ACTO

Association of Clinical Trials Organizations

ACTO NEWSLETTER № 29

1st Half of 2024

MOSCOW 2024

CONTENTS

SUMMARY

In the first half of 2024, the Ministry of Health of the Russian Federation issued 251 approvals to conduct clinical trials of all types. This is the lowest figure since 2012. In the period 2012–2023, the total number of approvals issued in a half-year did not fall below 300.

The number of new international multicenter clinical trials (IMCTs) after February 2022 fell from an average of 140.8 in the first half of the five pre-war years (2017–2021) to ten or less. In the first half of 2024, there are only eight new IMCTs, and five of them are launched by Russian sponsors. Before the war, IMCTs accounted for approximately 40% of the Russian clinical trials market; in the first half of 2024, this share was 3.2%.

In the first half of 2024, foreign sponsors received 13 approvals for local projects, which is slightly less than the 15.8 average for the first half of 2017–2021. Foreign sponsors received 23 approvals for bioequivalence studies, which is also lower than the pre-war average of 31.8. In 2012–2021, bioequivalence studies by foreign sponsors accounted for approximately 12% of all approvals, and their local projects for another 6%. In the first half of 2024, these shares amounted to 9.2% and 5.2%, respectively.

Since 2022, the geography of countries from which foreign sponsors come who want to start local trials in Russia, including bioequivalence studies, has begun to change. In 2021, European companies accounted for almost half of new projects of this type (45.7%), while the share of Indian companies was closer to a quarter (27.6%), but by the end of 2023 they had switched places. In the first half of 2024, Indian sponsors accounted for 45.5% of new local trials, while all European sponsors accounted for 24.2% in total. Another 12.1% of approvals were received by companies from Belarus (in 2021 it was slightly less, 10.5%), 9.1% — by sponsors from Iran (in 2021, they were not present in the Russian market).

The number of approvals issued to Russian sponsors for local trials in the first half of 2024 amounted to 56. The average indicator for the first half of 2017–2021 for this type of trials was 62, meaning that activity in this sector has also decreased somewhat. At the same time, the share in the total market volume has changed little: before the war it was about one fifth, and in the first half of 2024 it was 22.3%.

Russian sponsors received 151 approvals for bioequivalence studies, which is almost twice as many as the 77.6 average for the first half of 2017–2021. This market segment began to grow around the second half of 2020, and the outbreak of the military conflict did not slow down its growth: in 2021–2023, the results for the half-year always exceeded the results for the same period of the previous year. However, the figure for the first half of 2024 was a third lower than for the same period in 2023 (151 to 227), which may indicate that the growth potential for this type of studies has been exhausted. Their share has become the largest in the market in recent years, against the backdrop of a decline in other types of studies: 60.1% in the first half of 2024, compared to approximately 20% in the pre-war period.

An analysis of the distribution of issued approvals by therapeutic areas shows that in the IMCT sector, the most popular was oncology (three out of eight studies, 37.5%), and in local studies of generics and biosimilars — cardiology and cardiovascular diseases (11 out of 33 protocols of foreign sponsors, i.e. 33.3%, and 32 out of 181 Russian, i.e. 17.7%). The most popular substance among manufacturers of generic drugs in the first half of 2024 was amlodipine — it was included in five protocols, separately and in combinations. In local trials of original drugs from Russian developers, neurology was the leader among therapeutic areas (five out of 24 protocols, i.e. 20.8%). Foreign sponsors have received only two approvals for local testing of original drugs, one in the field of infectious diseases, the other in the field of oncology.

Among other things, in this issue the reader will find a story about how officials, in order to satisfy the plans set before them, are trying to radically change the established processes of conducting studies. The continued survival of an already seriously damaged pharmaceutical sector is at stake.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

It is quite difficult to choose the intonation to describe the clinical trials market in Russia in mid-2024. Immediately after the war began, the market experienced a breakdown, a rupture of connections and a whole series of more specific, but also dramatic changes, which set an alarming tone for the description of these transformations in our newsletters. But now, two and a half years later, a paradoxical situation has arisen. On the one hand, no sharp changes are occurring over short periods of time, and it would seem that we can move on to the ordinary monotonous listing of small discrepancies between the results of the first half of 2024 and the same period of the previous year. But, on the other hand, the whole situation remains deeply anomalous and extraordinary. The market, limited in its activity by military action and economic sanctions, has frozen in an unnatural position. To describe it neutrally without any special qualifications would be to pretend that everything has returned to normal, albeit some kind of "new normal," but that would be deceiving the reader. No, there is no new normal, it's just that the emergency that began in February 2022 has dragged on, and the market continues to exist within it in some distorted form. We describe this distorted form and its variations in our newsletters of recent years. We ask readers to remember this and not to succumb to the illusion of "stabilization."

To make it easier to keep the context, in Table 1 the key indicators for the half-year are compared not only with the same period of the previous year, as we usually do, but also with the results of the first half of 2022, which became a transitional period between the normal and abnormal state of the market, since approvals continued to be issued for applications submitted before the start of the war, as well as with the average results of January-June for the five pre-war years, 2017-2021, when the market was still functioning in normal mode.

Table 1

Approvals for Conduct Clinical Trials: H1 2024 vs H1 2023 vs H1 2022						
Year	**Total**	**International Multicenter CTs**	**Local CTs (Foreign Sponsors)**	**Bioequivalence Studies (Foreign Sponsors)**	**Local CTs (Local Sponsors)**	**Bioequivalence Studies (Local Sponsors)**
H1 2024	251	8	13	23	56	151
H1 2023	341	10	8	46	50	227
H1 2024 vs H1 2023, %	-26.4%	-20.0%	62.5%	-50.0%	12.0%	-33.5%
H1 2022	425	111	10	43	90	171
H1 2024 vs H1 2022, %	-40.9%	-92.8%	30.0%	-46.5%	-37.8%	-11.7%
The average number of approvals issued in H1 2017-2021	328	140.8	15.8	31.8	62	77.6
H1 2024 vs The average number of approvals issued in H1 2017-2021, %	-23.5%	-94.3%	-17.7%	-27.7%	-9.7%	94.6%

Data from www.grls.rosminzdrav.ru

In the first half of 2024, the Ministry of Health of the Russian Federation issued 251 approvals to conduct clinical trials. This is 26.4% less than the figure for the first half of 2023 (341 approvals[1]), 40.9% less than in the first half of 2022 (425 approvals) and 23.5% less than the average issued for the same period in 2017–2021 (328 approvals). Thus, the first half of 2024 is characterized by a decrease in overall activity in the Russian clinical trials market compared to similar periods of at least the previous seven years. But, as it will be seen below in Diagram 1, this statement is also true for an earlier period.

[1] The 2023 figures presented in this issue of the ACTO Newsletter differ slightly from those published in the 2023 H1 Newsletter, as the data were adjusted at the end of 2023.

The number of new international multicenter clinical trials (IMCTs) in the first half of 2024 was 20% lower than in the first half of 2023: eight new projects versus ten. But we must not lose sight of the fact that this is very significant, 92.8% less than in the first half of 2022, when 111 approvals of the same type were issued (most of them never started[2]) and 94.3% less than the average result for the first half of 2017–2021 (140.8 approvals).

It is also worth recalling that in the ACTO newsletters we classify as IMCT only those trials the information of which is posted in international databases[3]. In the register of the Ministry of Health of Russia for the first half of 2024, 12 studies have the status of IMCTs, but only eight of them meet our criteria; we consider the remaining four in this issue as local.

The number of approvals received by foreign sponsors for local trials amounted to 13, which is 62.5% more than the figure for the first half of 2023 (eight), 30% more than the figure for the first half of 2022 (ten), and 17.7% less than the average in January-June 2017–2021 (15.8 new protocols). The number of bioequivalence study approvals issued to foreign sponsors in the first half of 2024 is 23, which is 50% less than in the first half of 2023 (46), 46.5% less than the results of the first half of 2022 (43) and 27.7% less than the average for the first half of the year in 2017–2021 (31.8 new projects).

The number of approvals for local trials by Russian sponsors was 56, which is slightly, 12%, higher than the figure for the same period in 2023 (50 approvals), but at the same time 37.8% less than in January-June 2022 (there were 90), and 9.7% less than the average for January-June 2017-2021 (62 exactly).

The reduction in the number of approvals issued to Russian sponsors for bioequivalence studies is noteworthy: 151, 33.5% less than in the first half of 2023 (227 approvals) and 11.7% less than in the first half of 2022 (171 approvals). Only comparison with the average for the first half of 2017–2021 (77.6 approvals) shows an increase of 94.6%. The reduction is noteworthy because, firstly, this market segment has been the largest since 2022, and secondly, it grew rapidly in 2021–2023. The results for the first half of 2024 suggest that this growth has stopped. Further observations will help to understand whether this is true.

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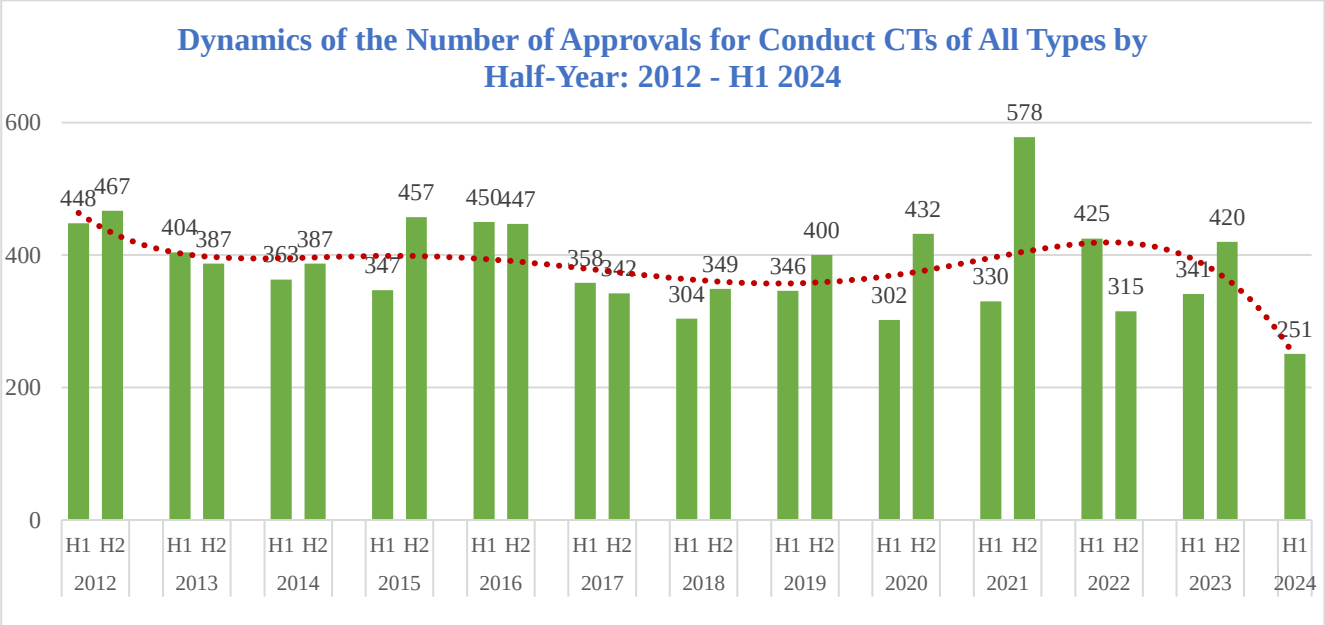
Diagrams 1–6 show the dynamics of the number of approvals by half-year starting in 2012 for studies of all types in total (diagram 1) and for each type separately (diagrams 2–6). The data is supplemented with a trend line that smooths out fluctuations.

