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REVIEW

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Review of medicines approved by the Food and Drug Administration from 2012 to 2024

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The aim. To describe the key characteristics of medical products approved by the Food and Drug Administration (FDA) and released by pharmaceutical companies from 2012 to 2024.

Materials and methods. The analysis is based on data from FDA publications related to the approval of medical products from 2012 to 2024. The products were systematized by year, pathway and reason for approval, nature of the active substance (synthetic, semi-synthetic, natural or biological) and target disease (indication for use) in accordance with the codes of the Anatomical Therapeutic Chemical (ATC) classification.

Results. During the analyzed period, the FDA approved a significant number of medicines, while maintaining a stable proportion of small molecules with a significant upward trend in the number of approved biologicals (monoclonal antibodies, CAR-T, siRNA, gene therapy, etc.). The largest proportion was accounted for by antitumor drugs and immunomodulators (group L according to ATC), demonstrating steady growth with projected growth in the future. Interest in drugs for the treatment of metabolic disorders and diseases of the nervous system remained steadily high, with the emergence of innovative therapeutic approaches. A gradual increase in the number of repositionings and extensions of indications was noted. The COVID-19 pandemic did not have a significant impact on the overall structure of approvals, and only two specific medicines for the treatment of COVID-19 were approved. There has been an increase in approvals for orphan diseases and the emergence of innovative therapeutic approaches: gene therapy, RNA interference, cell technologies, and bispecific antibodies.

Conclusion. In the period from 2012 to 2024, the pharmaceutical industry has seen a fundamental shift towards biotechnological development methods, personalized medicine, and targeted therapy. During the period under review, the

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proportion of small molecule approvals remained fairly stable, but a steady (compared to previous periods) increase in the number of biotechnology product approvals (monoclonal antibodies, gene and RNA therapy) can be noted. The largest increase was noted in class L (antitumor drugs and immunomodulators), which reflects the focus of global pharmaceutical companies on the fundamental study and discovery of pharmacotherapy opportunities in the oncology and immunity. It is necessary to note the trend towards the development of drugs for the treatment of rare (orphan) diseases. In the field of therapy for metabolic disorders, during the specified period, drugs were approved that revolutionized understanding of an entire cluster of diseases and approaches to therapy, and a new standard of therapy was formed due to SGLT2 inhibitors and agonists of the incretin system receptors, including molecules with a multi-targeted effect. The COVID-19 pandemic led to a limited number of drug approvals for the treatment of this infection but thanks to it, the "door" to the development of new generation vaccines has been opened, which are largely fundamentally different from those currently existing. The discovery of new means to combat infectious agents of various nature (bacteria, protozoa, viruses, fungi, and parasites) is also one of the priority goals of pharmaceutical companies, as evidenced by a significant proportion of approvals of drugs with a similar effect. In terms of "reasons for registration," the main share fell on original drugs; the contribution of new combinations and dosage forms was at its peak in the middle of the period and then decreased. Due to the expiration of patent protection for many drugs and the accumulation of data on their effects in the post-marketing period, a gradual increase in the number of repositionings and extensions of indications can be logically noted.

Keywords: FDA; ATC; targeted therapy; trends in drug design; approved medicines; new medicines

Abbreviations: HSC — hematopoietic stem cells; GIT — gastrointestinal tract; iDPP4 — dipeptidyl peptidase 4 inhibitor; iSGLT2 — sodium-glucose cotransporter 2 inhibitor; LH — luteinizing hormone; mRNA — messenger ribonucleic acid; NSCLC — non-small cell lung cancer; DM — diabetes mellitus; DM1 — type 1 diabetes mellitus; DM2 — type 2 diabetes mellitus; SMA — spinal muscular atrophy; FSH — follicle-stimulating hormone; COPD — chronic obstructive pulmonary disease; CMV — cytomegalovirus; CNS — central nervous system; CD — cluster of differentiation; CGRP — calcitonin gene-related peptide; FDA — Food and Drug Administration; IFN — interferon; IL — Interleukin; mAb — monoclonal antibody; siRNA — small interfering ribonucleic acid; VEGF — vascular endothelial growth factor.

Обзор лекарственных средств, одобренных FDA в период с 2012 по 2024 годы

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Цель. Описать ключевые характеристики лекарственных препаратов, одобренных Управлением по санитарному надзору за качеством пищевых продуктов и медикаментов (Food and Drug Administration, FDA), выпущенных фармацевтическими компаниями за период 2012–2024 гг.

Материалы и методы. Анализ произведен по данным из публикаций FDA, относящихся к одобрению лекарственных препаратов за период с 2012 по 2024 год. Препараты систематизировали по году, пути и поводу одобрения, характеру действующего вещества (синтетический, полусинтетический, природный или биологический) и целевому заболеванию (показание к применению) в соответствии с кодами анатомо-терапевтическо-химической классификации (АТХ).

Результаты. За анализируемый период FDA одобрило значительное количество лекарственных препаратов, при этом сохранялась стабильная доля малых молекул при значимом тренде роста числа одобренных биологических препаратов (моноклональные антитела, CAR-T, siRNA, генная терапия и др.). Наибольшую долю составили противоопухолевые препараты и иммуномодуляторы (группа L по АТХ), демонстрирующие устойчивый рост с прогнозируемым ростом в будущем. Стабильно высоким остался интерес к препаратам для лечения метаболических нарушений и заболеваний нервной системы с появлением инновационных терапевтических подходов. Отмечен постепенный рост числа репозиционирований и расширений показаний. Пандемия COVID-19 не оказала существенного влияния на общую структуру одобрений и было одобрено лишь два специфических препарата для лечения COVID-19. Отмечен рост одобрений для орфанных заболеваний и появление инновационных терапевтических подходов: генной терапии, РНК-интерференции, клеточных технологий и биспецифических антител.

Заключение. В период с 2012 по 2024 год в фармацевтической индустрии отмечается фундаментальный сдвиг в сторону биотехнологических методов разработки, персонализированной медицины и таргетной терапии. В течение рассматриваемого периода доля одобрения малых молекул оставалась достаточно стабильной, но можно отметить устойчивый (по сравнению с предыдущими периодами) рост числа одобрений биотехнологических продуктов (моноклональные антитела, генная и РНК-терапия). Наибольший прирост отмечен в классе L (противоопухолевые препараты и иммуномодуляторы), что отражает фокус внимания глобальных фармацевтических компаний к фундаментальному изучению и открытию возможностей фармакотерапии в области онкологии и иммунитета. Необходимо отметить тренд на разработку лекарственных средств для лечения редких (орфанных) заболеваний. В области терапии метаболический расстройств, за указанный период, одобрены препараты, которые перевернули понимание целого кластера болезней и подходов к терапии, сформировался новый стандарт терапии за счёт ингибиторов SGLT2 и агонистов рецепторов инкретиновой системы, включая молекулы оказывающее мультитаргетное влияние. Пандемия COVID-19 привела к ограниченному числу одобрений лекарственных препаратов для лечения инфекции, благодаря ей приоткрыта «дверца» к разработке вакцин нового поколения, во многом принципиально отличающихся от существующих в настоящее время. Открытие новых средств для борьбы с инфекционными агентами различной природы (бактерии, простейшие, вирусы, грибки и паразиты) также являются одной из приоритетных целей фармацевтических компаний, о чем свидетельствует значительная доля одобрения препаратов с подобным действием. По «поводам регистрации» основная доля приходилась на оригинальные препараты; вклад новых комбинаций и лекарственных форм был максимальным в середине периода и затем снижался. В связи с прекращением действия патентной защиты на многие препараты и накоплений данных об их эффектах в постмаркетинговом периоде можно закономерно отметить постепенный рост числа репозиционирований и расширений показаний.

Ключевые слова: FDA; АТХ; таргетная терапия; тенденции лекарственного дизайна; одобренные лекарственные препараты; новые лекарственные препараты

Список сокращений: ГСК — гемопоэтические стволовые клетки; ЖКТ — желудочно-кишечный тракт; иДПП4 — ингибитор дипептидилпептидазы 4 типа; иНГЛТ2 — ингибитор натрий-глюкозного контранспортёра 2 типа; ЛГ — лютеинизирующий гормон; мРНК — матричная рибонуклеиновая кислота; НМРЛ — немелкоклеточный рак лёгкого; СД — сахарный диабет; СД1 — сахарный диабет первого типа; СД2 — сахарный диабет второго типа; СМА — спинальная мышечная атрофия; ФСГ — фолликулостимулирующий гормон; ХОБЛ — хроническая обструктивная болезнь лёгких; ЦМВ — цитомегаловирус; ЦНС — центральная нервная система; CD — кластер дифференцировки (Cluster of differentiation); CGRP — пептид, связанный с геном кальцитонина; FDA — управление по санитарному надзору за качеством пищевых продуктов и медикаментов (Food and drug administration); IFN — интерферон; IL — интерлейкин (Interleukin); mAb — моноклональное антитело; siRNA — малая интерферирующая рибонуклеиновая кислота; VEGF — фактор роста эндотелия сосудов.

INTRODUCTION

Modern pharmacotherapy for most diseases differs significantly from the one existed several decades ago. Knowledge and understanding of the disease, achievements of fundamental sciences more and more precisely determine the target for therapeutic intervention, allowing the treatment process to be carried out not only effectively, but also at a level that is as comfortable for the patient. The development of original medicines meets the needs of society, the doctor and the patient, offering a new means for treating the disease, while the development of a new dosage form of the original drug, the creation of a generic drug or the inclusion of the active substance

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in the composition of a combined drug is aimed more at increasing the convenience and satisfaction of the patient [1, 2]. The expansion of scientific knowledge and technical capabilities of humans determines the evolution of pharmacotherapy for almost every known disease. The processes that make up the life cycle of a medicinal product are extremely diverse, but they are united by characteristics such as innovation, high quality standards, cost and complex formal regulation [3–5].

Strategies for creating new drugs have not changed significantly over the past few decades. Pharmaceutical developments are still represented by both original drugs and their copies, various combinations, as well as new dosage forms of already known active substances, including those in relation to which the so-called repositioning occurred, as a result of which the prospect of use in diseases different from the original goals of molecule development was established. It should be noted that the qualitative level of the developed products has changed significantly, since there is a noticeable trend of pharmaceutical companies investing in the search for and satisfaction of patients' needs in terms of the convenience of drug therapy [6–8].

The development of medicinal products is a risky, lengthy and costly process at all stages of the life cycle, since investments in the creating product do not stop almost until it is completely withdrawn from the market, which happens quite rarely [9, 10]. If we focus directly on the process of developing an original medicinal product, then, with some assumptions, it can be divided into the search for and justification of a target for therapeutic intervention, the selection of the best compound from a number of compounds in terms of its ability to affect the therapeutic target, optimization of the characteristics of the selected compound and the study of its pharmacodynamic, pharmacokinetic and toxicokinetic properties, the implementation of registration studies, registration and obtaining post-registration data [9, 11, 12]. It is important to note that the time, labor and financial costs are most significant up to the registration of the medicinal product, however, the information obtained at the post-registration stage, that is, during the sales period, is fundamental for future developments or modernization of existing ones. It is the analysis of various aspects of drug circulation that allows us to identify patient needs and societal demands, which determines the prospect, indicates the direction of the market and the beacons of successful implementation of new products for developers [5, 13]. Considering that the development of an original medical product requires an ever-increasing amount of resources every year and, as a rule, the original medicinal product to a greater extent meets the criteria of the needs of the doctor and society, the creation of generic drugs, new dosage forms, combinations, delivery systems, etc., requires significantly fewer resources, since these areas are more focused on the patient's needs [7, 8, 14].

The pharmaceutical industry is certainly an important component of the state's economy and the most attractive in terms of investment. Acting as the main beneficiary of the results of fundamental sciences and the main driver of their applied function, pharmacy demonstrates significant progress in the treatment of diseases that were previously considered incurable. It is important to note that modern pharmacy is increasingly using a patient-centric paradigm in drug development, presenting patients with drugs in new dosage forms, combinations, doses and methods of delivery. The proportion of drugs created by biotechnological means continues to increase. The segment of orphan medicines is also gradually increasing [15–17].

The presented data are of interest, indicating trends in drug development and demonstrating the ability of modern pharmaceutical companies to offer sometimes "revolutionary" solutions to previously unsolvable problems of medical and preventive services [18–20].

Global analytics and monitoring of the pharmaceutical market allow us to determine the current situation and vectors of development, as well as problems with current developments or products, which is a source of valuable information for healthcare, pharmaceutical marketing and industry purposes.

The presented work reflects the history of approvals by the Food and Drug Administration (FDA) of medicinal products manufactured by foreign pharmaceutical companies, including leaders in the pharmaceutical market.

THE AIM. To identify and describe the key characteristics of medicinal products approved by the Food and Drug Administration (FDA) and

released by foreign pharmaceutical companies for the period 2012–2024.

MATERIALS AND METHODS

Data for the analysis were collected from official sources, taking into account all medicinal products approved by the FDA for the period from 2012 to 2024. The drugs were systematized by year, route and reason for approval, the nature of the active substance (synthetic, semi-synthetic, natural or biological) and the target disease (indication for use) in accordance with the codes of the anatomical-therapeutic-chemical classification (ATC). The following approval routes are highlighted: original medicinal product, generic medicinal product (generic), new dosage form, new combination, new use, new manufacturer, re-registration.

The term "Biosimilar medicinal product" (biosimilar, biosimilar medicinal product, biosimilar) meant a biological medicinal product that contains a version of the active substance of the registered biological original (reference) product and for which similarity (similarity) has been demonstrated on the basis of comparative studies with the reference product in terms of quality, biological activity, efficacy and safety.

The term "Generic medicinal product" (generic) meant a medicinal product that has the same quantitative and qualitative composition of active substances and the same dosage form as the original product, and whose bioequivalence to the original medicinal product is confirmed by appropriate bioavailability studies. Different salts, esters, isomers, mixtures of isomers, complexes or derivatives of the active substance are recognized as the same active substance if their safety and efficacy do not differ significantly. Different oral dosage forms with immediate release are recognized as the same dosage form within the framework of bioavailability studies.

Also, the category "Generic drug" (exclusively within the framework of this article, for ease of perception of information) conditionally included a hybrid medicinal product — a medicinal product that does not fall under the definition of a generic medicinal product when it is impossible to confirm its bioequivalence using bioavailability studies, as well as if changes have occurred in this drug active substance (substances), indications for use, dosage, dosage form or route of administration compared to the original drug.

The drugs were divided by areas of application in accordance with the codes of the anatomical-therapeutic-chemical classification (ATC):

- Code A: Alimentary tract and metabolism;
- Code B: Blood and Blood Forming Organs;
- Code C: Cardiovascular System;
- Code D: Dermatologicals;
- Code G: Genito Urinary System and Sex Hormones;
- Code H: Systemic Hormonal Preparations, excl. Sex Hormones and Insulins;
- Code J: Antiinfectives for Systemic Use;
- Code L: Antineoplastic and Immunomodulating Agents;
- Code M: Musculo-Skeletal System;
- Code N: Nervous System;
- Code P: Antiparasitic Products, Insecticides and Repellents;
- Code R: Respiratory System;
- Code S: Sensory Organs;
- Code V: Various.

Data on the indications of medicinal products, as well as information on the mechanism of action, were taken from the published summary of product characteristics (SmPC) published on the Drugs.com website. Drugs.com reports were also used to describe previously registered medicinal products for which a new indication is presented. The search for literature data on fundamental studies concerning the mechanisms of action of the presented medicinal products was carried out in the PubMed, ResearchGate, Google Scholar and elibrary.ru databases.

For systematization, calculation of proportions and trends, as well as visualization of the obtained results, the R software package was used: R version 4.5.1 (2025-06-13 ucrt), ggplot2 version 3.5.2, RStudio 2025.05.1 Build 513.

RESULTS

When analyzing the approval history, the total number of approvals, approvals of new molecules, combinations, dosage forms and/or indications for use, as well as reproduced drugs were taken into account; changes in the manufacturer or re-registration were taken into account in the "other" category (not presented in the text description).

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2012

In 2012, 65 drugs were approved. Among them there were 27 new original molecules. As previously, except for 2016, the largest share was accounted for by antitumor drugs and immunomodulators (class L). For 14 drugs, the approval was associated with a change of manufacturer and for 5, re-registration was carried out. 11 new combinations and 9 new dosage forms were registered. A new indication was added for 6 drugs. The distribution by ATC classes and chemical type is presented in Figure 1.

Vismodegib (Erivedge®) is approved for the treatment of metastatic basal cell carcinoma or this disease in the late stages. It acts through the Hedgehog signaling pathway: selectively inhibits the Smoothened protein, which suppresses the pathological activation of the Hedgehog signal, characteristic of some basal cell carcinomas[1]

Glucarpidase (Voraxaze®) is an enzyme (carboxypeptidase) that converts methotrexate into inactive metabolites, reducing its plasma concentration. It is used as a means to treat methotrexate overdose, leading to renal failure and subsequent reduction of its clearance[2].

A strong opioid agonist — fentanyl (Subsys) — in the form of a spray for sublingual administration for accelerated absorption has been approved. It is used to relieve episodes of intractable pain in patients with tumors receiving opioid treatment and resistant to them[3].

Taliglucerase alfa (Elelyso®) is recombinant human glucocerebrosidase for enzyme replacement therapy for Gaucher disease has been approved. The enzyme complements the insufficient lysosomal activity, promoting the breakdown of accumulated glucosylceramide. Elelyso® (finished product of taliglucerase alfa) is produced using plant cell culture (expression system in carrot cells) - this is the first FDA-approved drug produced using the plant ProCellEx® platform[4].

A radiopharmaceutical drug containing florbetapir F-18 (Amyvid®) as an active substance has been approved. It is used in positron emission tomography to visualize β-amyloid in the brain. The diagnostic procedure helps in assessing the presence of dense amyloid plaques associated with Alzheimer's disease[5].

A gel for topical use based on ingenol mebutate (Picato®) has been created. The active substance combines a direct cytolytic effect on affected keratinocytes and promotes an inflammatory response at the site of the lesion, which is used to treat actinic keratoses[6].

In 2012, a pegylated peptide peginesatide (Omontys®) was developed, which is an agonist of the erythropoietin receptor. The drug based on it was planned to be used to stimulate erythropoiesis in patients with anemia caused by dialysis for chronic kidney disease. It is noteworthy that despite the approval, in 2013 this drug was discontinued and a recall of all released series was announced, since the PEARL study revealed that the drug was inferior to the reference drugs (darbepoetin alfa) in terms of safety in relation to the cardiovascular system.

2013

In 2013, the FDA approved 73 drugs, 28 of which were represented by new molecules (including 10 molecules of biological origin), 11 were new combinations of drugs; in 15 drugs had a new dosage form or a new indication for use. The distribution by ATC classes and chemical type is presented in Figure 2.

Examples of drugs that have been approved: ceritinib (Zykadia®; a drug for the treatment of inoperable or metastatic non-small cell lung cancer [NSCLC] with a specific mutation)[7] tisagenlecleucel (Kymriah®; the first gene therapy approved for the treatment of acute lymphoblastic leukemia in children and young people)[8], nivolumab (Opdivo®; a drug for the treatment of various types of cancer, including melanoma and lung cancer), durvalumab (Imfinzi®; approved for the treatment of lung cancer, in particular, for patients with locally advanced disease not amenable to surgical intervention)[9], Entresto® (sacubitril + valsartan; a combined drug for the treatment of chronic heart failure)[10].

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[5] Drugs.com. Amyvid. Avavilable from: https://www.drugs.com/amyvid.html
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The pomalidomide (Pomalyst®) is approved as a new antitumor agent[11]. This is a derivative of thalidomide[12] is a representative of the next generation of immunomodulators after lenalidomide, its peculiarity lies in the ability to inhibit both tumor cells and vascular compartments of myeloma cancer [21].

The approval of canagliflozin (Invokana®), the second, but far from the last, approved gliflozin not only for the treatment of T2DM, but also for the prevention of its cardiovascular complications, deserves special attention[13].

Riociguat (Adempas®) is the first-in-class soluble guanylate cyclase stimulator for the treatment of chronic thromboembolic pulmonary hypertension and pulmonary arterial hypertension[14]. The second approved drug macitentan (Opsumit®) for the treatment of the same disease is an antagonist of two subtypes of endothelin receptors A and B[15]. The third drug for the treatment of arterial hypertension is treprostinil (Orenitram®) — an artificial prostacyclin that causes vasodilation in the lungs[16].

The NS3/4A protease inhibitor simeprevir (Olysio™)[17] and the hepatitis C virus NS5B protein inhibitor sofosbuvir (Sovaldi)[18] are the first two drugs in the class for the treatment of hepatitis C.

For the treatment of homozygous familial hypercholesterolemia, the second-generation antisense oligonucleotide mipomersen (Kynamro™)[19] has been approved, which binds to messenger RNA encoding apolipoprotein B-100, its formula is resistant to nucleases and therefore it can be administered to the patient weekly [22].

2014

In 2014, 92 drugs received FDA approval, 46 of which were original molecules (including 15 of biological origin), and 15 were new combinations; 15 drugs had a new dosage form or a new indication for use (Fig. 3).

The trametinib (Mekinist®) and dabrafenib (Tafinlar®) received accelerated approval for combination therapy of melanoma[20]. Examples of approved drugs were glatiramer acetate (Copaxone®; approval of a three-times-a-week dosing regimen of 40 mg/mL for the treatment of multiple sclerosis)[21], ecallantide (Kalbitor®; approval of expanded use for the treatment of hereditary angioedema in patients aged 12 years and older)[22], dabigatran etexilate mesylate (Pradaxa®; approval for the treatment of deep vein thrombosis and pulmonary embolism)[23], panitumumab (Vectibix®; approval of first-line use in combination with FOLFOX for patients with metastatic colorectal cancer of the wild type KRAS)[24], human immunoglobulin (Octagam® 10%; approval for the treatment of chronic immune thrombocytopenic purpura)[25], tiotropium bromide (Spiriva® Respimat®; approval for maintenance treatment of COPD)[26], adalimumab (Humira®; approval for the treatment of Crohn's disease in pediatric patients)[27], ramucirumab (Cyramza®; approval in combination with paclitaxel for the treatment of late-stage gastric adenocarcinoma after previous

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chemotherapy)[28], simeprevir (Olysio™; approval in combination with sofosbuvir for the treatment of chronic hepatitis C genotype 1)[29].

Gliflozins — dapagliflozin (Farxiga®)[30] and empagliflozin (Jardiance®)[31], — as well as GLP-1 agonists albiglutide (Tanzeum™)[32] and dulaglutide (Trulicity®)[33] are approved for the treatment of T2DM and concomitant pathologies (heart failure, CKD or reduction of the risk of CVDs).

