ACTO

ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

ACTO NEWSLETTER № 26

Summary of 2022 results

MOSCOW 2023

CONTENTS

This issue of the newsletter is the second after the start of the Russian military operation in Ukraine. For some immediately, for other a little bit later, but it became clear that the outbreak of the geopolitical crisis is leading to the collapse of the market for international clinical trials in Russia, at least in the current historical period.

Even disregarding the political and emotional component, it is clear that the international pharmaceutical business is not ready to launch long-term investment projects in an unstable situation of armed conflict: the risks of failure to complete what has been started are too great. As a consequence, international sponsors stopped submitting applications for new trials. As a result, the number of approvals of international multicenter clinical trials (IMCTs) fell from 73 in Q1 2022 to only two in Q4, and the result of "124 approvals for IMCTs per year" became the lowest since the beginning of ACTO observations (since 2004). The survey conducted by the Association among the market participants showed that less than 15% of IMCTs approved by the regulator in 2022 have actually started or, as far as their sponsors expect, will start soon.

The previous issue mentioned the Bristol Myers Squibb's leaving Russia. Since then, two more members of ACTO have left the local market: Medpace and Dokumeds contract research organizations. Many of the remaining employees have already faced staff reductions, some have launched large-scale programs to relocate specialists or tried to switch them to remote project management in other countries. Companies faced many challenges with the projects that have already started. This includes complication of logistics solutions, as well as problems with payment due to the introduced financial restrictions.

In this issue, we continue to observe in real time the collapse of the former "IMCT empire" in Russia and the further transformation of the clinical trials market in favor of domestic, primarily generic manufacturers.

SUMMARY

The total number of approvals issued for clinical trials in Russia in 2022 decreased by 18.5% and amounted to 740 vs 908 in 2021. The sharpest decrease was in the number of approvals for international multicenter clinical trials (IMCTs), by 66.2% (124 vs 367 in 2021). This is the worst figure in 19 years of observation. Other types of trials of foreign sponsors were also affected: the number of approvals for local trials of therapeutic efficacy and safety fell by 55.6% (16 vs 36, also a historical low since 2004), for bioequivalence studies - by 18.4% (71 vs 87). In contrast, indicators of domestic sponsors showed an increase: by 21.8% for local trials (162 approvals vs 133 a year earlier), and by 28.8% for bioequivalence studies (367 vs 285, the maximum value for the entire observation period). The reason for the increased activity of Russian developers, which, however, was observed only in H1 2022, we believe is not the geopolitical crisis, as is the case with international trials, but the continued impact of the Covid-19 pandemic. In the H2, the activity of Russian developers reclaimed the levels of 2021.

The refusal of the majority of international sponsors to launch new IMCTs meant that in reality, not many trials, applications for which were approved by the regulator, will launch. The ACTO interviewed companies about the fate of their approvals and obtained information on 89 out of 124 IMCTs. Of these 89, almost half (43 trials) have been discontinued and will not be conducted in Russia. When it comes to a one third of those whose fate is known (30 projects), sponsors are still "on hold", but with the passage of time the chances are fading. Only 14 international trials have started, with a high probability of launching two more.

A significant transformation of the market forced us to abandon most of the traditional sections. Thus, in this newsletter, readers will not find the usual distributions of IMCTs by phases and regions of Russia. We also did not calculate the rating of medical organizations active in holding IMCTs. These distributions and ratings built on the data of approvals received would be too far from the real state of affairs, they would not clarify anything, but only create the illusion of activity where it no longer exists. We have decided not to “build Potemkin villages” with the help of diagrams.

An analysis of local trials (excluding bioequivalence studies) showed that foreign sponsors tested generics in 50% of cases, Russian sponsors tested generics and their new combinations in 30.2% of trials, another 11.7% were biosimilars. Adding bioequivalence studies to these data, we see that 93% of all local trials of foreign sponsors and 78% of domestic ones accounted for generic drugs. Majority of the trials of foreign generics was attributable to manufacturers from Belarus (30.9% of the total) and India (29.6%). The most popular among generic manufacturers were rivaroxaban (26 trials), vildagliptin (13), metformin and molnupiravir (ten trials each).

The analysis of the principal market participants drew attention to the significant reduction in the number of foreign players. Thus, the number of IMCT sponsors was 58 vs 115 in 2021, and the number of contract research organizations involved in the IMCT was 19 vs 31. The number of foreign sponsors of local trials has also decreased: 34 vs 54 a year earlier. The number of contract research organizations that were planned to be involved in local trials was 24 vs 28 in 2021. Only the number of Russian manufacturers increased: 117 vs 98 in 2021.

The newsletter ends with data on the behavior pattern of clinical trials markets in the post-Soviet countries.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

In the fall of 2022, after the results of the first half of the year were summed up and it became clear that the number of international trials in Russia was declining very quickly, the media started publishing disturbing materials about this[1]. In them, the experts explained that, according to the current laws, only such a medicine can enter the Russian market, in the trials of which Russian patients took part. This means that the reduction in the number of international trials will eventually lead to the fact that many modern innovative drugs will become unavailable to the inhabitants of the country. The Ministry of Industry and Trade and the Ministry of Health of Russia then tried to calm everyone down and assured other media that the number of trials was not decreasing, and the number of breakthrough therapy protocols was even growing[2]. In this issue of the newsletter, we would like to show the reader a remote debate that has not arisen on our initiative (we are only stating what is happening) with those who see and describe in the press the prospects for the Russian clinical trials market in an emphatically positive way. Information from ACTO is presented in the text, the position of those who opposed us - in the form of quotes and links to media materials. But we will start, as usual, with statistics on issued approvals.

TASS RUSSIAN NEWS AGENCY 9 SEP 2022

Clinical trials of drugs for "breakthrough therapy" in Russia grew by 17%

The Ministry of Health of Russia stressed that the total number of clinical trials of drugs in the country, including international and local ones, "retains an upward trend." "If in 2020, 449 clinical trials were conducted in our country for the first eight months, and in 2021 for the same period - 486, then currently 507 clinical trials are being conducted for the same period. More than three-quarters of all new trials has traditionally been initiated in the leading therapeutic areas: oncology, pulmonology, diseases of the cardiovascular system, endocrinology, rheumatology.

In 2022, the Ministry of Health of Russia issued 740 approvals for clinical trials compared to 908 in 2021, an annual decrease of 18.5% (Table 1). This happened primarily due to a sharp decrease, by 66.2%, in the number of approvals for international multicenter clinical trials (IMCTs): 124 vs 367 in 2021. A significant decline was also observed in other types of trials of foreign sponsors: the number of approvals for local trials of therapeutic efficacy and safety decreased by 55.6%: 16 approvals vs 36 a year earlier, for bioequivalence studies - by 18.4% (71 approvals vs 87). The indicators of Russian sponsors, on the contrary, showed an increase: the number of approvals for local trials of domestic drugs increased by 21.8% (162 vs 133 in 2021), and for bioequivalence studies – by 28.8% (367 approvals vs 285). But this rather significant increase could not compensate for the drop in the total number of reported trials.

Table 1

Approvals for Conduct Clinical Trials: 2022 vs 2021						
Year	**Total**	**International Multicenter CTs**	**Local CTs (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CTs (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
2022	740	124	16	71	162	367
2021	908	367	36	87	133	285
2022 vs 2021, %	-18.5%	-66.2%	-55.6%	-18.4%	21.8%	28.8%

Data from www.grls.rosminzdrav.ru

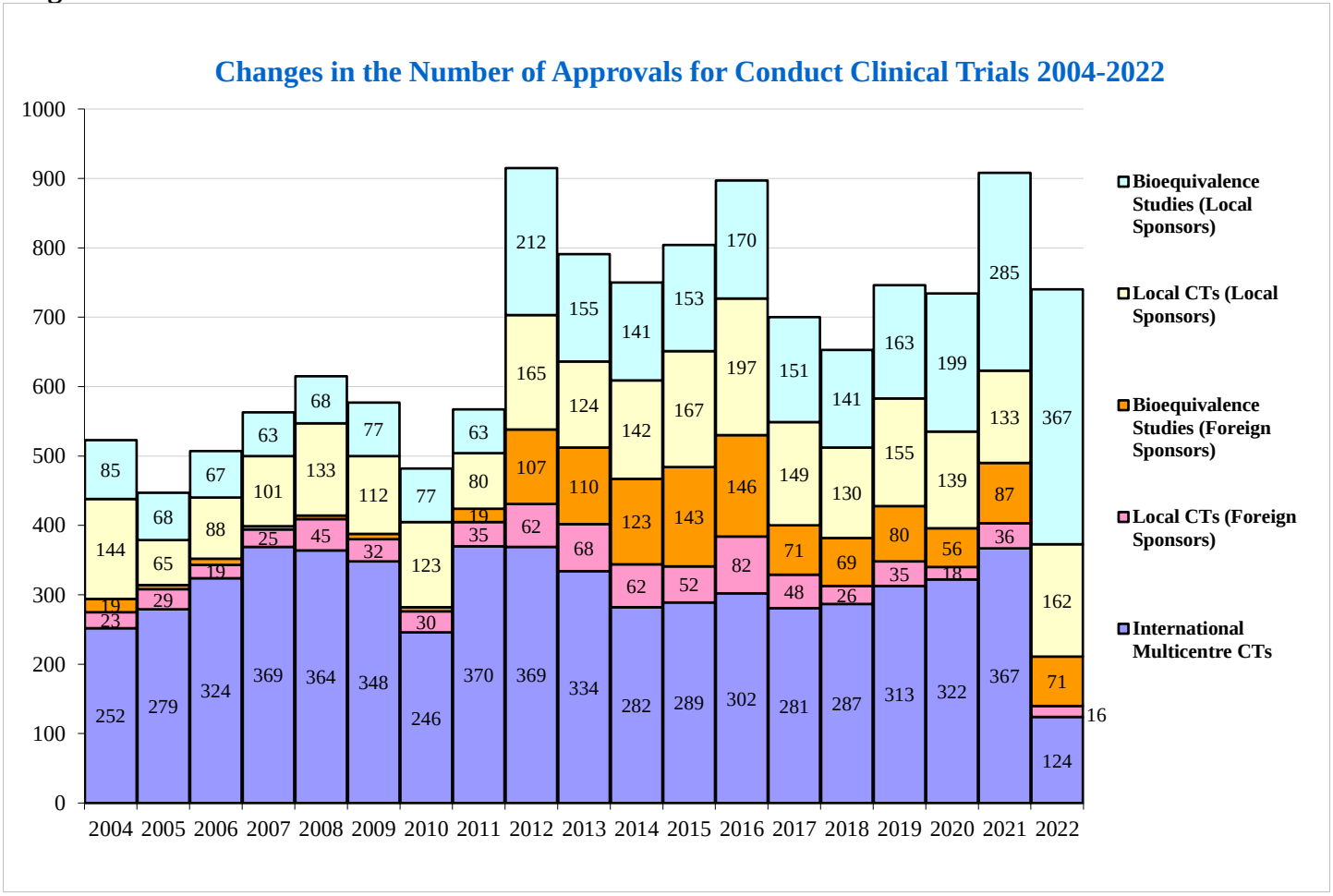
Diagram 1 shows the changes in the number of approvals issued for each type of trials since 2004. It can be seen that for the IMCT 2022 was the worst year for the entire observation period, as well as for local trials of

[1] " The medicines of the future are fading into the past. International companies suspend development in Russia ", Kommersant dated 09 September 2022. "States can't afford development of innovative drugs ", News.ru dated 09 September 2022

[2] "Clinical trials of drugs for "breakthrough therapy" in Russia grew by 17%", TASS dated 09 September 2022

foreign sponsors. But for bioequivalence studies of Russian sponsors, the past year was, on the contrary, the best. The latter have been steadily growing over the past five years: in 2018, 141 approvals of this type were issued, in 2019 - 163 approvals (annual increase of 15.6%), in 2020 - 199 (an increase of 22.1%), in 2021 - 285 (43.2%). In 2022, growth continued, although its pace slowed down a little, amounting, as already mentioned, to 28.8% compared to the previous year. Local trials of Russian sponsors did not break records: in 2012, 2015 and 2016, their performance was better than in 2022. Bioequivalence studies of foreign sponsors show a result close to the average for the previous five years.

Diagram 1



Data from www.grls.rosminzdrav.ru

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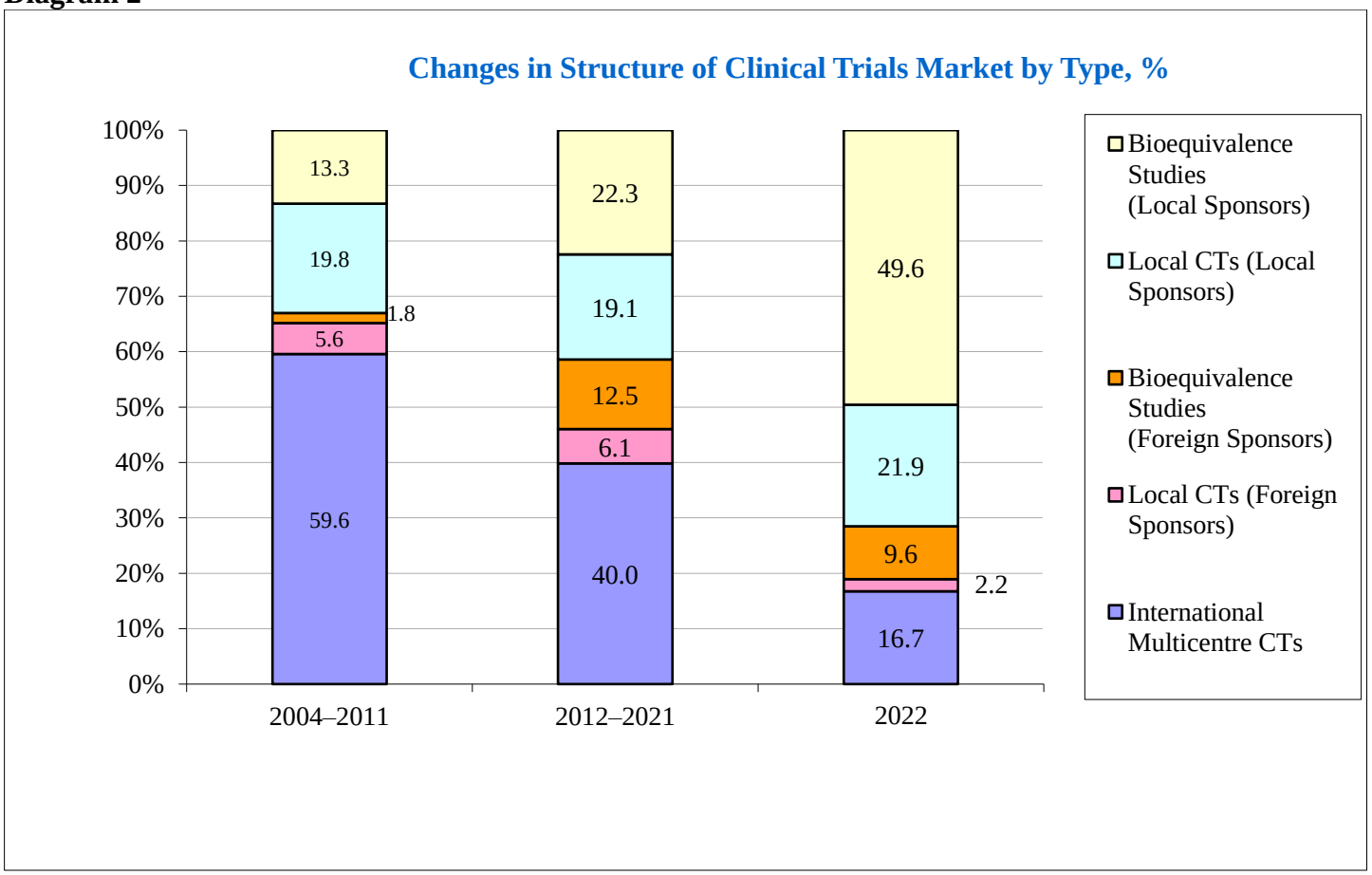
Such significant changes in the number of approvals issued for various types of trials could not but affect the overall structure of the market. Diagram 2 shows how the ratio of the shares of different types of trials has changed over different periods of time. Since the beginning of ACTO observations (since 2004), the market structure has undergone two significant transformations: the adoption of the law "On the Circulation of Medicines" in 2010 and a sharp decrease in the activity of foreign companies after the outbreak of hostilities in Ukraine in 2022. The diagram distinguishes two periods, within each of which the indicators remained relatively stable: 2004–2011, 2012–2021 (the average values for each type for the corresponding period are given for them) and, finally, 2022 standing apart.

Diagram 2



Data from www.grls.rosminzdrav.ru

The presented diagram shows that the “golden age” of IMCTs in Russia fell on the first decade of the 21st century, when they accounted for almost 60% of all trials conducted in the country. With the adoption of the Federal Law "On the Circulation of Medicines", the share of IMCTs lost almost 20 percentage points. But, as we remember from Diagram 1, this happened not due to a decrease in the number of IMCTs conducted, but due to an increase in the number of other types of trials. And then there was a collapse in 2022, the share of IMCTs reached a historic low of 16.7%. At the same time, it should be kept in mind that the presented diagram does not fully reflect reality, since it is based on data on approvals issued, and not on projects that have really started. In fact, the share of IMCTs in the total volume of trials conducted in Russia today is, by all means, even lower.

Compared to the average figures for the previous ten years, in 2022 the shares of other trials of foreign sponsors also decreased: from 12.5% to 9.6% of bioequivalence studies and from 6.1% to 2.2% of other local trials. But in this case the drop is not as dramatic as with the IMCT.

Naturally, against the background of a reduction in the share of IMCTs and local trials of foreign drugs, the share of trials of domestic sponsors in 2022, on the contrary, increased. To a lesser extent, this applies to local trials, which have added compared to the average for 2012-2021. Less than three percentage points (21.9% vs 19.1%). But studies of the bioequivalence of Russian generics accounted for almost half of the total number of trials: their share reached a historical maximum of 49.6%, which is more than twice the average for the previous ten years (22.3%). As already mentioned, the growth of this category of trials has continued over the past five years, most actively manifesting itself since the beginning of the pandemic. So, if in 2015-2019. From 18.9% to 21.8% of all approvals passed for trials on Russian generics, in 2020 their share was 27.1%, and in 2021 - already 31.4%. But even against this background, the results of 2022 stand out strongly, since the previously observed trend of an increase in the number and share of trials of local generics in this case was accompanied by a decrease (in the case of IMCTs, a landslide) of trials by foreign sponsors.

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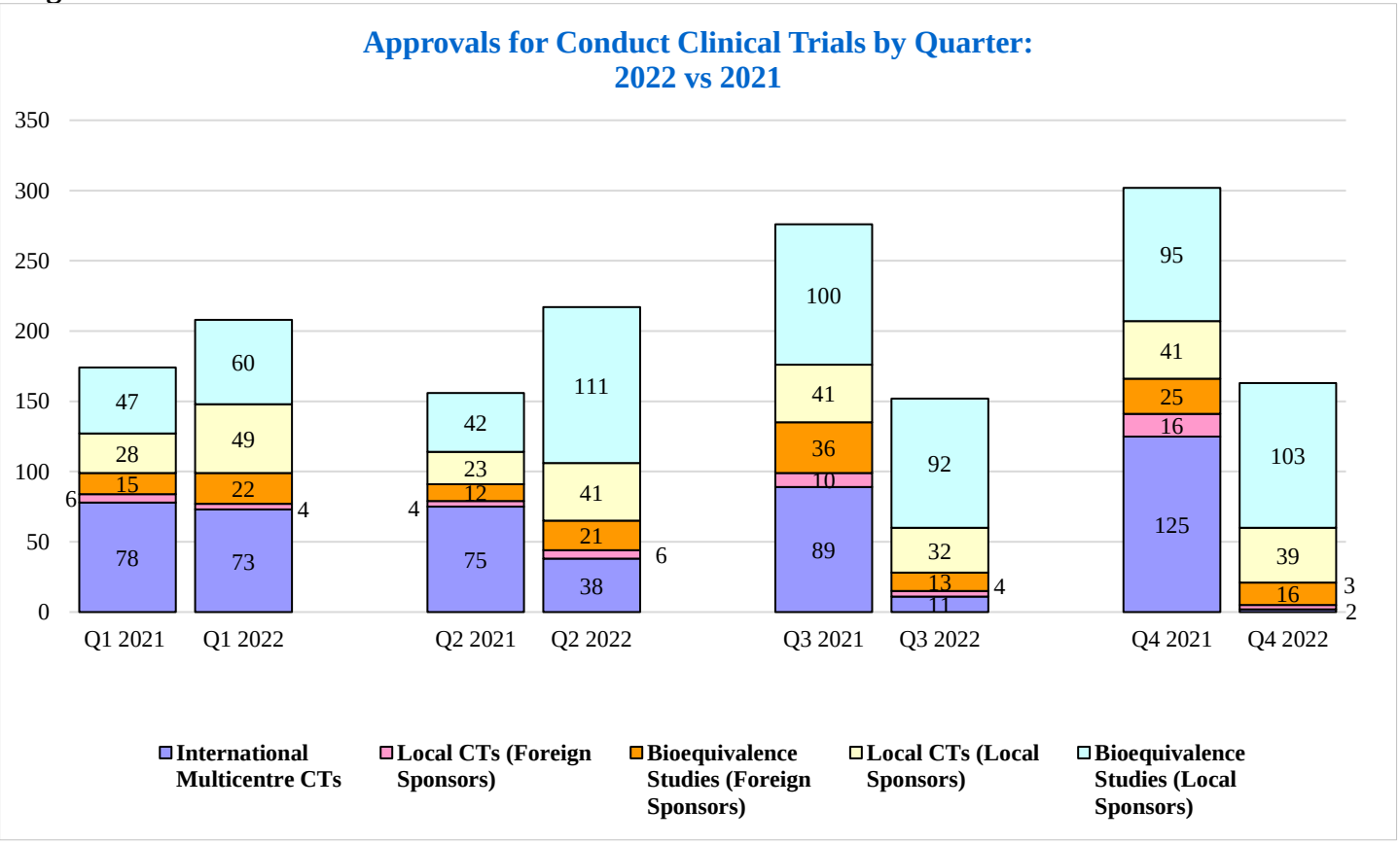
Since 2022 turned out to be a year transformations for the Russian market, it is worth analyzing in detail how the number of approvals for certain types of trials changed during the year. Diagram 3 shows the dynamics of approvals issued quarterly in comparison with the data for the corresponding quarter of the previous year.