Diagram 1 shows that 251 approvals is the minimum figure for the half-year; in the period 2012–2023 it did not fall below 300. The diagrams below will help you understand which types of studies are contributing to the decline in overall industry activity.

[2] See the newsletters with the results of the first half of the year and the overall results for 2022.
[3] ClinicalTrials.gov, EU Clinical Trials Register and CTRI.NIC.in.

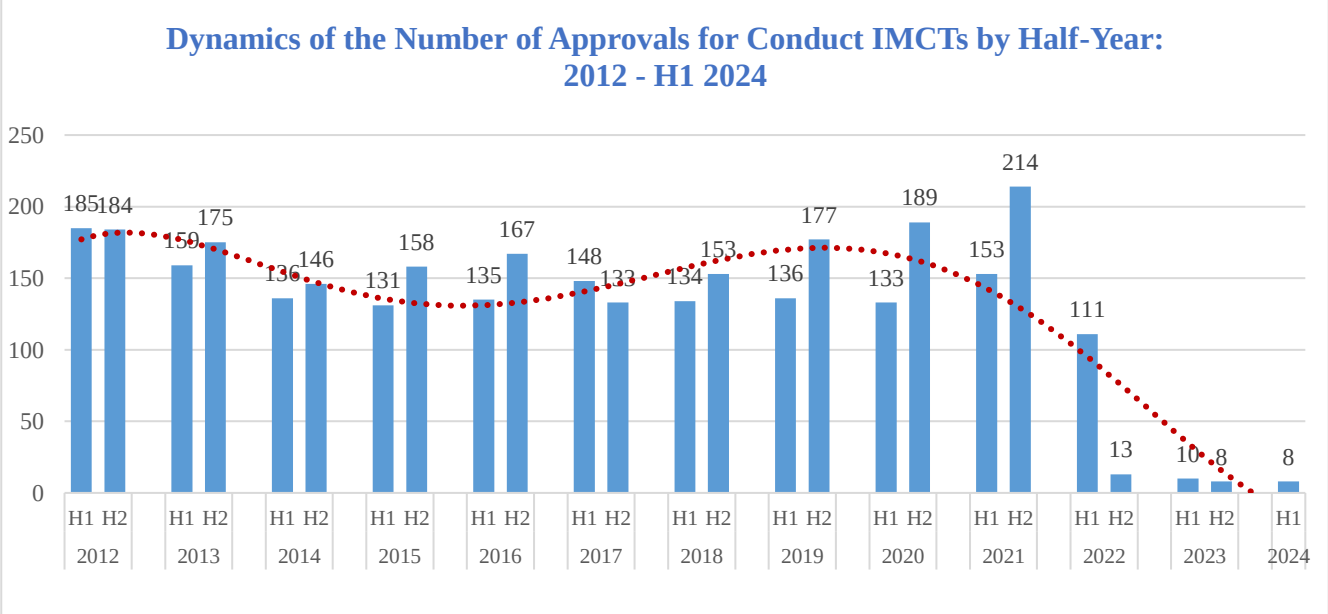
Diagram 1



Data from www.grls.rosminzdrav.ru

The number of new IMCTs, as shown in Diagram 2, fell sharply after the start of the war and, although approvals for which applications were submitted before 24 February 2022 continued to be issued, overall, this market segment has shrunk significantly and from the second half of 2022 to the first half of 2024 shows the lowest figures in the period of ACTO observations. Before the war, IMCTs accounted for approximately 40% of the Russian market (see Diagram 7 below), so the loss of these studies has a very noticeable impact on the overall level of activity in the field of clinical trials in Russia.

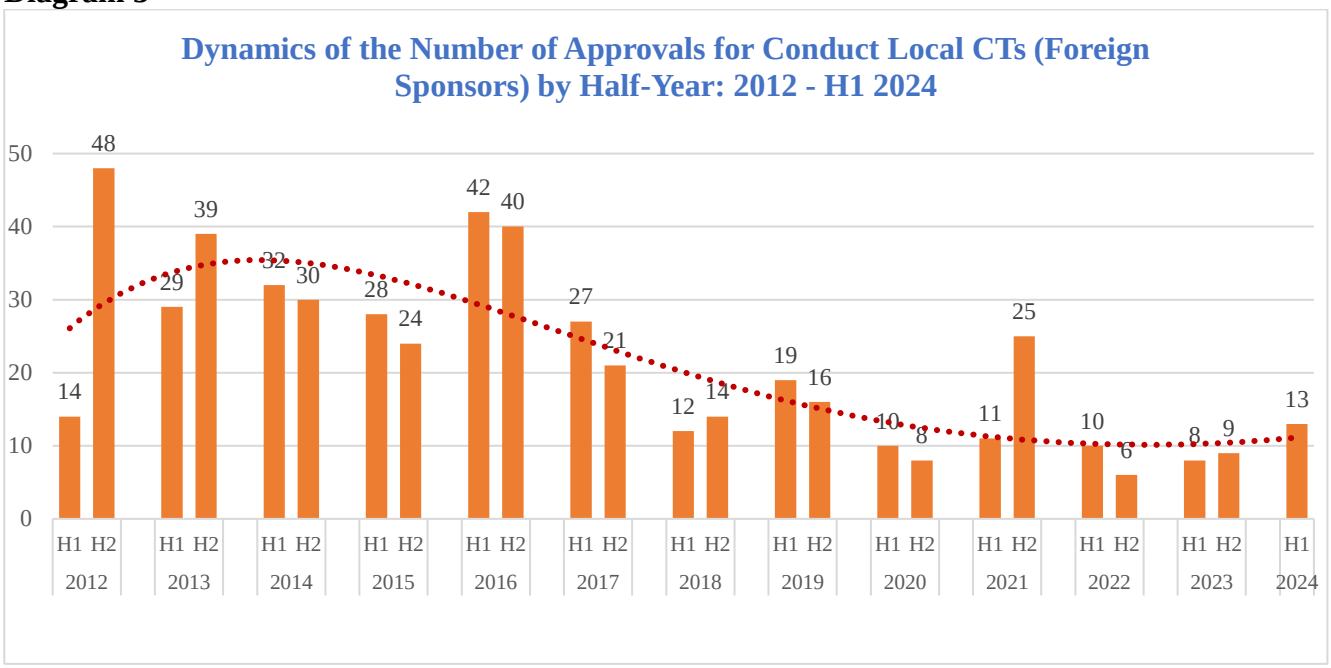
Diagram 2



Data from www.grls.rosminzdrav.ru

Local trials by foreign sponsors, although not as dramatic as IMCTs, also declined with the start of the war and remain at low levels (Diagram 3). A slight increase in activity in the first half of 2024 compared to the same periods in 2023 and 2022 occurs against the backdrop of a change in the geography of foreign sponsors who are declaring their readiness to conduct studies in Russia. In particular, Iranian companies entered the local market in 2023 (see details below in the section on therapeutic areas).

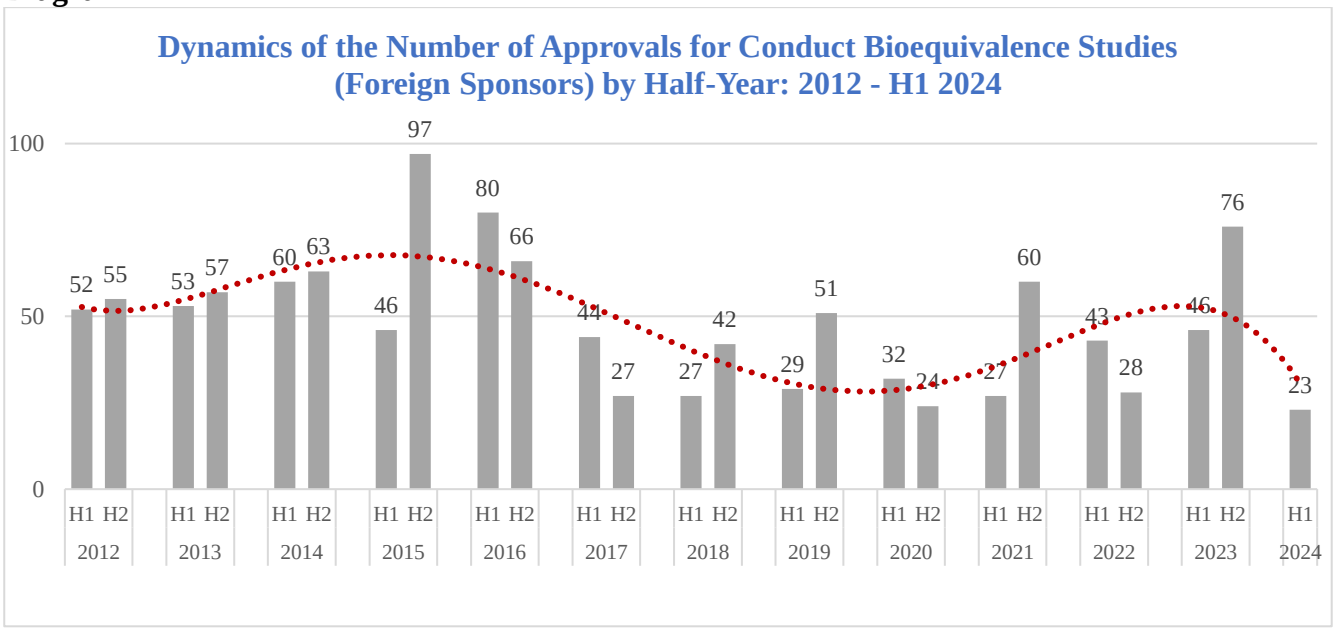
Diagram 3



Data from www.grls.rosminzdrav.ru

The number of approvals issued to foreign sponsors for bioequivalence studies in the first half of 2024 (23 studies) is lower than any other half-year indicator in the 2012–2024 period. The closest result was during the pandemic: 24 approvals in the second half of 2020. Before the war, bioequivalence studies by foreign sponsors accounted for about 12% of the market, and their reduction, although less than IMCTs, also affects overall activity.

