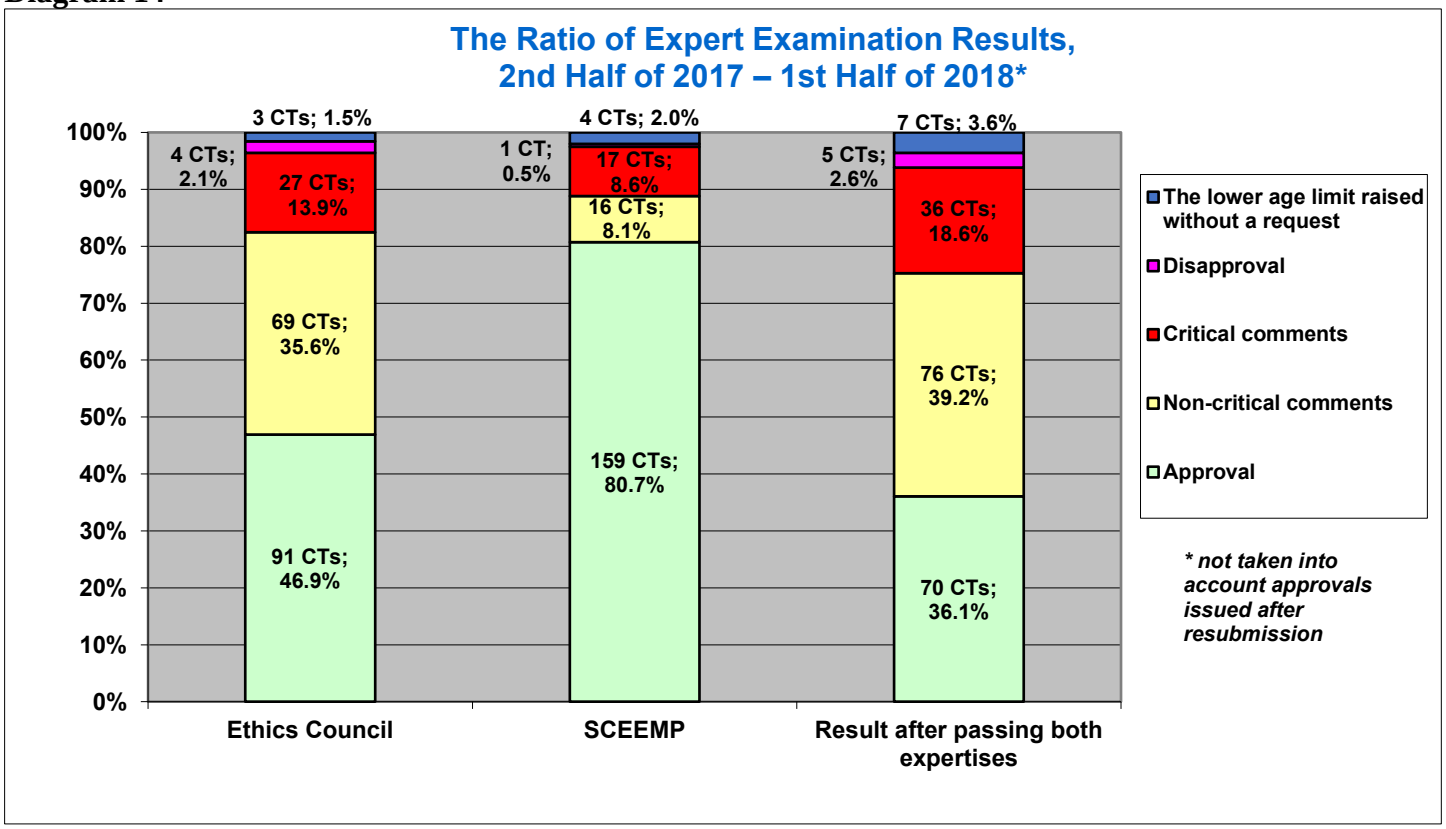
Shown in Diagram 14 is a comparison of expert evaluation results of clinical trials documents by two expert organisations: Scientific Centre for Expert Evaluation of Medicinal Products (SCEEMP) and the Ethics Council, as well as the total results of work by both bodies. At this point a new category of the possible outcome is worth mentioning: a trial is approved without comments, but the lower age limit for children is raised. This category is added to more traditional "disapproval", "critical request/comment" and "without comments" categories.

This is how it works: the applicant submits a package of documents to the Ministry of Health, requesting a paediatric trial or a trial with adult and children's population involved at the same time. Expert bodies do not send any requests or comments concerning the age of potential participants in principle and give their approval, but the applicant learns from the approval that the lower age limit for children has been raised. For example, a trial was requested for the 1–18 age group, but the approval reads "12–18 age group". And no explanation as to why younger children were excluded.

Diagram 14



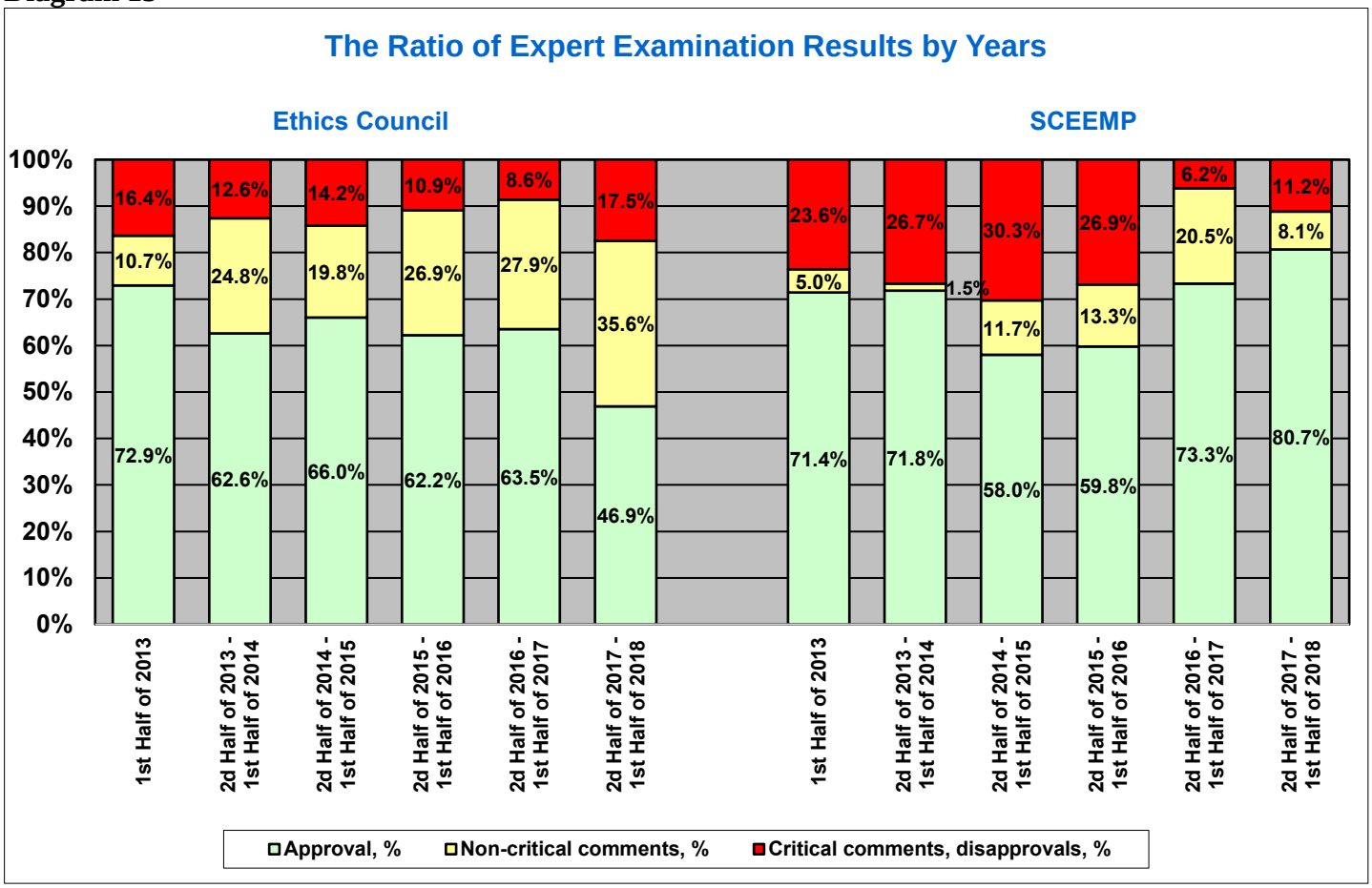
Data from poll of ACTO members

Such cases can be observed since last year. It's often hard for the applicant to understand who objects to the requested age limit, since neither SCEEMP nor the Ethics Council made no comments to this effect. They have to send one more request to the Ministry of Health. It should be noted that such outcomes did not occur in 100% of all cases (see below the statistics of results of reviewing pediatric protocols). But the very fact of this procedural novelty made us introduce a new category: "the lower age limit raised without a request." It can be seen from Diagram 14 that SCEEMP and the Ethics Council arrive at the age reduction decision using different logic. Three protocols were thus "truncated" based on the results of the Ethics Council's expert evaluation and four protocols – based on the results of SCEEMP expert evaluation. The results of both expert evaluations (third column) shows that unfortunately these were all different trials: eventually seven IMCTs were thus affected.

But let's get back to other results. We also see from Diagram 14 that the share of cases approved by SCEEMP without comments is way higher this year as compared to those approved by the Ethics Council. The share of trials that passed SCEEMP expertise without comments (80.7%) has grown by 7.4 percentage points year-on-year and has become the best during the entire history of ACTO monitoring (Diagram 15).

On the contrary, the number of cases approved by the Ethics Council without comments has been all time low this year: 46.9%. The share of critical comments and/or disapprovals by this expert body has risen from 8.6% a year before to 17.5%, whereas the share of noncritical comments has grown from 27.9% to 35.6%. These are the maximums for both categories registered during the monitoring period.

Diagram 15



Data from poll of ACTO members

The statistics obtained back the perception of market participants. In recent months ACTO has been receiving an ever growing number of complaints about the Ethics Council's expert evaluation. Complaints are caused by both the increased number of comments and their content. Thus, the number of comments made by the Ethics Council amounted to 17 for one trial only (and we are talking about international trials on which documents pass the ethics expert examination in different countries).

The nature of comments also reveals divergent stances taken by applicants and the Ethics Council members as well as the radicalization of approaches taken by the latter. So, the requirement to develop a special informed consent form for a female trial participant or participant's female partner who gets pregnant suddenly became mandatory (in a number of trials this form was originally present, but this is not a legitimate pretext for demanding it in all other cases and delaying the beginning of a trial because of its absence). Another novelty that perplexed ACTO regards the requirement to enter a full-time communication phone number to the patient emergency card for oncological trials (it turned out that some Ethics Council experts did not even know the purpose of this card, believing it to be a phone number for patients). The Ethics Council's approach to additional (including genetic) trials became very categorical. For some reason the Ethics Council members decided that

such trials can be legitimate only if they are specified in the protocol (which only shows that the Ethics Council experts are poorly versed in the current world trends).

Requirements to submit documents not specified in the law more and more frequently occur in the expert body's comments. This would be justified only if the Ethics Council was an independent ethics committee, as it is construed by ICH GCP. Yet this is not the case in our context: the given body was established for the sole purpose of performing assignments of the Russian Ministry of Health. All the Ethics Council's procedures, including a closed list of documents to be submitted for expert evaluation, are regulated by the Russian law. The Ethics Council is not entitled to act outside of this framework. This is not what experts believe, though. The Ethics Council proudly answered to ACTO's first query regarding the mounting problems with ethics expert examination that it is "empowered to express its opinion from humanistic, moral and biomedical ethic perspectives in those cases which are not reflected in the law."

The "above the law" stance is very convenient, but representatives of the international clinical trials industry should not be treated as amateurish in matters of ethic. The industry is fully capable of a conducting a dialogue on morality and humanism, especially when there are trials on the scales, participation in which gives specific patients a real chance at least to improve the quality of life or even to extend it.

ACTO is partly to blame for what has happened to the Ethics Council's review. We focused too long on SCEEMP where things with expert evaluation were a lot worse before. Moreover, compared to SCEEMP, comments by the Ethics Council have long seemed more like an itching nuisance than a serious problem. Moreover, most often they were not crucial, caused "conditional approvals"[5], and it was often easier for companies to accept them instead of making a case for their righteous cause.

As we passionately addressed other urgent matters, we overlooked a radical change of the trend, when a dragon matured. But even though we closed the stable door after the horse has bolted, ACTO still has fair chances to be heard. At any rate, the first attempt at a dialogue did take place and we brought home to the expert body some questions of the business community regarding its activities. We suppose that some time later it will be clear whether our hopes for an amicable settlement with regard for the best interests of all sides are justified: primary beneficiaries would be Russian patients for whom participation in international trials is getting ever more important, given the precarious situation with healthcare in Russia.