L-threo-dihydroxyphenylserine (L-DOPS, Droxidopa) was first described in 1971 [23], but approved for the treatment of hypotension only in 2014 (Northera®). L-DOPS is a synthetic amino acid precursor that acts as a prodrug to the neurotransmitter norepinephrine (noradrenaline), acts as a non-selective α- and β-adrenergic receptor agonist, increases norepinephrine levels in the peripheral nervous system[34]. For the treatment of lipodystrophy in 2014, a synthetic leptin analogue — metreleptin (Myalept®) was approved, the use of which reduces blood glucose and body weight[35]. Dantrolene sodium (Ryanodex®) is a postsynaptic muscle relaxant (inhibits the release of Ca^{2+} ions from sarcoplasmic reticulum stores by antagonizing ryanodine receptors), a hydantoin derivative, but unlike phenytoin, it does not exhibit antiepileptic activity, it is approved for the treatment of malignant hyperthermia[36]. For the treatment of insomnia, the first orexin receptor antagonist (lemborexant, Dayvigo®; approved in 2019)[37] and daridorexant, Quviviq®; approved in 2022)[38] — suvorexant (Belsomra®)[39] — acts as a selective dual antagonist of orexin receptors 1 and 2.

For the treatment of opioid-induced constipation, a polyethylene glycol-modified α-naloxol derivative — naloxegol (Movantik®)[40] has been approved, which inhibits the binding of opioids to μ-opioid receptors in the gastrointestinal tract (GIT), thereby preventing slowing of passage, hypertonus and increased fluid reabsorption in the GIT [24].

The first-in-class drug for the treatment of idiopathic pulmonary fibrosis is pirfenidone (Esbriet®) has been approved, which acts by reducing the production of growth factors and procollagens I and II[41].

For the treatment of acromegaly (previously, in 2012, approved for the treatment of Cushing's disease), pasireotide (Signifor®)[42] has been approved — this is a somatostatin analogue, which has a 40-fold higher affinity for somatostatin receptor 5. Ivermectin (Soolantra®) was described in 1975 [25], for its discovery Satoshi Omura (Kitasato University) and William Campbell (Merck) received half of the Nobel Prize in 2015. This substance is widely used as an antiparasitic agent, and in 2014 it was approved for the treatment of rosacea. The drug binds to glutamate-gated chloride channels, opening them increases the flow of chloride ions, which leads to hyperpolarization of the cell membranes of parasites, including *Demodex folliculorum* mites[43]. Avermectin group drugs stimulate the release of γ-aminobutyric acid (GABA) from nerve endings and increase the affinity of GABA to receptor sites on the postsynaptic membrane of muscle cells, which blocks the transmission of nerve impulses [26].

Liraglutide (Saxenda®) (approved in 2010) was approved in 2014 for use in obesity[44], which on the one hand is another successful example of adapting the undesirable effects of a drug for medical purposes, and on the other hand opens up the potential for a multiple expansion of prescriptions for drugs with similar effects.

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2015

In 2015, 99 drugs were registered in the USA, including 41 original drugs (including 21 biologicals), 20 new combinations, only 1 generic drug glatiramer acetate (Copaxone®)[45] and 1 drug with a new indication for use. In particular, deferasirox (Jadenu®; a new form of iron chelating drug that simplifies the treatment of patients with chronic iron overload)[46], esomeprazole magnesium (Nexium® 24HR; an over-the-counter version of the drug for the treatment of acid reflux)[47], levetiracetam (Spritam®; the first 3D-printed drug for the treatment of epilepsy)[48], lobelia and ivacaftor (Orkambi®; a combination drug for the treatment of cystic fibrosis)[49], palbociclib (Ibrance®; a drug for the treatment of breast cancer)[50], ceritinib (Zykadia®; for the treatment of metastatic NSCLC)[51], venetoclax (Venclexta®; for the treatment of chronic lymphocytic leukemia)[52], eliglustat (Cerdelga®; for the treatment of Gaucher's disease)[53], cariprazine (Vraylar®; for the treatment of schizophrenia and bipolar disorder)[54], lenvatinib (Lenvima®; for the treatment of thyroid cancer)[55] were approved (Fig. 4).

The approval history began with the new drug edoxaban (Savaysa®; an anticoagulant, a direct factor Xa inhibitor) for the prevention of stroke and systemic embolism[56]. Solution for renal replacement therapy (Phoxillum®) approved as a means for dialysis[57].

The synthesis of eluxadoline (μ- and κ-opioid receptor agonist and δ-opioid receptor antagonist in the enteric nervous system) was first described in 2006, but it was approved only 9 years later for clinical use in the treatment of diarrhea and abdominal pain in people with irritable bowel syndrome with a predominance of diarrhea (Viberzi®)[58]. The first in the class of NS5A inhibitors daclatasvir (Daklinza®)[59] was approved in 2015, developed by scientists from Bristol Myers Squibb and indicated for the treatment of hepatitis C also for the treatment of this disease the drug Technivie™ was approved, consisting of three active components: ombitasvir (NS5A inhibitor), paritaprevir (acylsulfonamide inhibitor of NS3-4A serine protease), ritonavir (enhances the effects of other protease inhibitors)[60]. Of particular note is the approval of dichlorphenamide (Keveyis®) for the treatment of primary hypokalemic and hyperkalemic periodic paralysis[61]; the effectiveness of the drug against glaucoma has been known since 1958 [27], and epilepsy since 1978 [28]. Flibanserin (Addyi®) was originally developed as an antidepressant (predominantly activates 5-HT1A receptors in the prefrontal cortex, increases dopamine and norepinephrine levels, and reduces serotonin levels), but was approved as a drug for the treatment of women in premenopause with hypolibidemia[62].

As an antiemetic (during chemotherapy), a selective neurokinin-1 receptor (NK1 receptor) antagonist, rolapitant (Varubi™), was approved, originally developed by Schering-Plough®, information about the effects is available since 2006[63].

Cariprazine (Vraylar®)[64] is an atypical neuroleptic from Gedeon Richter® Company, which acts as a partial agonist of D3R (highly selective), D2R dopamine receptors and 5-HT1A serotonin receptors, and as an antagonist of 5-HT2B and 5-HT2A receptors. In 2022, the drug was approved as an adjunct for major depressive disorder. Brexpiprazole (Rexulti®) is approved for the treatment of Schizophrenia and major depressive disorder, is a derivative of

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[64] Drugs.com. Vraylar. Available from: https://www.drugs.com/vraylar.html

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aripiprazole (aripiprazole lauroxil is an N-acyloxymethyl prodrug of aripiprazole, which is administered intramuscularly once every 4–8 weeks for the treatment of Schizophrenia; approved in 2015), like the previous drug, it is a partial agonist of serotonin 5-HT1A and dopamine D2R and D3R receptors. The generic was approved in 2022 and since 2023 it can be used to relieve agitation in Alzheimer's disease[65].

Olopatadine (Pazeo®)[66] is a selective histamine H1 receptor antagonist, patented in 1986, its use in the clinic began in 1997, in 2015 it was approved as an ophthalmic solution for allergic conjunctivitis, since 2020 it has been available over-the-counter in the USA.

Asfotase alfa (Strensiq®) is a drug for enzyme replacement therapy, a recombinant glycoprotein with the catalytic domain of tissue-specific alkaline phosphatase, a genetic defect in which causes hypophosphatasia[67]. Another drug for enzyme replacement therapy in the form of a solution for intravenous infusions is sebelipase alfa (Kanuma™) — recombinant lysosomal acid lipase[68].

The antidote sugammadex (Bridion®) is the first in class substance that selectively binds relaxant to reverse neuromuscular blockade caused by rocuronium and vecuronium during general anesthesia and, compared to other reversal agents, potentially has fewer side effects[69].

Lesinurad (Zurampic®) inhibits URAT1 (a protein that is responsible for the reabsorption of uric acid in the kidneys) and OAT4 (associated with diuretic-induced hyperuricemia)[70].

Selexipag (Uptravi®) and its active metabolite ACT-333679 act on the prostacyclin receptor in the lungs, which leads to vasodilation of arteries, reduced cell proliferation and inhibition of platelet aggregation; approved for the treatment of pulmonary hypertension[71].

For the treatment of HIV in 2015, 4 new combination drugs were approved — Evotaz® (atazanavir [HIV protease inhibitor] and cobicistat [cytochrome P450 enzyme inhibitor])[72], Prezcobix® (cobicistat and darunavir [HIV protease inhibitor])[73], Dutrebis® (lamivudine [HIV nucleoside reverse transcriptase inhibitor] and raltegravir [approved since 2007; HIV integrase inhibitor])[74], Stribild® (cobicistat, elvitegravir [approved since 2014; HIV integrase inhibitor], emtricitabine [approved since 2003; synthetic nucleoside analog of cytidine, HIV nucleoside reverse transcriptase inhibitor] and tenofovir alafenamide [tenofovir prodrug, nucleotide reverse transcriptase inhibitor])[75].

In the field of diabetes treatment, three combination drugs were approved in 2015 — Glyxambi® (empagliflozin [SGLT2i] and linagliptin [DPP4i])[76], Synjardy® (empagliflozin [SGLT2i] and metformin)[77], Ryzodeg® 70/30 (insulin degludec [long-acting] and insulin aspart [rapid-acting]); two drugs containing insulin glargine were approved in a new dosage form (more concentrated solution)[78]; Tresiba® (insulin degludec) — basal insulin with ultra-long action (over 24 hours)[79].

2016

In 2016, only 69 drugs were approved, of which 24 were original (including 13 biologicals), 13 were new combinations, 2 were generic drugs, and 18 had a new dosage form or a new indication for use. 2016 is the only year in the studied period in which class L drugs were not the predominant group: that year, 13 antimicrobial drugs for systemic action (class J) were also registered (Fig. 5).

In particular, nusinersen (Spinraza®; for the treatment of spinal muscular atrophy in children and

[65] Drugs.com. Rexulti. Available from: https://www.drugs.com/rexulti.html
[66] Drugs.com. Pazeo. Available from: https://www.drugs.com/mtm/pazeo.html
[67] Drugs.com. Strensiq. Available from: https://www.drugs.com/strensiq.html
[68] Drugs.com. Kanuma. Available from: https://www.drugs.com/mtm/kanuma.html
[69] Drugs.com. Bridion. Available from: https://www.drugs.com/mtm/bridion.html
[70] Drugs.com. Zurampic. Available from: https://www.drugs.com/zurampic.html
[71] Drugs.com. Uptravi. Available from: https://www.drugs.com/uptravi.html
[72] Drugs.com. Evotaz. Available from: https://www.drugs.com/evotaz.html
[73] Drugs.com. Prezcobix. Available from: https://www.drugs.com/prezcobix.html
[74] Drugs.com. Dutrebis. Available from: https://www.drugs.com/history/dutrebis.html
75 Drugs.com. Stribild. Available from: https://www.drugs.com/stribild.html
[76] Drugs.com. Glyxambi. Available from: https://www.drugs.com/glyxambi.html
[77] Drugs.com. Synjardy Available from: https://www.drugs.com/synjardy.html
[78] Drugs.com. Ryzodeg FlexTouch Pen. Available from: https://www.drugs.com/ryzodeg-70-30.html
[79] Drugs.com. Tresiba. Available from: https://www.drugs.com/tresiba.html

adults)[80], rucaparib (Rubraca®; for the treatment of a certain type of ovarian cancer in women[81], crisaborole (Eucrisa®; for the treatment of mild to moderate eczema [atopic dermatitis] in patients over 2 years of age)[82], bezlotoxumab (Zinplava®; to reduce the risk of recurrence of infection caused by *Clostridium difficile* in patients over 18 years of age)[83], olaratumab (Lartruvo®; for the treatment of adults with certain types of soft tissue sarcoma)[84], Exondys 51® (eteplirsen; for the treatment of patients with Duchenne muscular dystrophy)[85], Adlyxin® (lixisenatide; to improve glycemic control)[86], Xiidra® (lifitegrast; for the treatment of signs and symptoms of dry eye syndrome)[87], Epclusa® (sofosbuvir+velpatasvir; for the treatment of all six major forms of the hepatitis C virus)[88] were approved.

Pimavanserin (Nuplazid™) is a selective inverse agonist of the serotonin 5-HT2A receptor and significantly less active against 5-HT2C; received breakthrough antipsychotic therapy status in 2014, was approved in 2016 for the treatment of hallucinations and delusions in Parkinson's disease, and in 2018 it became available in new dosage forms[89].

Brivaracetam (Briviact®) is chemically similar to levetiracetam, which has anticonvulsant (antiepileptic) properties by binding to synaptic vesicle glycoprotein 2A, approved for the relief of epileptic seizures[90].

Defibrotide (Defitelio®) is a mixture of single-stranded oligonucleotides purified from the intestinal mucosa of pigs; polydeoxyribonucleotide sodium salt; approved for the treatment of hepatic veno-occlusive disease in people who have undergone bone marrow transplantation, acts as an endothelial protector, enhances the function of tissue-type plasminogen activator (tPA) and promotes plasminogen activation-1 (PAI-1)[91].

Obeticholic acid (Ocaliva®)[92] is a semi-synthetic bile acid analogue, chemically 6α-ethyl-chenodeoxycholic acid, a farnesoid X receptor agonist, approved for the treatment of primary biliary cholangitis. The prototype of this compound, chenodeoxycholic acid, was identified in 1999.

Lifitegrast (Xiidra®) inhibits integrin, lymphocyte function-associated antigen 1 (LFA-1), from binding to intercellular adhesion molecule 1 (ICAM-1). This mechanism suppresses T-lymphocyte-mediated inflammation. It is used to treat dry eye symptoms[93].

Phentermine hydrochloride (phenyl-tertiarybutyl amine) (Qsymia®) is a TAAR1 agonist (like amphetamine, which was approved in early 2016 for the treatment of attention deficit hyperactivity disorder), enhances the release of norepinephrine (to a greater extent), dopamine and serotonin (to a lesser extent) in neurons, blunts hunger, enhances fat catabolism (by stimulating peripheral secretion of norepinephrine and epinephrine)[94]. It was first used to suppress appetite in 1959.

Eteplirsen (Exondys 51®) is a morpholino antisense oligomer that triggers exon 51 skipping during pre-mRNA splicing of the dystrophin RNA transcript, which alters the downstream reading frame of dystrophin; eteplirsen administration to patients with specific nonsense mutations causing Duchenne muscular dystrophy[95]. Eteplirsen restores the reading frame of dystrophin mRNA and leads to the production of functional (albeit modified due to the presence of an internal deletion consisting of both the patient's original defect and the therapeutically altered dystrophin protein) dystrophin protein [29]. The second antisense oligonucleotide nusinersen (Spinraza®) is the first approved drug for the treatment of spinal muscular atrophy, which is caused by mutations in the *SMN1* gene, which encodes the survival motor neuron protein. Nusinersen modulates alternative splicing of the *SMN2* gene, functionally converting it into

[80] Drugs.com. Spinraza. Available from: https://www.drugs.com/spinraza.html
[81] Drugs.com. Rubraca. Available from: https://www.drugs.com/rubraca.html
[82] Drugs.com. Eucrisa. Available from: https://www.drugs.com/eucrisa.html
[83] Drugs.com. Zinplava. Available from: https://www.drugs.com/zinplava.html
[84] Drugs.com. Lartruvo: Package Insert / Prescribing Info. Available from: https://www.drugs.com/ pro/lartruvo.html
[85] Drugs.com. Exondys 51. Available from: https://www.drugs.com/exondys-51.html
[86] Drugs.com. Adlyxin. Available from: https://www.drugs.com/adlyxin.htm
[87] Drugs.com. Xiidra. Available from: https://www.drugs.com/xiidra.html
[88] Drugs.com. Epclusa. Available from: https://www.drugs.com/epclusa.html
[89] Drugs.com. Nuplazid. Available from: https://www.drugs.com/nuplazid.html
[90] Drugs.com. Briviact. Available from: https://www.drugs.com/briviact.html
[91] Drugs.com. Defitelio. Available from: https://www.drugs.com/mtm/defitelio.html
[92] Drugs.com. Ocaliva. Available from: https://www.drugs.com/ocaliva.html
[93] Drugs.com. Xiidra. Available from: https://www.drugs.com/xiidra.html
[94] Drugs.com. Qsymia. Available from: https://www.drugs.com/qsymia.html
[95] Drugs.com. Exondys 51. Available from: https://www.drugs.com/exondys-51.html

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the *SMN1* gene, thereby increasing the level of SMN protein in the central nervous system (CNS) [30].

Crisaborole (Eucrisa®) is a non-steroidal anti-inflammatory drug for topical use in mild to moderate atopic dermatitis (eczema) in adults and children, which acts as an inhibitor of phosphodiesterase 4B (PDE-4B), suppressing the release of tumor necrosis factor α (TNFα), interleukin (IL) 12, IL-23 and other cytokines, proteins that are believed to be involved in the immune response and inflammation[96]. Interestingly, in 2014, a drug containing tavaborole (Kerydin™) was approved, which is structurally similar to crisaborole, but acts as an inhibitor of fungal cell leucyl-tRNA synthetase, blocking protein synthesis and, accordingly, slowing growth; it is used to treat onychomycosis[97].

Oxymetazoline hydrochloride (Kovanaze™) (an imidazoline derivative, a mixed α1 / α2 adrenergic receptor agonist) and tetracaine hydrochloride (a local anesthetic, blocks Na^+ ion channels necessary for the initiation and conduction of neural impulses) are approved in spray form for local anesthesia during dental treatment, which is an alternative to injections[98].

Three drugs were approved for the treatment of diabetes mellitus in 2016: a new form of lixisenatide (Adlyxin™) (aGLP-1)[99], a combination of lixisenatide with insulin glargine (a basal insulin analogue) (Soliqua 100/33)[100], and a combination of insulin degludec (an ultra-long-acting basal insulin analogue) and liraglutide (aGLP-1) (Xultophy®)[101].

Three new combination drugs have been approved for the treatment of chronic hepatitis: Zepatier® (elbasvir [hepatitis C virus NS5A protein inhibitor] and grazoprevir [NS3/4A inhibitor])[102], Epclusa® (sofosbuvir [NS5B polymerase inhibitor] and velpatasvir [NS5A polymerase inhibitor])[103], Viekira® (dasabuvir [NS5B polymerase inhibitor], ombitasvir [NS5A polymerase inhibitor], paritaprevir [NS3-4A serine protease inhibitor] and ritonavir [originally developed as an HIV protease inhibitor])[104] and one new drug: tenofovir alafenamide (Vemlidy®) — a nucleotide reverse transcriptase inhibitor and a prodrug of tenofovir (previously approved for the treatment of HIV)[105].

For the treatment of anorexia, a drug containing dronabinol (Syndros™) is a delta-9-tetrahydrocannabinol, which, in addition to stimulating appetite, has an analgesic effect and is effective for nocturnal apnea, has been approved[106].

In the field of treatment of cardiovascular diseases, the following were approved: ephedrine sulfate (Akovaz®) (treatment of hypotension; new manufacturer)[107], Byvalson™ (a combination of nebivolol [a cardioselective third-generation β-blocker] and valsartan [an angiotensin II receptor blocker])[108], nitroglycerin in a new dosage form for the prevention of angina pectoris (GoNitro™)[109], lisinopril in a new dosage form (Qbrelis®) approved for the treatment of hypertension[110], and aspirin with omeprazole in the form of a new combination (Yosprala®) approved for the prevention of ischemic stroke[111].

2017

In 2017 were approved 103 drugs, including 42 original drugs (from them 27 biologicals), 12 new combinations, 2 reproduced drugs, as well as 27 drugs in a new dosage form or with new indications for use. Examples of approved drugs in 2017 are Zolgensma® (onasemnogene abeparvovec; gene therapy for the treatment of spinal muscular atrophy [SMA]), Kymriah® (tisagenlecleucel; the first CAR-T therapy for the treatment of relapsed acute myeloid leukemia in children and young people), Takhzyro® (lanadelumab; for the prevention of angioedema attacks) (Fig. 4).

Plecanatide (Trulance®) is a 16-amino acid peptide with an amino acid sequence similar to uroguanylin. It

[96] Drugs.com. Eucrisa. Available from: https://www.drugs.com/eucrisa.html
[97] Drugs.com. Kerydin. Available from: https://www.drugs.com/kerydin.html
[98] Drugs.com. Kovanaze. Available from: https://www.drugs.com/pro/kovanaze.html
[99] Drugs.com. Adlyxin Available from: https://www.drugs.com/adlyxin.html
[100] Drugs.com. Soliqua. Available from: https://www.drugs.com/soliqua.html
[101] Drugs.com. Xultophy. Available from: https://www.drugs.com/xultophy.html
[102] Drugs.com. Zepatier. Available from: https://www.drugs.com/zepatier.html
[103] Drugs.com. Epclusa. Available from: https://www.drugs.com/epclusa.html
[104] Drugs.com. Viekira. Available from: https://www.drugs.com/viekira.html
[105] Drugs.com. Vemlidy. Available from: https://www.drugs.com/vemlidy.html
[106] Drugs.com. Syndros Available from: https://www.drugs.com/mtm/syndros.html
[107] Drugs.com. Ephedrine (Monograph). Available from: https://www.drugs.com/monograph/ephedrine.html
[108] Drugs.com. Byvalson. Available from: https://www.drugs.com/byvalson.html
[109] Drugs.com. Nitroglycerin (oral/sublingual). Available from: https://www.drugs.com/mtm/ nitroglycerin-oral-sublingual.html
[110] Drugs.com. Qbrelis. Available from: https://www.drugs.com/mtm/qbrelis.html
[111] Drugs.com. Yosprala. Available from: https://www.drugs.com/yosprala.html

activates guanylate cyclase-C on endothelial cells of the gastrointestinal tract, which leads to phosphorylation mediated by protein kinase A and protein kinase G II of the cystic fibrosis transmembrane conductance regulator protein, upon activation of which negatively charged ions (Cl^- and HCO_3^-) are released into the lumen of the gastrointestinal tract. This ensures the entry of Na^+ and water ions, providing a laxative effect. It is indicated for the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation[112].

Etelcalcetide (Parsabiv®) is a new drug for the treatment of secondary hyperparathyroidism in people undergoing hemodialysis, acts through activation of the calcium-sensing receptor in the parathyroid gland, which leads to a decrease and suppression of parathyroid hormone secretion. Interestingly, by nature it is a peptide consisting mainly of D-amino acids instead of the usual L-amino acids[113].

Abaloparatide (Tymlos®) is a synthetic analogue of parathyroid hormone, consisting of 34 amino acids, acts as an anabolic agent on bone tissue through selective activation of parathyroid hormone receptor 1, expressed in osteoblasts and osteocytes. Approved for the treatment of postmenopausal osteoporosis[114].

The first tryptophan hydroxylase inhibitor (involved in serotonin biosynthesis) is a telotristat (Xermelo®) approved for the treatment of adults with diarrhea associated with carcinoid syndrome[115].