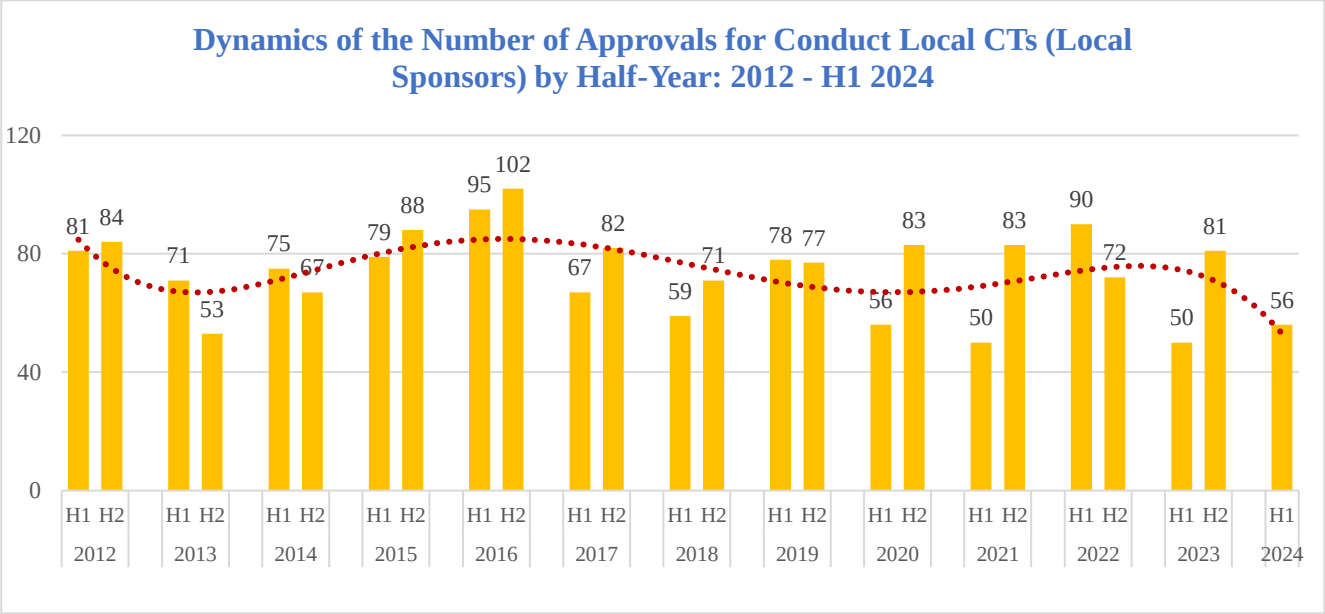
Diagram 4



Data from www.grls.rosminzdrav.ru

In the first half of 2024, Russian sponsors received more approvals for local trials than in the same period of the previous year, but still less than the average for the half-year in 2012–2023 (the average is close to 75), and since this type of studies accounts for about one-fifth of the market, below-average activity negatively affects the overall picture.

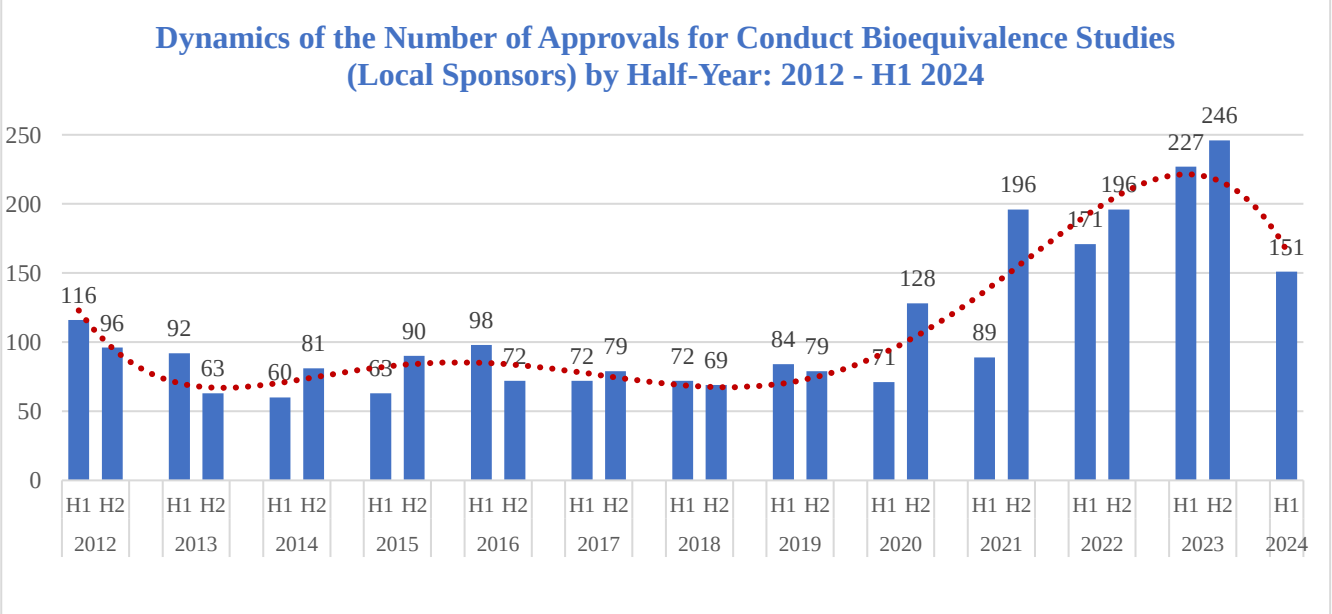
Diagram 5



Data from www.grls.rosminzdrav.ru

In 2012–2020, Russian sponsors were issued an average of 82.5 approvals per half-year to conduct bioequivalence studies. There was a surge in 2021–2023, clearly visible in Diagram 6, with an average of 187.5 over the half-year. The growth of this segment in 2022–2023 almost offset the sharp decline in IMCTs, so that the market indicators as a whole for this period were close to pre-war levels. But in the first half of 2024, the graph went down and bioequivalence studies of Russian sponsors was no longer able to compensate for the contraction in other sectors. Since 2022, they account for the largest share of the clinical trials market in Russia, approximately 50–60%, so it was the reduction in their number that made the largest contribution to the decrease in the total number of new trials in the first half of 2024.

Diagram 6



Data from www.grls.rosminzdrav.ru

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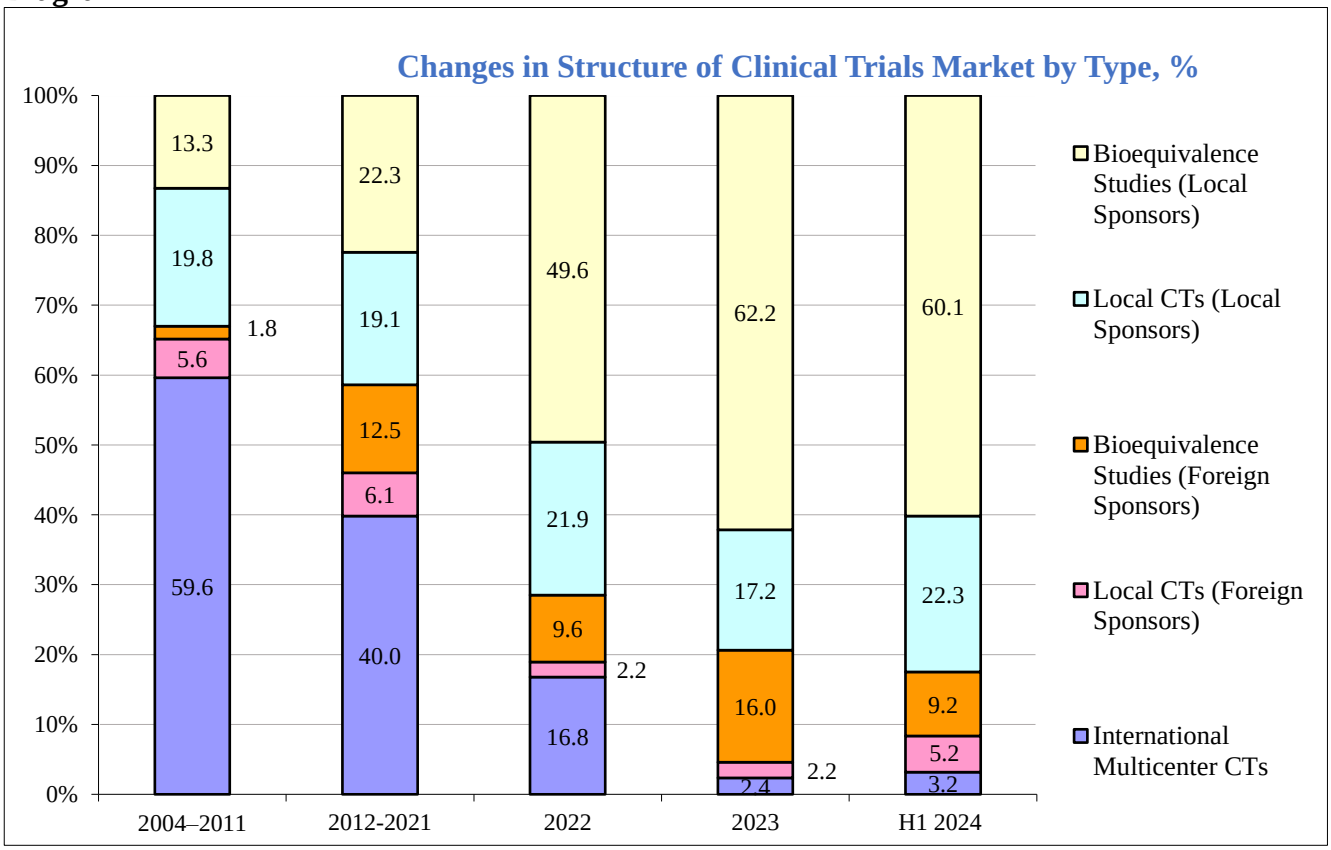
Diagram 7 reflects changes in the market structure by types of studies. The first half of 2024 is compared with 2023, with 2022, and also with two periods, 2004–2011 and 2012–2021, within which the indicators of individual types of studies, although they fluctuated, were generally close, so the average for the specified period of time is given for them. The gap between 2011 and 2012 is due to changes in the rules of the game in the market that followed the adoption of the law "On Circulation of Medicines". In 2022, there was a breakdown associated with the outbreak of war, but the year itself was rather a transitional one between the normal and the new abnormal state, since approvals continued to be issued, applications for which had been submitted before the outbreak of hostilities. The year 2023 and the first half of 2024 already fully reflect the new distorted state of the market.

If we outline the difference with the pre-war situation in broad strokes, the point is that before the war (2012–2021), the ratio between studies by foreign and Russian sponsors was approximately 60% to 40%, and after (2023 and the first half of 2024), it changed to approximately 20% to 80%. Specific fluctuations in the number of approvals for individual types of studies are much less informative than this rough generalization.