But let's get back to the stats. Unfortunately, despite an impressive improvement of SCEEMP's expert evaluation parameters, the "failure" of the Ethics Council notably aggravated the cumulative results of both expert examinations (see Table 1). During the period under review the share of positive conclusions based on the results of both expert evaluations was only 36.1%, down by 9.8 percentage points year-on-year. This is one more all monitoring time low. The "credit" should apparently be given to the Ethics Council's experts.

Table 1

Dynamics of the positive outcome of reviewing IMCT materials based on the results of both expert evaluations; distribution by years						
The period included in the analysis	**1st Half of 2013**	**2d Half of 2013 – 1st Half of 2014**	**2d Half of 2014 – 1st Half of 2015**	**2d Half of 2015 – 1st Half of 2016**	**2d Half of 2016 – 1st Half of 2017**	**2d Half of 2017 – 1st Half of 2018**
The share of positive conclusions based on the results of both expert evaluations in reviewing IMCT materials	**51.5%**	**43.7%**	**42.6%**	**38.3%**	**45.9%**	**36.1%**

Data from poll of ACTO members

[5] Approvals issued under conditions that corrections required in the comments would be made.

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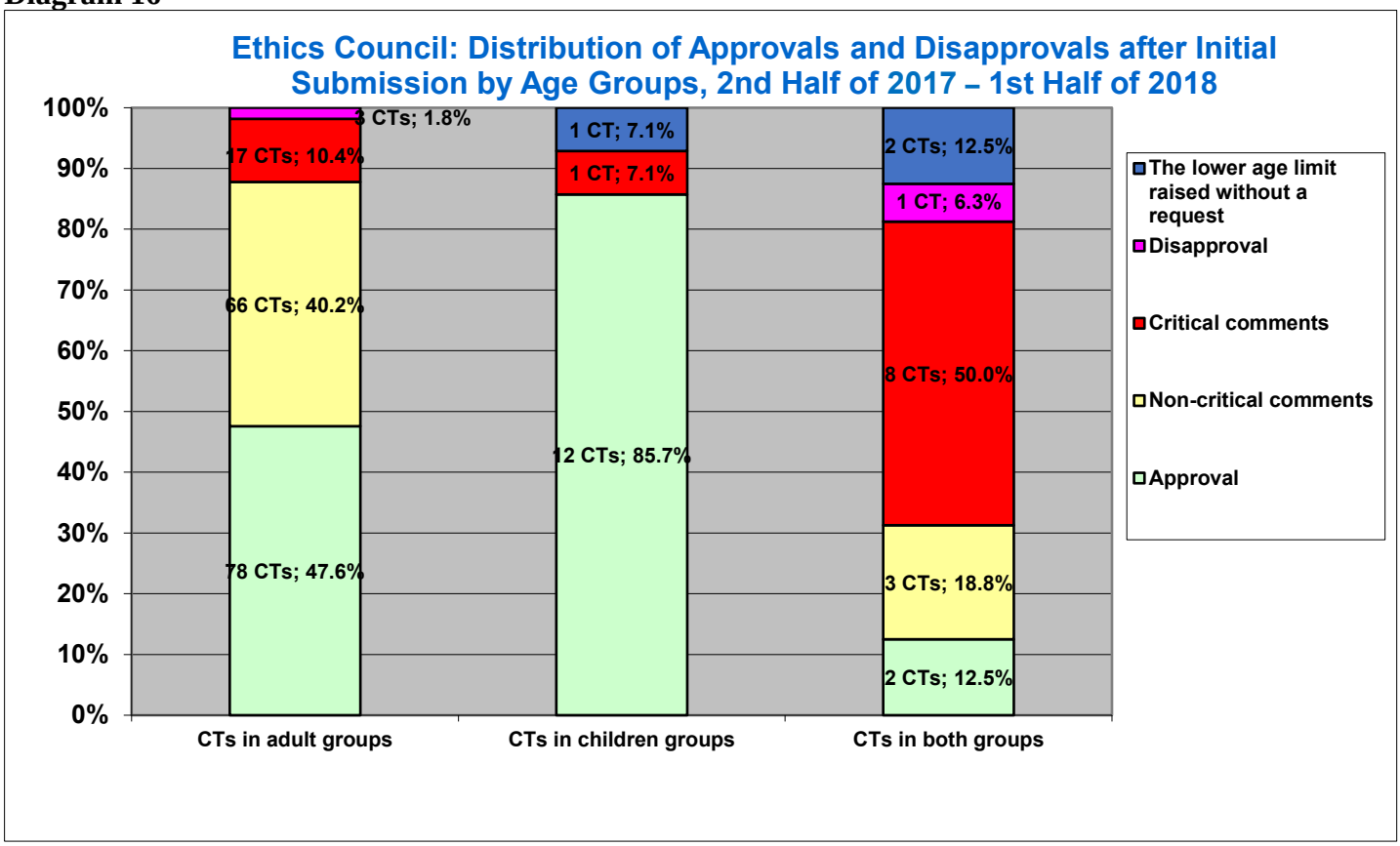
You may see on Diagrams 16 and 17, what decisions were taken by the Ethics Council and SCEEMP depending on the age group of potential participants (adults, children or both populations at one time).

Diagram 16



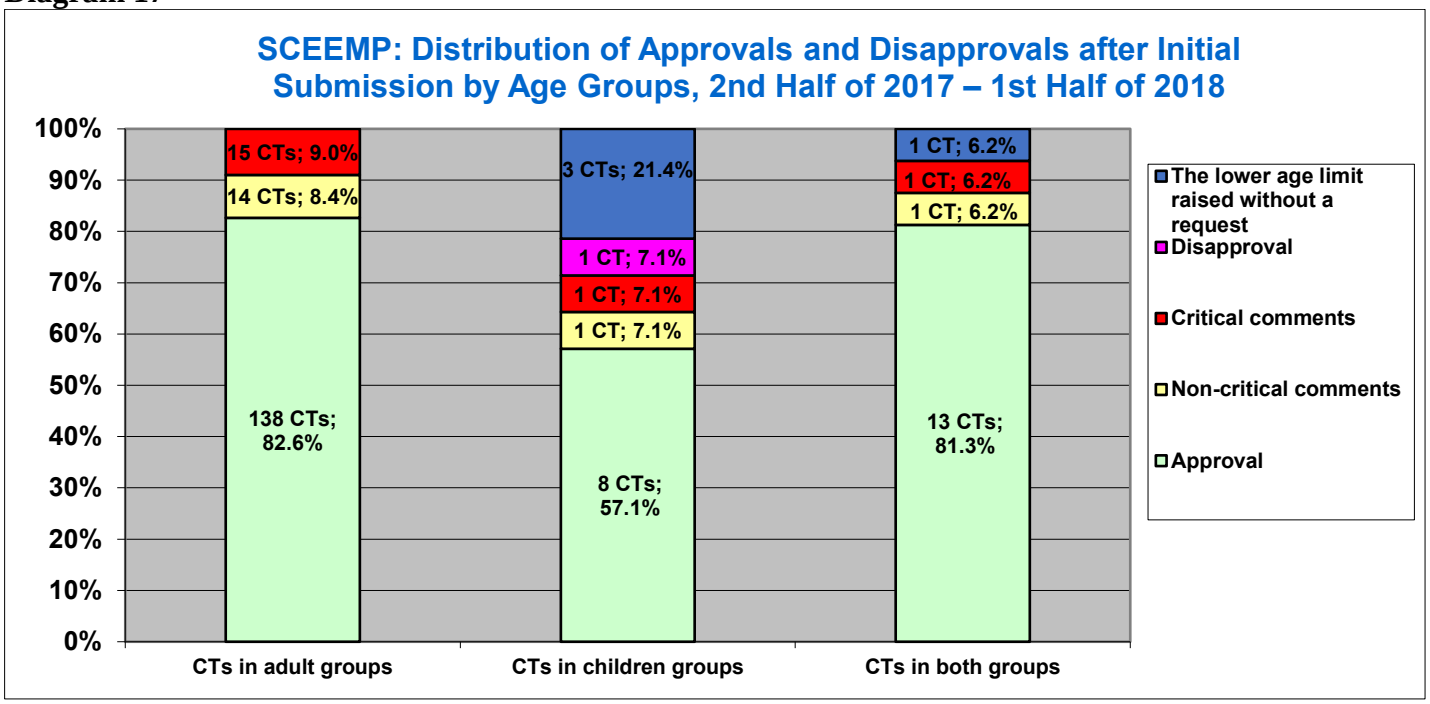
Data from poll of ACTO members

The situation with approval by the Ethics Council of trials where solely a children's population is going to participate looks rather decent (Diagram 16). The share of approvals at the first try go (85.7%) proved here twice as high as in trials with the involvement of adults. Up by 22.1 percentage points year-on-year (63.6%). The situation was a lot worse in trials with both age groups involved. The share of cases approved at the first try was minimum, only 12.5%, whereas the share of censored requests and disapprovals stood at 56.3%. Another 12.5% fell to the share of lower age limit reduction for trial participants without notifying the sponsor.

The distribution pattern of SCEEMP critical comments is more predictable (Diagram 17). It is pediatric trials that accounted for the minimum of trials approved at the first try – 57.1%. This is better than a year earlier, when their share stood at 50%. One trial each (7.1%) was disapproved, received a critical or noncritical comment. In three IMCTs (21.4%) the age of participants was raised without forwarding a query to a sponsor.

In trials with both age groups involved the share of cases approved at the first try (81.3%) was almost the same as for trials where only adults were involved (82.6%). For comparison: last year's indicator rose by 18.8 percentage points. One trial each (6.2%) received a critical/noncritical comment. In yet another trial the age of participants was raised without any comment forwarded to the sponsor.

Diagram 17



Data from poll of ACTO members

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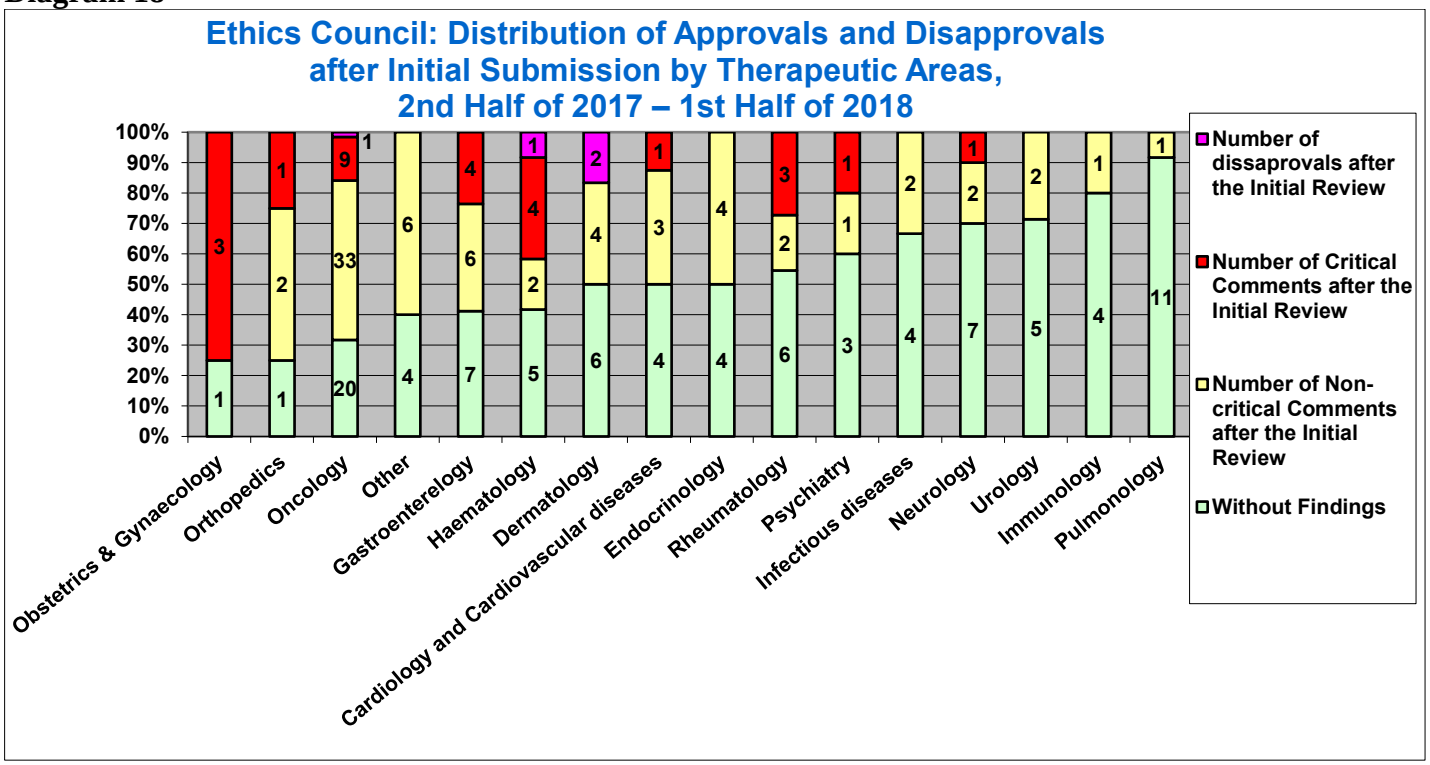
The distribution of results for expert evaluation by the Ethics Council, depending on a therapeutic area of planned trials is shown in Table 2 and Diagram 18 that follows.

