ACTO

ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

ACTO NEWSLETTER № 25

1st Half of 2022

MOSCOW 2022

CONTENTS

ACTO has been issuing biannual newsletters with an overview of the Russian clinical trials market for more than ten years. During this time, the traditional column system has taken shape. Thus, the biannual issues usually contain analyses of expert evaluations, material relating to inspections by supervisory bodies, rankings of principal investigators, etc.

In 2022 it was decided to abandon most of the traditional themes, since in the current political and economic situation they do not look relevant or even quite appropriate. The state of affairs in 2022 is out of the ordinary, it is different from anything described in the ACTO newsletters of previous years. During ACTO's observation period, the Russian economy has gone through a number of crises, including those associated with the breakdown of international ties. However, never before has what government experts have dubbed "structural transformation" affected Russia's clinical trials market so noticeably. Therefore, it was decided to devote the current issue of the newsletter to fixing those changes in the industry, which can be traced on the statistical data for the first half of 2022.

IMCT: EPICRISIS

At the end of February 2022, with the start of the military operation in Ukraine, Russia entered an acute crisis phase, characterized by a sharp breakdown in international ties in general and, in particular, by the disruption of supply chains and cash flows in business. This crisis affected various sectors of the economy in different ways; somewhere it was predictable, somewhere the situation developed and continues to develop according to a not quite expected scenario. In the field of international clinical trials, it was almost immediately clear that this was the beginning of the end. The specific nature of the business is a single project for a number of countries, requiring clear and coordinated action from all participants. This is impossible to achieve in the unstable conditions of a major geopolitical conflict, not to mention the economic sanctions and international isolation that followed. So in fact, from the very beginning it became clear that from now on, the prospects for international multicenter clinical trials (IMCTs) in Russia appear in an extremely gloomy. The only question was how long the "old stock" (previously started projects) would last.

Now, after the lapse of the first half of 2022, we can only register an intermediate stage, realizing that the fall into the abyss is not yet over. And we can also share the impressions of the included observation of how things have developed for a single industry.

Unlike our Ukrainian colleagues, for whom the situation understandably developed in a much more dramatic scenario, the Russian segment of the industry faced logistical problems in the first wave. First, in the centers located in the southern regions of the country. We remind the reader that flight restrictions have been imposed on a number of cities in southern Russia since 24 February. Consequently, it became impossible to rapidly collect biological samples from centers located in these cities. With a wealth of experience in dealing with complex logistical challenges, reinforced by the recent Covid-19 pandemic accompanied by lockdowns, companies have rushed to tackle the new challenge. From bad to worse. The subsequent closure of airspace over the European Union to Russian carriers and Russia's retaliation against a number of Western carriers has significantly limited the window of opportunity. The need to organise roundabout flights – via Georgia, Turkey, Bahrain – has inevitably led to delays in the delivery of ambient samples to central laboratories. Despite the efforts of the logistics staff and transporters, some of the samples deteriorated during transportation. As a stopgap solution, sponsors began to look for opportunities to switch to local laboratories at least for those laboratory indicators that suffered from time delays in the first place. Here again, the experience of previous years came in handy. Recall that in 2007, the industry had already experienced several months of stoppage of exports of biological samples from Russia. In addition to problems with the biological samples export, issues of supplying preparations and necessary materials to Russia were also addressed. There was no restriction on the drugs importation into the country, yet due to general problems with air transportation, the flow of goods on the remaining available routes was significantly densified, which also caused temporary delays, especially in the beginning. In addition, the restrictions imposed by the Government on the export of medical devices have created difficulties with the return of equipment after its use in a trial.

But the problems did not end there. The financial sanctions caused difficulties in settlements with suppliers of goods and services. Work with certain Russian market entities has become significantly more difficult or completely impossible after the introduction of political and economic measures by other states and international organizations.

The uncertainty of the overall situation created a serious risk for the IMCT sponsors of not being able to conduct a full-fledged trial program. In addition, as the geopolitical conflict escalated, so did the tempers in the economic spheres, which also affected the clinical trial industry. The sharp deterioration of the country's image in the eyes of the international community has also had a negative impact on the attractiveness of the Russian clinical trials market, which was predictable. All of these factors together led one after another to the decision by sponsoring companies to postpone the launch of new international projects in Russia or to abandon them altogether. Companies continue with ongoing trials, except in the case of Bristol Myers Squibb, which has decided to shut down the whole of its business in Russia, but for the vast majority of projects, new recruitment has been discontinued. How big these decisions were and how they affected the statistics for the first half of 2022 is clear from the data in the next section.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

To begin with, let's look at the overall numbers of approvals received. Contrary to our assumption about a decrease in the total number of trials due to the expected reduction in the number of IMCTs, it increased compared to the first half of 2021. In January-June 2022, the Ministry of Health of the Russian Federation issued 425 approvals for conducting clinical trials (Table 1). This represents an increase of 95 approvals or 28.8% compared to the same period the previous year, when 330 approvals were issued.

The number of approvals for IMCTs dropped by more than a quarter (27.5%): 111 in the first half of 2022, compared with 153 in the first half of 2021. The number of approvals issued to foreign sponsors for local trials also decreased slightly: 10 in the first half of 2022 and 11 in the same period of 2021.

But in the other three categories of trials there was a significant increase. Foreign sponsors received 43 approvals for bioequivalence studies in January-June 2022, a 59.3% increase over the same period in 2021 (27 approvals). The number of approvals for Russian sponsors' local trials increased by 80%: 90 approvals in the first half of 2022 and 50 a year earlier. The maximum growth, 92.1%, was recorded in the sector of Russian sponsors' bioequivalence studies: 171 approvals in January-June 2022, compared to 89 for the same period in 2021.

As a result, despite the decrease in the number of planned IMCTs, the total number of approvals issued showed a significant increase compared to the same period of the previous year.

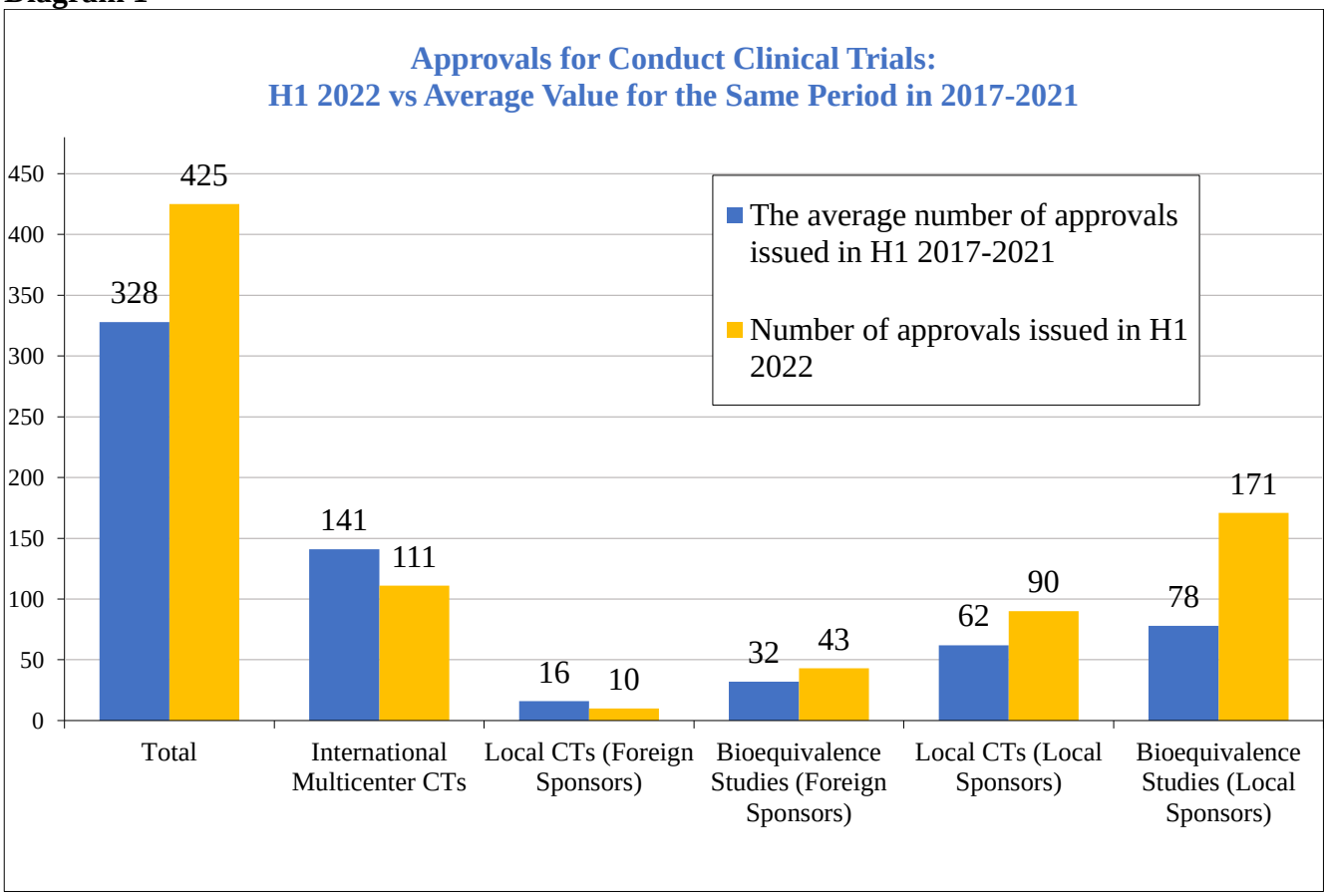
Table 1

Approvals for Conduct Clinical Trials: H1 2022 vs H1 2021						
Year	**Total**	**International Multicenter CTs**	**Local CTs (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CTs (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
H1 2022	425	111	10	43	90	171
H2 2021	330	153	11	27	50	89
H1 2022 vs H2 2021, %	28.8%	-27.5%	-9.1%	59.3%	80.0%	92.1%

Data from www.grls.rosminzdrav.ru

To what extent these changes in indicators are typical or unusual can be understood by placing them in a broader temporal context. Diagram 1 compares the results of the first half of 2022 with the January-June average of the previous five years. You can see that the total number of approvals received in the first half of 2022 is quite significantly, 29.6% higher than the average for the same period of 2017–2021 (425 vs 328). The number of approvals issued for IMCTs was 21.3% lower than the average (111 vs 141). The foreign sponsors' local research sector also showed a tangible decrease – 37.5% less than the average for the previous five years (10 vs 16). The remaining three categories, as compared to last year's data, showed growth. The number of approvals issued for foreign sponsors' bioequivalence studies was 34.4% higher (43 vs 32), and for Russian sponsors' local trials was 45.2% higher (90 vs 62). The absolute leader of the increase was the number of approvals issued for Russian sponsors' bioequivalence – 119.2% more than the average for the same period in the previous five years (171 vs 78).

Diagram 1

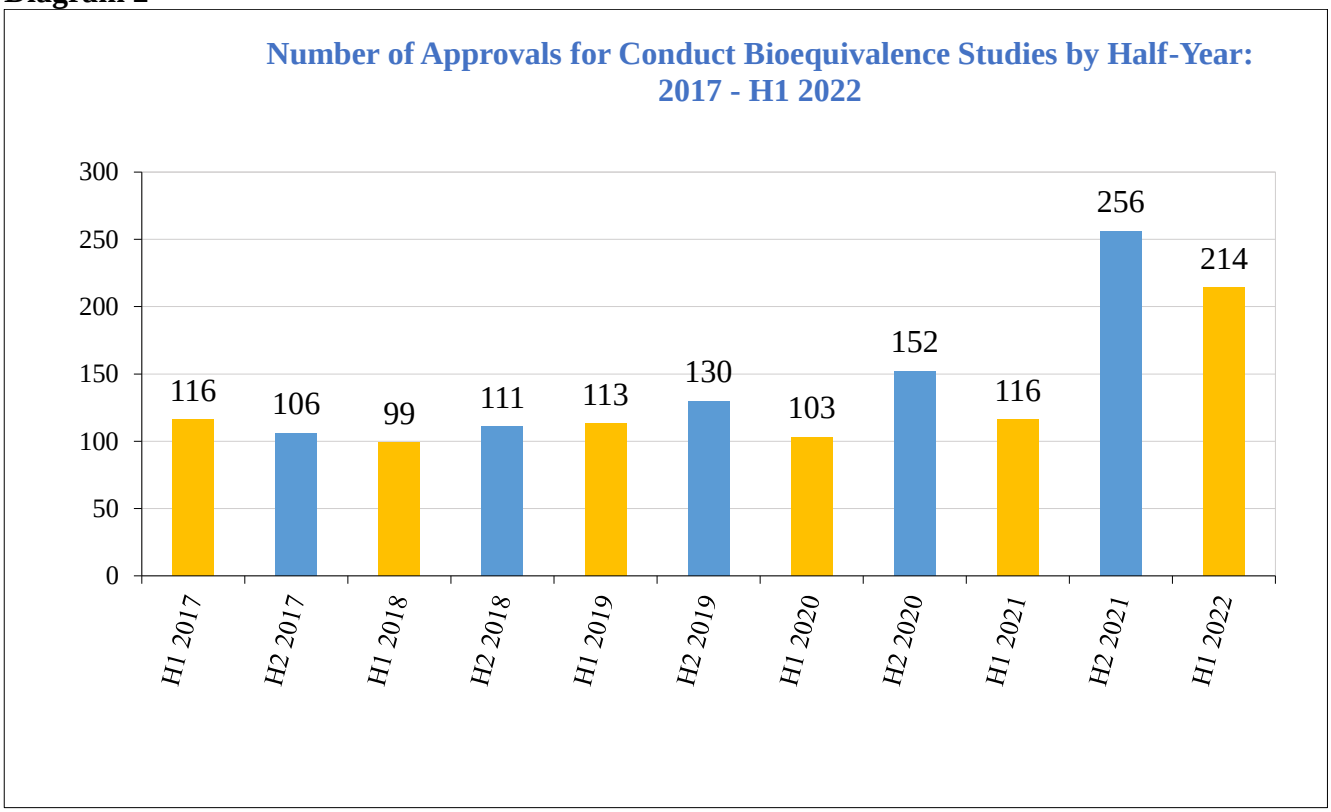


Data from www.grls.rosminzdrav.ru

Comparing the data in Table 1 and Diagram 1, we can state that both on a short time scale (when comparing with the same period of the previous year), and on a longer time scale (when comparing with the average indicator of similar periods of the previous five years), the first half of 2022 is characterized, first, by a significant reduction in the number of new international projects, and second, by a rapid growth of bioequivalence studies, especially those with Russian sponsors.

