ACTO

ASSOCIATION OF CLINICAL TRIALS ORGANIZATIONS

ACTO NEWSLETTER № 27

1st Half of 2023

MOSCOW 2023

CONTENTS

SUMMARY

In the first half of 2023 the Ministry of Health of the Russian Federation issued 340 approvals for conducting clinical trials. This is a 20% decrease from 425 approvals issued in the first half of 2022.

The number of approvals for international multicenter clinical trials (IMCTs) reduced by 92.8%: eight vs 111 approvals in the previous year. According to ACTO, the sponsor is no longer going to launch at least one of the approved trials in Russia, and four other trials are so called ‘extension studies’ to which only participants from the earlier completed protocols are invited. In total, over a year and a half, the share of the IMCTs in the total market structure decreased from 40% to a paltry 2.4%.

The number of issued approvals for local trials of therapeutic efficacy and safety of Russian medicinal products also decreased from 90 in the first half of 2022 to 51 in the first half of 2023. (43.3%). But the number of bioequivalence studies for domestic generics rose: 229 approvals vs 171 in the previous year (33.9%). Bioequivalence studies conducted by the Russian sponsors are the only type of trials demonstrating a sustained growth throughout the 2020s. In the first half of 2023, they accounted for a record 67.4% of all approvals issued.

The number of approvals for local trials and bioequivalence studies conducted by foreign sponsors generally remained the same as compared with the previous year: nine approvals in the first half of 2023 vs ten approvals in the previous year for local projects, and 43 approvals in both cases for bioequivalence studies.

Cardiology and cardiovascular diseases (CVD) represented the most popular therapeutics area for the manufacturers of biosimilars and generics. 17 protocols in this area were approved by foreign sponsors which accounted for 34.7% of all approvals of this type. Russian manufacturers of generics received 66 approvals in this area, i.e. 25.6% of the total volume. This was due to the popularity of particular molecules: rivaroxaban (20 approvals in six months), apixaban (eight approvals), indapamide and perindopril (seven approvals each, tested mostly in combinations). As for non-cardiac substances, the antidiabetic agent vildagliptin (seven protocols) attracted the most interest among manufacturers of generics.

There is no point in analyzing the distribution of IMCTs by therapeutics areas due to a negligible number of studies of that type.

VOLUME AND DYNAMICS OF THE CLINICAL TRIALS MARKET

In the first half of 2023 the Ministry of Health of the Russian Federation issued 340 approvals for conducting clinical trials (Table 1). This is a 20% decrease from the number of approvals issued over the same period of 2022 (425 approvals).

The number of international multicenter clinical trials (IMCTs) showed a dramatic decline by 92.8%. In the first half of the previous year, when predominantly applications submitted prior to war were approved, 111 approvals for conducting IMCTs were issued. Over the first six months of 2023, only eight new international trials were approved.

Table 1

Approvals for Conduct Clinical Trials: 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 2023	340	8	9	43	51	229
H2 2022	425	111	10	43	90	171
H1 2023 vs H2 2022, %	-20.0%	-92.8%	-10.0%	0.0%	-43.3%	33.9%

Data from www.grls.rosminzdrav.ru

There's a point to be made here. The registry maintained by the Ministry of Health of the Russian Federation, which is a source we are extracting data from, categorizes 16 projects as IMCTs over a period of time from January to June 2023. However, historically we verify all trials and in our statistics we consider only those trials to be international which are mentioned (as international ones) in other databases: ClinicalTrials.gov, EU Clinical Trials Register. Otherwise, we consider a study to be local, even if the applicant has indicated otherwise in the registry maintained by the Ministry of Health of the Russian Federation. “Why is it so?”, the reader would ask us. In addition to the provision of the WMA Declaration of Helsinki[1], the formal fulfillment of which the Russian registry may be barely considered because of the limited information placed there, we should not forget about the requirements of every decent academic periodical. No such periodical will accept for publication the results of a study that has not been publicly announced in advance. On the other hand, the chances are paltry that a medicinal product will enter the global market if both the academic community and general public know next to nothing about the development of this product. Therefore, from our perspective, the lack of information about a trial in the generally acknowledged international registries means that the trial sponsor does not intend to enter the international market and is going to limit its circulation to the local market of Russia or those countries where the regulatory system is not so committed to international standards of pharmaceutical product development.

By the way, the reverse process also occurs. Sometimes sponsors enter IMCTs into the registry as regular (local) clinical trials by mistake. Accordingly, when revealing such a situation, we consider the study as an IMCT. As a result, our statistics are always slightly different from what is shown in the registry maintained by the Ministry of Health of the Russian Federation. Usually the discrepancies are not that significant. For example, in 2018–2021, the discrepancy between our data and the registry maintained by the Ministry of Health of the Russian Federation ranged from minus 0.7% (2018, 2 trials were reclassified from local trials to IMCTs and 4 trials were reclassified from IMCTs to local trials) to plus 0.5% (2021, 13 trials were reclassified from local trials to IMCTs, 11 trials were reclassified from IMCTs to local trials). The percentage of data discrepancy increased in 2022 reaching 8.8%. And it was caused not by the increase in the number of cases of disagreement, but by the decrease in the "base", i.e.

[1] “Every research study involving human subjects must be registered in a publicly accessible database before recruitment of the first subject” (para. 35 of the WMA Declaration of Helsinki).

the total number of approvals issued for IMCTs. But this year, because the IMCT sector has reduced to minimum, this difference has become significant. When searching in the international databases, we could not find half of the protocols (eight of 16, or 50%) declared by sponsors as IMCTs. Hence, they are categorized as local trials in our statistics. They included three trials by Biocad JSC, two trials by Pharmasyntez-Nord JSC, two trials by Dr Reddy's Laboratories Ltd., and one trial by Generium JSC. It should be mentioned that we classified another trial by Biocad JSC as an IMCT because information on this trial was found in the registry at ClinicalTrials.gov. However, the list of countries where it is planned to be conducted is limited to the Russian Federation and the Republic of Belarus.

But let's get back to the stats. Generally, the number of local trials and bioequivalence studies by foreign sponsors remained the same as in the previous year: nine approvals in the first half of 2023 vs ten approvals in the first half of 2022 (-10%) for local trials of therapeutic efficacy and safety, and 43 approvals (the same number as in the previous year) for bioequivalence studies.

The number of approvals for local trials applied for by Russian sponsors decreased by 43.3% as compared with the same period of the previous year: 51 vs 90 protocols. However, the number of bioequivalence studies initiated by the Russian companies increased by 33.9%: 229 vs 171 approvals in the previous year. This is the only type of trials that has been demonstrating a sustained growth throughout the 2020s, as discussed below.

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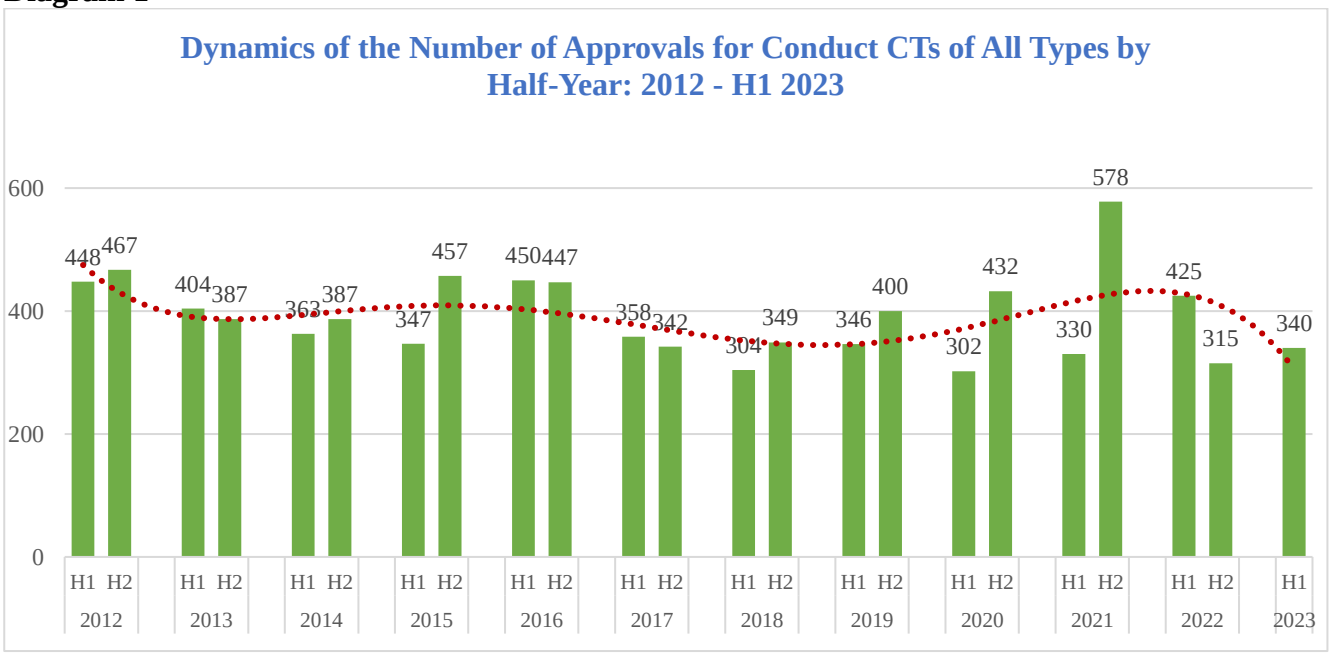
Diagrams 1–6 are shown below, where the first half of 2023 totals are given among other semi-annual totals starting from 2012. The data is supplemented by a polynomial trend line, which helps to mitigate the noise of random fluctuations and allows for better tracking of dynamics.

