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Strategic Indicators in the Development of Original Medicinal Products in 2024: Analysis of Pipelines of International Pharmaceutical Leaders

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ABSTRACT

INTRODUCTION. Major international pharmaceutical companies play a crucial role in the development of original medicines. To determine the directions for original medicines development in Russia, it is essential to analyze global trends and emerging weak signals (tendencies) – early indicators of future-significant innovations.

AIM. This study aimed to identify trends and emerging weak signals that could shape pharmaceutical development in Russia through an analysis of the pipeline of original medicines being developed by global pharma leaders.

MATERIALS AND METHODS. An analysis was conducted on the medicinal product development plans for 2024 of the 20 largest pharmaceutical companies globally, which have the highest research and development budgets. The focus was on original medicines scheduled for clinical trials Phase 1 from January to May 2024. A descriptive research approach was applied, based on retrospective analysis of secondary data. The study measured the number of original medicines under development, research directions, target classes, medicine types, and groups. Both quantitative and qualitative evaluations were used to identify key trends and tendencies (emerging weak signals) in pharmaceutical development of medicines.

RESULTS. During the analysed period, 17 out of 20 leading pharmaceutical companies initiated Phase 1 trials for a total of 84 original medicines. The most active research areas included oncology, endocrinology and metabolism, cardiovascular system, and immunology. Notably, 40 medicines entered Phase 1 trials in oncology. The largest share (42%) of the medicines in development consists of high molecular weight molecules. Based on the number of medicines developed by multiple companies, trends were identified for the following medicine classes: "Large molecule" – bispecific antibodies (10 medicines, 5 developers); monospecific antibodies (8 medicines, 7 developers); antibody-drug conjugates (8 medicines, 3 developers); "Small molecule" – enzyme inhibitors (9 medicines, 6 developers); "Cell therapy" – CAR-T-based therapies (6 medicinal products, 2 developers).

CONCLUSIONS. Current trends in targeted therapy development include the creation of bispecific antibodies and next-generation antibody-drug conjugates, alongside CAR-T therapies based on autologous T cells, predominantly for the treatment of malignant neoplasms. The study of multispecific antibodies is shaping a new direction in targeted cancer therapy. The development of low-molecular-weight enzyme inhibitors is establishing a trend in various therapeutic areas. Specifically, enzyme inhibitors of targets based on synthetic lethality principle (such as WRN and PRMT5) are emerging as a key tendency in small-molecule medicine development for targeted cancer therapy.

Keywords: original drugs; medicinal products; global trends; tendencies; emerging weak signals; pipeline; Phase I; clinical trials; drug development

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Стратегические индикаторы в разработке оригинальных препаратов в 2024 году: анализ пайплайнов международных фармацевтических лидеров

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РЕЗЮМЕ

ВВЕДЕНИЕ. Ключевое влияние на планирование разработки оригинальных лекарственных препаратов оказывают крупнейшие зарубежные фармацевтические компании. Для определения направлений разработки оригинальных препаратов в России актуален анализ мировых трендов и слабых сигналов (тенденций) – ранних индикаторов значимых в будущем инноваций.

ЦЕЛЬ. Выявление трендов и тенденций, способных оказать влияние на фармацевтическую разработку в России, путем анализа спектра разрабатываемых оригинальных препаратов крупнейшими зарубежными компаниями.

МАТЕРИАЛЫ И МЕТОДЫ. Проведен анализ планов разработки препаратов на 2024 г. 20 крупнейших на мировом рынке зарубежных фармацевтических компаний, имеющих наиболее высокие бюджеты на исследования и разработки. Проанализированы оригинальные препараты, запланированные к изучению в клинических исследованиях I фазы за период январь-май 2024 г. Применена концепция описательного исследования, которая базируется на ретроспективном анализе вторичных данных. Измерениями проведенного анализа являлись номенклатура разрабатываемых оригинальных препаратов, направления разработки, целевые классы, виды и группы препаратов. На основании количественной и качественной оценки проводилось определение трендов и тенденций (слабых сигналов) в разработке оригинальных препаратов.

РЕЗУЛЬТАТЫ. За анализируемый период 17 из 20 крупнейших фармацевтических компаний включили в исследования I фазы 84 оригинальных препарата. Больше всего разрабатываемых молекул определено в направлениях: онкология, эндокринология и обмен веществ, сердечно-сосудистая система, иммунология. 40 препаратов включены в исследования I фазы в направлении онкология. Наибольшее количество препаратов (42%) относится к молекулам с относительно высокой молекулярной массой. На основании выявленного количества препаратов у нескольких разработчиков сделано предположение о наличии трендов разработки для следующих классов: «Большая молекула» – биспецифическое антитело (10 препаратов, 5 разработчиков); моноспецифическое антитело (8 препаратов, 7 разработчиков); конъюгат антитело-лекарственное средство (8 препаратов, 3разработчика); «Малая молекула» – ингибиторы ферментов (9 препаратов, 6 разработчиков); «Препарат клеточной терапии» – препараты на основе CAR-T технологии (6 препаратов, 2 разработчика).