Safinamide (Xadago®) (synthesized in 1993) is approved for the treatment of Parkinson's disease[116]. Like selegiline and rasagiline, it is a selective inhibitor of monoamine oxidase B, but unlike them, it is reversible. Safinamide also affects the metabolism of glutamate, dopamine and serotonin, interacts with sigma receptors, blocks Ca^{2+}- and Na^+-channels.

Valbenazine (Ingrezza®) is a prodrug, an ester of [+]-α-dihydrotetrabenazine with the amino acid L-valine, the first drug approved for the treatment of drug-induced dyskinesia. It acts as an inhibitor of the presynaptic vesicular monoamine transporter type 2 in humans, reducing dopamine secretion[117].

Cerliponase α (Brineura®) is the first drug for the treatment of Batten disease (juvenile form of a group of diseases called neuronal ceroid lipofuscinoses), which occurs as a result of a genetic mutation in battenin — a protein encoded by the *CLN3* gene and causing a deficiency of tripeptidylpeptidase-1. The drug is an enzyme replacement agent (functions as a serine protease, a recombinant form of TPP1)[118].

Another anticoagulant drug has been approved — betrixaban (Bevyxxa®) — a direct inhibitor of activated coagulation factor X, for the prevention of venous thrombosis, is practically not metabolized by cytochrome CYP3A4 and does not have significant renal excretion, which distinguishes it from drugs with a similar mechanism of action[119].

For the treatment of precocious puberty, triptorelin (Triptodur®) has been approved (patented in 1975 and approved for medical use in 1986) — a decapeptide and agonist of gonadotropin-releasing hormone, suppresses the expression of luteinizing hormone (LH) and follicle-stimulating hormone, reduces the secretion of androgens and estrogens[120].

Secnidazole (Solosec®) (a 5-nitroimidazole derivative, structurally similar to metronidazole) is approved as an antimicrobial and antiprotozoal agent. It has a bactericidal effect against most anaerobic bacteria and many protozoa, including trichomonads. The mechanism of action is based on the ability to disrupt the coiling of DNA of microbial cells, cause a break in its strands; suppress the synthesis of nucleic acids; inhibit reduction processes characteristic of anaerobes[121].

Exenatide (Bydureon BCise) is approved as a new antidiabetic drug (GLP-1 receptor agonist), which, unlike its predecessor, is administered once a week instead of 2 injections per day[122]. A drug containing another synthetic GLP-1 analogue, semaglutide

[112] Drugs.com. Trulance. Available from: https://www.drugs.com/trulance.html
[113] Drugs.com. Parsabiv. Available from: https://www.drugs.com/mtm/parsabiv.html
[114] Drugs.com. Tymlos. Available from: https://www.drugs.com/tymlos.html
[115] Drugs.com. Xermelo. Available from: https://www.drugs.com/xermelo.html
[116] Drugs.com. Xadago. Available from: https://www.drugs.com/xadago.html
[117] Drugs.com. Ingrezza. Available from: https://www.drugs.com/ingrezza.html
[118] Drugs.com. Brineura. Available from: https://www.drugs.com/brineura.html
[119] Drugs.com. Bevyxxa. Available from: https://www.drugs.com/bevyxxa.html
[120] Drugs.com. Triptodur. Available from: https://www.drugs.com/mtm/triptodur.html
[121] Drugs.com. Solosec. Available from: https://www.drugs.com/solosec.html
[122] Drugs.com. Bydureon. Available from: https://www.drugs.com/bydureon.html

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(Ozempic®), has also been approved for the treatment of T2DM and to reduce the risk of its cardiovascular complications[123]. Ertugliflozin (Steglatro®), a sodium / glucose cotransporter 2 inhibitor, and its combinations with metformin (biguanide) (Segluromet®)[124] or sitagliptin (DPP-4i; Steglujan®)[125] have also been approved as antihyperglycemic agents.

Voretigene neparvovec (Luxturna®) — AAV2 vector containing human cDNA RPE65 with a modified Kozak sequence, is indicated for the treatment of people with vision loss due to inherited retinal dystrophy with confirmed biallelic RPE65 mutations, and who have a sufficient number of viable retinal cells (the first gene therapy drug for the treatment of congenital Leber's amaurosis, the first approved gene therapy)[126].

For the diagnosis of growth hormone deficiency, macimorelin (Macrilen®) (D-tryptophanamide, 2-methylalanyl-N-[(1R)-1-(formylamino)-2-(1H-indol-3-yl) ethyl] acetate; ghrelin receptor agonist, causing the release of growth hormone from the pituitary gland) has been approved. Traditionally, growth hormone deficiency was diagnosed using an insulin tolerance test or a glucagon stimulation test [31]. These two agents are administered parenterally, whereas the approved macimorelin is administered orally[127].

Glycopyrrolate (Lonhala Magnair®) was first used in 1961 to treat peptic ulcer disease. Since 1975, intravenous glycopyrronium has been used before surgery to reduce salivary, tracheobronchial, and pharyngeal secretions — a muscarinic receptor antagonist, inhibits cholinergic transmission and is approved for the treatment of COPD [32]. In 2021, it was approved for therapy in peptic ulcer due to its ability to reduce hydrochloric acid secretion[128].

The first-in-class drug letermovir (Prevymis®) is approved for the prevention of cytomegalovirus (CMV) infection and other diseases in allogeneic stem cell transplant recipients. It acts as a specific inhibitor of the CMV-terminase complex, which is encoded by the CMV genes *UL56*, *UL51*, and *UL89*. This inhibition prevents the cleavage of CMV DNA concatamers, resulting in long, unprocessed DNA and non-infectious viral particles. Letermovir is active only against CMV and does not affect other herpes viruses[129].

Vestronidase α (Mepsevii®) deserves attention as the only drug for the treatment of Sly syndrome (mucopolysaccharidosis type VII) and is a recombinant form of the human enzyme β-glucuronidase[130]. Macimorelin (Macrilen®) is an agonist of receptors that enhance the secretion of growth hormone (ghrelin receptors) from the pituitary gland and is used for diagnostic purposes in adults[131].

2018

In 2018, the FDA approved 110 drugs, 57 of which were new molecular entities (including 37 biologicals), 13 were new drug combinations, 2 were reproduced drugs; 28 drugs had a new dosage form or a new indication for use. It should also be noted that 19 drugs were first-in-class, 34 drugs were intended for the treatment of rare diseases, and seven biosimilars were approved. Examples of registered drugs were cannabidiol[132] (Epidiolex®; the first drug derived from marijuana approved for the treatment of epilepsy associated with Lennox-Gastaut and Dravet syndromes)[133], stiripentol (Diacomit®; the second drug approved for the treatment of Dravet syndrome [severe myoclonic epilepsy of infancy])[134], migalastat (Galafold®; the first oral drug for the treatment of Fabry disease [an extremely rare lysosomal storage disease])[135], burosumab (Crysvita®; the first drug for the treatment of X-linked hypophosphatemic rickets)[136], pegvaliaza (Palynziq®; the first approved drug for the treatment of phenylketonuria)[137], as well as three new drugs for the prevention of migraine —

[123] Drugs.com. Ozempic. Available from: https://www.drugs.com/ozempic.html
[124] Drugs.com. Segluromet. Available from: https://www.drugs.com/segluromet.html
[125] Drugs.com. Steglujan. Available from: https://www.drugs.com/steglujan.html
[126] Drugs.com. FDA Approves Luxturna. Available from: https://www.drugs.com/newdrugs/fda-approves-luxturna-voretigene-neparvovec-rzyl-gene-therapy-patients-rare-inherited-vision-loss-4662.html
[127] Drugs.com. Macrilen. Available from: https://www.drugs.com/mtm/macrilen.html
[128] Drugs.com. Lonhala Magnair Starter Kit (inhalation). Available from: https://www.drugs.com/ mtm/lonhala-magnair-starter-kit-inhalation.html
[129] Drugs.com. Prevymis. Available from: https://www.drugs.com/prevymis.html
[130] Drugs.com. Mepsevii. Available from: https://www.drugs.com/mtm/mepsevii.html
[131] Drugs.com. Macrilen. Available from: https://www.drugs.com/mtm/macrilen.html
[132] Starting in 2018, cannabidiol (i.e. CBD oil) is no longer prohibited under the S8 Cannabinoids category.
[133] Drugs.com. Epidiolex Available from: https://www.drugs.com/epidiolex.html
[134] Drugs.com. Diacomit. Available from: https://www.drugs.com/diacomit.html
[135] Drugs.com. Galafold. Available from: https://www.drugs.com/galafold.html
[136] Drugs.com. Crysvita. Available from: https://www.drugs.com/mtm/crysvita.html
[137] Drugs.com. Palynziq. Available from: https://www.drugs.com/palynziq.html

erenumab (Aimovig®)[138], fremanezumab (Ajovy®)[139] and galcanezumab (Emgality®)[140] (Fig. 7).

In 2018, tolvaptan (Jynarque®) was approved for the treatment of adults at risk of rapidly progressing autosomal dominant polycystic kidney disease, which was previously used to treat hypervolemic and euvolemic hyponatremia, and which acts as a selective competitive vasopressin receptor 2 antagonists[141]. Lofexidine hydrochloride (Lucemyra®) is the first non-opioid drug for the treatment of opioid withdrawal syndrome, acting as an α2-adrenergic receptor agonist and is structurally similar to clonidine, but unlike the latter, it reduces blood pressure to a lesser extent[142]. Widely known in veterinary practice moxidectin, a macrocyclic lactone of the milbemycin class, widely known in veterinary practice (macrolides, first isolated in 1972 from *Streptomyces hygroscopicus*), the mechanism of action associated with the opening of glutamate-sensitive chlorine channels in neurons and myocytes of invertebrates, which leads to hyperpolarization and blocking of signal transmission [33], is approved for use in onchocerciasis[143].

The antibiotic plazomicin (Zemdri®) (first submitted for review in 2012, derived from sisomicin, which is structurally closest to gentamicin) acts as an aminoglycoside antibiotic and is approved for the treatment of complicated urinary tract infections[144].

Glycopyrronium (Qbrexza®) (blocks muscarinic receptors and suppresses cholinergic transmission; does not penetrate the blood-brain barrier) was first used in 1961 to treat peptic ulcer disease, and since 1975 its intravenous administration has been used before surgery to reduce salivary, tracheobronchial, and pharyngeal secretions [32], and in 2018 it was approved for the treatment of hyperhidrosis[145].

Tecovirimat (TPOXX®) is an antiviral drug active against orthopoxviruses, such as smallpox and monkeypox (mpox), the first in its class (synthesis published in 2004), suppresses the function of the orthopoxvirus envelope protein VP37, the main envelope protein required for the production of extracellular virus, prevents the virus from leaving the infected cell, preventing the spread of the virus in the body[146].

For the prevention and treatment of malaria, tafenoquine (Krintafel® and Arakoda®)[147,148] (structurally similar to primaquine [first produced in 1946], chloroquine [was discovered in 1934] and mefloquine [developed in the 1970s]) has been approved, which belongs to the family of 8-aminoquinoline drugs, the mechanism of antimalarial action is poorly understood.

Elagolix (Orilissa®) was first described in 2008 [34], but was approved for medical use only in July 2018, as a potent and selective competitive antagonist of the gonadotropin-releasing hormone (GnRH) receptor of the "second generation" due to its non-peptide, low molecular weight nature, which allows it to be used orally. The drug is used to treat moderate to severe pain caused by endometriosis[149]. The drug is the first in its class, after it relugolix was created (approved in 2022 for the treatment of prostate cancer).

Eravacycline (Xerava®) is a new synthetic halogenated antibiotic of the tetracycline class[150], also from this group (tetracyclines) sarecycline (Seysara®) (a narrow-spectrum antibiotic) was approved for the treatment of acne[151]. Unlike other antibiotics in this group, the drug has a long C7 fragment, thanks to which it directly interacts with bacterial mRNA. This compound was obtained during chemical experiments with tetracycline cascades, which also resulted in the development of another third-generation tetracycline antibiotic — omadacycline (Nuzyra®) for the treatment of community-acquired bacterial pneumonia and acute skin infections[152].

[138] Drugs.com. Aimovig. Available from: https://www.drugs.com/aimovig.html
[139] Drugs.com. Ajovy. Available from: https://www.drugs.com/ajovy.html
[140] Drugs.com. Emgality. Available from: https://www.drugs.com/emgality.html
[141] Drugs.com. Jynarque. Available from: https://www.drugs.com/mtm/jynarque.html
[142] Drugs.com. Lucemyra. Available from: https://www.drugs.com/lucemyra.html
[143] Drugs.com. FDA Approves Moxidectin. Available from: https://www.drugs.com/newdrugs/fda-approves-moxidectin-river-blindness-4766.html
[144] Drugs.com. FDA Approves Zemdri. Available from: https://www.drugs.com/newdrugs/zemdri-plazomicin-approved-fda-adults-complicated-urinary-tract-infections-cuti-4770.html
[145] Drugs.com. Qbrexza (glycopyrronium cloth). Available from: https://www.drugs.com/mtm/qbrexza-glycopyrronium-cloth.html
[146] Drugs.com. TPOXX. Available from: https://www.drugs.com/tpoxx.html
[147] Drugs.com. Krintafel. Available from: https://www.drugs.com/mtm/krintafel.html
[148] Drugs.com. Arakoda. Available from: https://www.drugs.com/arakoda.html
[149] Drugs.com. Orilissa Play pronunciation. Available from: https://www.drugs.com/orilissa.html
[150] Drugs.com. Xerava. Available from: https://www.drugs.com/mtm/xerava.html
[151] Drugs.com. Seysara. Available from: https://www.drugs.com/seysara.html
[152] Drugs.com. Nuzyra (oral/injection). Available from: https://www.drugs.com/mtm/nuzyra-oral-injection.html

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Baloxavir marboxil (Xofluza®) is a prodrug, an inhibitor of the enzyme that synthesizes viral mRNA. It is used as an antiviral agent, including for the treatment of acute uncomplicated influenza in people aged twelve years and older who are at risk of influenza complications (since 2019)[153].

Latanoprost (Xelpros®) is a prostaglandin analogue (prostaglandin F2α) in the form of eye drops for the treatment of glaucoma and high intraocular pressure, by stimulating the outflow of aqueous humor through the uveoscleral pathway; prodrug — inactive until hydrolyzed in the cornea from ether to biologically active acids[154].

For the treatment of COPD, an inhalation solution containing revefenacin (Yupelri®) has been approved — a bronchodilator, a long-acting muscarinic receptor antagonist[155].

Prucalopride (Motegrity®) acts as a selective, high-affinity 5-HT4 receptor agonist for the treatment of chronic intestinal pseudo-obstruction[156].

2019

In 2019, the FDA approved 100 drugs, and 57 drugs registration was made for original molecules (including 31 of biologicals), in 14 — for new combinations, in 2 — for reproduced drugs; 16 drugs had a new dosage form or a new indication for use. Notable examples of approved drugs are tafamidis (Vyndaqel®; for the treatment of transthyretin familial amyloid polyneuropathy)[157], fedratinib (Inrebic®; for the treatment of myelofibrosis)[158], luspatercept (Reblozyl®; for the treatment of anemia associated with β-thalassemia)[159], romosozumab (Evenity®; for the treatment of osteoporosis in postmenopausal women)[160], upadacitinib (Rinvoq®; for the treatment of rheumatoid arthritis)[161] (Fig. 8).

Triclabendazole (Egaten®) is approved for the treatment of fascioliasis[162] (previously used to combat paragonimiasis), unlike classic benzimidazoles, does not have a carbamate group, but the structure contains a chlorinated benzene ring; all drugs in this class bind to β-tubulin, thereby preventing microtubule polymerization [35]. It has had non-proprietary drug status since 1990.

Allopregnanolone (3-α,5-α-tetrahydroprogesterone, 3α,5α-THP; Zulresso®) is a metabolite of allopregnanedione (synthesized from progesterone; a progesterone receptor agonist, a positive allosteric modulator of the GABAA receptor, and a negative allosteric modulator of the GABAA-rho receptor), synthesized both by the adrenal cortex and directly in the brain with the participation of 5-α-reductase and 3-α-hydroxysteroid oxidoreductase. It plays a multifaceted role in the development of the central nervous system, binding to a special structural site on its surface and modulating the activity of the GABA-A receptor [36]. Zulresso® is approved for the treatment of postpartum depression[163].

Esketamine (Spravato®), which has a high antagonism to NMDA receptors, deserves attention. Approved as a nasal spray for the treatment of resistant depression and major depressive disorder with concomitant suicidal thoughts or behavior[164].

Duobrii® is approved for the treatment of psoriasis — the first combination of halobetasol (topical corticosteroid; has immunosuppressive, anti-inflammatory, and antiproliferative effects) and tazarotene (third-generation retinoid, agonist of retinoic acid receptors (RAP-α, RAP-β, RAP-γ; normalizes the differentiation of keranocytes, inhibits their proliferation, and reduces the expression of inflammatory markers; approved in the same year as a single drug for the treatment of acne). The effects of these substances organically complement each other, reducing the irritating effect (of tazarotene) or prolonging the action (of halobetasol)[165].

Qternmet XR® is approved for the treatment

[153] Drugs.com. Xofluza. Available from: https://www.drugs.com/xofluza.html
[154] Drugs.com. Xelpros. Available from: https://www.drugs.com/mtm/xelpros.html
[155] Drugs.com. Yupelri Inhalation. Available from: https://www.drugs.com/yupelri.html
[156] Drugs.com. Motegrity. Available from: https://www.drugs.com/motegrity.html
[157] Drugs.com. Vyndaqel. Available from: https://www.drugs.com/vyndaqel.html
[158] Drugs.com. Inrebic. Available from: https://www.drugs.com/inrebic.html
[159] Drugs.com. Reblozyl. Available from: https://www.drugs.com/reblozyl.html
[160] Drugs.com. Evenity. Available from: https://www.drugs.com/evenity.html
[161] Drugs.com. Rinvoq. Available from: https://www.drugs.com/rinvoq.html
[162] Drugs.com. Triclabendazole (Monograph). Available from: https://www.drugs.com/monograph/ triclabendazole.html
[163] Drugs.com. Zulresso. Available from: https://www.drugs.com/zulresso.html
[164] Drugs.com. Spravato. Available from: https://www.drugs.com/spravato.html
[165] Drugs.com. Duobrii. Available from: https://www.drugs.com/duobrii.html

of T2DM — the first combination of dapagliflozin, metformin hydrochloride, and saxagliptin[166].

Tafamidis meglumine (Vyndaqel®; selective transthyretin stabilizer; binds to two thyroxine-binding sites of transthyretin in its native [tetrameric] form, which prevents dissociation of the complex into monomers and slows amyloidogenesis) is approved for the treatment of cardiomyopathy and amyloidosis[167].

Onasemnogene abeparvovec (Zolgensma®) is approved — the first drug for gene therapy for spinal muscular atrophy, for use in children under 2 years old[168].

Budesonide (Ortikos®) is approved for the treatment of Crohn's disease[169].

Bremelanotide (Vyleesi®)[170] is used for low sexual desire that occurs before menopause. Bremelanotide is a non-selective agonist of melanocortin receptors MC1–MC5 (except MC2 — the ACTH receptor), but acts primarily as an agonist of MC3 and MC4 receptors. It is a cyclic heptapeptide lactam analog of αmelanocyte-stimulating hormone (α-MSH), an active metabolite of melanotan II, which lacks the Cterminal amide group [37]. In addition to melanotan II and endogenous melanocyte-stimulating hormones, such as α-MSH, other peptide analogs of the same family as bremelanotide include afamelanotide (NDP-α-MSH), modimelanotide, and setmelanotide [38].

Amlodipine besylate (Katerzia™) in a new dosage form is approved for the treatment of hypertension and coronary artery disease[171].

Recarbrio™ is approved for the treatment of genitourinary infections — a combination of imipenem (synthetic β-lactam antibiotic), cilastatin (human dehydropeptidase inhibitor that prevents the degradation of imipenem), and relabactam (β-lactamase inhibitor).

A new anti-tuberculosis drug has been approved. Pretomanid (Dovprela®)[172] is activated in mycobacteria by deazaflavin-dependent nitroreductase (Ddn) and converted into a highly active metabolite. This metabolite attacks the DprE2 synthesis enzyme, which is necessary for the synthesis of the cell wall arabinogalactan, to which mycolic acid will be attached; this mechanism is common with delamanid [39].

Tenapanor (Ibsrela®) is an inhibitor of the Na^+/H^+ exchanger (NHE3), the antiport protein is located in the kidneys and intestines, regulating the levels of sodium absorbed and excreted by the body), selectively inhibits sodium absorption in the intestine, limiting the amount absorbed from food, and thereby reduces the level of sodium in the body, which may be potentially useful in kidney disease and/or hypertension [40]. In October 2023, tenapanor was approved by the FDA for the treatment of hyperphosphatemia[173].

Semaglutide (Rybelsus®) (aGLP-1) is approved in tablet form for oral administration[174].

Trifarotene (Aklief®) is approved as a drug for the topical treatment of acne. It is a retinoid — a selective agonist of the fourth-generation retinoic acid receptor RAR-γ[175].

Lasmiditan (Reyvow®) — a selective agonist of 5-HT1F serotonin receptors selectively binds to this subtype of receptors, and the lack of affinity for 5-HT1B and 5-HT1D increases its safety[176].

Minocycline (Amzeeq®) (binds to the 30S ribosomal subunit of bacteria and thereby inhibits protein synthesis), which was patented in 1961, has been approved as a drug for the topical treatment of acne (foam)[177].

For the first time, a triple combination for the treatment of cystic fibrosis has been approved — elexacaftor, tezacaftor, and ivacaftor (Trikafta®). All substances are classified as cystic fibrosis transmembrane regulators (CFTR) in cystic fibrosis[178].

A new combination of amoxicillin (antibiotic, aminopenicillins of the penicillin family; inhibits cross-links between linear polymer chains of peptidoglycan, which is the main component of the bacterial cell

[166] Drugs.com. Qternmet XR. Available from: https://www.drugs.com/qternmet-xr.html
[167] Drugs.com. Vyndaqel Play pronunciation. Available from: https://www.drugs.com/vyndaqel.html
[168] Drugs.com. Zolgensma. Available from: https://www.drugs.com/zolgensma.html
[169] Drugs.com. Ortikos. Available from: https://www.drugs.com/mtm/ortikos.html
[170] Drugs.com. Vyleesi. Available from: https://www.drugs.com/vyleesi.html
[171] Drugs.com. Katerzia. Available from: https://www.drugs.com/mtm/katerzia.html
[172] Drugs.com. FDA Approves Pretomanid. Available from: https://www.drugs.com/newdrugs/fda-approves-pretomanid-highly-resistant-forms-tuberculosis-5029.html
[173] Drugs.com. Ibsrela. Available from: https://www.drugs.com/ibsrela.html
[174] Drugs.com. Rybelsus. Available from: https://www.drugs.com/rybelsus.html
[175] Drugs.com. Aklief. Available from: https://www.drugs.com/aklief.html
[176] Drugs.com. Reyvow. Available from: https://www.drugs.com/reyvow.html
[177] Drugs.com. Amzeeq. Available from: https://www.drugs.com/mtm/amzeeq.html
[178] Drugs.com. Trikafta. Available from: https://www.drugs.com/trikafta.html

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wall; developed in the 1960s), omeprazole (proton pump inhibitor, patented in 1978), and rifabutin (antibiotic, blocks DNA-dependent RNA polymerase, discovered in 1975) — the drug Talicia® has been approved for the treatment of Helicobacter pylori infection[179].