Apart from such areas as obstetrics and gynaecology as well as orthopedics with a small number of initiated trials, oncology accounts for the least share of trials approved without comments from the Ethics Council – only 32%. A year ago this indicator stood at 52%, which is also an extremely poor result.

Diagram 18



Data from poll of ACTO members

But now it has become prohibitively low with only a third of oncologic trials getting no critical comments from the Ethics Council's experts. Even though most comments (52% of the total number) are noncritical, we should not forget that even a noncritical comment is a problem in international trials. The Ethics Council experts may think that "conditional approvals" means nothing for an applicant. But not a single IMCT sponsor (let alone CRO) may enter any corrections without notifying the headquarters. In other words, a comment needs to be translated, forwarded to the central team which makes a decision to correct the document or write explanations, their reply will be sent to the Ministry of Health and, finally, if the regulator is satisfied with the response, the much-desired approval will be granted. This takes time – the most valuable asset in any clinical trial. In this case time is often tantamount to the survival of oncological patients. As for competitive enrollment, it can be a chance for Russian patients to be included in an international trial.

And what is on the other side of the scale? Some comment of the Ethics Council that documents lack a informed consent form by clinical trials participant's female partner, should she suddenly become pregnant. In a trial exploring a remedy for the prostate cancer (a real case). What if a prostate cancer patient's female partner suddenly gets pregnant indeed, despite all warnings, and her consent to the observation will be needed? To promote "humanism, morality and biomedical ethic", it's better to get this form beforehand just in case, even if the recruitment of Russian patients is delayed because of this nuisance.

In addition to oncology, a low share of trials approved without comments by the Ethics Council in haematology (42%) is another reason for concern. In last year's survey the indicator for this therapeutic field was also the lowest, but then it stood at 47.4%. Now it has sunk by another five percentage points. Unlike oncology, where the total share of critical comments and disapprovals amounted to 15.9%, in haematology this is 41.6% – an outrageously high percentage for such a sensitive field.

We have to state with regret that the already grim general picture of the Ethics Council's expert evaluations looks absolutely depressing if we review specific therapeutic fields. This deterioration dealt the hardest blow on those fields where patient's life is threatened like nowhere else: oncology and haematology. May it lie heavy on the conscience of experts.

Table 2

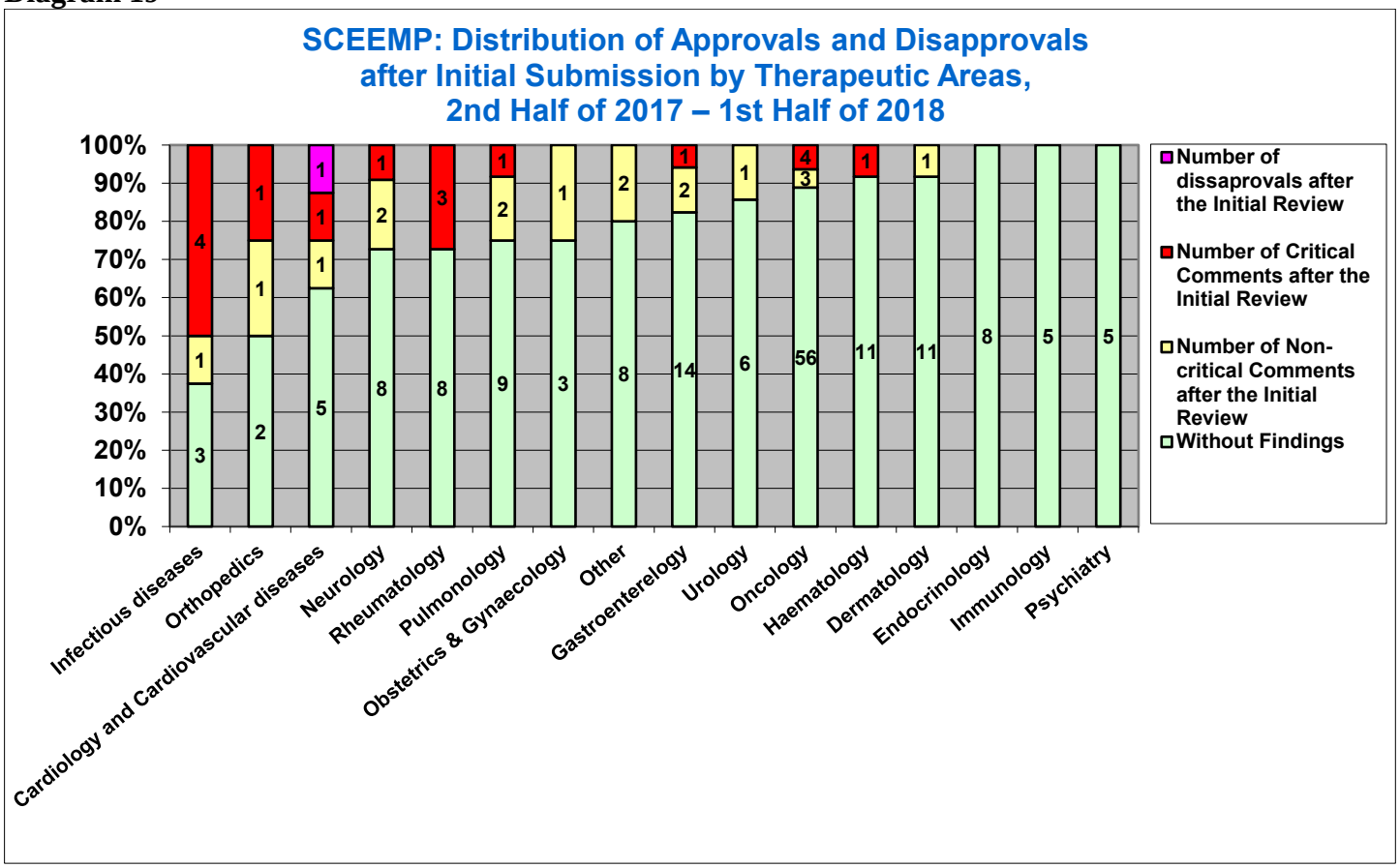
Ethics Council: Distribution of Approvals and Disapprovals by Therapeutic Areas									
Therapeutic Areas	**Total Number of Initial Submissions**	**Without Findings**	**Without Findings, % of Total**	**Number of Non-critical Comments after the Initial Review**	**Non-critical Comments after the Initial Review, % of Total**	**Number of Critical Comments after the Initial Review**	**Critical Comments after the Initial Review, % of Total**	**Number of Dissaprovals after the Initial Review**	**Number of Dissaprovals after the Initial Review, % of Total**
Oncology	63	20	32%	33	52%	9	14.3%	1	1.6%
Gastroenterelogy	17	7	41%	6	35%	4	23.5%	0	0.0%
Haematology	12	5	42%	2	17%	4	33.3%	1	8.3%
Dermatology	12	6	50%	4	33%	0	0.0%	2	16.7%
Pulmonology	12	11	92%	1	8%	0	0.0%	0	0.0%
Rheumatology	11	6	55%	2	18%	3	27.3%	0	0.0%
Neurology	10	7	70%	2	20%	1	10.0%	0	0.0%
Cardiology and Cardiovascular diseases	8	4	50%	3	38%	1	12.5%	0	0.0%
Endocrinology	8	4	50%	4	50%	0	0.0%	0	0.0%
Urology	7	5	71%	2	29%	0	0.0%	0	0.0%
Infectious diseases (except HIV/HCV/tuberculosis)	6	4	67%	2	33%	0	0.0%	0	0.0%
Immunology	5	4	80%	1	20%	0	0.0%	0	0.0%
Psychiatry	5	3	60%	1	20%	1	20.0%	0	0.0%
Obstetrics & Gynaecology	4	1	25%	0	0%	3	75.0%	0	0.0%
Orthopedics	4	1	25%	2	50%	1	25.0%	0	0.0%
Other	10	4	40%	6	60%	0	0.0%	0	0.0%
Total	194	92	47%	71	37%	27	13.9%	4	2.1%

Data from poll of ACTO members

Table 3 and Diagram 19 show the distribution of SCEEMP expert evaluation results by therapeutic areas. Here the lowest percentage of trials approved without comments falls to the share of infectious diseases: 37.5%. And 50% of all cases considered in this field got critical comments. Compared to the previous survey, the indicators underwent serious degradation: back then they were also low, standing at 66.7% of cases approved at the first go plus 33.3% of trials with critical comments. Unfortunately, this result fully coincides with the perception of applicants: it is in the field of infectious diseases that SCEEMP expert examination is most questionable.

In other areas the situation is a lot better and, looking at Diagram 19, we may rejoice again at such remarkable changes for the better in expert evaluations by the given federal institution.

Diagram 19



Data from poll of ACTO members

Table 3

SCEEMP: Distribution of Approvals and Disapprovals by Therapeutic Areas									
Therapeutic Areas	**Total Number of Initial Submissions**	**Without Findings**	**Without Findings, % 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 Dissaprovals after the Initial Review**	**Number of Dissaprovals after the Initial Review, % of Total**
Oncology	**63**	**56**	**88.9%**	**3**	**4.8%**	**4**	**6.3%**	**0**	**0.0%**
Gastroenterelogy	**17**	**14**	**82.4%**	**2**	**11.8%**	**1**	**5.9%**	**0**	**0.0%**
Haematology	**12**	**11**	**91.7%**	**0**	**0.0%**	**1**	**8.3%**	**0**	**0.0%**
Dermatology	**12**	**11**	**91.7%**	**1**	**8.3%**	**0**	**0.0%**	**0**	**0.0%**
Pulmonology	**12**	**9**	**75.0%**	**2**	**16.7%**	**1**	**8.3%**	**0**	**0.0%**
Neurology	**11**	**8**	**72.7%**	**2**	**18.2%**	**1**	**9.1%**	**0**	**0.0%**
Rheumatology	**11**	**8**	**72.7%**	**0**	**0.0%**	**3**	**27.3%**	**0**	**0.0%**
Other	**10**	**8**	**80.0%**	**2**	**20.0%**	**0**	**0.0%**	**0**	**0.0%**
Infectious diseases (except HIV/HCV/tuberculosis)	**8**	**3**	**37.5%**	**1**	**12.5%**	**4**	**50.0%**	**0**	**0.0%**
Cardiology and Cardiovascular diseases	**8**	**5**	**62.5%**	**1**	**12.5%**	**1**	**12.5%**	**1**	**12.5%**
Endocrinology	**8**	**8**	**100.0%**	**0**	**0.0%**	**0**	**0.0%**	**0**	**0.0%**
Urology	**7**	**6**	**85.7%**	**1**	**14.3%**	**0**	**0.0%**	**0**	**0.0%**
Immunology	**5**	**5**	**100,0%**	**0**	**0.0%**	**0**	**0.0%**	**0**	**0.0%**
Psychiatry	**5**	**5**	**100.0%**	**0**	**0.0%**	**0**	**0.0%**	**0**	**0.0%**
Obstetrics & Gynaecology	**4**	**3**	**75.0%**	**1**	**25.0%**	**0**	**0.0%**	**0**	**0.0%**
Orthopedics	**4**	**2**	**50.0%**	**1**	**25.0%**	**1**	**25.0%**	**0**	**0.0%**
Total	**197**	**162**	**82.2%**	**17**	**8.6%**	**17**	**8.6%**	**1**	**0.5%**