Diagram 1

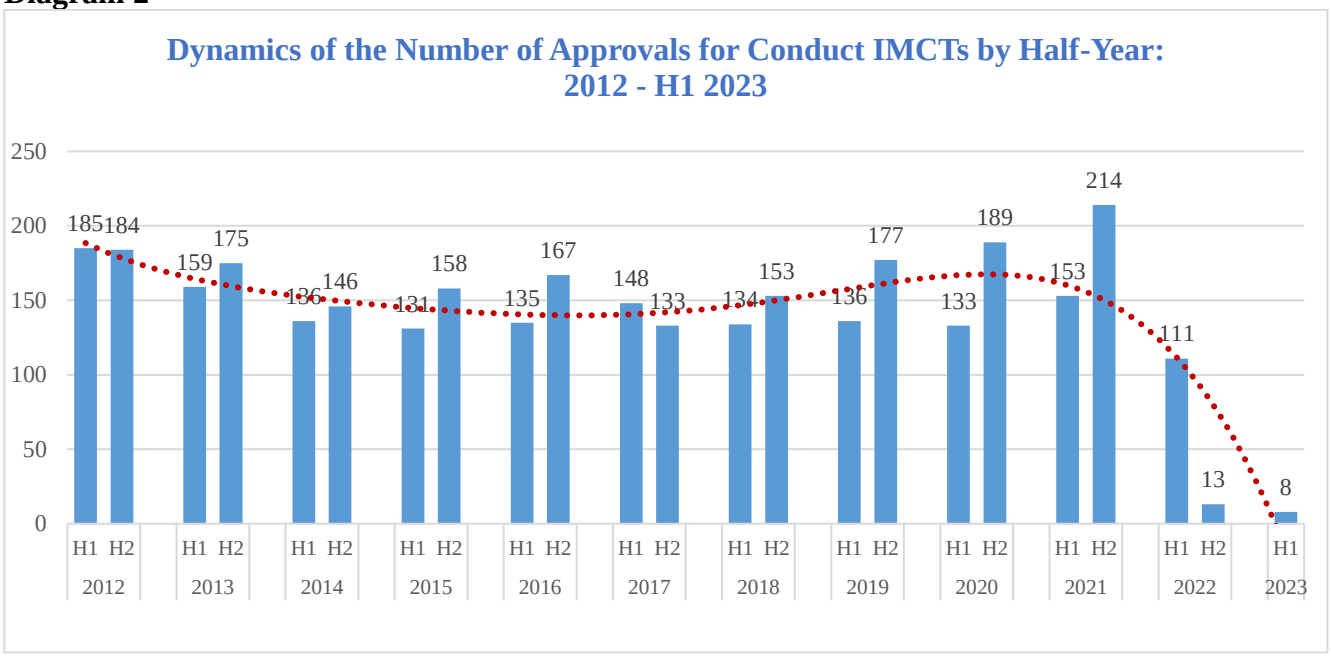


Data from www.grls.rosminzdrav.ru

Diagram 1 with semi-annual sums of approvals issued for all types of trials starting from 2012, shows that the market taken as a whole has so far maintained its usual volume. The rates over the first six months of 2023 are inferior to those obtained over the same period of 2022, but it should be taken into account that the latter one is among the three most productive periods on ACTO's record (only the first half of 2012 and 2016 were more productive). However, many of the IMCT approvals issued in 2022 remained ink on paper, the trials did not start, but formally the January-June 2022 figure remains high. Between 2012 and 2023, the average number of approvals issued in the first half of the year was rarely more than 400 and never fewer than 300, so in this data series, the results for the first half of 2023 look completely typical. They turn out to be atypical not quantitatively, but qualitatively. To see it is true, we need to look at each type of trial individually.

For example, Diagram 2 represents the dynamics of approvals for IMCTs. The preservation of the usual scale cannot be implied here. The trend line, which curvature corresponds to the rate of changes, drops sharply downward in 2022 through the first half of 2023. The collapse looks particularly pronounced because of the market's growth from 2019 through 2021, spurred by the coronavirus pandemic, among other factors. However, during the first half of 2022, the IMCT rates subsided markedly (111 approvals), and during the second half of 2022 and the first half of this year they were — in the language of chemical metaphors — found only in trace amounts (13 and eight, respectively). The reasons are obvious: the outbreak of war and the breakdown of international economic relations.

Diagram 2

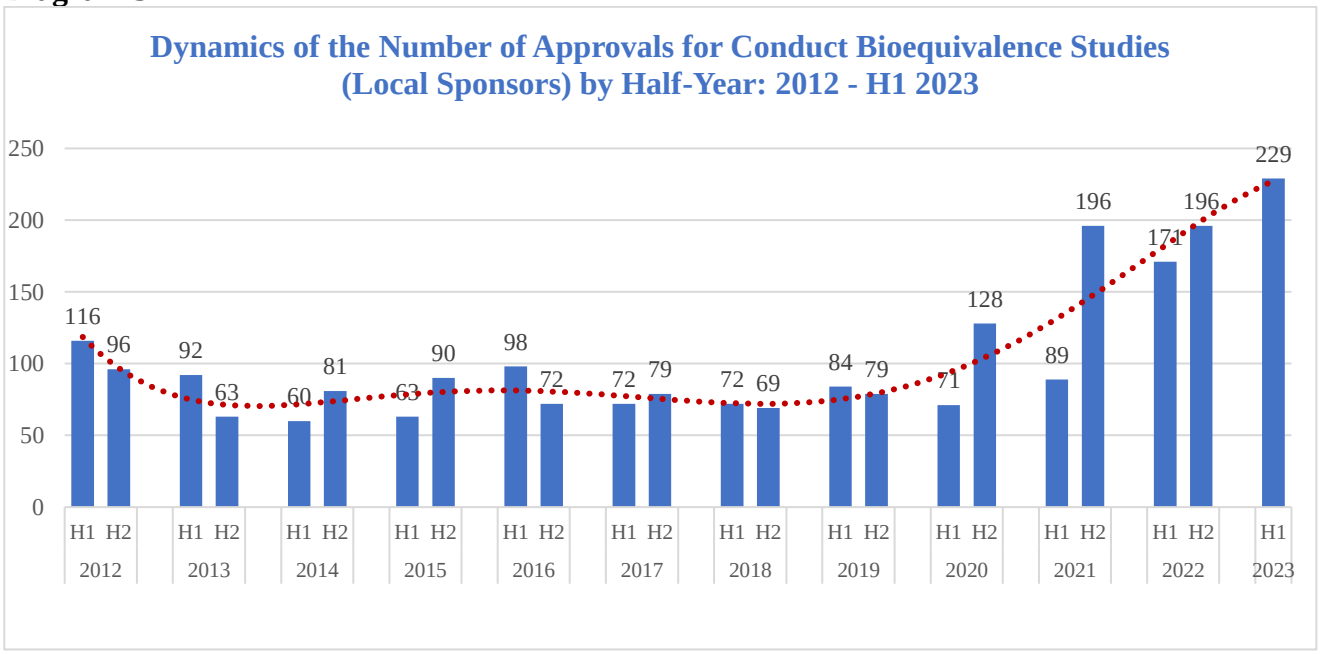


Data from www.grls.rosminzdrav.ru

Undoubtedly, since the number of approvals for IMCTs is rapidly decreasing, while the market volume generally remains the same, some other types of trials should be increasing in number.

Diagram 3 shows that the number of bioequivalence studies by Russian sponsors has been intensively increasing since 2020.