ВЫВОДЫ. Актуальными трендами в развитии таргетной терапии является разработка биспецифических антител и конъюгатов «антитело–лекарство» нового поколения, параллельно с разработкой CAR-T препаратов на основе аутологичных Т-клеток, преимущественно для терапии злокачественных новообразований. Исследование препаратов группы мультиспецифических антител формирует тенденцию разработки препаратов для таргетной терапии рака. Создание низкомолекулярных ингибиторов ферментов определяет тренд разработки препаратов в различных терапевтических областях. Разработка ингибиторов ферментов, воздействующих на мишени, основанные на принципе синтетической летальности (такие как WRN и PRMT5), является тенденцией в разработке малых молекул для прицельной терапии злокачественных опухолей.

Ключевые слова: оригинальные лекарственные препараты; мировые тренды; тенденции; слабые сигналы; пайплайн; клинические исследования I фазы

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Финансирование. Работа выполнена в инициативном порядке, без спонсорской поддержки. Исследование проведено при финансовой поддержке Минздрава России, направленной на обеспечение деятельности координационного центра исследований и разработок в области медицинской науки ФГБУ «ЦНИИОИЗ» Минздрава России в рамках реализации федерального проекта «Медицинская наука для человека».

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INTRODUCTION

Major global pharmaceutical companies exert significant influence on the range of original medicinal products (MPs) under development. Effective strategies that facilitate the advancement of promising MP research enable these companies to maintain competitive edge, create long-lasting business models, and shape shifts in conventional clinical paradigms by offering innovative solutions. This ultimately determines their long-term success in the pharmaceutical market [1].

Analysis of global trends and tendencies (weak signals) in the development of original MPs is one of the key tools for understanding potential growth vectors for the Russian manufacturers. It helps identify target medical conditions, new therapeutic targets and development approaches most justified in terms of proven clinical effect, meeting patient needs, and commercial viability.

The aim of this study is to identify trends and tendencies that may affect pharmaceutical development in Russia by analysing the range of original medicinal products developed by the largest foreign companies.

Research tasks: to analyse 2024 MP development plans of 20 largest international pharmaceutical companies; to identify MPs scheduled for study in clinical trials (CT) Phase I; to analyse the distribution of MPs by therapeutic areas/medical fields and indications; to develop an approach to MPs classification; to determine drug targets; to identify trends and tendencies (weak signals) in MPs development.

MATERIALS AND METHODS

MP development pipelines were analysed for 2024, focusing on 20 largest pharmaceutical companies in the global market with the highest R&D budgets for MPs in 2023[1]. The companies' pipelines (Merck & Co., Roche, Novartis, Johnson & Johnson, AstraZeneca, Pfizer, Eli Lilly, Bristol Myers Squibb, GSK, AbbVie, Sanofi, Gilead Sciences, Boehringer Ingelheim, Moderna, Takeda, Amgen, Novo Nordisk, Regeneron Pharmaceuticals, Bayer, Otsuka Pharmaceutical)[2] are publicly available on the companies' official websites and were used to assess the range of MPs under development. Data provided by the companies as of May 2024 were used for the analysis; this limitation is due to differing update schedules on company websites.

MPs scheduled for study in CT Phase I were identified for all companies listed over January-May 2024. Pharmaceutical companies were ranked by their R&D investment scopes and the number of original MPs scheduled for first-in-human trials during the analysed period. MPs were categorised by therapeutic areas/medical fields.

Development areas and indications for these MPs were assessed according to the International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10).

MPs were categorised by classes, types and groups. In this work, a class denotes a typically

[1] Drug Discovery and Development. Top 25 investors in pharma R&D 2023.

[2] https://www.merck.com/research/product-pipeline/; https://www.roche.com/solutions/pipeline/; https://www.novartis.com/research-development/novartis-pipeline; https://www.investor.jnj.com/pipeline/development-pipeline/default.aspx; https://www.astrazeneca.com/our-therapy-areas/pipeline.html; https://www.pfizer.com/science/drug-product-pipeline; https://www.lilly.com/discovery/clinical-development-pipeline; https://www.bms.com/researchers-and-partners/in-the-pipeline.html; https://www.gsk.com/en-gb/innovation/pipeline/; https://www.abbvie.com/science/pipeline.html; https://www.sanofi.com/en/our-science/our-pipeline; https://www.gilead.com/science-and-medicine/pipeline; https://www.boehringer-ingelheim.com/human-pharmaclinical-pipeline; https://www.modernatx.com/research/product-pipeline; https://www.takeda.com/science/pipeline/; https://www.amgen-pipeline.com/; https://www.novonordisk.com/science-and-technology/r-d-pipeline.html; https://www.regeneron.com/pipeline-medicines/investigational-pipeline; https://www.bayer.com/en/pharma/development-pipeline; https://www.otsuka.co.jp/en/research-and-development/pipeline/

common chemical structure of molecules. MP class names are given according to formulations proposed in the pipelines (with Russian translations). MPs are systematised by type and group within classes based on commonalities in MP development technologies; the system was proposed by the project coordination center "Medical Science for Humanity". MP type refers to biological and/or chemical synthesized medicinal products. MP group refers to biological and/or chemical synthesized medicinal products united by a common specific development technology and potential physicochemical or chemical interaction with targets.