Data from poll of ACTO members

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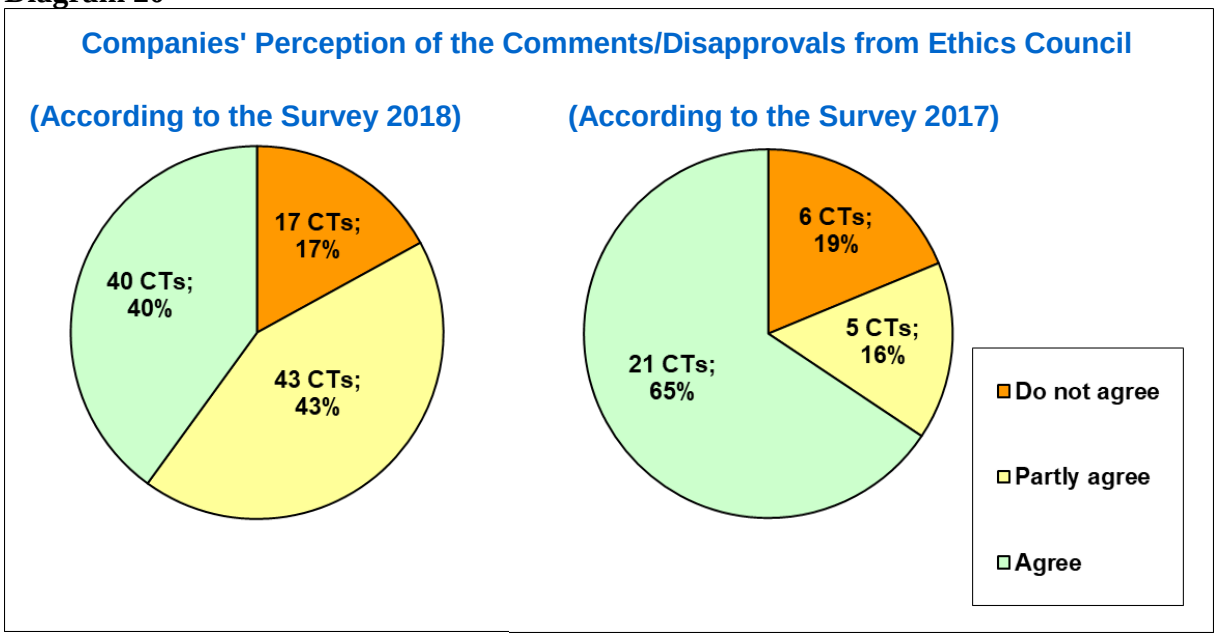
As usual, we asked companies to assess, among other things, the fairness of comments from expert organisations. The results of this assessment have tangibly changed compared to the previous year.

Thus, you may see from Diagram 20, how companies perceived the Ethics Council's comments last year and this year. The share of disagreements with the Ethics Council's assessment has grown, albeit not considerably: from 14% to 17%. Yet the shares of "agreed" and "partly agreed" segments have changed significantly. Thus, the percentage of agreements with comments of the expert body has plummeted from 63% down to 40%. Only in 2014 there was less agreement (39%). The share of partial agreement has increased almost proportionately – from 23% in the survey of 2017 to 43% in this year's survey.

What's the meaning of these data? Traditionally, applicants took expert evaluations of the Ethics Council easier than those of SCEEMP for one simple reason: the comments were not so sharp and potentially not so difficult to incorporate. To a certain extent, this affects an subjective assessment: it's easier to accept them, than to explain the gist of objections. But, as we can see, the above-mentioned problem of the Ethics Council's expert examination quality deterioration directly affected the perception of companies.

Diagram 20

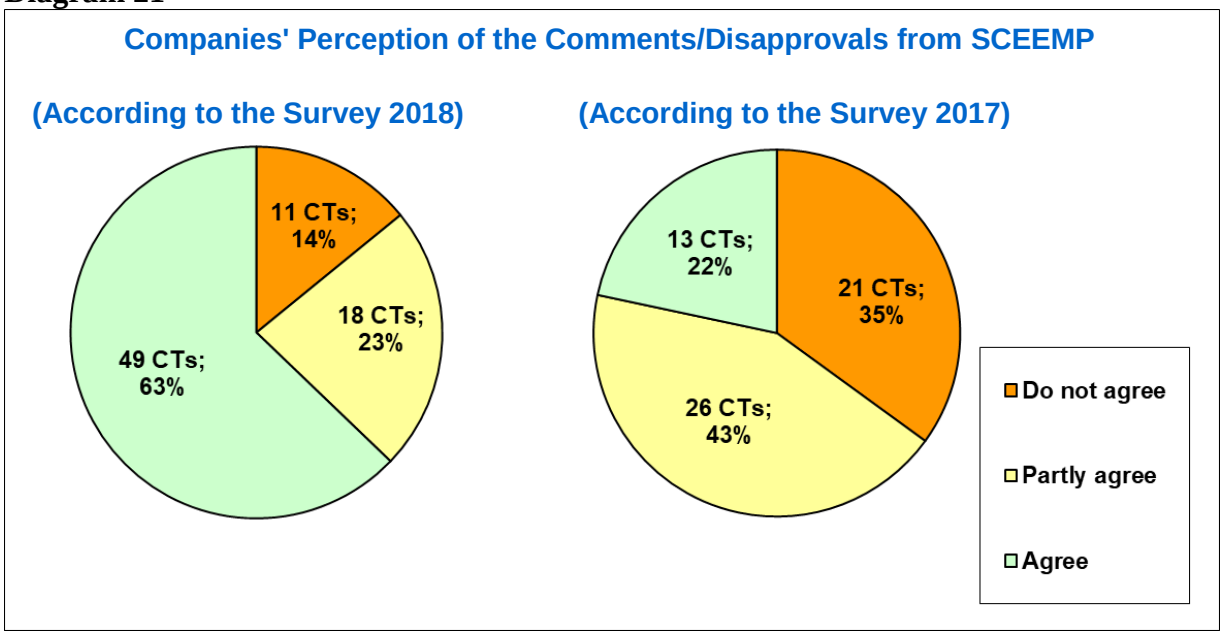


Data from poll of ACTO members

You may see companies assessing SCEEMP comments in 2018 and 2017 on Diagram 21. Changes took place here as well, but for the better. Thus, the share of disagreement during the past year went down from 35% to 19%. This is an absolute record for the entire time of our monitoring. For comparison: it stood at 75% in 2014!

Other assessments have changed as well. Thus, the share of cases where companies were "partly agree" with SCEEMP comments has dropped from 43% to 16%, whereas the share of "agreements" has risen from 22% (previous maximum) to 65% – an apparent recognition of positive changes at this institution.

Diagram 21



Data from poll of ACTO members

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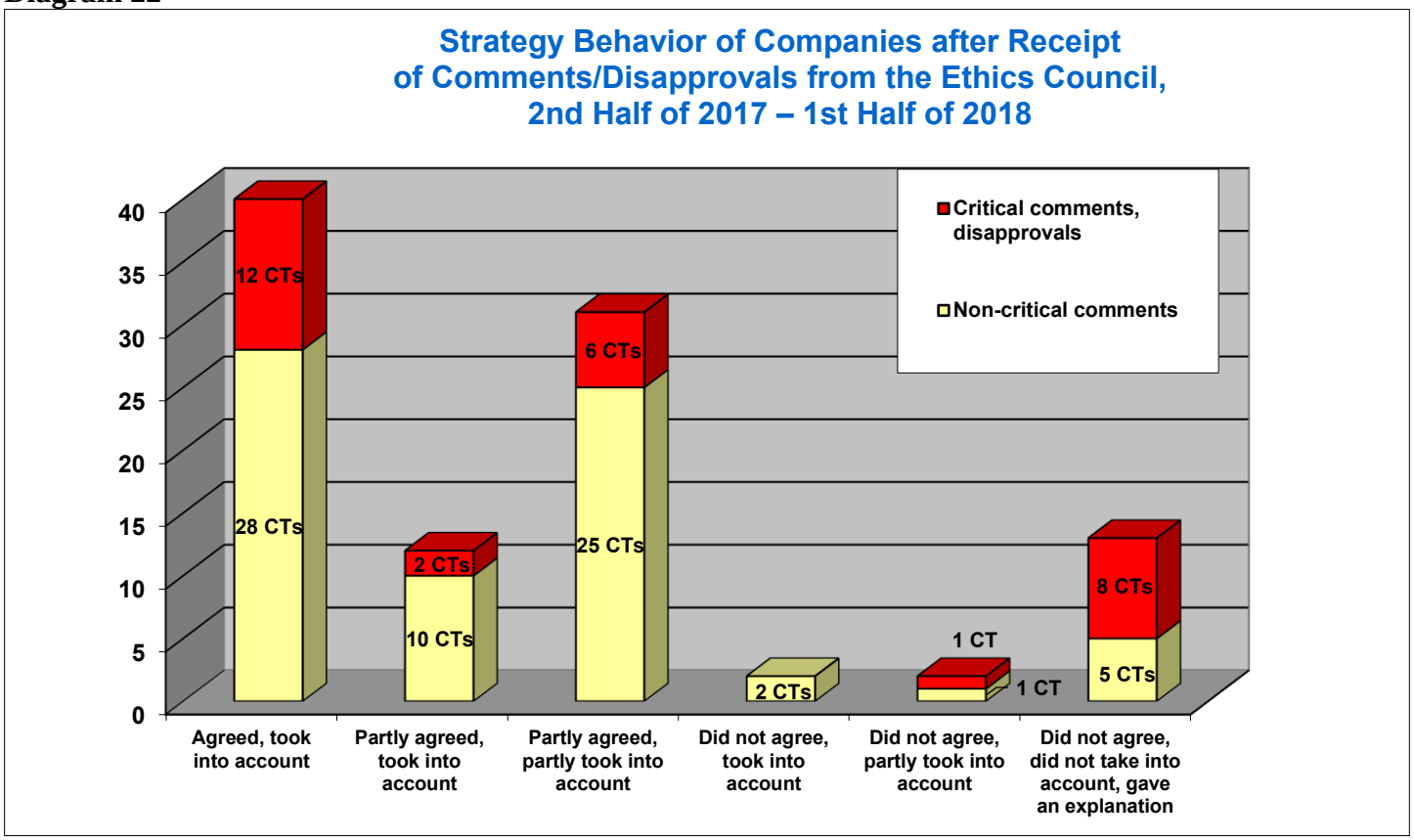
Diagrams 22 and 23 show the strategy chosen by companies that receive requests and comments from expert bodies. As usual, the most common attitude towards the expert evaluation of the Ethics Council among applicants has been "agreed" in 40% of all cases (62% in last year's survey). Slightly less than a third (31%) opt for the "partly agree, partly took into account" strategy. A year earlier only 8.1% of all cases fell within this category. Finally, the third most common strategy has been "did not agree, did not take into account, gave an explanation" that accounted for 13% of all cases versus 6.8% a year ago.

Diagram 22

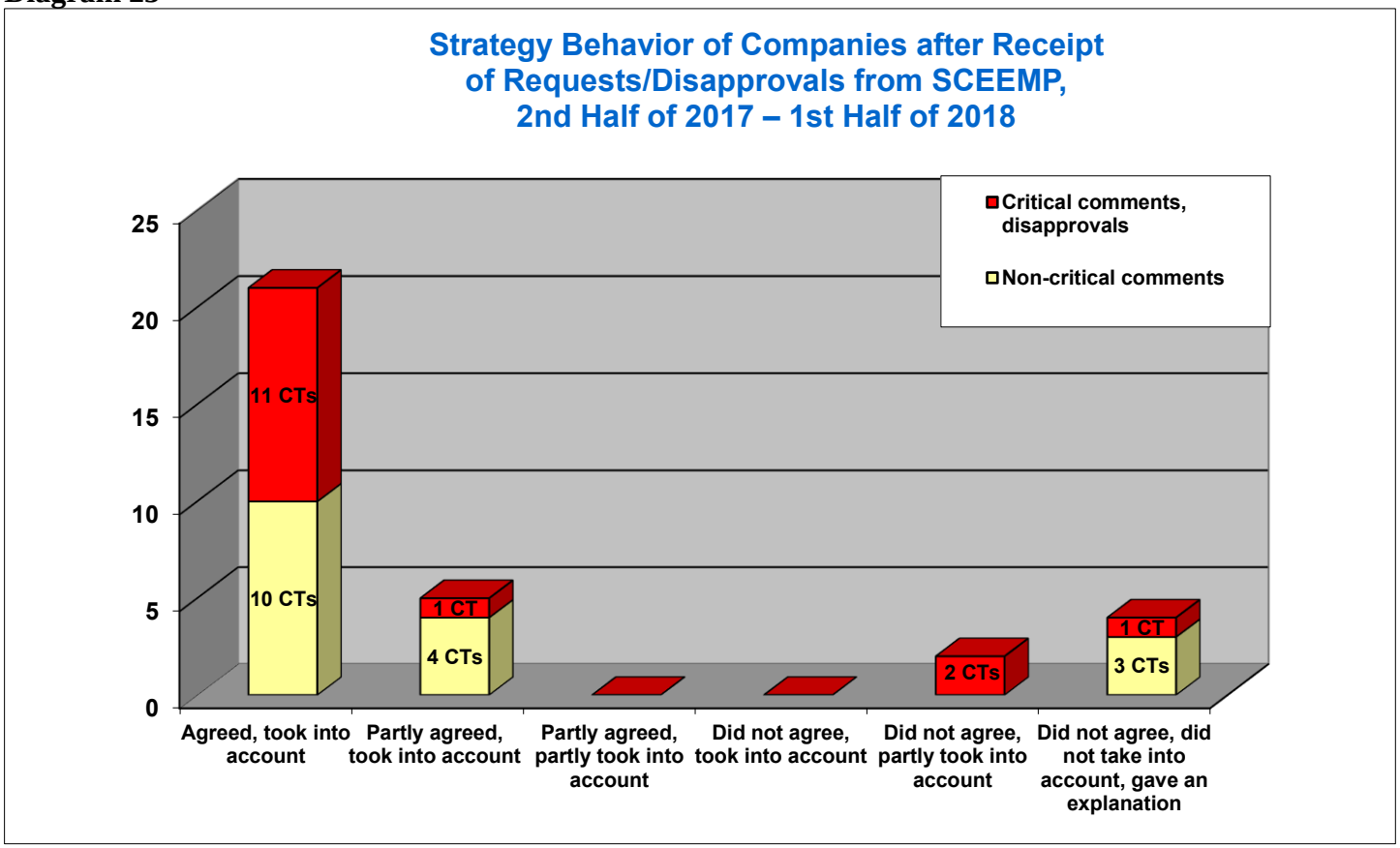


Data from poll of ACTO members

When receiving SCEEMP comments (Diagram 23) companies most often resorted to the strategy "agreed, took into account" during the period under review – in 65.6% of all cases (versus 22% a year earlier). Following next is the category "partly agreed, took into account"– 15.6% of all cases (the survey of 2017 yielded almost the same result of 17%). The third most common strategy is "did not agree, did not take into account, gave an explanation" – 12.5% (versus 20.3% in 2017). Finally, the rarest line of conduct has been "did not agree, partly took into account" – 6.3% (6.8% a year ago).