It is worth stating that the growth in the number of bioequivalence studies cannot be fully attributed to the specifics of the first half of 2022. Diagram 2 shows the evolution of the number of approvals issued for such studies (in general, regardless of the sponsoring country) by half-years, starting in 2017. The first and second halves of the year in Russia differ in terms of the number of business days due to the January and May holidays, which creates seasonal fluctuations, and therefore the indicators for the first and second halves of the year are shown in different colors on the diagram. If we abstract away from seasonal fluctuations, we can see that the growth in the number of bioequivalence studies is not in 2022, but earlier, starting in 2019. The Covid-19 pandemic was probably one of the catalysts for activity in this case (we will be able to test this hypothesis in the therapeutic areas review section of the newsletter), but other factors also seem to influence the resulting pattern.

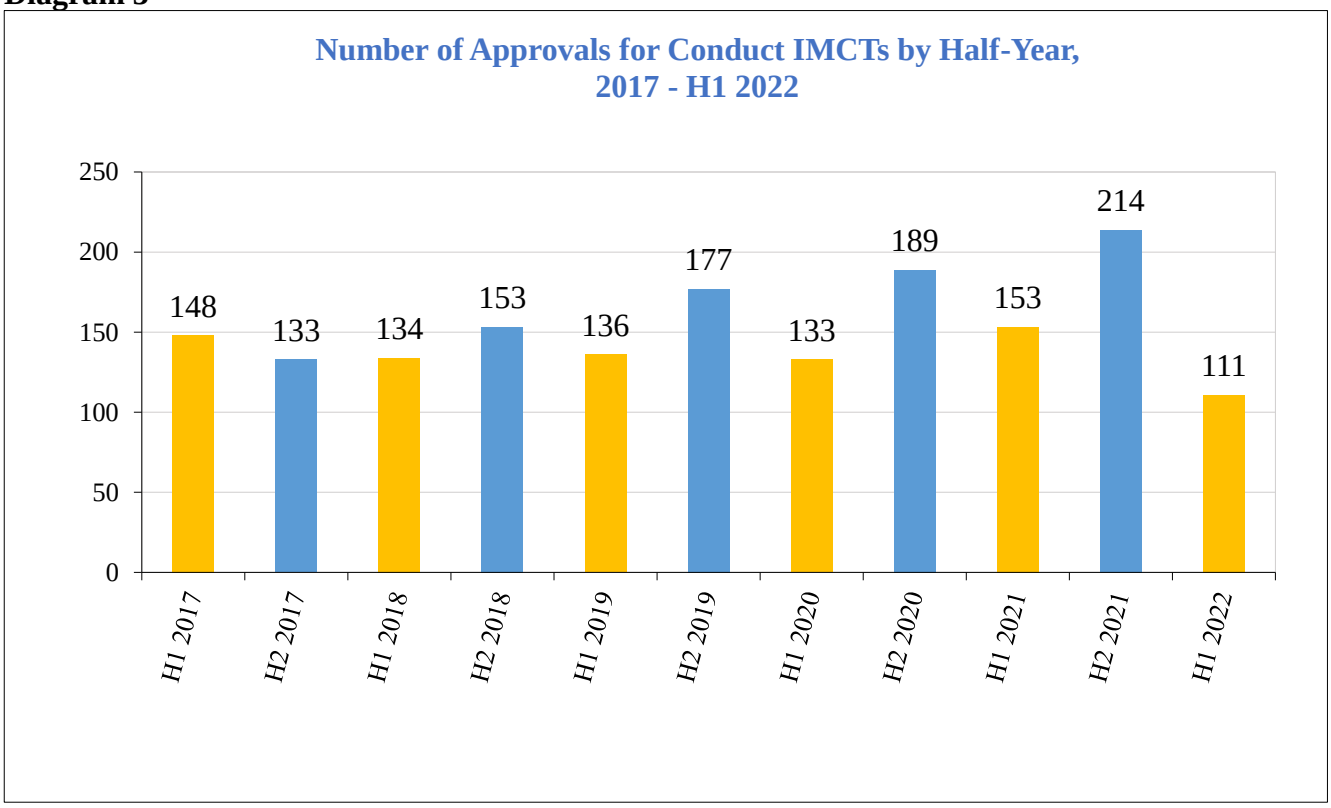
Diagram 2



Data from www.grls.rosminzdrav.ru

The decrease in the number of approvals issued for international projects, as opposed to bioequivalence studies, is much more specific to 2022 (Diagram 3) and we believe deserves more detailed consideration.

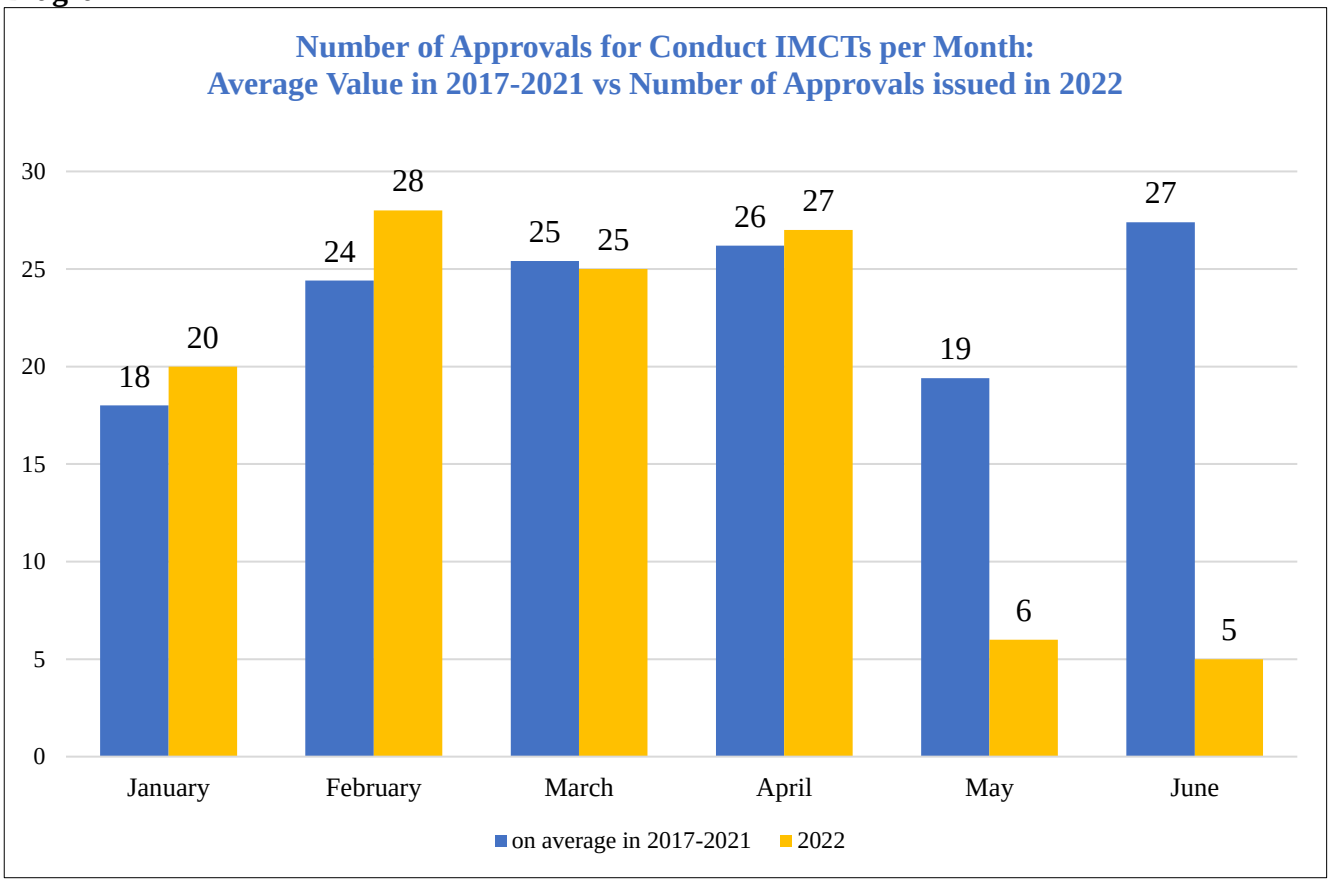
Diagram 3



Data from www.grls.rosminzdrav.ru

Diagram 4 shows the number of approvals for IMCTs issued in the first half of 2022 on a monthly basis compared to the average number of approvals for the same month in 2017–2021. We can see that the number of approvals for IMCTs in the first four months of the year roughly corresponded to the average indicators for this type of trials in the same months of the previous five years, and even exceeded them slightly in January, February, and April. A sharp drop and a gap with the average begins in May 2022. And this is understandable - the approval period for a clinical trial is three to four months, and the approvals received in January and March were for applications submitted as early as the end of 2021. The decline in sponsor activity, which began in March, became clearly visible from May, and the picture is likely to get worse for the foreseeable future.

Diagram 4

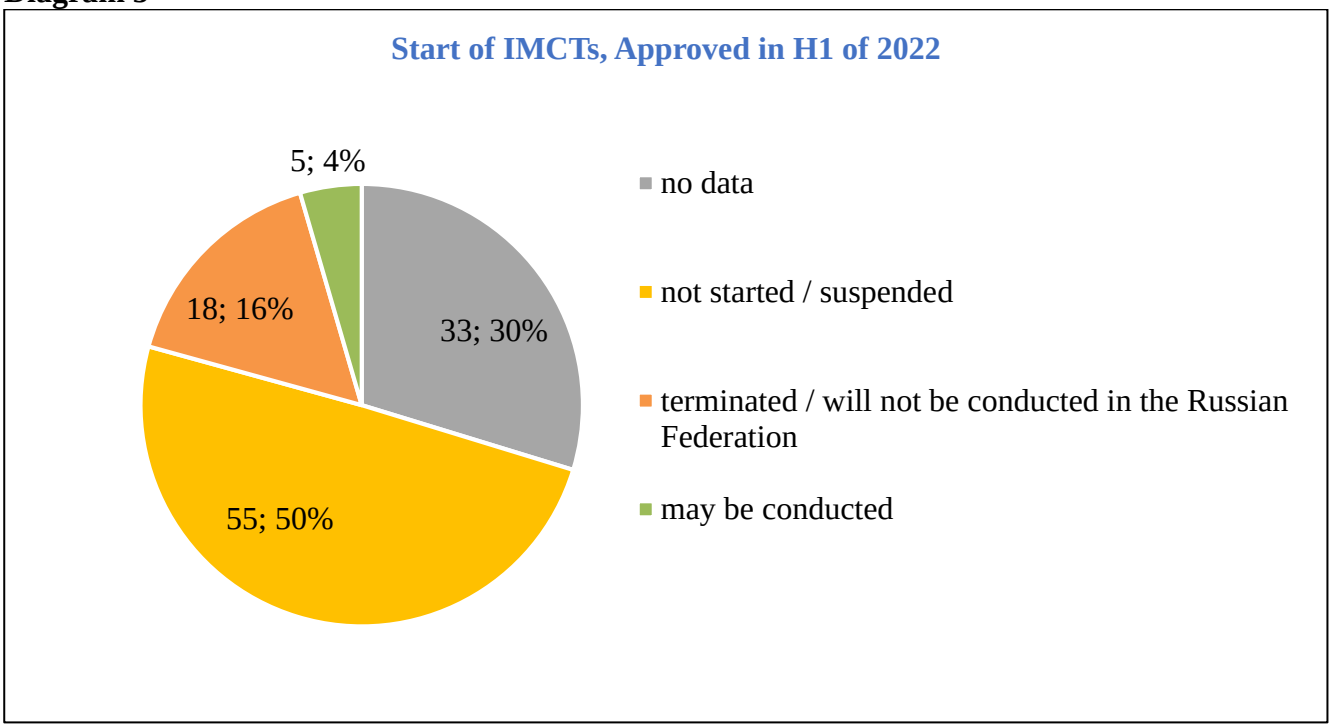


Data from www.grls.rosminzdrav.ru

Given the already mentioned decisions of Western sponsors to freeze the launch of new projects in Russia, it was also obvious to us that the number of approvals issued clearly does not match the number of IMCTs that have been actually launched. To assess the real picture, ACTO conducted a survey and collected information on sponsors' decisions regarding the launch of IMCTs, for which approvals were obtained in the first half of 2022, i.e. 70.3%. The survey data is shown in Diagram 5. They show that at least half of the new international projects (55) as of July 2022 were "on hold", their launch has been stopped. It is now definitively known that 18 IMCTs (16%) will not take place in Russia. And only 5 IMCTs (4%) were reported by their organizers as potentially active. One of these five trials was approved back in early January, recruitment was initiated and patients are now in treatment, but recruitment of new participants has been suspended. Three trials have not yet started, but have a chance to start, and all three are expected to include patients who previously participated in a study of the same drug (extension or roll-over studies for current patients). Finally, the fifth, active and forthcoming study was initiated by a sponsor from India.

When reading Diagram 5, it is also worth bearing in mind that it is a snapshot of a constantly changing situation. The longer the protocol is on hold, the less chance it has of being launched in Russia. Therefore, unless the overall situation changes, the share of IMCTs with "terminated" status will gradually increase at the expense of the "not started" share.