A descriptive research concept was applied based on retrospective analysis of secondary data. The object were the original MPs in development, development vectors and therapeutic areas, target classes, types and groups of MPs.

To determine trends in original MP development, classes, types, and groups of MPs developed by the largest number of companies and in the greatest amount were identified. In this work, trends were understood as identified similarities in the choice of MPs developed by several companies (at least two), indicating a common pathway of pharmaceutical development.

Classes with the largest numbers of MPs were evaluated for emerging tendencies (weak signals). In pharmaceutics, a tendency (weak signal) is an early, often faint sign of a potential change that may interfere with the industry in the future. Such signals require monitoring, since they can lead to new trends. Thus, weak signals are indicators of potentially significant events in the future; applied to the pharmaceutical industry, they mark the emergence of promising new developments. It was assumed that a tendency (weak signal) in drug development could be MPs forming a fundamentally new group of products and meeting three proposed qualitative criteria to determine the tendency status:
1) published information indicating potential clinical significance of MPs in the new group;
2) no currently registered MPs worldwide that could be classified into this group;
3) publications reporting that several MPs of this group have been advanced to clinical trial stages.

Based on information about several MPs of the same class being developed that have the similar target, an assumption was also made about existing tendency in MP development *(Fig. 1)*.

RESULTS AND DISCUSSION

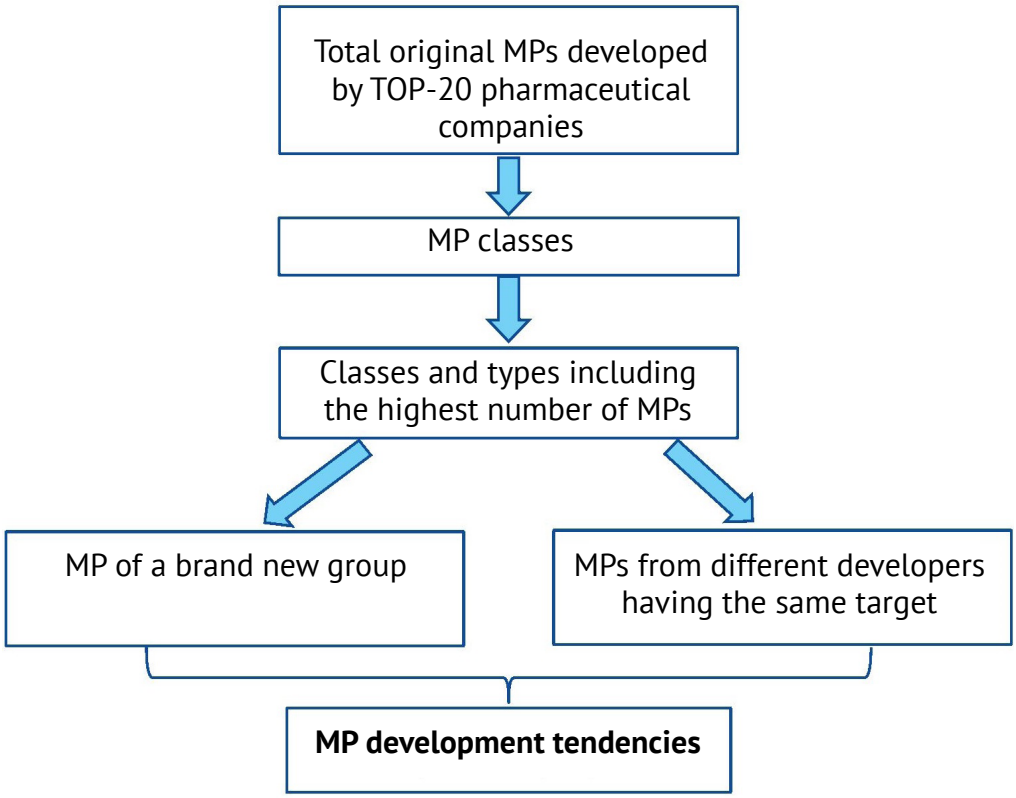
During the study period (January-May 2024), 17 out of 20 companies initiated CT Phase 1 for a total of 84 new original MPs *(Table 1)*. Leaders by number of new MPs in pipelines were AstraZeneca (n=18), Pfizer (n=13), and Bristol Myers Squibb (n=9). Analysis of Merck, Takeda and Otsuka Pharmaceutical pipelines did not reveal any new molecules scheduled for Phase I trials.

Analysis of therapeutic areas/fields and indications. MPs included in CT Phase I can be classified into 12 development areas *(Table 2)*. Forty MPs (48%) concern Oncology, underlining its priority status. AstraZeneca (n=11), Pfizer (n=8), Bristol Myers Squibb (n=6), and Novartis (n=5) showed high activity in this therapeutic area. Other priority development areas include Endocrinology and Metabolism, Immunology, and Cardiovascular system.