In their relationship with SCEEMP companies never opted for the strategy "did not agree, took into account" during the period under review (8.5% of all cases in the 2017 survey), or the strategy "partly agreed, partly took into account" (the most common line of conduct a year before – 25.4% of all cases).

Diagram 23



Data from poll of ACTO members

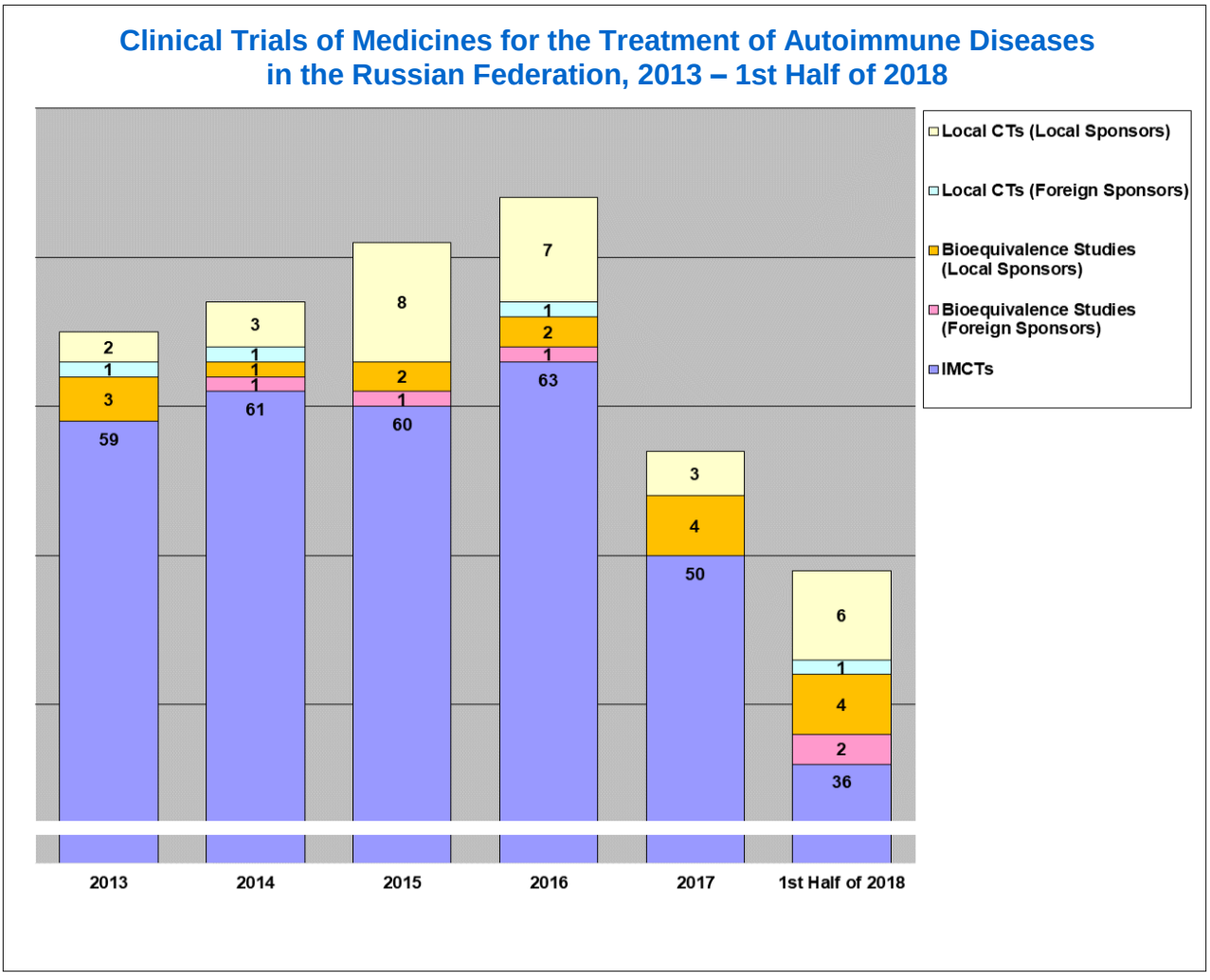
SITUATION WITH CLINICAL TRIALS OF MEDICINAL PRODUCTS FOR THE TREATMENT OF AUTOIMMUNE DISEASES

The object of analysis were clinical trials for which approvals for conducting in Russia according to the Ministry of Health's register were received from January 2013 to July 2018. The sample was formed on the basis of the disease mentioned in the protocol, and in the lack of this mention – on the basis of indications for the medicine under study. Autoimmune diseases may belong to various therapeutic areas; thus, the trials under study belong to gastroenterology[6], haematology [7], dermatology [8], neurology [9], rheumatology [10], and other areas. We excluded remedies for certain specific diseases from our sample[11], leaving them for possible future review.

Clinical trials' market structure of medicinal products for the treatment of autoimmune diseases

Diagram 24 gives a general idea of the market structure.

Diagram 24



Data from www.grls.rosminzdrav.ru

[6] Ulcerative colitis, Crohn's disease and others.
[7] Primary immune thrombocytopenia, autoimmune hemolytic anemia and others.
[8] Psoriasis.
[9] Multiple sclerosis, myasthenia gravis and others.
[10] Rheumatoid arthritis, systemic lupus erythematosus, primary Sjogren's syndrome, dermatomyositis and others.
[11] Medicines for lgA-nephropathy, chronic neutropenia, APDS/PASLI, primary immunodeficiencies, diabetes mellitus type 1.

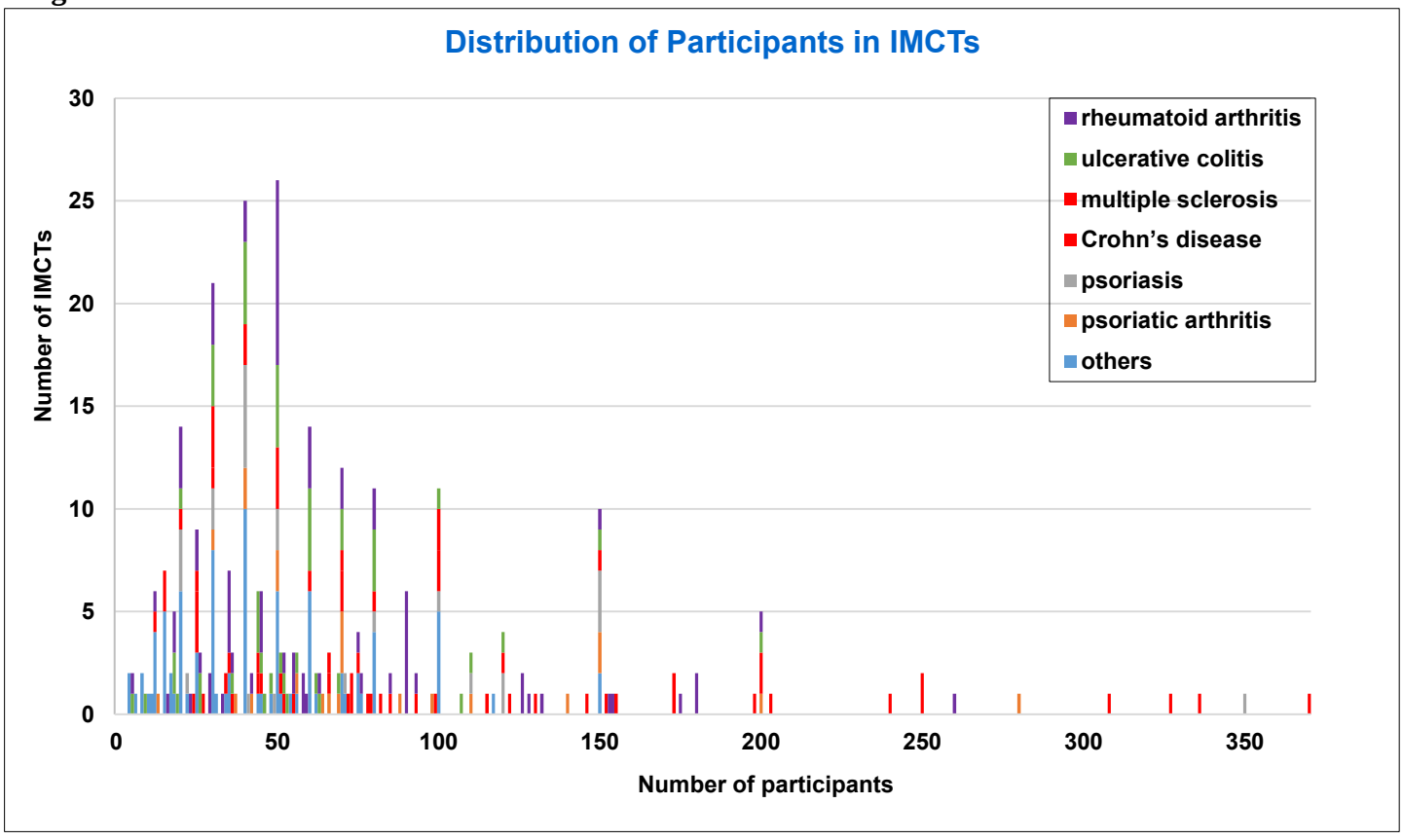
In 2013 – first half of 2018 approvals for conducting 383 trials of medicines for treatment of autoimmune diseases were provided in Russia, of which 329, i.e. 86% were international multicentre ones. The rest 54 trials were distributed between: local trials of Russian sponsors (29), local trials of foreign sponsors (4), bioequivalence studies initiated by Russian companies (16) and bioequivalence studies by foreign sponsors (5).

From the beginning of 2013 to the middle of 2018 the ratio between the trials of different types remained almost unchanged. We see just a small reduction of IMCT number in 2017, down by 18% from the average in four previous years (2013–2016). We can also see nonuniform activity of Russian sponsors in local trials: in 2015, 2016 and apparently in 2018 it is higher than in 2013, 2014 and 2017. But with such low absolute figures this can be explained by random fluctuations.

IMCTs

Out of 329 IMCTs 200 trials belong to phase III, 97 to phase II, 11 to phase IV, 9 to phase I. The rest 12 IMCTs are trials of phases I/II, I/III, II/III and III/IV. The announced number of IMCT participants varies between 4 and 750, in 80% of cases between 20 and 150 people; the average number of participants is 71; the median is 50. The distribution of participants in IMCTs is shown in Diagram 25.

Diagram 25[12]



Data from www.grls.rosminzdrav.ru

The top ten diseases mentioned in protocols looks like this: rheumatoid arthritis – 74 IMCTs, ulcerative colitis – 46, multiple sclerosis – 41, Crohn's disease – 29, psoriasis – 25, psoriatic arthritis – 24, axial spondyloarthritis[13] – 23, systemic lupus erythematosus – 17, juvenile idiopathic arthritis – 13, lupus nephritis – 9.

INNs mentioned in protocols more often than others are presented in Table 4. They account for 36% of all IMCTs of autoimmune disease medicinal products, conducted in Russia for 5.5 years.