Diagram 3



Data from www.grls.rosminzdrav.ru

There were almost the same number of approvals for IMCTs in Q1 2022 as for the same period in 2021, 73 vs 78. This is understandable, hostilities began on February 24, which did not affect the flow of approvals issued before and for some time after that: applications for these approvals were submitted as early as 2021 (the average period for obtaining an approval in 2021 was 111 days). Nevertheless, already in Q2 2022, we saw a decrease in the number of approvals for IMCTs compared to the same period in 2021: 38 vs 75 (49.3% less). In Q3 this number fell to 11 vs 89 for the same period of the previous year. In Q4 there were only two of them vs 125 (a drop of 98.4%).

With bioequivalence studies of Russian sponsors, the situation is different. They actively added to the indicators of the previous year in Q1 (60 approvals vs 47 in 2021) and especially Q2 (111 vs 42). However, since the second half of 2022, such a rapid growth, demonstrated in the first half, has stopped. In Q3, the number of approvals issued was even lower than in 2021 (92 vs 100), in Q4 there was a slight, incomparable in scale with the first half of the year, an excess of the result of 2021 (103 vs 95).

A similar situation, but with a slightly less noticeable difference in indicators, was also observed in local trials of the safety and therapeutic efficacy of domestic sponsors: an increase in the number of approvals issued in the first half of the year and its termination, and even a loss to the indicators of 2021 in the second.

There was an opinion in the media that Russian companies were “replacing” the leaving Western ones on the market[3], that the reduction in the activity of foreign companies allowed domestic companies to "feel more confident"[4]. But if this were the case, the number of new trials by Russian sponsors would grow not only in the first half of 2022, but also later. We believe that it is impossible to make such bold conclusions about the relationship between the decline in the activity of foreign companies and the increase in Russian ones, which was confirmed by the results of the year. In our opinion, the behavior pattern of IMCTs and the behavior pattern of bioequivalence studies of Russian sponsors do not depend on each other, they can simultaneously go down, as it was in 2014, or up, as it was in 2021, or be multidirectional, as in the first half of 2022 Not to mention the fact that bioequivalence studies of generic drugs that have lost patent protection cannot, in principle, “replace” complex protocols for testing innovative drugs.

ФАРММЕДПРОМ NEWS

Russian pharmaceutical companies take over the clinical trials market

#clinical trials 18 November 2022 News

In total, for the period from January to September of this year, the Ministry of Health of the Russian Federation issued 576 approvals to conduct clinical trials (CTs) of drugs. At the same time, 340 of them accounted for Russian companies, while in the previous year there were only 226 of them. In a sense, it can be said that domestic manufacturers are replacing companies that have left the clinical trials market, but this is true only for the US players.

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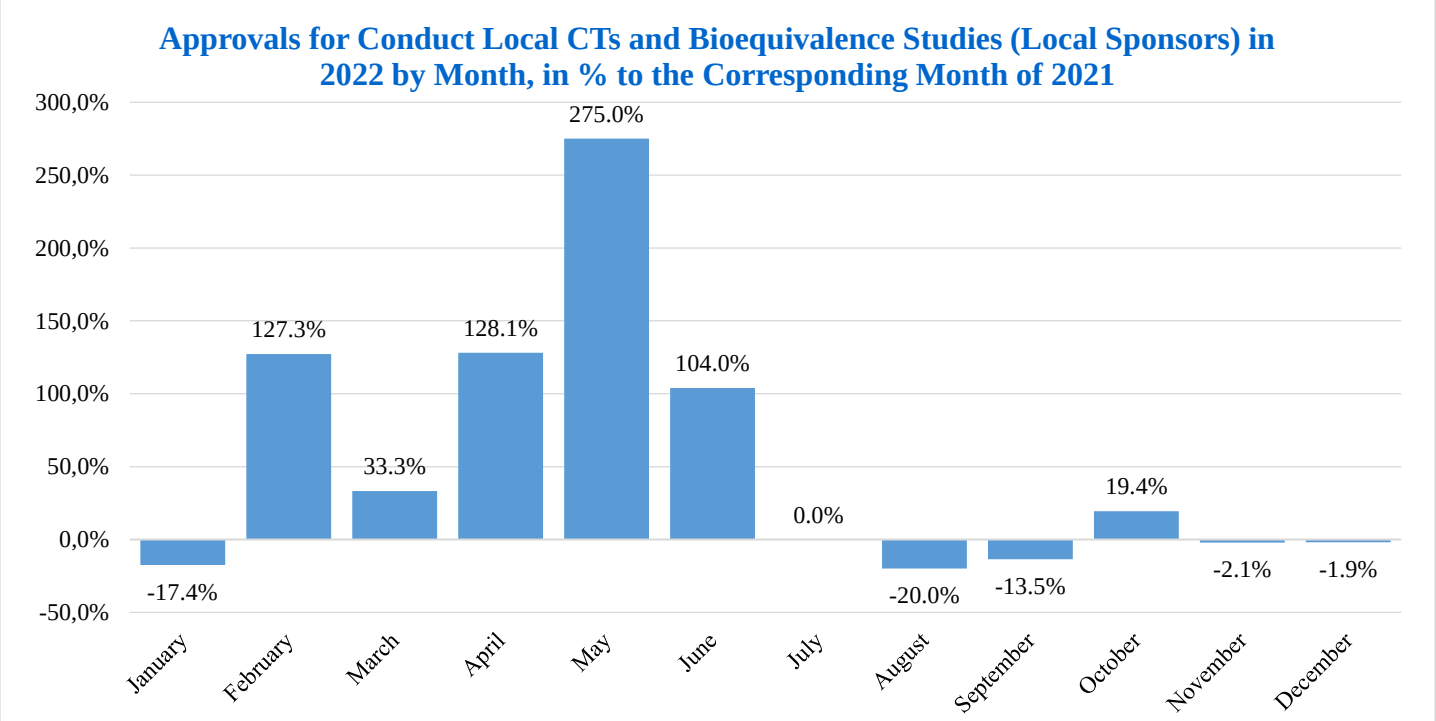
Diagrams 4 and 5 make it possible to see the monthly dynamics of 2022 for certain types of trials as a percentage of previous periods. Thus, Diagram 4 shows the behavior pattern of the issuance of approvals for trials by Russian sponsors (including trials of both original and generic drugs) as a percentage of the corresponding month of the previous year. It can be seen that the largest excess of 2021 indicators took place in February, April, May and June. In other months, this excess was either not so significant, or the indicators for 2022 turned out to be lower than in 2021.

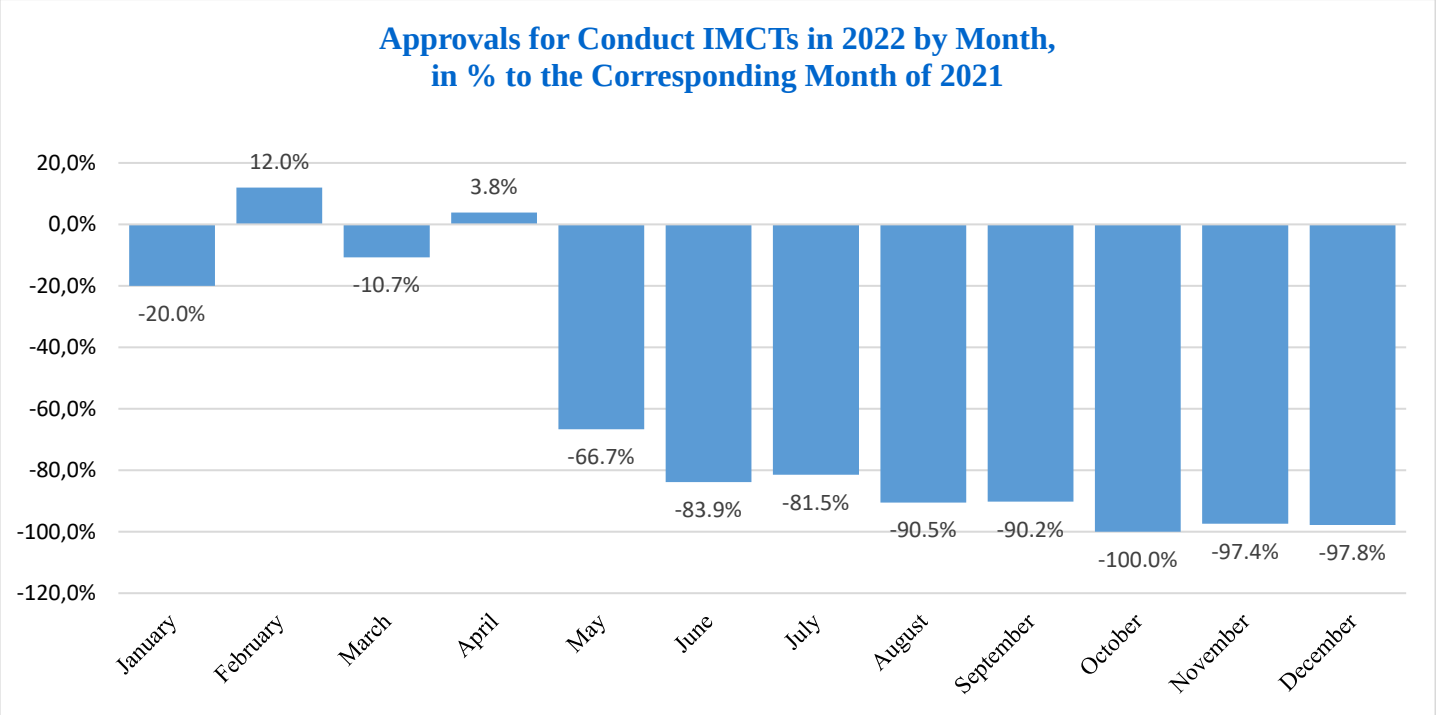
Diagram 4



Data from www.grls.rosminzdrav.ru

[3] "Russian pharmaceutical companies take over the clinical trials market" Pharmmedprom dated 18 November 2022
[4] “There are fewer clinical drug trials in Russia: how critical is this?”, Pharmmedprom dated 26 January 2023

Diagram 5



Data from www.grls.rosminzdrav.ru

The monthly comparison for IMCTs looks completely different (Diagram 5). For the first four months of the year, there is no stability in relation to the same periods of the previous year, one month is a little worse, the other a little better. The sharp drop in indicators begins in May, when the number of approvals issued decreases to 1/3 of the figure for the same month in 2021 (6 vs 18). This is followed by a collapse, and since October, approvals for IMCTs have practically ceased to be issued. At the same time, in October 2022, the Ministry of Health told the press that the total number of ongoing trials, including international ones, is stable and does not decrease, that the Russian market remains attractive and has real development prospects[5], and in January 2023, articles were published alleging an increase in the number of clinical trials in Russia[6].

TASS RUSSIAN NEWS AGENCY 19 OCT 2022

The Ministry of Health denies the decrease in the number of clinical trials of drugs in the territory of the Russian Federation

"The total number of ongoing clinical trials in the Russian Federation, including international and local ones, is stable and does not decrease. <...> The results of a comprehensive analysis of the main general economic trends in the economies of different countries, regional potentials and the development of demographic situations allow us to conclude that the Russian market for clinical drug trials retains its attractiveness and has real development prospects.

TASS RUSSIAN NEWS AGENCY 24 JAN 2023

Murashko announced an increase in the number of clinical trials of drugs conducted in Russia

The head of the Ministry of Health urged to support the promotion of domestic medicines so that import substitution takes place, and to explain that they are of the same quality as foreign ones

MOSCOW, January 24. /TASS/. The number of clinical trials of drugs conducted in the Russian Federation has grown mainly due to domestic manufacturers, Russian Health Minister Mikhail Murashko said on Tuesday.

[5] "The Ministry of Health denies the decrease in the number of clinical trials of drugs in the territory of the Russian Federation", TASS dated 19 October 2022

[6] "Murashko announced an increase in the number of clinical trials of drugs conducted in Russia", TASS dated 24 January 2023

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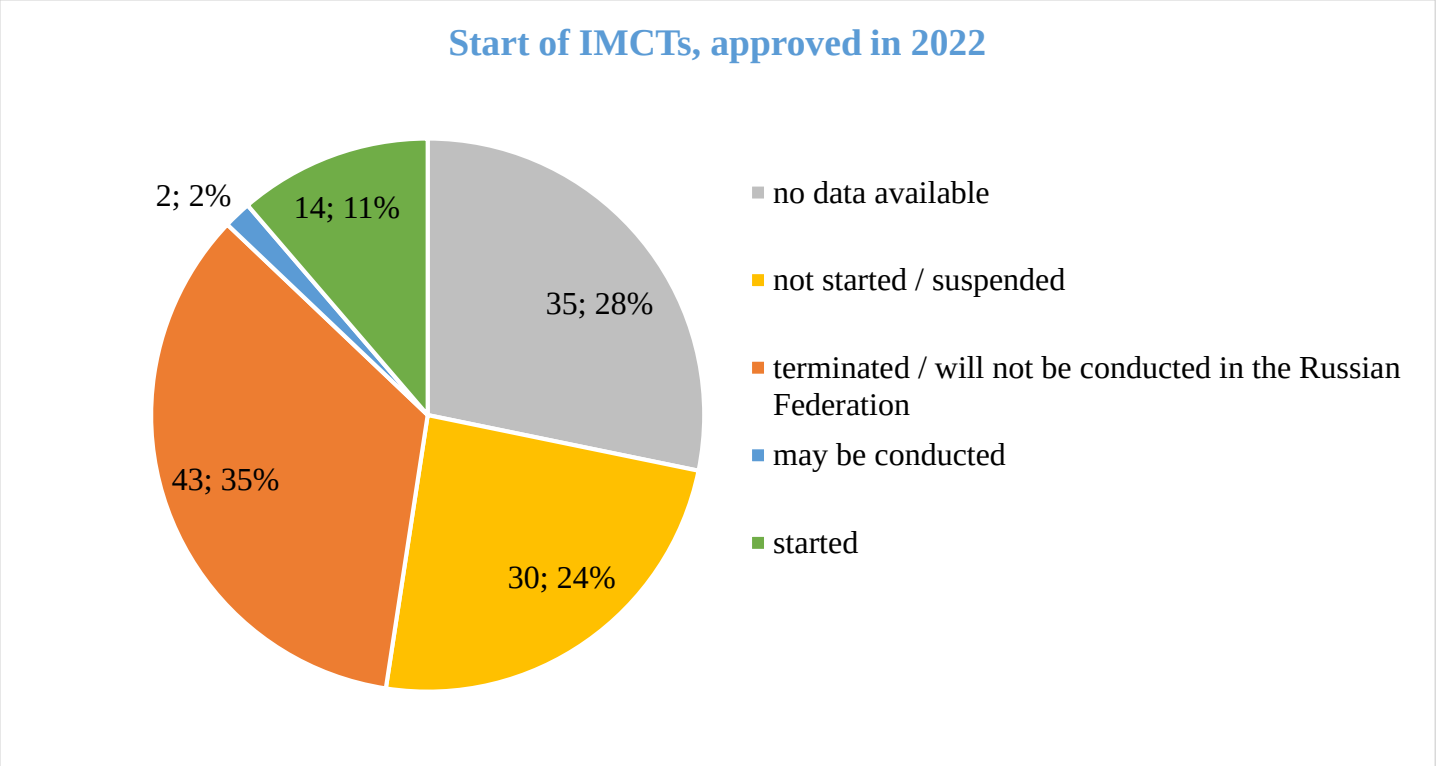
As mentioned earlier, the number of approvals issued for IMCTs does not really reflect the current situation. After the majority of international sponsors announced the suspension of new projects in Russia, it became clear that not all trials approved by the regulator will actually start. In order to more clearly present the real state of affairs, in mid-2022, ACTO conducted a survey of companies involved in the organization of trials, and tried to find out the fate of approvals issued for holding IMCTs in the 1st half of 2022. The results were published in the previous issue of the newsletter. At the end of the year, we decided to repeat the survey and today we can present data for the whole of 2022 (diagram 6).

Diagram 6



Data from poll of ACTO members

We managed to obtain information about 89 out of 124 approvals for IMCTs (72%), the fate of another 35 projects (28%) remained unknown to us. 43 IMCTs (35% of all those approved in 2022, or almost half of those whose fate is known) will definitely not be held in Russia. At least 30 more trials (24% of the total number or a third of those known to us) are kept on hold by sponsors. 14 international trials have started (11% of the total). Of these 14, ten protocols represent extensions of therapy for patients previously enrolled in another trial of the same drug (so-called extension or roll-over trials for current patients). It is clear that the number of participants in these trials was extremely limited - in total it amounted to 156 persons. Three more startup projects are sponsored by a Russian developer, one by a Chinese one. And, finally, two more IMCTs (2%), as their organizers assumed at the beginning of February, have a chance to start soon.

Taking into account that information about another 38 international projects is unknown to us, the shares of both started and not started projects may turn out to be slightly higher, but the approximate ratio according to the pattern we have received is generally clear.

All of the above does not prevent individual experts from giving optimistic assessments of the prospects for the Russian market[7]: "shallow recession" in general, "sharp spurt" of domestic pharmaceutical companies, which are advised to "take advantage of the situation", whatever that means, etc. True, in order to maintain optimism, the material published at the end of January 2023 uses the statistics of 2021 (by the way, one of the most successful years for the Russian market since 2004, more approvals for all types of trials were issued only in 2012) and an unknown method of calculation. We, for our part, prefer to face the truth, even if it is extremely unpleasant.

ФАРММЕДПРОМ NEWS

There are fewer clinical drug trials in Russia: how critical is this?

#clinical trials 26 January 2023 News

Firstly, the behavior pattern of CI in Russia **has always been characterized by cyclicity**: ups and downs alternating from year to year. And the recession of 2022 is not the deepest yet, Andrey Alasheev noted. In 2020, 734 clinical trials were approved (that is, 5 less than in 2022), and in 2017 and 2018, against the backdrop of a politically favorable situation, there were only 700 and 653, respectively. It turns out that the past year is not the most disastrous.

And yet, along with a decrease in the share of other countries in the CI market, **there was a sharp leap forward in favor of domestic pharmaceutical companies**. Over the year, the share of clinical trials of domestic drugs increased from 45% to 71%. And this suggests that they are gradually replacing foreign drugs, which means that the Russian pharmaceutical industry is finally starting to feel more confident.

Russia now ranks **19th in the world** in terms of the number of approved CTs of drugs, according to 2021 data. But there are no signs of disaster here. In the top five is Iran, which has been living under sanctions for 70 years. Time will tell how the situation will develop and who will take the vacant positions in the trial market. So far, it is clear that the conditions are in favor of Russian producers, and they should take advantage of the situation.

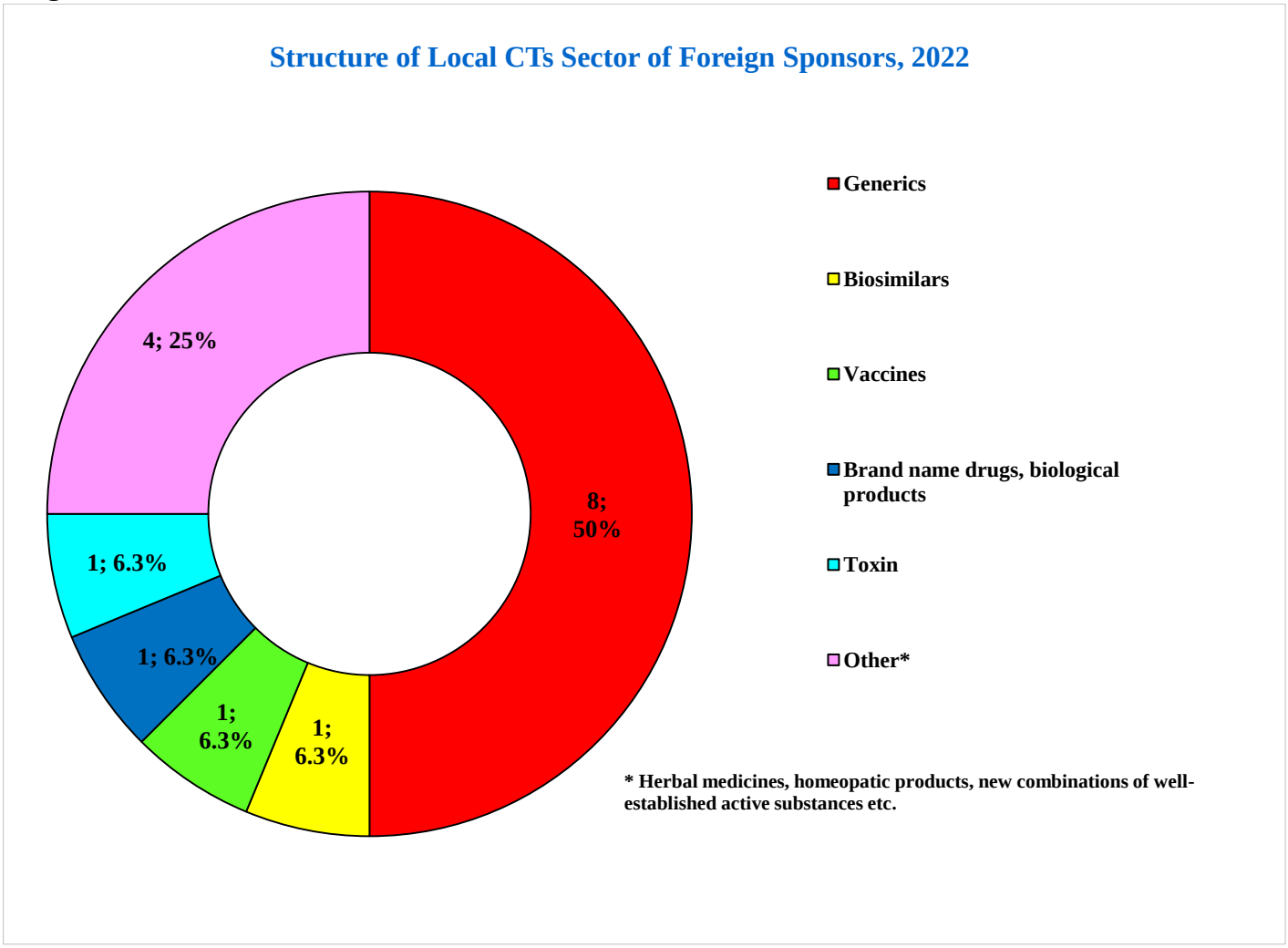
[7] "There are fewer clinical drug trials in Russia: how critical is this?", Pharmmedprom dated 26 January 2023

STRUCTURE OF THE MARKET FOR LOCAL TRIALS THERAPEUTIC EFFICACY AND SAFETY BY TYPE OF DRUGS

Diagrams 7 and 8 allow you to see which types of drugs were studied in local trials of therapeutic efficacy and safety by foreign and Russian sponsors, respectively.