Diagram 5

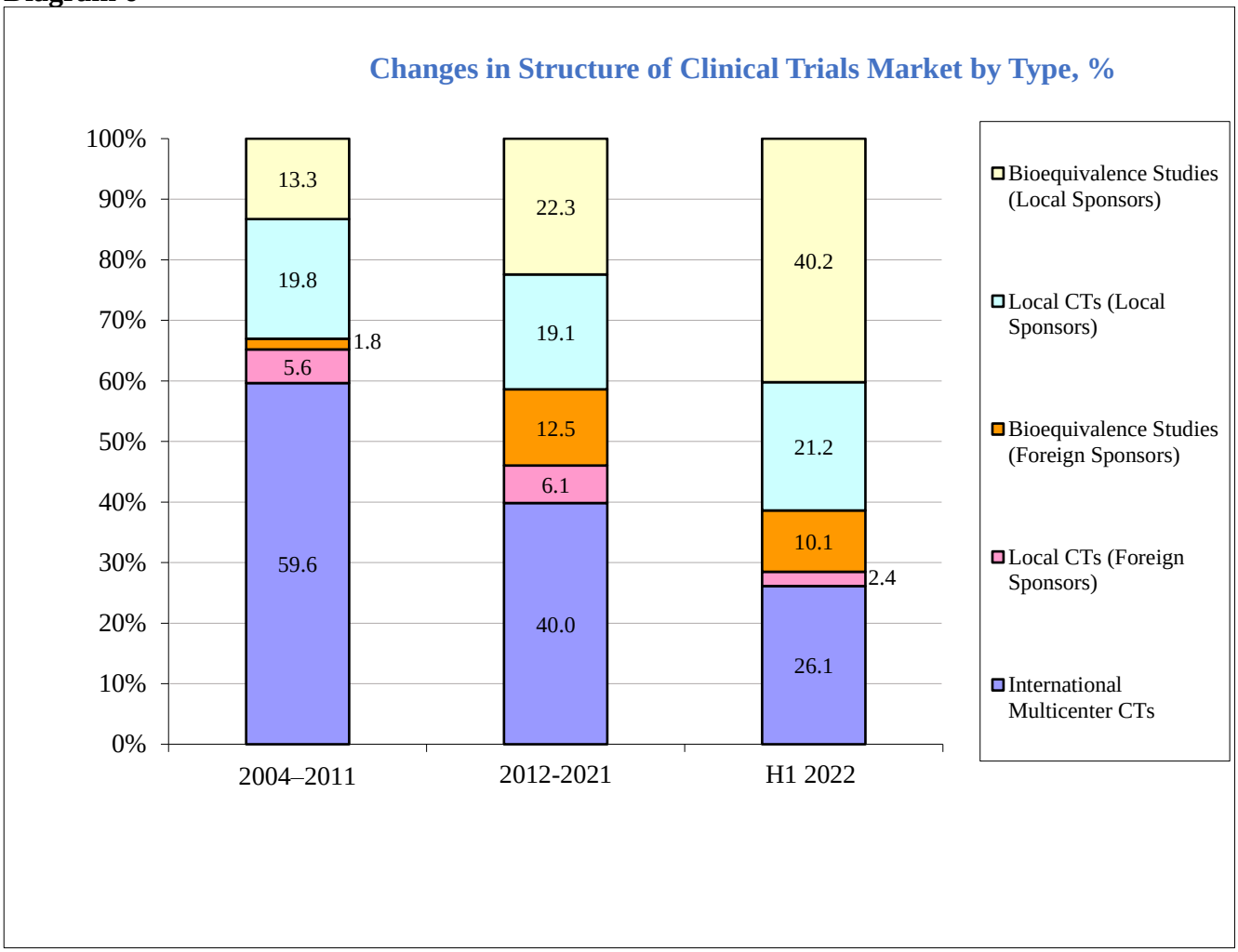


Data from poll of ACTO members

STRUCTURE AND DYMAMICS OF THE CLINICAL TRIALS MARKET BY TYPE

Diagram 6 shows what global qualitative changes in the market began in the first half of 2022. In the left column we see what the average share of different types of trials in 2004–2011 (the so-called "pre-reform" period) was; in the middle column we see average figures for the period 2012–2021 (after the law "On Circulation of Medicines" came into force). Finally, the right column is the figures for the first half of the year 2022. The features of the H1 2022 that we have already noted are also evident here: first, the share of IMCTs dropped sharply (to 26.1%, with the usual 40% and more in recent years), and second, the share of Russian sponsors' bioequivalence studies increased dramatically (to 40.2%, with an average of 22.3% since 2012). As for the IMCTs share, there is every reason to believe that at the end of the year, we will see a much more depressing picture: recall that the reduction in the number of approvals for this type of trial has only been noticeable since May.

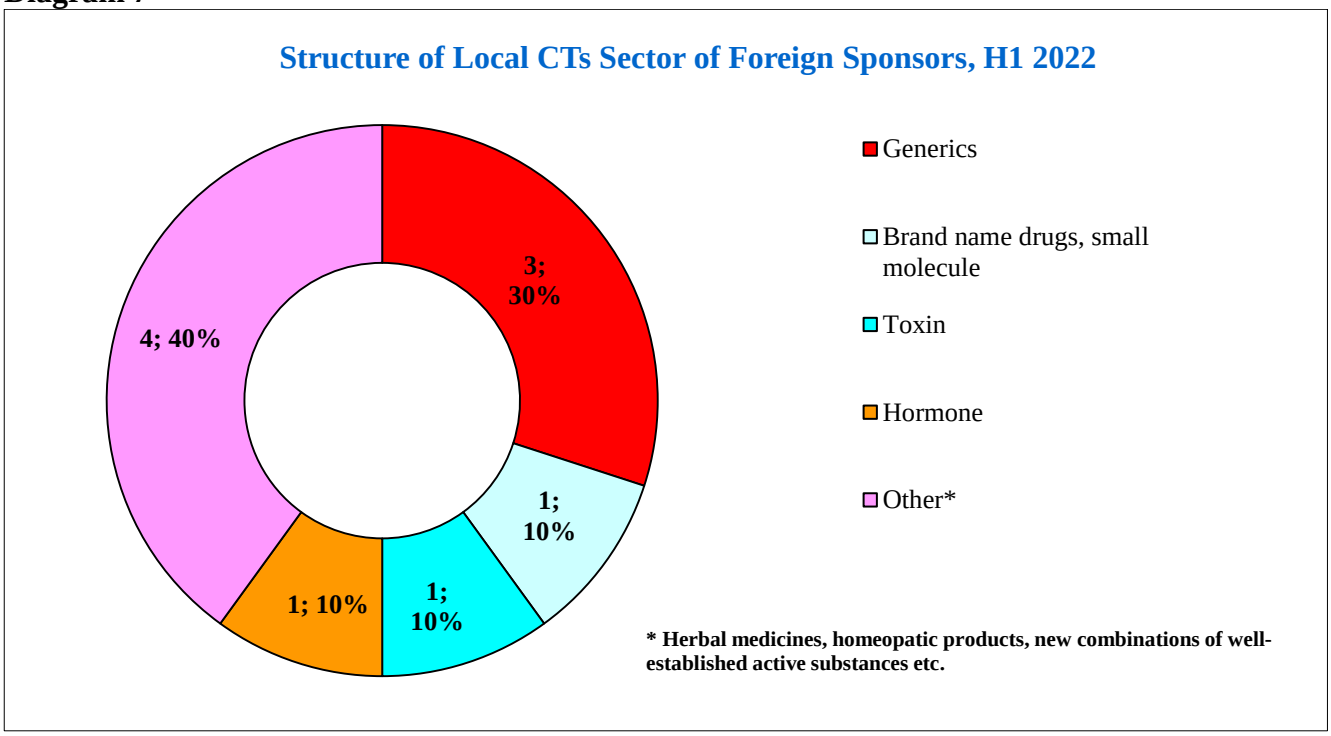
Diagram 6



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

The following two diagrams show which types of drugs were predominantly tested in local therapeutic efficacy and safety trials in the first half of 2022. Diagram 7 shows the ratio of different groups of drugs in foreign sponsors' trials (not including bioequivalence studies). Three out of ten protocols studied generics, one protocol each for a hormone, a toxin and an original small molecule, and four other active substances belong to the "other" category, under which ACTO newsletters group plant and animal derived products as well as homeopathic and some other products.

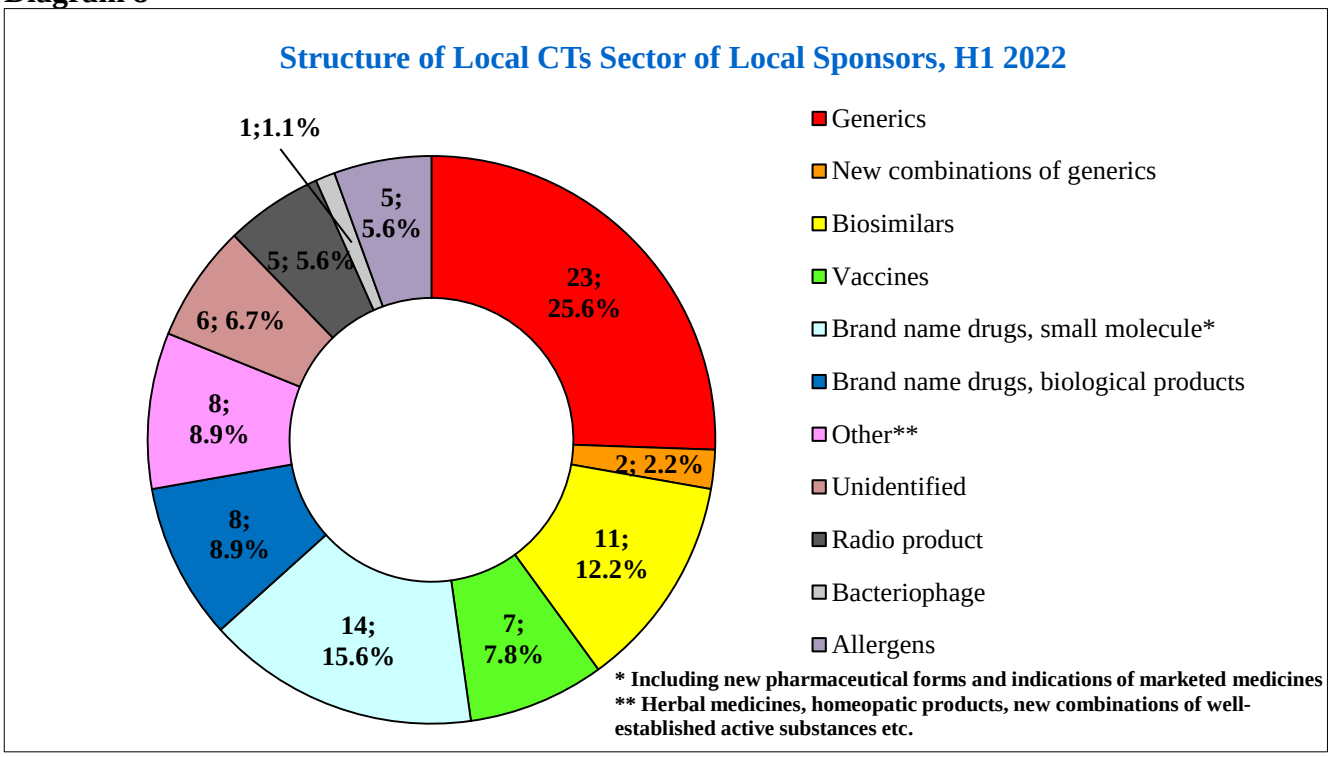
Diagram 7



Data from www.grls.rosminzdrav.ru

A more complex picture is the ratio of different groups of drugs in Russian sponsors' local trials (Diagram 8). In 23 out of 90 new protocols, generics were supposed to be studied (a quarter of the local trials), another two studied combinations of generics, and 11 (12.2%) studied biosimilars. Fourteen trials (15.6% share) studied original small molecules, eight (8.9%) – original biological products, seven (7.8%) – vaccines, five (5.6%) – radiopharmaceuticals, another five (5.6%) – allergens, and one additional protocol studied a bacteriophage. In addition, eight approvals (8.9%) were issued to study medicine we placed in the "other" category. In another six cases (6.7%), it was not possible to classify the active substance.

Diagram 8



Data from www.grls.rosminzdrav.ru

STRUCTURE OF THE CLINICAL TRIALS MARKET BY THERAPEUTIC AREA

Usually this column is not included in our biannual issues; according to the established practice, we analyze the therapeutic areas to which the trials conducted in Russia is devoted when we summarize the year's results. However, this time, given the serious structural changes taking place on the Russian clinical trials market, we decided to do it now. It was all the more important for us to understand why the bioequivalence studies sector has grown so much, which has been noted in previous sections of the newsletter.

Let's start with IMCTs. Table 2 shows the international protocols approved in the first half of 2022. Given that the vast majority of these trials have not started, and very likely never will, this table might better be called “what we have been deprived of”.

The five protocols we mentioned as active or for which activity is probable relate to drugs to be used in rheumatology/immunology, neurology, hepatology, oncology and ophthalmology.

Table 2

Distribution of International Multicenter CTs by Therapeutic Areas, H1 2022			
Therapeutic Area	**Number of IMCTs**	**Share (%)**	**The number of planned participants**
Oncology	33	29.7%	2 150
Neurology	14	12.6%	2 404
Rheumatology	10	9.0%	362
Psychiatry	7	6.3%	1 159
Oncohaematology	6	5.4%	149
Endocrinology	5	4.5%	360
Cardiology and CVD	5	4.5%	218
Infectious Diseases (except HIV/HCV/tuberculosis, covid-19)	4	3.6%	264
Ophthalmology	4	3.6%	183
Hepatology	3	2.7%	220
Nephrology	3	2.7%	164
Gastroenterology	3	2.7%	135
Haematology	3	2.7%	38
Covid-19	2	1.8%	2 610
Otorhinolaryngology	2	1.8%	150
Pulmonology	2	1.8%	44
Obstetrics	1	0.9%	120
Intensive Care	1	0.9%	100
Dermatology	1	0.9%	64
Cosmetology	1	0.9%	51
Urology	1	0.9%	25
TOTAL	111	100.0%	10 970

Data from www.grls.rosminzdrav.ru

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Table 3 contains data on local therapeutic efficacy and safety trials and bioequivalence studies of foreign generics. It shows that the overwhelming number of trials of this type (41.3%, 19 protocols) were for medicines used in cardiology and the treatment of cardiovascular diseases (CVDs). Looking ahead, six out of these 19 trials involved rivaroxaban, a drug that is also actively used in Covid-19 therapy. As well as vildagliptin, metformin and sitagliptin, which accounted for three of the six protocols we attributed to endocrinology, sharing second to third place with neurology (shares of 13% each). In the latter, however, four of the six trials involved levetiracetam, all four initiated by a single sponsor.