Diagram 7



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

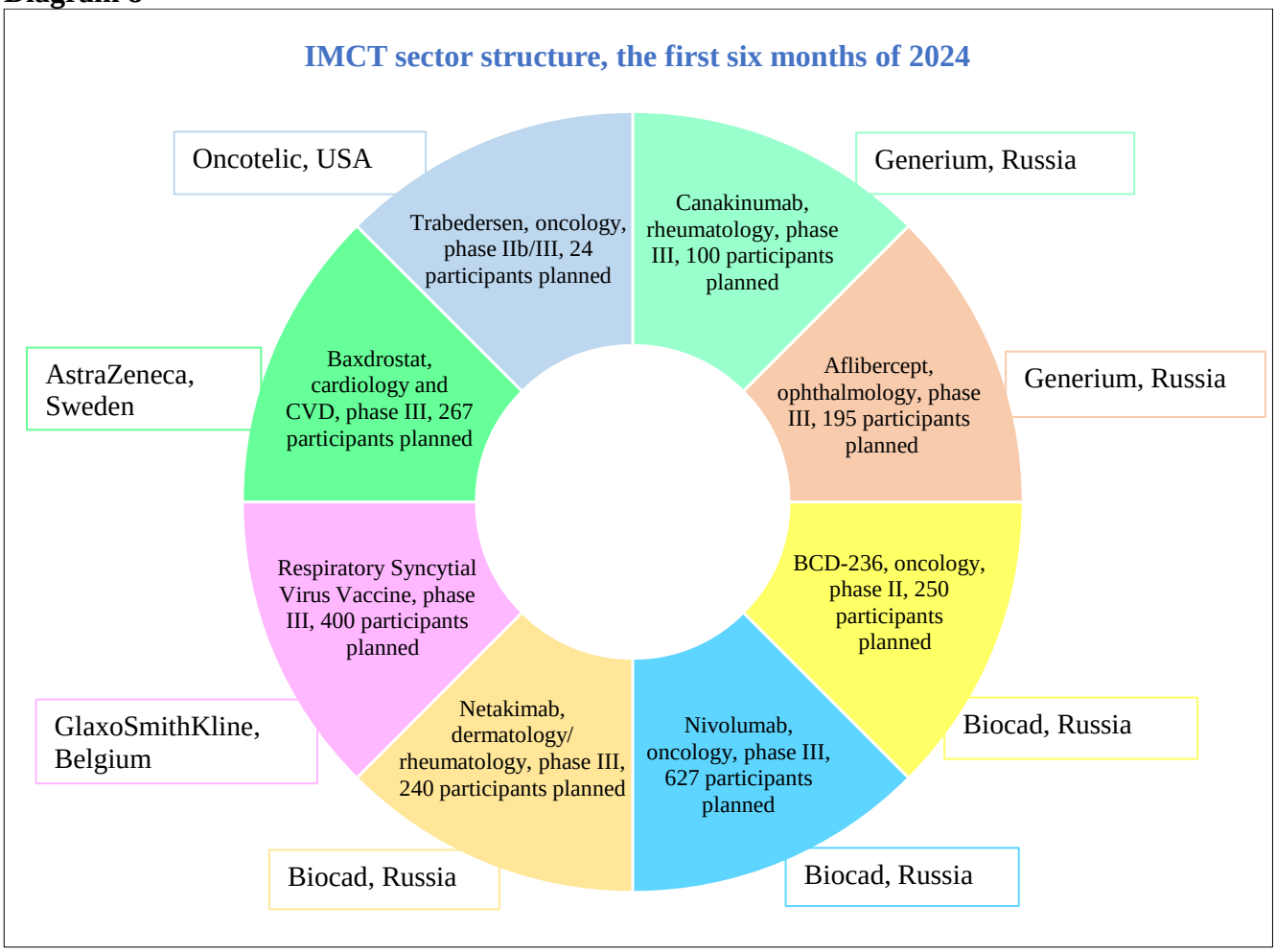
STRUCTURE AND DYNAMICS OF THE CLINICAL TRIALS MARKET BY TYPE

Diagram 8 summarizes information on eight clinical trials the international status of which we were able to confirm. Let us recall that in total, 12 new projects were included in the IMCT category in the register of the Ministry of Health of the Russian Federation for the first half of 2024, but we did not find four of them in international databases and classified them as local.

In the first half of 2024, five out of eight new IMCTs were initiated by Russian sponsors, or 62.5%. Three of the five approvals were received by Biocad, two by Generium; for more details on these protocols, see the diagram.

The remaining three IMCTs were conducted by foreign sponsors. GlaxoSmithKline announced a protocol for a follow-up to a previously completed trial of a vaccine to prevent respiratory syncytial infection in people over 60. Oncotelic received an approval to study an antisense oligonucleotide in patients with pancreatic cancer (in addition to Russia, two American centers are listed in the trial, and for some reason, only they are listed in the clinicaltrials.gov registry, without the Russian ones). AstraZeneca has also planned a full-fledged independent international trial, dedicated to studying the drug Baxdrostat in the Asian population with uncontrolled arterial hypertension. In addition to Russia, centers from Australia, Argentina, China (including Hong Kong), India, Japan, the Republic of Korea, the Philippines, Turkey and Vietnam have announced plans to participate in the study.

Diagram 8



Data from www.grls.rosminzdrav.ru

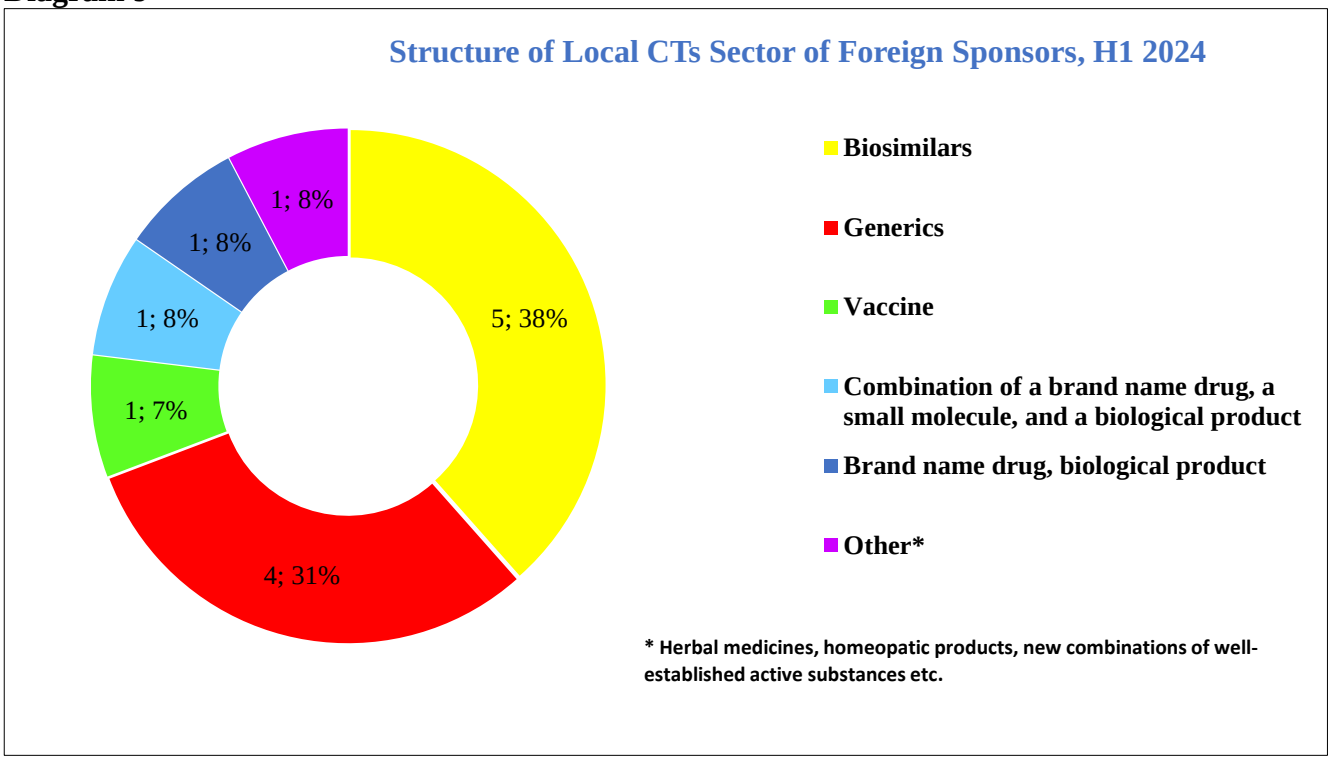
In the structure of the sector of local trials by foreign sponsors in the first half of 2024, which, we recall, is built without taking into account bioequivalence studies, the first thing that stands out is the

unusually large share of biosimilars: five out of 13 protocols or 38.5% (Diagram 9), while in 2015–2023 their share did not exceed 20% (Diagram 10).

Generics (four protocols in the first half of 2024) and their combinations (one more protocol) also together account for a share of 38.5%, which, on the contrary, is unusually small: in 2015–2023 it was no less than 45%. Let's see whether the change in proportions will remain until the end of the year or whether the approvals issued in July-December will smooth it out.

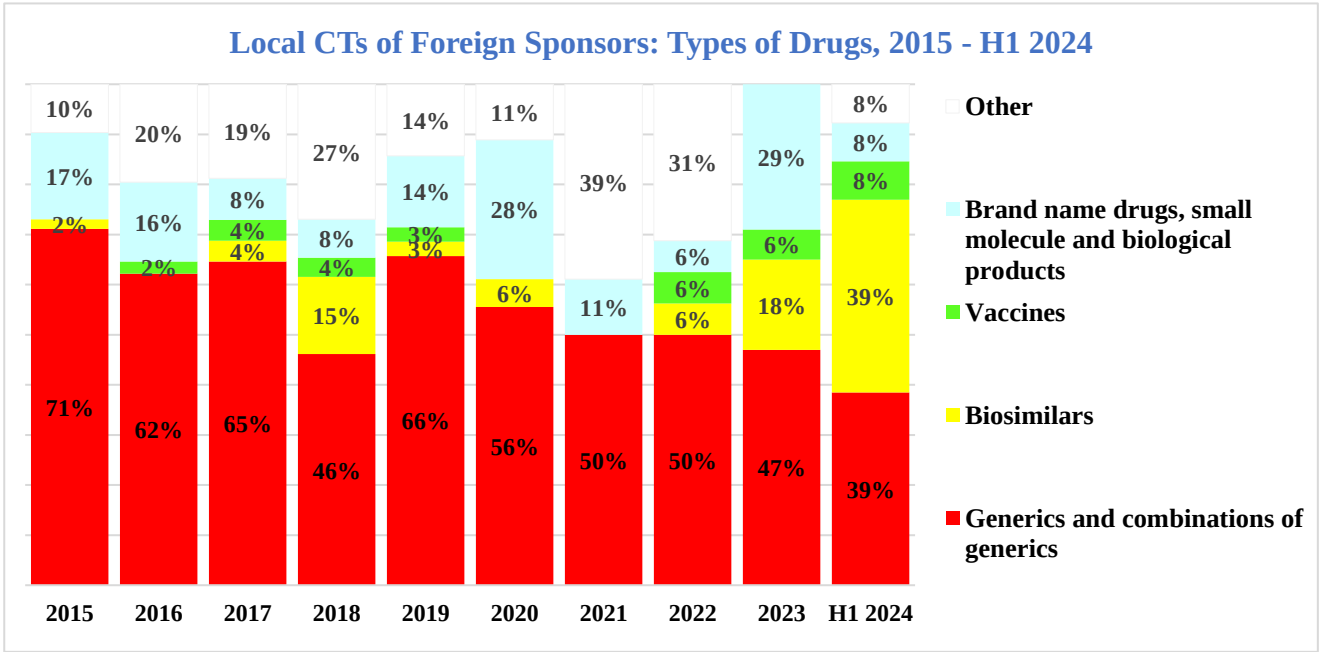
Two more protocols (7.7% each) include a vaccine against chickenpox, an original biologic product, which is a combination of durvalumab and oleclumab, and capsules containing bacterial lysates, which we classified as “other.”