Diagram 3

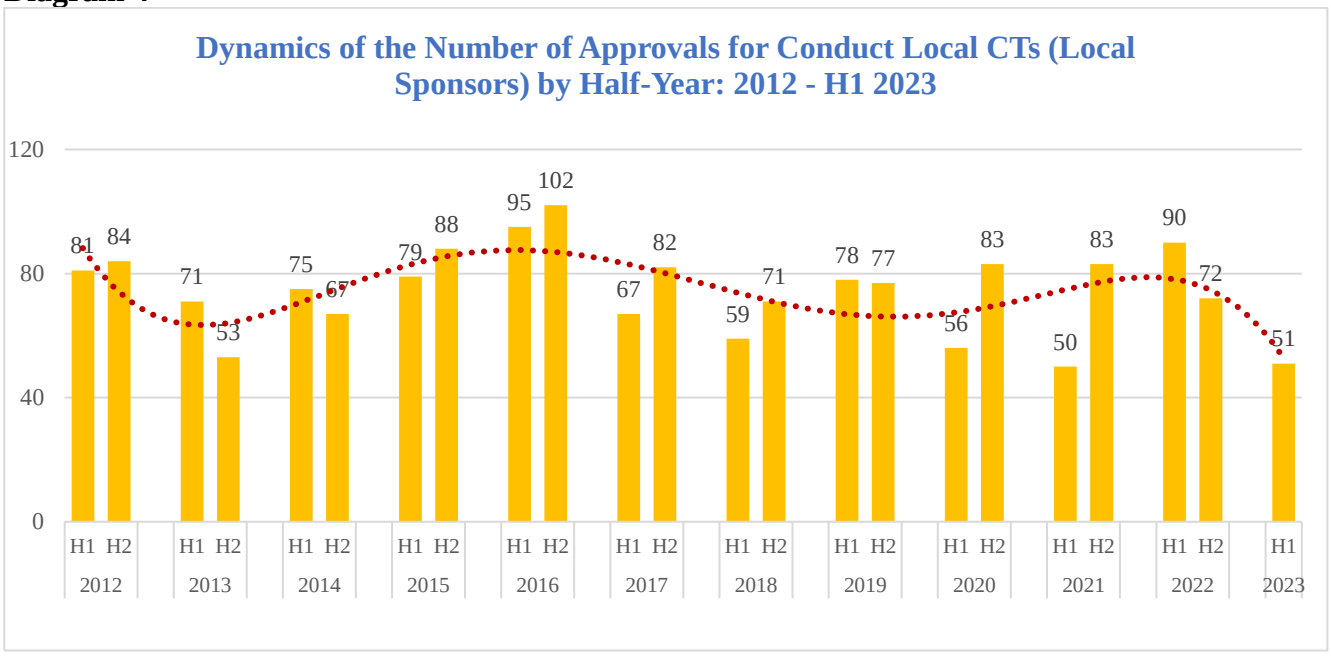


Data from www.grls.rosminzdrav.ru

In 2013–2019, the number of approvals issued for this type of trials did not exceed the token threshold of 100 approvals per a half-year period. A noticeable increase in their number followed in the second half of 2020 (128 approvals), later, in the second half of 2021 Russian manufacturers of generics took a quantum leap (196 approvals over a half-year period) and in 2022 kept the figures close to 200. In the period from January till June 2023, for the first time in the history of ACTO's monitoring, Russian sponsors received more than two hundred approvals for bioequivalence studies in six months.

Diagram 4 shows that, as opposed to bioequivalence studies, the number of local trials by Russian sponsors is not increasing, but is staying within a more or less usual range.

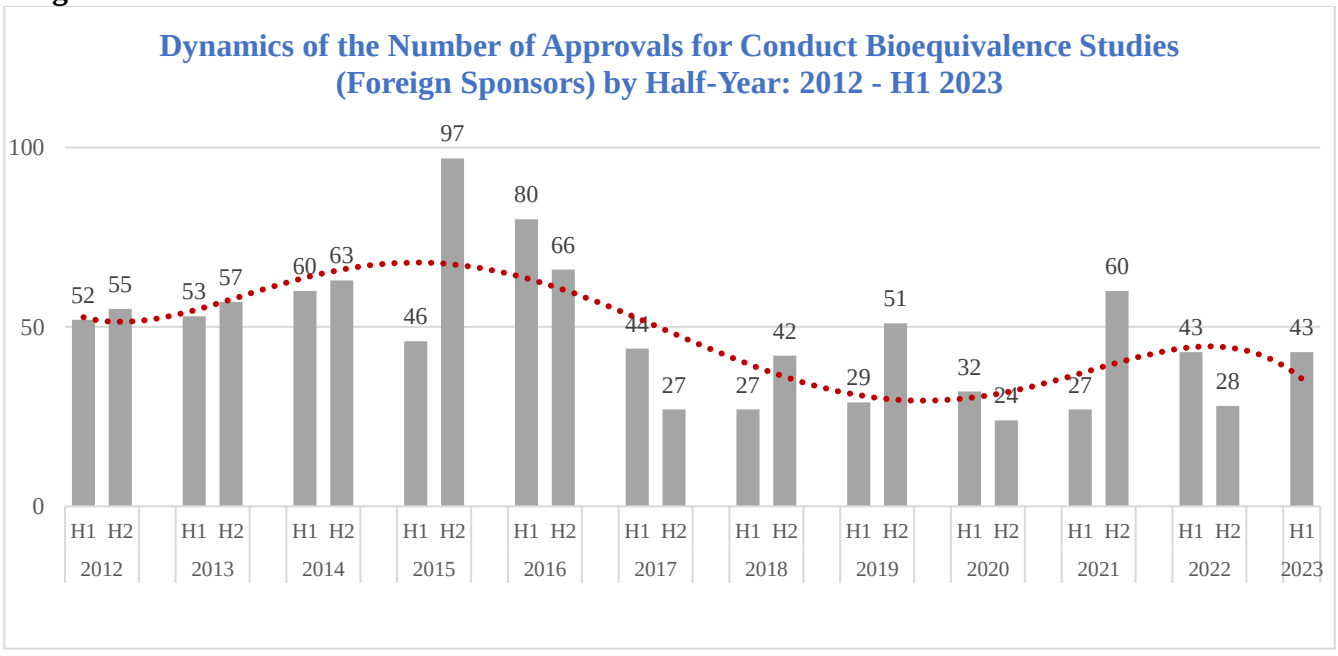
Diagram 4



Data from www.grls.rosminzdrav.ru

A remarkable trend in the dynamics of the trials (both local trials and bioequivalence studies) conducted by foreign sponsors over the period of 2012–2023 is a decrease in the average number of approvals starting from 2017 (Diagrams 5 and 6).

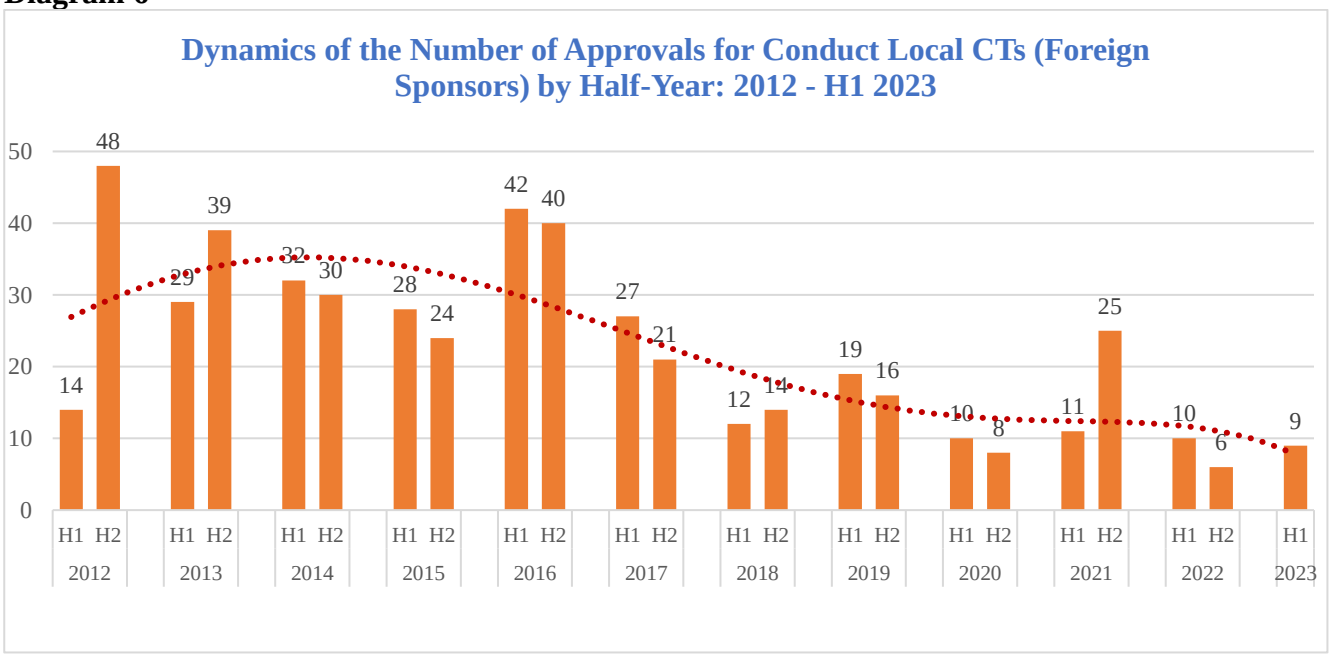
Diagram 5



Data from www.grls.rosminzdrav.ru

Various factors had an impact on this situation. Firstly, since 2016, when applying for marketing authorisation of certain dosage forms of generics (parenteral aqueous solutions, oral solutions, gases, etc.) it has become unnecessary to submit the results of "therapeutic equivalence" studies. Secondly, at the same time the requirement to submit the results of the manufacturing site inspection conducted by the Russian inspectorate as a part of the marketing authorisation application came into force. And in general, the rules of product launch to the Russian pharmaceutical market for foreign participants were becoming increasingly stricter every year, forcing them to think once again if the game was worth the candle.