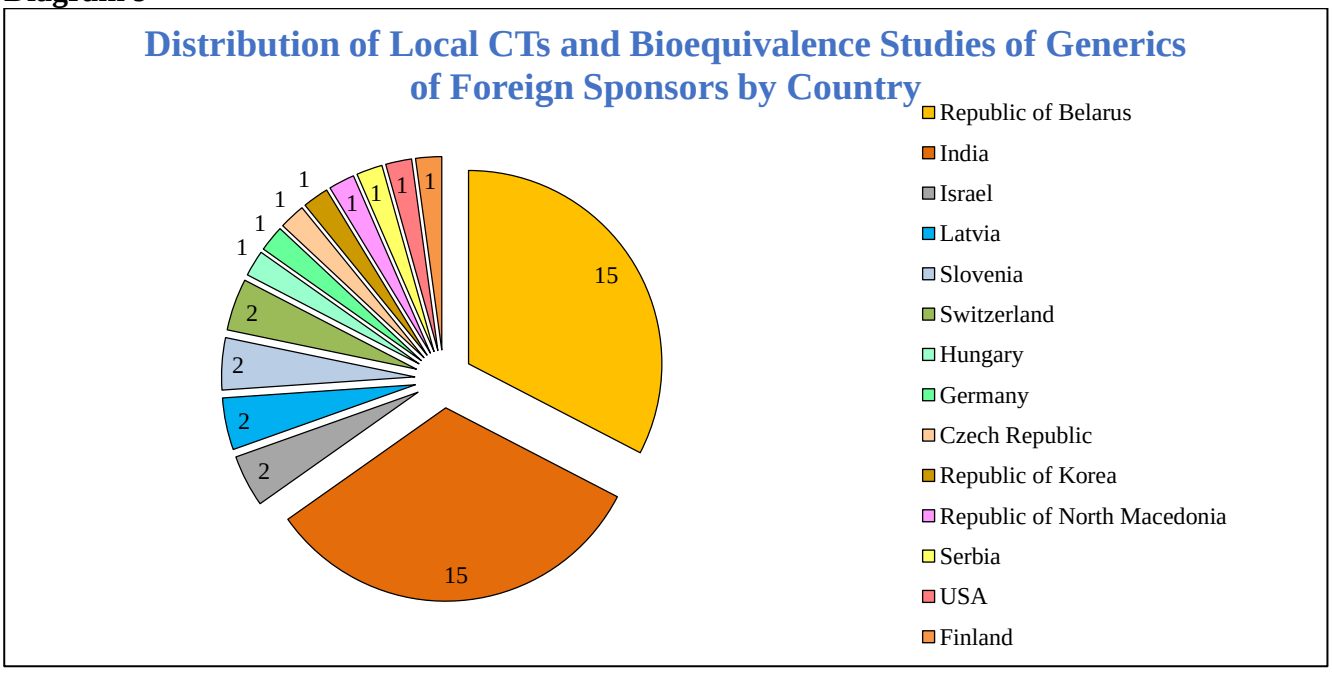
Table 3

Distribution of Local CTs and Bioequivalence Studies of Generics of Foreign Sponsors, H1 2022			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Cardiology and CVD/Vascular surgery	19	41.3%	1 107
Endocrinology	6	13.0%	504
Neurology	6	13.0%	293
Analgesic and NSAIDs	4	8.7%	140
Infectious Diseases (except HIV/HCV/tuberculosis, covid-19)	3	6.5%	126
Pulmonology	2	4.3%	500
Gastroenterology	2	4.3%	165
Psychiatry	2	4.3%	102
Gynecology	1	2.2%	128
Allergology	1	2.2%	28
TOTAL	46	100.0%	3 093

Data from www.grls.rosminzdrav.ru

Among other things, we decided to look at which countries were the sponsors who initiated these trials (Diagram 9). 15 trials (32.6% each) were conducted by sponsors from India and the Republic of Belarus.

Diagram 9



Data from www.grls.rosminzdrav.ru

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Table 4 shows the distribution of local efficacy and safety trials and bioequivalence studies of generics and domestic biosimilars. As we recall, it was the bioequivalence studies of local sponsors that led to a boom in the number of approvals issued in the first half of 2022.

So, 54 protocols (26.1%) were for drugs used in cardiology and treatment of CVDs. Once again, out of these 54 protocols, nine were for rivaroxaban, three for apixaban, and another three for enoxaparin sodium. Thus, it is likely that interest in actively developing generics of these, as well as some other drugs, was motivated precisely by the possibility of using them in Covid-19 therapy. The next large group of medicines (21 protocols, 10.1% of the total number of approvals) were drugs used to treat infectious diseases (it should be noted that we did not include medicines to treat infections such as HIV/HCV/TB, as well as Covid-19, which we identified as independent groups). The third place was taken by neurology, with 17 protocols or 8.2% of the total number of trials, and the fourth by drugs for use directly in the treatment of Covid-19: 13 protocols or 6.3%. Nine of these 13 trials were for molnupiravir. In the next largest number of trials in the therapeutic group, endocrinology (11 protocols, 5.3%), at least four trials were devoted to generics, which also have the potential to be used in the coronavirus infection treatment.

Another ten protocols were for generics or biosimilars of drugs used in hematology, and nine were for oncology. The remaining therapeutic areas accounted for a smaller number of trials.

Table 4

Distribution of Local CTs and Bioequivalence Studies (Generics and Biosimilars), Conducted by Local Sponsors, H1 2022			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Cardiology and CVD	54	26.1%	2 359
Infectious Diseases (except HIV/HCV/tuberculosis, covid-19)	21	10.1%	885
Neurology	17	8.2%	699
Covid-19	13	6.3%	3 955
Endocrinology	11	5.3%	516
Haematology	10	4.8%	769
Oncology	9	4.3%	596
HIV	8	3.9%	574
Oncohaematology	8	3.9%	305
Analgesic and NSAIDs	7	3.4%	435
Gastroenterology	7	3.4%	292
Psychiatry	6	2.9%	217
Hepatology	5	2.4%	347
Phlebology	4	1.9%	249
Immunology	4	1.9%	170
Gynecology	3	1.4%	420
Urology	3	1.4%	128
Pulmonology	3	1.4%	127
Allergology	3	1.4%	96
Dermatology	2	1.0%	644
Otorhinolaryngology	2	1.0%	570
Rheumatology	2	1.0%	200
Intensive Care	2	1.0%	104
Nephrology	1	0.5%	304
Parasitology	1	0.5%	50
Surgery/Dermatology	1	0.5%	24
TOTAL	207	100.0%	15 035

Data from www.grls.rosminzdrav.ru

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Table 5 presents the molecules that most frequently appeared in trials of generics and biosimilars from both foreign and Russian manufacturers. We see that rivaroxaban was the most popular (15 trials), followed by molnupiravir (nine protocols), then ticagrelor and pomalidomide (six protocols each).

Analyzing these data as a whole, we can conclude that a significant portion of the generic and biosimilar medicinal products trials for which approvals were obtained in the first half of 2022 were for drugs directly or indirectly used in Covid-19 therapy. A conservative estimate is that such 'two-in-one' medicines accounted for 15–20% of all generic trials conducted by domestic manufacturers, and even more for foreign sponsors – about 26%. We believe that our earlier hypothesis that the rapid growth of bioequivalence studies is largely a continuation of the trend that emerged at the height of the Covid-19 pandemic has been further confirmed by the data presented here.

Table 5

Most Requested INN Used in Clinical Trials of Generics in H1 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	9	15	Cardiology and CVD, surgery, covid-19
Molnupiravir	–	9	9	Covid-19
Tikagrelor	1	5	6	Cardiology and CVD
Pomalidomide	–	6	6	Oncohaematology
Vildagliptin (separately and in fixed combinations)	2	3	5	Endocrinology, perhaps covid-19
Levetiracetam	4	1	5	Neurology
Amlodipin (separately and in fixed combinations)	2	2	4	Cardiology and CVD
Amoxicillin	–	4	4	Infectious diseases
Dapagliflozin	1	3	4	Endocrinology
Apixaban	1	3	4	Cardiology and CVD, perhaps covid-19
Perindopril (in fixed combinations)	1	2	3	Cardiology and CVD
Metformin (in fixed combinations)	2	1	3	Endocrinology, perhaps covid-19
Dabigatran etexilate	–	3	3	Cardiology and CVD/surgery
Indapamide (separately and in fixed combination)	1	2	3	Cardiology and CVD
Melatonin	1	2	3	Neurology
Paracetamol (in fixed combinations)	–	3	3	Analgesic and NSAIDs, infectious diseases
Sitagliptin (separately and in fixed combinations)	1	2	3	Endocrinology, perhaps covid-19
Azithromycin	1	2	3	Infectious diseases
Macitentan	–	3	3	Cardiology and CVD
Torasemide	–	3	3	Cardiology and CVD
Rosuvastatin (separately and in fixed combination)	1	2	3	Cardiology and CVD
Rebamipide	1	2	3	Gastroenterology
Ramipril (separately and in fixed combination)	2	1	3	Cardiology and CVD
Clopidogrel	–	3	3	Cardiology and CVD
Enoxaparin sodium	–	3	3	Cardiology and CVD, surgery, perhaps covid-19

Data from www.grls.rosminzdrav.ru

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Finally, let's look at what the local trials of the original drugs were like. Table 6 shows the distribution by therapeutic area of such trials of foreign sponsors, and Table 7 by domestic sponsors. And, as we can see, the main area on which domestic developers continue to be focused is still Covid-19.

Table 6

Distribution of Local CTs of Brand Name Drugs of Foreign Sponsors, H1 2022			
Therapeutic Area	**Number of CTs**	**Number of planned participants**	**Developer's country**
Gastroenterology	2	260	Germany
Obstetrics	1	1244	Belgium
Pulmonology	1	794	Slovenia
Otorhinolaryngology	1	505	Poland
Cosmetology	1	196	Republic of Korea
HIV	1	110	USA
TOTAL	7	3 109	

Data from www.grls.rosminzdrav.ru

Table 7

Distribution of Local CTs of Brand Name Drugs (Including Biological Products) of Local Sponsors, H1 2022			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Covid-19	16	29.6%	10 413
Oncology	8	14.8%	889
Infectious Diseases (except HIV/HCV/tuberculosis, covid-19)	6	11.1%	1 011
Pulmonology	4	7.4%	1 617
Neurology	4	7.4%	532
Allergology	4	7.4%	140
Rheumatology	3	5.6%	722
Endocrinology	2	3.7%	300
Surgery	1	1.9%	900
Phlebology/vascular surgery	1	1.9%	460
Analgesic and NSAIDs	1	1.9%	280
Otorhinolaryngology	1	1.9%	250
Dermatology	1	1.9%	175
Cardiology and CVD	1	1.9%	170
Gastroenterology	1	1.9%	26
TOTAL	54	100.0%	17 885

Data from www.grls.rosminzdrav.ru

CLINICAL TRIALS IN POST-SOVIET STATES

Statistical data from the previous sections show that the number of new international projects in Russia in the first half of 2022 decreased sharply, and this process is actively continuing. It is absolutely clear that the clinical trials market in Ukraine has also suffered a heavy blow. The importance of these two markets to the international clinical trials industry is great.

Although Russia's share of the global market is small, about 2% (Table 8), the country's competitive advantage has always been its ability to recruit a large number of patients in a fairly short period of time. Good enrollment rates were also provided by Ukraine. In some projects, aggregate enrollment in Russia and Ukraine could reach 30% of the world's total. But now, after the stoppage of new international trials in Russia and under conditions when it is objectively more difficult to conduct them in Ukraine, pharmaceutical companies have a need to compensate for lost opportunities. It made them look more closely at the possibilities of other countries. The processes in Ukraine are likely to be quickly restored after the cessation of hostilities, since the country's image has not suffered in any way, and international ties have only grown stronger. In fact, even now, according to available information, the launch of new projects in the country is being resumed. But the Russian market and the opportunities for patient enrolment that it provided now look like they have been lost for a long time. Accordingly, sponsors will have to seriously explore new markets in order to restore the usual level of activity. This process is already underway, with companies showing interest in countries that have not previously been as actively involved in research, such as the UAE, Kuwait, Tunisia, Morocco, and Saudi Arabia. Of the former USSR Countries, Georgia, for example, is currently attracting a lot of interest. There are occasional questions about other post-Soviet states as well. Moreover, those sponsors who would not want to lose the opportunity to sell the medicine in Russia in the future are showing increased interest in the EAEU countries, as trials conducted in one of these countries allow the drug to be registered in all states of the economic union in the future.

Another factor we think is worth mentioning is the redistribution of human capital. The outbreak of hostilities has caused large numbers of people to migrate not only from Ukraine, but also from Russia. The clinical trial industry has opened up a major opportunity for the relocation of specialists. Professionals are actively leaving for different regions, from those where the trial market is developed (United Kingdom, Germany, USA, Canada, etc.) to the more exotic ones, like Argentina and Serbia. But not everyone is ready to leave, given family or other personal circumstances. In this context, a large number of highly qualified specialists remain in Russia, whose future is still very uncertain. It cannot be ruled out that the solution for them will be a greater activation of clinical trials processes in other post-Soviet states.

As changes in the Russian segment of the industry are also evident outside of Russia, in this issue of the newsletter we have decided to give a very general overview of the current situation of clinical trials in the countries that were once part of the USSR, perhaps going into a little more detail about some of them.