Recall that the number of such trials of foreign sponsors (this does not include bioequivalence studies) was extremely limited - only 16 projects. In half of the cases (eight protocols), generics were tested. One trial each included immunoglobulin, hepatitis A vaccine, botulinum toxin, and progesterone. The remaining four trials tested so-called "other medicines", where we include substances of herbal and animal origin, homeopathic preparations, combinations of well-studied substances, etc.

Diagram 7

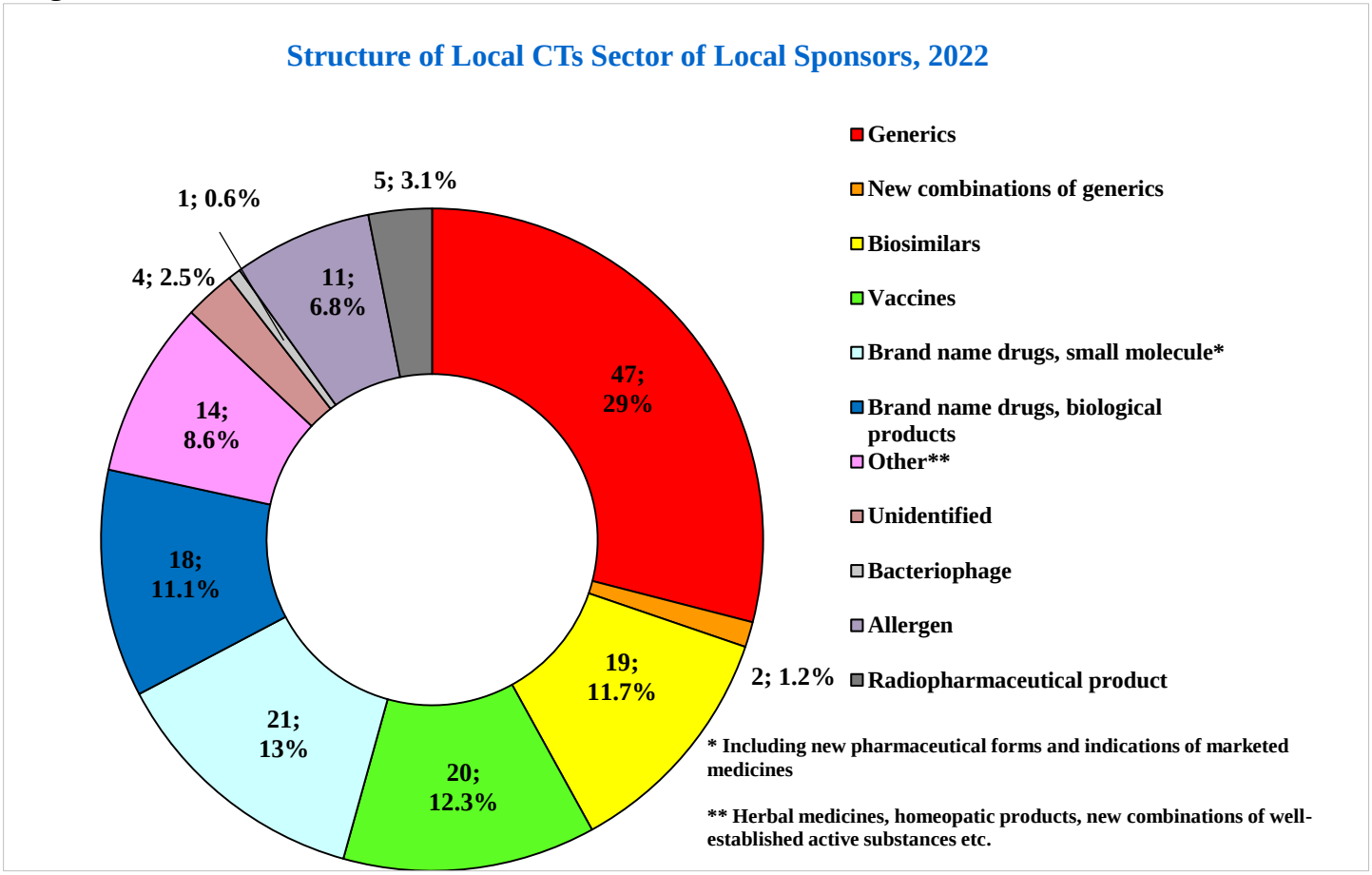


Data from www.grls.rosminzdrav.ru

In local trials of Russian sponsors (there were 162 of them, not counting bioequivalence studies), generics and their new combinations accounted for 30.2% (47 protocols for individual drugs and two more for combinations), another 11.7% - for biosimilars (19 trials). Original drugs (small molecules) took a share of 13% (21 protocols), another 19 trials (shares of 11.7% each) accounted for original biological drugs and vaccines. Allergens were studied in 6.8% of trials (11 protocols) and radiopharmaceuticals in 3.1% (five). Another approval was issued for the trial of bacteriophage. In 8.6% of the trials (14 protocols), it was supposed to test preparations

based on substances of herbal or animal origin, homeopathic preparations, etc. In four cases, the drug could not be identified.

Diagram 8



Data from www.grls.rosminzdrav.ru

STRUCTURE OF THE CLINICAL TRIALS MARKET BY THERAPEUTIC AREAS

Table 2 shows the distribution of IMCTs approved in 2022 by therapeutic area. Let us remind you again that these are the statistics of issued approvals, which in most cases remained unrealized, the trials themselves have not started. To get an idea of how many IMCTs in each specific therapeutic area are actually going on or have a chance to start, the ACTO survey data in the last column of the table helps.

Due to the sharp decline in the number of new international projects in Russia, it would not be entirely correct to fully compare the indicators of 2022 with those of previous years. One can only try to estimate the losses by comparing the absolute number of approvals received. Oncology, traditionally the most approved, has fallen by two-thirds, with 35 approved protocols in 2022 vs 108 in the previous year. Of these 35, according to the ACTO survey, 12 will definitely no longer be carried out in Russia, four have been suspended, two have started (since both protocols include patients who previously participated in the trial of the same drug, both protocols account for only seven participants), one (four more participants of the earlier protocol) there is a chance to start, there is no information on 16. In oncohaematology, eight approvals were obtained, up from 37 a year earlier, with only one trial known to have started with three persons. Gastroenterology accounted for three protocols with 22 in 2021. Neurology dropped from 34 to 16 approvals (two trials started with 72 participants), rheumatology from 28 to ten (three trials started with 137 participants), cardiology and cardiovascular diseases (CVD) - from 17 projects to seven (two trials started with 46 participants, there is also a chance for another one with 27 patients), pulmonology - from 19 to three (all three did not start), haematology from 12 to three (all three will no longer be carried out in Russia). New trials of medicines against Covid-19 were also approved less often: 16 trials in 2021 and only two in 2022, but the gradual decline in developer interest in this disease could also have an effect here.

It is clear that a decrease in the number of new IMCTs means a decrease in the number of patients who could potentially take part in them. In 2021, it was planned to recruit 39 thousand persons for treatment within the framework of international trials (of which 10,500 patients with oncological and oncohaematological diseases), in 2022 - 11.5 thousand in all therapeutic areas, and this comes from the data on approvals. If we take into account the information available in ACTO about the fate of projects, we get the following: without trials, which will definitely not be carried out in the Russian Federation, the total planned number of participants will be 7,300, and if we take only IMCTs that have already started or have this is a chance, then only 379 persons.

Table 2

Distribution of International Multicenter CTs by Therapeutic Areas, 2022				
Therapeutic Area	**Number of IMCTs**	**Share (%)**	**The number of planned participants**	**Status as of February 2023 according to the ACTO survey (for studies that have started, the number of declared participants is given in parentheses)**
Oncology	35	28.2%	2 219	2 – started (7), 1 – may be conducted (3), 4 – not started / suspended, 12 – terminated / will not be conducted in the Russian Federation, 16 – no data available
Neurology	16	12.9%	2 518	2 – started (72), 7 – not started / suspended, 4 – terminated / will not be conducted in the Russian Federation, 3 – no data available
Rheumatology	10	8.1%	362	3 – started (137), 3 – not started / suspended,

				4 – terminated / will not be conducted in the Russian Federation
Oncohaematology	8	6.5%	172	1 – started (3), 5 – not started / suspended, 1 – terminated / will not be conducted in the Russian Federation, 1 – no data available
Psychiatry	7	5.6%	1 159	5 – terminated / will not be conducted in the Russian Federation, 2 – no data available
Cardiology and CVD	7	5.6%	275	2 – started (46), 1 – may be conducted (27), 1 – not started / suspended, 2 – terminated / will not be conducted in the Russian Federation, 1 – no data available
Endocrinology	6	4.8%	510	4 – terminated / will not be conducted in the Russian Federation, 2 – no data available
Ophthalmology	5	4.0%	333	1 – started (30), 2 – not started / suspended, 1 – terminated / will not be conducted in the Russian Federation, 1 – no data available
Infectious Diseases (except HIV/HCV/tuberculosis, COVID-19)	4	3.2%	264	2 – not started / suspended, 1 – terminated / will not be conducted in the Russian Federation, 1 – no data available
Nephrology	4	3.2%	174	1 – started (10), 1 – not started / suspended, 1 – terminated / will not be conducted in the Russian Federation, 1 – no data available
Hepatology	3	2.4%	220	1 – started (24), 1 – terminated / will not be conducted in the Russian Federation, 1 – no data available
Gastroenterology	3	2.4%	135	1 – not started / suspended, 1 – terminated / will not be conducted in the Russian Federation, 1 – no data available
Pulmonology	3	2.4%	74	2 – not started / suspended, 1 – terminated / will not be conducted in the Russian Federation
Haematology	3	2.4%	38	3 – terminated / will not be conducted in the Russian Federation
Covid-19	2	1.6%	2 610	2 – no data available
Otorhinolaryngology	2	1.6%	150	1 – not started / suspended, 1 – no data available
Dermatology	2	1.6%	37	1 – not started / suspended, 1 – terminated / will not be conducted in the Russian Federation
Obstetrics and gynecology	1	0.8%	120	1 – no data available
Allergology	1	0.8%	100	1 – started (20)
Cosmetology	1	0.8%	64	1 – terminated / will not be conducted in the Russian Federation
Urology	1	0.8%	20	1 – no data available
TOTAL	124	100.0%	11 554	

Data from www.grls.rosminzdrav.ru, poll of ACTO members

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Table 3 shows the distribution by therapeutic area of local trials initiated by foreign sponsors (including bioequivalence studies) of generics and biosimilars. Their total number has fallen from 105 to 81 compared to 2021.

In general, in this category of trials, the reduction was primarily due to the loss of certain therapeutic areas not presented in 2022: HIV (there were six approvals in 2021), ophthalmology (there were four), dermatology and oncohaematology (three each), etc. The shares of seven of the 16 therapeutic areas presented in table 3 decreased slightly compared to the previous year (by 2 percentage points on average), six showed a slight increase (by 1.5 percentage points on average). A noticeable increase against the general background is demonstrated only by drugs used in cardiology and CVD, neurology, as well as analgesics and non-steroidal anti-inflammatory drugs (NSAIDs).

The field of cardiology and cardiovascular diseases, including vascular surgery and intensive care, not only remained in first place, but also grew the most compared to 2021: 30 approvals and a share of 37% in 2022 with 24 and 22.9% a year earlier. The demand for drugs used in the complex therapy of Covid-19 and the complications caused by it could contribute to its growth. Analgesics and NSAIDs were in second place in 2022: 10 new trials, 12.3% of all in this category (in 2021 there were eight trials, the share was 7.6%). In third place is neurology with nine protocols and a share of 11.1% (six trials and 5.7% a year earlier). Fourth place belongs to endocrinology, some drugs of which are also used in Covid-19: eight trials, a share of 9.9%. Fifth place was shared by gastroenterology and infectious diseases: five approvals each, shares of 6.2%. It should be reminded that data on infectious diseases are given without taking into account HIV, tuberculosis, hepatitis C and Covid-19, which are traditionally separated into separate categories in ACTO newsletters. Yet in 2022, foreign sponsors did not receive approvals for trials of generics and biosimilars of drugs for the treatment of these specific diseases.

Table 3

Distribution of Local CTs and Bioequivalence Studies (Generics and Biosimilars) of Foreign Sponsors, 2022			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Cardiology and CVD/Vascular surgery/Intensive care	30	37.0%	1 993
Analgesic and NSAIDs	10	12.3%	944
Neurology	9	11.1%	417
Endocrinology	8	9.9%	495
Gastroenterology	5	6.2%	460
Infectious Diseases (except HIV/HCV/tuberculosis, COVID-19)	5	6.2%	336
Allergology	2	2.5%	618
Pulmonology	2	2.5%	500
Phlebology	2	2.5%	404
Psychiatry	2	2.5%	102
Haematology	1	1.2%	128
Cosmetology	1	1.2%	110
Gynecology	1	1.2%	80
Immunology	1	1.2%	46
Rheumatology	1	1.2%	40
Urology	1	1.2%	36
TOTAL	81	100.0%	6 709

Data from www.grls.rosminzdrav.ru

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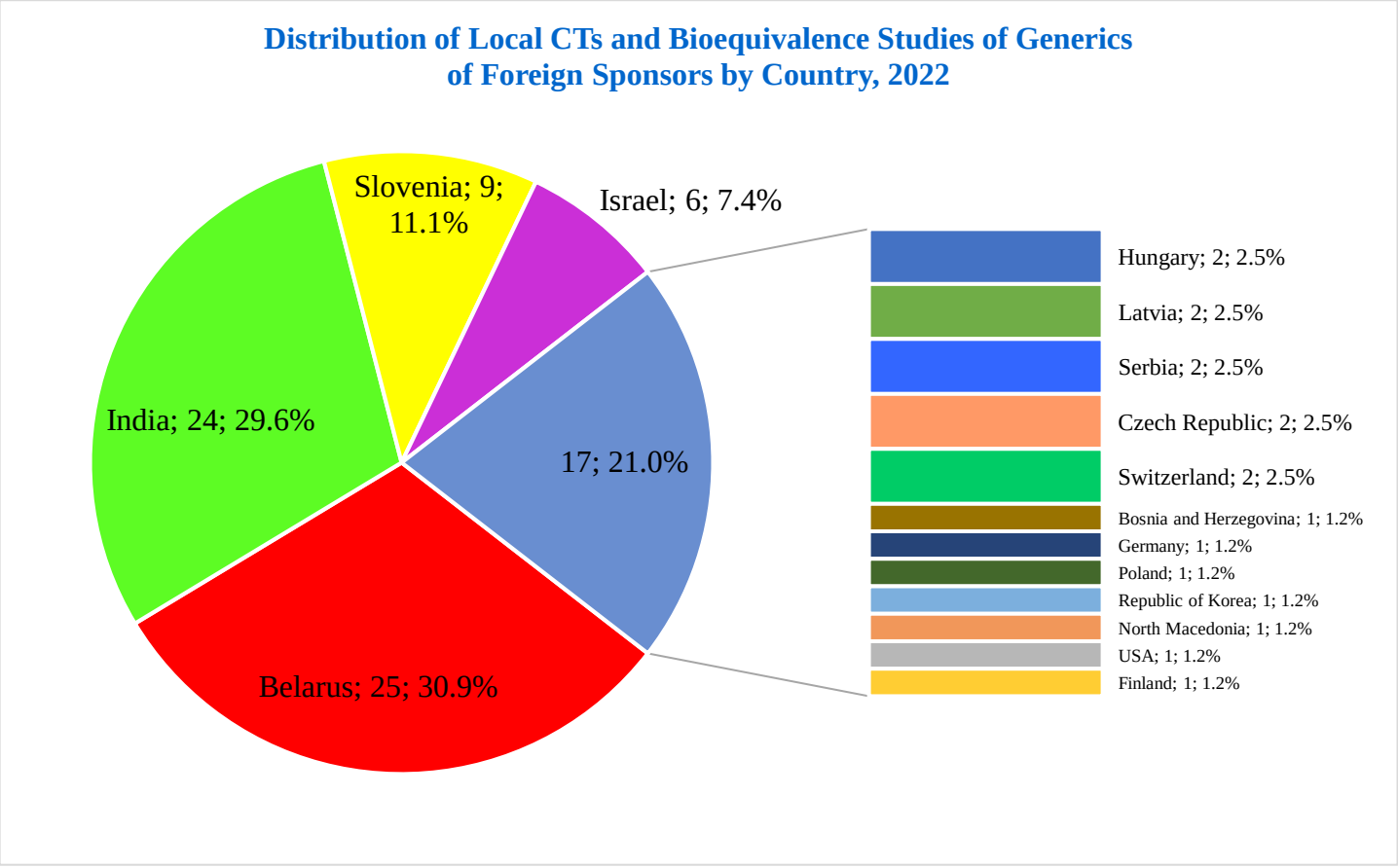
Against the backdrop of a decrease in the activity of foreign companies in Russia, it becomes interesting from which countries come sponsors who want to conduct local trials of generics and biosimilars here (Diagram 9).

Belarus and India lead by a wide margin. Sponsors from Belarus have 25 approvals, which account for 30.9% of all issued for this type of trials. Sponsors from India have almost the same number: 24 approvals or 29.6% in total. Notable are Slovenia (11.1%, nine protocols) and Israel (7.4%, six trials). The remaining 12 countries account for one or two approvals each, their total share is slightly more than a fifth, 21%.

If grouped by regions: 30.9% accounts for Belarus, 29.6% - for India, the same percentage, 29.6% - for European countries (including Switzerland and others that are not members of the European Union), 7.4% - for Israel, another 2.4% - for the United States and South Korea put together. For comparison: in 2021, Belarus accounted for 10.5% of trials of this kind (11 approvals), India - 27.6% (29), sixteen European countries (including those outside the EU) - 45, 7% (48 trials, ten of them sponsored by Germany, six each from Hungary and Slovenia), Israel - 11.4% (12), USA and South Korea - 3.8% (two each) and another 1 % (one trial) - to Turkey.

Diagram 9



Data from www.grls.rosminzdrav.ru

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Table 4 shows the distribution by therapeutic area of local trials (including bioequivalence studies) of generics and biosimilars licensed to Russian sponsors. This is a growing market segment: an increase from 345 in 2021 to 435 in 2022 corresponds to an increase of 26%.

The main growth of the sector was provided by cardiology and CVD, oncology, endocrinology and Covid-19. In 2022 cardiology and CVD (this year we included anticoagulants in this category, which were previously classified either as surgery or intensive care) accounted for the highest quantity of approvals: 108 new protocols, 24.8% of the total. In 2021, cardiology and CVD accounted for 50 new trials, or 14.5%, and even if we supplement this therapeutic area with trials on intensive care and surgery, we get 16% of the total (55 trials), which is significantly less than in 2022. Oncology came in second with 46 approvals, 10.6% (26 and 7.5% a year earlier). Neurology and endocrinology shared third place with 35 trials and a share of 8% each (in 2021 endocrinology scores were 11 protocols and 3.2%). In fifth place are infectious diseases excluding HIV, hepatitis C, tuberculosis and Covid-19: 25 approvals or 5.7% (27 and 7.8% a year earlier). HIV, hepatitis C and tuberculosis in total accounted for 23 new protocols or 5.3% (28 and 8.1% in 2021), Covid-19 another 22 or 5% (eight and 2.3% in 2021). Thus, if separate categories had not been singled out from the field of infectious diseases, it would have been the second most popular among Russian sponsors testing generics and biosimilars with 70 new projects and a total share of 16.1%. We also recall that certain drugs, which, according to their main indications, relate to cardiology and CVD, endocrinology and neurology, are also used in the treatment of symptoms and complications of Covid-19, which undoubtedly served as such an active interest of generic manufacturers in the context of the ongoing pandemic.

The shares of 13 out of 26 therapeutic areas decreased slightly compared to 2021, by an average of 1.66 percentage points. The most noticeable reductions are in neurology (35 trials in 2022 and 8% of the total vs 56 trials and 16.2% in 2021) and analgesics and NSAIDs (12% and 2.8% vs 21% and 6.1% a year earlier). The other 13 therapeutic areas have grown, with nine of them gaining less than or about one percentage point, which can be attributed to random fluctuations.

Table 4

Distribution of Local CTs and Bioequivalence Studies (Generics and Biosimilars), Conducted by Local Sponsors, 2022			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Cardiology and CVD/Vascular surgery/Intensive care	108	24.8%	4 957
Oncology	46	10.6%	3 667
Neurology	35	8.0%	1 874
Endocrinology	35	8.0%	1 740
Infectious Diseases (except HIV/HCV/tuberculosis, COVID-19)	25	5.7%	1 217
HIV/HCV/Tuberculosis	23	5.3%	1 264
Covid-19	22	5.1%	7 550
Oncohaematology	17	3.9%	799
Gastroenterology/Coloproctology	16	3.7%	980
Haematology	14	3.2%	1 154
Rheumatology	12	2.8%	1 106
Analgesic and NSAIDs	12	2.8%	611
Pulmonology	12	2.8%	533
Psychiatry	10	2.3%	352
Immunology	8	1.8%	310
Urology	7	1.6%	294
Hepatology	6	1.4%	393
Phlebology/ Vascular surgery	5	1.1%	273
Allergology	5	1.1%	150
Obstetrics and gynecology	4	0.9%	445
Dermatology	3	0.7%	944

Surgery	3	0.7%	90
Otorhinolaryngology	2	0.5%	366
Nephrology	2	0.5%	332
Parasitology	1	0.2%	50
Narcology	1	0.2%	38
Not identified	1	0.2%	32
TOTAL	435	100.0%	31 521

Data from www.grls.rosminzdrav.ru

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Table 5 lists the molecules that appeared more often in trial approvals for generics and biosimilars from Russian and foreign sponsors. As in 2020–2021, rivaroxaban was the most popular (26 trials in 2022). Vildagliptin alone and in combinations was in second place (13 trials), metformin alone and in combinations shared third place with molnupiravir (10 protocols each).

A comparison of Table 5 with similar ones from previous years shows that even before the spread of coronavirus infection, Russian sponsors relatively often tested generics of rivaroxaban, vildagliptin, and metformin, but since the onset of the pandemic, these molecules have become even more popular and, starting from 2020, have been fixed at the top of the rating. Molnupiravir, as a drug first approved for use in late 2021, naturally appeared in the statistics later. In the results of the first half of 2022, it took second place right from the beginning, and at the end of the year it became one of those who took third. In general, it can be argued that in 2022, as in 2020-2021, anti-coronavirus drugs are still of great interest to Russian companies producing generics and biosimilars. Moreover, looking at the presented table, it can be assumed with a high degree of confidence that more than half of the trials presented in them were primarily motivated by the fight against Covid-19.