A new antibiotic, cefiderocol (Fetroja®), has been approved, which is structurally similar to cefepime and ceftazidime, but the chlorocatechol group at the end of the C-3 side chain further increases its stability to β-lactamase and makes it a siderophore (small, high-affinity iron-chelating compounds, one of the strongest known Fe^{3+} chelators)[180].

Cenobamate (Xcopri®) is a blocker of potential-dependent Na^+ channels, predominantly inhibiting the constant sodium current, additionally enhances the presynaptic release of γ-aminobutyric acid, increasing inhibitory GABAergic neurotransmission, and is approved for use in epilepsy[181].

Golodirsen (Vyondys 53®) is approved for the treatment of Duchenne muscular dystrophy, causing exon skipping in the dystrophin gene and thereby increasing the amount of dystrophin protein available to muscle fibers[182].

Levamlodipine (Conjupri®) — the pharmacologically active enantiomer of amlodipine — a dihydropyridine calcium channel blocker used as an antihypertensive and antianginal agent, the key advantage of which (like all enantiomers) is a 2-fold reduction in the effective dose compared to traditional amlodipine drugs (patented in 1982)[183].

Lumateperone (Caplyta®) is approved for the treatment of Schizophrenia and the depressive phase of bipolar disorder, both as monotherapy and as adjunctive therapy (with lithium or valproate), acts as a 5-HT2A receptor antagonist and an antagonist of several dopamine receptor subtypes (D1R, D2R, and D4R), but with lower affinity. It moderately inhibits serotonin transporter reuptake and has additional off-target antagonism against α-1 receptors, without noticeable antimuscarinic or antihistaminergic properties, limiting the side effects associated with other atypical antipsychotics[184].

Lemborexant (Dayvigo®) is a dual orexin antagonist (orexin receptor antagonist OX1 and OX2) that is used to treat insomnia and, unlike suvorexant, has a short duration of action[185]. Ubrogepant (Ubrelvy®) is approved for the treatment of migraine and acts as an antagonist of the calcitonin gene-related peptide receptor[186].

2020

In 2020, against the backdrop of the COVID-19 pandemic, 104 drugs were registered, including 50 original ones (including 30 biologicals), 14 new combinations, 3 reproduced drugs, and 21 drugs in a new dosage form or with a new indication for use. A high proportion of biologicals, including antibodies and therapeutic vaccines, as well as drugs intended for the treatment of orphan diseases, also persisted, which underscores the importance of developing therapies for small groups of patients. Among the approved drugs, remdesivir (Veklury®; antiviral agent for the treatment of COVID-19)[187], formoterol bromide and glycopyrronium bromide (Breztri Aerosphere®; for the treatment of chronic obstructive pulmonary disease [COPD])[188], carfilzomib (Kyprolis®; for the treatment of relapsed or refractory multiple myeloma)[189], loncastuzumab (Zynlonta®; for the treatment of relapsed or refractory non-Hodgkin's lymphoma)[190], and teplizumab (Tzield®; to slow the progression of type 1 diabetes)[191] can be distinguished (Fig. 9).

A new dosage form (nasal spray) for diazepam[192] (Valtoco®) (a benzodiazepine, a positive allosteric modulator of GABA type A receptors, a derivative of

[179] Drugs.com. Talicia. Available from: https://www.drugs.com/mtm/talicia.html
[180] Drugs.com. Fetroja. Available from: https://www.drugs.com/mtm/fetroja.html
[181] Drugs.com. Xcopri. Available from: https://www.drugs.com/xcopri.html
[182] Drugs.com. Vyondys 53. Available from: https://www.drugs.com/vyondys-53.html
[183] Drugs.com. Conjupri. Available from: https://www.drugs.com/mtm/conjupri.html
[184] Drugs.com. Caplyta. Available from: https://www.drugs.com/caplyta.html
[185] Drugs.com. Dayvigo. Available from: https://www.drugs.com/dayvigo.html
[186] Drugs.com. Ubrelvy. Available from: https://www.drugs.com/ubrelvy.html
[187] Drugs.com. Veklury. Available from: https://www.drugs.com/veklury.html
[188] Drugs.com. Breztri. Available from: https://www.drugs.com/breztri-aerosphere.html
[189] Drugs.com. Kyprolis. Available from: https://www.drugs.com/kyprolis.html
[190] Drugs.com. Zynlonta. Available from: https://www.drugs.com/zynlonta.html
[191] Drugs.com. Tzield. Available from: https://www.drugs.com/tzield.html
[192] Decree of the Government of the Russian Federation of June 30, 1998 No. 681 "On Approval of the List of Narcotic Drugs, Psychotropic Substances and their Precursors Subject to Control in the Russian Federation" (with Amendments and additions). Available from: https://base.garant.ru/12112176/. Russian

chlordiazepoxide [approved in 1960] has been available for clinical use since 1963) [41] has been approved for the relief of epileptic seizures, including in children[193].

A triple combination of hypoglycemic drugs — Trijardy XR® (empagliflozin [SGLT2i], linagliptin [DPP-4i], and metformin hydrochloride [biguanide]) has been approved for the treatment of T2DM[194].

Pizensy®, a drug containing lactitol (a disaccharide sugar alcohol, a derivative of lactose), which was previously widely used as an excipient, has been approved for the treatment of chronic idiopathic constipation[195].

Bempedoic acid (Nexletol®) has been app roved as the first in-class drug for the treatment of hypercholesterolemia[196]. It is a prodrug that is transformed into a thioether with the participation of coenzyme A and the enzyme acyl-CoA synthetase with a very long chain SLC27A2 in the liver, after which it inhibits ATP-citrate lyase, which is involved in cholesterol biosynthesis in the liver above HMG-CoA reductase, an enzyme that is blocked by statins. Almost immediately after this registration, a drug containing bempedoic acid and ezetimibe (Nexlizet®), which inhibits the absorption of cholesterol from the small intestine and reduces the bioavailability of cholesterol, was approved. Ezetimibe blocks a critical mediator of cholesterol absorption, Niemann-Pick C1-Like 1 protein (NPC1L1) on gastrointestinal epithelial cells, and in hepatocytes it blocks aminopeptidase N and disrupts the caveolin 1 — annexin A2 complex involved in cholesterol transport [42] The drug is also approved for the treatment of heterozygous familial hypercholesterolemia[197].

Rimegepant (Nurtec® ODT) is a small molecule antagonist of the calcitonin gene-related peptide receptor (for oral administration) approved for the treatment and prevention (in 2021) of migraine[198]. Eptinezumab (Vyepti®; intravenous injections), a fully human monoclonal antibody that blocks the binding of calcitonin gene-related peptide to its receptor, has been approved for the same indication[199].

Osilodrostat (Isturisa®) (an inhibitor of steroidogenesis enzymes) — steroid 11β-hydroxylase and aldosterone synthase for the treatment of adults with Cushing's disease[200].

Ozanimod (Zeposia®) is approved for the treatment of relapsing multiple sclerosis and ulcerative colitis, acting as an agonist of the sphingosine-1-phosphate receptor (S1PR), which causes its internalization and degradation via the ubiquitin-proteasome pathway, leading to the isolation of lymphocytes in peripheral lymphoid organs and away from sites of chronic inflammation[201]. This compound is more selective than siponimod, fingolimod, and mocravimod.

Selumetinib (Koselugo®) is approved as a drug for the treatment of children aged two years and older with neurofibromatosis type I (NF-1), a genetic disorder of the nervous system that causes tumors to grow on nerve tissue; it is a kinase inhibitor (selective inhibitor of the enzyme mitogen-activated protein kinase kinase [MAPK kinase] subtypes 1 and 2), which is part of the MAPK/ERK pathway that regulates cell proliferation and is overactive in many types of cancer[202].

Mitomycin (Jelmyto®) (discovered in 1955 by Japanese scientists in cultures of the microorganism *Streptomyces caespitosus*; structurally similar to rifamycin and ansamycin), is a potent DNA crosslinker, which is effective for killing bacteria. As an alkylating agent, it inhibits the transcription of DNA into RNA, stopping protein synthesis and depriving cancer cells of the ability to multiply[203].

Opicapone (Ongentys®) is approved for the treatment of Parkinson's disease, effectively blocking the enzyme catechol-O-methyltransferase (>90% at therapeutic doses), which breaks down levodopa, sele ctively and reversibly, and only outside the central nervous system, which ensures greater penetration into the CNS and increased efficacy[204].

Monomethyl fumarate (Bafiertam®) is approved

[193] Drugs.com. Valtoco. Available from: https://www.drugs.com/valtoco.html
[194] Drugs.com. Trijardy XR. Available from: https://www.drugs.com/trijardy-xr.html
[195] Drugs.com. Pizensy. Available from: https://www.drugs.com/pro/pizensy.html
[196] Drugs.com. Nexletol. Available from: https://www.drugs.com/nexletol.html
[197] Drugs.com. Nexlizet. Available from: https://www.drugs.com/nexlizet.html
[198] Drugs.com. Nurtec ODT. Available from: https://www.drugs.com/nurtec-odt.html
[199] Drugs.com. Vyepti. Available from: https://www.drugs.com/vyepti.html
[200] Drugs.com. Isturisa. Available from: https://www.drugs.com/isturisa.html
[201] Drugs.com. Zeposia. Available from: https://www.drugs.com/zeposia.html
[202] Drugs.com. Koselugo. Available from: https://www.drugs.com/koselugo.html
[203] Drugs.com. Jelmyto (gel). Available from: https://www.drugs.com/mtm/jelmyto-gel.html
[204] Drugs.com. Ongentys. Available from: https://www.drugs.com/ongentys.html

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for the treatment of multiple sclerosis[205], acting by altering the nuclear transcription factor associated with erythroid factor 2 (nuclear factor erythroid 2-related factor 2, NFE2L2) — a basic leucine zipper protein — which regulates the expression of antioxidant proteins that protect against oxidative damage caused by trauma and inflammation [43]. Several drugs that stimulate the NFE2L2 pathway are being studied for the treatment of diseases caused by oxidative stress.

Two precursors, dimethyl fumarate (in 2013) and diroximel fumarate (in 2019), were previously approved. The first medical use of fumaric acid for the treatment of psoriasis was described in 1959 (local form), and the oral form appeared in 1994 [44].

Leuprorelin (Camcevi®) (was patented in 1973 and approved for medical use in 1985) is an analogue of GnRH, acting as an agonist of pituitary GnRH receptors, increases the secretion of LH and FSH by the anterior pituitary gland, increases serum estradiol and testosterone levels via the hypothalamic-pituitary-gonadal axis (HPG axis) [45]. Approved for the treatment of precocious puberty[206]. A combination containing leuprorelin / norethisterone acetate was previously approved (2012) for the treatment of endometriosis.

Artesunate (water-soluble hemisuccinate of dihydroartemisinin, a derivative of artemisinin; developed, like lumefantrine, piperaquine, and pyronaridine) is approved for the treatment of malaria. The first publications appeared in 1979. It is used both in monotherapy and in combinations (artesunate / pyronaridine, arterolan/ piperaquine, artemisinin base / piperaquine, and artemisinin / naphthoquine)[207].

Trigheptanoin (Dojolvi®) is approved as a drug for the treatment of children and adults with molecularly confirmed long-chain fatty acid oxidation disorders[208].

Remimazolam (Byfavo®)[209] — a benzodiazepine, enhances the action of the endogenous neurotransmitter GABA on GABAA receptors (increasing the frequency of Cl^- channel opening) — a drug that was synthesized in the late 1990s [46], approved as an alternative to midazolam (patented in 1974) for the induction and maintenance of procedural sedation in adults during invasive diagnostic or surgical procedures lasting 30 minutes or less[210].

Nifurtimox (Lampit®) began to be used in medicine in 1965, and received FDA approval for the treatment of Chagas disease only in 2020. Its mechanism of action is similar to metronidazole (1950s, nitroimidazole) (forms a nitro-anion-radical metabolite that reacts with the nucleic acids of the parasite, causing significant DNA breakage)[211].

The first oral drug for the treatment of spinal muscular atrophy, risdiplam (Evrysdi®)[212] (a pyridazine derivative), has been approved — an RNA splicing modifier aimed at the survival of motor neuron 2 (reduces the decrease in survival motor neuron protein; the first drug with a similar mechanism of action was nusinersen [approved in 2016; see above]). Viltolarsen (Viltepso®)[213] has been approved for the treatment of Duchenne muscular dystrophy, which, like eteplirsen (approved in 2016) and golodirsen (approved in 2019), is a phosphorodiamidate antisense morpholino oligonucleotide, a structural analogue of DNA that binds to exon 53 of dystrophin pre-mRNA, implementing its alternative splicing by skipping during mRNA processing and thereby (by restoring the reading frame) ensuring the synthesis of an internally truncated but functional dystrophin. The production of the latter compensates for the critical deficiency of this protein in Duchenne muscular dystrophy [47].

Clascoterone (Winlevi®) (cortexolone 17α-propionate) is approved as the first in-class drug for the treatment of hidradenitis suppurativa (inverse acne — an androgen-dependent skin disease), which acts as an antiandrogen or androgen receptor antagonist, the biological target of androgens such as testosterone and dihydrotestosterone[214].

[205] Drugs.com. Bafiertam. Available from: https://www.drugs.com/mtm/bafiertam.html
[206] Drugs.com. Camcevi. Available from: https://www.drugs.com/pro/camcevi.html
[207] Drugs.com. FDA Approves Artesunate. Available from: https://www.drugs.com/newdrugs/fda-approves-artesunate-severe-malaria-5244.html
[208] Drugs.com. Dojolvi. Available from: https://www.drugs.com/dojolvi.html
[209] ConsultantPlus. List of psychotropic substances whose turnover in the Russian Federation is limited and for which certain control measures may be excluded in accordance with the legislation of the Russian Federation and international treaties of the Russian Federation (List III). Available from: https://www.consultant.ru/document/cons_doc_LAW_136206/99b9c00551ec8df9db44dea714007a 82d2595d3d/. Russia
[210] Drugs.com. Byfavo. Available from: https://www.drugs.com/mtm/byfavo.html
[211] Drugs.com. Lampit. Available from: https://www.drugs.com/lampit.html
[212] Drugs.com. Evrysdi. Available from: https://www.drugs.com/evrysdi.html
[213] Drugs.com. Viltepso. Available from: https://www.drugs.com/viltepso.html
[214] Drugs.com. Winlevi. Available from: https://www.drugs.com/winlevi.html

Somapacitan (Sogroya®) is approved as the first human growth hormone therapy for adults with its deficiency, binding to serum albumin, which slows its elimination[215].

Atoltivimab / maftivimab / odesivimab (Inmazeb®) is the first drug containing a fixed combination of three monoclonal antibodies directed against the glycoprotein of the Ebola virus[216]. Remdesivir (Veklury®) is approved for the treatment of COVID-19, which acts as an inhibitor of RNA-dependent RNA polymerase (a direct-acting antiviral agent), an enzyme necessary for the replication of a number of RNA viruses (ebolaviruses and coronaviruses)[217]. For the treatment of infection caused by the Ebola virus, a drug containing ansuvimab (Ebanga®) (a neutralizing antibody, was isolated from the blood of a person who survived an outbreak of the disease caused by the Ebola virus in 1995)[218] has also been approved.

Lonafarnib (Zokinvy®) (a synthetic tricyclic halogenated carboxamide with potential antineoplastic properties), a farnesyltransferase inhibitor, is approved as an oral medication to help prevent the accumulation of defective progerin or progerin-like protein in Hutchinson-Gilford progeria syndrome[219].

Lumasiran (Oxlumo®) (a double-stranded small interfering ribonucleic acid [siRNA]), is approved to reduce the level of the enzyme glycolate oxidase by targeting the messenger mRNA HAO1 in hepatocytes via RNA interference, resulting in a reduction in the amount of glyoxylate available, a substrate for oxalate formation[220].

Setmelanotide (Imcivree®) is approved for the treatment of a rare form of obesity. The compound binds to and activates MC 4 receptors in the paraventricular nucleus of the hypothalamus and in the lateral hypothalamic area—areas involved in appetite regulation. This action is believed to underlie its appetite-suppressing effects. In addition to reducing appetite, setmelanotide increases resting energy expenditure in both obese animals and humans [48–50]. Importantly, unlike some other MC 4 receptor agonists, setmelanotide does not cause an increase in heart rate or blood pressure[221].

Berotralstat (Orladeyo®) is approved for the prevention of hereditary angioedema, acts as an inhibitor of plasma kallikrein, which leads to the blockade of bradykinin release — a key biological peptide that contributes to swelling and pain[222].

Vibegron (Gemtesa®) is approved as a drug for the treatment of overactive bladder, acts as a selective β3-adrenergic receptor agonist (discovered in 1980; initially considered as a potential target for the treatment of obesity and diabetes [51]) located in the kidneys, urinary tract, and bladder[223].

2021

In 2021, a total of 94 drugs were approved, of which 65 were original (including 44 biologicals), 10 were new combinations, 1 was a generic drug, and 11 had a new dosage form or a new indication for use. The main categories of approved drugs were for the treatment of oncological and orphan diseases (26 drugs). In particular, ribociclib (Kisqali®; for the treatment of breast cancer)[224], tirzepatide (Mounjaro®; for the treatment of type 2 diabetes)[225], tebentafusp (Kimmtrak®; for the treatment of unresectable or metastatic uveal melanoma)[226], olutasidenib (Rezlidhia®; for the treatment of relapsed acute myeloid leukemia with IDH1 mutation)[227], anifrolumab (Saphnelo®; for the treatment of systemic lupus erythematosus)[228], aducanumab (Aduhelm®; the first anti-amyloid antibody for the treatment of Alzheimer's disease)[229] were approved (Fig. 10).

Vericiguat (Verquvo®) is approved as the first-in-class drug to reduce cardiovascular risks in patients with heart failure, acting as a direct stimulator

[215] Drugs.com. Sogroya. Available from: https://www.drugs.com/sogroya.html
[216] Drugs.com. Inmazeb. Available from: https://www.drugs.com/pro/inmazeb.html
[217] Drugs.com. Veklury. Available from: https://www.drugs.com/veklury.html
[218] Drugs.com. Ebanga. Available from: https://www.drugs.com/pro/ebanga.html
[219] Drugs.com. Zokinvy. Available from: https://www.drugs.com/zokinvy.html
[220] Drugs.com. Oxlumo. Available from: https://www.drugs.com/mtm/oxlumo.html
[221] Drugs.com. Imcivree. Available from: https://www.drugs.com/imcivree.html
[222] Drugs.com. Orladeyo. Available from: https://www.drugs.com/orladeyo.html
[223] Drugs.com. Gemtesa. Available from: https://www.drugs.com/gemtesa.html
[224] Drugs.com. Kisqali. Available from: https://www.drugs.com/kisqali.html
[225] Drugs.com. Mounjaro. Available from: https://www.drugs.com/mounjaro.html
[226] Drugs.com. Kimmtrak. Available from: https://www.drugs.com/kimmtrak.html
[227] Drugs.com. Rezlidhia. Available from: https://www.drugs.com/rezlidhia.html
[228] Drugs.com. Saphnelo. Available from: https://www.drugs.com/saphnelo.html
[229] Drugs.com. Aduhelm. Available from: https://www.drugs.com/aduhelm.html

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of soluble guanylate cyclase, interacting with the β-subunit of its regulatory site[230].

Paliperidone palmitate (Invega Hafyera®) is approved for the treatment of Schizophrenia under a new brand name. This drug was originally approved in 2006 under the brand name Invega, in 2009 the indications were expanded (schizoaffective disorder) and an injectable form was approved, and in 2014 it became available for use by adolescents; in 2021, this drug was approved under a new formulation (Invega Hafyera®, extended-release suspension)[231].

Voclosporin (Lupkynis®) is approved as the first-in-class calcineurin inhibitor for the treatment of lupus nephritis, acting as an immunosuppressant and exerting an immunomodulatory effect on T-cells, stabilizing podocytes[232].

Evinacumab (Evkeeza®) is approved for the treatment of homozygous familial hypercholesterolemia[233]. This is the first-in-class drug, the mechanism of action of which is associated with the effect on angiopoietin-like protein 3, which slows down the work of enzymes involved in the breakdown of fats in the body [52].

Casimersen (Amondys 45™) is approved for the treatment of Duchenne muscular dystrophy[234], is an antisense phosphorodiamidate morpholino oligonucleotide for binding to exon 45 of the pre-mRNA of the Duchenne muscular dystrophy (*DMD*) gene, which prevents its exclusion into mature RNA before translation, which causes the production of an internally shortened dystrophin protein [53].

Fosdenopterin (Nulibry®) is approved to reduce the risk of death due to a rare genetic disorder known as molybdenum cofactor deficiency type A. It is a replacement drug for intravenous administration, a metabolic precursor of molybdopterin necessary for the enzymatic activity of sulfite oxidase, xanthine dehydrogenase/oxidase, and aldehyde oxidase[235].

The combination of serdexmethylphenidate (a prodrug of dexmethylphenidate) and dexmethylphenidate (Azstarys®) is approved for the treatment of attention deficit hyperactivity disorder in patients over 6 years of age[236]. Another drug for the treatment of this mental disorder is viloxazine (Qelbree®; extended-release form)[237], which also acts as a selective norepinephrine reuptake inhibitor and has been used as an antidepressant for more than 30 years (in immediate-release form). This is a racemic compound with two stereoisomers — the (S)-(–)-isomer is five times more pharmacologically active than the (R)-(+)-isomer — first used in 1974 [54].

Dasiglucagon (Zegalogue®) is the first glucagon product (approved for medical use in 1960) that comes in a ready-to-use aqueous formula. Like endogenous glucagon, dasiglucagon consists of 29 amino acids, but with 7 amino acid substitutions, which ensures its physical and chemical stability in an aqueous environment. It is intended for the relief of hypoglycemia; previously, drugs containing glucagon in the form for subcutaneous injections (in dimethyl sulfoxide) or powder for intranasal administration (approved in 2019) were approved for use for this indication[238].

The first-in-class antifungal drug — ibrexafungerp (triterpenoid) (Brexafemme®) —an inhibitor of glucan synthase and a blocker of the synthesis of 1,3-β-D-glucan of Candida fungi that cause vaginal candidiasis (potentially active against many pathogens of life-threatening fungal lesions) has been approved[239].