Table 8 compiles indicators such as the absolute number of active interventional trials registered with the ClinicalTrials.gov database as of July 2022, the country's global market share for this indicator, the population, and the number of trials per million inhabitants. Russia remained the leader in terms of number of trials (1,400 protocols) and global market share (1.8%) of the countries presented in the table at mid-2022. It is followed by Ukraine (595 protocols or 0.77% of all trials worldwide) and Lithuania (223 trials, 0.29%). Unexpectedly Georgia took fourth place (195 trials, 0.25%). Although the fact that the Georgian market has been quite active recently was not news, the fact that it managed to rise so high surprised us. Next come Estonia and Latvia (173 and 172 trials respectively, 0.22% in both cases), Belarus (a country that clearly has a similar fate to Russia in the area of clinical trials), Moldova, Kazakhstan, etc. At the end of the table is Tajikistan, with one active trial at the time of data collection. And there is no Turkmenistan, as no studies were reported in this country in the ClinicalTrials.gov database.

Table 8

The level of participation in clinical trials by country (as of 07.19.2022)				
Region	**Number of active interventional CTs**	**Share in the global CT market**	**Population, mln**	**Number of CTs, per million population**
In the world	77 750			
Russia	1 400	1.80%	145.6	9.6
Ukraine	595	0.77%	41.2	14.5
Lithuania	223	0.29%	2.8	79.7
Georgia	195	0.25%	3.7	52.9
Estonia	173	0.22%	1.3	129.9
Latvia	172	0.22%	1.9	91.7
Belarus	90	0.12%	9.3	9.7
Moldova	69	0.09%	2.6	26.5
Kazakhstan	28	0.04%	19.1	1.5
Armenia	16	0.02%	3.0	5.3
Uzbekistan	10	0.013%	35.6	0.3
Kyrgyzstan	6	0.008%	6.7	0.9
Azerbaijan	3	0.004%	10.2	0.3
Tadjikistan	1	0.001%	9.5	0.1

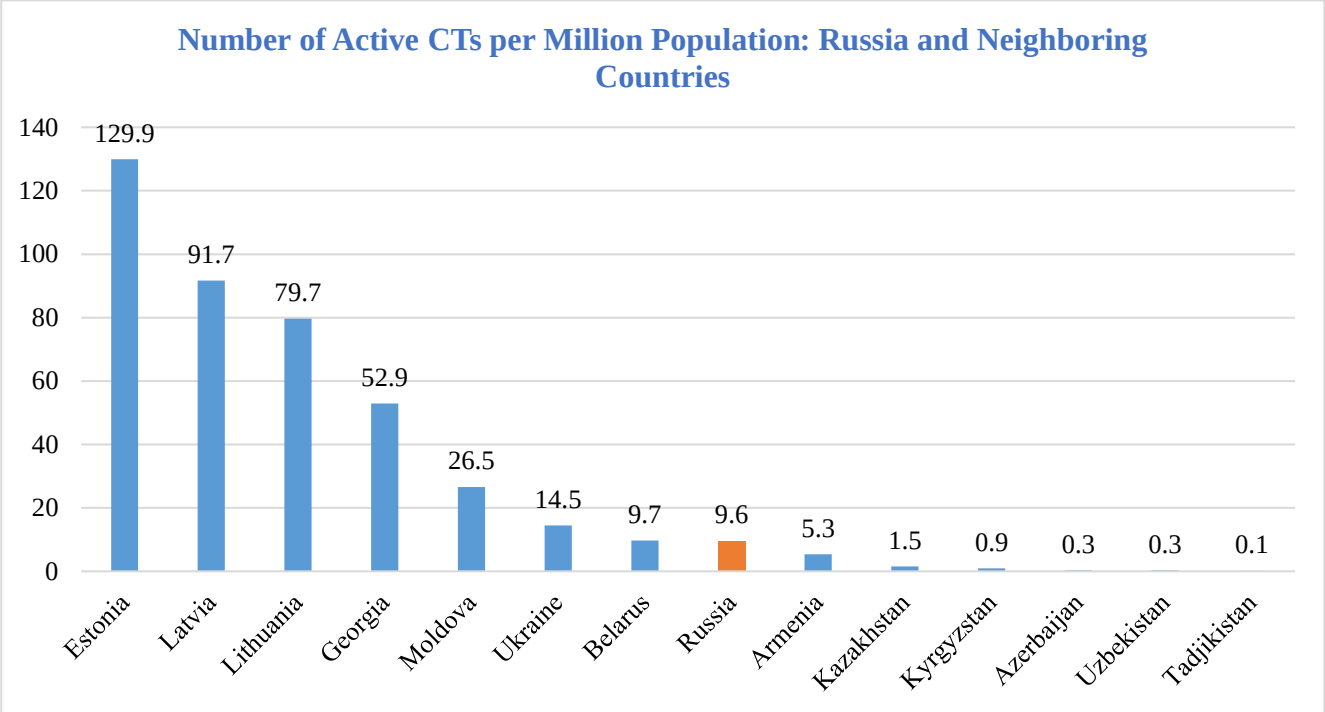
Data from www.clinicaltrials.gov; data from official statistical bodies of countries as of 01.01.2022

If we rank the countries according to the number of trials per million population (Diagram 10), the Baltic States are in the lead: Estonia (129.9), Latvia (91.7), Lithuania (79.7). This seems logical, since all three countries since 2004 are members of the European Union, have long been integrated and live under common European rules, which undoubtedly affects the choice of sponsors of these countries as participants in international projects.

The Baltic countries with a very good result of 52.9 trials per million population are followed by Georgia. Let us again be surprised and delighted by these figures, because ten years ago, when the clinical trials industry in Russia was long mature and developed, the industry in Georgia was only taking its first steps.

Next comes Moldova with 26.5 trials per million population, Ukraine with 14.5, Belarus with 9.7 and only behind, with an indicator of 9.6 is Russia. It should be understood that the clinical trials market in Belarus is by no means considered to be developed, but the country has managed to outperform Russia, even if only slightly, on this indicator. In assessing the Russian figures, though, a small caveat is necessary: we have some doubts as to whether the official statistics on Russia's population correspond to the true situation. There is reason to believe that the real population in the country is smaller, and has certainly declined substantially in the last six months. If our doubts are correct, Russia's figures may be slightly better than those presented. However, even if it outperformed Belarus, this would not change the overall picture.

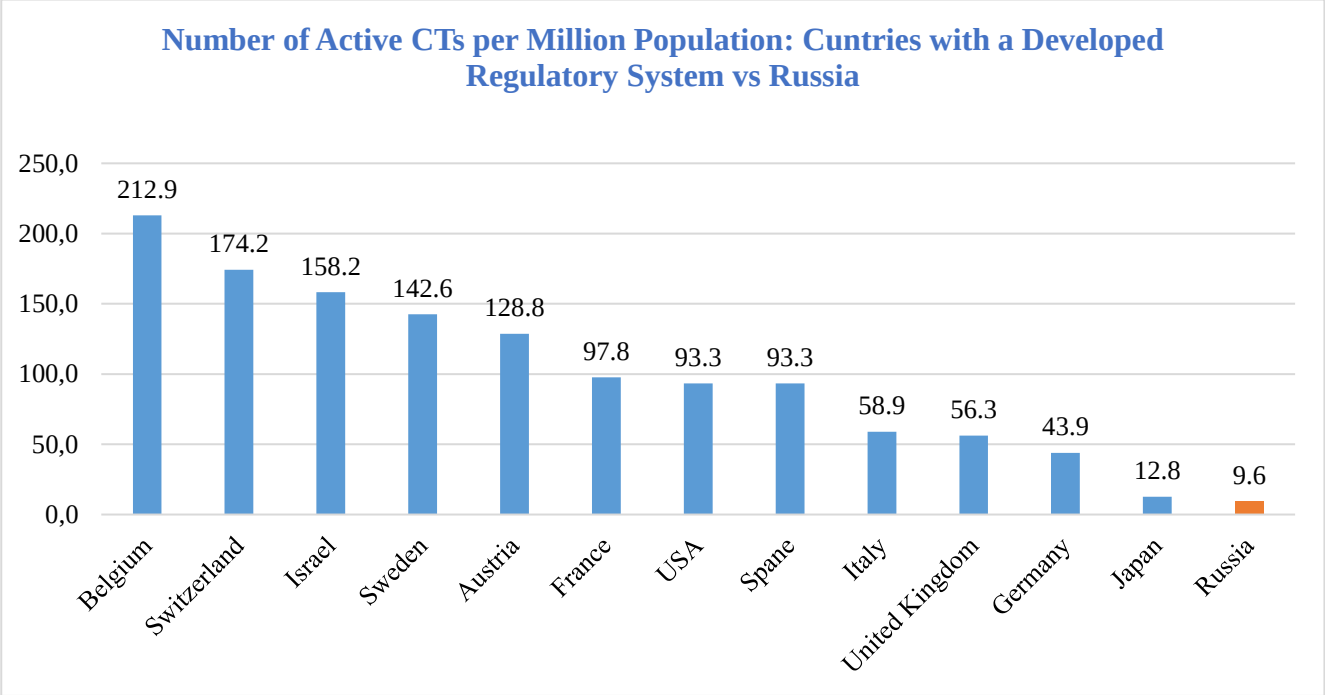
Diagram 10



Data from www.clinicaltrials.gov

For a visual comparison of the data presented with the situation in countries with a developed regulatory system, we also did a sample rating of some such countries, placing Russia in it for reference (Diagram 11).

Diagram 11



Data from www.clinicaltrials.gov

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When characterizing the clinical trials market in individual countries, the issue of the quality of the trials being conducted cannot be overlooked. The most convenient and accessible mechanism for evaluation in this case seems to be the use of the database of inspections conducted by the FDA on investigators from a particular country[1].

We searched by country and included the data obtained in the table (Table 9), the first part of which presents the results of FDA inspections in post-Soviet states, and the second part presents the results of inspections in some other countries of the world for general comparison. This data includes inspections conducted from 1 October 2008 to the present. Here we should stipulate that the FDA database used to include inspections for an earlier period, but it was changed at some time, and it is not available now.

To better understand the data, let's explain the classification used by the FDA:

NAI (No Action Indicated) – a result indicating that there are no comments;

VAI (Voluntary Action Indicated) – individual non-critical comments that do not require regulatory intervention, the correction of which is the responsibility of the investigator;

OAI (Official Action Indicated) – serious violations requiring FDA intervention or sanctions.

Thus, the higher the proportion of inspections with an NAI result, the better. When comparing results, it must be taken into account that FDA activity varies from country to country, so the total number of inspections carried out in a country must also be considered. The higher this number, the more accurate the overall assessment of the quality of trials conducted in the country.

Table 9

Comparative Table of the Results of US FDA Inspections, 2008, October - 2022, July							
Country	**Total number of FDA Inspections**	**NAI**	**NAI, % of Total**	**VAI**	**VAI, % of Total**	**OAI**	**OAI, % of Total**
Post-Soviet countries							
Georgia	**10**	**10**	**100.0%**	**0**	**0.0%**	**0**	**0.0%**
Belarus	**2**	**2**	**100.0%**	**0**	**0.0%**	**0**	**0.0%**
Russia	**63**	**50**	**79.4%**	**13**	**20.6%**	**0**	**0.0%**
Ukraine	**35**	**27**	**77.1%**	**8**	**22.9%**	**0**	**0.0%**
Latvia	**9**	**6**	**66.7%**	**3**	**33.3%**	**0**	**0.0%**
Estonia	**6**	**3**	**50.0%**	**3**	**50.0%**	**0**	**0.0%**
Lithuania	**4**	**2**	**50.0%**	**2**	**50.0%**	**0**	**0.0%**
Other countries of the world							
Japan	**31**	**27**	**87.1%**	**4**	**12.9%**	**0**	**0.0%**
Israel	**15**	**12**	**80.0%**	**3**	**20.0%**	**0**	**0.0%**
Finland	**4**	**3**	**75.0%**	**1**	**25.0%**	**0**	**0.0%**
Poland	**136**	**97**	**71.3%**	**39**	**28.7%**	**0**	**0.0%**
Belgium	**24**	**16**	**66.7%**	**8**	**33.3%**	**0**	**0.0%**
Germany	**90**	**60**	**66.7%**	**30**	**33.3%**	**0**	**0.0%**
Hungary	**40**	**26**	**65.0%**	**14**	**35.0%**	**0**	**0.0%**

[1] https://www.accessdata.fda.gov/scripts/cder/CLIIL/index.cfm

Spane	**51**	**33**	**64.7%**	**17**	**33.3%**	**1**	**2.0%**
Netherlands	**28**	**18**	**64.3%**	**10**	**35.7%**	**0**	**0.0%**
Czech Republic	**39**	**25**	**64.1%**	**14**	**35.9%**	**0**	**0.0%**
Italy	**57**	**36**	**63.2%**	**21**	**36.8%**	**0**	**0.0%**
France	**78**	**49**	**62.8%**	**29**	**37.2%**	**0**	**0.0%**
Denmark	**12**	**7**	**58.3%**	**5**	**41.7%**	**0**	**0.0%**
United Kingdom	**44**	**25**	**56.8%**	**19**	**43.2%**	**0**	**0.0%**
Sweden	**4**	**2**	**50.0%**	**2**	**50.0%**	**0**	**0.0%**
Austria	**13**	**5**	**38.5%**	**8**	**61.5%**	**0**	**0.0%**

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

Not all countries are included in the table: Armenia, Azerbaijan, Moldova, Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan and Uzbekistan did not have FDA inspections during this period.

As the above data clearly show, the results of FDA inspections of investigators' activities from post-Soviet states are no less good, and often even better, than those of their colleagues from other countries.