Diagram 6



Data from www.grls.rosminzdrav.ru

We could see some revival in 2021, which also maintained in 2022 for bioequivalence studies. Among other things, this could result from the pandemic, which has acted as a booster for the pharmaceutical industry worldwide. And now there is a new slump. Its severity will be seen in the not-too-distant future.

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Now that we have looked at each type of trial individually, we can get back to generalizations.

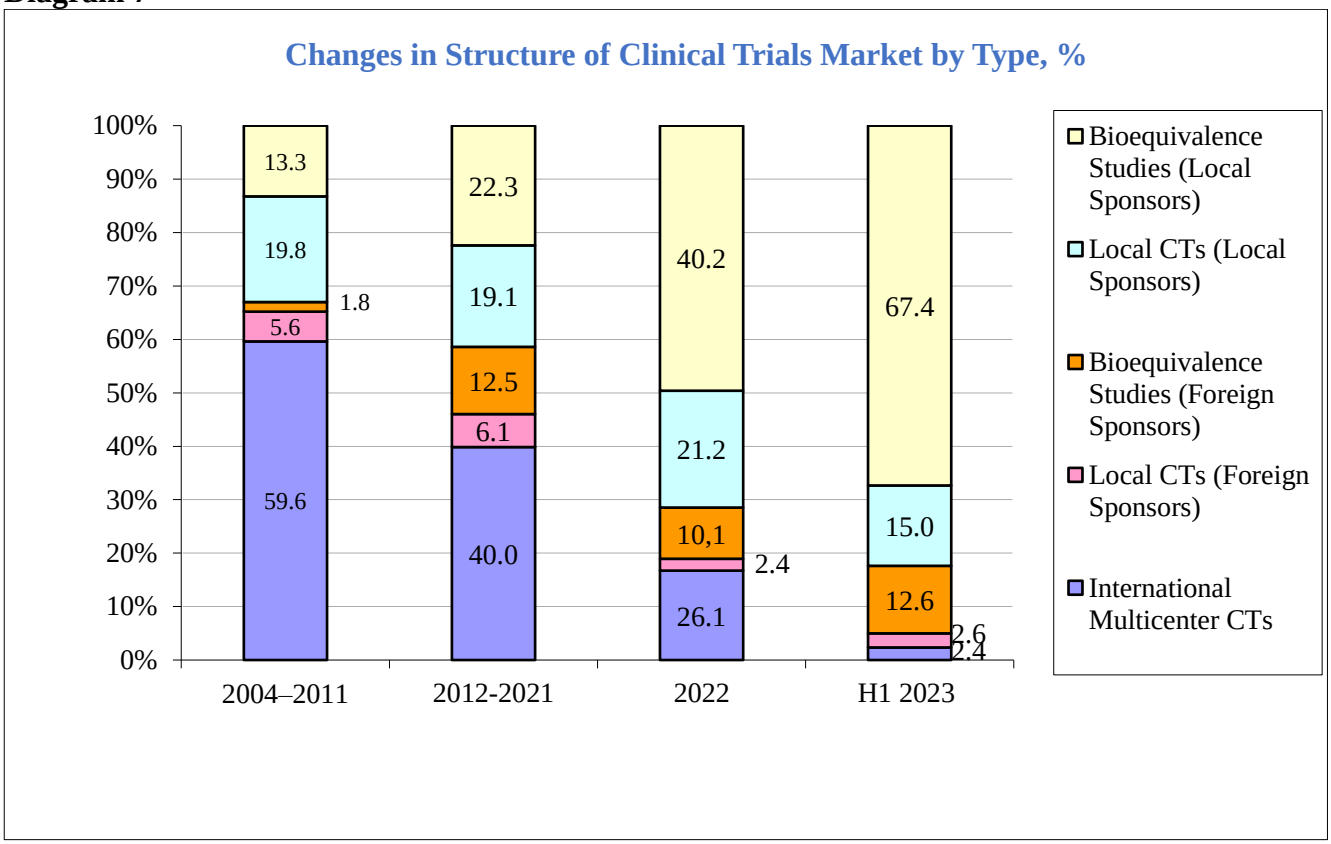
Diagram 7 shows the differences in the structure of the Russian clinical trials market in different periods: before the adoption of the current law "On Circulation of Medicines" (2004–2011), in the period after the legislative reform (2012–2021) and at present (2022 and the first six months of 2023).

After the reform, in 2012–2021, the percentage of bioequivalence studies by Russian and foreign sponsors increased (from 13.3% to 22.3% and from 1.8% to 12.5%, respectively), the percentage of IMCTs proportionally decreased (from 60% to 40%), and the percentage of local trials remained close to pre-reform levels.

The percentage of IMCTs fell to 16.8% at the end of 2022 and to a barely discernible 2.4% in the first half of 2023. Nearly half of all approvals issued in 2022 (49.6%) accounted for the bioequivalence studies applied for by Russian sponsors. And in the first half of 2023, they already accounted for two-thirds (67.4%).

The percentage of local trials by foreign sponsors over the past year and a half decreased from 6% (average for 2012–2021) to about 2.5%. The sector of local trials applied for by domestic manufacturers also showed some decline in the first half of this year: 15% vs almost 22% in the previous year. But it is a bit early to draw conclusions based on data from a half-year period, it will be easier to judge by the results of the whole year.

Diagram 7



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

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Summarizing this section of the newsletter, we can state that the number of new international clinical trials (and it is in these trials that the most modern and promising medicinal products are studied) in Russia has fallen to its lowest values over the last 20 years. The state of this market sector seems to have entered a terminal stage. In the country there are on-going projects that started before February 24, 2022, but the average duration of IMCTs is about three years. This means that very soon we will witness a rapid decline not only in the number of approvals issued for new IMCTs, but also in the number of active international trials in Russia. And what comes next? Assessment of the geopolitical outlook is beyond our competence, but the way in which political decisions affect drug development in Russia is something we will continue to monitor as long as we can.

And a few words about the regulatory authority's reaction to such a dramatically changing market situation. Our readers may remember that the previous issue of the newsletter abundantly quoted the officials from the Ministry of Health and the Ministry of Industry and Trade of the Russian Federation, who were very touchy about the news of the decrease in the number of IMCTs in the country and tried to publicly deny the inevitable fact of the collapse of the international trials market in Russia. Trying to put the best face on matters, they juggled with statistics; despite the presence of an obvious problem, they continued to insist that everything was going well, that the number of studies was not falling, but even growing.

But not everyone has Konashenkov's[2] talent. And this year, the number of such claims from the Ministry of Health has dropped drastically. Now, officials hardly mention specific figures anymore, but they are still trying to save face: "no one has left us, but if necessary, we are ready to manufacture everything by ourselves".

[2] Lieutenant General Igor Konashenkov is the chief spokesman for the Ministry of Defense of the Russian Federation.

TASS RUSSIAN NEWS AGENCY

31 MAY 2023

Foreign companies continue to submit applications for drug trials in Russia

RYAZAN, May 31. /TASS/. A significant part of foreign companies continue to apply to the Ministry of Health of the Russian Federation for approvals for conducting clinical trials of drug products in Russia. This was reported by the Deputy Minister of Health of the Russian Federation, Sergei Glagolev on Wednesday.

"We have seen the unconstructive position of some foreign drug developers who stopped submitting applications for multicentre clinical trials of new drugs. Despite such actions, a significant part of foreign representatives continue to apply to us for these approvals, and, in addition, the situation with ongoing clinical trials of medicines was practically unaffected," he said at the XXV All-Russian Conference "Pharmmedobrazheniya-2023", dedicated to the aspects of the state regulation in the sphere of circulation of medicines and medical devices.

interfax INTERNATIONAL INFORMATION GROUP

14 Jun 2023

The Ministry of Health states that almost all foreign drugs can be reproduced in Russia

Moscow, June 14, INTERFAX.RU - Deputy Head of the Ministry of Health of the Russian Federation, Sergey Glagolev believes that almost the entire range of foreign drugs can be reproduced in Russia.

"Almost the entire range of foreign medicines can be reproduced *(in Russia - IF)*, innovative medicines can be created. The key limiting factor is patent legislation," Glagolev said during the "Drug Safety" forum that took place as a part of St. Petersburg International Economic Forum on Wednesday.