[12] Clinical trial of a drug for rheumatoid arthritis with 750 participants was excluded from the trial.
[13] Including ankylosing spondylitis.

Table 4

INN in IMCTs of medicines for the treatment of autoimmune diseases in Russia in 2013 – 1st half of 2018			
INN	**Number of IMCTs**	**Disease and number of IMCTs**	**Company and number of IMCTs**
Secukinumab	22	psoriasis – 7	Novartis – 22
		psoriatic arthritis – 6	
		axial spondyloarthritis – 6	
		rheumatoid arthritis – 1	
		juvenile idiopathic arthritis – 1	
		multiple sclerosis – 1	
Adalimumab	17	rheumatoid arthritis – 8	Amgen – 2, Boehringer – 2, Fujifilm – 2, Pfizer – 1, Hexal – 1
		psoriasis – 5	Boehringer – 2, Coherus – 2, Merck – 1, Milan – 1
		Crohn's disease (CD) – 2	Boehringer – 1, AbbVie – 1
		axial spondyloarthritis – 1	AbbVie – 1
		ulcerative colitis (UC) – 1	AbbVie – 1
Upadacitinib	14	rheumatoid arthritis – 8	AbbVie – 14
		Crohn's disease (CD) – 3	
		ulcerative colitis (UC) – 2	
		psoriatic arthritis – 1	
Tofacitinib	12	psoriatic arthritis – 3	Pfizer – 12
		rheumatoid arthritis – 3	
		juvenile idiopathic arthritis – 3	
		axial spondyloarthritis – 2	
		ulcerative colitis (UC) – 1	
Filgotinib	12	rheumatoid arthritis – 6	Gilead – 3, Galapagos – 3
		Crohn's disease (CD) – 3	Gilead – 2, Galapagos – 1
		ulcerative colitis (UC) – 3	Gilead
Ozanimod	11	Crohn's disease (CD) – 4	Celgene – 4
		multiple sclerosis – 4	Receptos – 7
		ulcerative colitis (UC) – 3	
Bimekizumab	8	axial spondyloarthritis – 3	Biopharma – 8
		psoriasis – 3	
		psoriatic arthritis – 2	
Ixekizumab	8	axial spondyloarthritis – 4	Eli Lilly – 8
		psoriasis – 2	
		psoriatic arthritis – 2	
Sarilumab	8	rheumatoid arthritis – 6	Sanofi – 8
		juvenile idiopathic arthritis – 2	
Etanercept	7	rheumatoid arthritis – 4	Pfizer – 2, Hexal – 1, Coherus – 1
		psoriasis – 2	Hexal – 1, Coherus – 1
		psoriatic arthritis – 1	Amgen – 1
The rest 117 INN	*210*		

Data from www.grls.rosminzdrav.ru

Rating of companies leading in conducting of IMCTs of medicines for the treatment of autoimmune diseases looks like this (Table 5). These companies initiated the total of 68% of all IMCTs under review.

Table 5

Companies conducting IMCTs of medicines for the treatment of autoimmune diseases in Russia, 2013 – 1st half of 2018		
Ranking	**Company**	**Number of IMCTs**
1	Novartis	35
2–3	AbbVie Pfizer	21 each
4	Eli Lilly	16
5	Janssen-Cilag	15
6	F. Hoffmann-La Roche	12
7–9	Gilead Sciences, Sanofi, Biopharma	9 each
10–11	Amgen, Takeda	8 each
12–15	Bristol-Myers Squibb, GlaxoSmithKline, Merck, Receptos	7 each
16–17	Actelion, Boehringer	6 each
18–21	Biogen, Celgene, Galapagos, Genzyme	5 each
	The remaining 62 companies	***106 total***

Data from www.grls.rosminzdrav.ru

Local trials

Most local trials were conducted by Russian sponsors. Biocad with 17 trials of ten medicines during 5.5 years is an absolute leader here. Four of these ten products are original developments [14] studied in eight out of 17 trials [15]. In other nine trials Biocad studied five biosimilars and one generic [16].

Valenta Pharm conducted two trials of fampridine improving the gait of multiple sclerosis patients. Ten more Russian companies conducted one trial each. There are no original developments among these trials, but there are two cases of in-licensing: olokizumab belongs to R-Pharm and theralizumab – to TheraMAB.

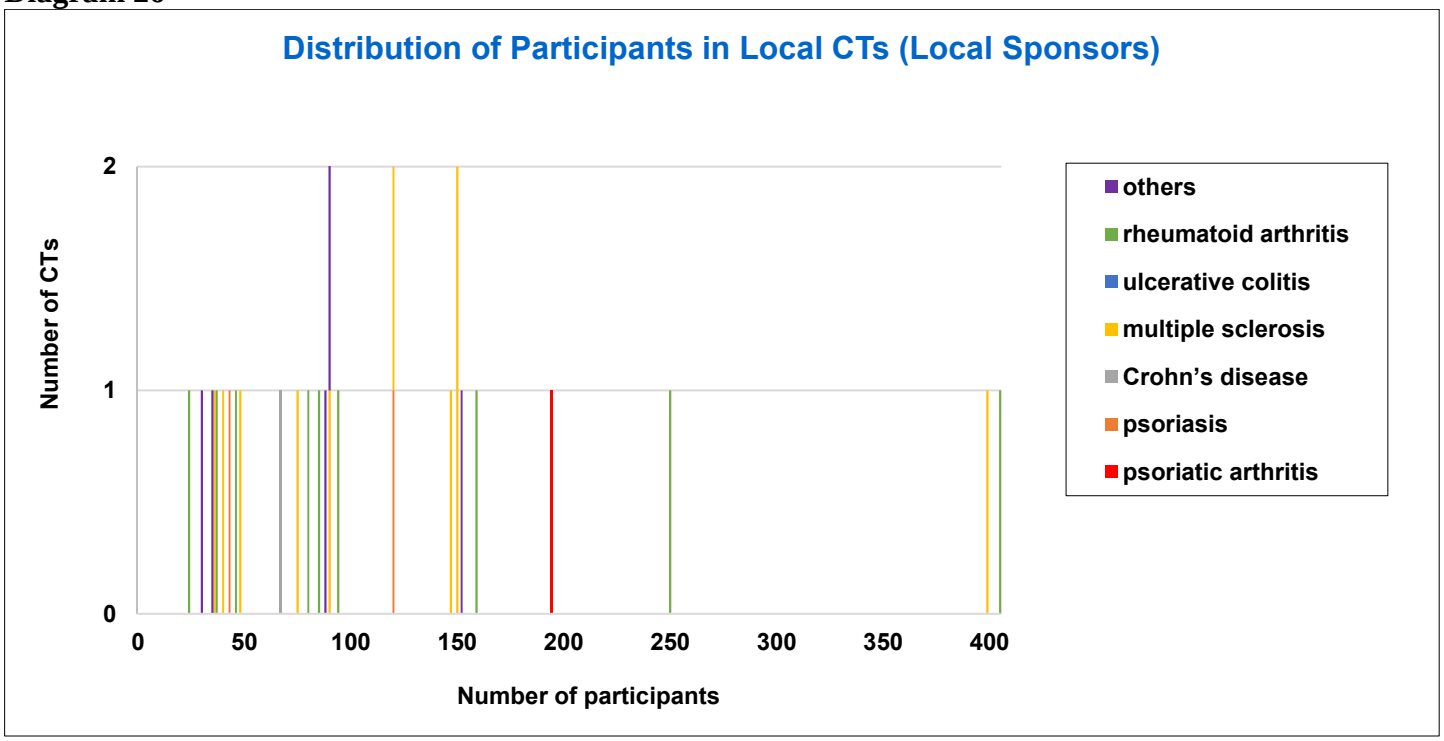
Main diseases in local protocols of domestic companies include: multiple sclerosis (ten trials), rheumatoid arthritis (eight) and ankylosing spondylitis (three).

Foreign sponsors conducted four local trials. InteKrin studied INT131 (besylate) for multiple sclerosis. Pharmacyclics in a joint venture with Janssen Biotech conducted the trial of ibrutinib for autoimmune hemolytic anemia. AbbVie initiated a third-phase trial of risankizumab for psoriasis. And finally, Croatian company Belupo studied the efficacy and safety of betamethasone in the form of a spray, also for psoriasis.

In each of the 33 local trials, according to Ministry of Health's register, from 24 to 405 people participated, the average being 116 (Diagrams 26, 27), median value – 88.

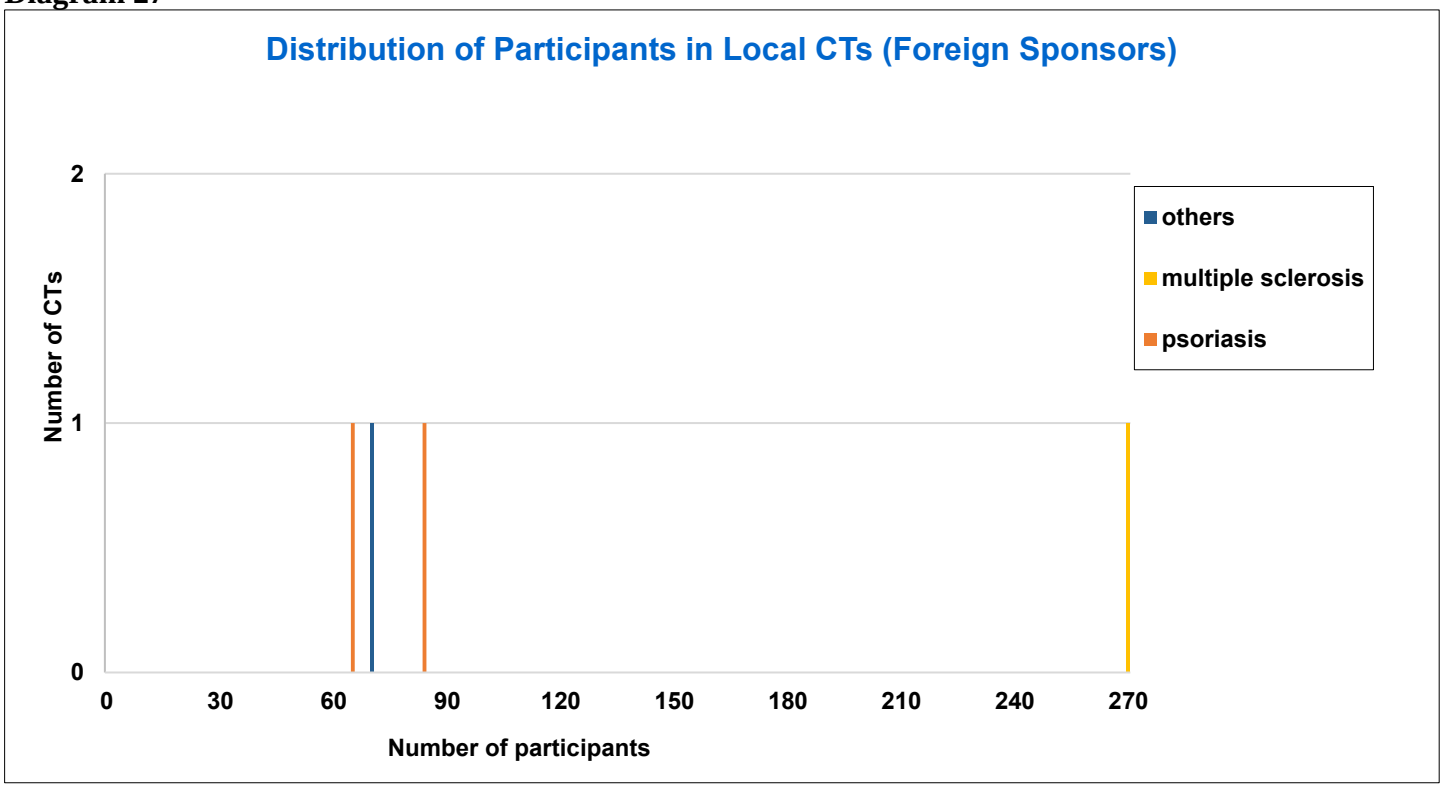
[14] BCD-085 – a monoclonal antibody against interleukin-17; BCD-121 – a bio-specific monoclonal antibody against TNF-alpha and interleukin-17 at one time; BCD-132 – a monoclonal antibody against CD20; BCD-089 – a monoclonal antibody against interleukin-6.
[15] BCD-085 featured in five protocols.
[16] Biosimilars of interferon beta-1a, peginterferon beta-1a (two trials), adalimumab, infliximab (three trials) and rituximab as well as Timexon generic (glatiramer acetate).

Diagram 26



Data from www.grls.rosminzdrav.ru

Diagram 27



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Bioequivalence studies

Out of 16 bioequivalence studies initiated by Russian sponsors six focused on fingolimod – INN of Gilenya medication whose formula patent protection expires in 2019. It is used in multiple sclerosis therapy. Fingolimod caught the eyes of Novosibhimfarm (two trials), Biocad, Pharmasyntez, Nativa and Medisorb.