A new antiviral drug for the treatment of smallpox is brincidofovir (Tembexa®)[240], which is a prodrug of cidofovir (conjugated to a lipid molecule that facilitates penetration into the cell, in which cidofovir is phosphorylated, turning into an active diphosphate, acting as an acyclic nucleotide [incorporated into the viral DNA chain and stops the synthesis of viral DNA]). Currently, the drug is being investigated for activity against other dangerous viruses [55].

Semaglutide (Wegovy®) — a GLP-1RA in the form of injections is approved for weight loss[241].

[230] Drugs.com. Verquvo. Available from: https://www.drugs.com/verquvo.html
[231] Drugs.com. Invega Hafyera. Available from: https://www.drugs.com/invega-hafyera.html
[232] Drugs.com. Lupkynis. Available from: https://www.drugs.com/lupkynis.html
[233] Drugs.com. Evkeeza. Available from: https://www.drugs.com/evkeeza.html
[234] Drugs.com. Amondys 45. Available from: https://www.drugs.com/amondys-45.html
[235] Drugs.com. Nulibry. Available from: https://www.drugs.com/mtm/nulibry.html
[236] Drugs.com. Azstarys. Available from: https://www.drugs.com/azstarys.html
[237] Drugs.com. Qelbree. Available from: https://www.drugs.com/qelbree.html
[238] Drugs.com. Zegalogue. Available from: https://www.drugs.com/zegalogue.html
[239] Drugs.com. Brexafemme. Available from: https://www.drugs.com/brexafemme.html
[240] Drugs.com. Tembexa. Available from: https://www.drugs.com/tembexa.html
[241] Drugs.com. Wegovy. Available from: https://www.drugs.com/wegovy.html

Finerenone (Kerendia®) is approved as the first-in-class drug for the treatment of kidney diseases associated with T2DM, which is an oral non-steroidal antagonist of mineralocorticoid receptors containing the S810L mutation. Unlike eplerenone and spironolactone, it has less affinity for other steroid hormone receptors[242].

Another representative of the "first-in-class" drugs is approved for the treatment of chronic graft-versus-host disease — belumosudil (Rezurock®) — an inhibitor of serine / threonine kinase (Rho-associated coiled-coil containing protein kinase 2, ROCK2), also affects oxidative phosphorylation and angiogenesis[243].

Fexinidazole is a drug that continues the trend of forming new indications for known drugs (fexinidazole was first described in 1978). The drug has been approved for the treatment of African trypanosomiasis (sleeping sickness; the active metabolites in vivo are sulfoxide and sulfone) caused by *Trypanosoma brucei gambiense*[244]. Fexinidazole is less effective than nifurtimox in combination with eflornithine in severe cases of the disease, but it has the advantage that it can be taken orally (acoziborole is in clinical trials). This is the first drug in 30 years intended for the treatment of late-stage sleeping sickness.

Odevixibat (Bylvay®) is the first-in-class drug — a reversible, selective, low-molecular-weight inhibitor of the ileal sodium/bile cotransporter, which is responsible for the reabsorption of most bile acids in the distal ileum, which leads to a decrease in FXR (farnesoid X receptor) stimulation, reducing the inhibition of bile acid synthesis [56]. Bylvay® is indicated for the treatment of pruritus in people aged 3 months and older with progressive familial intrahepatic cholestasis[245].

A new combination (Twyneo®) containing a fixed dose of tretinoin (vitamin A derivative) / benzoyl peroxide (oxidizing agent) for the treatment of acne has been approved.

In the continuation of new drugs developed for enzyme replacement therapy, avalglucosidase α (Nexviazyme®)[246] has been approved — consists of the human enzyme α-acid glucosidase, which is conjugated with a pair of tetramannose glycans bis-mannose-6-phosphate. The substance binds to the cation-independent mannose-6-phosphate receptor located on skeletal muscles and enters the cell, where, penetrating into lysosomes, it undergoes proteolytic cleavage, subsequently acting as an enzyme for the treatment of glycogen storage disease type II (Pompe disease) [57].

The first-in-class inhibitor of hypoxia-inducible factor-2α (HIF2; binds to HIF-2α and, under hypoxia or impaired VHL protein function, blocks the formation of the HIF-2α-HIF-1β transcription complex, reduces transcription and expression of HIF-2α target genes) belzutifan (Welireg®) is approved for the treatment of renal cell carcinoma associated with von Hippel-Lindau disease[247] (extensive studies have indicated its effectiveness against Pachak-Zhuang syndrome with polycythemia and paragangliomas in adolescents [58]).

Also approved was the first-in-class selective κ-opioid receptor agonist difelikefalin (Korsuva®)[248], which acts as an analgesic (unlike pentazocine and phenazocine, it has no side effects associated with CNS effects [59]), activating these receptors on peripheral nerve endings (reduces the intensity of pain signal transmission) and immune system cells (reduces the release of pro-inflammatory nerve-sensitizing mediators, such as prostaglandins) [60, 61]. Indicated for the treatment of pruritus associated with chronic kidney disease.

Lonapegsomatropin (Skytrofa®), which is a somatotropin prodrug, has been approved for hormone replacement therapy in growth hormone deficiency[249].

Atogepant (Qulipta®) is approved for migraine prevention. It is a low molecular weight oral antagonist of the calcitonin gene-related peptide receptor (CGRP; blocks the binding of CGRP to the receptor, preventing its activation). Unlike 5-HT1 receptor agonists (triptans), its use does not cause vasoconstrictor effects[250].

Maralixibat chloride (Livmarli®) for the treatment

[242] Drugs.com. Kerendia. Available from: https://www.drugs.com/kerendia.html
[243] Drugs.com. Rezurock. Available from: https://www.drugs.com/rezurock.html
[244] Drugs.com. Fexinidazole. Available from: https://www.drugs.com/pro/fexinidazole.html
[245] Drugs.com. Bylvay. Available from: https://www.drugs.com/bylvay.html
[246] Drugs.com. Nexviazyme. Available from: https://www.drugs.com/mtm/nexviazyme.html
[247] Drugs.com. Welireg. Available from: https://www.drugs.com/welireg.html
[248] Drugs.com. Korsuva. Available from: https://www.drugs.com/korsuva.html
[249] Drugs.com. Skytrofa. Available from: https://www.drugs.com/skytrofa.html
[250] Drugs.com. Qulipta. Available from: https://www.drugs.com/qulipta.html

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of cholestatic pruritus in people with Alagille syndrome, acts as a reversible inhibitor of the apical sodium-dependent bile acid transporter (ASBT), reducing the reabsorption of bile acids (mainly salts) from the terminal ileum, which is accompanied by a decrease in itching[251].

Another "first-in-class" drug, avacopan (Tavneos®), is approved for the treatment of vasculitis associated with anti-neutrophil cytoplasmic autoantibodies, including granulomatosis with polyangiitis and microscopic polyangiitis[252]. It acts as a C5a complement receptor blocker for oral administration, and also suppresses neutrophil migration and activation [62].

The allogeneic processed thymus tissue product (Rethymic®)[253] has been approved for restoring immunity in patients with athymia (an extremely rare disease in which children are born without a thymus, leading to profound immunodeficiency). Recipient T-cell precursors from the bone marrow migrate to the implanted allogeneic thymus tissue sites, where they develop into native immunocompetent T-cells [63].

Varenicline (Tyrvaya®) was originally developed as a cytisine analogue and used to facilitate smoking cessation, as both compounds are full or partial agonists of various subtypes of nicotinic acetylcholine receptors (varenicline exhibits full agonism at α7 nicotinic acetylcholine receptors and is a partial agonist of α4β2, α3β4 and α6β2 subtypes)[254]. Their use, unlike nicotine, causes a smaller dopamine release effect and at the same time prevents the effects of nicotine on these receptors, provoking and stimulating the mesolimbic dopamine system [64]. This is similar to the action of buprenorphine in the treatment of opioid addiction. The implementation of varenicline as a drug for the treatment of nicotine addiction ceased in 2006, and in 2021 it was approved in the form of a nasal spray for the treatment of dry eye syndrome, the mechanism of action is associated with a specific irritating effect of the compound on the endings of the vagus nerve on the mucous membrane of the nasal sinuses, which causes intense lacrimation.

Ropeginterferon α-2b (Besremi®) is approved as a "first-in-class" drug for the treatment of polycythemia vera[255]. It is an interferon (IFN) α-2b (recombinant) covalently linked to monomethoxypolyethylene glycol (mPEG), and exerts cellular effects in the bone marrow as a result of binding to the transmembrane IFNα receptor, triggering a cascade of downstream signals through kinase activation, affecting the expression of individual genes [65].

Another first-in-class drug of 2021 was vosoritide (Voxzogo®) for the treatment of achondroplasia (a congenital disease resulting from a missense mutation in the fibroblast growth factor receptor 3 gene [*FGFR3*], leading to increased function that negatively regulates endochondral bone growth)[256]. Under normal conditions, FGFR3 is expressed both during embryonic (promotes proliferation) and postnatal (suppresses growth during puberty) development. Vosoritide is an analogue (with a longer duration of action) of C-type natriuretic peptide (CNP) — a signaling molecule that is primarily responsible for stimulating chondrocytes and long bone growth. Binding of CNP (or vosoritide) to its corresponding natriuretic peptide B receptor (NPR-B) leads to inhibition of the MAPK / ERK pathway by blocking RAF-1, which promotes chondrocyte proliferation and differentiation. This activity serves to counteract the downstream signal resulting from FGFR3 and its resulting effect on bone growth [66].

Initially, rapamycin was developed as an antifungal agent, but after the discovery of its immunosuppressive and antiproliferative effects (1994), its use was directed towards influencing immunity (immunosuppression in transplantation) and cancer (suppression of proliferation) [67]. In 2021, sirolimus (Fyarro®) was approved for the treatment of malignant perivascular epithelioid cell tumor (in 2022 it was approved for the treatment of angiofibromas)[257].

Efgartigimod-α (Vyvgart®) (antibody fragment) is the first-in-class neonatal Fc receptor blocker, preventing the recirculation of immunoglobulin G back into the blood, reducing its total amount and preventing the degradation of acetylcholine receptors by autoantibodies that cause myasthenia gravis[258].

[251] Drugs.com. Livmarli. Available from: https://www.drugs.com/livmarli.html
[252] Drugs.com. Tavneos. Available from: https://www.drugs.com/tavneos.html
[253] Drugs.com. Rethymic. Available from: https://www.drugs.com/pro/rethymic.html
[254] Drugs.com. Tyrvaya. Available from: https://www.drugs.com/tyrvaya.html
[255] Drugs.com. Besremi. Available from: https://www.drugs.com/besremi.html
[256] Drugs.com. Voxzogo. Available from: https://www.drugs.com/voxzogo.html
[257] Drugs.com. Fyarro. Available from: https://www.drugs.com/mtm/fyarro.html
[258] Drugs.com. Vyvgart. Available from: https://www.drugs.com/vyvgart.html

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Cabotegravir (Apretude®) is approved for the treatment of HIV / AIDS as a drug with antiretroviral activity[259], is an integrase strand transfer inhibitor, i.e. blocks the HIV integrase enzyme, thereby preventing the integration of its genome into human cell DNA; structurally similar to dolutegravir, which was approved in 2013.

Inclisiran (Leqvio®)[260] is an siRNA that acts as a proprotein convertase inhibitor, specifically inhibiting the translation of the PCSK9 protein (a serine protease produced and secreted by the liver, the binding and action of which on low-density lipoprotein receptors [LDL] leads to their increased lysosomal degradation in hepatocytes, resulting in an increase in circulating LDL cholesterol levels, and inhibition of this process leads to a decrease in LDL) [68] — the first-in-class drug for the treatment of high LDL cholesterol in people with atherosclerotic cardiovascular disease, as well as with heterozygous familial hypercholesterolemia.

Levoketoconazole (Recorlev®)[261] is the levorotatory enantiomer of ketoconazole (an antifungal agent, an imidazole derivative, first synthesized in 1977), an inhibitor of the enzymes CYP11B1 (11β-hydroxylase), CYP17A1 (17α-hydroxylase/17,20-lyase) and CYP21A2 (21-hydroxylase), CYP11A1 (cholesterol side-chain cleavage enzyme), CYP51A1 (lanosterol-14α-demethylase); inhibits the biosynthesis of glucocorticoids, reducing their level, which determines its use in Cushing's syndrome [69].

2022

In 2022, approval was received for 80 drugs, including 37 original drugs (27 of them is biologicals), 4 new combinations, 4 reproduced drugs, as well as 20 drugs in a new dosage form or with new indications for use. These drugs cover a wide range of medical conditions, including cancer, dermatological diseases, rare diseases, and autoimmune disorders. Notably, 31% of the drugs approved in 2022 are intended for the treatment of various types of cancer, including non-Hodgkin's lymphoma, NSCLC, and relapsed myeloid leukemia. 14% of approved drugs were intended for the treatment of neurological diseases (including amyotrophic lateral sclerosis and transthyretin amyloid polyneuropathy). In particular, tebentafusp (Kimmtrak®; for the treatment of unresectable or metastatic uveal melanoma)[262], mosunetumab (Lunsumio®; for the treatment of relapsed or refractory follicular lymphoma)[263], olutasidenib (Rezlidhia®; for the treatment of relapsed acute myeloid leukemia with IDH1 mutation)[264], tirzepatide (Mounjaro®; injectable drug for the treatment of type 2 diabetes)[265], deucravacitinib (Sotyktu®; for the treatment of psoriasis)[266] were approved (Fig. 11).

Tebentafusp (Kimmtrak®) is an anticancer drug (therapy for inoperable or metastatic uveal melanoma), the first-in-class bispecific gp100-peptide-HLA-directed activator of cluster of differentiation (CD) 3+ T-cells for intravenous infusions[267].

Faricimab (Vabysmo®) is approved for the treatment of neovascular age-related macular degeneration and diabetic macular edema[268], and is the first bispecific monoclonal antibody to vascular endothelial growth factor and angiopoietin 2. By blocking the action of these two growth factors, faricimab reduces the migration and replication of endothelial cells, inhibiting angiogenesis [70].

Sutimlimab (Enjaymo®) is the first-in-class monoclonal antibody for the treatment of adults with cold agglutinin disease, which, by acting on the C1s enzyme and inhibiting its enzymatic spread along the classical complement pathway, prevents the formation of the C3-convertase enzyme and complement-enhanced activation of autoimmune B cells[269].

Mitapivat (Pyrukynd®) is approved as the first-in-class drug for the treatment of hemolytic anemia[270], acting as a pyruvate kinase activator, binding to it and, by activating it, enhances the activity of the glycolytic pathway, increasing the level of adenosine triphosphate (ATP) and reducing the level of 2,3-diphosphoglycerate (2,3-DPG). Mutations in pyruvate kinase cause pyruvate

[259] Drugs.com. Apretude. Available from: https://www.drugs.com/apretude.html
[260] Drugs.com. Leqvio. Available from: https://www.drugs.com/leqvio.html
[261] Drugs.com. Recorlev. Available from: https://www.drugs.com/recorlev.html
[262] Drugs.com. Kimmtrak. Available from: https://www.drugs.com/kimmtrak.html
[263] Drugs.com. Lunsumio. Available from: https://www.drugs.com/lunsumio.html
[264] Drugs.com. Rezlidhia. Available from: https://www.drugs.com/rezlidhia.html
[265] Drugs.com. Mounjaro. Available from: https://www.drugs.com/mounjaro.html
[266] Drugs.com. Sotyktu. Available from: https://www.drugs.com/sotyktu.html
[267] Drugs.com. Kimmtrak. Available from: https://www.drugs.com/kimmtrak.html
[268] Drugs.com. Vabysmo. Available from: https://www.drugs.com/vabysmo.html
[269] Drugs.com. Enjaymo. Available from: https://www.drugs.com/enjaymo.html
[270] Drugs.com. Pyrukynd. Available from: https://www.drugs.com/pyrukynd.html

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kinase deficiency, which prevents adequate glycolysis of red blood cells (RBCs), leading to the accumulation of the glycolysis intermediate 2,3-DPG and a deficiency of the pyruvate kinase product ATP [71].

Dexmedetomidine (Igalmi®) is approved for sedation (approved in veterinary practice since 2006) in acute agitation associated with schizophrenia or bipolar disorder, available as a solution for injection or intravenous administration, as well as in the form of a buccal or sublingual film[271]. It acts similarly to clonidine (8 times more selective), as an α2-adrenergic receptor agonist in certain parts of the brain, without having a depressant effect on respiration and more closely mimicking natural sleep, and to a lesser extent causing amnesia [72].

Mavacamten (Camzyos®) is approved as the first-in-class drug for the treatment of obstructive hypertrophic cardiomyopathy, affecting sarcomere hypercontractility, which is one of the characteristics of hypertrophic cardiomyopathy, and also inhibits excessive formation of myosin and actin cross-bridges, shifting the overall myosin population towards an energy-saving, recruitable, super-relaxed state[272].

Tirzepatide (Mounjaro®) is the first-in-class dual agonist of incretin system receptors (glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1) — a drug used to treat T2DM and for weight loss (since 2023) and moderate to severe obstructive sleep apnea (since 2024)[273].

A new triple combination (Voquezna Triple Pak®) has been approved for the treatment of *Helicobacter pylori* infection, consisting of a potassium-competitive acid transporter blocker vonoprazan, amoxicillin (β-lactam antibiotic) and clarithromycin (macrolide antibiotic)[274].

Vutrisiran (Amvuttra®) is approved as an orphan drug for the treatment of polyneuropathy of hereditary transthyretin-mediated amyloidosis (hATTR) in adults. It is a double-stranded small interfering RNA that prevents the expression of the transthyretin gene (*TTR*; a serum protein produced in the liver, the main function of which is to transport vitamin A and thyroxine). Rare mutations in the transthyretin gene lead to the accumulation of large amyloid deposits of misfolded transthyretin molecules, most noticeably in the peripheral nerves and heart, which provokes the development of polyneuropathy, progressing to cardiomyopathy[275].

Betibeglogene autotemcel (Zynteglo®) is approved for gene therapy for β-thalassemia in people who do not have the β0/β0 genotype and who are suitable for hematopoietic stem cell transplantation (HSCT) but lack a related HLA-matched HSCT donor. Betibeglogene autotemcel is produced individually for each recipient from stem cells collected from their blood, administered as an autologous intravenous infusion, the dose depends on the recipient's body weight; before administration, the recipient undergoes preliminary chemotherapy to cleanse the bone marrow of cells[276].

Olipudase-α (Xenpozyme®) is approved as the first-in-class enzyme replacement therapy for the treatment of acid sphingomyelinase deficiency type A/B or type B (Niemann-Pick disease) not associated with the CNS[277].

Spesolimab (Spevigo®) is approved as the first-in-class drug for the treatment of generalized pustular psoriasis, is a monoclonal antibody that acts as an IL-36 receptor antagonist[278].

Daxxibotulinumtoxin A (Daxxify®) is approved for the temporary improvement in the appearance of moderate to severe glabellar lines (wrinkles between the eyebrows)[279], later (in 2024) letibotulinumtoxin A was approved for use for the same purpose, and earlier (in 2010) botulinum toxin was approved for the prevention of chronic migraine (intramuscular injections) and, in 2016 (abobotulinumtoxin A), for the treatment of spasticity of the lower extremities in children aged two years and older. Botulinum toxin exerts its effect by cleaving key proteins required for nerve activation. After binding to the nerve ending, the toxin enters the vesicle via receptor-mediated endocytosis, from which it is released into the cytoplasm, where the toxin cleaves SNARE proteins (proteins that mediate the fusion of vesicles with their target membrane-bound compartments) and

[271] Drugs.com. Igalmi (buccal/sublingual). Available from: https://www.drugs.com/mtm/igalmi-buccal-sublingual.html
[272] Drugs.com. Camzyos. Available from: https://www.drugs.com/camzyos.html
[273] Drugs.com. Mounjaro. Available from: https://www.drugs.com/mounjaro.html
[274] Drugs.com. Voquezna Triple Pak. Available from: https://www.drugs.com/voquezna-triple-pak.html
[275] Drugs.com. Amvuttra. Available from: https://www.drugs.com/amvuttra.html
[276] Drugs.com. Zynteglo. Available from: https://www.drugs.com/zynteglo.html
[277] Drugs.com. Xenpozyme. Available from: https://www.drugs.com/xenpozyme.html
[278] Drugs.com. Spevigo. Available from: https://www.drugs.com/spevigo.html
[279] Drugs.com. Daxxify. Available from: https://www.drugs.com/daxxify.html

acetylcholine vesicles cannot bind to the intracellular cell membrane, preventing the cell from releasing neurotransmitter vesicles. This stops nerve signaling, resulting in flaccid paralysis. This blockade is slowly removed as the toxin loses activity and SNARE proteins are slowly regenerated by the affected cell. The first use of botulinum toxin A dates back to 1977, it was administered to patients with strabismus, and the first FDA approval was obtained in 1989 for the treatment of strabismus and blepharospasm in adults.

Deucravacitinib (Sotyktu®), a first-in-class drug, a highly selective allosteric inhibitor of non-receptor tyrosine-protein kinase 2 (TYK2) approved for the treatment of moderate to severe plaque psoriasis[280]. It is noteworthy that the molecule of the active substance contains methylamide, in which all three hydrogen atoms are replaced by deuterium, which is a promising trend in modern medicinal chemistry [73].

Elivaldogene autotemcel (Skysona®) is a gene therapy (single; autologous hematopoietic stem cell therapy in which stem cells are mobilized and collected from the patient and genetically modified to transfer a functional copy of the *ABCD1* gene using a lentiviral vector) for the treatment of cerebral adrenoleukodystrophy (cerebral adrenoleukodystrophy is caused by a mutation in the *ABCD1* gene on the X chromosome, which encodes the ALD protein, which helps transport very long chain fatty acids (VLCFA) into peroxisomes for degradation, when the *ABCD1* gene is dysfunctional, they degrade incorrectly and accumulate abnormally in the blood and CNS, penetrate the BBB and are incorporated into white matter, damaging myelin)[281].

Omidenepag isopropyl (Omlonti®) is approved for the treatment of glaucoma and high intraocular pressure, is a prodrug that, upon hydrolysis, is converted to the active metabolite omidenepag, a selective prostaglandin E2 receptor agonist[282].

Teplizumab (Tzield®) is a first-in-class drug that is a humanized monoclonal antibody (mAb) targeting the CD3+ antigen co-expressed with the T-cell receptor on the surface of T lymphocytes, which is the first approved treatment shown to delay the onset of stage 3 type 1 diabetes in people with stage 2 type 1 diabetes[283]. The Fc region of the mAb was designed not to interact with the Fc receptor to avoid side effects (e.g., cytokine release) associated with an intact Fc. The mechanisms of action of teplizumab appear to include weak agonistic activity in signaling through the CD3+ T-cell receptor complex associated with the development of anergy, unresponsiveness, and/or apoptosis, especially of unwanted activated effector T lymphocytes. The mechanism may involve partial agonistic signaling and deactivation of autoreactive T lymphocytes of pancreatic β-cells, leading to an increase in the proportion of regulatory T-cells and exhausted CD8+ T-cells in the peripheral blood [74]. It is important to note that this is the only drug for use as a prophylactic rather than a therapeutic agent in people at high risk of diabetic ketoacidosis.