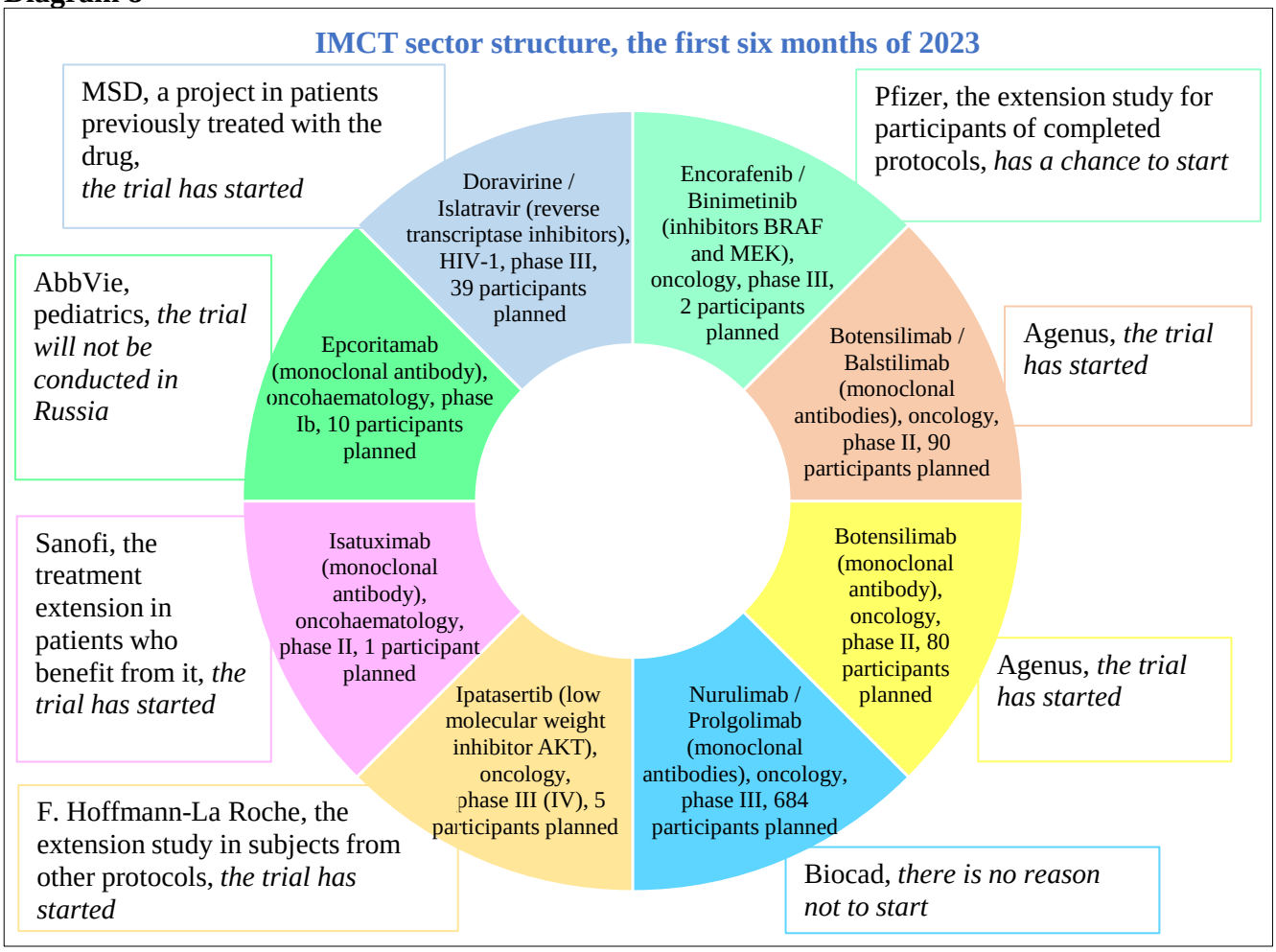
STRUCTURE AND DYMAMICS OF THE CLINICAL TRIALS MARKET BY TYPE

As we remember from the first section, there were only eight IMCTs approved during the first six months of 2023. Therefore, it is possible to discuss each of them in details (Diagram 8).

Four out of the eight protocols are so-called extension studies, which involve patients who participated in the company's previous trials of the same drug. Projects of this type typically include a small number of patients (in this particular case, one, two, five and 39 subjects). As far as we know, three of these four studies have already started, and the last one is about to start.

Of the remaining four trials, two are adequate international Phase II trials - these are trials by the US company Agenus, which are designed to study the monoclonal drug botensilimab alone and in combination with balstilimab, and involve 80 and 90 cancer patients. As far as we know, both studies have already started.

Diagram 8



Data from www.grls.rosminzdrav.ru

According to ACTO, another project approved in the first half of 2023 will not be conducted in Russia: AbbVie had applied for conducting the IMCT under the protocol *"A single-arm, open-label, phase 1b trial of Epcoritamab in pediatric patients with relapsed/refractory aggressive mature B-cell neoplasms"* before the war started. As is often the case with pediatric protocols, the regulatory authority stalled, hesitated, and asked additional questions; as a result, it has taken over a year to grant an approval. By the end of this period, the sponsor's interest in the participation of Russian centers in this project has become irrelevant.

Finally, the sponsor of the eighth trial under the protocol *"A randomized study of the efficacy and safety of neoadjuvant therapy with BCD-217 (nurulimab + prolgolimab) versus standard adjuvant*

therapy with pembrolizumab in patients with resectable stage III skin melanoma" was the Russian company, Biocad. We have already mentioned it in the previous section - among the company's five studies approved during the first half 2023, this trial was the only one that we have categorized as an IMCT. However, it should be reminded that this trial is claimed to be conducted only in two countries, Russia and Belarus.

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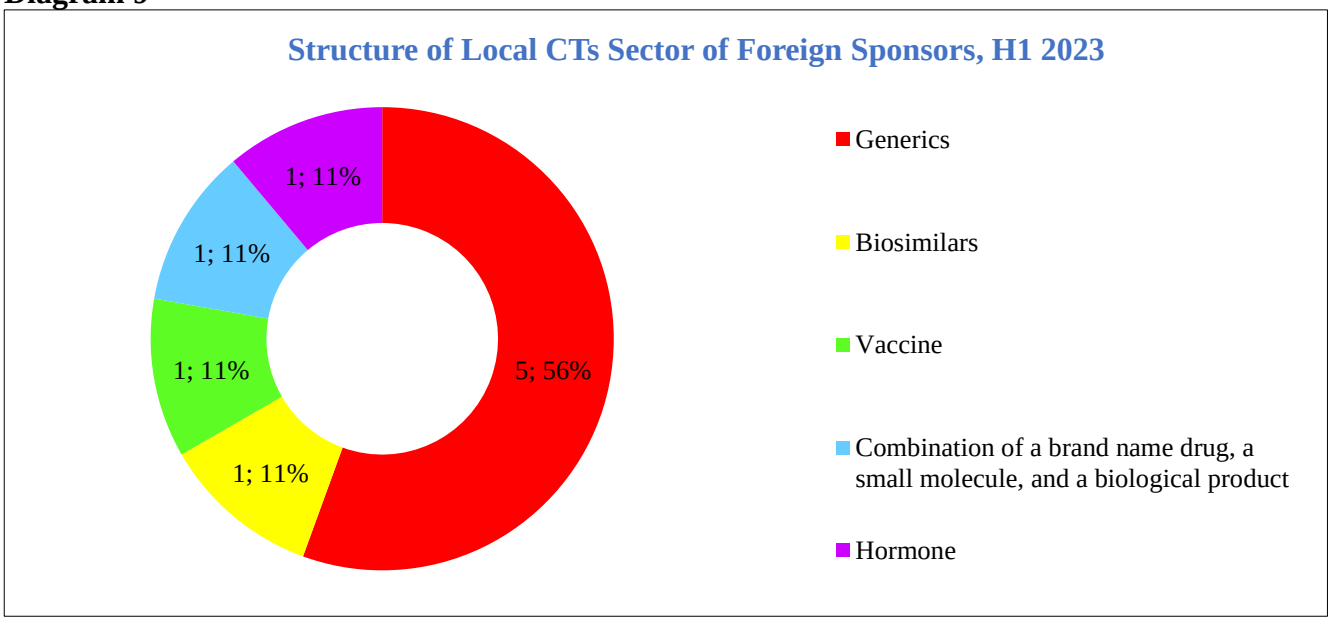
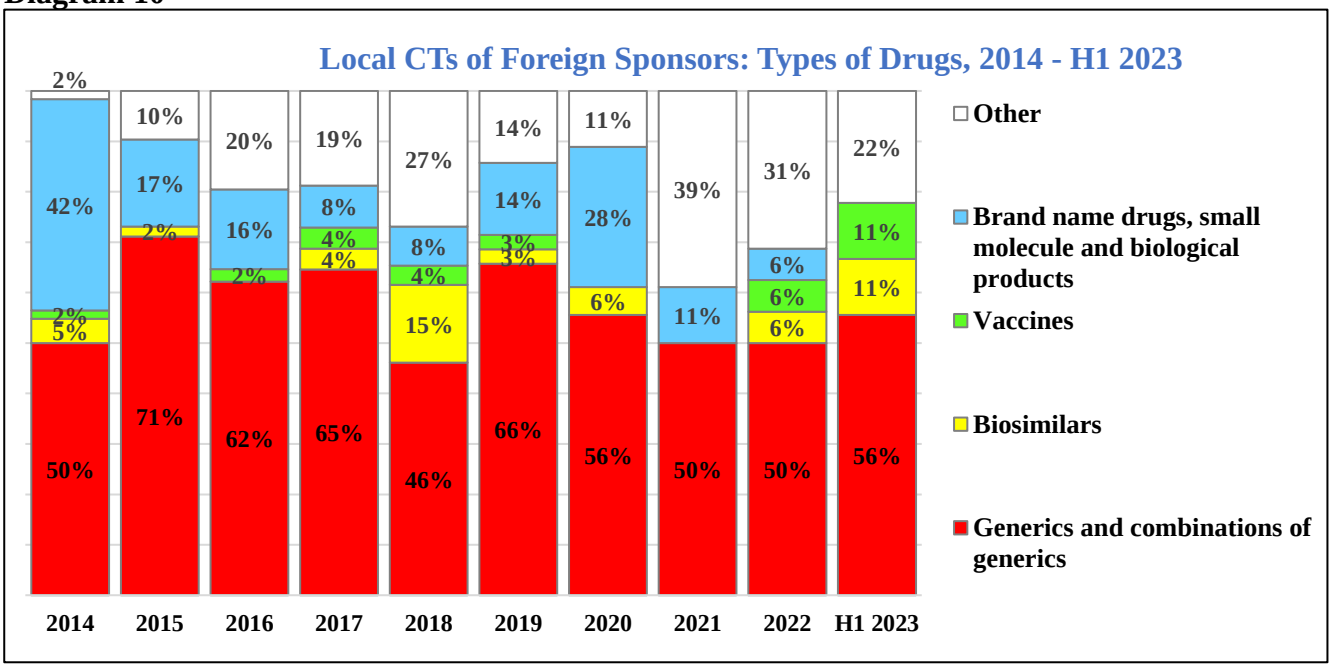
The structure of the sector of local trials by foreign sponsors looks rather typical as compared with the pattern of previous years (Diagrams 9 and 10). Five out of the nine protocols approved in the first half of the year (56%) account for generics, with one trial each for a biosimilar (tocilizumab), a vaccine to prevent meningococcal infections, a hormone (estradiol) and a combination of a biologic drug + a small molecule (durvalumab and ceralasertib for lung cancer). The total number of trials of this type is traditionally small, so even small fluctuations shift the proportions considerably, but the principle of "at least half are generics" is generally maintained.