Four trials focused on leflunomide used to treat rheumatoid and psoriatic arthritis. Six Russian companies have passed the state registration of leflunomide-based medicines since 2011. Including Berezovsky pharmaceutical plant, Medimeks and EvoPharm that conducted trials in 2013–2018. Incomepharm was still conducting a trial of this medicine in late August of 2018.

In three bioequivalence studies teriflunomide used in treating multiple sclerosis and included in the "Seven Nosologies" programme in 2017 was tested. Those trials were sponsored by Biocad, Drugs Technology and Valenta Pharm.

Biocad and Chemical Diversity Research Institute also conducted one trial of dimethyl fumarate each, another medication for multiple sclerosis. The trial of immunosuppressor hydroxychloroquine, conducted by Biocom in 2014–2016, enabled the company to get this medicine registered in Russia in 2017.

Five more bioequivalence studies were conducted in Russia by foreign sponsors. Hetero Labs, Long Sheng Pharma Rus and Teva tested their own generics of fingolimod. The latter company also conducted a trial of teriflunomide. Lastly, a representative office of the Indian Simpex Pharma studied a leflunomide generic.

Thus, in their bioequivalence studies Russian and foreign companies in 2013–2018 gave preference to multiple sclerosis medicines (15 out of 21 trials), fingolimod in the first place (eight trials). The rest six are rheumatoid and psoriatic arthritis medications.

From 34 to 90 people participated in bioequivalence studies, the average number being 54 (Diagrams 28 and 29); the median is 51.

Diagram 28

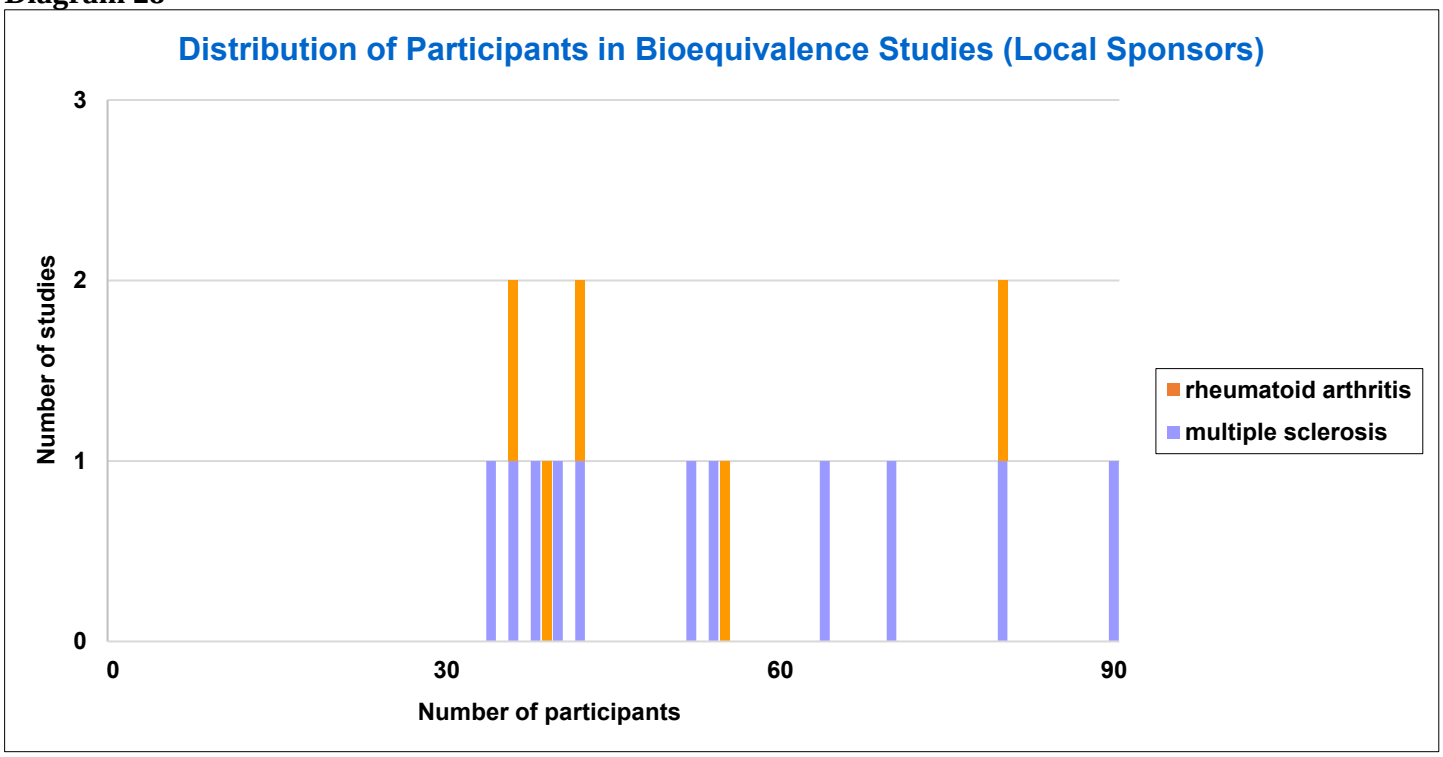

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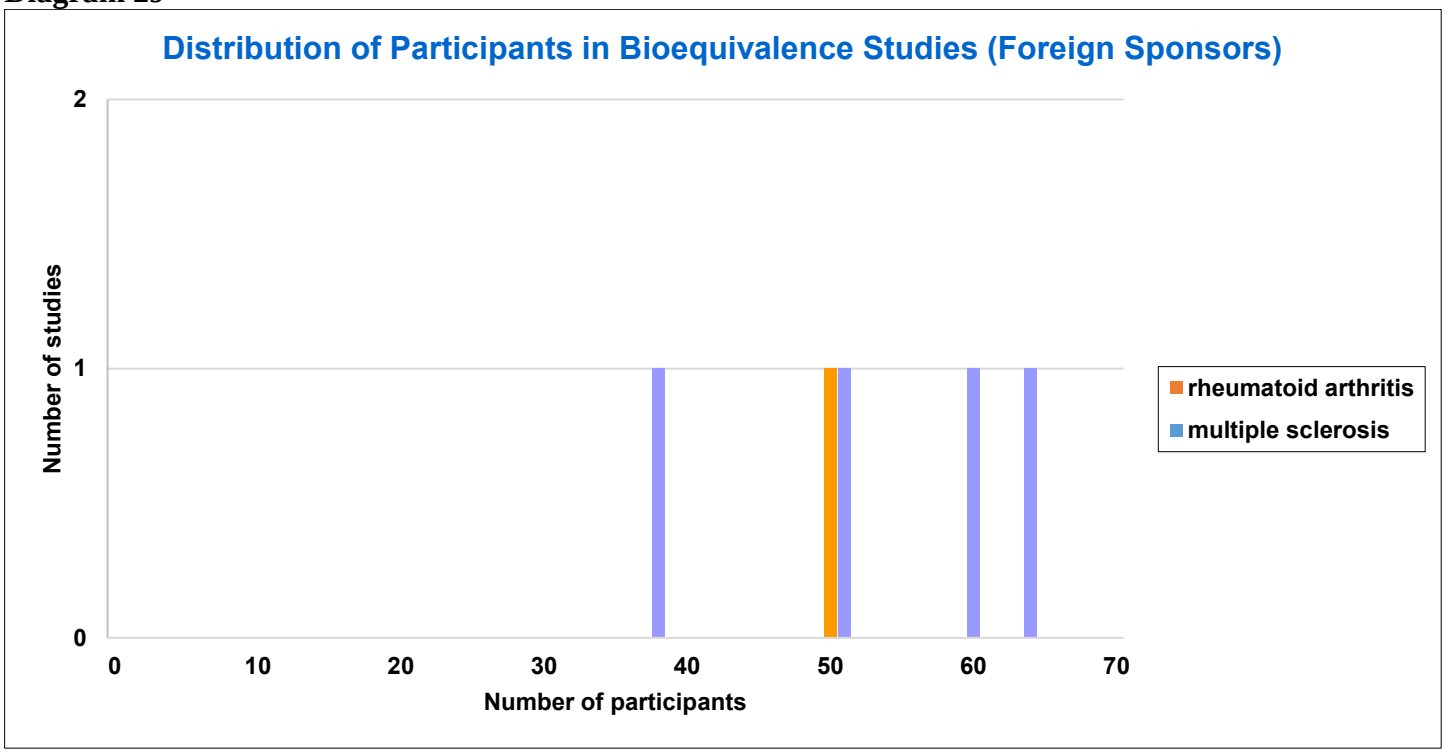
Diagram 29



Data from www.grls.rosminzdrav.ru

Comparing the Russian and world markets

We do not have enough data for direct comparison, but the search at www. clinicaltrials.gov by diagnoses of certain autoimmune diseases [17] shows that the top ten diseases most often mentioned in protocols is little different from the same IMCTs rating of trials conducted in the Russian Federation (see Table 6). The only difference is that primary immune thrombocytopenia [18] hit the top ten of the world rankings, whereas juvenile arthritis [19] was included only in Russian rankings.

Table 6

Clinical trials of medicines for the treatment of autoimmune diseases according to data from www.clinicaltrials.gov, 2013 – 1st half of 2018	
Disease	**Number of CTs**
rheumatoid arthritis	162
multiple sclerosis	130
ulcerative colitis	123
Crohn's disease	121
psoriasis	115
lupus nephritis	98
systemic lupus erythematosus	62
primary immune thrombocytopenia	32
ankylosing spondylitis	31
psoriatic arthritis	31

Data from www.clinicaltrials.gov

[17] Only interventional trials that kicked off from 01.01.2013 to 30.06.2018 were taken into account, where intervention was described as "drug", "biological" and "genetic", while "behavioral", "device", "test" and "other" categories were excluded.
[18] In Russia for the period under review there were two trials in patients with this pathology, plus another trial in patients suffering from immune thrombocytopenic purpura.
[19] 17 trials at www.clinicaltrials.gov.

In terms of quality the Russian market does not appear to be isolated from the world market, as regards the trials of medicinal products for "most popular" diseases. So, all recently approved FDA medications for rheumatoid arthritis (baricitinib, sarilumab, tofacitinib) passed trials at Russian clinical centres, as part of international projects. Most popular INN in the protocols of this disease are also little different (adalimumab, infliximab, upadacitinib, enteracept) in Russian IMCTs and those registered on www.clinicaltrials.gov. We see the same picture with respect to multiple sclerosis: recently approved FDA medicines daclizumab and ocrelizumab were studied in Russia, although the latter had already been approved in the United States. The same is true for ulcerative colitis and Crohn's disease.

On the whole, clinical trials registered at www.clinicaltrials.gov cover a wider spectrum of autoimmune diseases, which can be expected. Thus, during the period under review no trials of medicines for sarcoidosis (17 trials at www.clinicaltrials.gov), vitiligo (12 trials), alopecia areata (12 trials) and others were conducted in Russia.

Thus, if all trials of medicines for autoimmune diseases were divided into "centre" where "most popular" diseases are located with respective medication actively studied in a large number of clinical trials, and "peripheral" with a smaller number of clinical trials for "less popular" diseases, we may say that the centre is adequately represented in the Russian market, but as we move towards the peripheral, the likelihood of a clinical trial to be conducted in Russia as well keeps falling. This leaves the Russian market with significant quality growth potential.