Analysis showed that out of 84 MPs, 76 (90%) could be aligned with ICD-10 classes and groups, while eight (8) MPs (10%) were difficult to allocate due to broad range of indications (e.g., fibrosis). For Immunology, ICD-10 analysis was a challenge because of the wide spectrum of indications specified by developers (autoimmune diseases, inflammation etc.). Therefore, instead of Immunology, the next most numerous area, Cardiovascular system, was analysed. Systematised quantitative distribution of the developed original MPs according to their indications as per ICD-10 classes and groups is presented in *Table 3 "Distribution of Indications for Investigational Original Drugs Scheduled for First-in-Human Trials in 2024 by Total Drug Count, Classes and ICD-10 Groups"* (published on the journal website[3]).

Analysis of MP classes, types, and groups. Among 84 original MPs included in pipelines for CT Phase I, 11 drugs could not be classified, so 73 MPs were included in the class-based analysis. MP distribution is presented in *Table 4 "Distribution of Investigational Original Drugs Scheduled for First-in-Human Trials in 2024 by Class, Type and Group"* (published on the journal website[4]).

[3] https://doi.org/10.30895/1991-2919-2025-752-annex
[4] Ibid.



The figure is prepared by the authors / Рисунок подготовлен авторами

Fig. 1. *Flowchart for identifying tendencies (weak signals) in the development of original medicinal products*

Рис. 1. *Схема определения тенденций (слабых сигналов) в разработке оригинальных лекарственных препаратов*

The most frequently developed MP classes are: Large molecule (42%); Small molecule (27%); Cell therapy product (12%). To identify trends, the number of MPs with similar structures and the number of companies initiating their development were assessed.

The Large Molecule class lists the following MP groups that define the trends: monospecific antibody (monoclonal antibody, MAb); antibody-drug conjugate (ADC); bispecific antibody (BsAb). ADCs and BsAbs have reached the global market relatively recently, and to date, a comparatively small number of these products have been registered [5].

Within the Large molecule class, noteworthy is Multispecific antibody group represented by a single drug candidate being developed *(Table 4)*. Despite being the only MP assigned to this fundamentally new group, it still defines a development tendency (weak signal) within the Large Molecule class. This conclusion is justified by combination of the following criteria: published information on the potential clinical significance of MPs belonging to the Multispecific antibody group [2]; currently absent MPs authorised worldwide that could be classified within this group [3]; and the confirmed clinical development stage of a number of multispecific antibodies [4].

Within the Small molecule class, the dominant group defining development trend is enzyme inhibitors *(Table 4)*. In this group, the fact that several developers have multiple MPs designed for the same biological target suggests emerging tendencies in the development of WRN inhibitors and PRMT5 inhibitors.

In the Cell therapy products, prevalent MPs belong to one group that defines the development trend: CAR-T based on autologous T-lymphocytes. No additional tendencies were identified for this class.

It is reasonable to deem the above MP groups as the current key development areas among the analysed foreign pharmaceutical companies and to consider them in more detail in connection with the new drug candidates presented by these companies.

Large Molecule class. Monoclonal antibodies have been widely marketed since 1986 [6].

Table 1. *Distribution of pharmaceutical companies by R&D investment scope and number of original medicines scheduled for first-in-human trials in 2024*
Таблица 1. *Распределение фармацевтических компаний по объемам инвестиций в R&D и количеству оригинальных препаратов, запланированных к первому применению у человека в 2024 г.*

Company *Название компании*	**Rank of R&D investments, 2023** *Место компании в рейтинге инвестиций в R&D в 2023 г.*	**R&D investments, 2023 ($ billion)** *Инвестиции в R&D в 2023 г. (млрд $)*	**Number of medicinal products** *Количество наименований препаратов*
Merck & Co	1	30,5	0
Roche	2	14,7	5
Novartis	3	13,6	6
Johnson & Johnson	4	11,9	3
Astra Zeneca	5	10,9	18
Pfizer	6	10,6	13
Eli Lilly	7	9,3	7
Bristol Myers Squibb	8	9,2	8
GSK	9	7,7	6
AbbVie	10	7,6	1
Sanofi	11	7,2	5
Gilead Sciences	12	5,7	2
Boehringer Ingelheim	13	5,6	3
Moderna	14	4,84	1
Takeda	15	4,80	0
Amgen	16	4,78	2
Novo Nordisk	17	4,70	4
Regeneron Pharmaceuticals	18	4,4	1
Bayer	19	3,5	1
Otsuka Pharmaceutical	20	2,0	0

The table is prepared by the authors using official websites of pharma companies as of December 2024 / Таблица составлена авторами по данным, размещенным на официальных интернет-ресурсах фармацевтических компаний по состоянию на май 2024 г.

Note. *R&D, Research and Development.*
Примечание. *R&D – Исследования и разработки.*

Currently, the U.S. Food and Drug Administration (FDA) has approved more than 100 therapeutic monoclonal antibodies, which have made breakthroughs in tumour immunotherapy and substantially improved survival of patients with certain tumours and other diseases [7]. MAbs have changed the framework of cancer therapy thanks to precise targeting of tumour surface antigens; however, MAbs alone are often insufficient [8]. The ADC concept emerged to bridge the gap between MAbs and cytotoxic agents, thereby improving the therapeutic window. The key idea behind ADC is targeted delivery of a cytotoxic drug to tumour cells while minimising systemic toxicity. ADCs can also recruit immune cells to eliminate target cells [9].