Diagram 9



Data from www.grls.rosminzdrav.ru

Diagram 10



Data from www.grls.rosminzdrav.ru

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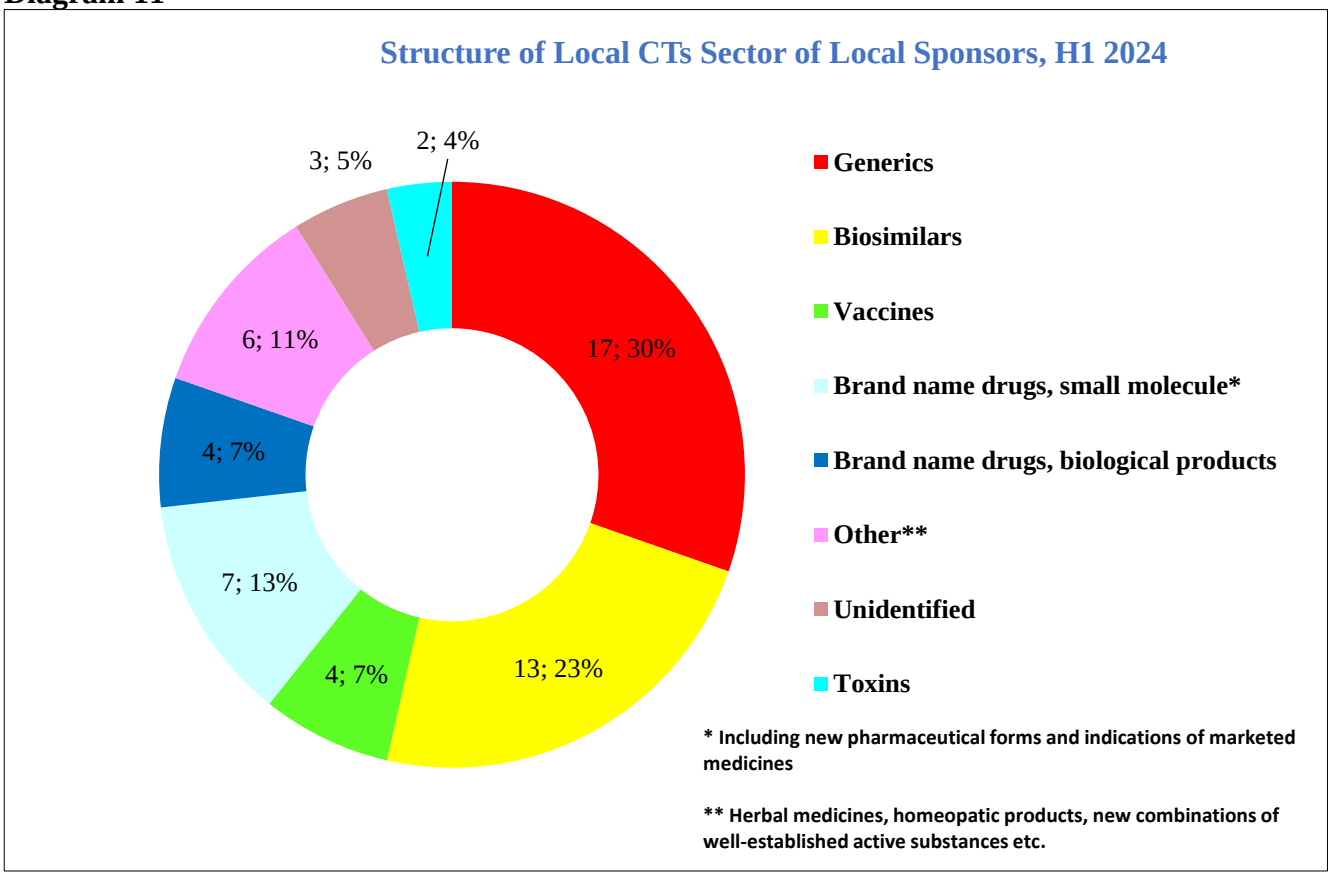
In the structure of the sector of local trials by Russian sponsors in the first half of 2024, generics traditionally predominate: 17 out of 56 protocols, which is 30.4% (Diagram 11). Biosimilars in second place: 13 protocols or 23.2%. Please note that the diagrams in this section are constructed without taking into account bioequivalence studies.

The share of biosimilars in local trials of Russian sponsors in 2015–2022 was 15% or less (Diagram 12). For the first time, we recorded an excess of this value at the end of the first half of 2023 (33%). By the end of 2023, the share of biosimilars had decreased slightly to 28%, but still significantly exceeded the standard figures of previous years. The results of the first half of 2024 show that the interest of Russian companies in studying biosimilars has steadily increased. Moreover, we are talking primarily about specific companies that collectively initiated more than half of the biosimilar studies in the first half of 2024: Geropharm (four out of 13 protocols, all in the field of endocrinology) and Generium (three more, two in the field of endocrinology and one rheumatology).

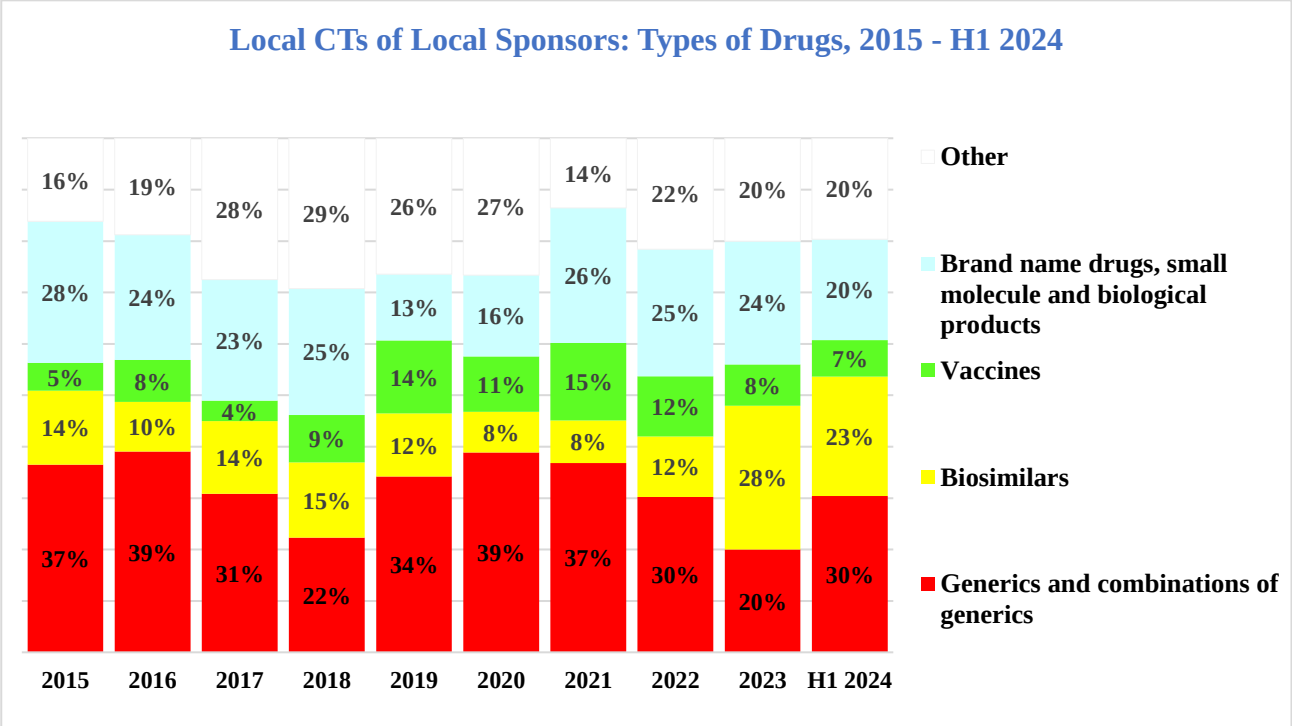
In addition to generics and biosimilars, Russian sponsors received approvals for local trials of original small molecules (seven protocols, 12.5%), original biological products (four protocols, 7.1%), vaccines, which we single out in a separate category (also four protocols and 7.1%), botulinum toxin (two studies, 3.6%), as well as various drugs of plant and animal origin, such as, for example, polypeptides of the cerebral cortex of cattle, etc. (six studies, 10.7%). In another three protocols (5.4%), it was not possible to identify the active substances, since the developers only named the drug codes and did not publish any information in open sources that would clarify the mechanism of their action.

Diagram 11



Data from www.grls.rosminzdrav.ru

Diagram 12



Data from www.grls.rosminzdrav.ru

STRUCTURE OF THE CLINICAL TRIALS MARKET BY THERAPEUTIC AREA

In the previous section, we already talked about eight IMCTs, approvals for which were issued in the first half of 2024. Table 2 presents the same information broken down by therapeutic areas.

Three of the eight protocols relate to oncology: the Russian Biocad is studying BCD-236 in breast cancer and nivolumab in melanoma, and the American company Oncotelic is studying trabedersen in pancreatic cancer.

Other approvals (one for each field) were issued for studies in the fields of ophthalmology (Generium, aflibercept for diabetic macular edema), rheumatology (Generium, canakinumab for Still's disease), cardiology and cardiovascular diseases (AstraZeneca, baxdrostat for arterial hypertension), and infectious diseases (GlaxoSmithKline, a vaccine for the prevention of respiratory syncytial virus infection). The latest protocol is a study at the intersection of dermatology and rheumatology (Biocad, netakimab in plaque psoriasis).

Table 2

Distribution of International Multicenter CTs by Therapeutic Areas, H1 2024			
Therapeutic Area	**Number of IMCTs**	**Share (%)**	**The number of planned participants**
Oncology	3	37.5%	901
Ophthalmology	1	12.5%	195
Dermatology/Rheumatology	1	12.5%	100
Cardiology and CVD	1	12.5%	267
Infectious Diseases (except HIV/HCV/tuberculosis, covid-19)	1	12.5%	400
Rheumatology	1	12.5%	240
TOTAL	8	100.0%	2 103

Data from www.grls.rosminzdrav.ru

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Table 3 shows the distribution by therapeutic areas of local studies of generics and biosimilars that were initiated by foreign sponsors in the first half of 2024.

As usual, cardiology and cardiovascular diseases are in the lead: this therapeutic area accounts for a third of the approvals, 11 out of 33. Three protocols each (9.1% share) for oncology, rheumatology and infectious diseases (excluding HIV, tuberculosis, hepatitis C and Covid-19). Two protocols (6.1% each) for HIV, neurology and urology. Another seven therapeutic areas had one protocol each (3.0% each).