Table 5

Most Requested INN Used in Clinical Trials of Generics in 2022				
Substance	**Number of CTs of foreign generics**	**Number of CTs of local generics**	**All clinical trials to a given INN**	**Therapeutic Area**
Rivaroxaban	6	20	26	Cardiology and CVD, surgery, covid-19
Vildagliptin (separately and in fixed combinations)	2	11	13	Endocrinology, perhaps covid-19
Metformin (separately and in fixed combinations)	2	8	10	Endocrinology, perhaps covid-19
Molnupiravir	–	10	10	Covid-19
Apixaban	3	6	9	Cardiology and CVD, perhaps covid-19
Indapamide (separately in fixed combination)	6	3	9	Cardiology and CVD
Perindopril (separately in fixed combination)	3	6	9	Cardiology and CVD
Ticagrelor	2	7	9	Cardiology and CVD
Amlodipin (separately and in fixed combinations)	5	3	8	Cardiology and CVD
Dabigatran Etexilate	–	7	7	Cardiology and CVD, surgery
Dapagliflozin	2	5	7	Endocrinology
Pomalidomide	–	7	7	Oncohaematology
Sitagliptin (separately and in fixed combinations)	1	6	7	Endocrinology, perhaps covid-19
Ibuprofen (separately and in fixed combinations)	1	5	6	Analgesic and NSAIDs
Levetiracetam	4	2	6	Neurology
Nimesulid	5	1	6	Analgesic and NSAIDs
Hydrochlorothiazide (in fixed combinations)	1	4	5	Cardiology and CVD

Diosmin (separately and in fixed combinations)	2	3	5	Phlebology, coloproctology, vascular surgery
Lercanidipine (separately and in fixed combinations)	2	3	5	Cardiology and CVD
Loperamide	2	3	5	Gastroenterology
Nirmatrelvir	–	5	5	HIV, covid-19
Raltegravir	–	5	5	HIV
Ramipril (separately and in fixed combinations)	2	3	5	Cardiology and CVD
Rosuvastatin (separately and in fixed combinations)	1	4	5	Cardiology and CVD
Enoxaparin Sodium	–	5	5	Cardiology and CVD, surgery, intensive care, perhaps covid-19
Valsartan (in fixed combinations)	2	2	4	Cardiology and CVD
Ambroxol (separately and in fixed combinations)	1	3	4	Pulmonology
Amoxicillin	–	4	4	Infectious diseases
Clopidogrel	–	4	4	Cardiology and CVD
Lapatinib	–	4	4	Oncology
Macitentan	–	4	4	Cardiology and CVD
Melatonin	1	3	4	Neurology
Nilotinib	–	4	4	Oncohaematology
Paracetamol (in fixed combinations)	–	4	4	Analgesic and NSAIDs, infectious diseases
Telmisartan (separately and in fixed combinations)	3	1	4	Cardiology and CVD
Umifenovir	1	3	4	Infectious diseases incl. covid-19
Eltrombopag	1	3	4	Haematology
Ethylmethylhydroxypyridine succinate	–	4	4	Neurology, Covid-19
Etravirine	–	4	4	HIV

Data from www.grls.rosminzdrav.ru

Another molecule included in the rating of the most demanded, to which we would like to draw the reader's attention, is loperamide. The substance was first synthesized over 50 years ago, back in 1969. The last time a generic trial of loperamide was conducted in Russia in 2017. In 2022, we see as many as five bioequivalence studies of this drug: two from the foreign sponsor and three from the domestic ones. At the same time, the original drug is consistently present on the Russian market, and its generics are represented in large numbers as well. How to explain the surge of interest in loperamide in 2022, we do not know.

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Tables 6 and 7 show the distribution of local trials of original medicines (including biological medicines) by therapeutic areas with foreign and domestic sponsors respectively. The total number of such projects of foreign sponsors has been reduced by three times compared to 2021, from 18 to six. Russian increased by 30.5%: from 72 in 2021 to 94 in 2022.

Table 6

Distribution of Local CTs of Brand Name Drugs of Foreign Sponsors, 2022			
Therapeutic Area	**Number of CTs**	**Number of planned participants**	**Sponsor's Country**
Infectious Diseases (except HIV/HCV/tuberculosis, COVID-19)	2	1 074	Slovenia, China
Gastroenterology	2	260	Germany
Obstetrics	1	1 244	Belgium
Otorhinolaryngology	1	196	Poland
TOTAL	6	2 774	

Data from www.grls.rosminzdrav.ru

Covid-19 remains the most popular therapeutic area for Russian developers, which had been ranking first since 2020. Of the 20 anti-coronavirus trials in 2022, nine (45%) accounted for vaccines. In the area of other infectious diseases, which is in second place, the share of vaccines is even higher: 11 out of 16 or 69%. The third place was shared by oncology and allergology (ten trials each). In fifth place is neurology (nine trials, two of which are aimed at eliminating the neurological consequences of Covid-19), in sixth place is rheumatology (eight new projects).

Table 7

Distribution of Local CTs of Brand Name Drugs (Including Biological Products) of Local Sponsors, 2022			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Covid-19	20	21.5%	29 209
Infectious Diseases (except HIV/HCV/tuberculosis, COVID-19)	16	17.2%	4 306
Oncology	10	10.8%	1 460
Allergology	10	10.8%	350
Neurology	9	9.7%	1 415
Rheumatology	8	8.6%	1 814
Surgery/Traumatology/Anesthesiology	3	3.2%	1 550
HIV/HCV	2	2.2%	725
Vascular Surgery/Phlebology	2	2.2%	630
Pulmonology	2	2.2%	498
Urology	2	2.2%	434
Cardiology and CVD	2	2.2%	62
Gynecology	1	1.1%	272
Otorhinolaryngology	1	1.1%	250
Dermatology	1	1.1%	175
Oncohaematology	1	1.1%	84
Haematology	1	1.1%	70
General therapy	1	1.1%	60
Hepatology	1	1.1%	32
Gastroenterology	1	1.1%	26
TOTAL	94	100.0%	43 422

Data from www.grls.rosminzdrav.ru

PARTICIPATION OF MEDICAL ORGANIZATIONS IN BIOEQUIVALENCE STUDIES

Medical organizations that were most often involved in conducting bioequivalence studies are presented in Table 8. Of the clinics listed in it, 18 were in the top 25 for the previous year. The newcomers were the Clinical Hospital No. 9, Yaroslavl (20 trials, place 10–11), and the Professor's Clinic, Perm (five trials, place 18–20).

Medical organizations among the leaders, the activity of which has grown especially noticeably compared to 2021, is Clinical Hospital No. 3, Yaroslavl (55 trials vs 21 a year earlier and first place vs 6–8), the Rostov Central District Hospital (30 vs 10, fifth place in 2022 and 13–15 in the previous year) and the Sechenov University, Moscow (21 trials vs four, 8–9 vs 20–24).

The clinics with the most significant decrease in activity compared to 2021 are RZD-Medicine, Yaroslavl (only eight new bioequivalence studies at 38 a year earlier, ranked 15–16 after the first in 2021), Medical Center Probiotech, Serpukhov (5 trials vs 20, rank 18–20 vs ninth a year earlier), and Clinical Hospital No. 2, Yaroslavl (20 new protocols vs 31, rank 10–11 vs second in 2021).

Table 8

Top-20 medical organizations on the activity of participation in bioequivalence studies (approvals issued in 2022)					
Place in ranking	**Name of medical organization**	**Total number of bioequivalence studies**	**Number of bioequivalence studies conducted by local sponsors**	**Number of bioequivalence studies conducted by foreign sponsors**	**Number of bioequivalence studies and sites ranking on approvals issued in 2021**
1	Clinical Hospital № 3, Yaroslavl	55	51	4	21 (6–8)
2	Eco-Safety Research Center, St. Petersburg	38	38	–	26 (4)
3–4	Yaroslavl Regional Clinical Narcological Hospital, Yaroslavl	32	29	3	28 (3)
3–4	Cardiology Dispensary, Ivanovo	32	27	5	17 (11)
5	Rostov Central District Hospital, Yaroslavl region, Rostov	30	30	–	10 (13–15)
6	Certa Clinic, Moscow	25	19	6	21 (6–8)
7	X7 Clinical Research, St. Petersburg	22	10	12	24 (5)
8–9	Bessalar clinic, Moscow	21	20	1	10 (13–15)
8–9	I. M. Sechenov First Moscow State Medical University, Russian Ministry of Health, Moscow	21	17	4	4 (20–24)
10–11	Clinical Hospital № 9, Yaroslavl	20	20	–	n/a
10–11	Clinical Hospital № 2, Yaroslavl	20	16	4	31 (2)
12	N.P. Bekhtereva Institute of Human Brain of the Russian Academy of Sciences, Saint Petersburg	19	17	2	19 (10)
13–14	Ligand Research, Moscow	18	6	12	21 (6–8)
13–14	Lopukhin Federal Research and Clinical Center of Physical-Chemical Medicine of Federal Medical Biological Agency, Moscow	18	11	7	7 (18)
15–16	Tomsk National Research Medical Center of the Russian Academy of Sciences, Tomsk	8	6	2	10 (13–15)
15–16	Clinical Hospital "RZD-Medicine", Yaroslavl	8	4	4	38 (1)
17	Mordovia Republican Central clinical hospital, Saransk	6	5	1	4 (20–24)
18–20	Medical Center Probiotech, Serpukhov	5	5	–	20 (9)
18–20	The Professor’s Clinic, Perm	5	5	–	n/a
18–20	Perm Clinical Center of the Federal Medical and Biological Agency, Perm	5	5	–	3 (25)

Data from www.grls.rosminzdrav.ru

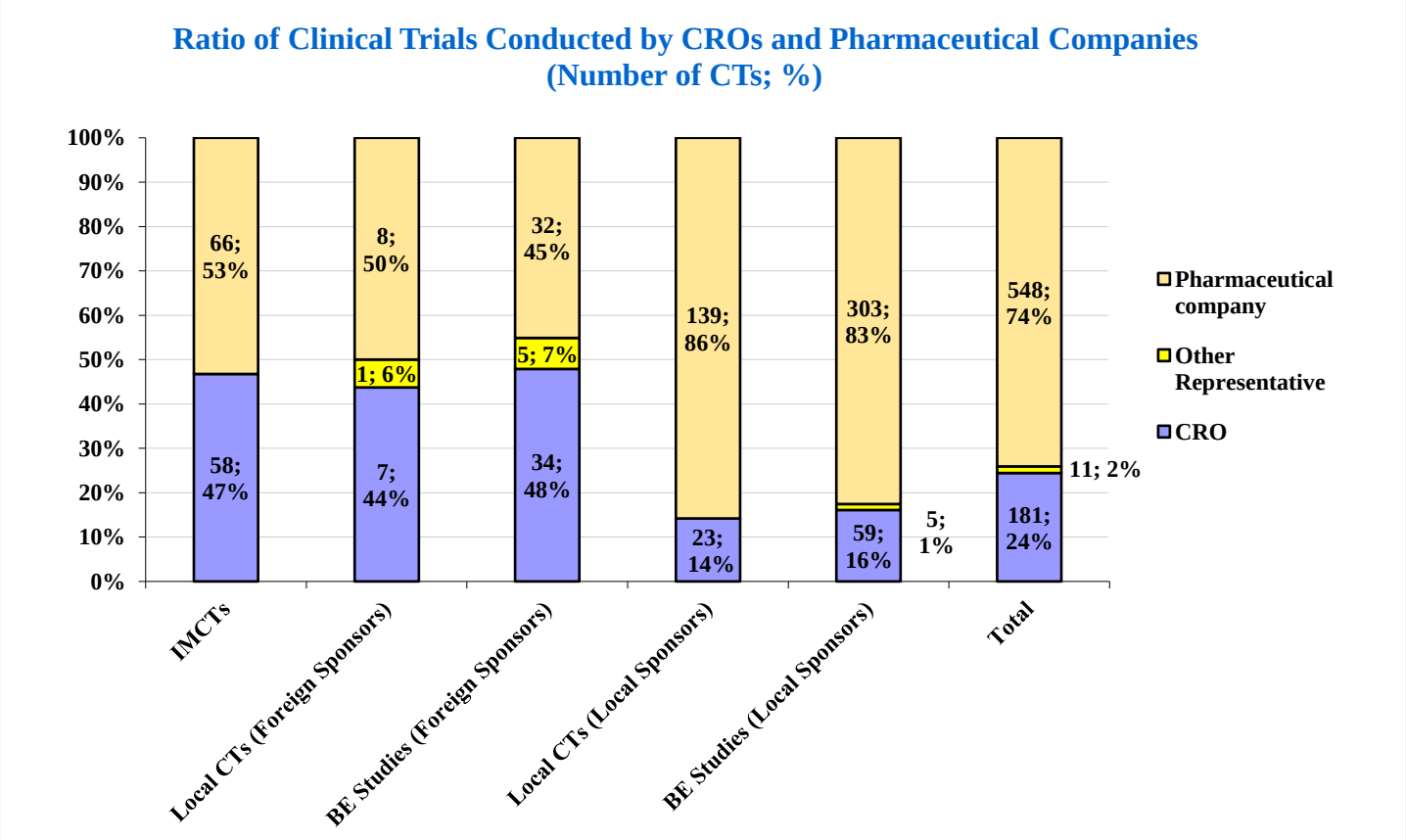
MAIN PLAYERS ON THE RUSSIAN CLINICAL TRIALS MARKET – 2022

This section contains data on the main participants in the Russian clinical trials market for 2022. In addition to the standard division into sponsors and contract research organizations (CROs), we traditionally single out the "other representative" category, which includes legal entities that are not CROs in the full sense, yet they provide certain types of services for launching the drug in the Russian market. Before proceeding with the analysis of the statistics below, we recall again that in 2022, approval was not necessarily followed by the start of a trial. First of all, this concerned IMCTs and international sponsors and CROs.

Sponsors and CROs, general structural distribution

Diagram 10 shows the ratio of approvals issued for those trials that the sponsors intended to conduct themselves, and those for which it was planned to involve the CRO. It should be noted that sponsors do not always indicate that they are going to involve a contracting organization in the trial, so the figures given may not accurately reflect the actual state of affairs.

Diagram 10



Data from www.grls.rosminzdrav.ru

For IMCTs, the ratio of 53% (sponsored) to 47% (CRO involved) is identical to that observed in 2020 and 2021. In local trials, the share of projects that pharmaceutical companies were going to implement on their own over the past year increased with foreign sponsors to 50% vs 36% a year earlier and for Russian sponsors to 86% vs 83%. On the contrary, in bioequivalence studies, the percentage of protocols that sponsors planned to work without involving intermediaries decreased: for foreign ones from 59% in 2021 to 45% in 2022 and for Russian sponsors from 87% to 83%.

If we evaluate the market as a whole, without division into types, the percentage of trials that sponsors, according to their applications, were preparing to conduct on their own, increased to 74%. For comparison: in 2016–2021 it was 63–69%. The share of trials involving contract research organizations decreased to 24% from 25–35% in 2016–2021. Deviations from the usual indicators are explained by the fact that in 2022 the number of new IMCTs in Russia decreased, where CROs traditionally participate in about half of the projects, so the indicators of other types of trials, in which CROs are involved less often, had a more noticeable impact on the final ratio. Only the share of 2% of "other representatives" has not changed.

International multicentre clinical trials, sponsors

Table 9 shows the leaders in terms of the number of approvals for IMCTs in 2022. It would be incorrect to conduct a detailed comparison with the previous year, given that in 2022 the activity of international companies came to almost nought compared to the usual figures. We only note that the number of IMCTs, on average, accounted for the top ten at the end of 2021, was 19.2 trials, at the end of 2022 - only 6.8 trials. That is, the activity of the leaders of this rating fell by almost three times. And this is if we evaluate only by the issued approvals, while we know that the majority of IMCTs for which approvals were granted never started.

Table 9

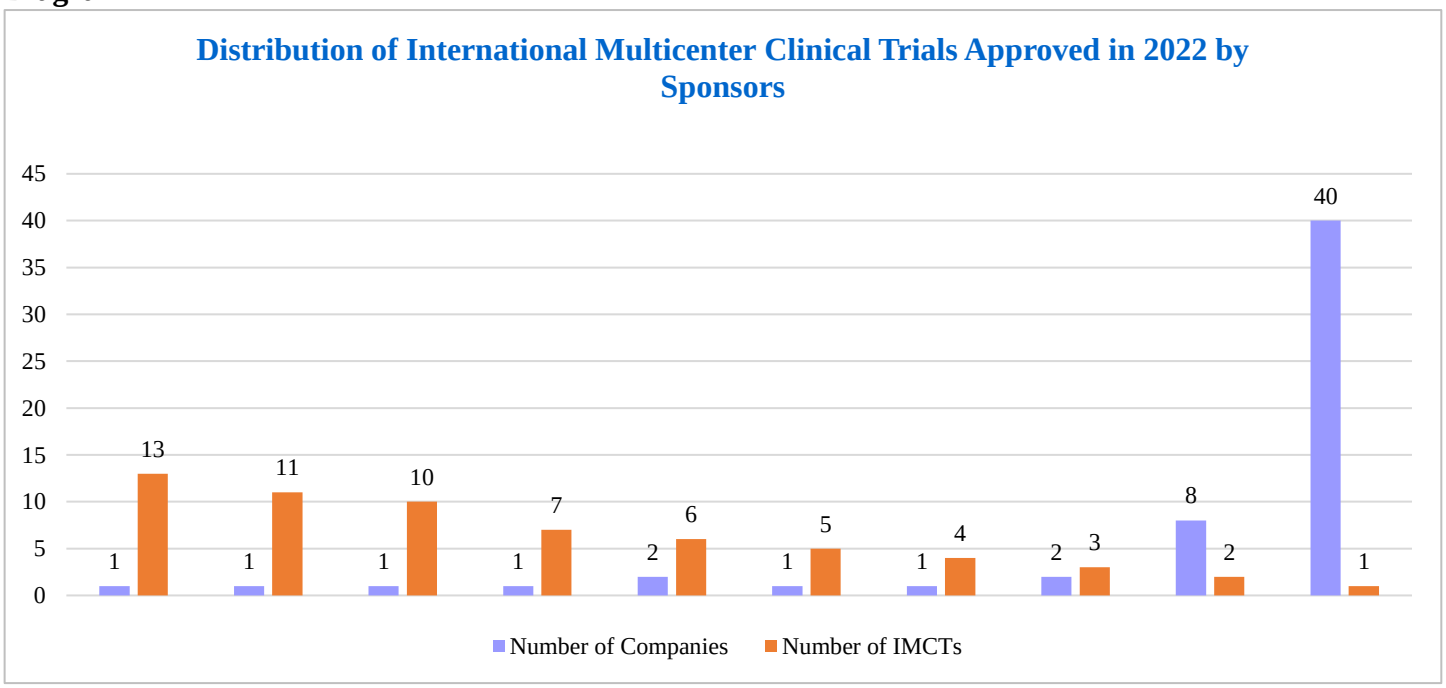
Top-10 Leading Pharmaceutical Companies on Approvals for International Multicenter CTs, 2022					
Rating in 2022	**Company (including separate companies, associated in group of companies, as well as independent divisions of the company)**	**Total**	**Conducted by themselves**	**Conducted by CRO**	**Number of IMCTs; Ranking in 2021**
1	Novartis	13	13	–	30 CTs; 2
2	Merck & Co.	11	11	–	26 CTs; 3
3	F. Hoffmann-La Roche	10	10	–	25 CTs; 4
4	AstraZeneca AB (incl. Alexion Pharmaceuticals)	7	5	2	34 CTs; 1
5–6	Janssen Pharmaceutica (incl. Actelion Pharmaceuticals)	6	4	2	17 CTs; 5
5–6	GSK	6	5	1	10 CTs; 9-10
7	AbbVie	5	5	–	9 CTs; 11-12
8	Novo Nordisk	4	4	–	12 CTs; 8
9–10	Boehringer Ingelheim	3	1	2	6 CTs; 14-16
9–10	R-Pharm International	3	3	–	n/a

Data from www.grls.rosminzdrav.ru

Places in the top 10 at the end of the year retained more than half of the companies. Sanofi (two protocols), Pfizer (one IMCT) and Eli Lilly (also one) were eliminated. In 2021, they had 15, 13 and ten new IMCTs, respectively. AbbVie (five projects), Boehringer Ingelheim (3 trials) and R-Pharm, Russia (3), replaced the top ten places. In 2021, these companies received nine, six and zero approvals to hold IMCTs, respectively.

Diagram 11 shows the overall distribution of approvals for IMCTs for 2022 by sponsors. Only two companies have received more than ten approvals, four - from six to ten, four more - from three to five approvals each, eight - two and 40 - one approval each. Compared to 2021, the total number of sponsors who received approval to host IMCTs during the year decreased from 115 to 58.

Diagram 11



Data from www.grls.rosminzdrav.ru

International multicentre clinical trials, CROs

Table 10 lists the 12 contract research organizations most likely to be recruited by sponsors to host IMCTs under the 2022 approvals. Again, most of these approvals never translated into actual trials.

As with sponsors of IMCTs, the activity of international trials CROs has dropped dramatically compared to the previous year. Here are some illustrations. IQVIA in 2022, as a year earlier, took first place, but in 2021 the company received 22 approvals for IMCTs, and in 2022 only 13. Syneos Health ranked fifth in 2021 with 17 approvals and was in second in 2022 with seven. Parexel's activity has dropped from 20 to five approved IMCTs, while its position in the ranking has not changed (3rd in 2021 and 3-4 in 2022).

More than half of the CROs were presented in a similar table for 2021. Labcorp dropped out (11 IMCTs in 2021 and none in 2022). PRA became part of ICON (22 approvals from PRA and six from ICON in 2021, and only four from the combined company in 2022). The lower half of the table has been updated, but a detailed analysis of the performance of these companies due to the general decrease in activity in the IMCT sector will not be informative.