ADCs are targeted agents in which a cytotoxic substance connects to a MAb via a chemical linker. ADCs enable focused delivery of cytostatic to target cells with reduced systemic toxicity [10]. The first ADC, Mylotarg (gemtuzumab ozogamicin), was approved in 2000 for the treatment of acute myeloid leukaemia [11]. Currently, a notable expansion of targets and indications for ADCs is observed. Existing strategies for developing next-generation ADCs suggest high potential of this category for advancing targeted cancer therapy and potential replacement of traditional chemotherapy in the future [12].

Three companies focus on ADC development *(Table 4)*. Most ADCs being developed target solid tumour antigens. One of the eight ADCs in CT Phase I (BL-B01D1, Bristol Myers Squibb) is first-in-class[5]. It is a bispecific antibody-drug conjugate targeting human epidermal growth factor receptor type 3 (HER3) and epidermal growth factor receptor (EGFR). EGFR and HER3 are highly expressed in epithelial tumours.

[5] «Первые в классе» («First-in-class») — препараты, имеющие механизм действия, отличный от механизма действия препаратов, применяемых в существующей практике.

Table 2. *Distribution of original medicines scheduled for first-in-human trials in 2024 by therapeutic area*
Таблица 2. *Распределение фармацевтических компаний по объемам инвестиций в R&D и количеству оригинальных препаратов, запланированных к первому применению у человека в 2024 г.*

Area of development *Направление разработки*	Number of medicinal products *Количество препаратов*	
	Units *Ед.*	%
Oncology Онкология	40	47
Endocrinology and metabolic diseases Эндокринология и обмен веществ	9	11
Immunology Иммунология	8	10
Cardiovascular system Сердечно-сосудистая система	7	8
Rheumatology Ревматология	4	4,8
Infectious diseases Инфекционные болезни	4	4,8
Clinical neurology Клиническая неврология	4	4,8
Respiratory system Дыхательная система	2	2,4
Gastroenterology and hepatology Гастроэнтерология и гепатология	2	2,4
Pathology Патологическая анатомия	2	2,4
Coloproctology Колопроктология	1	1,2
Allergology Аллергология	1	1,2
Total Итого	84	

The drug contains a novel topoisomerase I inhibitor (Ed-04), released after antibody-mediated internalisation. Preclinical studies of BL-B01D1 demonstrated broad potential efficacy across various solid tumours with an acceptable safety profile [13].

Bispecific antibodies belong to a new generation of MAbs targeting two antigens or epitopes. This induces multiple physiological responses or anti-tumour effects and provides substantial therapeutic effects resulting from synergy. Bispecific antibody-based drugs began entering clinical practice considerably later than ADCs. The first drug, blinatumomab, was approved in the USA in 2014 and is used to treat relapsed acute lymphoblastic leukaemia. In Russia, the drug was authorised in 2023[6]. Bispecific antibodies have already shown clinical advantages over monospecific antibodies. For example, blinatumomab is so far the most effective antibody-based anti-tumour drug, with dosages as low as hundreds of micrograms per entire treatment course, whereas 5–20 g of monospecific antibodies are required per patient per year [14].

Most developed bispecific antibodies target oncological diseases, some are designed for chronic inflammatory, autoimmune, neurodegenerative, vascular, and infectious diseases. Since 2014, the FDA has approved 9 bispecific antibody-based drugs[7]. Roche leads in the number of approved drugs (4 MPs), followed by Johnson & Johnson (3 MPs). BsAb sales exceeded $2.4 billion in Q1 2024, with more than 60% sold in the USA. In 2023, global BsAbs sales exceeded $8 billion[8], confirming their commercial potential.

Analysis showed that most developed bispecific antibodies target solid tumours. In 2024, five companies scheduled Phase I CT for bispecific antibodies *(Table 4)*. Among the 10 MPs being developed, three (3) can be considered potentially first-in-class[5], as there are currently no drugs with a similar mechanism of action.

Bispecific antibody JNJ-9968 (Johnson & Johnson) is intended to treat haematologic malignancies: it selectively targets cells with mutations in the calreticulin gene. Mutant calreticulin (CALRmut) expressed on the surface of tumour cells is a novel therapeutic target for treating myeloproliferative malignant neoplasms. The product acts as a bridge between CALR-mutant tumour cells and T-cells by inducing activation of T-cell cytotoxicity, as observed in studies of $CD34^+$ CALR-mutant cells [15].

Bispecific γδT-cell activator PF-08046052 (Pfizer) for treating progressive solid tumours targets EGFR. The product acts predominantly on EGFR-positive tumour cells and may expand therapeutic options for patients resistant to standard anti-tumour therapy by activating the pool of γδT-cells [16].