Etranacogene dezaparvovec (Hemgenix®) is another gene therapy (also has breakthrough status) for the treatment of hemophilia B (absence or insufficient levels of blood clotting factor IX). It is a vector gene therapy based on an adeno-associated virus carrying the blood clotting factor IX gene. In 2022, this therapy was the most expensive in the world[284].

Another gene therapy based on an adenovirus vector is approved for the treatment of non-muscle-invasive bladder cancer unresponsive to Bacillus Calmette-Guerin with carcinoma *in situ* with or without papillary tumors — nadofaragene firadenovec (Adstiladrin®); created using an excipient (Syn-3) that facilitates gene transfer through the urothelium and promotes transduction of the human *IFNα2b* gene (induces apoptosis in human bladder cancer cells unresponsive to BCG by inducing the production of autocrine TNFα associated with apoptosis-inducing ligand). Localized expression of this gene causes antitumor effects[285].

The herbal preparation anacaulase-bcdb (NexoBrid®) has been approved for the removal of eschar in adults with deep partial and/or full thickness thermal burns[286]. The drug is a mixture of proteolytic enzymes extracted from the stems of pineapple plants (*Ananas comosus* [L.] Merr.). It mainly consists (80–95% by weight) of proteins such as stem

[280] Drugs.com. Sotyktu. Available from: https://www.drugs.com/sotyktu.html
[281] Drugs.com. Skysona. Available from: https://www.drugs.com/skysona.html
[282] Drugs.com. Omlonti. Available from: https://www.drugs.com/omlonti.html
[283] Drugs.com. Tzield. Available from: https://www.drugs.com/tzield.html
[284] Drugs.com. Hemgenix. Available from: https://www.drugs.com/hemgenix.html
[285] Drugs.com. Adstiladrin. Available from: https://www.drugs.com/adstiladrin.html
[286] Drugs.com. Nexobrid. Available from: https://www.drugs.com/pro/nexobrid.html

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bromelain, ananain, jacalin-like lectin, bromelain inhibitors and phytocystatin inhibitor, as well as saccharides, both free monosaccharides and N-linked glycan of stem bromelain and low molecular weight metabolites [75].

A new form of vigabatrin (Vigpoder®; developed in the 1980s, first approved for medical use since 2009) — a solution for oral administration[287] (in 2024, the ready-made solution is approved for use in children from 1 month) is approved for the treatment of patients with infantile spasms. Vigabatrin is an inhibitor of GABA-AT aminotransferase: its administration leads to an increase in GABA levels in the brain.

2023

In 2023, the FDA approved 111 drugs, 55 of which were new, which corresponds to the average for the last 5 years. The share of biologicals exceeded the 40% threshold in 2023 — to date, this is a record value for this group of drugs. The main categories of approved drugs included the following:

- monoclonal antibodies: 12 approved drugs, which is a record for this category;
- peptides and oligonucleotides: 9 approved drugs, including 5 peptides and 4 oligonucleotides;
- biologicals: 17 new biologicals, which corresponds to the average for recent years.

The drugs registered in 2023 were intended for the treatment of a wide range of diseases, including orphan diseases, as well as neurological disorders and oncological diseases. In the period under study, the largest number of registrations for the treatment of oncological diseases occurred in 2023 (Fig. 12).

In particular, the following drugs were approved: lecanemab (Leqembi®; for the treatment of Alzheimer's disease)[288], pirtobrutinib (Jaypirca®; for the treatment of relapsed or refractory mantle cell lymphoma)[289], elacestrant (Orserdu®; for the treatment of estrogen receptor-positive breast cancer)[290], peguigalsidase α (Elfabrio®; for the treatment of Fabry disease)[291]. During 2023, several drugs were approved that should be emphasized due to their impact on the creation and approval process.

Lovotibeglogene autotemcel (Lyfgenia®), a gene therapy drug for sickle cell anemia, is surprising not only for its approach to gene modification of the patient's own cells with their subsequent return to the body, but also for its agreed cost[292].

The approval of tirzepatide (Mounjaro® in 2022 and Zepbound® in 2023)[293, 294] caused excitement throughout the GLP-1 market, while the first dual agonist of key incretin receptors may significantly affect the effectiveness of therapy for many patients. Cantharidin, being a well-known chemical substance, the use of which has historically been reckless (as an aphrodisiac) due to its high toxicity, has been approved as a remedy for molluscum contagiosum (Ycanth®)[295]. Lotilaner 0.25% ophthalmic solution (Xdemvy®) for the treatment of demodecosis blepharitis is widespread in veterinary medicine[296].

A drug containing sildenafil citrate (Liqrev®) is registered as a drug for the treatment of pulmonary hypertension, which is symbolic, given the history of its creation and use[297].

The combination of hyaluronic acid and lidocaine (Skinvive by Juvéderm®) is approved for reducing the severity of wrinkles on the face[298], which can be considered a step towards expanding the pharmaceutical market or accelerating its expansion into the field of aesthetic medicine.

New gliflozins have been approved for the treatment of T2DM (bexagliflozin; Brenzavvy®)[299] and heart failure (sotagliflozin; Inpefa®)[300]. The first drug (donaisel; Lantidra®) for cell therapy of type 1 diabetes has appeared on the pharmaceutical market[301], which is an allogeneic (donor) cell therapy of pancreatic islets

[287] Drugs.com. Vigpoder. Available from: https://www.drugs.com/vigpoder.html
[288] Drugs.com. Leqembi. Available from: https://www.drugs.com/leqembi.html
[289] Drugs.com. Jaypirca. Available from: https://www.drugs.com/jaypirca.html
[290] Drugs.com. Orserdu. Available from: https://www.drugs.com/orserdu.html
[291] Drugs.com. Elfabrio. Available from: https://www.drugs.com/elfabrio.html
[292] Drugs.com. Lyfgenia. Available from: https://www.drugs.com/lyfgenia.html
[293] Drugs.com. Mounjaro. Available from: https://www.drugs.com/mounjaro.html
[294] Drugs.com. Zepbound. Available from: https://www.drugs.com/zepbound.html
[295] Drugs.com. Ycanth. Available from: https://www.drugs.com/ycanth.html
[296] Drugs.com. Xdemvy. Available from: https://www.drugs.com/xdemvy.html
[297] Drugs.com. Liqrev. Available from: https://www.drugs.com/liqrev.html
[298] Drugs.com. Skinvive. Available from: https://www.drugs.com/skinvive.html
[299] Drugs.com. Brenzavvy. Available from: https://www.drugs.com/brenzavvy.html
[300] Drugs.com. Inpefa. Available from: https://www.drugs.com/inpefa.html
[301] Drugs.com. Lantidra. Available from: https://www.drugs.com/lantidra.html

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obtained from a donor, and which is administered once into the portal vein of the liver against the background of preliminary immunosuppression.

Nodosiran (Rivfloza®) is another product (patisiran, govosiran, lumasiran, inclisiran were previously approved) created on the basis of siRNA (selective "silencing" of genes necessary for the synthesis of unnecessary / defective proteins; for the description of this mechanism, scientists Andrew Fire and Craig Mello received the Nobel Prize in 2006) for the treatment of primary hyperoxaluria type 1[302].

A drug containing eflornithine (Iwilfin®; ornithine decarboxylase inhibitor) has been approved for the treatment of neuroblastoma[303]. It has been developed as an antitumor agent since the 1970s, but until 2023 it was used for hirsutism and African trypanosomiasis [77].

Cyclosporine (Vevye®) has been approved for the treatment of dry eye syndrome. This compound has been used for medical purposes for more than 40 years (since 1983), mainly for the treatment and prevention of graft-versus-host disease, treatment of rheumatoid arthritis, psoriasis, nummular keratitis after adenovirus keratoconjunctivitis, acute severe ulcerative colitis[304].

Colchicine (Lodoco®) has been approved to reduce cardiovascular risk in people with atherosclerosis or recent myocardial infarction; previously (since 1961), its medical use was limited to anti-gout properties. Colchicine was most effective in combination therapy with lipid-lowering and anti-inflammatory drugs[305]. The mechanism of this effect of colchicine is unknown.

Delandistrogene moxeparvovec (Elevidys®) is a gene therapy for children with Duchenne muscular dystrophy, which works by delivering a gene that is necessary for the production of microdystrophin, a shortened protein (138 kDa compared to the dystrophin protein of normal muscle cells weighing 427 kDa), which contains selected domains of the dystrophin protein present in normal muscle cells[306].

Somatrogon (Ngenla®) is approved for the treatment of children with growth retardation due to endogenous growth hormone deficiency, is a glycosylated protein created from human growth hormone and a small part of human chorionic gonadotropin[307].

Valoctocogene roxaparvovec (Roctavian®) is approved as a gene therapy that uses adeno-associated virus 5, which carries the human coagulation factor VIII (antihemophilic globulin) gene, along with a human liver-specific promoter that stimulates translation in hepatocytes, rather than in endothelial and sinusoidal liver cells, where coagulation factor VIII is normally synthesized[308].

Lotilaner ectoparasiticidal (Xdemvy®) is an antiparasitic drug, the first in its class for the treatment of blepharitis (inflammation of the eyelid) caused by Demodex (Demodex mite) infection. It is used in the form of eye drops, acts as an inhibitor of chloride channels activated by GABA in ticks[309].

Zuranolone (Zurzuvae®) is approved for the treatment of postpartum depression, inhibits a pregnane neurosteroid, a positive allosteric modulator of the GABAA receptor[310].

Avacincaptad pegol (Izervay®) is approved for the treatment of age-related macular degeneration — an RNA aptamer covalently linked to a branched polyethylene glycol molecule, an inhibitor of complement C5 (cleaved into C5a and C5b, and this is the last stage of the complement cascade, where a membrane-attacking complex (MAC) is formed, causing cell death) based on oligonucleotides[311]. By inhibiting the cleavage of complement C5, avacincaptad pegol can weaken inflammatory processes, thereby slowing down damage and degeneration of retinal cells [78].

Poselimab (Veopoz®) (first in class) is a recombinant human IgG4 monoclonal antibody (directed against the terminal complement protein C5, inhibits terminal complement activation by blocking the cleavage of C5 into C5a (anaphylatoxin) and C5b, thereby suppressing the formation of the MAC C5b-C9, which mediates cell lysis.), approved for the treatment of protein-losing enteropathy caused by CD55 deficiency (CHAPLE disease; complement hyperactivation), a complement inhibitor[312].

[302] Drugs.com. Rivfloza. Available from: https://www.drugs.com/rivfloza.html
[303] Drugs.com. Iwilfin. Available from: https://www.drugs.com/iwilfin.html
[304] Drugs.com. Vevye. Available from: https://www.drugs.com/vevye.html
[305] Drugs.com. Lodoco. Available from: https://www.drugs.com/lodoco.html
[306] Drugs.com. Eevidys. Available from: https://www.drugs.com/elevidys.html
[307] Drugs.com. Ngenla. Available from: https://www.drugs.com/ngenla.html
[308] Drugs.com. Roctavian. Available from: https://www.drugs.com/roctavian.html
[309] Drugs.com. Xdemvy. Available from: https://www.drugs.com/xdemvy.html
[310] Drugs.com. Zurzuvae. Available from: https://www.drugs.com/zurzuvae.html
[311] Drugs.com. Izervay. Available from: https://www.drugs.com/izervay.html
[312] Drugs.com. Veopoz. Available from: https://www.drugs.com/veopoz.html

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A	Pancrelipase Taliglucerase Alfa Teduglutide Crofelemer Linagliptin and Metformin Hydrochloride Lorcaserin Sodium Picosulfate, Magnesium Oxide, and Citric Acid Phentermine and Topiramate Linaclotide Cysteamine Hydrochloride
B	Peginesatide Fibrin Sealant Apixaban
C	Icosapent Ethyl Epinephrine Lomitapide
D	Tazarotene
G	Testosterone Mifepristone Avanafil Mirabegron
H	Prednisolone Pasireotide
J	Meningococcal C and Y, Haemophilus influenzae B, Tetanus Toxoid Conjugate Vaccine Influenza Virus Vaccine Inactivated Raxibacumab Varicella Zoster Immune Globulin Intravenous Immunoglobulin Cobicistat, Elvitegravir, Emtricitabine, and Tenofovir Bedaquiline
L	Pertuzumab Ziv-Aflibercept Filgrastim Ingenol Mebutate Mitomycin Omacetaxine Melesuccinate Axitinib Vismodegib Carfilzomib Vincristine Sulfate Liposome Enzalutamide Bosutinib Teriflunomide Regorafenib Tofacitinib Cabozantinib Ponatinib
M	Alendronate
N	Fentanyl Methylphenidate Perampanel Loxapine
P	Invermectin
R	Lucinactant Ciclesonide Beclomethasone Dipropionate Ivacaftor Azelastine and Fluticasone Aclidinium Bromide
S	Ocriplasmin Tafluprost
V	Glucarpidase Florbetapir F-18

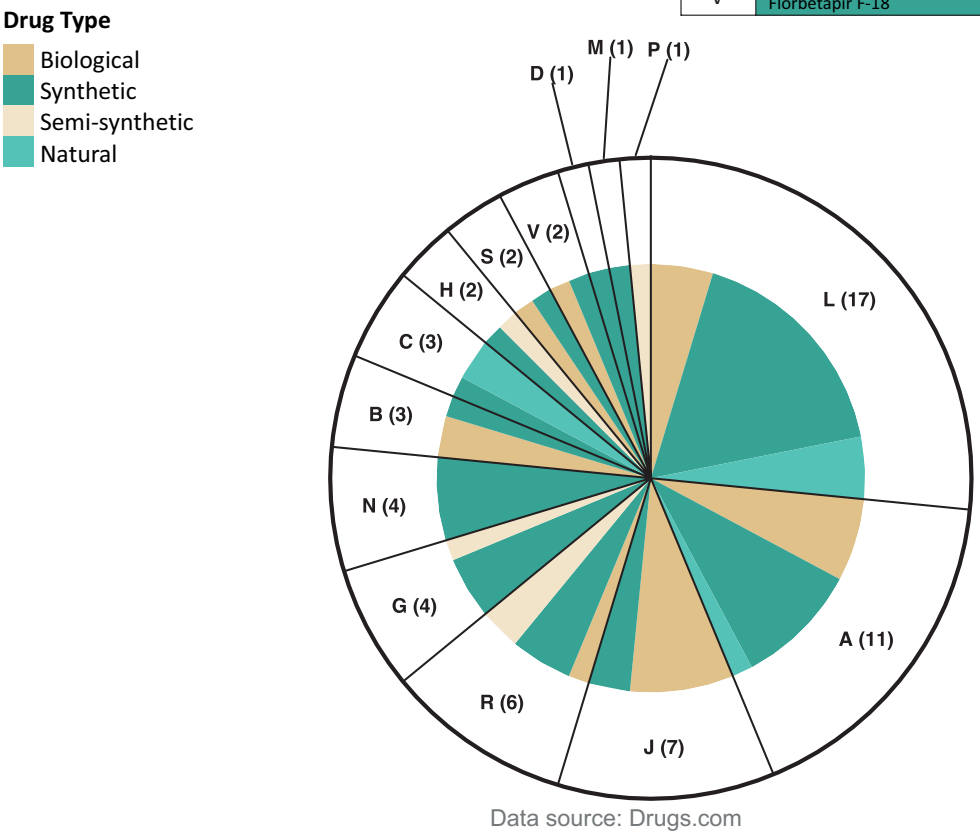
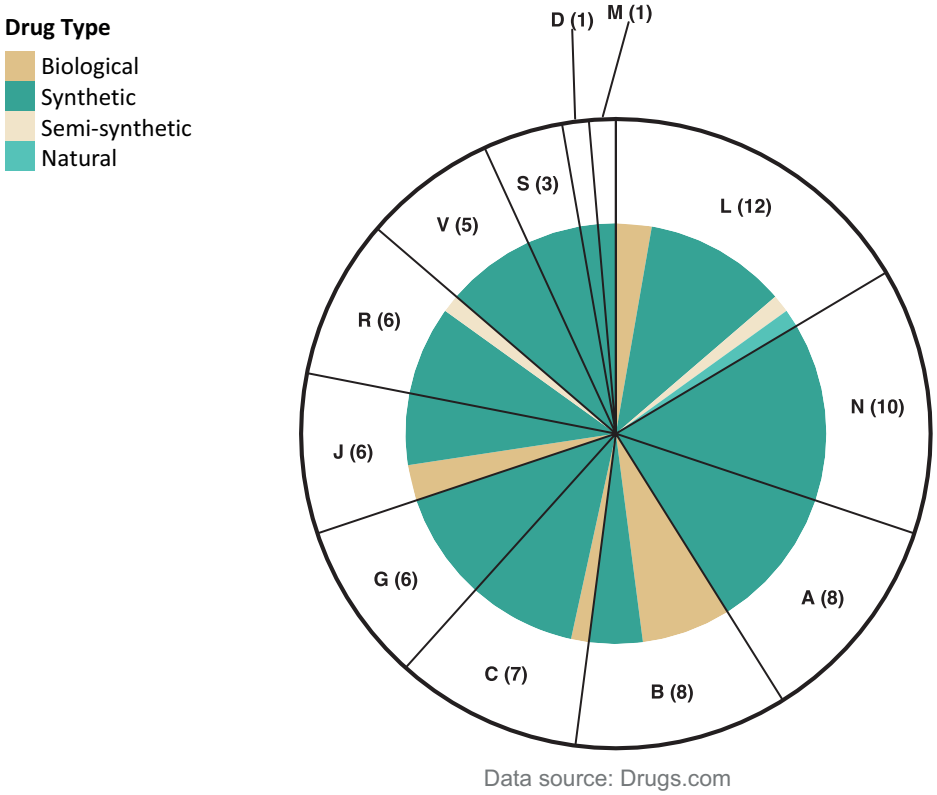


Figure 1 – FDA Approvals of Original Drugs in 2012.
Note: The outer ring corresponds to the proportions of drugs according to the first letter of their ATC class; the segments of the inner ring correspond to the proportion of drug types – biological, synthetic, semi-synthetic, or of natural origin.

A	Alogliptin Alogliptin and Metformin Alogliptin and Pioglitazone Mesalamine Glycerol Phenylbutyrate Canagliflozin Doxylamine and Pyridoxine Cysteamine Bitartrate
B	Pooled Plasma (Pooled) Prothrombin Complex Concentrate, Human Coagulation Factor IX, Recombinant Turoctocog Alfa Coagulation Factor XIII A-Subunit, Recombinant Ferric Carboxymaltose Clinolipid Treprostinil
C	Mipomersen Atorvastatin and Ezetimibe Nimodipine Enalapril Maleate Riociguat Macitentan Polidocanol
D	Luliconazole
G	Levonorgestrel Oxybutynin Ospemifene Levonorgestrel/Ethinyl Estradiol and Ethinyl Estradiol Ethinyl Estradiol and Norethindrone, Ethinyl Estradiol and Ferrous Fumarate Bazedoxifene and Conjugated Estrogens
J	Tobramycin Influenza Virus Vaccine, Inactivated Acyclovir Dolutegravir Simeprevir Sofosbuvir
L	Golimumab Obinutuzumab Tacrolimus Ado-trastuzumab Pomalidomide Dimethyl Fumarate Dabrafenib Trametinib Afatinib Mechlorethamine Methotrexate Ibrutinib
M	Diclofenac
N	Sumatriptan Aripiprazole Buprenorphine and Naloxone Paroxetine Mesylate Бупренорфин и Buprenorphine and Naloxone Desvenlafaxine Levomilnacipran Topiramate Vortioxetine Eslicarbazepine Acetate
R	Budesonide Chlorpheniramine and Hydrocodone Carbinoxamine Fluticasone and Vilanterol Hydrocodone Umeclidinium Bromide and Vilanterol
S	Bromfenac Brimonidine and Brinzolamide Brimonidine
V	Tilmanocept Gadoterate Meglumine Radium-223 Dichloride Flutemetamol F-18 Sucroferric Oxyhydroxide



Data source: Drugs.com

Figure 2 – FDA Approvals of Original Drugs in 2013.

Note: The outer ring corresponds to the proportions of drugs according to the first letter of their ATC class; the segments of the inner ring correspond to the proportion of drug types — biological, synthetic, semi-synthetic, or of natural origin.