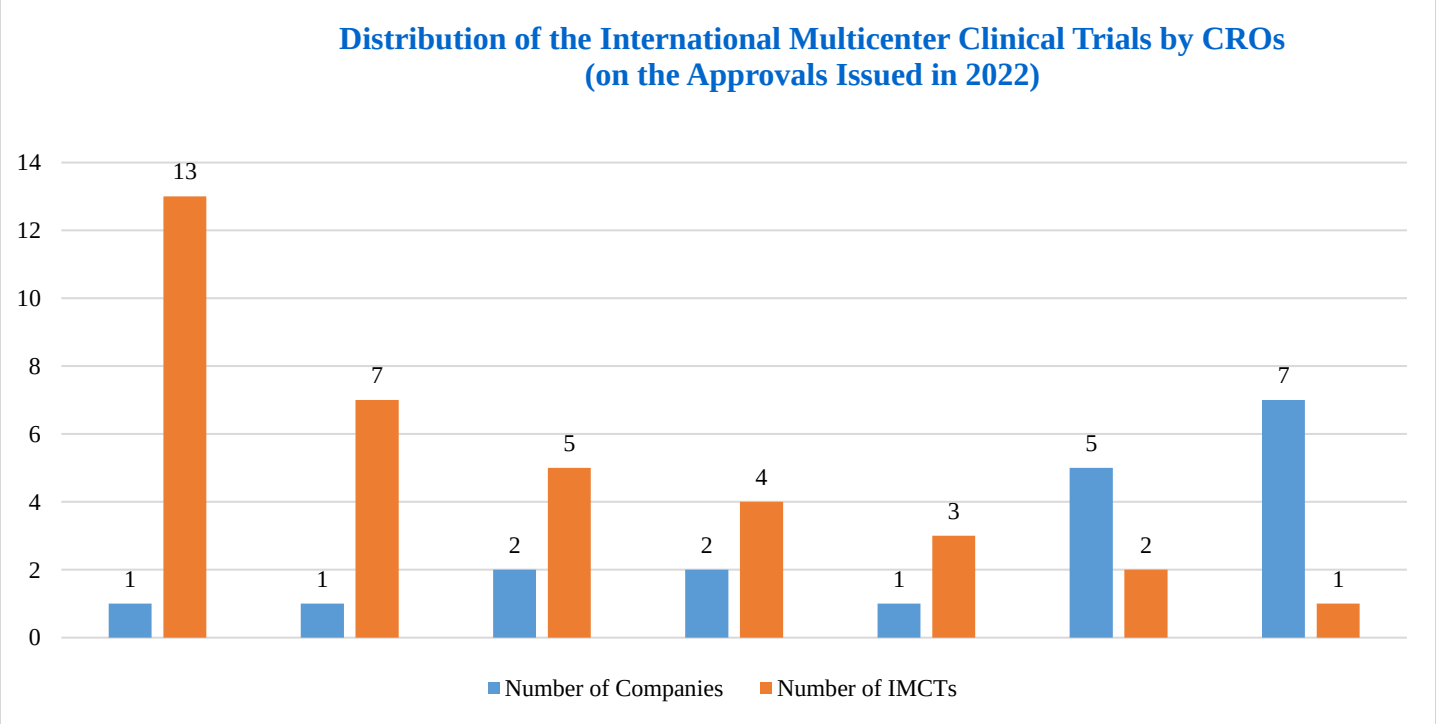
Table 10

Ranking of Leading CROs on Approvals for International Multicenter CTs, 2022				
Ranking in 2022	**Company**	**Number of IMCTs**	**Number of Sponsors**	**Number of IMCTs; Ranking in 2021**
1	IQVIA	13	10	22 CTs; 1-2
2	Syneos Health	7	7	17 CTs; 5
3–4	Parexel	5	3	20 CTs; 3
3–4	PPD	5	5	19 CTs; 4
5–6	ICON (incl. PRA Health Sciences)	4	4	22 CTs; 1-2 - PRA Health Sciences; 6 CTs; 9 - ICON
5–6	Cromos Pharma (K-Research)	4	3	1 CT; 20-31
7	MB Quest	3	3	1 CT; 20-31
8–12	Medpace	2	2	11 CTs; 6-7
8–12	OCT Rus	2	2	2 CTs; 13-19
8–12	PSI	2	2	8 CTs; 8
8–12	Premier Research	2	2	2 CTs; 13-19
8–12	Synergy Research Group	2	2	3 CTs; 10-12

Data from www.grls.rosminzdrav.ru

Diagram 12 shows the distribution of approvals for IMCTs by CRO. More than ten approvals accounted for one contract research organization, more than five IMCTs for one more, 3–5 approved projects accounted for five CROs, two IMCTs for another five and one for seven organizations. The total number of CROs potentially involved in IMCTs decreased from 31 in 2021 to 19 in 2022.

Diagram 12



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies, foreign sponsors

Table 11 summarizes the top foreign sponsors in terms of the number of approvals received for local trials and bioequivalence studies.

The first place was shared by Novartis, which received seven approvals (four new projects and a place 5–10 a year earlier) and the Borisov Plant of Medical Preparations (BZMP) (not included in the 2021 ranking). Tied for places 3-5 with six approvals is Teva (2021 leader with 12 trials), Dr. REDDY's Lab. (second place with ten protocols in 2021) and Lekpharm (not included in the previous year's ranking). Rubikon is in sixth place with five approvals (one trial in 2021). Lines 7-9 of the rating with four approvals are occupied by KRKA (fourth place and six trials a year earlier), Sun Pharma and Pharmtechnology (there were two new projects each). Rounding out the table are Berlin-Chemie with three approvals each (third place and seven approvals in 2021) and Simpex Pharma (two approvals in 2021).

Out of the top 10 in 2021 were Emcure Pharmaceuticals, Gedeon Richter, Hetero Labs, Pharmland, and Servier Laboratories (all ranked 5-10 with four trials).

A feature of the 2022 rating is a significant number of sponsors from Belarus among the leaders. These include BZMP, Lekpharm, Rubikon and Pharmtechnology. Sponsors from Belarus were in the same rating in previous years, the only unusual thing is that this time there are four of them at once.

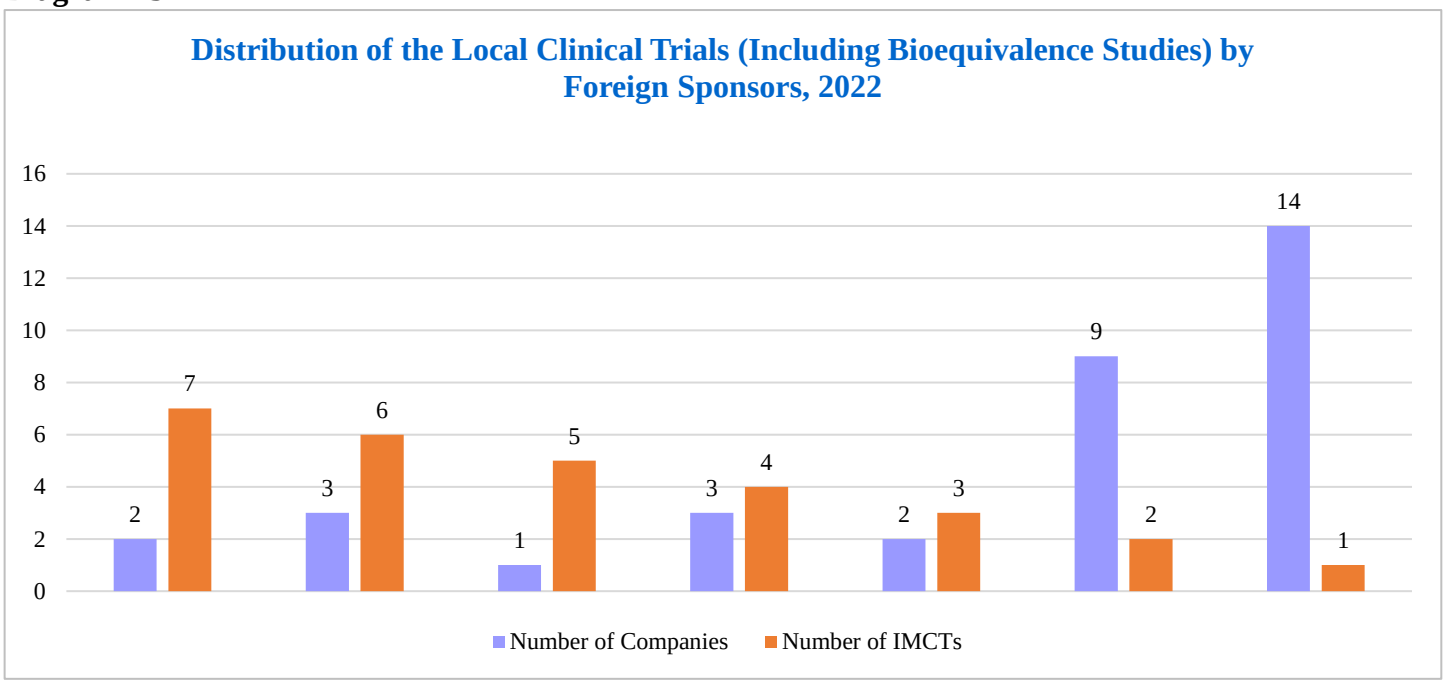
Table 11

Ranking of Foreign Sponsors on Approvals for Local CTs and Bioequivalence Studies, 2022					
Ranking in 2022	**Company**	**Total**	**Conducted by themselves**	**Conducted by CROs/other representatives**	**Number of CTs; Ranking in 2021**
1–2	Novartis (incl. Sandoz d.d., Lek d.d.)	7	7	–	4 CTs; 5-10
1–2	BZMP	7	6	1	n/a
3–5	Dr. REDDY's Lab.	6	6	–	10 CTs; 2
3–5	Lekpharm	6	–	6	n/a
3–5	Teva	6	6	–	12 CTs; 1
6	Rubikon	5	–	5	1 CT; 26-54
7–9	KRKA	4	4	–	6 CTs; 4
7–9	Sun Pharma	4	4	–	2 CTs; 16-25
7–9	Pharmtechnology	4	–	4	2 CTs; 16-25
10–11	Berlin-Chemie	3	–	3	7 CTs; 3
10–11	Simpex Pharma	3	–	3	2 CTs; 16-25

Data from www.grls.rosminzdrav.ru

The distribution of new local trials and bioequivalence studies among foreign companies is shown in Diagram 13. The total number of sponsors in this category in 2022 was 34, which is significantly less than the previous year (54 companies).

Diagram 13



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies, domestic sponsors

Table 12 shows the top Russian sponsors in terms of the number of approvals received in 2022 for bioequivalence studies and other types of local trials.

Promomed managed to rise to first place with 53 approvals (third place and 26 approvals a year earlier), pushing Pharmasyntez to second place with 37 new protocols (first place and 35 approvals in 2021). Renewal Production Pharmaceutical Company with an indicator of 27 approvals this time was in third place (fourth line and 19 trials a year earlier), and Canonpharma with 21 protocols in fourth place (second place and 28 approvals in 2021). R-Pharm moved up to the fifth place, it received 19 approvals (in 2021, only six, place 18–20). It should also be recalled here that the company also entered the top 10 in international trials (three protocols, 9-10 lines in the rating). Solopharm is in sixth place with 18 new trials (up from nine projects and eleventh place a year earlier). Wertex and Bright Way Industries shared 7th–8th positions in the rating, having received 17 approvals each (in 2021, Wertex was in seventh with 13 and Bright Way Industries was in eighth with 12 new trials). Biocad has 14 approvals and ninth place in 2022 (seven trials and lines 13-17 in 2021). And Microgen, which closes the top ten, has one less, 13 approvals (five trials and a place of 21-29 a year earlier).

If we compare the activity of the top 10 in 2021 and 2022, then the average number of approvals received by companies from the top ten increased from 18.7 to 23.6 approvals, i.e. by 26%.

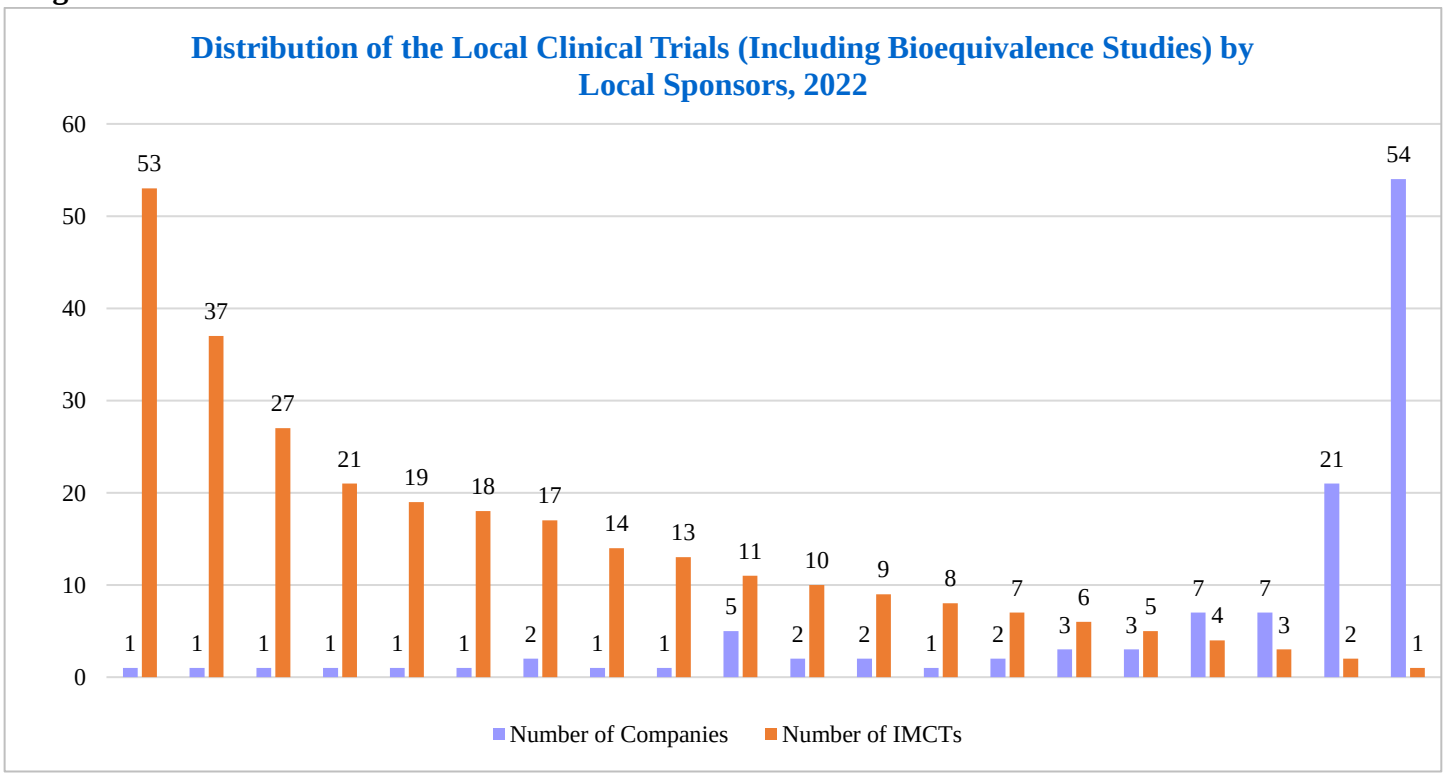
Table 12

Top-15 Leading Local Sponsors on Approvals for Local Clinical Trials and Bioequivalence Studies, 2022					
Ranking in 2022	**Company**	**Total**	**Conducted by themselves**	**Conducted by CRO**	**Number of CTs; Ranking in 2021**
1	Promomed Rus (incl. Biokhimik)	53	53	–	26 CTs; 3
2	Pharmasyntez (incl.Pharmasyntez-Nord, Pharmasyntez-Tyumen, Saterex)	37	37	–	35 CTs; 1
3	Renewal	27	27	–	19 CTs; 4
4	Canonpharma Production	21	21	–	28 CTs; 2
5	R-Pharm (incl. Technology of Medicines)	19	19	–	6 CTs; 18-20
6	Solopharm	18	18	–	9 CTs; 11
7–8	Werteks	17	17	–	13 CTs; 7
7–8	Bright Way Group (incl. Velpharm)	17	15	2	12 CTs; 8
9	Biocad	14	14	–	7 CTs; 13-17
10	NPO Microgen	13	13	–	5 CTs; 21-29
11–15	AVVA RUS (incl. Pollo)	11	11	–	7 CTs; 13-17
11–15	Valenta Pharm	11	11	–	16 CTs; 6
11–15	Advanced Pharma	11	11	–	3 CTs; 36-44
11–15	Izvarino Pharma (incl. Nanopharma Development)	11	–	11	10 CTs; 9-10
11–15	Moscow Endocrine Plant	11	11	–	18 CTs; 5

Data from www.grls.rosminzdrav.ru

The distribution of new trials by Russian sponsors is shown in Diagram 14. A total of 117 companies obtained this type of approval in 2022, a notable increase from 98 in 2021.

Diagram 14



Data from www.grls.rosminzdrav.ru

Local trials and bioequivalence studies, CROs

Table 13 includes the top CROs in 2022 in terms of approvals for local trials, including bioequivalence studies. Compared to the previous year, the changes are almost exclusively quantitative, only SCT can be classified as conditionally new names - the company last entered the top ten in 2019.

Probiotech remained in first place, increasing the number of approvals to 28 from 16 in 2021. MDA moved up to rank two with 14 projects (eight approvals and third a year earlier), iPharma was able to rank third with 11 protocols (four approvals, 10–12 in 2021), and X7 Clinicals and Pharmaceuticals Research - place 4-5 with eight (seven protocols and fourth place a year earlier), sharing it with the SCT. Three companies are on the lines 6-8 with seven new trials: Vita Aeterna, Ligand Research and Accellena Research and Development, of which in 2021 only the last one was in the top 10, the rest were only in the third ten. In ninth place is ClinPharmDevelopment with six approvals (a year earlier, the company was second with nine). In tenth place is ARS, with four trials (sixth and fifth place in 2021).

The average number of approvals for local trials handled by top 10 CROs increased from seven to ten in 2021.

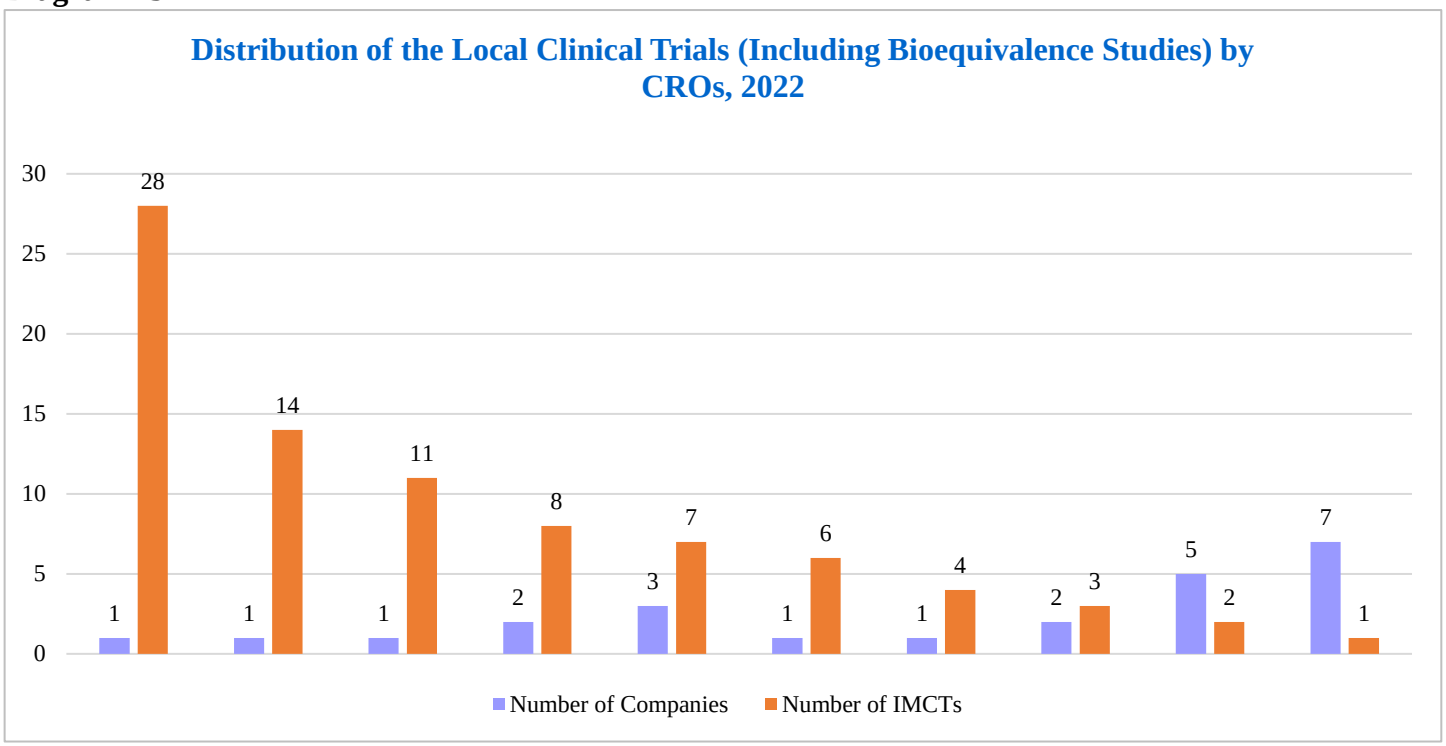
Table 13

Top-10 CROs Involved in the Local CTs and Bioequivalence Studies (on Approvals Issued in 2022)						
Ranking in 2022	**Company**	**Total number of local CTs, 2022**	**Number of CTs of foreign sponsors**	**Number of CTs of local sponsors**	**Number of sponsors**	**Number of CTs; Ranking in 2021**
1	Probiotech	28	7	21	9	16 CTs; 1
2	Medical Development Agency (MDA)	14	2	12	9	8 CTs; 3
3	IPHARMA	11	–	11	4	4 CTs; 10-12
4–5	X7 Research	8	6	2	5	7 CTs; 4
4–5	SCT	8	–	8	1	n/a
6–8	Vita Aeterna	7	4	3	5	1 CT; 21-28
6–8	Ligand Research	7	2	5	3	1 CT; 21-28
6–8	Accellena Research and Development	7	–	7	5	5 CTs; 6-9
9	ClinPharmDevelopment	6	3	–	5	9 CTs; 2
10	ARS	4	4	–	2	6 CTs; 5

Data from www.grls.rosminzdrav.ru

Diagram 15 shows the distribution of local trials and bioequivalence studies by contract research organizations. A total of 24 CROs were planned to be involved in these types of trials in 2022, four fewer than in 2021.