Diagram 9



Data from www.grls.rosminzdrav.ru

Diagram 10



Data from www.grls.rosminzdrav.ru

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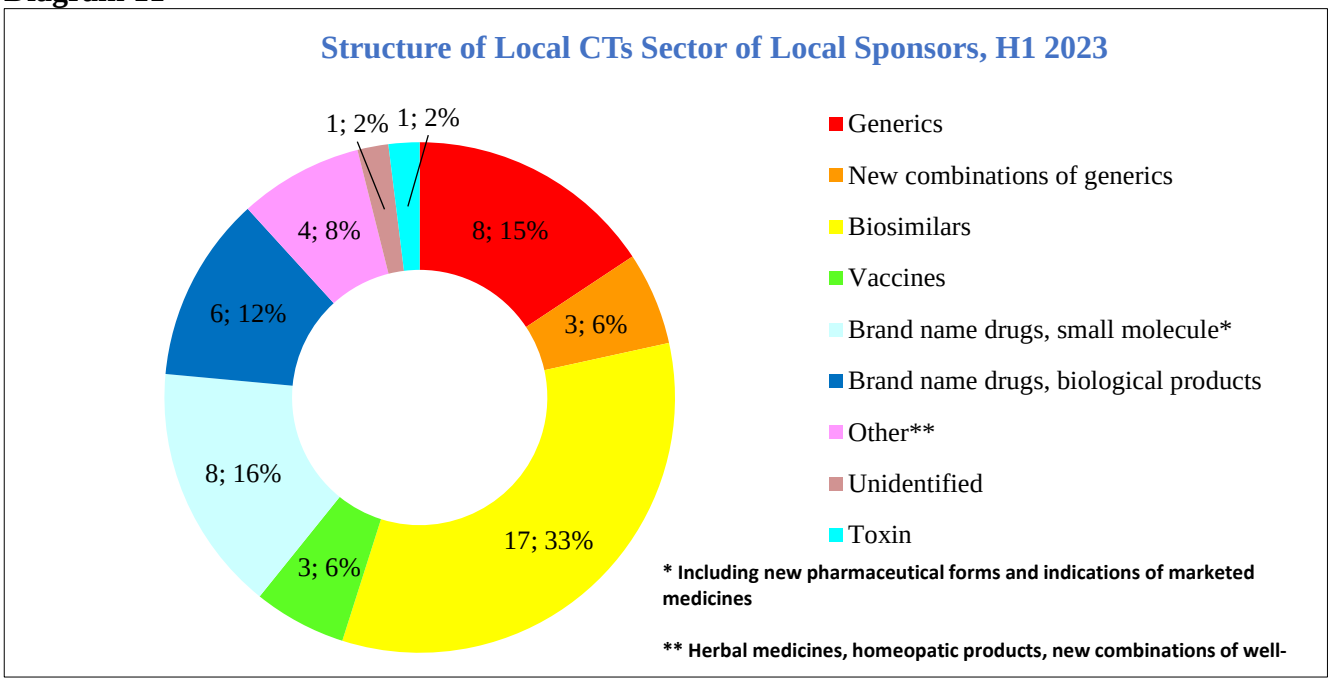
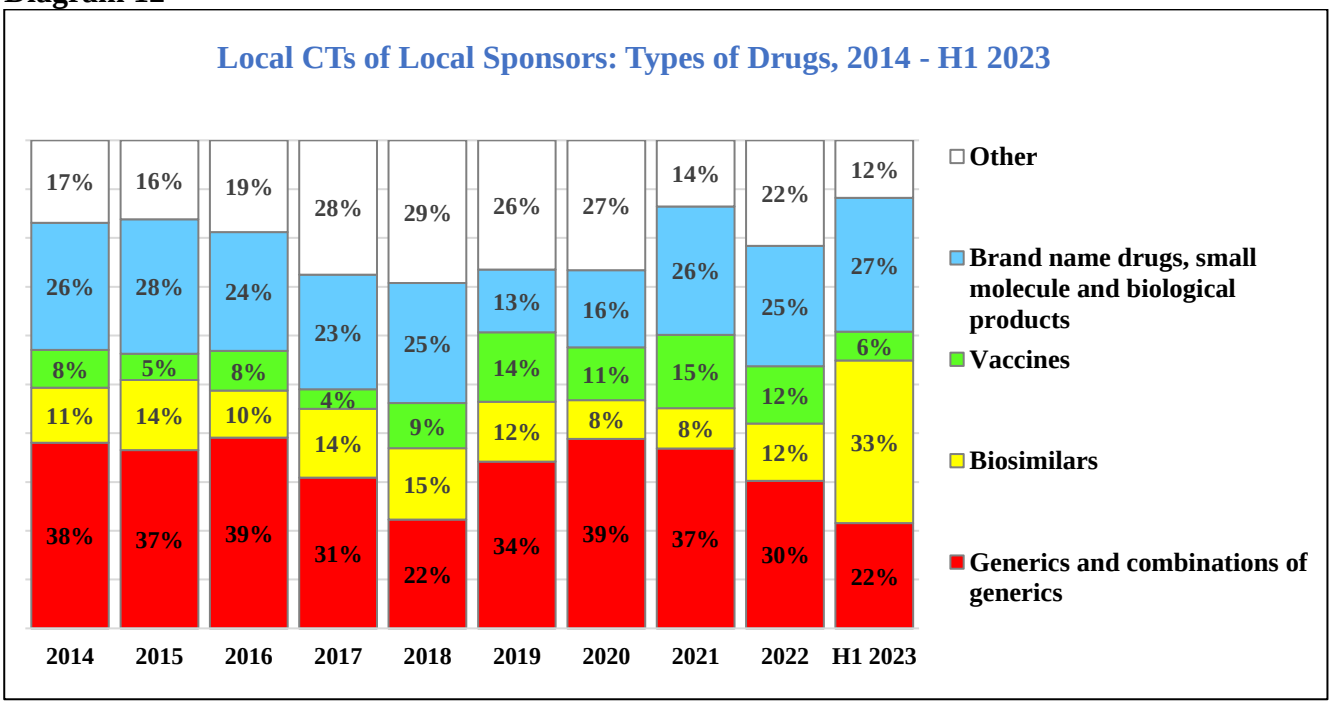
The sector structure for local trials by Russian sponsors is not so sustained (Diagrams 11 and 12). Compared to previous years, the percentage of generics and their combinations decreased in the first half of 2023. Usually these two groups together accounted for more than a third of the approvals, but in the first six months of 2023 they accounted for only 22% (eight trials of generics, and another three trials of their new combinations). On the contrary, the percentage of biosimilars trials increased markedly. With a standard rate of 15% or less, it reached 33% (17 protocols) in the first half of 2023. The growth was driven by two companies, Generium and Geropharm; they obtained four approvals each, although in 2019–2022 these companies initiated one to five trials of biosimilars per year in total.