Annex

IMCT STATISTICS FOR ONCOLOGY AND ONCOHAEMATOLOGY, 2017

Table 7

Distribution of IMCTs by therapeutic areas, 2017			
Therapeutic area	**Number of IMCTs**	**Share (%)**	**The number of planned participants**
Oncology and oncohaematology	88	31.7%	5 935
Rheumatology	28	10.0%	2 422
Neurology	25	8.9%	2 641
Haematology	20	7.1%	301
Endocrinology	19	6.8%	3 255
Gastroenterology	16	5.7%	1 048
Pulmonology	15	5.3%	2 700
Cardiology and CVD	15	5.3%	3 957
Infectious Diseases (except HIV/HCV/tuberculosis)	10	3.6%	744
Psychiatry	8	2.8%	673
Nephrology	8	2.8%	1 269
HIV/HCV/tuberculosis	6	2.1%	447
Dermatology	5	1.4%	187
Gynaecology	4	1.4%	436
Otorhinolaryngology	4	1.4%	251
Surgery	3	1.1%	300
Ophthalmology	2	0.7%	138
Allergology	2	0.7%	155
Geriatrics	2	0.7%	140
Immunology	1	0.4%	30
TOTAL	281	100.0%	27 029

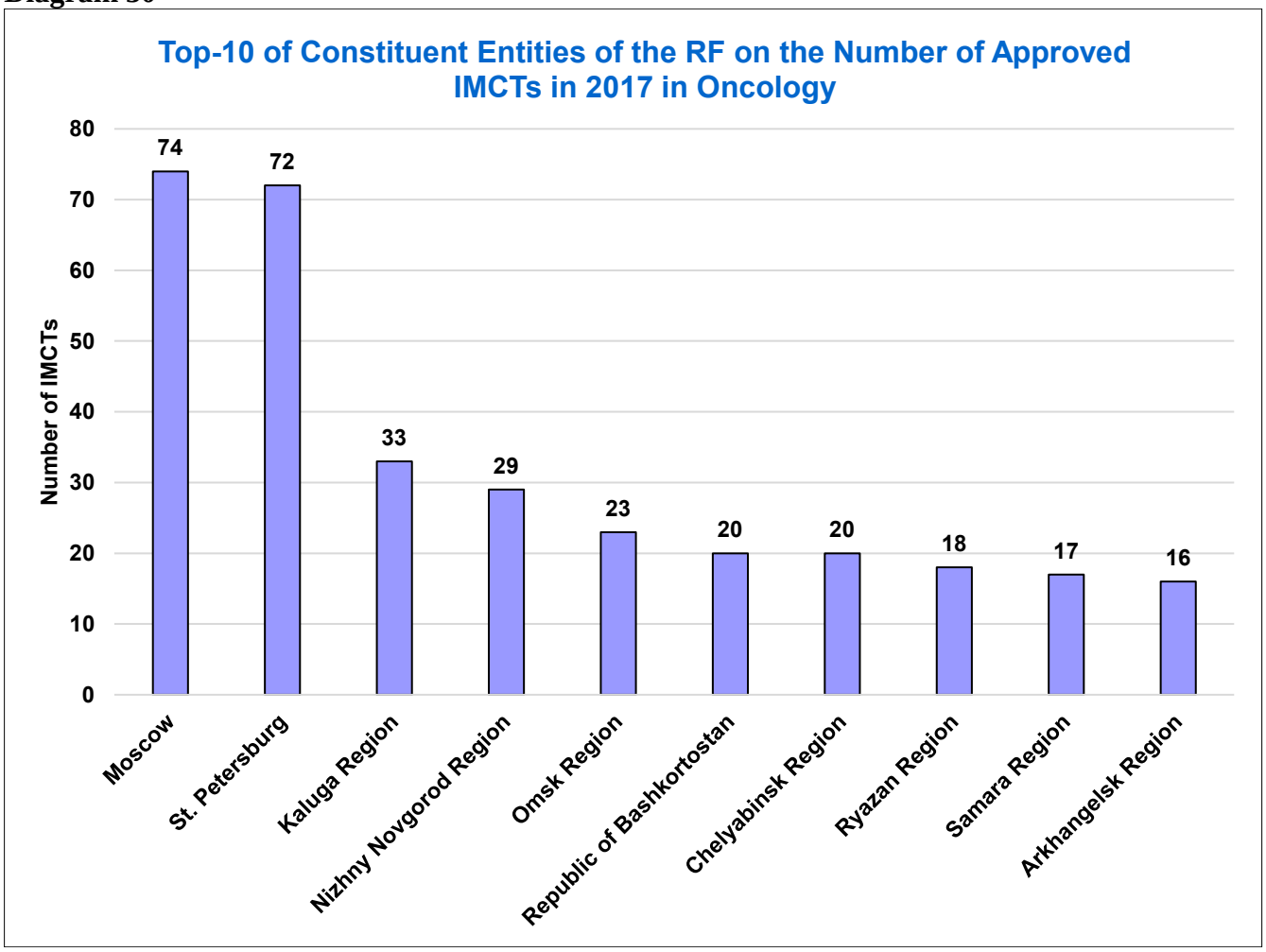
Data from www.grls.rosminzdrav.ru

Table 8

IMCT distribution in oncology and oncohaematology, 2017			
No	**Disease type**	**Number of IMCTs**	**Claimed number of subjects**
1	Lung and pleural cavity tumours	18	1 808
2	Kidney and urinary excretory system tumours	13	956
3	Leukemia (including hemoblastosis and lymphocytic leukemia)	10	510
4	Breast tumour	8	738
5	Gastrointestinal tumours	6	277
6	Multiple myeloma	6	183
7	Prostate tumour	5	247
8	Tumours without known localisation	5	123
9	Lymphoma	5	120
10	Female reproductive system tumours	4	372
11	Melanoma	3	217
12	Head and neck tumours	2	179
13	Liver tumours	1	170
14	Myelofibrosis	1	20
15	CNS tumours	1	15
	TOTAL	88	5 935

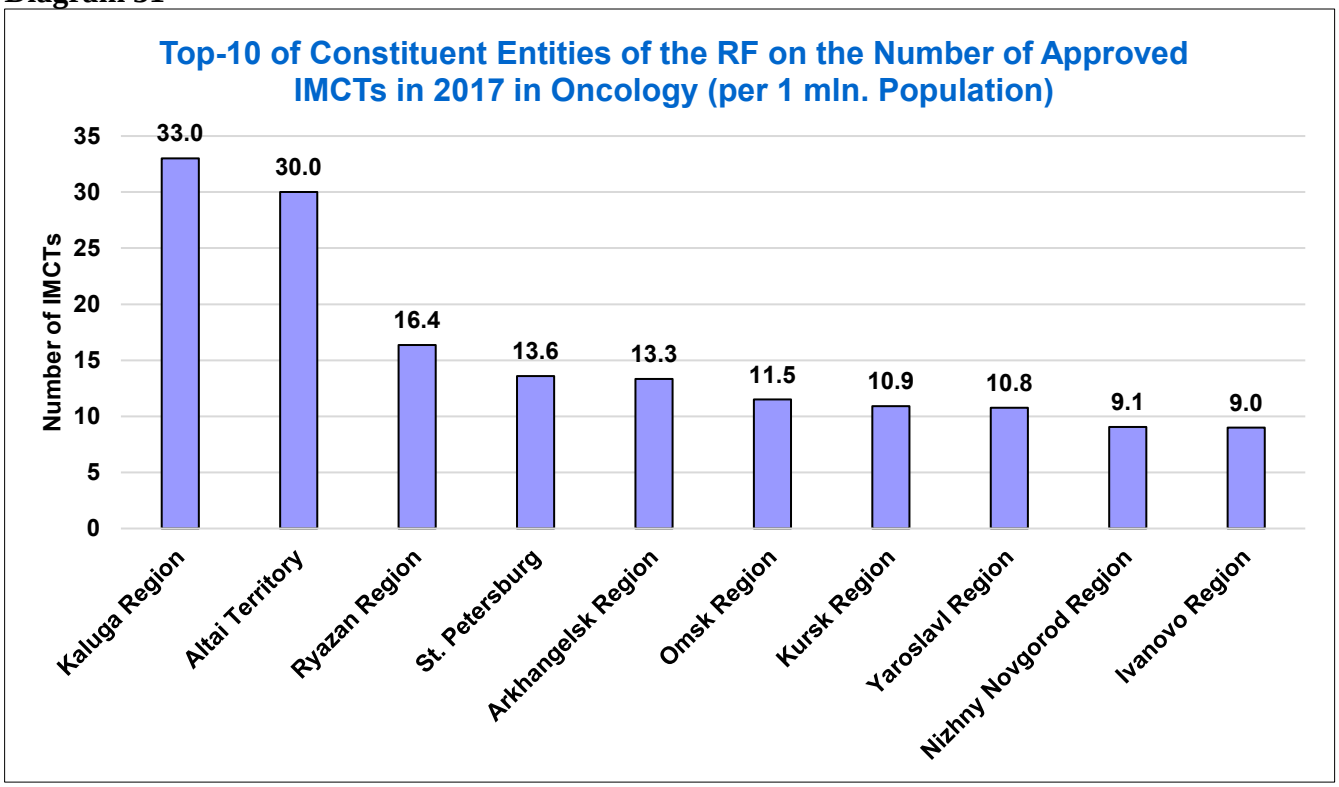
Data from www.grls.rosminzdrav.ru

Diagram 30



Data fromwww.grls.rosminzdrav.ru

Diagram 31



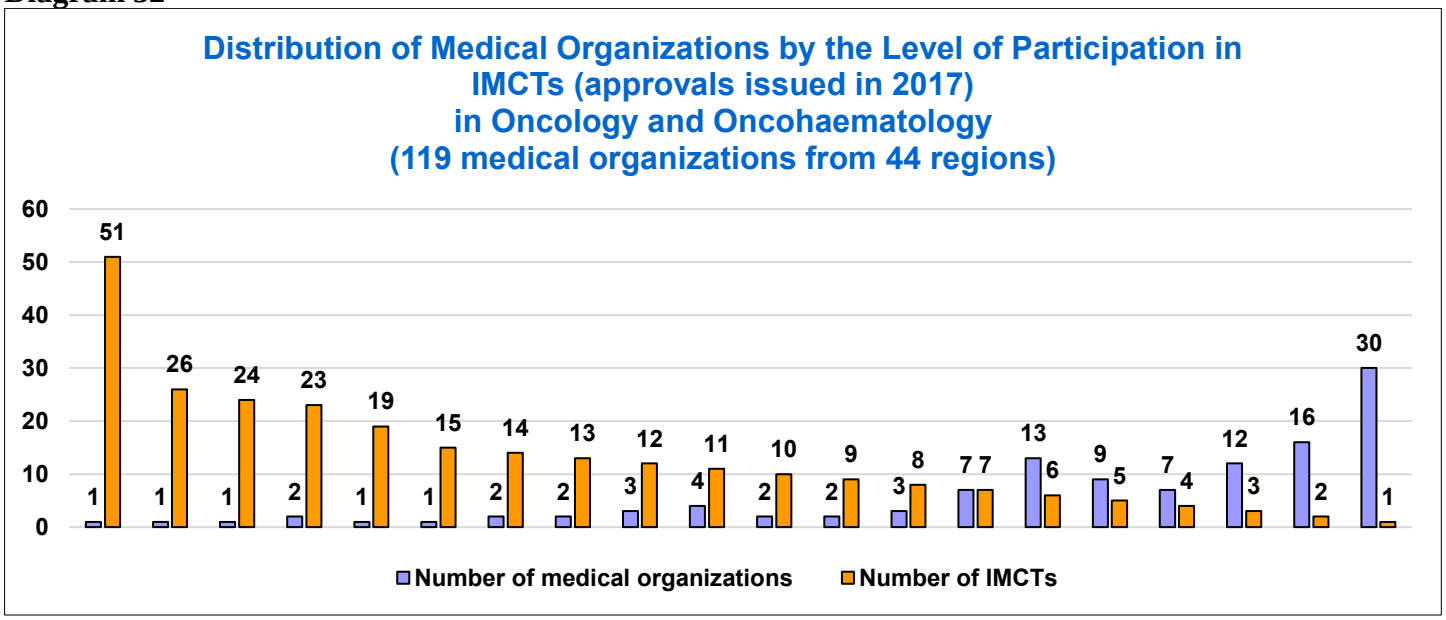
Data from www.grls.rosminzdrav.ru

Table 9

Top of medical organizations on the activity of participation in IMCTs in oncology and oncohaemotology approved in 2017			
Place in ranking	**Name of medical organization**	**Number of IMCTs approved in 2017 with participation of this medical organization**	**Number of centres approved in 2017 for conducting IMCTs**
1	N.N. Blokhin Russian Cancer Research Centre, Russian Ministry of Health, Moscow	51	61
2	National Medical Research Radiology Centre, Russian Ministry of Health, Obninsk	26	32
3	St. Petersburg City Clinical Oncological Dispensary, St. Petersburg	24	25
4	Clinical Oncological Dispensary, Omsk	23	27
5	N.N. Petrov Research Institute of Oncology, Russian Ministry of Health, St. Petersburg	23	23
6	St. Petersburg Clinical Practical Research Centre for Specialised Types of Medical Aid (Oncological), St. Petersburg	19	19
7	Arkhangelsk Clinical Oncological Dispensary, Arkhangelsk	15	15
8	Republican Clinical Oncological Dispensary, Ufa	14	15
9	Scientific Center for X-ray Radiology, Moscow	14	14
10–11	Republican Clinical Oncology Dispensary of the Ministry of Healthcare of Tatarstan Republic, Kazan	13	13
10–11	Leningrad Regional Oncology Center, St. Petersburg	13	13
12–14	I.P. Pavlov First St. Petersburg State medical University, Russian Ministry of Health, St. Petersburg	12	12
12–14	Kursk Regional Clinical Oncology Center, Kursk	12	12
12–14	Volga Federal Medical Research Center of the Ministry of Health of the Russian Federation, Nizhny Novgorod	12	12

Data from www.grls.rosminzdrav.ru

Diagram 32



Data from www.grls.rosminzdrav.ru