Diagram 15



Data from www.grls.rosminzdrav.ru

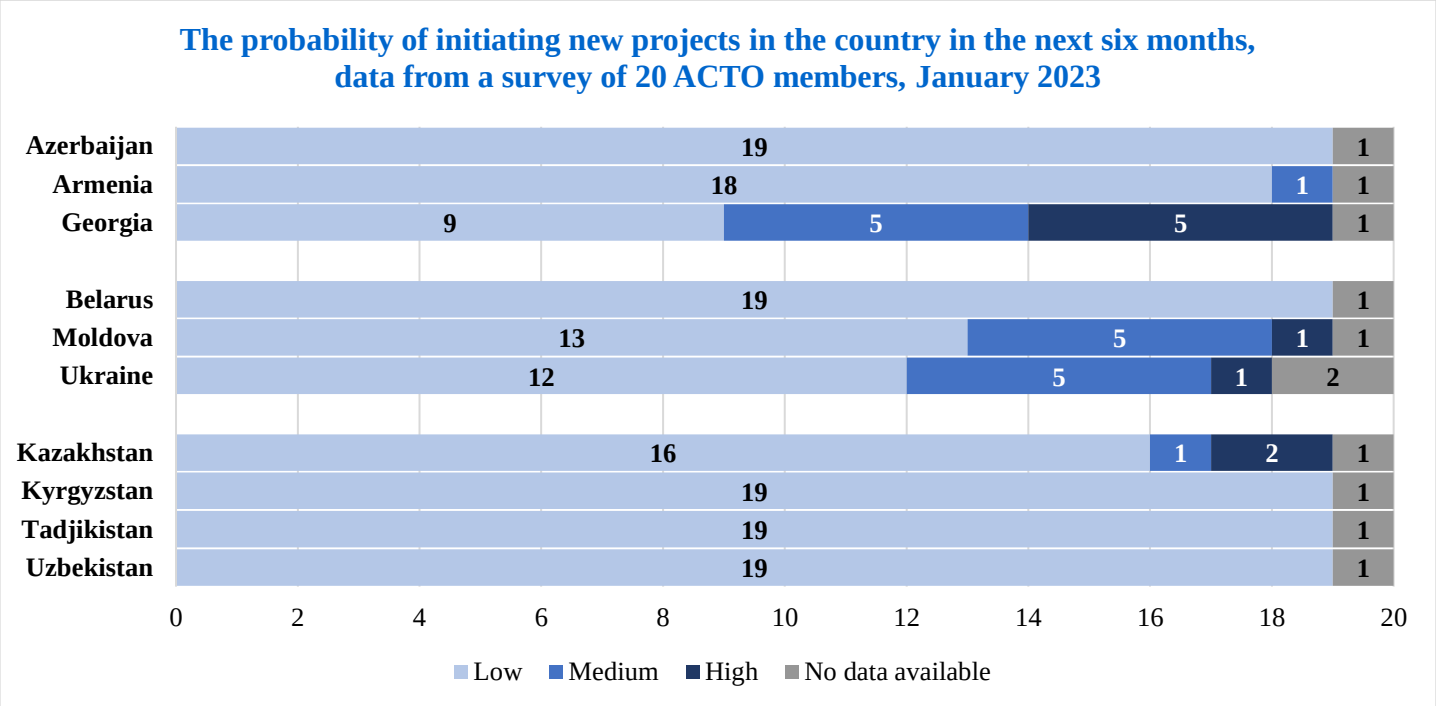
It was periodically discussed in the Russian professional community throughout 2022 whether CROs, who have always worked with international trials, now that the number of IMCTs has fallen, will be more actively involved in local trials. For our part, we were rather skeptical about this possibility. And, as the results of 2022 confirmed, no shift of international players into the local trials sector is visible. The CROs involved in IMCTs and in local trials are still different groups that hardly overlap. There are a small number of companies that work with projects of both types (for example, in 2022, K-Research had four international and three local trials, and OCT Rus had two local and two international trials), but expansion of their account of contract research organizations specializing in IMCTs is not observed.

CLINICAL TRIALS
IN THE NEIGHBOR COUNTRIES OF THE RUSSIAN FEDERATION

In the newsletter with the results of the first half of 2022, ACTO for the first time tried to assess the activity in the clinical trials markets of the neighboring countries of the Russian Federation[8] . The following is an updated statistical summary of these markets.

In January 2023, ACTO conducted a survey on the activity of members of the Association in neighboring countries. 20 respondents shared their estimates of the likelihood of launching new clinical trials in the next six months. The results of the survey for ten states, grouped by region, are presented in Diagram 16. It is clearly seen that ACTO members are most optimistic about Georgia (five companies consider the probability of new trial high, five more medium). This pattern confirms the conclusions of our previous issue that Georgia is currently playing the role of the most actively developing player in the post-Soviet space, clearly attractive to sponsors. A little less, but still optimistic, despite the ongoing hostilities, companies look at Ukraine, as well as Moldova (for each of the countries, one company chose the answer “high probability” and five companies “medium”). Of the Central Asian countries, only Kazakhstan is expected to launch new projects of ACTO members, two respondents rated the chances as high and one as medium. Finally, one member expressed cautious optimism about Armenia, estimating the likelihood of launching a new project there as medium.

Diagram 16



Data from poll of ACTO members

Further, in Table 14, for each of the countries of the post-Soviet space, the number of active intervention trials in the ClinicalTrials.gov database as of mid-February 2023 is given. The global market share is calculated, as well as the number of trials per million population. To calculate the latter indicator, population data for the beginning of 2023, published by the official statistical body of the country concerned, were used, and in the absence of such data, the data of the medium scenario from the UN forecast for 2023 were used.

[8] See the last section of ACTO Newsletter No. 25 on http://acto-russia.org/en/.

Table 14

The activity of clinical trial markets in the neighboring countries of the Russian Federation as of 02/13/2023 (data for 07/19/2022 are also given in parentheses)				
Region	**Number of active interventional CTs**	**Share in the global CT market**	**Population, mln**	**Number of CTs, per million population**
In the world	**78 014** (77 750)			
Russia	**1 264** (1 400)	**1.62** (1.80)	**146.4** (145.6)	**8.6** (9.6)
Ukraine	**517** (595)	**0.66** (0.77)	**41.2** (41.2)	**12.5** (14.5)
Lithuania	**218** (223)	**0.28** (0.29)	**2.9** (2.8)	**75.2** (79.7)
Georgia	**198** (195)	**0.25** (0.25)	**3.7** (3.7)	**53.5** (52.9)
Estonia	**164** (173)	**0.21** (0.22)	**1.4** (1.3)	**117.1** (129.9)
Latvia	**164** (172)	**0.21** (0.22)	**1.8** (1.9)	**91.1** (91.7)
Belarus	**82** (90)	**0.11** (0.12)	**9.5** (9.3)	**8.6** (9.7)
Moldova	**61** (69)	**0.08** (0.09)	**3.5** (2.6)	**17.4** (26.5)
Kazakhstan	**25** (28)	**0.03** (0.04)	**19.8** (19.1)	**1.3** (1.5)
Armenia	**16** (16)	**0.02** (0.02)	**2.8** (3.0)	**5.7** (5.3)
Uzbekistan	**10** (10)	**0.013** (0.013)	**36.0** (35.6)	**0.3** (0.3)
Kyrgyzstan	**10** (6)	**0.013** (0.008)	**7.0** (6.7)	**1.4** (0.9)
Azerbaijan	**3** (3)	**0.004** (0.004)	**10.4** (10.2)	**0.3** (0.3)
Tadjikistan	**2** (1)	**0.003** (0.001)	**10.1** (9.5)	**0.2** (0.1)

Data from www.clinicaltrials.gov; data from official statistical bodies of countries as of 01.01.2023 and The United Nations' world population prospect for 2023 (medium variant)

We are well aware that a step of six months is too small to draw far-reaching conclusions about certain changes. However, we decided to compare how much the percentage of active intervention trials reported by country in the ClinicalTrials.gov database has changed since the previous survey (July 2022) (Diagram 17).

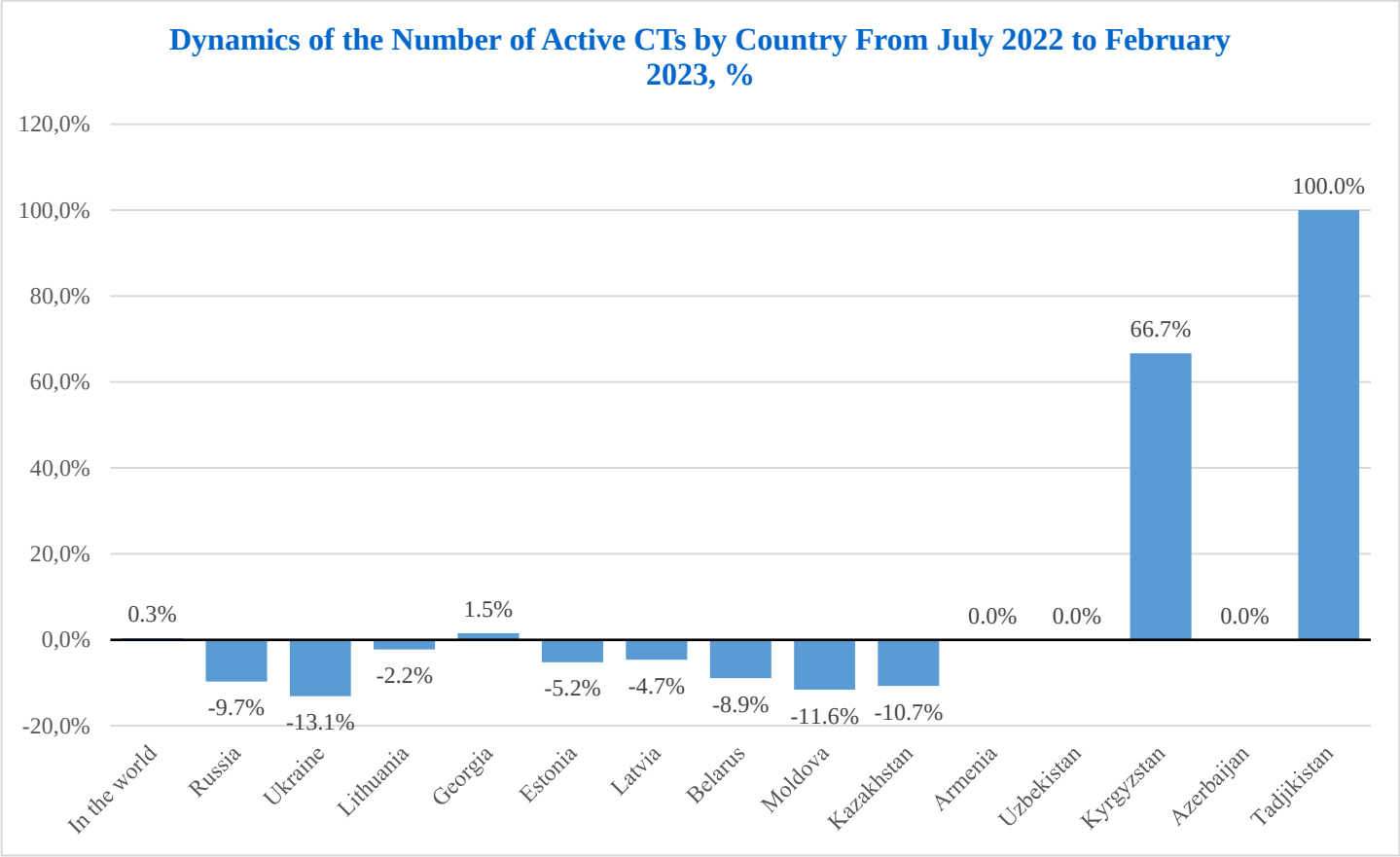
Despite the fact that the number of active trials in the world as a whole increased slightly (by 0.3%), we see that in most countries of the post-Soviet space it has decreased. Maximum reduction (-13.1%) was observed in Ukraine. This is followed by Moldova (-11.6%) and Kazakhstan (-10.7%). Following are Russia (-9.7%) and Belarus (-8.9%). Slightly less, but the markets of Estonia (-5.2%), Latvia (-4.7%) and Lithuania (-2.2%) also lost ground. If the results of Ukraine, Russia and Belarus were quite expected for us: they were clearly the result of a direct military conflict, then the situation in Moldova and Kazakhstan was somewhat surprising at first. Although, after some reflection, it seemed logical: perhaps the resulting pattern reflects the fears of sponsors that the conflict will spread to neighboring regions: Moldova, Kazakhstan, the Baltic countries. It remains to be hoped that the above-described results of the survey of ACTO members correctly reflect the intentions of the sponsors, and the interest in starting new projects in Ukraine, Moldova and Kazakhstan will find its practical implementation.

Against the background of "risk" regions, the situation in Armenia, Uzbekistan and Azerbaijan looks stable. The indicator in all three countries has not changed over the past six months. Although, it must be admitted that, in general, the extremely small number of new trials in these states does not yet give grounds for excessive optimism.

The only countries in the post-Soviet space where the number of active trials has increased over the past six months are Georgia (1.5% growth), and, quite unexpectedly, Kyrgyzstan and Tajikistan. The situation in Georgia fully reflects the current popularity of this country among sponsors, recall again the results of the survey, where it scored the maximum number of votes for the likely placement of new trial in the near future. We hope that the political situation in the country will not interfere with these plans.

As for the results of Kyrgyzstan (an increase in the number of trials by 66.7%) and Tajikistan (100%), then, keeping in mind the law of small numbers, one should not rush to perceive them as a serious signal yet. The 100% growth of Tajikistan is due to the fact that, unlike one trial, reflected in the database six months ago, now there are two of them. The same could be said about Kyrgyzstan. But still, there the increase seems to be more noteworthy: ten trials vs only six months ago. Perhaps it is worth observing the country and trialing the information in more detail.

Diagram 17

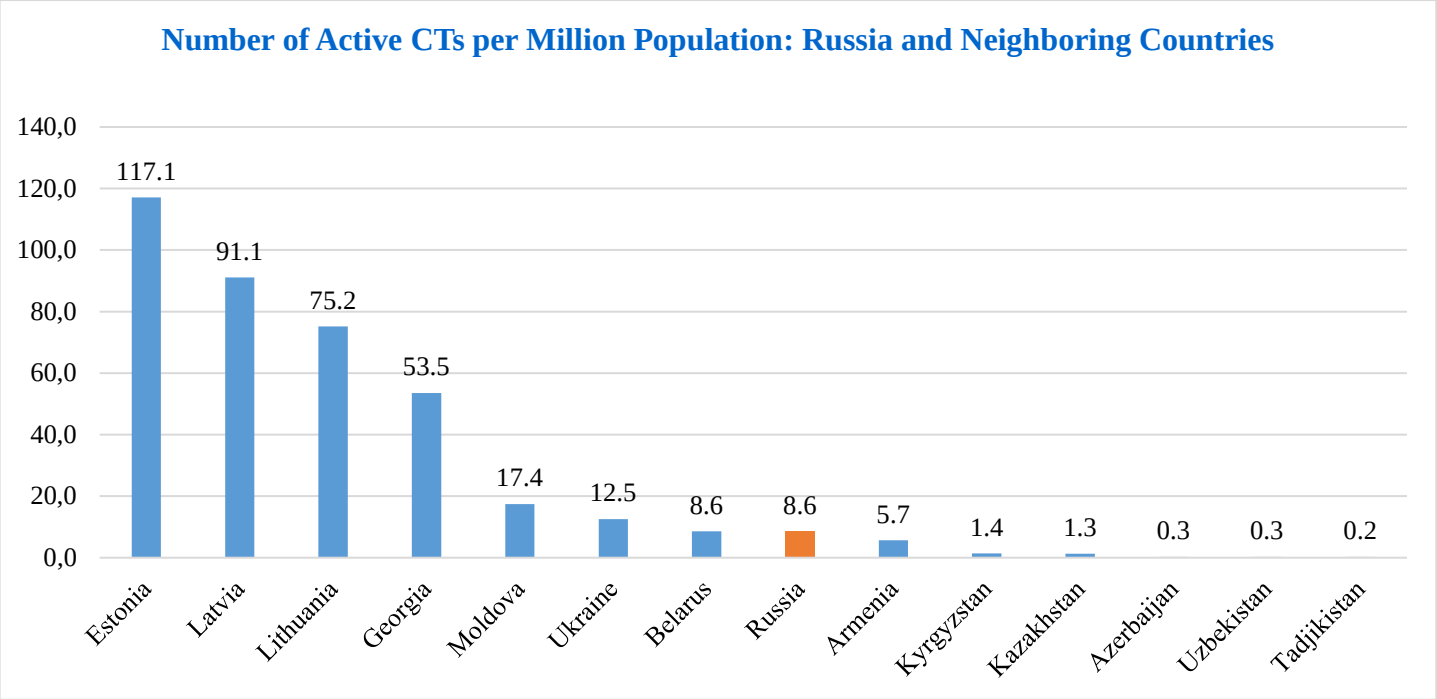


Data from www.clinicaltrials.gov

Diagram 18 allows comparing the countries of the post-Soviet space in terms of the number of trials per million population. The only visible change in the presented ranking since July 2022 is that Kyrgyzstan, due to the already mentioned unexpected increase in the number of trials, overtook Kazakhstan in it. The rest of the countries remained in their places, except that Russia equalized its result with Belarus (in July 2022, Belarus showed a result of 9.7 trials per million population, Russia - 9.6).

Comparison of directly numerical indicators gives us a pattern similar to the previously analyzed one: most countries showed a decrease in the number of active trials per million population. This applies to the Baltic countries, Moldova, Ukraine, Belarus, Russia and Kazakhstan. The indicators of two countries have not changed: Azerbaijan and Uzbekistan. Finally, an increase of 0.6 trial per 1 million population was recorded in Georgia (53.5 vs 52.9 in July 2022), followed by Kyrgyzstan with an increase of 0.5 (1.4 vs 0.9), Armenia, which improved this indicator by 0.4 (5.7 vs 5.3), and, finally, Tajikistan with an increase of 0.1 (0.2 vs 0.1 six months ago).

Diagram 18



Data from www.clinicaltrials.gov

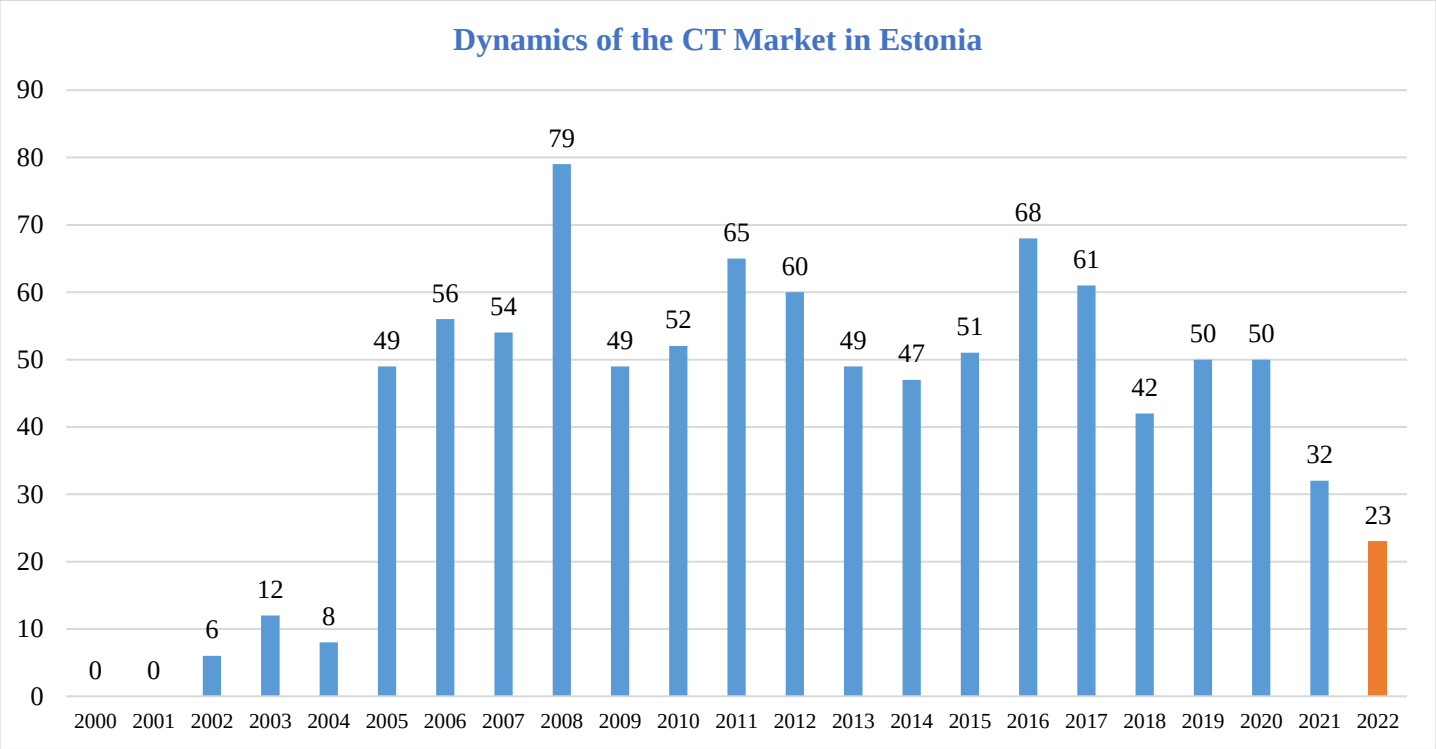
Diagrams 19–32 below show the annual changes in the number of new clinical trials in the post-Soviet countries according to the ClinicalTrials.gov registry. These data were already presented in our previous issue of the newsletter, now they are supplemented, which allows us to assess what 2022 has become for these countries. The statistics include the intervention trials first posted from January 1 to December 31 of the respective year.

In most of the countries reviewed, the number of new clinical trials in 2022 decreased compared to 2021. The largest reduction can be observed in Ukraine (-77.5%), followed by Latvia (-59.5%), Russia (-52.8%), Georgia (-42.9%), which is somewhat inconsistent with the previously discussed a positive trend for the country, but it should be noted that in 2021 a historical maximum was reached in the number of new trials in the country, Moldova (-41.7%), Kazakhstan (-38.5%), Estonia (-28, 1%) and Lithuania (-18.8%).

Kyrgyzstan and Uzbekistan repeated the result of 2021 (three and two new trials per year, respectively).