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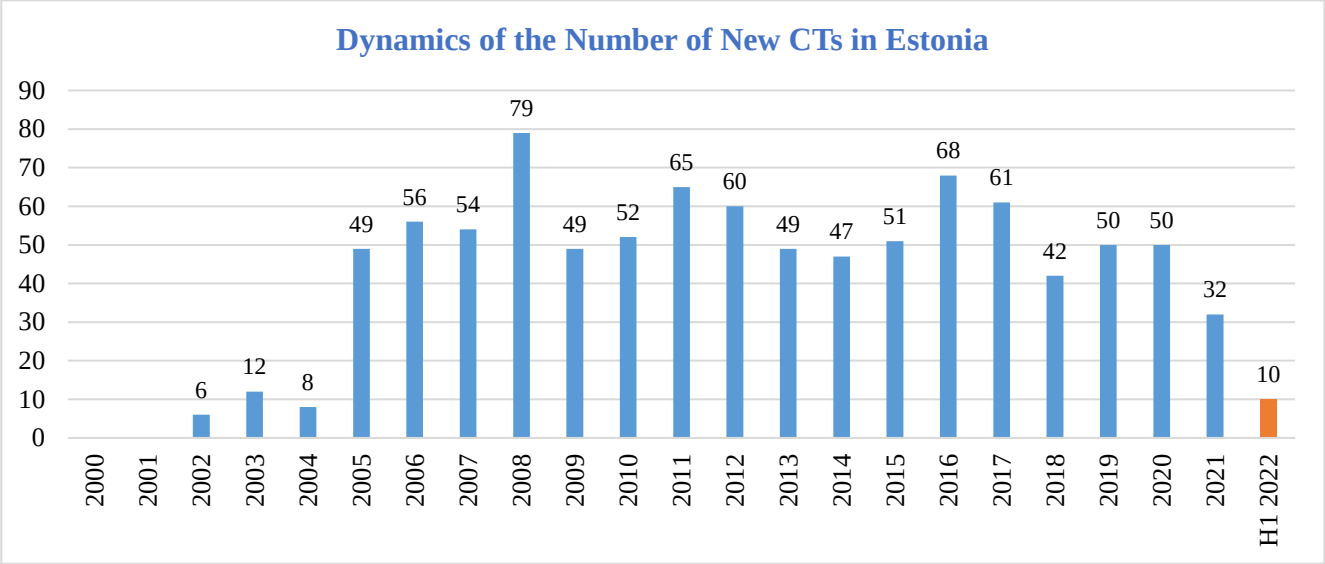
It is also interesting to look in retrospect at how the post-Soviet states came to their current state of the clinical trials market. To do this, we decided to track how the number of new clinical trials varied by country from year to year. ClinicalTrials.gov registry statistics were used, with values corresponding to the number of interventional trials that first appeared in the database ("first posted") between 1 January and 31 December of the respective year.

The market for clinical trials started to form earliest (approximately from the beginning of the 2000s) in the Baltic States, Russia and Ukraine.

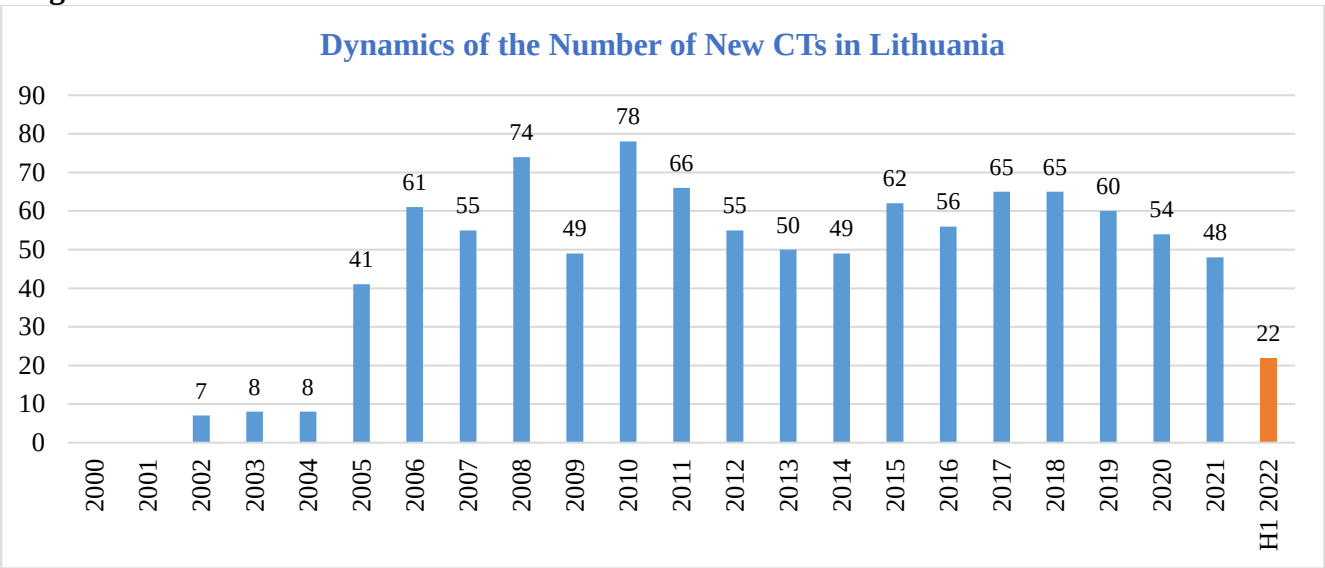
The graphs of all three Baltic countries (diagrams 12–14) are similar to each other: a small number of trials in the first years of formation, then a noticeable growth and then slight fluctuations from year to year. The average number of trials conducted in all three countries is also comparable with each other. The maximum values were observed in Estonia in 2008 (79 trials) and 2016 (68), in Lithuania in 2010 and 2008 (78 and 74 trials, respectively), in Latvia in 2015 and 2007 (65 and 64 trials). It is worth noting that some of the decline observed in 2013–2014 was global in nature and was noticed by us back then. In the last few years, the number of trials in all three countries has also been decreasing slightly. It is likely that further development of the markets is hindered to some extent by the relatively low population size: as we remember from Diagrams 10 and 11, the number of active trials per million population in the Baltic States is quite comparable with that of the developed European countries.

Diagram 12



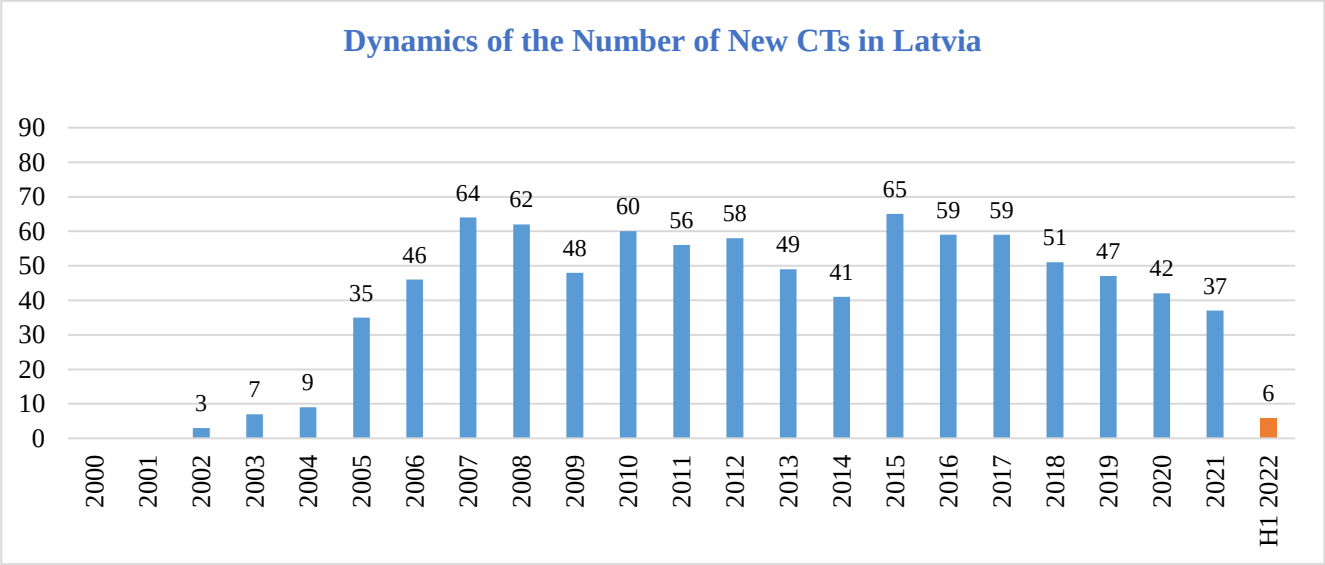
Data from www.clinicaltrials.gov

Diagram 13



Data from www.clinicaltrials.gov

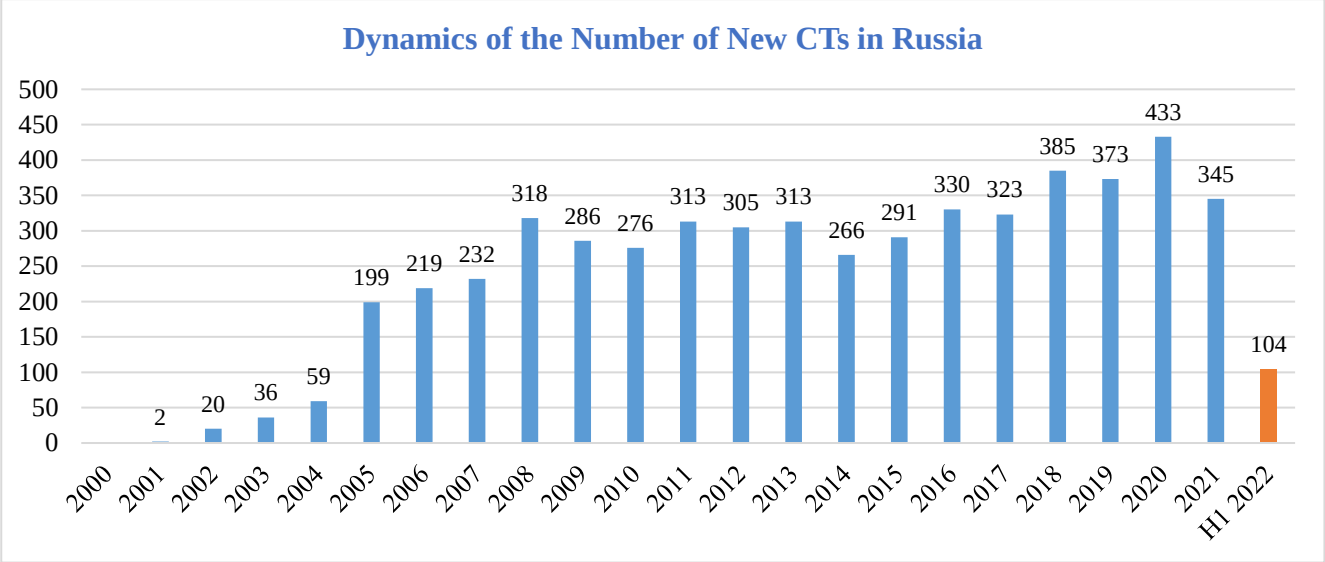
Diagram 14



Data from www.clinicaltrials.gov

Diagram 15 shows the evolution of the number of trials in Russia. Here we also see an initial progressive growth up to 2008, then a slight decline and growth again, a dip in 2014 and a new growth. The maximum number of trials was in the pandemic year 2020, with 433 new projects in the ClinicalTrials.gov registry database. And remembering the data in Diagram 4, judging by the indicators of the first four months of this year, we can assume that it could well become a record for Russia. It could have been, but it all went down the drain. As a result, given the size of the population, Russia's enormous potential in the field of clinical trials has never been fully realized, at least not in this historical period.

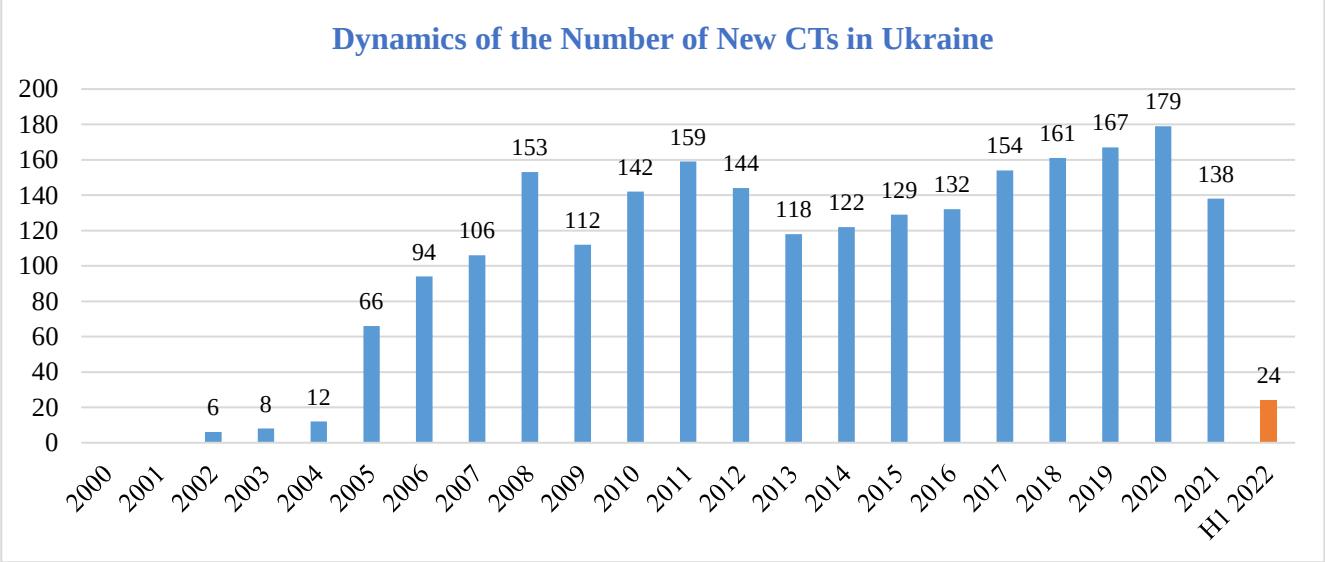
Diagram 15



Data from www.clinicaltrials.gov

The performance of the Ukrainian market (Diagram 16) showed similar trends – a small increase in the first years, and then, starting in 2005, a breakthrough growth in the number of trials. Excellent figures in 2008 (153 trials). Then some decline in 2009 and 2013, followed by a resumption of growth until 2020, when a historical high of 179 trials was reached. The results of 2022 are still difficult to predict. It is clear that due to the military conflict, a failure in the normal functioning of the sector is inevitable. But as noted above, unlike Russia, the Ukrainian market has much better prospects for speedy recovery.