Table 3

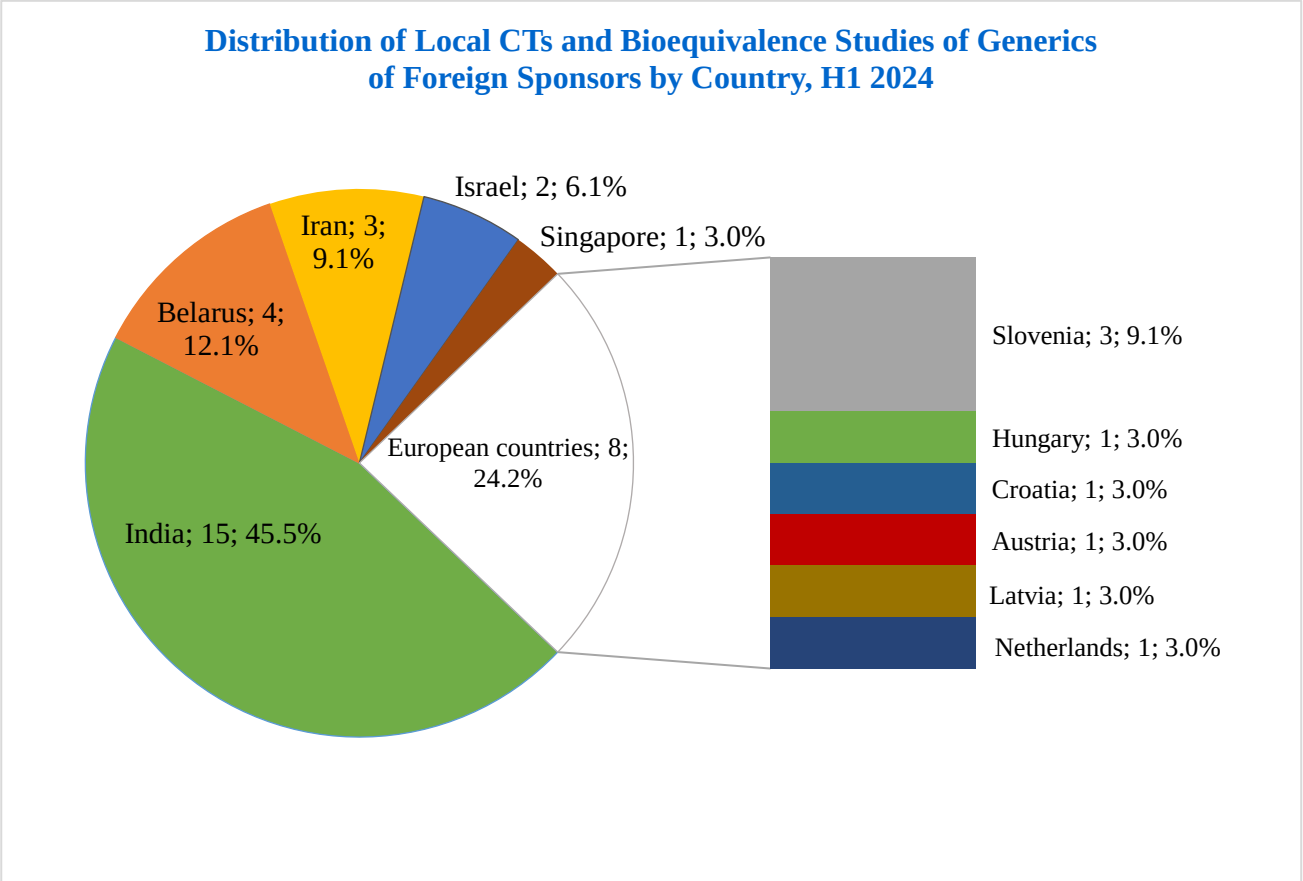
Distribution of Local CTs and Bioequivalence Studies (Generics and Biosimilars) of Foreign Sponsors, H1 2024			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Cardiology and CVD	11	33.3%	581
Infectious Diseases (except HIV/HCV/tuberculosis, covid-19)	3	9.1%	1 116
Oncology	3	9.1%	640
Rheumatology	3	9.1%	183
Urology	2	6.1%	160
HIV	2	6.1%	101
Neurology	2	6.1%	68
Dermatology	1	3.0%	688
Analgesic and NSAIDs	1	3.0%	220
Ophthalmology	1	3.0%	120
Pulmonology	1	3.0%	84
Gastroenterology	1	3.0%	70

Haematology	1	3.0%	46
Psychiatry	1	3.0%	32
TOTAL	33	100.0%	4 109

Data from www.grls.rosminzdrav.ru

After the war began, we started tracking the geography of foreign sponsors who conduct studies in the Russian Federation. The distribution of sponsors by country in the first half of 2024 is shown in Diagram 13, and changes in this distribution from 2021 onwards are shown in Diagram 14.

Diagram 13



Data from www.grls.rosminzdrav.ru

Sponsors from India received the most approvals in the first half of 2024: 15 (of which six are from divisions of the Hetero group of companies, three from Dr. Reddy's Laboratories, two each from Intas Pharmaceuticals and Sun Pharmaceutical Industries, one each from Mylan Laboratories and Agio Pharmaceuticals). The share of studies by Indian companies grew to 44.4% by the end of 2023 and remains at approximately the same level: 45.5% in the first half of 2024.

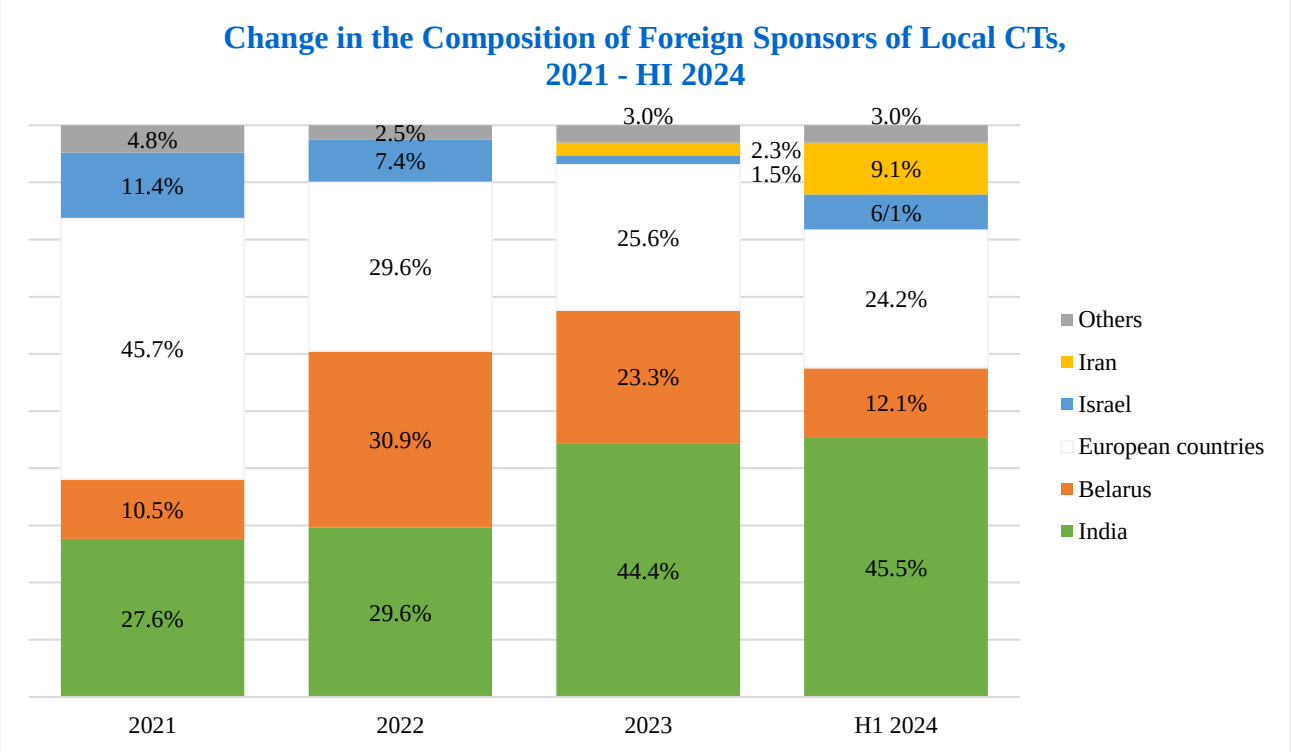
Sponsors from Belarus received four out of 33 approvals (Pharmland two, AmantisMed and Pharmtechnology one each). The share of new studies launched in the Russian market by companies from Belarus increased to 30.9% in the first year of the war, but by the end of 2023 it had decreased to 23.3%, and in the first half of 2024 it was only 12.1%.

European sponsors received eight approvals (two from KRKA, two more from Sandoz, including Lek, one each from Belupo, Olainfarm, Egis and Synthon BV). The share of local trials by European sponsors, including companies from countries outside the European Union, in the Russian market before the war was almost half, by the end of 2023 it had shrunk to a quarter and in the first half of 2024 remains approximately the same, 24.2%.

Three approvals have been issued to CinnaGen from Iran. Iran first appeared in our geographic diagrams at the end of 2023, when its share was a modest 2.3% of the total number of approvals, but as we can see, in the first half of 2024 it grew to 9.1%.

Finally, two more approvals were received by Israel's Teva and one by PVP Labs PTE from Singapore.

Diagram 14



Data from www.grls.rosminzdrav.ru

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Table 4 shows the distribution of approvals for local studies of generics and biosimilars obtained by Russian sponsors in the first half of 2024 by therapeutic areas.

The five areas that together accounted for more than half of the new studies were cardiology and cardiovascular diseases (32 or 17.7% of the total number of approvals issued), oncology and endocrinology (22 protocols each or 12.2%), gastroenterology together with proctology as a single therapeutic area (12 or 6.6%), and neurology (also 12 or 6.6%). In the first half of 2023, the list of leading regions was the same, with cardiology still in its usual first place.

Table 4

Distribution of Local CTs and Bioequivalence Studies (Generics and Biosimilars), Conducted by Local Sponsors, H1 2024			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Cardiology and CVD	32	17.7%	1 453
Oncology	22	12.2%	1 851
Endocrinology	22	12.2%	1 322
Gastroenterology/Coloproctology	12	6.6%	1 260
Neurology	12	6.6%	859
Infectious Diseases (except HIV/HCV/tuberculosis, covid-19)	10	5.5%	639
Analgesic and NSAIDs	9	5.0%	367
HIV/HCV/Tuberculosis	8	4.4%	451
Rheumatology	7	3.9%	641

Haematology	7	3.9%	591
Pulmonology	6	3.3%	718
Obstetrics and Gynecology	6	3.3%	244
Allergology	5	2.8%	414
Hepatology	4	2.2%	226
Dermatology	3	1.7%	462
Urology	3	1.7%	270
Transplantology/Immunology	2	1.1%	179
Oncohaematology	2	1.1%	116
Psychiatry	2	1.1%	115
Phlebology	2	1.1%	92
Dentistry	1	0.6%	237
Traumatology	1	0.6%	154
Parasitology	1	0.6%	52
Unidentified	1	0.6%	40
Otorhinolaryngology	1	0.6%	30
TOTAL	181	100.0%	12 783

Data from www.grls.rosminzdrav.ru

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Amlodipine, a calcium channel blocker with antianginal and hypotensive effects, was the most frequently mentioned drug in the protocols for studies of generics and biosimilars in the first half of 2024 (Table 5). It was planned to be studied separately and in combination with other drugs in five new studies.