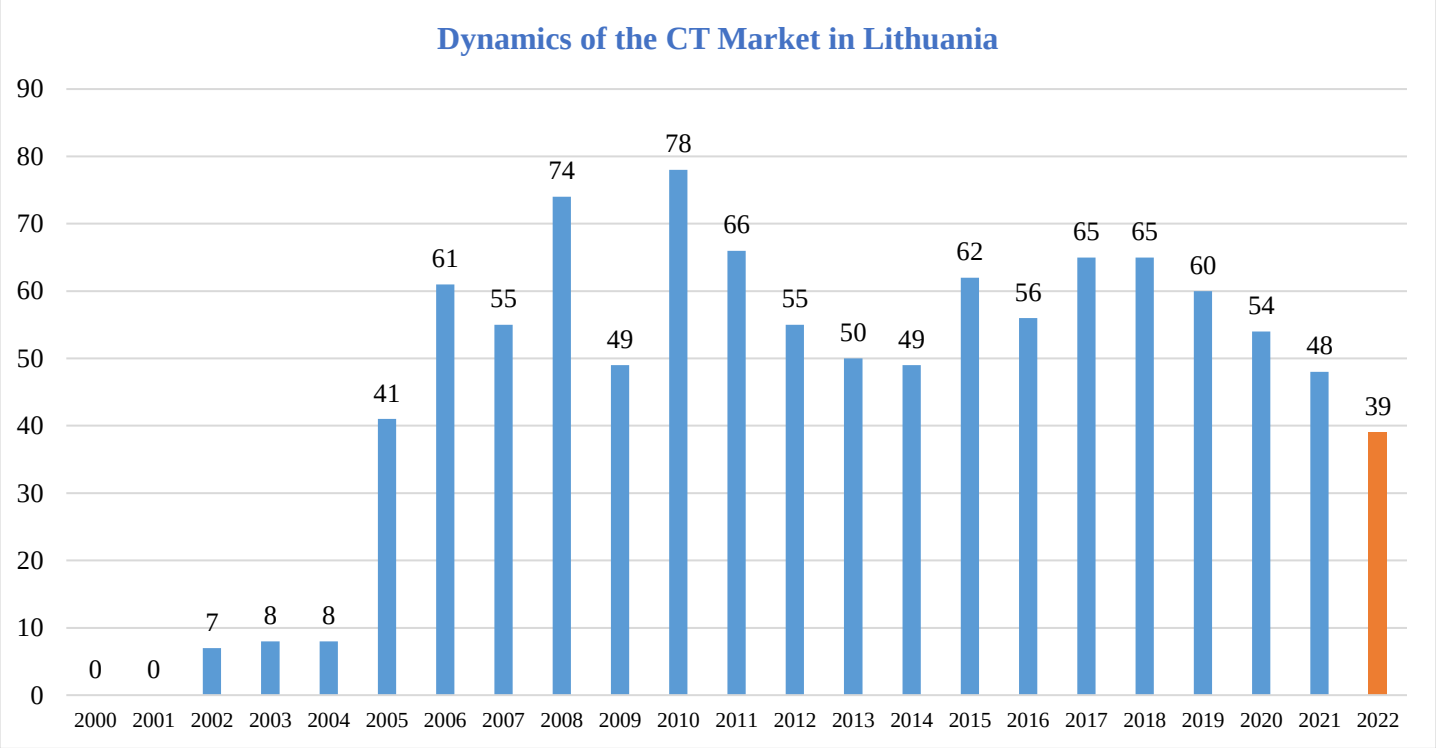
The countries where the past year was better than the previous one were Tajikistan (one trial in 2022 and none in 2021), Azerbaijan (two trials vs one), Armenia (nine vs seven, this was the maximum value for the country for all years) and Belarus (16 vs nine a year earlier). The rather unexpected positive result of Belarus is due to the fact that the decline in indicators began there earlier: 2021 turned out to be even worse for the country than 2022, while from 2017 to 2020 it was even worse. 24 to 27 new trials were consistently recorded in the country.