Bispecific antibody AZD1163 (AstraZeneca) is an inhibitor of enzymes peptidyl arginine

[6] Блинцинто, лиофилизат для приготовления концентрата для приготовления раствора для инфузий (МНН: блинатумомаб; ДРУ: Амджен Европа Б.В., Нидерланды; РУ № ЛП-(002210)-(РГ-RU) от 19.04.2023).
[7] FDA. Bispecific antibodies: An area of research and clinical applications.
[8] Global Bispecific Antibody Market, Drugs Sales, Patent, Price and Clinical Trials Insight 2029.

deiminases 2 and 4 (PAD2 and PAD4) developed for treating rheumatoid arthritis. Inhibition of PAD2 and PAD4 prevents formation of several citrullinated autoantigens recognised by autoantibodies in patients with rheumatoid arthritis. Preclinical results show robust inhibitory activity against PAD2 and PAD4, indicating prospective impact of the MP on one of the important pathogenetic links controlling formation of autoantigens in rheumatoid arthritis [17].

Despite clinical success of monospecific and bispecific antibodies, therapeutic effect for treating malignant tumours is still limited, such as low response rates, treatment resistance etc., indicating the promise of researching multispecific antibodies (MsAbs). To date, there is no uniform definition of MsAbs. D. Keri et al. [18] consider MsAbs to be antibodies recognising ⩾2 epitopes, whereas A. Amash et al. [19] consider antibodies targeting ⩾3 targets as MsAbs. To distinguish general trends and tendencies in therapeutic antibody development, this analysis defines MsAbs as mAbs targeting three or more targets.

Currently, there are many MsAbs at the clinical trials [4]. However, no MsAb has yet been approved for clinical use [3].

Clinical significance of MsAbs as potential immunotherapy drugs includes [2]:
- ability to simultaneously bind three or more distinct antigens;
- enhanced activation of immune cells or immunosuppression blockade using a flexible target combination, enabling precise and effective tumour eradication;
- lower molecular weight compared to traditional high-molecular-weight agents (such as scFv format – a single-chain variable fragment or a short-format antibody capable of recognising the target antigen but lacking the fragmented crystallizing (Fc) part, which is the basic functional unit for MsAb development), enabling higher permeability.

Advantages of MsAbs may also include reduced manufacturing costs and fewer clinical trials compared with CAR-T or combination of antibody therapies [2].

An example of a multispecific antibody is AbbVie's NK-cell and $CD8^+$ T-cell activator for solid tumours, code ABBV-303. The candidate drug targets three antigens simultaneously: hepatocyte growth factor receptor (c-Met), activating NK-cell receptor (NKG2D), and NK-cell receptor CD16a. Binding of ABBV-303 to NKG2D and CD16a redirects both innate (NK cells) and adaptive ($CD8^+$ T cells) immune cells to lyse tumour cells expressing c-Met. ABBV-303 is expected to be used in combination with a wide range of other immune oncology drugs, as well as with other traditional approaches, such as chemotherapy and radiotherapy [20].

Small Molecule class. Of all low-molecular-weight drugs classified as Small Molecule (*Table 4 "Distribution of Investigational Original Drugs Scheduled for First-in-Human Trials in 2024 by Class, Type and Group"*, published on the journal website[9]), enzyme inhibitors are the most frequently developed (9 MPs, 6 developers). Enzyme inhibition is a recognised strategy for treating pathological conditions such as inflammation, diabetes, microbial infections, HIV, and tumours.

Among target enzymes, developers focus on enzyme molecules involved in the pathogenesis of malignancies. Several companies are developing MPs that inhibit the same enzymes, notably protein arginine N-methyltransferase 5 (PRMT5) and Werner syndrome helicase (WRN). Both are "synthetic lethal" targets[10] and are currently considered promising for targeted therapies.

Arginine N-methyltransferase 5 (PRMT5) belongs to the family of protein arginine N-methyltransferases. Currently, nine (9) PRMTs have been identified in human cells. PRMT5 activity is critical for haematopoiesis, regulation of cellular apoptosis, cell-cycle progression and inflammation, demonstrating its potential as a drug target in various diseases, including haematological and solid cancers [21]. It has been determined that PRMT5 levels are elevated in tumours with deletions of the MTAP

[9] https://doi.org/10.30895/1991-2919-2025-752-annex

[10] Синтетическая летальность — взаимодействие между двумя генетическими событиями, при котором совместное возникновение этих двух генетических событий приводит к гибели клетки, но каждое событие в отдельности не приводит к этому, — может быть использована для терапии рака. Процессы восстановления ДНК могут быть синтетическими летальными целями, поскольку многие виды онкологических заболеваний приводят к нарушению пути восстановления ДНК, следствием чего может стать зависимость от специфических белков восстановления.

gene (MTAP del). The PRMT5 enzyme has been identified as a "synthetic lethal" target for this cancer genotype. This gene encodes MTA phosphorylase that accumulates in patients with MTAP del. Loss of MTAP activity sensitizes cells to PRMT5 inhibition. PRMT5 inhibition may slow down or suppress tumour growth [22, 23].

Currently, AstraZeneca is conducting a CT Phase I of a PRMT5 inhibitor (code AZD3470), intended to treat Hodgkin lymphoma and solid tumours. Bristol Myers Squibb is developing a PRMT5 inhibitor (code MRTX1719) for treating solid tumours. These drug candidates are expected to overcome limitations associated with first-generation PRMT5 inhibitors, which demonstrate mechanism-based toxicity and lack of selective action on the MTAP del cancer genotype [24].