There are four protocols each for apixaban, valsartan, indapamide, perindopril, paracetamol, ibuprofen and ademetionine, of which apixaban and ademetionine are only declared independently, perindopril and paracetamol only in combinations, and the rest both separately and together with other molecules. It is easy to see that five of the eight most popular drugs are cardiological, except for paracetamol and ibuprofen, which we classify as analgesics and non-steroidal anti-inflammatory drugs, as well as the hepatoprotector ademetionine.

There are three protocols each for ticagrelor, eltrombopag, raltegravir and rabeprazole (separately), as well as for vildagliptin, bisoprolol and fluticasone (separately and in combinations), of which ticagrelor and bisoprolol are also used in cardiology.

The remaining active substances were mentioned in only one or two protocols. Among them, surprisingly, is rivaroxaban, which has led this ranking for four years in a row, but is only mentioned in one protocol for the first half of 2024. Only two protocols feature the hypoglycemic drug metformin, which was in second place in 2023 and was popular in previous years. Further observations will help to understand whether the list of drugs that generic manufacturers are interested in is really being updated.

Table 5

Most Requested INN Used in Clinical Trials of Generics and Biosimilars in H1 2024				
Substance	**Number of CTs of foreign generics**	**Number of CTs of local generics**	**All clinical trials to a given INN**	**Therapeutic Area**
Amlodipin (separately and in fixed combinations)	3	2	5	Cardiology and CVD
Apixaban	2	2	4	Cardiology and CVD, perhaps covid-19
Valsartan (separately and in fixed combinations)	2	2	4	Cardiology and CVD
Indapamide (separately and in fixed combination)	–	4	4	Cardiology and CVD
Perindopril (in fixed combinations)	2	2	4	Cardiology and CVD

Paracetamol (in fixed combinations)	1	3	4	Analgesic and NSAIDs, Infectious Diseases
Ibuprofen (separately and in fixed combinations)	–	4	4	Analgesic and NSAIDs
Ademethionine	–	4	4	Hepatology
Vildagliptin (separately and in fixed combinations)	–	3	3	Endocrinology, perhaps covid-19
Tikagrelor	2	1	3	Cardiology and CVD
Eltrombopag	1	2	3	Haematology
Raltegravir	1	2	3	HIV
Bisoprolol (separately and in fixed combinations)	1	2	3	Cardiology and CVD
Rabeprazole	–	3	3	Гастроэнтерология
Fluticasone (separately and in fixed combinations)	–	3	3	Pulmonology, Allergology

Data from www.grls.rosminzdrav.ru

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Table 6 shows the therapeutic areas of local trials of original drugs, for which foreign sponsors obtained approvals in the first half of 2024. There are only two such approvals, one less than in the first half of the previous year. One was awarded to China's Changchun BCHT Biotechnology to study a live attenuated vaccine against chickenpox, and the second to AstraZeneca to study a combination of durvalumab and oleclumab in patients with lung cancer.

Table 6

Distribution of Local CTs of Brand Name Drugs of Foreign Sponsors, H1 2024			
Therapeutic Area	**Number of CTs**	**Number of planned participants**	**Developer's country**
Infectious Diseases (chicken pox vaccine)	1	160	China
Oncology	1	50	Great Britain
TOTAL	2	210	

Data from www.grls.rosminzdrav.ru

In the first half of 2024, Russian sponsors received 24 approvals to conduct local trials of original drugs, including biological ones, which is two more than in the same period in 2023. Their distribution by therapeutic areas is shown in Table 7.

More than half of the new studies are in the three most popular therapeutic areas: neurology (five approvals), infectious diseases and cardiology (four each). Let us recall that we take cardiology into account together with cardiovascular diseases, and from infectious diseases we single out HIV, tuberculosis, viral hepatitis C and Covid-19 and count them separately. If tuberculosis were included in infectious diseases, there would be one more protocol for this area. By the way, for the first time since 2020, there are no anti-Covid-19 drugs in the distribution in Table 7.

Table 7

Distribution of Local CTs of Brand Name Drugs (Including Biological Products) of Local Sponsors, H1 2024			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Neurology	5	20.8%	1 239
Infectious Diseases (except HIV/HCV/tuberculosis, covid-19)	4	16.7%	1 504
Cardiology and CVD	4	16.7%	2 306
Urology	3	12.5%	556
Pulmonology	2	8.3%	291

Obstetrics and Gynecology	2	8.3%	204
Gastroenterology	1	4.2%	36
Tuberculosis	1	4.2%	25
Toxicology	1	4.2%	42
Phlebology	1	4.2%	230
TOTAL	24	100.0%	6 433

Data from www.grls.rosminzdrav.ru

PLUS DIGITALIZATION OF THE ENTIRE COUNTRY…

"Communism is Soviet power plus electrification of the entire country"

V.I. Lenin

Another topic we want to cover in this issue concerns legislative changes that threaten to have an impact on the clinical studies industry in Russia no less than the "special military operation" ("SVO" by the first letters in Russian) announced two and a half years ago. But if the victims of the "SVO" were primarily international projects, the situation™[4] with the new law threatens, if not death, then serious disability for all those remaining. We are talking about a new procedure for obtaining informed consent from subjects to participate in studies, namely, the introduction of a mandatory electronic form of such consent. And it would be half the trouble if the conversation was only about the mandatory nature of electronic ICF, but according to the new law, the consent must be obtained exclusively using a single (that is, state) identification and authentication system. But first things first.

It all started out quite peacefully and even loyally towards business. Back in 2020, the Ministry of Health began preparing a bill that was supposed to amend the current law "On Circulation of Medicines". The goal is to bring the latter into line with the legislation of the Eurasian Economic Union (EAEU). At first, the project was quite brief, focusing exclusively on recognizing the priority of EAEU law.

However, over time, the document began to acquire details that went beyond the originally stated goals. Thus, among other things, in terms of regulating studies, the Ministry of Health proposed supplementing the procedure for obtaining consent to participate in a study with an electronic form. Moreover, the proposal consisted precisely of an alternative: consent was supposed to be received either, as usual, on paper, or in electronic form. The planned innovation received full support from the industry, as it responded to international trends towards a gradual transition to an increasingly active use of new technologies and the spread of a decentralized approach to conducting clinical trials. Moreover, many still remembered what a help the possibility of using remote communication methods had been during the Covid-19 pandemic. So, the initiative of the Ministry of Health was received with enthusiasm, although with some surprise at such an unexpected progressiveness of the approaches of the Russian regulator.

By the spring of 2023, the project had been discussed in detail and repeatedly with the expert and business community, had gone through several rounds of interdepartmental approvals, and had finally been sent by the Ministry of Health to the Government of the Russian Federation. In August 2023, the document was submitted to the State Duma already in the status of a government document. At that time, the text of the norm we are interested in remained unchanged: along with the written form of the ICF, the possibility of using an electronic form was created. But in the State Duma, in the second reading, which took place on 14 December 2023, the text of the bill was changed. In the part that interests us, it is significant. Now the norm on obtaining consent was as follows: *"The patient's voluntary consent to participate in a clinical trial of a medicinal product for medical use shall be confirmed by the enhanced qualified electronic signature or simple electronic signature (using a unified identification and authentication system) of the patient or the signature of his/her legal representative on the patient's information sheet generated in the form of an electronic document, and, at the request of the patient or his/her legal representative, by the signature of the said person on the patient's information sheet generated on paper."*

Translated from official language into human language, this means that the primary (and only) form of signature of the subject becomes electronic. And not just electronic, but confirmed in the state

[4] The word "situation" is used by Russian authorities as a euphemism for any kind of crisis, for example, to describe the invasion of the Ukrainian army into Russian territory.

information system, the so-called UIAS[5]. In addition to the electronic one, if the patient wishes, he/she can also sign on a paper ICF, but only as an additional document, and not as a choice of one of the options. Here it is also necessary to explain that the UIAS itself was created to gain access to information contained in state information systems, for example, when a citizen applies for services (such as obtaining a passport or registering property rights) on the Unified Portal of State Services. It was unclear how clinical trials conducted by pharmaceutical companies had anything to do with this. However, the law was adopted on 18 January 2024, and the entry into force of the new consent procedure was set for 1 January 2025.

At first, we, to tell the truth, decided that the authors of the amendment had mixed something up and had not figured it out. And who are they, the authors? Let us recall that the project proposed by the Ministry of Health was supported not only by all departments, but was ultimately approved by the Government. And there was no talk of any single system of identification and authentication, and the ICF was supposed to be signed in either paper or electronic format.

According to the bill's passport, the authors of the adopted amendments were 22 State Duma deputies, namely the members of the Health Protection Committee in full (19 persons), as well as the Deputy Chairman of the State Duma, member of the Budget and Taxes Committee V.A. Davankov, Deputy Chairman of the Competition Protection Committee S.F. Lisovsky, and Deputy Chairman of the Economic Policy Committee S.A. Naumov. None of the authors are specialists in the field of clinical studies. Who could have come up with the idea to ~~cross a snake with a hedgehog~~ try to connect the independent clinical studies system, operated by individual pharmaceutical companies, to the state information system? After all, even at the level of the state healthcare system, a unified electronic system does not yet exist, although plans to create one have been announced, and in some regions they are even trying (with varying degrees of success) to implement them. But implementation of such plans is still a long way off, considering the not always high technical equipment of healthcare institutions, especially those located at some distance from Moscow and St. Petersburg. Or are we missing something, and there are interested parties behind the industry trying to profit from creation of such a system? Or gain control over the flow of patients and their distribution in clinical trials? Sounds like nonsense. But maybe a monstrous mistake did occur, and if we explain it to officials, everything will be fixed?

The industry had no answers to these questions, but there was an understanding that this was a real problem. Moreover, one that will affect everyone. And in the conditions of a sector of international studies that has practically ceased to exist, this primarily falls on the shoulders of domestic developers and (here we again recall the market structure reflected in Diagram 7) manufacturers of domestic generics.

It was with these thoughts that the few and almost demotivated representatives of Western big pharma, having united with representatives of leading domestic companies, turned to the Ministry of Health of the Russian Federation for an explanation of the situation™ that had arisen. The platform chosen for communication was the working group in the field of pharmaceuticals and medical devices under the subcommittee on improving the control (supervisory) and permitting functions of federal executive authorities under the Government Commission for Administrative Reform. The very same one where, for more than three years, the discussion of the draft law took place, which resulted in such unpredictable consequences.