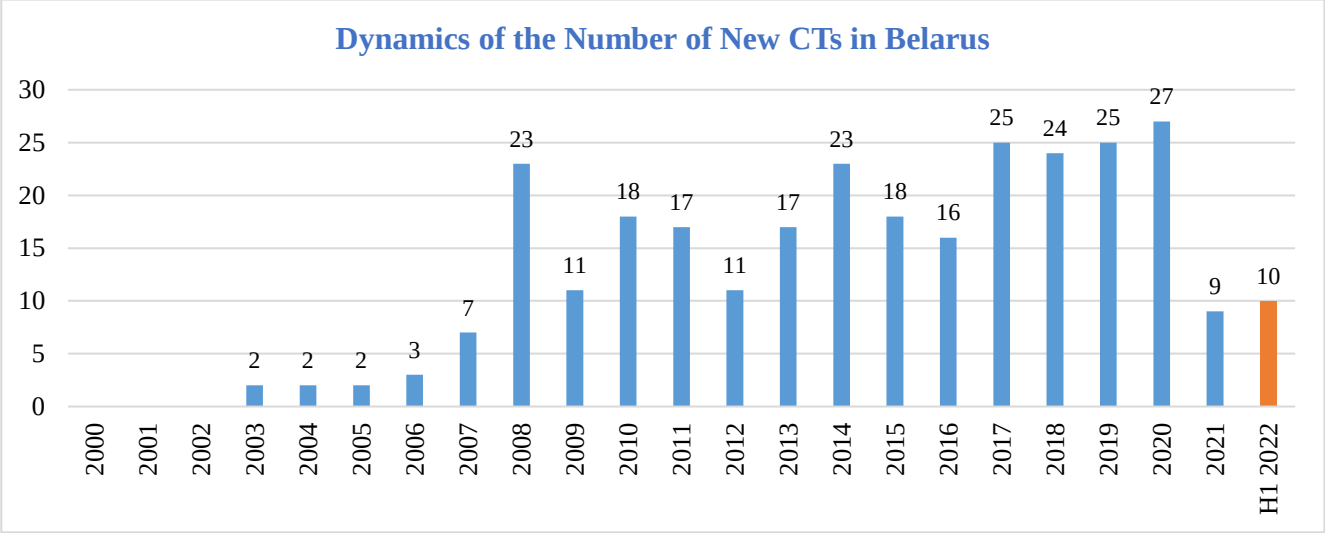
Diagram 16



Data from www.clinicaltrials.gov

The market performance of the Republic of Belarus looks quite unstable (Diagram 17). Attempts to "launch" the market in Belarus began about the same time as in the previously described countries. Unfortunately, this was never fully achieved. Despite the interest in the country on the part of a number of sponsors and contract clinical trial organizations, the development of the industry was hampered by serious restrictions on economic activity and rigid administrative management, typical for the country as a whole. For example, for many years in Belarus it was expressly forbidden to enter into a contract directly with investigators, only through the sites. There was also an attempt to adjust tariffs. It is clear that the investigators were totally unmotivated to do the work that the government assigned them, while limiting their ability to receive fair pay for their work. In the last few years, this problem seems to have been solved. But it was too late. As we can see, the number of new trials in the country has not risen above 25–27. Now the fate of the clinical trials market in Belarus is likely to be the same as in Russia.

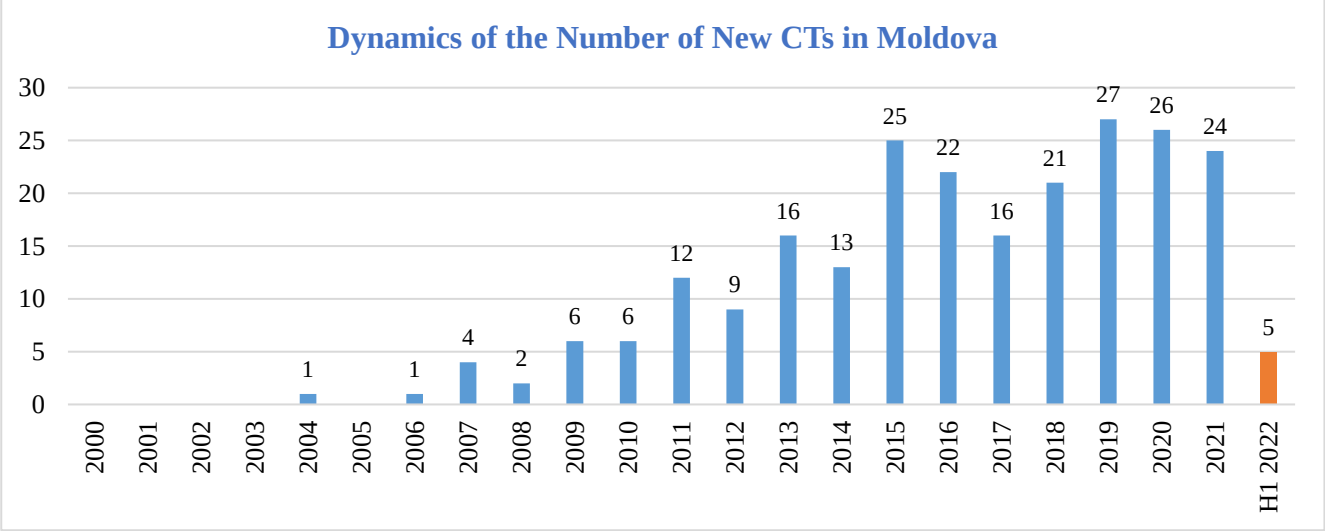
Diagram 17



Data from www.clinicaltrials.gov

We know almost nothing about how the Moldovan market developed. Usually this country is considered in the cluster of East European countries and, as we can see in the diagram (Diagram 18), until 2015 the country saw some growth in the number of trials, although this growth has not been equally stable each year. But the number of trials in the country never became significant, being limited to a maximum of 27 trials in 2019. Who knows, maybe now, as a result of the Russian and Ukrainian market crisis, the Moldovan market will get a new impetus for development.

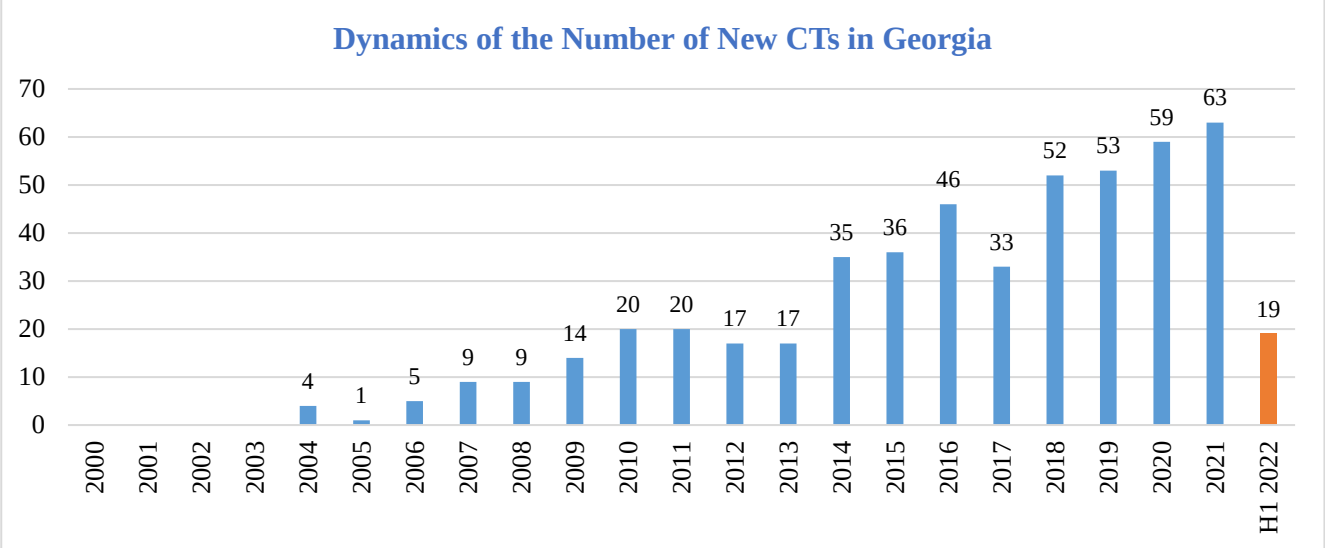
Diagram 18



Data from www.clinicaltrials.gov

The market development history of Georgia is extremely interesting (Diagram 19). The evolution of the new trials number in this country looks as if its formative period is not over and the country's potential is far from exhausted: since 2005 Georgia has demonstrated an almost constant growth in the number of new trials. Every five years their average number doubled: 11 in 2006–2010, 25 in 2011–2015, and 49 in 2016–2020. The maximum is in 2021 – 63 trials. Only 2012–2013 and 2017 fell out of the general trend and showed a slight decrease, which in general does not spoil the overall positive picture. Judging by the requests from sponsors, interest in the country is indeed high, despite its relatively small population (3.7 million). Reasonable local regulation and relatively short approval times contribute to this. Companies also note the high motivation of investigators and good patient enrolment. We can only be happy for our Georgian colleagues and wish them further development of the industry.

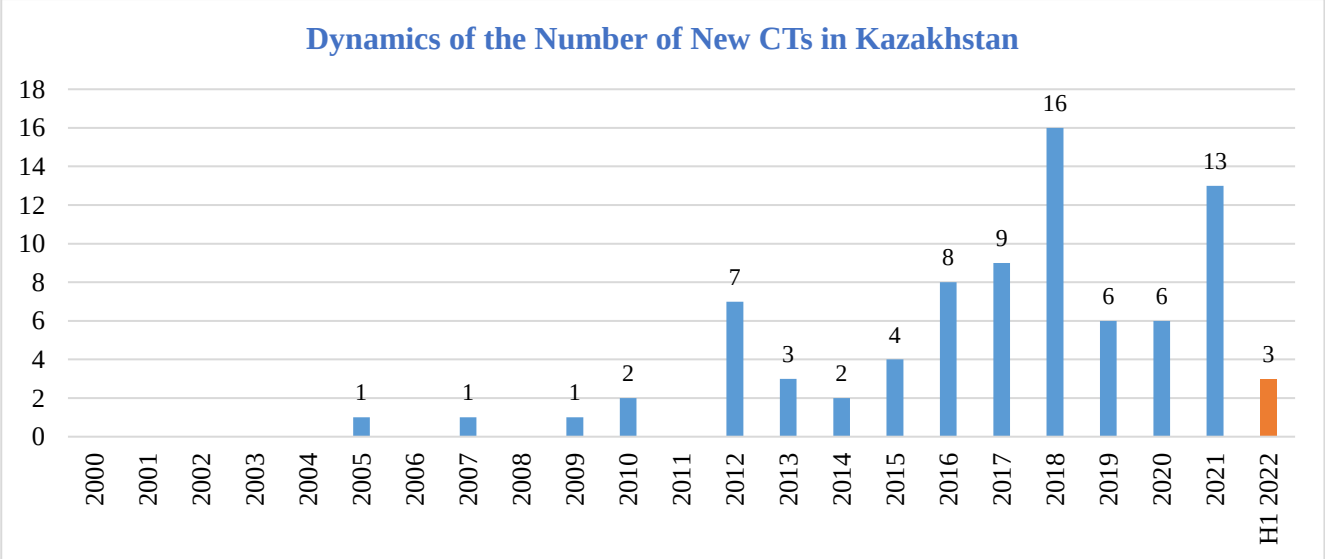
Diagram 19



Data from www.clinicaltrials.gov

For other countries, it is problematic to give a holistic description of market performance, because with a very small number of new trials per year, random fluctuations are too noticeable. But it cannot be overlooked that of these countries in our sampling, which are not yet active in clinical trials, Kazakhstan appears to have good prospects (Diagram 20).

Diagram 20



Data from www.clinicaltrials.gov

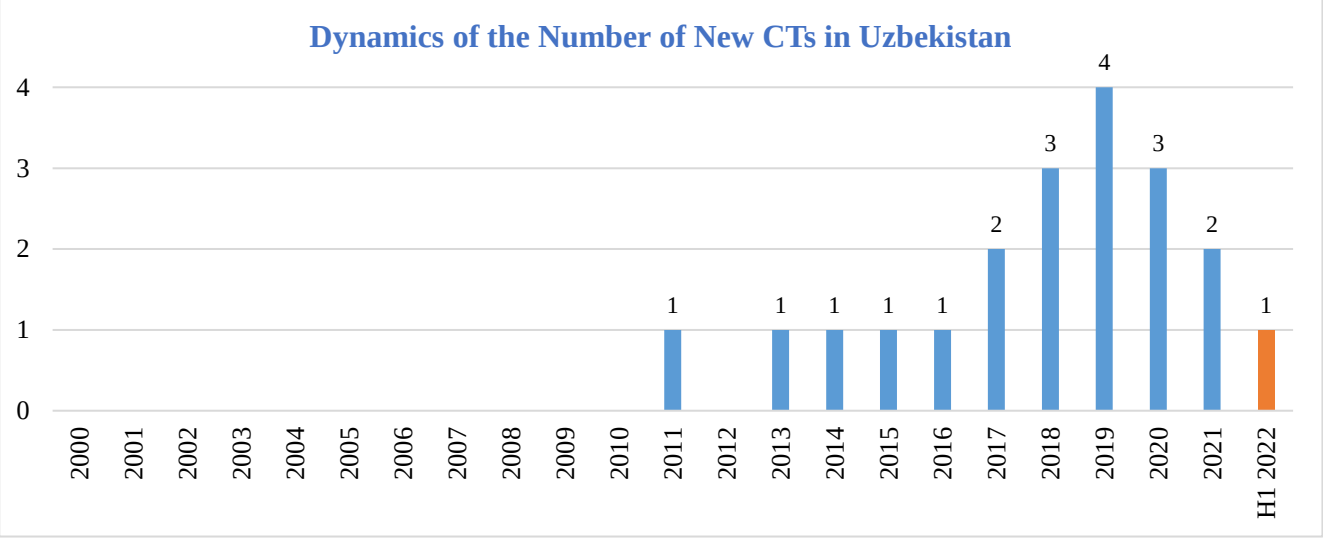
Attempts to develop the industry have long been made in Kazakhstan, as can be seen from the diagram. A state with a population of 19.5 million people is potentially interesting for large

pharmaceutical companies. But in the early years, attempts to launch the market were not entirely successful. The lack of clear sectoral laws was a hindrance. For example, for a number of years the export of biological materials was not regulated in the country, with the result that sponsors were unable to export samples to central laboratories. This problem was subsequently solved, but there was still no rapid growth. The country was not well known and perhaps not fully trusted. Thus, Kazakhstan "missed" its start at a time when many other post-Soviet states, already described above, were beginning to actively develop the industry. However, being "on the sidelines" of the process, Kazakhstan has not stood still – thanks to its accession to the EAEU, the country has adopted sectoral laws that is broadly harmonized with international laws and is based on the ICH GCP. Subsequent events in the form of the collapse of the two leading markets in Russia and Ukraine seem to have opened up new prospects for Kazakhstan. This includes the already mentioned membership in the EAEU, which allows, after conducting studies of a drug in Kazakhstan, to register it in other members of the Union. And a sufficiently high level of standards of medical care necessary for the country's participation in international projects. And the potential openness of Kazakhstan to the migration of industry professionals. And it seems that the leadership of the country understands this, as can be judged by a number of initiatives to develop the pharmaceutical industry. The general reset in the social, economic and political spheres announced by Kassym-Jomart Kemeluly Tokayev, President of Kazakhstan, after the events of January 2022 should also be noted. The impression that the country is ready to create a favorable environment for foreign investment was reinforced during ACTO's visit to Kazakhstan in June 2022 and talks with representatives of regulatory bodies, professional associations and research centers.