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

Table 2 shows the distribution of IMCTs approved in the first half of 2023 by therapeutics area. Of the eight approved protocols, five protocols focused on cancer medicines (see also Diagram 8 in the previous section). Two approvals are oncohaematological, but as far as we know, one of these IMCTs will not be conducted in Russia. Another approval has been issued to study an anti-HIV medicine. There is no point in comparing the distribution of IMCTs by therapeutics area with the results obtained for 2022 because of the drastic reduction in the total number of trials of this type.

Table 2

Distribution of International Multicenter CTs by Therapeutic Areas, H1 2023			
Therapeutic Area	**Number of IMCTs**	**Share (%)**	**The number of planned participants**
Oncology	5	62.5%	861
Oncohaematology	2	25.0%	11
HIV	1	12.5%	39
TOTAL	8	100.0%	911

Data from www.grls.rosminzdrav.ru

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Table 3 shows the distribution by therapeutics area for the local trials of generics and biosimilars initiated by foreign sponsors. Cardiology and cardiovascular diseases (CVD) occupies the leading position in the top list almost every time (this area has only come in second place three times since 2013, i.e. in 2014, 2015 and 2019). The first half of 2023 was no exception: with 17 approvals, it was well ahead of other areas in the same way as before.

Other therapeutics areas accounted for five or fewer approvals each. The numbers are small, so it will be more productive to make a comparison with earlier numbers at the year's end.

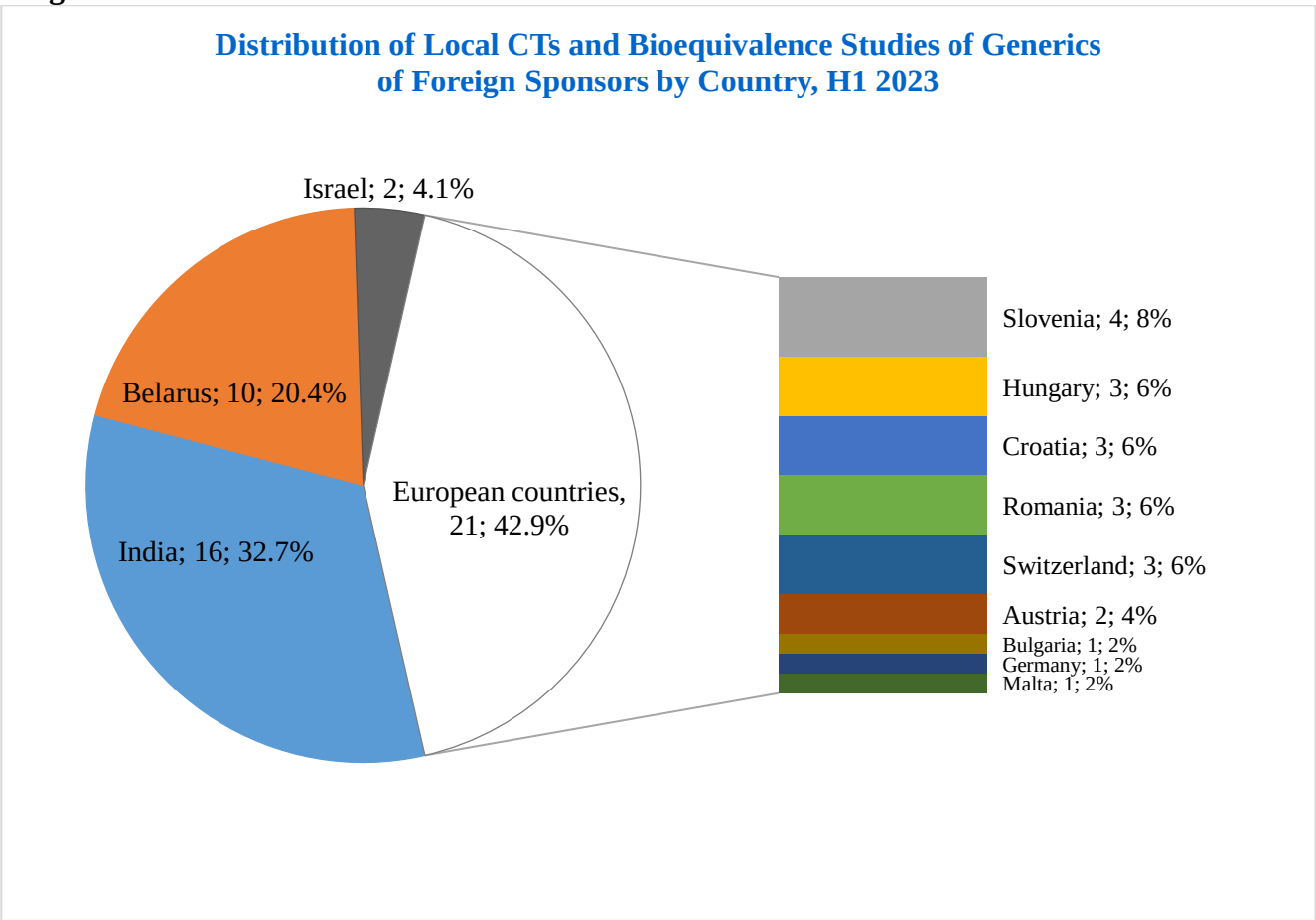
Table 3

Distribution of Local CTs and Bioequivalence Studies of Generics of Foreign Sponsors, H1 2023			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Cardiology and CVD/Vascular surgery	17	34.7%	979
Analgesic and NSAIDs	5	10.2%	393
Infectious Diseases (except HIV/HCV/tuberculosis, Covid-19)	4	8.2%	314
Gastroenterology	3	6.1%	320
Haematology	3	6.1%	197
Urology	3	6.1%	118
Endocrinology	3	6.1%	101
Dermatology	2	4.1%	302
Neurology	2	4.1%	106
Rheumatology	2	4.1%	78
Ophthalmology	1	2.0%	220
Phlebology	1	2.0%	70
Pulmonology	1	2.0%	44
Hepatology	1	2.0%	40
Oncology	1	2.0%	34
TOTAL	49	100.0%	3 316

Data from www.grls.rosminzdrav.ru

Diagram 13 shows which countries are represented by sponsor companies that have initiated local trials of generics/biosimilars and bioequivalence studies during the first half of 2023.

Diagram 13



Data from www.grls.rosminzdrav.ru

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Table 4 shows the distribution by therapeutics areas for the local trials of generics and biosimilars initiated by Russian sponsors. The five areas that together accounted for 60% of all approvals for trials of generics and biosimilars were: cardiology and CVDs (66 protocols, 25.6%), endocrinology (26 approvals, 10.1%), oncology (22 approvals, 8.5%), neurology (15 protocols, 5.8%), and gastroenterology and HIV/hepatitis C (14 approvals, 5.4% each).

Table 4

Distribution of Local CTs and Bioequivalence Studies (Generics and Biosimilars), Conducted by Local Sponsors, H1 2023			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Cardiology and CVD	66	25.6%	3 064
Endocrinology	26	10.1%	1 516
Oncology	22	8.5%	3 094
Neurology	15	5.8%	1 394
HIV/HCV	14	5.4%	671
Gastroenterology	14	5.4%	928
Infectious Diseases (except HIV/HCV/tuberculosis, Covid-19)	12	4.7%	673
Rheumatology	11	4.3%	1 093

Haematology	9	3.5%	489
Urology	8	3.1%	380
Oncohaematology	7	2.7%	286
Analgesic and NSAIDs	7	2.7%	232
Obstetrics and Gynecology	7	2.7%	814
Hepatology	5	1.9%	240
Immunology	5	1.9%	748
Covid-19	4	1.6%	320
Transplantology/ Immunology	4	1.6%	137
Allergology	4	1.6%	136
Psychiatry	4	1.6%	496
Otorhinolaryngology	3	1.2%	146
Phlebology	3	1.2%	364
Pulmonology	2	0.8%	138
Surgery	2	0.8%	130
Coloproctology	2	0.8%	60
Dermatology	1	0.4%	550
Dentistry	1	0.4%	42
TOTAL	258	100.0%	18 141

Data from www.grls.rosminzdrav.ru

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The most popular molecules in the trials of generics over the first half of 2023 are rivaroxaban (20 approvals), apixaban (eight approvals), vildagliptin (seven approvals), perindopril alone and in combination (seven approvals), and indapamide combination medicines (also seven approvals).