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A	Elosulfase Alfa Metreleptin Albiglutide Human Insulin Dulaglutide Liraglutide Dapagliflozin Empagliflozin Canagliflozin and Metformin Eliglustat Naloxegol Netupitant and Palonosetron Dapagliflozin and Metformin Hydrochloride
B	Coagulation Factor IX, Recombinant Antihemophilic Factor, Recombinant C1-Esterase Inhibitor, Recombinant Recombinant Antihemophilic Factor Vorapaxar Amino Acids, Electrolytes, Dextrose and Lipids
C	Omega-3-Acid Ethyl Esters Propranolol Hydrochloride Sotalol Hydrochloride
D	Efinaconazole Tavaborole Fluocinolone Acetonide Pirfenidone Benzoyl Peroxide and Clindamycin Phosphate
G	Testosterone Undecanoate Testosterone Ethinyl Estradiol and Norelgestromin
H	Pasireotide
J	Meningococcal Group B Vaccine Tobramycin 9-Valent Human Papillomavirus Vaccine, Recombinant Immunoglobulin and Hyaluronidase Dalbavancin Tedizolid Phosphate Doxycycline Hyclate Oritavancin Abacavir, Dolutegravir and Lamivudine Elvitegravir Ledipasvir and Sofosbuvir Ombitasvir/Paritaprevir/Ritonavir with Dasabuvir Ceftolozane and Tazobactam Peramivir
L	Ramucirumab Siltuximab Vedolizumab Peginterferon Beta-1a Pembrolizumab Alemtuzumab Blinatumomab Nivolumab Apremilast Nintedanib Mercaptopurine Ceritinib Belinostat Methotrexate Idelalisib Olaparib
M	Sodium Hyaluronate Indomethacin Dantrolene Diclofenac Sodium
N	Tasimelteon Droxidola Acetaminophen and Oxycodone Hydrochloride Topiramate Buprenorphine and Naloxone Naloxone and Oxycodone Suvorexant Bupropion and Naltrexone Donepezil and Memantine
P	Ivermectin Miltefosine
R	Diphenhydramine Hydrochloride and Naproxen Sodium Umeclidinium Phenylephrine Hydrochloride Fluticasone Propionate Olodaterol Fluticasone Furoate Hydrocodone Bitartrate
S	Ketorolac and Phenylephrine Finafloxacin
V	Ragweed Pollen Allergen Extract Florbetaben F18 Naloxone Hydrochloride Ferric Citrate Cobicistat Lipid Microspheres with Sulfur Hexafluoride

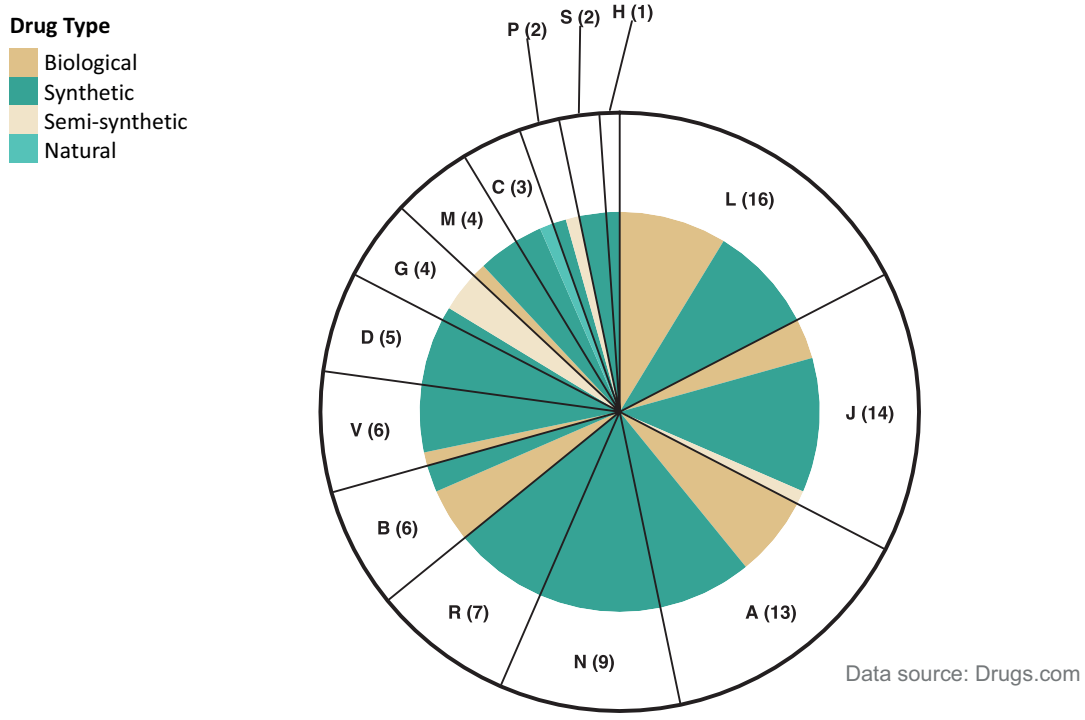

Figure 3 – FDA Approvals of Original Drugs in 2014.
Note: The outer ring corresponds to the proportions of drugs according to the first letter of their ATC class; the segments of the inner ring correspond to the proportion of drug types — biological, synthetic, semi-synthetic, or of natural origin.

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A	Insulin glargine Bile acid Deoxycholic acid Insulin degludec and insulin aspart Insulin degludec Asfotase alfa Sebelipase alfa Insulin glargine Empagliflozin and linagliptin Eluxadoline Empagliflozin and metformin Rolapitant Glycopyrrolate
B	Coagulation factor IX (recombinant) Fibrin sealant Antihemophilic factor (recombinant) Coagulation factor X (human) Antihemophilic factor (recombinant), pegylated Von Willebrand factor (recombinant) Edoxaban Ferric pyrophosphate citrate Cangrelor
C	Alirocumab Evolocumab Amlodipine besylate and perindopril arginine Ivabradine Sacubitril and valsartan Selexipag
D	Adapalene and benzoyl peroxide Betamethasone dipropionate and calcipotriene
G	Levonorgestrel Flibanserin
H	Parathyroid hormone
J	Meningococcal vaccine serogroup B Anthrax immune globulin Diphtheria and tetanus toxoids and acellular pertussis and inactivated poliovirus vaccine, DTaP-IPV Vaccine Influenza vaccine, adjuvanted Atazanavir and cobicistat Cobicistat and darunavir Lamivudine and raltegravir Avibactam and ceftazidime Isavuconazonium Ombitasvir, paritaprevir, and ritonavir Daclatasvir Cobicistat, elvitegravir, emtricitabine, and tenofovir alafenamide Ciprofloxacin
L	Secukinumab Filgrastim-sndz Dinutuximab Talimogene Laherparepvec Melolizumab Daratumumab Necitumumab Elotuzumab Tacrolimus ТрабектеTrabectedиндин Docetaxel Palbociclib Lenvatinib Panobinostat Glatiramer Acetate Sonidegib Tipiracil hydrochloride and trifluridine Irinotecan liposomal Cobimetinib Osimertinib Ixazomib Bendamustine hydrochloride Alectinib
M	Meloxicam Lesinurad
N	Morphine sulfate Carbidopa and levodopa Carbidopa and levodopa Paliperidone palmitate Brexpiprazole Levetiracetam Aspirin Cariprazine Arilpiprazole lauroxil Amphetamine Buprenorphine hydrochloride Methylphenidate hydrochloride
R	Albuterol sulfate Chlorpheniramine polistirex and codeine polistirex Olodaterol and tiotropium Chlorpheniramine and codeine Ivacaftor and lumacaftor Glycopyrrolate and indacaterol
S	Olopatadine HCl Dichlorphenamide
V	Idarucizumab Foscarnet Deferasirox Uridine triacetate Patiromer Naloxone Uridine triacetate Sugammadex

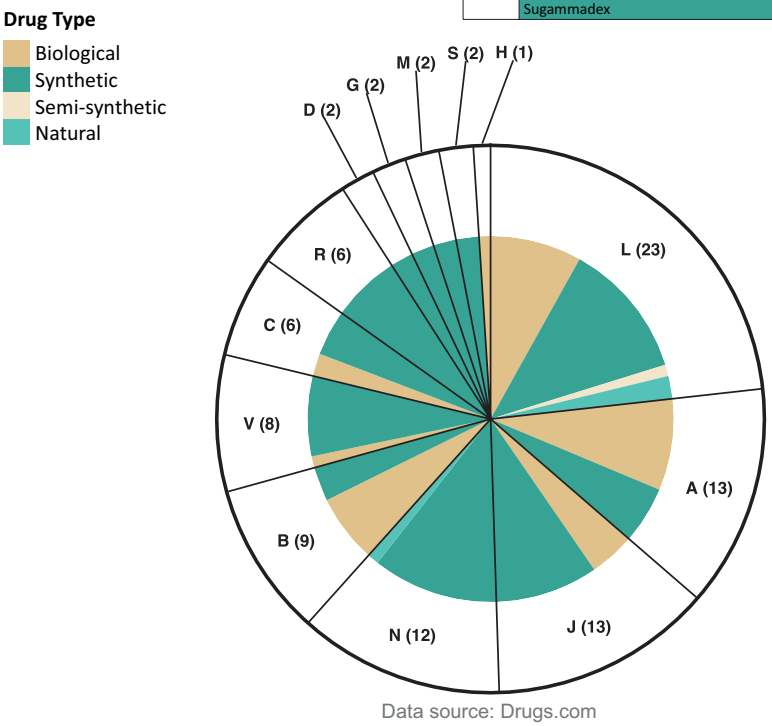

Figure 4 – FDA approvals of original drugs for 2015.

Note: the outer ring corresponds to the proportions of drugs according to the first letter of their ATC class; the segments of the inner ring correspond to the proportion of drug types — biological, synthetic, semi-synthetic or of natural origin.

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A	Lixisenatide
	Insulin degludec and liraglutide
	Obeticholic acid
	Calcifediol
	Dronabinol
	Granisetron
	Phentermine hydrochloride
	Aspirin and omeprazole
	Insulin glargine and lixisenatide
B	Coagulation factor IX (recombinant), albumin fusion protein
	Antihemophilic factor (recombinant)
	Defibrotide
	Antihemophilic factor (recombinant) single chain
C	Nebivolol and valsartan
	Nitroglycerin
	Lisinopril
D	Betamethasone dipropionate
	Crisaborole
G	Levonorgestrel
	Prasterone
J	Obiltoxaximab
	Influenza vaccine, inactivated
	Influenza vaccine, inactivated
	Cholera vaccine, live, oral
	Influenza vaccine, inactivated
	Human immunoglobulin
	Bezlotoxumab
	Elbasvir and Grazoprevir
	Emtricitabine, Rilpivirine and Tenofovir Alafenamide
	Emtricitabine, Rilpivirine and Tenofovir Alafenamide
	Sofosbuvir and Velpatasvir
	Dasabuvir, Ombitasvir, Paritaprevir and Ritonavir
	Tenofovir Alafenamide

L	Ixekizumab
	Infliximab-dyyb
	Atezolizumab
	Daclizumab
	Etanercept
	Adalimumab-atto
	Olaratumab
	Tofacitinib
	Melphalan
	Venetoclax
	Cabozantinib
	Aminolevulinic acid
	Rucaparib
N	Eteplirsen
	Nusinersen
	Amphetamine
	Sumatriptan
	Sumatriptan
	Brivaracetam
	Oxycodone
	Pimavanserin
	Buprenorphine
	Naltrexone and oxycodone
	Carbamazepine
P	Mebendazole
R	Reslizumab
	Ephedrine sulfate
	Acetylcysteine
	Formoterol fumarate and glycopyrrolate
	Fluticasone furoate
S	Bromfenac
	Ciprofloxacin and fluocinolone acetonide
	Oxymetazoline hydrochloride and tetracaine hydrochloride
	Lifitegrast
V	Fluciclovine F18
	Gallium 68

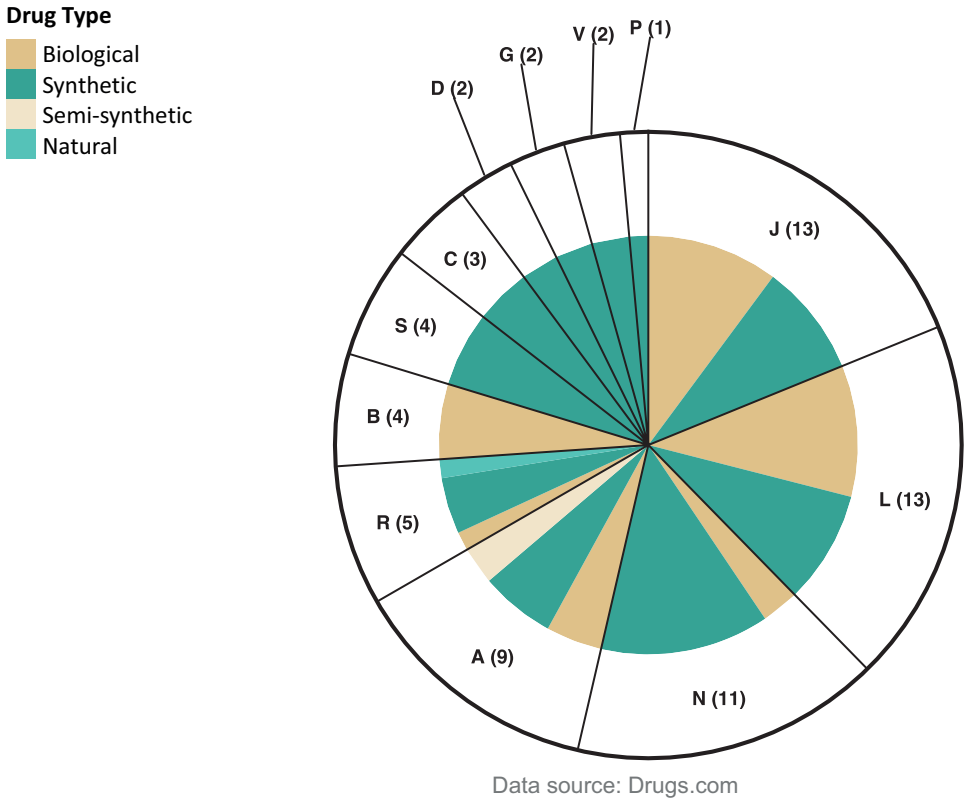

Figure 5 – FDA approvals of original drugs for 2016.
Note: the outer ring corresponds to the proportions of drugs according to the first letter of their ATC class; the segments of the inner ring correspond to the proportion of drug types — biological, synthetic, semi-synthetic or of natural origin.

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A	Cerliponase alfa Insulin aspart Exenatide Vestronidase alfa Semaglutide Insulin lispro Plecanatide Dapagliflozin and saxagliptin Telotristat ethyl Naldemedine Ascorbic acid Alrepitant Sodium picosulfate, magnesium oxide and anhydrous citric acid Glycopyrrolate Ertugliflozin Ertugliflozin and sitagliptin Ertugliflozin and metformin hydrochloride
B	Coagulation factor IX (recombinant), glycopegylated C1 esterase inhibitor (human) Emicizumab-kxwh Betrixaban
C	Angiotensin II Adrenaline Spironolactone Valsartan
D	Dupilumab Triamcinolone Acetonide Clobetasol Propionate Mometasone Furoate Ozenoxacin Hydrogen peroxide
H	Deflazacort Desmopressin Acetate Abaloparatide
J	Rabies Immunoglobulin Recombinant zoster vaccine Hepatitis B vaccine Delafloxacin Sofosbuvir, velpatasvir and voxilaprevir Glecaprevir and pibrentasvir Meropenem and vaborbactam Letermovir Dolutegravir and rilpivirine
L	Ixekizumab Infliximab-dyyb Atezolizumab Daclizumab Etanercept Adalimumab-atto Olaratumab Tofacitinib Melphalan Venetoclax Cabozantinib Aminolevulinic acid Acid Rucaparib
N	Eteplirsen Nusinersen Amphetamine Sumatriptan Sumatriptan Brivaracetam Oxycodone Pimavanserin Buprenorphine Naltrexone and oxycodone Carbamazepine
P	Mebendazole
R	Reslizumab Ephedrine sulfate Acetylcysteine Formoterol fumarate and glycopyrrolate Fluticasone furoate
S	Bromfenac Ciprofloxacin and fluocinolone acetonide Oxymetazoline hydrochloride and tetracaine hydrochloride Lifitegrast
V	Fluciclovine F18 Gallium 68

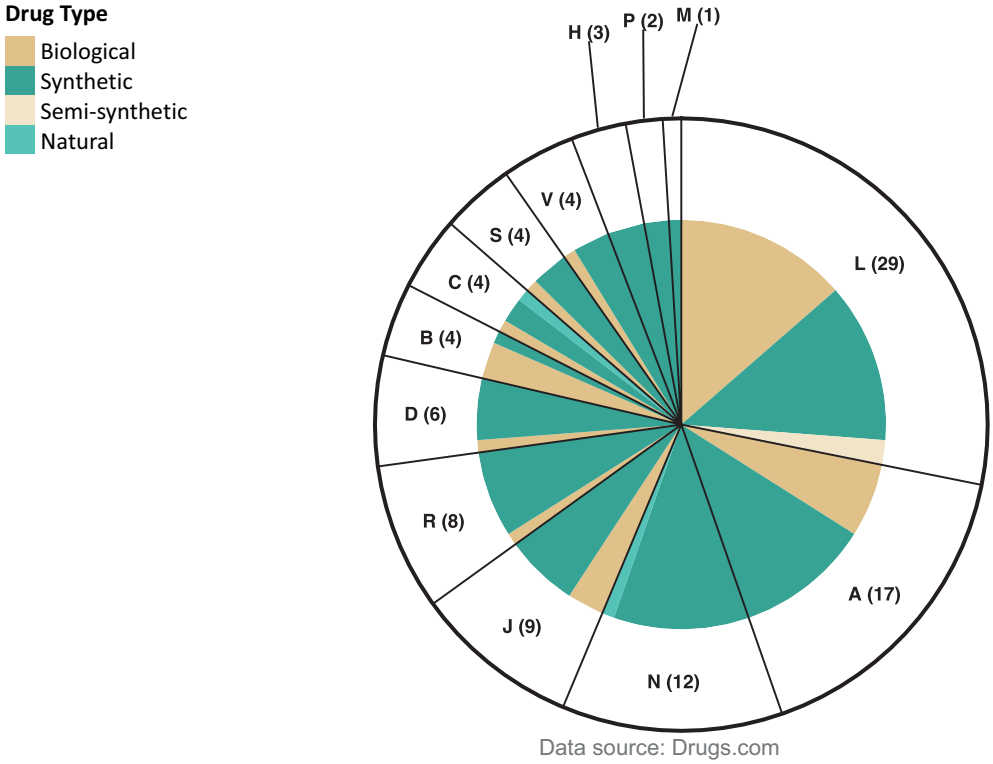
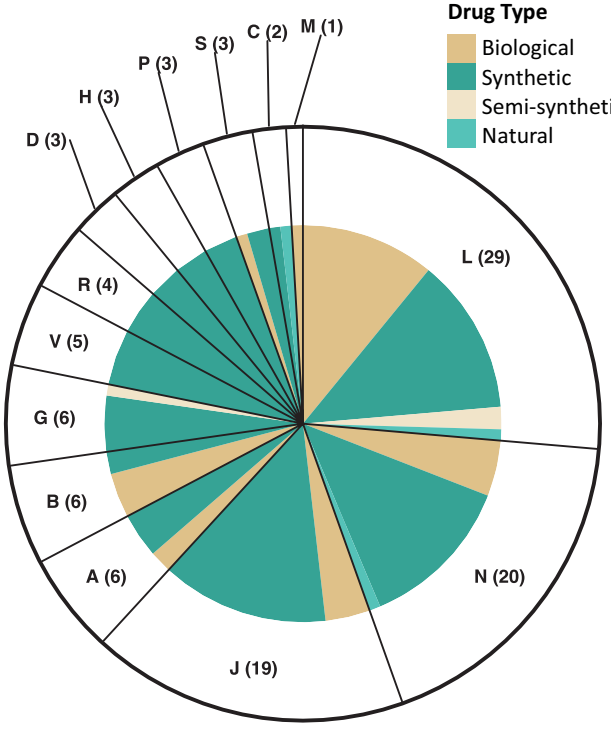


Figure 6 – FDA approvals of original drugs for 2017.

Note: the outer ring corresponds to the proportions of drugs according to the first letter of their ATC class; the segments of the inner ring correspond to the proportion of drug types — biological, synthetic, semi-synthetic or of natural origin.

ОБЗОР
DOI: 10.19163/2307-9266-2025-13-6-432-486

A	Pegvaliaza-pqpz
	Elapegademase-dmde
	Fosnetupitant and palonosetron
	Polyethylene glycol 3350 with electrolytes
	Migalastat
	Prucalopride
B	Blood clotting factor Xa
	Epoetin alpha-epbx
	Lanadelumab-fli
	Antihemophilic factor
	Avatrombopag
	Lusutrombopag
C	Epinephrine
	Amlodipine and celecoxib
D	Tretinoin
	Fluocinolone acetonide
	Halobetasol propionate
G	Testosterone enanthate
	Ethinylestradiol/levonorgestrel and ferrous bisglycinate
	Estradiol
	Elagolix
	Ethinylestradiol and segesterone acetate
	Estradiol and progesterone
H	Dexamethasone
	Desmopressin Acetate
	Dexamethasone
J	Vancomycin hydrochloride
	Ibalizumab-uiyk
	Rifamycin
	Hexavallent vaccine
	Efavirenz, lamivudine and tenofovir disoproxil fumarate
	Bictegravir, emtricitabine and tenofovir alafenamide
	Ламивудин и тенофовира дизопроксил фумарат
	Lamivudine and tenofovir disoproxil fumarate
	Plazomicin
	Tecovirimat
	Cobicistat, darunavir, emtricitabine and tenofvir alafenamide
	Eravacycline
	Doravirine
	Doravirine, lamivudine and tenofovir disoproxil fumarate
	Liposomal amikacin
	Sarecycline
	Omadacycline
	Baloxavir Marboxil
	Itraconazole
L	Tildrakizumab-asmn
	Pegfilgrastim
	Filgrastim-aafi
	Mogamulizumab-kpkc
	Cemiplimab rwlc
	Adalimumab-adaz
	Pegfilgrastim-cbqv
	Emapalumab-lsge
	Rituximab-abs
	Trastuzumab-pkrb
	Calaspargase Pegol-mknl
	Ravulizumab-cwvz
	Cyclosporine
	Moxetumomab Pasudotox-tdfk
	Tagraxofusl-erzs
	Apalutamide
	Fostamatinib
	Abiraterone Acetate
	Baricitinib
	Encorafenib
	Binimetinib
	Ivosidenib
	Duvelisib
	Dacomitinib
	Talazoparib
	Lorlatinib
	Glasdegib
	Larotrectinib
	Gilteritinib
M	Burosumab-tza
N	Erenumab-aooe
	Patisiran
	Fremanezumab-vfrm
	Galcanezumab
	Inotersen
	Cannabidiol
	Amantadine hydrochloride
	Acetaminophen and benzhydrocodone hydrochloride
	Lidocaine
	Lofexidine hydrochloride
	Risperidone
	Methylphenidate hydrochloride
	Stiripentol
	Riluzole
	Buprenorphine and naloxone
	Clobazam
	Sufentanil
	Amifampridine Phosphate
	Levetiracetam
	Levodopa
P	Moxidectin
	Tafenoquine
	Tafenoquine
R	Ivacaftor / Tezacaftor and Ivacaftor
	Glycopyrronium
	Revefenacin
	Albuterol sulfate
S	Cenegermin-bkbj
	Loepernol etabonate
	Latanoprost
V	Lutetium Lu 177 dotatate
	Tolvaptan
	Sodium zirconium cyclosilicate
	Iobenguane I 131



Data source: Drugs.com

Figure 7 – FDA approvals of original drugs in 2018.

Note: the outer ring corresponds to the proportions of drugs according to the first letter of their ATC class; the segments of the inner ring correspond to the proportion of drug types — biological, synthetic, semi-synthetic or natural origin.