But it cannot be ruled out that in the coming years, the opportunities that are opening up because of the Russian market transformation can be successfully used by other countries, those that have not yet stolen the show.

For example, during our trip to Kazakhstan, we learned that the country is competing with Uzbekistan for the role of Central Asia's leading pharmaceutical cluster. In particular, in the beginning of 2022 the President of the Republic of Uzbekistan adopted a decree "On additional measures for accelerated development of pharmaceutical industry of the Republic in 2022–2026", which separately mentions the issue of clinical trials development. For us this was surprising, initially we did not consider Uzbekistan as a serious contender to enter the clinical trials market: we remember that on the international map of clinical trials this country is practically absent (Diagram 21). Since 2011, only a few studies have been initiated in the country. But perhaps we were wrong. Given its large population of 35.6 million, Uzbekistan has undeniable potential. However, we do not yet know anything about the local laws, and we cannot say to what extent it allows the country to fit into the international process.

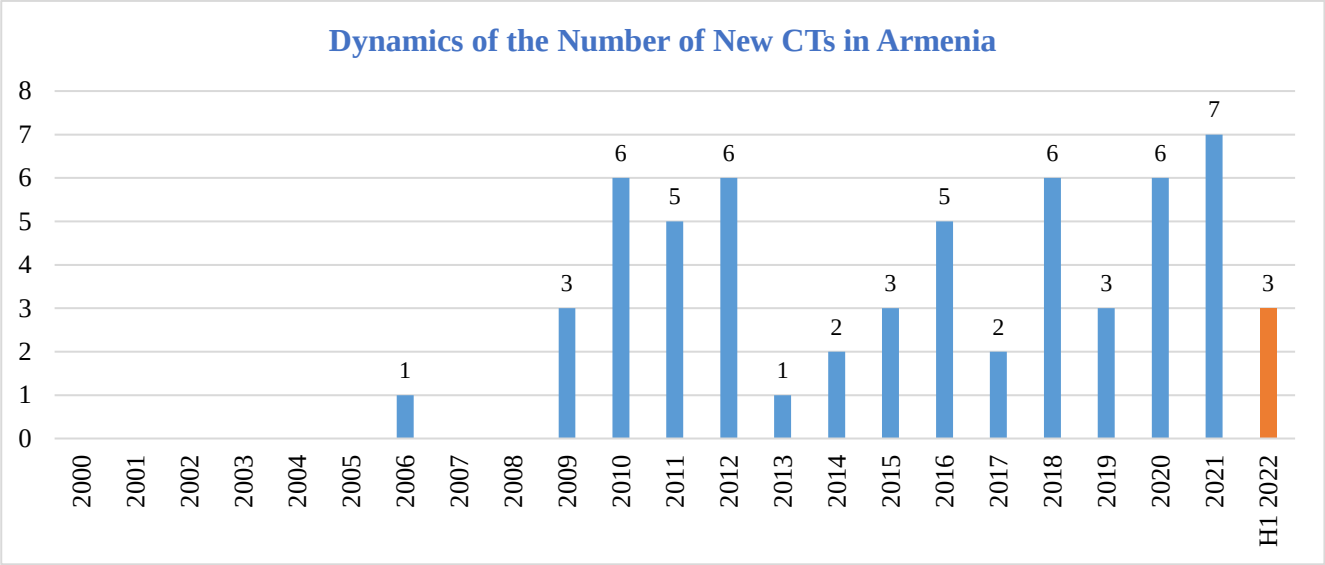
Diagram 21



Data from www.clinicaltrials.gov

It is probably worth saying a few words about two other countries that are members of the EAEU, along with Belarus, Kazakhstan, and Russia: Armenia and Kyrgyzstan. Both countries are still new to clinical trials. Armenia has already begun to take its first, still timid steps (Diagram 22); the number of new studies in this country does not yet exceed seven, but there is some stability.

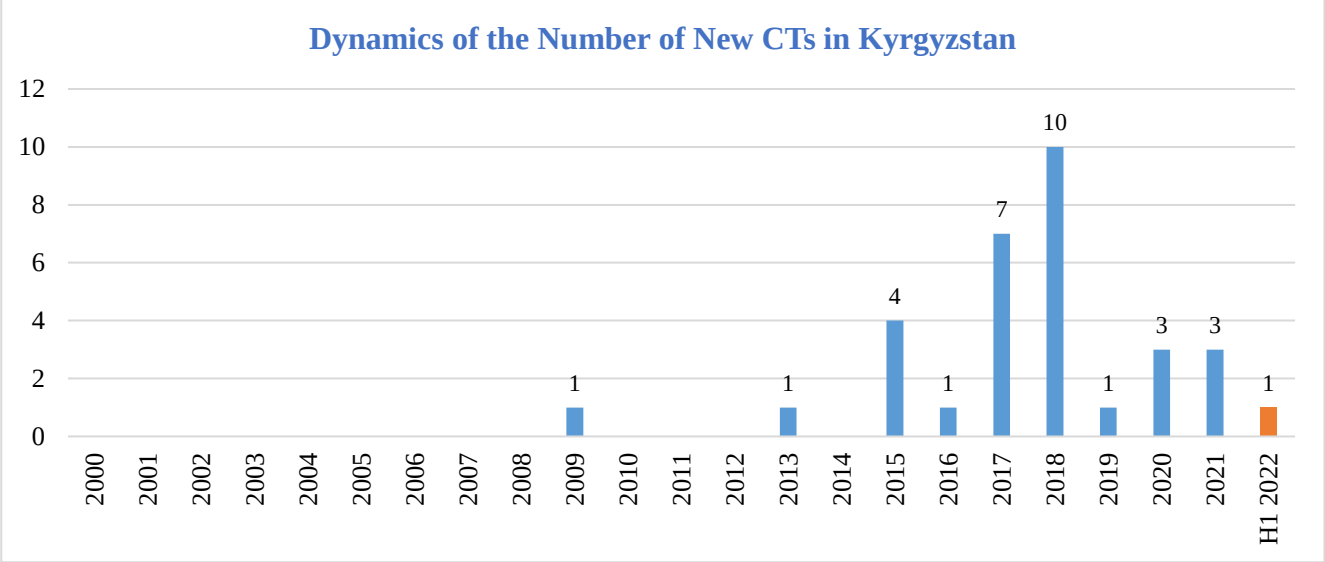
Diagram 22



Data from www.clinicaltrials.gov

Kyrgyzstan started later than many other post-Soviet states. The first study in this country appears in the ClinicalTrials.gov database only in 2009, the second only in 2013. But in 2017–2018, there was a spike - seven and ten new trials, then, just in time for the pandemic, there was again a lull. Given the historical proximity to Kazakhstan, we believe that the prospects for the development of the industry in Kyrgyzstan largely depend on the extent to which the stated ambitions of its larger neighbor can be realized.

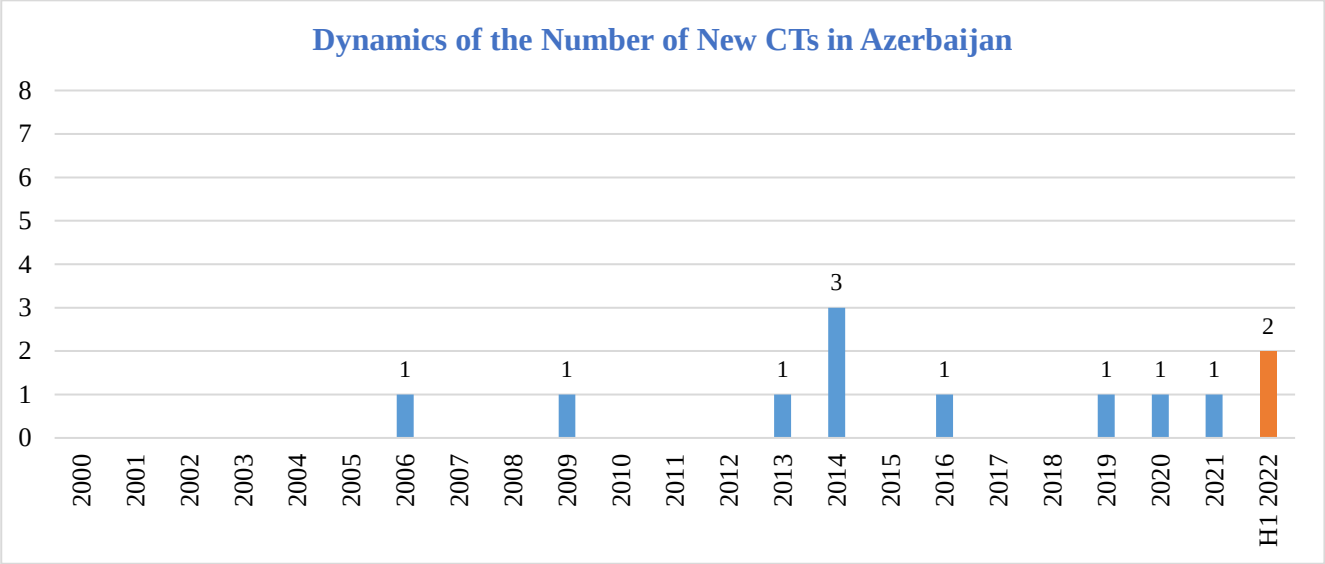
Diagram 23



Data from www.clinicaltrials.gov

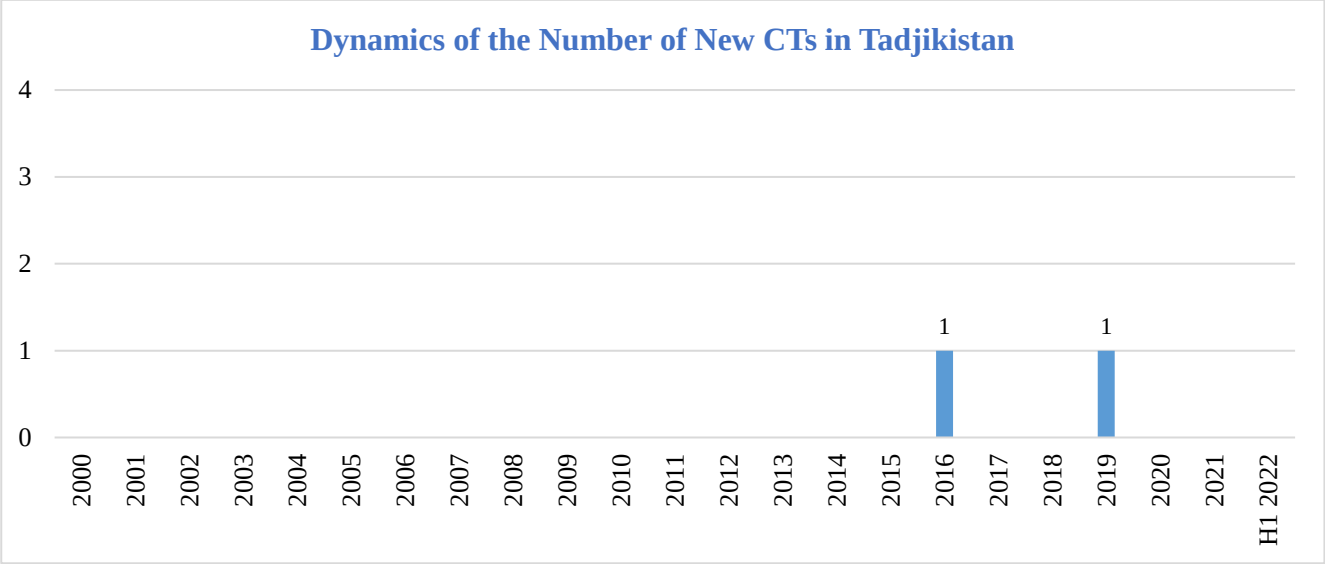
The remaining two countries on our list, Azerbaijan and Tajikistan, have very little to say about themselves in the field of clinical trials; their experience includes only sporadic projects (Diagrams 24 and 25, respectively). Finally, another post-Soviet state, Turkmenistan, has not yet been included in the ClinicalTrials.gov database.

Diagram 24



Data from www.clinicaltrials.gov

Diagram 25



Data from www.clinicaltrials.gov