Developers have chosen Werner syndrome helicase (WRN) as a target more recently (since 2019), when a therapeutically promising relationship between the WRN protein and tumours with a microsatellite instability (MSI) phenotype was independently noted in several publications [25–27]. WRN was shown to play an important role in various cellular processes highly significant for maintaining genome stability, including DNA replication, transcription, and repair. Further analysis showed that WRN depletion causes cell cycle arrest, mitotic defects, and apoptosis, especially in MSI cells, sparking interest in research of WRN inhibitors as targeted therapy for cancer [28]. WRN enzyme is a promising "synthetic lethal" target for MSI tumours [25].

In 2024, Roche and Novartis included selective covalent WRN inhibitors (codes RG6457 and HR0761, respectively) in their CT Phase I development plans for treatment of MSI solid tumours. By inhibiting WRN protein, these molecules can induce lethal genomic instability in cancer cells already compromised in their DNA repair capacity.

Developers are also focusing on inhibitors of DGKα and CDK2 targets for treating malignancies. Diacylglycerol kinase alpha (DGKα) is the first identified member of the diacylglycerol kinase family and is associated with progression of various tumour types. DGKα enzyme is highly expressed in various cancers and promotes cancer cell survival due to its anti-apoptotic and proliferative activity [29]. It was determined that DGKα expression in cancer cells promoted tumour growth via the AKT signalling pathway, suggesting DGKα as a potential target in tumour cells for targeted therapy. DGKα was shown to mediate T-cell dysfunction during anti-PD-1 therapy, exacerbating exhaustion of reinvigorated tumour-specific T-cells. Pharmacological antagonism of DGKα delayed T-cell exhaustion and hindered resistance to PD-1 blockade. DGKα inhibition may enhance the efficacy of anti-PD-1 therapy [30]. In 2024, Gilead initiated CT Phase I of a DGKα inhibitor, GS-9911, for patients with late-stage cancers. Use of this drug, including combination with other anti-tumour drugs, is expected to increase survival of patients with various malignancies resistant to standard therapies by suppressing proliferation of sensitive tumour cells, inducing apoptosis, relieving T-cell anergy and restoring their cytotoxic activity.

Cyclin-dependent kinase 2 (CDK2) belongs to enzymes essentially regulating cell division and proliferation. CDK2 overexpression is associated with abnormal cell cycle regulation and unfavourable outcomes in various cancers. In clinical use, first-generation inhibitors targeting CDK2 showed poor tolerability, likely due to off-target effects. Despite substantial development effort, no approved drugs selectively targeting CDK2 exist to date [31]. CDK2 inhibition is potentially able to overcome multiple resistance mechanisms to CDK4/6 inhibitors in breast cancer.

In 2024, AstraZeneca included a selective CDK2 inhibitor, code AZD8421, for therapy of solid tumours in CT Phase I. AZD8421 showed an improved therapeutic index and combined exposure potential in preclinical trials compared with other CDK2 modulators.

Non-receptor tyrosine-protein kinase, TYK2, is a potential target in nervous system diseases. TYK2 belongs to intracellular Janus kinase (JAK) family and mediates cytokine signaling (e.g., via interleukin-23) involved in pathogenesis of immune-mediated diseases. Genome-wide association studies in European populations have linked TYK2 with several autoimmune diseases, including rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel diseases, and other pathologies [32].

Bristol Myers Squibb included TYK2 inhibitor, code BMS-986465, in the development plan. Its active substance selectively binds to the unique regulatory domain of TYK2, blocking

TYK2 enzyme and the cellular signals it mediates. Disrupting these signals by targeting TYK2 is considered a promising way to suppress pronounced inflammation. At the same time, TYK2 does not block related JAK proteins, whose inhibition can cause serious adverse effects. The product is expected to show no systemic toxicity as the TYK2 signalling pathways it inhibits are limited to selected immune pathways, unlike the pathways of the other JAK family [33].

Bristol Myers Squibb developed the first TYK2 inhibitor, FDA-approved in 2022[11], based on two large trials that confirmed significantly higher efficacy compared to apremilast[12] in patients with psoriasis [34]. Information on the specific indication being developed by the company in 2024 was not provided. Available information suggests the investigated disease area relates to neuroinflammatory diseases.

Salt-inducible kinase (SIK) inhibitors have a potential in treating gastrointestinal diseases. SIKs are important regulators of metabolism, cell division, oncogenesis, and inflammation. Three (3) SIK isoforms are known to regulate production of pro-inflammatory cytokines by innate immune cells to a various degree. However, the mechanism is not fully elucidated. Pfizer has initiated development of a SIK inhibitor for ulcerative colitis therapy, code PF-07899895. Specific inhibition of this target is supposed to suppress hyperactivation of pro-inflammatory signaling pathways and reduce production of pro-inflammatory cytokines that maintain immune inflammation in the colon mucosa. The product is expected to expand options for controlling immune inflammation in ulcerative colitis (potentially in patients resistant to current medical treatment options), and may help achieve clinical and endoscopic remission (including steroid-free remission), improving patients' quality of life [35].