The initial impulse was to explain to the regulator the absurdity of the situation™ (and it was clear to all market participants, including sponsors and researchers), to demonstrate the risks to the industry and, above all, to express a lack of understanding of the goals of changing the procedure for obtaining consent, to which, it would seem, there had never been any complaints. And, of course, remembering that the initially proposed amendment to the law by the Ministry of Health was quite adequate, there was a desire to appeal to the unreasonableness of the deputies who ruined such a good

[5] Federal State Information System "Unified system of identification and authentication in the infrastructure providing information technology interaction of information systems used to provide state and municipal services in electronic form."

initiative by the regulator. In general, the appeal was in the style of the eternal Russian questions "who is to blame?" and "what is to be done?"

To our (naive, as we now understand) surprise, the Ministry of Health, represented by the relevant department representatives,[6] reacted by actively defending the adopted norm: "The law has been adopted, the text has been agreed upon by the Ministry of Health, it must be implemented." And when asked about implementation, they tried to redirect us to the digitalization department and the Ministry of Digital Development[7]. But the industry's questions were not only about technical feasibility; we were primarily interested in the legal and ethical aspects of the problem. For example, how the uncontested requirement to comply with the electronic ICF form is combined with the provisions of GCP and Russian legislation on electronic signatures. What to do with vulnerable patient groups and those potential participants who may not have an account in the UIAS. For example, elderly people or foreign citizens. How to ensure the confidentiality and protection of patients' personal data from the sponsor (if the operator of the electronic system is assumed to be the sponsor) or a third party (if, according to the officials, the operator is someone else). Considering that patient identification should be carried out using the UIAS, i.e. the state information system, how can one be linked to the other and, at the same time, meet the strict requirements for computerized GCP systems? Since representatives of the relevant department of the Ministry of Health demonstrated exceptional steadfastness of faith in the need to implement the innovation, finding it difficult to give clear answers to numerous questions, it was decided to hold a joint meeting, to which representatives of the Ministry of Digital Development, as the operator of the UIAS, would also be invited.

Such a meeting took place in mid-May. At the meeting, the representatives of the Ministry of Digital Development explained certain technical points regarding the operating procedure of the UIAS. In particular, they informed that currently more than 110 million accounts are registered in the UIAS, it is possible for children from 14 to 18 to create their own account, and for younger children, parents have the opportunity to register. However, the issue of integrating a third-party computerized system with the UIAS is not so simple. Today, the UIAS is primarily used to provide access to a certain trusted (by the Ministry of Digital Development) information system (primarily State Services). To become such a system, an organization should comply with certain regulations and meet the requirements of Government Resolution No. 1382 dated 22 December 2012. In particular, an agency/organization may join the UIAS if the need for interaction between information systems is directly provided for by federal laws, acts of the President or the Government of the Russian Federation, or if such joining is approved by a decision of the Presidium of the Government Commission. For commercial structures, the Ministry of Digital Development uses an external signature mechanism in the form of an enhanced qualified electronic signature, which is implemented in the "Gosklyuch" mechanism.

At the same time, representatives of the Ministry of Digital Development stated that they were somewhat surprised by the situation™ which had developed around the law, because for their part they had sent proposals to the Presidential Administration and the Government apparatus, firstly, allowing for variability of use of paper and electronic signatures, and secondly, suggesting use of not a simple electronic signature that requires integration with the UIAS, but an enhanced unqualified one. They consider the introduction of a non-alternative option in the form in which it is currently prescribed in the law to be "somewhat premature."

This turn of the conversation somewhat stunned the representatives of the Ministry of Health, but they did not give up, suggesting that they think in the time remaining before the law comes into force about how to implement its requirements. The issue was complicated by the fact that no one wanted to take on (admit) an interest in creating such a system. Moreover, during the conversation it was confirmed that the owner of a computerized system that involves working with patients' personal data should also register as a personal data operator. Initially, the Ministry of Health believed that proposals for development and use of such systems should come from healthcare institutions (clinical bases). The

[6]Department for Regulation of Circulation of Medicines and Medical Devices of the Ministry of Health of Russia

[7] Ministry of Digital Development, Communications and Mass Media

industry quickly proved that the interest of medical organizations in conducting clinical trials did not go that deep. As for studies sponsors, they will not be able to take on the responsibility of accessing subjects' personal data, as this would directly violate GCP. The remaining options are either that the system should be created under the control of the state/some government agency (but neither the Ministry of Health nor the Ministry of Digital Development planned to take on the creation of such a system, not to mention the lack of a budget), or by a third party on a reimbursable basis. The remaining issues (among others) were that this third party must be trusted not only by researchers and patients, but also, given commercial secrets and other sensitive business information, by sponsors.

For its part, the Ministry of Digital Development stated that they do not have any authority to accredit, validate or audit third-party computerized systems or operating companies. As for the UIAS, access to its audit by foreign companies or foreign government agencies is certainly not expected. At the same time, representatives of the agency acknowledged that in order to avoid abuse and possible falsification of data when using computerized systems developed by third parties, it may be necessary to develop complex technical regulations, which are unlikely to be ready in the remaining six months. In other words, having understood the importance of the questions posed, the employees of the Ministry of Digital Development just threw up their hands, clearly sympathizing with the business. The Ministry of Health suggested that the industry think about how to nevertheless implement the possibility of fulfilling the requirements of the law. At this point the parties parted ways, agreeing to meet again for further discussion.

The next meeting took place in June. The industry wanted answers from the Ministry of Health to the questions related to legal and ethical conflicts that could arise when trying to implement the law in practice. The Ministry of Health dismissed the existence of legal problems out of hand: the regulator does not see any discrepancies with the provisions of the GCP or the law “On Electronic Signatures” in the non-alternative method of obtaining a signature. It was slightly less categorical and confident when discussing the issue of what to do with participants in studies started before 1 January 2025, if there is suddenly a need to sign a new version of the ICF, should only the electronic form be followed? And will it be necessary to remove such patients from the study if they suddenly refuse to sign the electronic ICF or the system is not ready? Here, the department’s representatives, clearly not wanting to take responsibility for making the decision, preferred to give an extremely vague answer. It seems that the law does not clearly stipulate such cases, but there seems to be no strict requirement... Maybe everything is not as scary as it seems, no need to get worked up, because the law does not say yes or no... Besides, decision 79[8] does not contain such a basis for excluding patients from studies, which means that the provision of the Russian law will not be applicable here...

However, the Ministry of Health did not provide a final summary on this issue, suggesting that we think about it some more. At the same time, market participants should hardly expect an official response in the future. This behavior of officials can be considered as follows: “we will not specifically ask anyone about this aspect. But we also don’t want to take responsibility for the decision made. Do as you see fit, we are ready to turn a blind eye."

In addition to representatives of business and the Ministry of Health, the meeting was also attended by an IT company operating in the clinical trials market and having experience in conducting studies using electronic ICFs, although not within the strict framework prescribed by the new law. In their opinion, the technical possibility of implementing the provisions of the law exists, but there are both operational problems and a lack of understanding of the possibility of integration into the UIAS. In any case, even if the system is technically feasible, the losses for the clinical studies industry will be serious. Thus, according to the company’s estimates, enrolment capabilities will be reduced by 15–20%. Other market participants supported the theme, estimating (provided that the system is feasible and functional) that the potential losses in enrolment are higher — up to 20% in bioequivalence studies, and much higher for complex hospital projects, where the impact on enrolment threatens to be catastrophic.

[8] This refers to the Rules of Good Clinical Practice of the EAEU

The industry thus warned the regulator that the introduction of the mechanism would lead to a market collapse. It may not be so easy to fix (after all, this is not an easy calculation based on the number of approvals issued, but a decrease in the speed of enrolment). But ultimately this will also lead to delays in the registration of new drugs. And as a result, officials will have to somehow explain the drop in indicators.

At this point the meeting as a whole ended, the Ministry of Health expressed its readiness to continue the discussion, taking time for a break. They also called on the participants to consider what possible change to the law (not by abandoning the only way to obtain consent, since "we can't get away from digital," but perhaps by using some other signature option, in addition to the one that provides for integration with the UIAS) could be considered in order to reduce market losses.

Since then, there have been no new meetings or discussions, at least with the participation of the ACTO. Meanwhile, autumn was approaching...

Instead of a conclusion.

So, cui prodest[9]? The discussion that took place essentially showed that none of the market players were initially interested in changing the law in the form in which it was adopted. The Ministry of Digital Development (as the agency responsible for digitalization issues) acknowledged that the issue is too small and too complex to be of any independent interest to them. And in fact, it sided with the industry, supporting our concerns and doubts about the feasibility of the project within the specified time frame. Only the Ministry of Health is engaged in the defense of the project, proving that nothing is impossible, and "a journey of a thousand miles begins with a single step". At the same time, the regulator does not show any visible signs of interest in the implementation procedure. It is clear that they will be satisfied with any option that at least formally satisfies the requirements of the law. So where did the problem come from, who started this whole mess and why?

We will share with the reader the version sounded to us by a business consulting company. According to their assessment, the composition of the amendment's authors indicates that the true author was the Ministry of Health itself. Why did they change their own project? There are all the signs (and they concern not only the Ministry of Health and certainly not only the area of clinical studies) that plans for a ~~barrage~~ of digitalization are being passed down to departments from above, from the Government (in this connection, the name Grigorenko is heard). The Ministry of Health is already concerned about a whole series of initiatives, mysteriously called "incidents". Thus, there is "Incident 7", related to the introduction of electronic medical records, as well as "Incident 38", which involves the development and improvement of the efficiency of electronic registration with a doctor. And there is reason to believe that a KPI system has also been launched for officials concerning digitalization of various government services. The fact that, in a fit of bureaucratic zeal, someone, seeing the words "patient's electronic signature" in the text of the bill, attached to them the standard "using a single identification and authentication system" is well-intentioned. But one more area has been added to the list of assets, even if it formally does not affect the relationship "state – citizen/patient/consumer", so what? You can't make an omelette without breaking eggs... After all, "we can't escape digitalization." The fact that the future of Russian healthcare is here as eggs, well, that's sometime later, in the future. And the increase in KPI is today.

In fact, this entire dramatic story for a single industry fits perfectly into the paradigm of today's realities. All we can do is watch. "We" means the representatives, first and foremost, of the international clinical studies industry, of which there is almost nothing left in Russia anyway. So there is practically nothing to lose. Now all that remains is to watch as Russian officials decided to balance our chances of survival with domestic developers by thoroughly cutting off the branch under them.

There is, however, another option for Russian manufacturers to get out of current situation™ – simply ignore the law. Although such an approach will primarily hit honest players, who will not find it

[9] "Who benefits?" (Latin)

so easy to decide on such a radical decision. But it will give an advantage to those who are not so scrupulous. Well, the story in any case will receive some development, so we continue to observe.

P.S. Well, one more touch to the portrait. Just a few days ago, Pavel Pugachev, who oversaw the digital transformation of Russian healthcare in his post, left his post as Deputy Minister of Health. Evil tongues say that he failed. Was the sacrifice in vain?