Table 5

Most Requested INN Used in Clinical Trials of Generics in H1 2023				
Substance	**Number of CTs of foreign generics**	**Number of CTs of local generics**	**All clinical trials to a given INN**	**Therapeutic Area**
Rivaroxaban	3	17	20	Cardiology and CVD, surgery, Covid-19
Apixaban	5	3	8	Cardiology and CVD, perhaps Covid-19
Vildagliptin	1	6	7	Endocrinology, perhaps Covid-19
Indapamide (in fixed combination)	2	5	7	Cardiology and CVD
Perindopril (separately and in fixed combinations)	1	6	7	Cardiology and CVD
Tamsulosin (separately and in fixed combinations)	2	4	6	Urology
Telmisartan (separately and in fixed combinations)	1	5	6	Cardiology and CVD
Amlodipin (in fixed combinations)	3	2	5	Cardiology and CVD
Deferasirox	1	4	5	Haematology
Sofosbuvir(separately and in fixed combinations)	–	5	5	HCV
Hesperidin (in fixed combination)	1	3	4	Phlebology
Hydrochlorothiazide (in fixed combinations)	–	4	4	Cardiology and CVD

Gliclazide	1	3	4	Endocrinology
Dapagliflozin	–	4	4	Endocrinology
Dydrogesteron (separately and in fixed combinations)	–	4	4	Gynecology
Diosmin (in fixed combinations)	1	3	4	Phlebology
Lisinopril (separately and in fixed combinations)	2	2	4	Cardiology and CVD
Axitinib	–	3	3	Oncology
Valsartan (separately and in fixed combinations)	–	3	3	Cardiology and CVD
Gabapentin	1	2	3	Neurology
Dolutegravir	–	3	3	HIV
Dutasteride (in fixed combinations)	2	1	3	Urology
Clopidogrel	2	1	3	Cardiology and CVD
Sitagliptin	–	3	3	Endocrinology, perhaps Covid-19
Tikagrelor	–	3	3	Cardiology and CVD
Estradiol (in fixed combinations)	–	3	3	Gynecology

Data from www.grls.rosminzdrav.ru

Rivaroxaban is the INN of Xarelto, Bayer's blockbuster drug, which patent protection in Russia is expiring at the end of 2025. In November 2019, Xarelto became the best-selling medicine in the country[3]. In autumn of 2020, rivaroxaban was recommended by the Ministry of Health of the Russian Federation for the treatment of coronavirus infection[4] and over three incomplete years of the pandemic it became the second most purchased medicine for Covid-19 in monetary terms in the Russian public sector[5]. The number of studies of rivaroxaban analogues grew rapidly: six in 2019, 14 and 13 in 2020 and 2021, 26 in 2022, and finally 20 in the first half of 2023. In April 2021, the first generic produced by a local manufacturer was authorised in Russia and those produced by five more Russian companies were authorised in 2022–2023. Generics of rivaroxaban from Sandoz, as well as from Indian, Slovenian and Polish companies are also authorised in Russia. Bayer is trying to combat these real-life issues, and claims have been made against Russian developers, among others[6]. As a result of at least one case (involving a company which was issued the marketing authorisation for a generic product in the Russian Federation in 2021), Bayer managed to make a settlement agreement[7]. Legal proceedings involving other companies are still on-going.[8]. Meanwhile, some Russian companies that have received a marketing authorisation for their rivaroxaban product in the Russian Federation sell it to the public authorities in small lots[9] and do not put it on free sale.

Apixaban, like rivaroxaban, is an oral anticoagulant manufactured by Bristol Myers Squibb in collaboration with Pfizer under the brand name of Eliquis. This worldwide blockbuster[10] was a top five best-seller in Russia in 2020–2022[11]. Its patent protection formally expires after 2026. Until recently, apixaban has not been very popular with generic manufacturers: over 2019–2021, there were only three trials of this substance in total, of which one trial was by a Russian sponsor. In 2019 it was included in

[3] «A prescription drug has become a sales leader for the first time since Viagra," Vedomosti, November 7, 2019
[4] Temporary guidelines "Prevention, diagnosis and treatment of new coronavirus infection (COVID-19)" Version 9 (26.10.2020), .
[5] Sales of Covid drugs in Russia over 2 years exceeded ₽500 billion,", RBK, November, 9 2022 г.
[6] "Bayer sues Russian company trying to market generic Xarelto", The Pharma Letter, May 19, 2023.
[7] «Bayer and Berezovsky Pharmaceutical Plant entered into a settlement agreement," Kommersant, March 31, 2023.
[8] «Perm manufacturer of generic drugs may be banned from selling a medicine used for Covid-19," Vedomosti, May 16 2023
[9] «The Russian analogue of the most expensive anticoagulant will cost 20 rubles. per tablet", Pharmmedprom, April 27 2023
[10] "The top 20 drugs by worldwide sales in 2020", Fierce Pharma, May 3, 2021.
[11] «In 2022, Russians began to spend more on medicines in pharmacies," Pharmvestnik, February 08 2023

the regional Moscow program of free drug provision for citizens suffering from CVDs, and in 2020 it was included in the list of medicines used in the treatment of coronavirus infection, but this fact did not change the situation. The increase started later: nine approvals for trials of apixaban analogues were issued in 2022, six of them were obtained by Russian companies, with five approvals out of six issued in June and later. Interestingly, on June 3, it became known about the plans of the St. Petersburg authorities to conclude a so-called offset agreement, under which a part of the funds required to launch production of specific medicines is allocated from the budget. The rest of the funds is sought by the manufacturer, and the city authorities undertake to buy the medicines released by the manufacturer for an agreed period of time and at an agreed price[12]. St. Petersburg administration was going to organize manufacturing of several medicines, including apixaban, rivaroxaban, and vildagliptin.[13] Later, a similar contract also including apixaban was awarded by the Moscow Mayor's Office[14]. As of mid-August 2023, there are no Russian companies that have obtained a national marketing authorisation for their generics; only an analogue from Polish Polpharma is present in the registry. But by the time the patent expires, Russian sponsors will surely take advantage of the situation.

Vildagliptin is an antidiabetic medicine marketed by Novartis whose patent protection expired in December 2019. It ranked third in our 2019 list of popular generics, but the trials were initiated almost exclusively by foreign sponsors. In 2020, four Russian companies also tested its analogues. In 2021, these were two foreign and four Russian companies. At the same time, in 2021, the first Hungarian-made generic vildagliptin was authorised in Russia. But in 2022, the real growth in popularity among the local manufacturers began: there were 13 approvals, 11 of which were issued to Russian legal entities.

Indapamide/perindopril is a combination widely used to lower blood pressure. Both products have been on the market (the global and the Russian ones) long enough for their patent protection to have expired. Both medicines are on the list of vital and essential medicines, which means a stable demand for them, including on the part of the public authorities. The number of trials of their analogues is growing along with the general increase in the activity of Russian generics manufacturers after 2019.

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Tables 6 and 7 contain information on the therapeutics areas to which local trials of originator products by foreign and Russian sponsors belong, respectively.

There are only three protocols applied for by the foreign sponsors: Belgian Besins Healthcare initiated a study of its Estrogel® product in female patients with estradiol deficiency, Indian Serum Institute initiated a study of a meningococcal vaccine, and British AstraZeneca initiated a study of the combination of ceralasertib and durvalumab in patients with advanced or metastatic non-small cell lung cancer.

Table 6

Distribution of Local CTs of Brand Name Drugs of Foreign Sponsors, H1 2023			
Therapeutic Area	**Number of CTs**	**Number of planned participants**	**Developer's country**
Gynecology	1	332	Belgium
Infectious Diseases (except HIV/HCV/tuberculosis, Covid-19)	1	80	India
Oncology	1	55	Great Britain
TOTAL	3	467	

Data from www.grls.rosminzdrav.ru

[12] «Smolny will announce a competition for the first offset contract by the beginning of autumn," Vedomosti, June 03 2022

[13] «FV" found out a possible list of drugs for concluding the St. Petersburg offset", Pharmvestnik, August, 02 2022

[14] «R-Pharm won another offset contract for the supply of medicines," Pharmvestnik, March 17 2023

In 2020–2022, the most popular therapeutics area among Russian developers was Covid-19, but the pandemic ended, and in the first half of 2023, pulmonology and hematology shared the first place. However, there are only three protocols for each of these areas. If tuberculosis and Covid-19 were counted along with other infectious diseases in ACTO newsletters, this area would occupy the leading position. But we traditionally break them down into separate categories, so they were all lower in the rankings, along with rheumatology, psychiatry, and neurology. There were two protocols for each of these areas. And one protocol was issued for each of nephrology, oncology, urology and endocrinology.

Table 7

Distribution of Local CTs of Brand Name Drugs (Including Biological Products) of Local Sponsors, H1 2023			
Therapeutic Area	**Number of CTs**	**Share (%)**	**Number of planned participants**
Pulmonology	3	13.6%	335
Haematology	3	13.6%	164
Tuberculosis	2	9.1%	620
Infectious Diseases (except HIV/HCV/tuberculosis, Covid-19)	2	9.1%	530
Covid-19	2	9.1%	520
Rheumatology	2	9.1%	374
Psychiatry	2	9.1%	288
Neurology	2	9.1%	58
Urology	1	4.5%	632
Nephrology	1	4.5%	210
Oncology	1	4.5%	60
Endocrinology	1	4.5%	46
TOTAL	22	100.0%	3 837

Data from www.grls.rosminzdrav.ru