Diagram 19



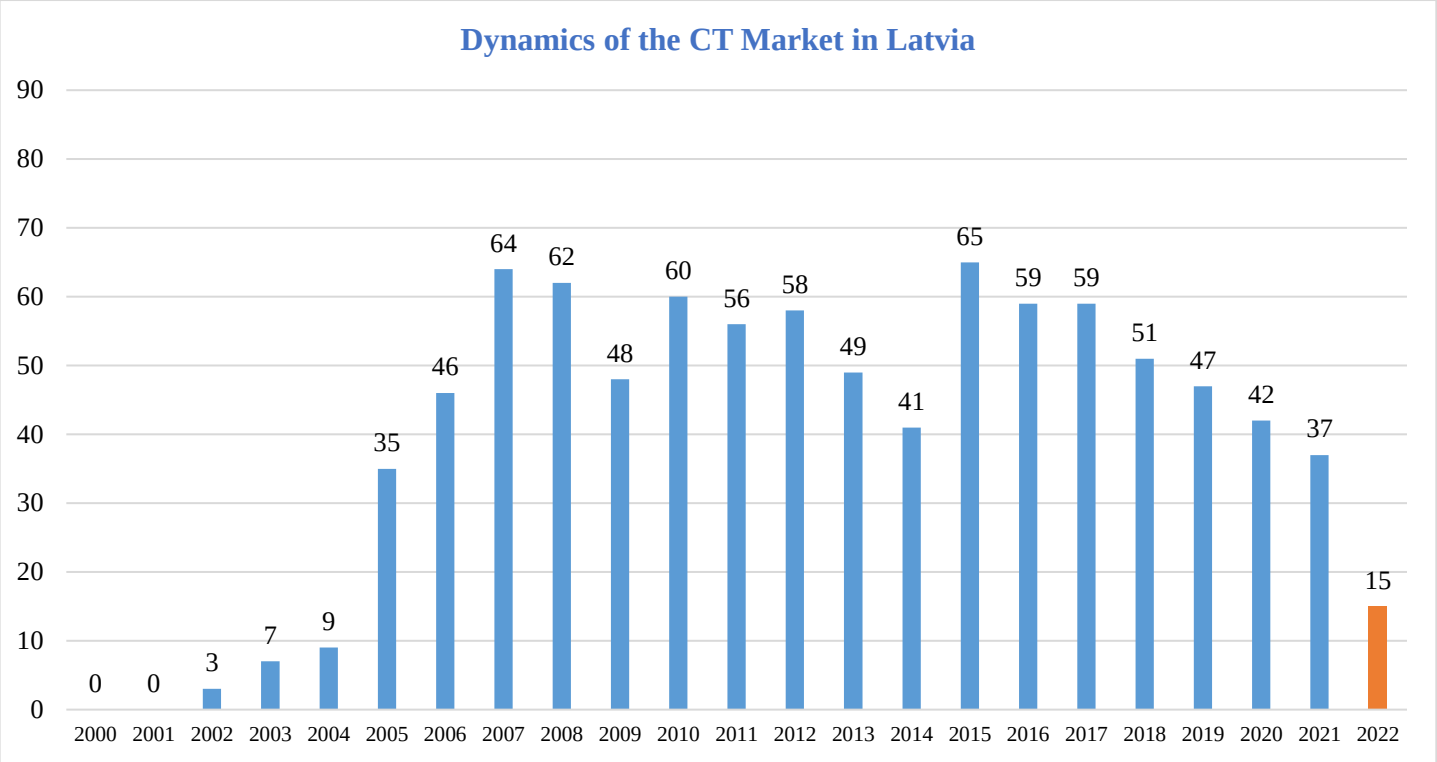
Data from www.clinicaltrials.gov

Diagram 20



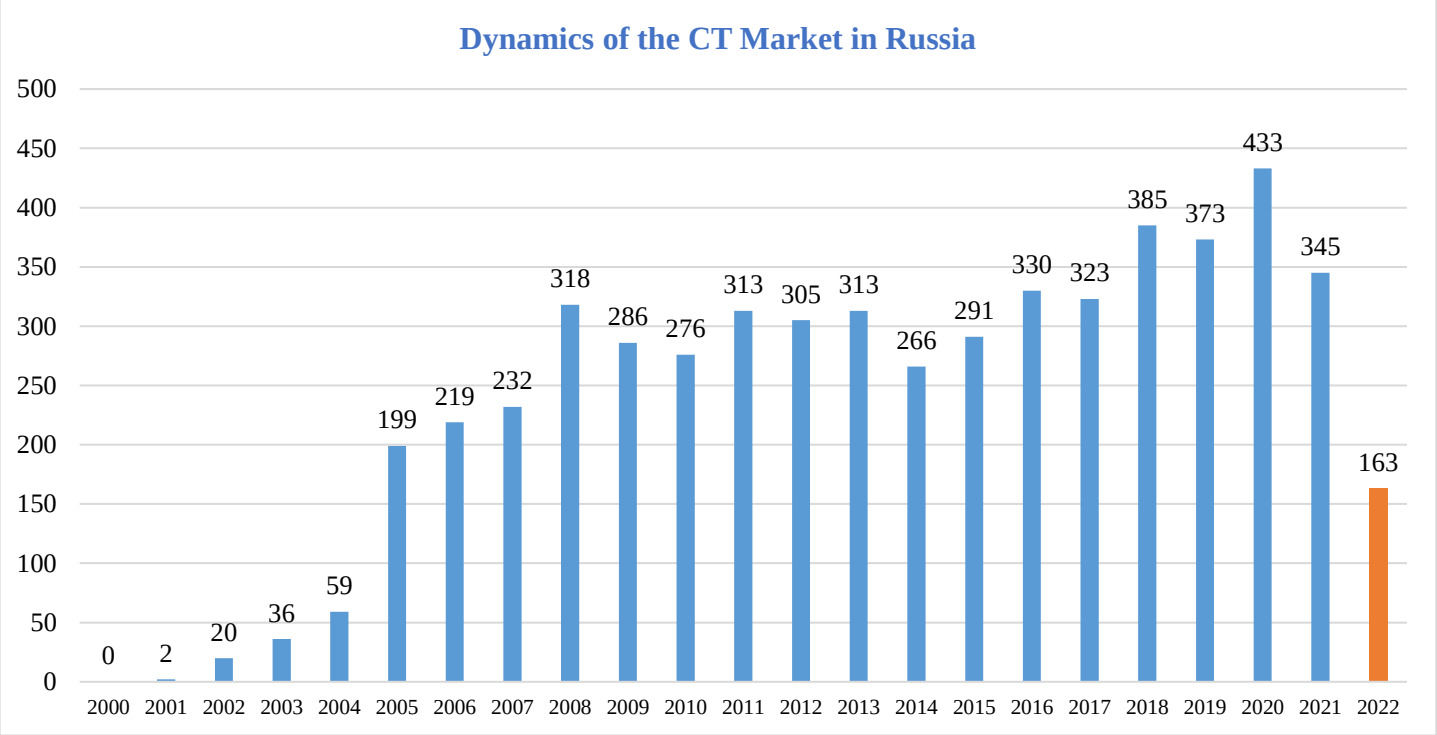
Data from www.clinicaltrials.gov

Diagram 21



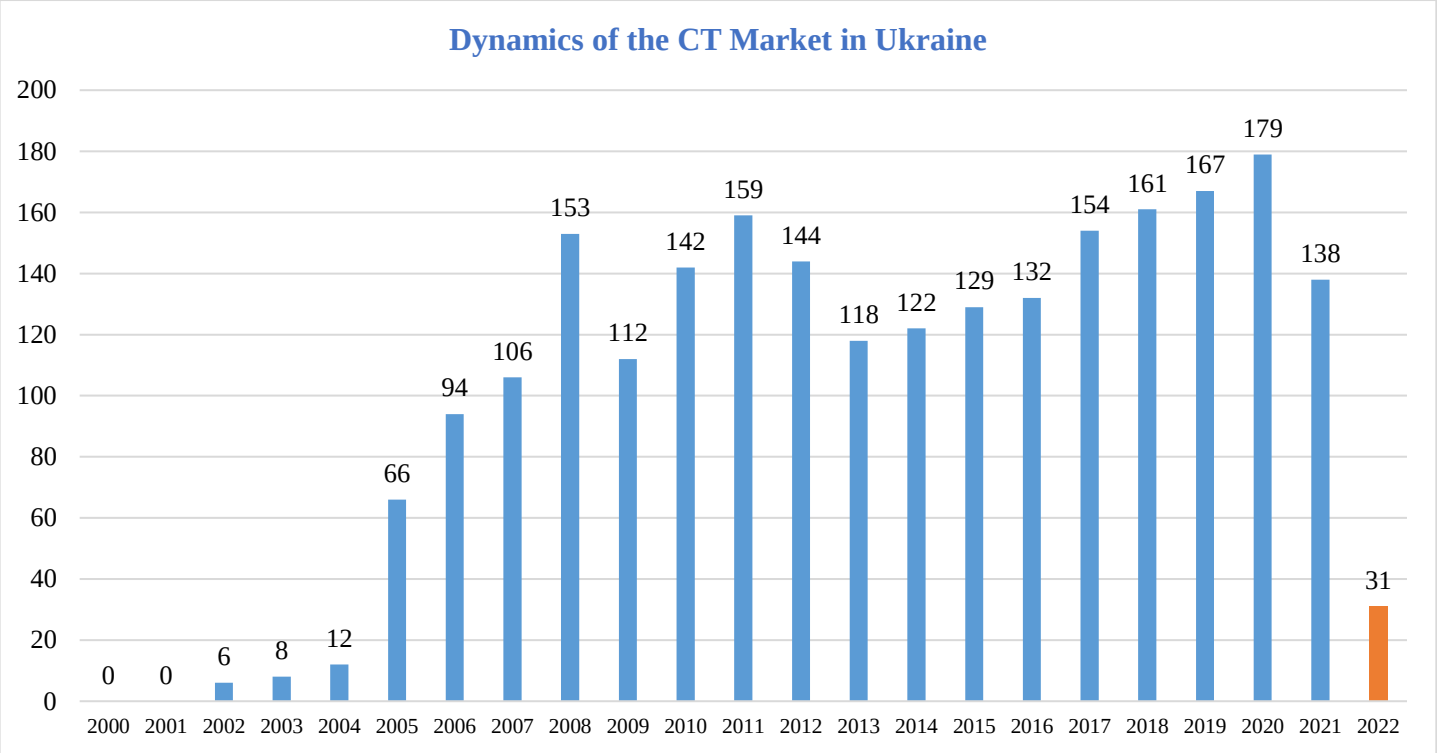
Data from www.clinicaltrials.gov

Diagram 22



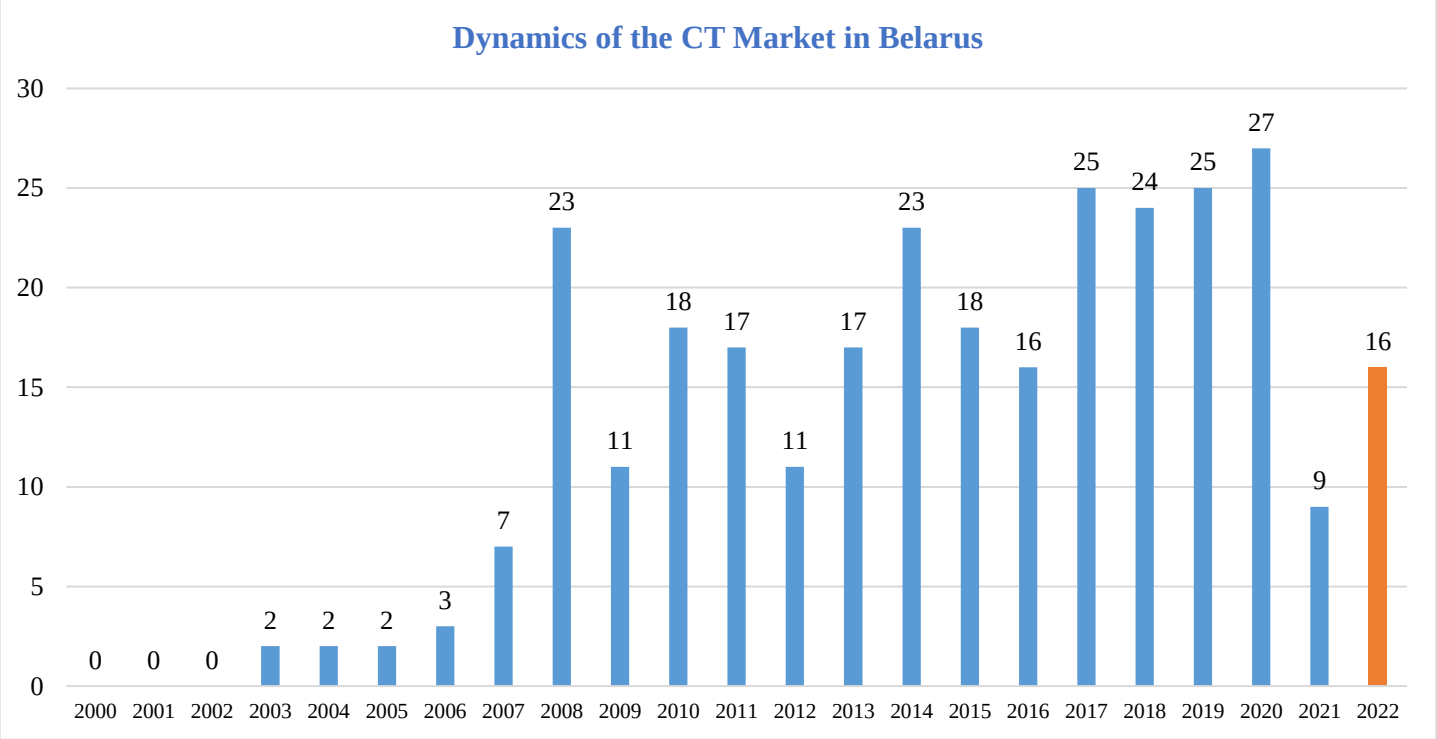
Data from www.clinicaltrials.gov

Diagram 23



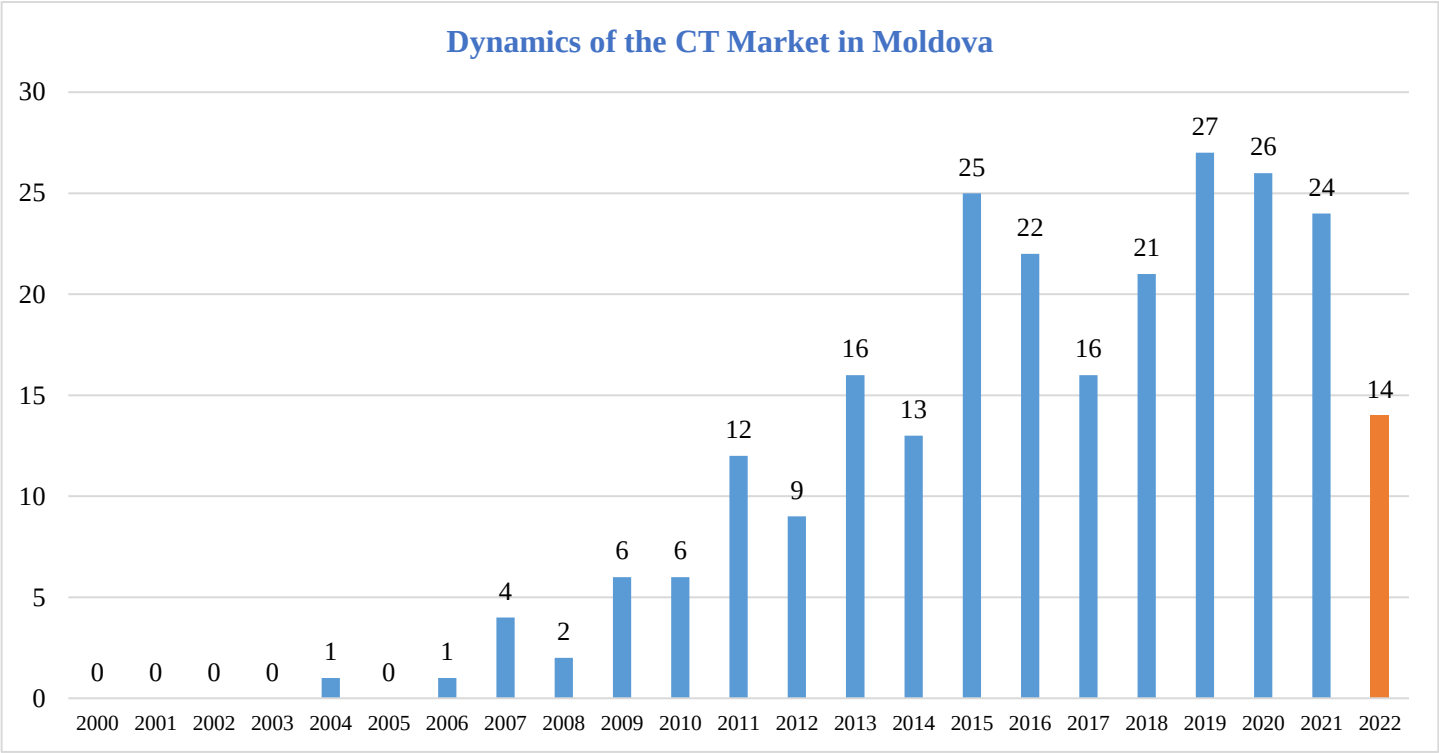
Data from www.clinicaltrials.gov

Diagram 24



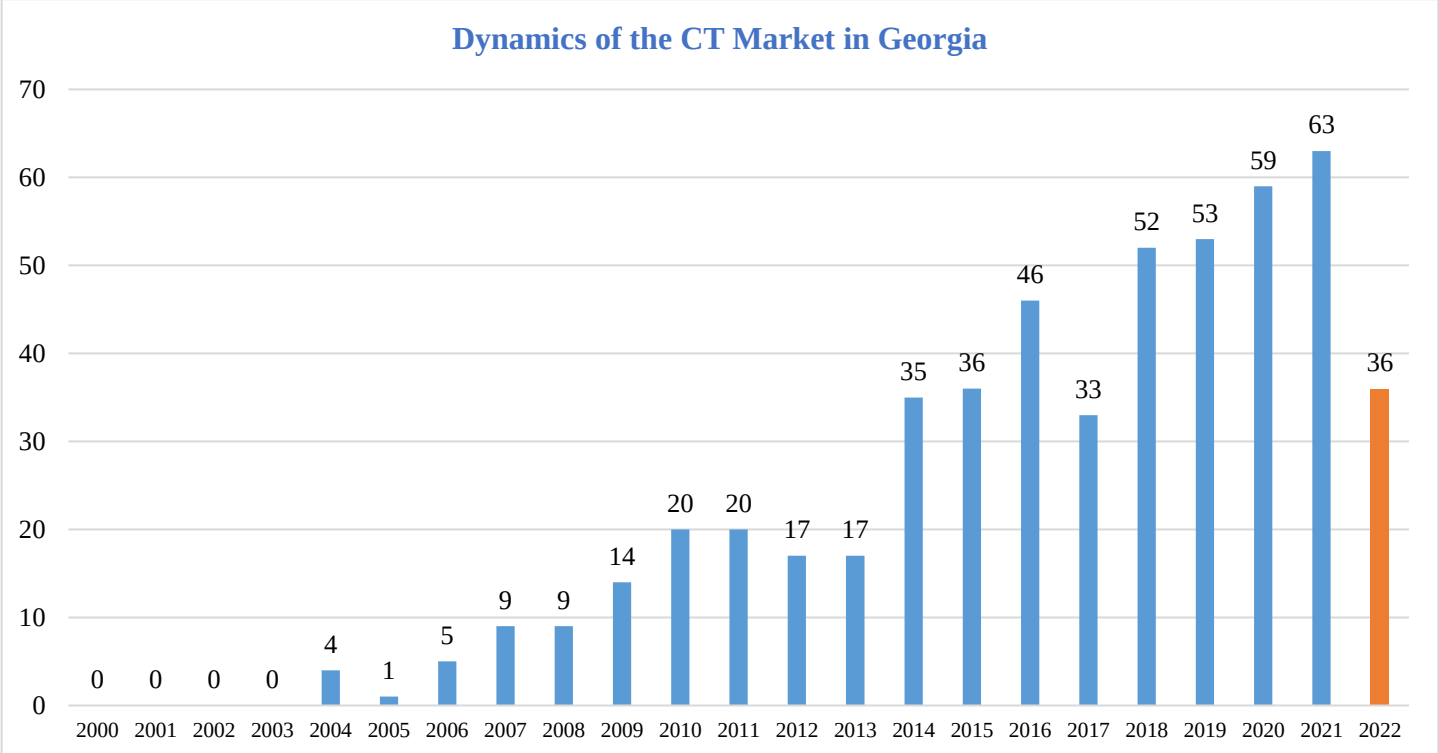
Data from www.clinicaltrials.gov

Diagram 25



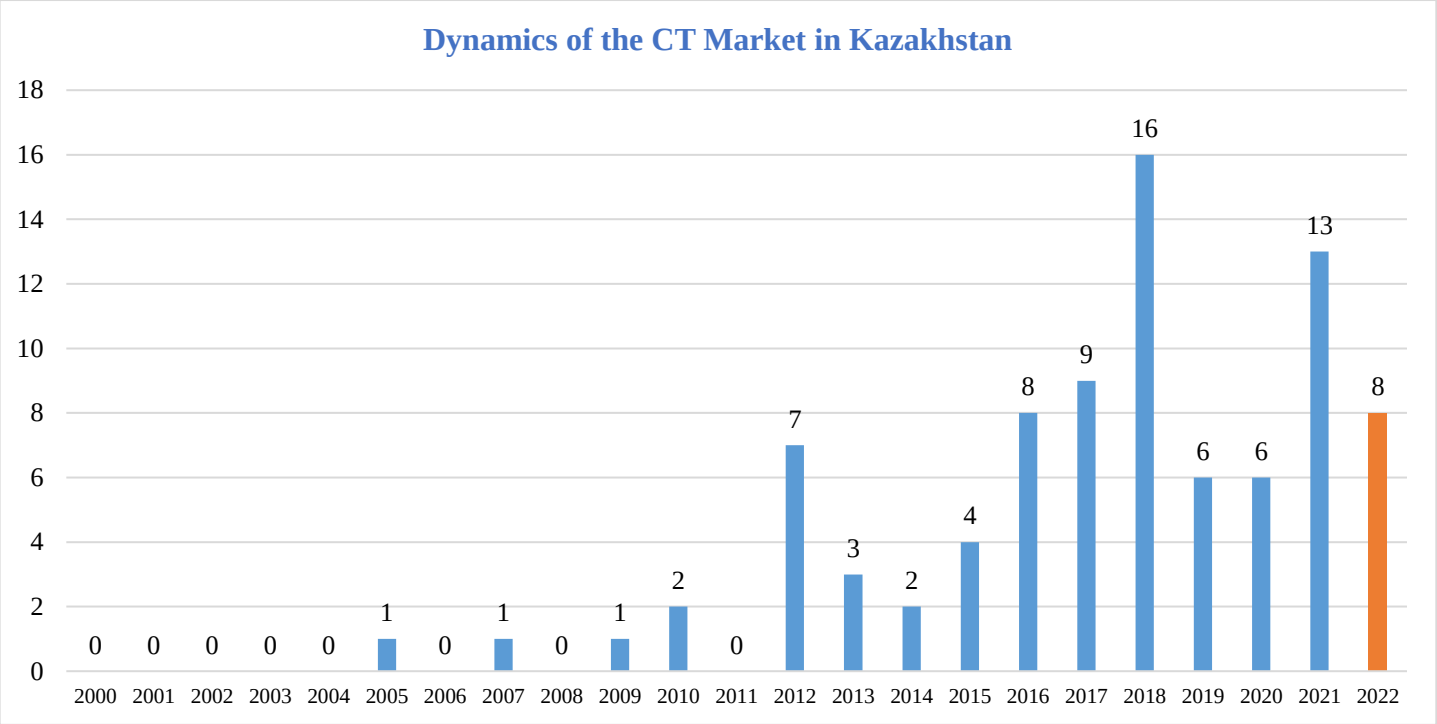
Data from www.clinicaltrials.gov

Diagram 26



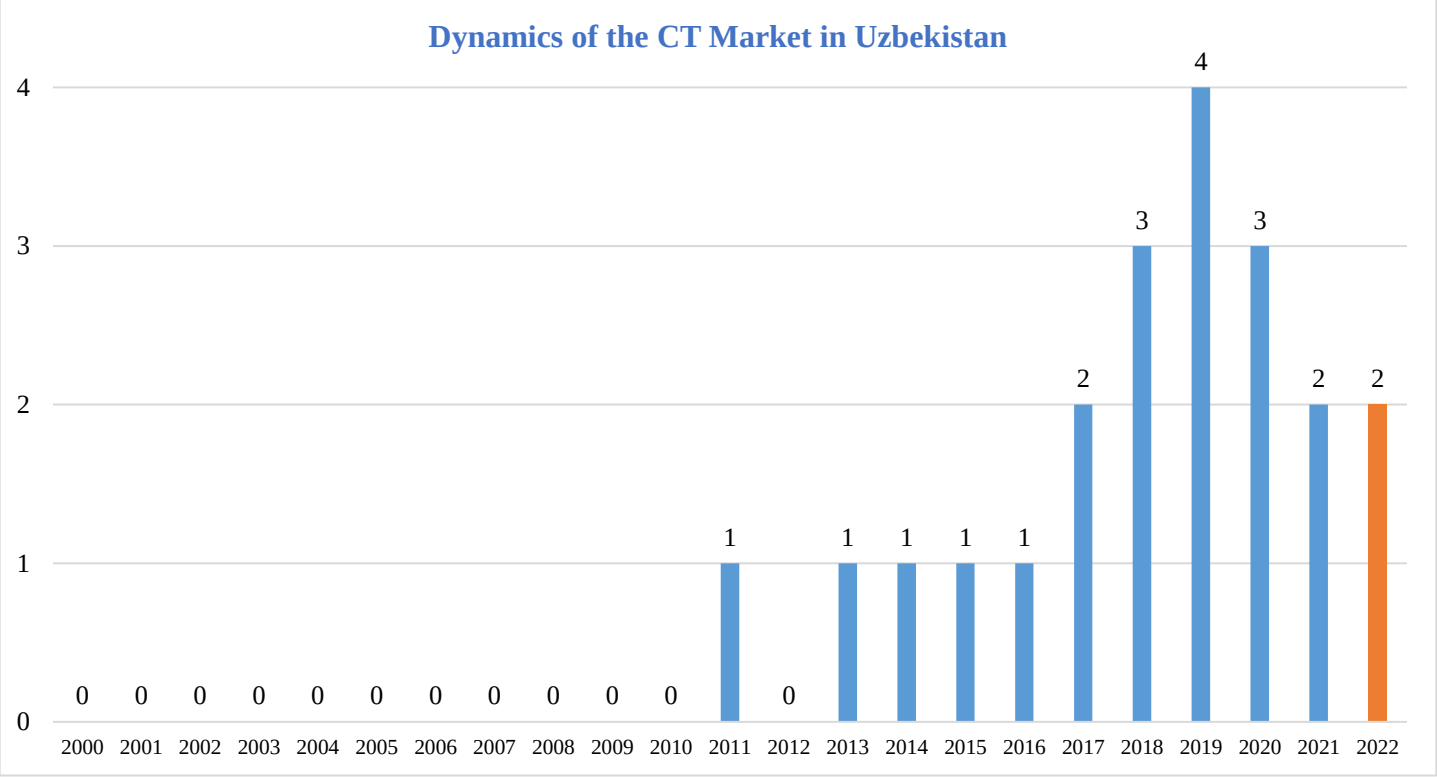
Data from www.clinicaltrials.gov

Diagram 27



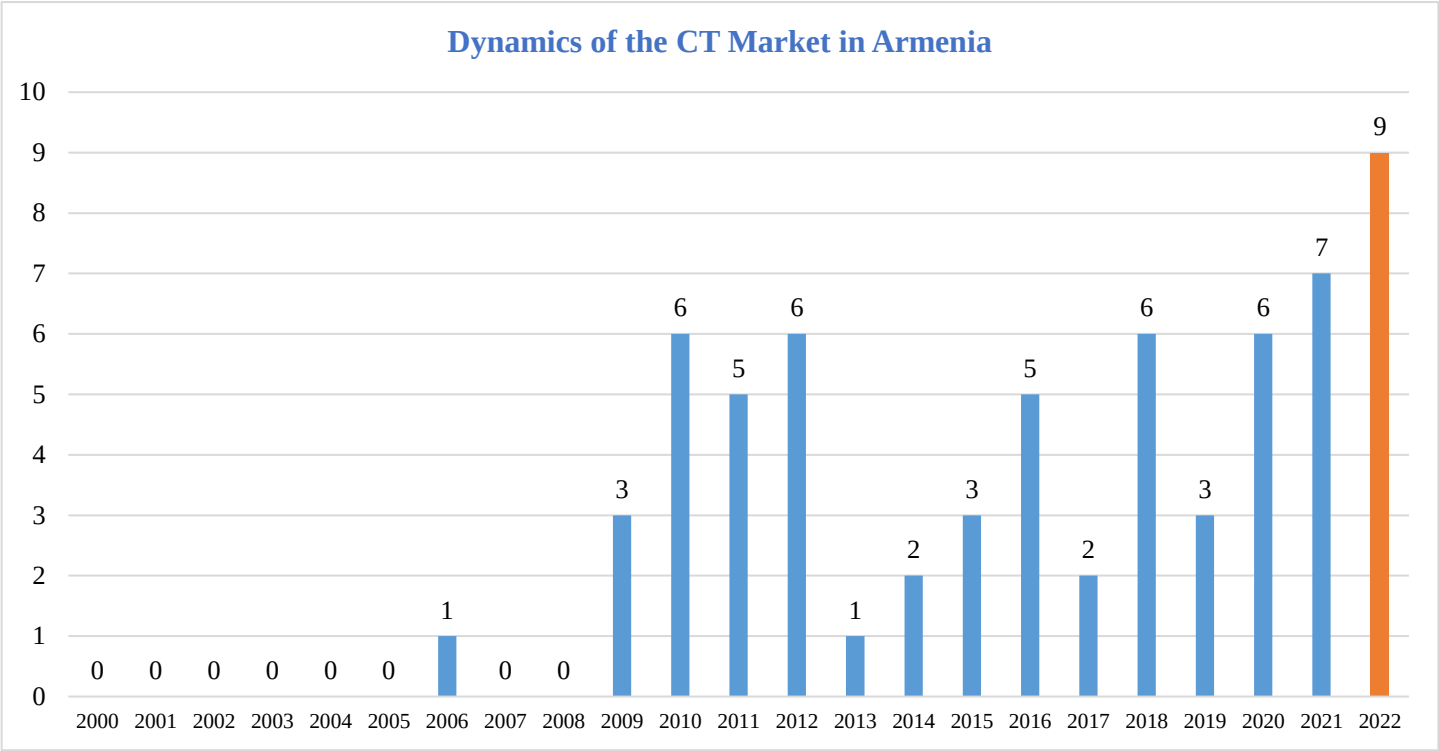
Data from www.clinicaltrials.gov

Diagram 28



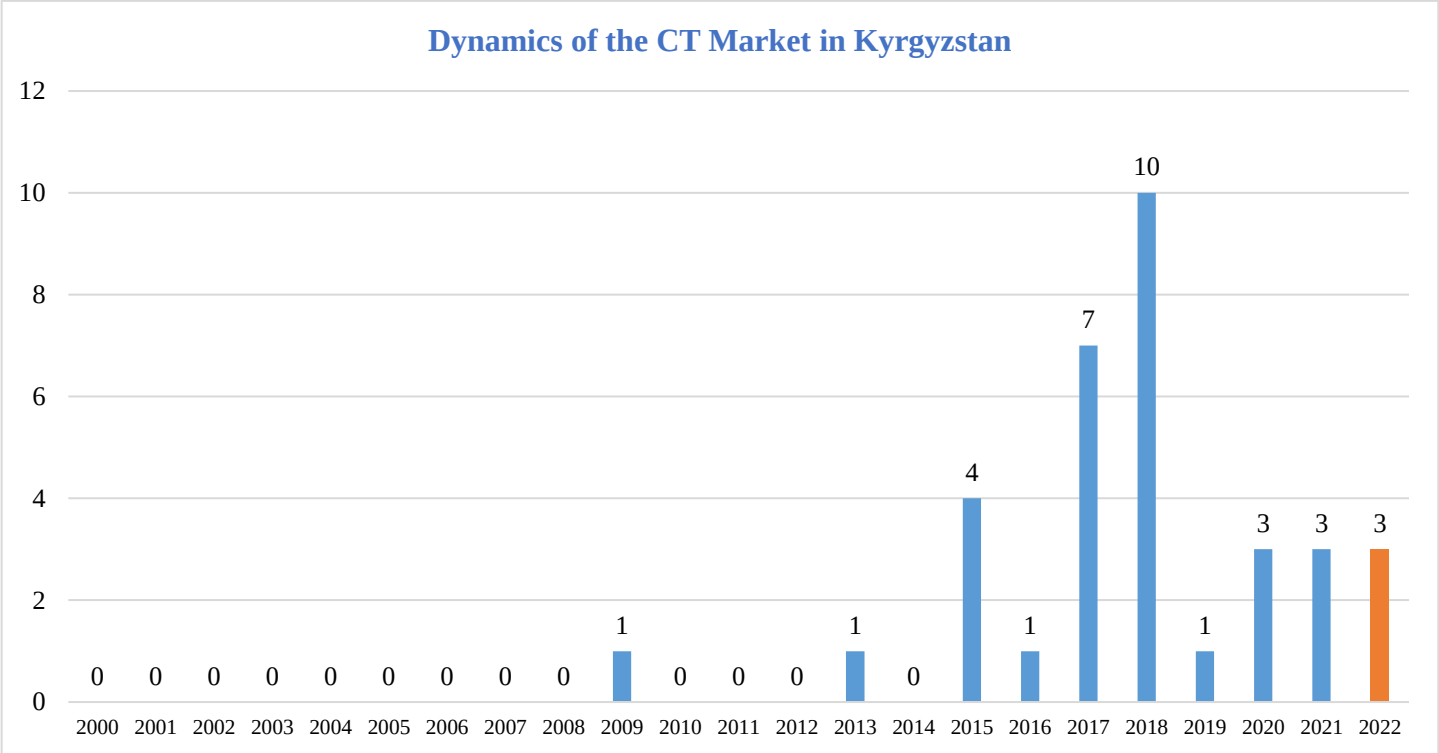
Data from www.clinicaltrials.gov

Diagram 29



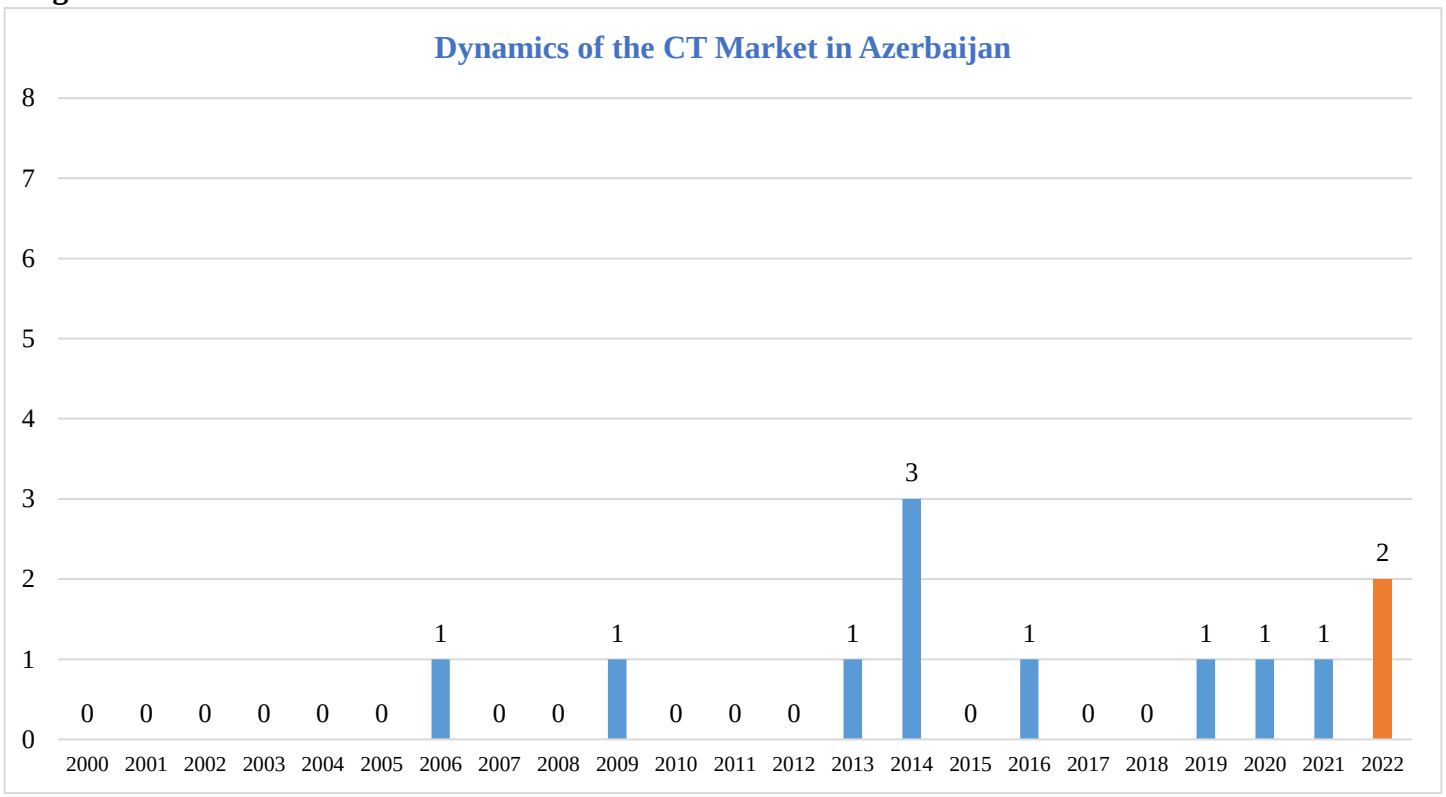
Data from www.clinicaltrials.gov

Diagram 30



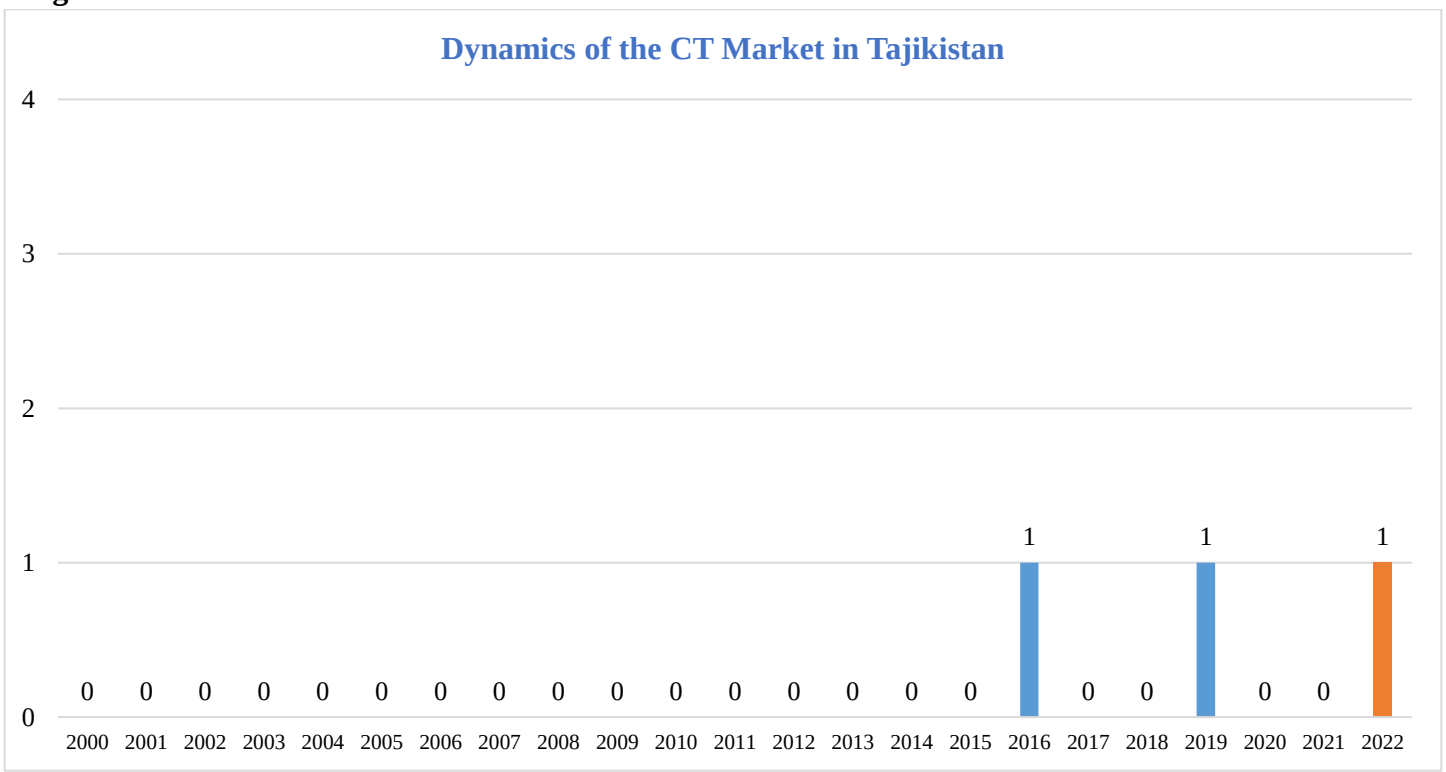
Data from www.clinicaltrials.gov

Diagram 31



Data from www.clinicaltrials.gov

Diagram 32



Data from www.clinicaltrials.gov