HIV reverse transcriptase (RT) is a well-known target for developing MPs in the highly active antiretroviral therapy (HAART) group. In 2024, Gilead began clinical development of a long-acting non-nucleoside reverse transcriptase inhibitor, code GS-1614. The candidate drug differs from analogues by its more prolonged action. Developers plan to investigate its efficacy in combination regimens with dosing possibly once every six (6|) months[13]. GS-1614 is expected to expand therapeutic options for patients resistant to antiretroviral drugs and improve compliance through long-lasting effect.

Cell therapy products. Cell therapy medicines are considered advanced therapy medicinal products (ATMP) [36]. Two main types of cell therapy exist: cellular immunotherapy and regenerative medicine [37]. Our analysis showed that among MPs included in CT Phase I, CAR-T-based products predominate[14] (autologous CAR-T based on autologous T-lymphocytes: 6 MPs, 2 developers). CAR-T therapy is a form of adoptive T-cell therapy recently introduced for the treatment of blood cancers. It involves *ex vivo* engineering of patient's autologous T-lymphocytes to express receptors targeting specific antigens on cancer cells, followed by reinfusion of genetically modified T-cells to mediate cytotoxicity directed toward tumour cells [38].

AstraZeneca and Bristol Myers Squibb prioritise CAR-T research. Notably, AstraZeneca has focused its CAR-T product development on solid tumour therapy (3 of 4 CAR-T medicinal products in development).

The CAR-T product (code AZD0754) may be considered first-in-class[5]. It is designed to treat prostate cancer and targets a novel antigen: 6th transmembrane epithelial antigen of the prostate type 2 (STEAP2) via chimeric antigen receptors on modified autologous T-lymphocytes. STEAP2 is a tumour cell antigen that demonstrates high homogeneous surface expression at all disease stages, with limited expression in normal tissues. Recently published data confirm the hypothesis that STEAP2 plays a functional role in controlling aggressive prostate cancer traits [39]. The product also co-expresses a dominant-negative TGF-β receptor II (dnTGFβRII) to reduce the immunosuppressive effects of transforming growth factor beta (TGF-β) on CAR-T cells; this approach has not been previously used for their protection [40].

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[11] SOTYKTU tablets, for oral use. Highlights of Prescribing Information. Initial U.S. Approval: 2022.

[12] ОТЕСЛА, таблетки, покрытые пленочной оболочкой, 10, 20, 30 мг. ДРУ: Амджен Европа Б.В. (Нидерланды), РУ № ЛП-003829 от 08.09.2016.

[13] CATIE. A potential long-acting treatment — GS-1614.

[14] Т-клеточная терапия с использованием химерных антигенных рецепторов.

Bristol Myers Squibb, in turn, is working on two CAR-T products based on autologous T-lymphocytes intended for multiple sclerosis and relapsed/refractory multiple myeloma.

CONCLUSIONS

Thus, out of the 20 largest pharmaceutical companies with the highest R&D budgets in 2023, 17 companies have initiated studies of original MPs in CT Phase I. The companies leading by number of MPs included in development plans in January-May 2024 were AstraZeneca, Pfizer, and Bristol Myers Squibb, with a total of 84 MPs included in CT Phase I. The main ICD-10-related MP classes under development (67%) are: II Neoplasms (C00–C97, Malignant neoplasms); IV Endocrine, nutritional and metabolic diseases (E00–E90); IX Diseases of the circulatory system (I00–I99). Oncology is the leading area of original MP development.

The largest share of MPs scheduled for first-in-human trials are molecules with a relatively high molecular weight (Large molecule class — 42%). MPs with a relatively low molecular weight (Small Molecule class – 27%) and cell therapy products (12%) were developed less frequently.

1. Based on estimated number of MPs with similar structures being developed by multiple developers, development trends are assumed for the following classes: 1) Large molecule – bispecific antibody (10 MPs, 5 developers); monospecific antibody (8 MPs, 7 developers); antibody-drug conjugate (8 MPs, 3 developers); 2) Small molecule — enzyme inhibitors (9 MPs, 6 developers); 3) Cell therapy products — CAR-T-based products (6 MPs, 2 developers). It should be noted that a current trend in targeted therapy development is the creation of next-generation bispecific antibodies and antibody-drug conjugates alongside development of CAR-T products based on autologous T-cells, mainly in oncology.

2. Proposed qualitative criteria for identifying the tendency allowed assuming that there was a weak development signal for the Large molecule class in the form of MPs comprising the multispecific antibody group. MPs in this group are expected to open a new era of targeted therapy for malignant neoplasms.

3. Based on the number of investigational MPs sharing identical target across several developers, a development tendency was assumed for the enzyme inhibitors group: PRMT5 inhibitors (2 MPs, 2 developers) and WRN inhibitors (2 MPs, 2 developers). Targets with synthetic lethality (such as WRN and PRMT5) are currently regarded as promising objectives for targeted cancer therapy with small molecules.

Identified trends and emerging weak signals can form the basis for planning activities of the Russian pharmaceutical industry to successfully implement pharmaceutical self-sufficiency and transition to personalised medicine.

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Additional information. Tables 3, 4 are published on the website of *Regulatory Research and Medicine Evaluation*.
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Дополнительная информация. На сайте журнала «Регуляторные исследования и экспертиза лекарственных средств» размещены таблицы 3 и 4.
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