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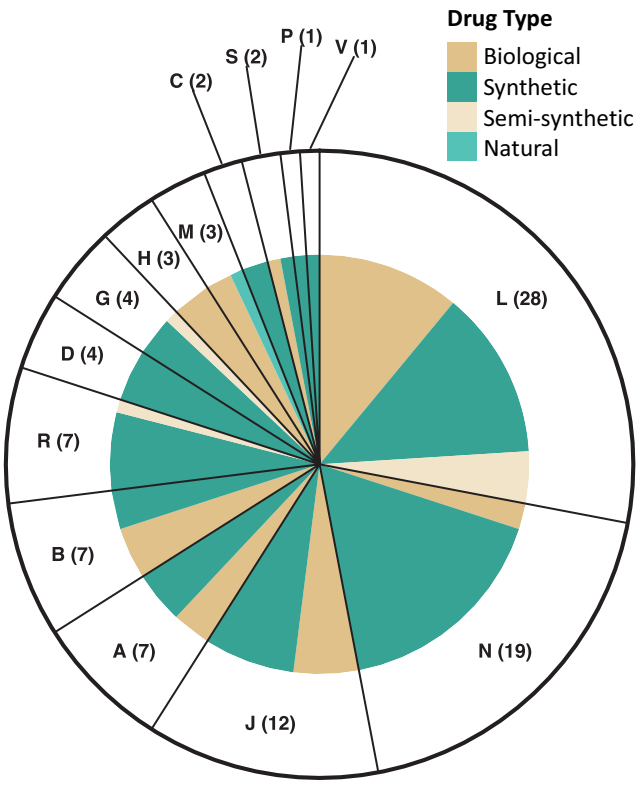
A	Human insulin in sodium chloride solution
	Semaglutide
	Givosiran
	Cellulose and citric acid
	Dapagliflozin, metformin hydrochloride and saxagliptin
	Tenalanor
	Amoxicillin, omeprazole and rifabutin
B	Caplacizumab
	Turoctocog Alfa Pegol
	Luspatercept-aamt
	Caplacizumab
	Iron maltol
	Voxelotor
	Cysteine hydrochloride
C	Amlodipine benzoate
	Левамлодипина малеат
D	Levamlodipine propionate and tazarotene
	Trifarotene
	Amafepanotide
	Tazarotene
G	Testosterone undecanoate
	Drospirenone
	Bremelanotide
	Ethinylestradiol and Etonogestrel
H	Glucagon
	Glucagon
	Teriparatide
J	Immunoglobulin
	Quadrivalent dengue fever vaccine
	Subcutaneous immunoglobulin
	Smallpox vaccine
	Ebola vaccine
	Acyclovir
	Dolutegravir and lamivudine
	Imipenem, cilastatin and relebactam
	Pretomanid
	Lefamulin
	Minocycline
	Cefiderocol
L	Trastuzumab
	Trastuzumab
	Risankizumab-rzaa
	Etanercept
	Trastuzumab-anns
	Bevacizumab
	Rituximab
	Adalimumab
	Pegfilgrastim-bmez
	Adalimumab
	Infliximab
	Trastuzumab and hyaluronidase
	Polatuzumab Vedotin
	Enfortumab Vedotin
	Fam-Trastuzumab Deruxtecan
	Silonimod
	Cladribine
	Erdafitinib
	Alpelisib
	Selinexor
	Darolutamide
	Pexidartinib
	Энтректиниб
	Fedratinib
	Uladacitinib
	Diroximel fumarate
	Zanubrutinib
	Methotrexate
M	Prabotulinumtoxin
	Romosozumab
	Colchicine
N	Onasemnogene Abeparvovec
	Golodirsen
	Sumatriptan
	Methylphenidate hydrochloride
	Esketamine
	Brexanolone
	Solriamfetol
	Tafamidis meglumine
	Amifampridine
	Midazolam
	Pitolisant
	Istradefylline
	Lasmiditan
	Asenapine
	Cenobamate
	Riluzole
	Lumateperone
	Lemborexant
	Ubrogepant
P	Triclabendazole
R	Budesonide
	Fluticasone Propionate and salmeterol
	Aclidinium bromide and formoterol fumarate
	Fluticasone propionate and sameterol
	Cetirizine hydrochloride
	Elexacaftor / Tezacaftor / Ivacaftor and Ivacaftor
	Phenylephrine hydrochloride
S	Brolucizumab
	Netarsudil and Latanoprost
V	Tiopronin



Data source: Drugs.com

Figure 8 – FDA approvals of original drugs in 2019.

Note: the outer ring corresponds to the proportions of drugs according to the first letter of their ATC class; the segments of the inner ring correspond to the proportion of drug types — biological, synthetic, semi-synthetic or natural origin.

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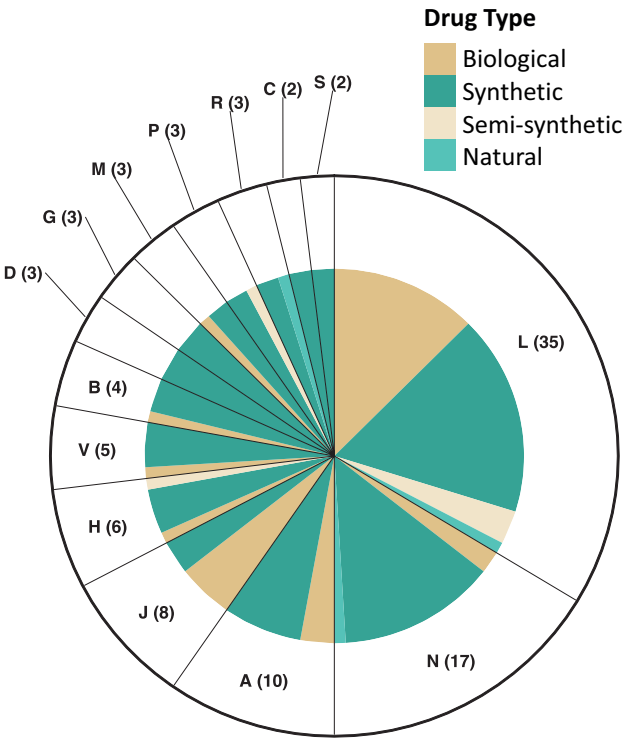
A	Insulin glargine Insulin lispro Lumasiran Empagliflozin, linagliptin and metformin hydrochloride Lactitol Lactic acid, citric acid and sodium bitartrate Metoclopramide Triheptanoin Cysteamine hydrochloride Sodium sulfate, magnesium sulfate and potassium chloride
B	Blood coagulation factor VIIa (recombinant)-jncw Ferric derisomaltose Mannitol Berotralstat
C	Bempedoic acid Bempedoic acid and ezetimibe
D	alcipotriene and betamethasone dipropionate Clascoterone Tirbanibulin
G	Ethinylestradiol and levonorgestrel Elagolix/estradiol/norethindrone acetate and Elagolix Vibegron
H	Somalacitan Hydrocortisone Osilodrostat Octreotide Setmelanotide Levothyroxine sodium
J	Monovalent influenza A vaccine Influenza vaccine, adjuvanted Meningococcal (groups A, C, Y, W) conjugate vaccine Atoltivimab, Maftivimab and Odesevimab Ansuvimab Minocycline Fostemsavir Remdesivir
L	Teprotumumab Isatuximab Pegfilgrastim Inebilizumab Adalilumab Brexucabtagene Autoleucel Tafasitamab Satralizumab Ofatumumab Naxitamab Margetuximab Rituximab Mitomycin Sacituzumab Govitecan Daratumumab and Hyaluronidase Balantamab mafodotin Avapritinib Tazemetostat Pemetrexed Ozanimod Selumetinib Pemigatinib Tucatinib Monomethyl fumarate Leuprolide acetate Capmatinib Selpercatinib Ripretinib Lurbinectedin Decitabine and cedazuridine Azacitidine Pralsetinib Lonafarnib Relugolix Pertuzumab, trastuzumab and hyaluronidase-zzxf
M	Collagenase Clostridium Histolyticum-aaes Meloxicam Celecoxib
N	Eptinezumab Viltoarsen Cocaine hydrochloride Diazepam Amisulpride Rimegepant Ibuprofen and acetaminophen Opicapone Apomorphine hydrochloride Fenfluramine Remimazolam Calcium, magnesium, potassium and sodium oxybates Oliceridine Risdiplam Bupivacaine hydrochloride Tramadol hydrochloride Fosphenytoin sodium
P	Artesunate Abametapir Nifurtimox
R	Ephedrine sulfate Oxymetazoline hydrochloride Budesonide/glycopyrrolate/formoterol fumarate
S	Bimatoprost Loteprednol etabonate
V	Peanut allergen extract Fluorestradiol F18 Flortaucipir F18 Medi 64 dotatate Gallium 68 PSMA-11



Data source: Drugs.com

Figure 9 – FDA approvals of original drugs in 2020.
Note: the outer ring corresponds to the proportions of drugs according to the first letter of their ATC class; the segments of the inner ring correspond to the proportion of drug types — biological, synthetic, semi-synthetic or natural origin.

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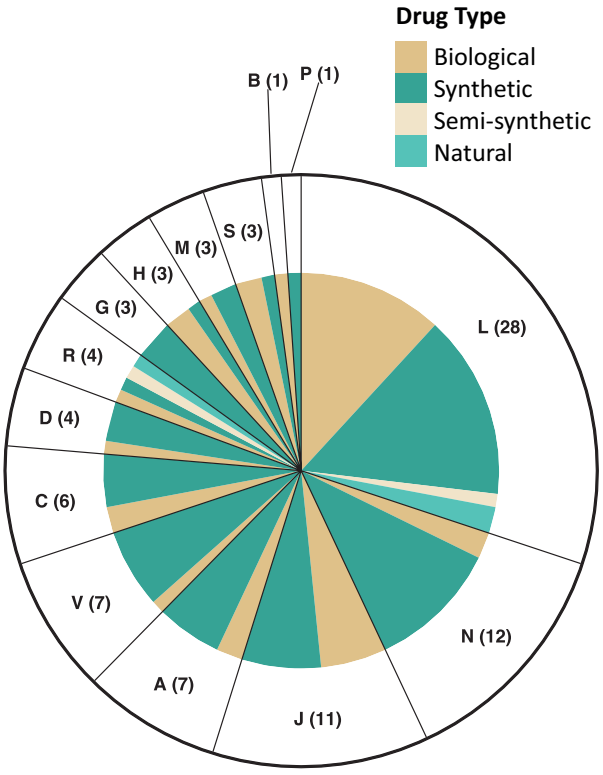
A	Semaglutide Avalglucosidase alpha Fosdenopterin Sotagliflozin Odevixibat Maralixibat Glycopyrrolate
B	Human plasminogen
C	Evinacumab Inclisiran Vericiguat Ezetimibe and rosuvastatin Torsemide Finerenone
D	Tralokinumab Tretinoin and benzoyl peroxide Triamcinolone acetonide Clindamycin phosphate
G	Drospirenone and estetrol Relugolix, estradiol and norethindrone acetate Finasteride and tadalafil
H	Dasiglucagon Lonapegsomatropin Levoketoconazole
J	Pneumococcal 20-valent conjugate vaccine Pneumococcal 15-valent conjugate vaccine Tick-borne encephalitis Vaccine against encephalitis COVID-19 vaccine Hepatitis B vaccine Cabotegravir and rilpivirine Oritavancin Ibrexafungerp Brincidofovir Maribavir Cabotegravir
L	Lisocabtagene Maraleucel Idecabtagen Wikileucel Dostarlimab Pegcetacoplan Amivantamab Asparaginase Erwinia Chrysanthemi (recombinant) Anifrolumab Tisotumab Ropeginterferon alfa-2b Adalimumab Efgartigimod Cyclosporine Sirolimus Loncastuximab Tesirine Voclosporin Umbralisib Trilaciclib Melphalan Flufenamide Tivazanib Ponesimod Leuprolide Mesylate Infigratinib Belumosudil Belzutifan Mobocertinib Ruxolitinib Avacopan Aciminib
M	Vosoritide Celecoxib and tramadol hydrochloride Baclofen
N	Casimersen Aducanumab Bupivacaine Dexmethylphenidate and serdexmethylphenidate Viloxazine hydrochloride Bupivacaine and meloxicam Olanzapine and samidorphan Paliperidone palmitate Dihydroergotamine mesylate Atogepant Varenicline Topiramate
P	Fexinidazole
R	Tezepelumab Ephedrine hydrochloride Budesonide Azelastine
S	Ranibizumab Ranibizumab Pilocarpine hydrochloride
V	Allogeneic processed thymus tissue Naloxone hydrochloride Piflufolastat F18 Difelikefalin Naloxone hydrochloride Paflocyanine Gallium 68 Gozetotide



Data source: Drugs.com

Figure 10 – 2021 FDA Original Drug Approvals.

Note: The outer ring corresponds to the proportions of drugs according to the first letter of their ATC class; the segments of the inner ring correspond to the proportion of drug types — biological, synthetic, semi-synthetic, or of natural origin.

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DOI: 10.19163/2307-9266-2025-13-6-432-486

A	Tirzepatide Olipudase alfa Fecal microbiota, live Триентин тетрагидрохлорид Amoxicillin, clarithromycin, and vonoprazan Omeprazole and sodium bicarbonate Aprepitant Sodium phenylbutyrate and taurursodiol Sodium phenylbutyrate
B	Betibeglogene autotemcel Etranacogene dezaparvovec Mitapivat
C	Amlodipine besylate Mavacamten Furosemide
D	Anacaulase Benzoyl peroxide Tapinarof
G	Testosterone Testosterone undecanoate
H	Terlipressin
J	COVID-19 vaccine Measles, mumps, and rubella vaccine, live Oteseconazole Lenacapavir
L	Tebentafusp Sumimlimab Filgrastim Ciltacabtagene autoleucel Nivolumab and relatlimab Bevacizumab Pegfilgrastim Pegfilgrastim Spesolimab Eflapegrastim Bevacizumab Tremelimumab Teclistamab Teplizumab Adalimumab Nadroparagene firadenovec Mosunetuzumab Ublituximab Sirolimus Mirvetuximab soravtansine Abrocitinib Pacritinib Alpelisib Deucravacitinib Futibatinib Olutasidenib Adagrasib
M	Daxibotulinumtoxin A Baclofen
N	Vutrisiran Elivaldogene autotemcel Daridorexant Donepezil Ganaxolone Dextroamphetamine Dexmedetomidine Edaravonен Vigabatrin Zonisamide Dextromethorphan and bupropion Chloroprocaine hydrochloride Phenobarbital sodium
R	Mometasone furoate and olopatadine hydrochloride Mometasone furoate monohydrate Roflumilast
S	Faricimab Ranibizumab Omidenepag isopropyl Latanoprost
V	Technetium Tc 99m succimer Gallium Ga 68 gozetotide Lutetium Lu 177 vipivotide tetraxetan Indigotindisulfonate sodium Sodium thiosulfate Gadopiclenol Xenon Xe 129 hyperpolarized

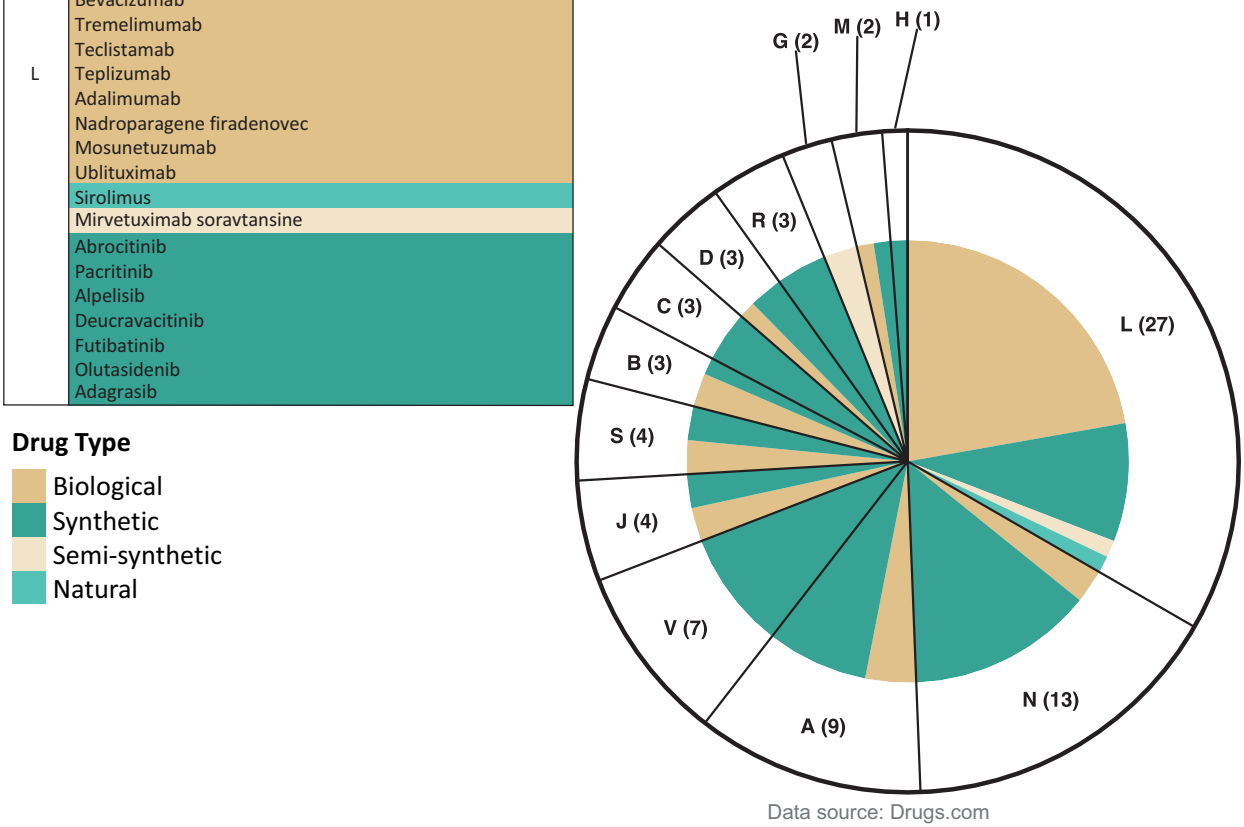

Figure 11 – 2022 FDA Original Drug Approvals.
Note: The outer ring corresponds to the proportions of drugs according to the first letter of their ATC class; the segments of the inner ring correspond to the proportion of drug types — biological, synthetic, semi-synthetic, or of natural origin.

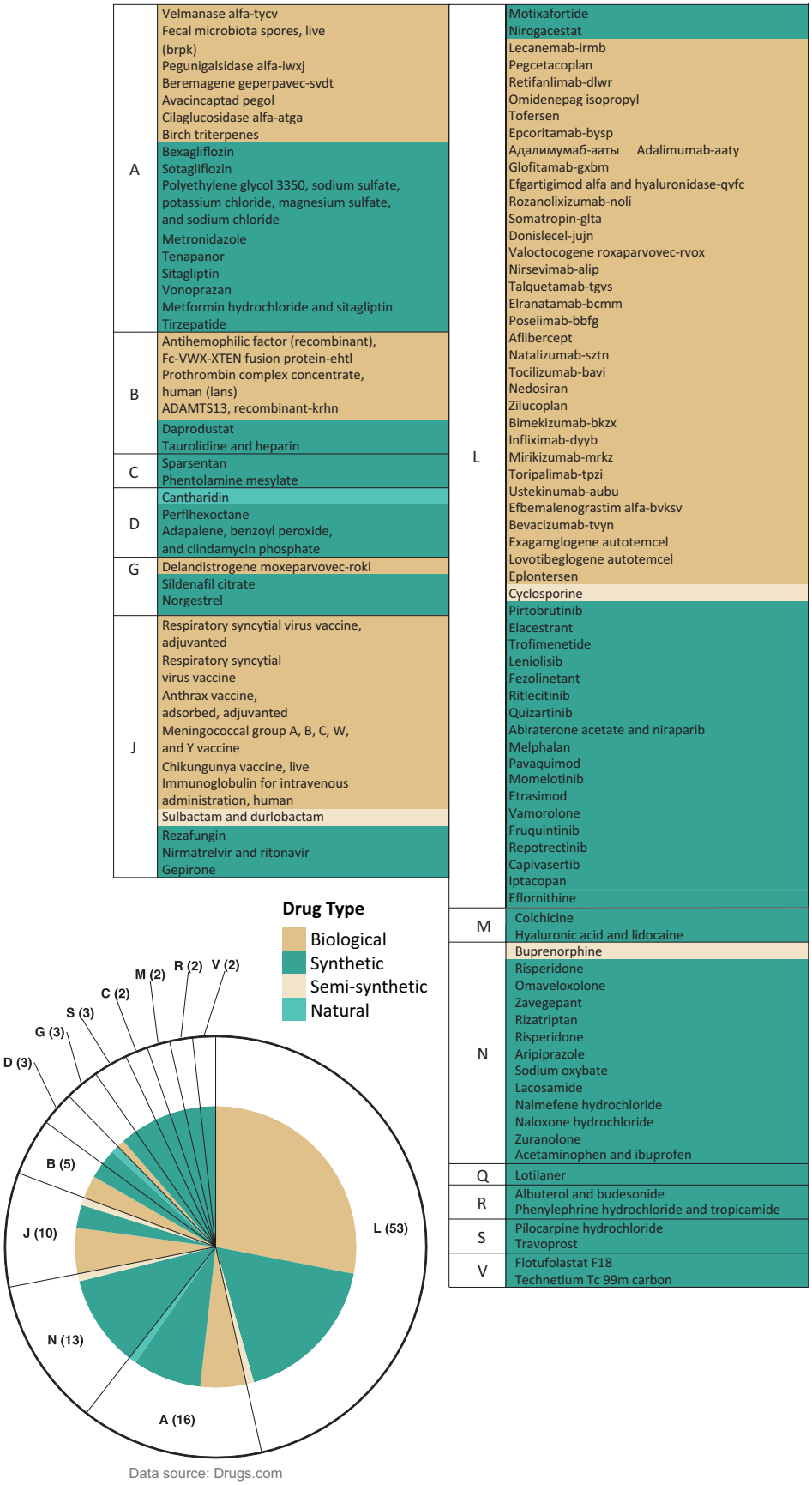

Figure 12 – 2023 FDA Original Drug Approvals.

Note: The outer ring corresponds to the proportions of drugs according to the first letter of their ATC class; the segments of the inner ring correspond to the proportion of drug types — biological, synthetic, semi-synthetic, or of natural origin.

ОБЗОР
DOI: 10.19163/2307-9266-2025-13-6-432-486

A	Seladelpar
	Elafibranor
	Resmetirom
B	Concizumab-mtci
	Marstacimab-hncq
	Vadadustat
C	Olezarsen
	Sotatercept-CSRK
	Landiolol
	Acoramidis
	Aprocitentan
D	Lebrikizumab-lbkz
	Nemolizumab-ilto
	Deucravacitinib
	Sofpironium
	Berdazimer
H	Palopegteriparatide
	Crinecerfont
J	Ceftobiprole medocaril sodium
	Cefepime and enmetazobactam
	Sulopenem and etzadroxil and probenecid
L	Danicopan
	Cosibelimab-ipdl
	Zenocutuzumab-zbko
	Zanidatamab-zfri
	Zolbetuximab-clzb
	Axatilimab-csfr
	Crovalimab-akkz
	Tarlatamab-dlle
	Nogapendekin alfa inbakicept-pmln
	Tislelizumab-jsgr
	Ensartinib
	Revumenib
	Ivosidenib
	Lazertinib
	Vorasidenib
	Imetelstat
	Mavorixafor
	Tovorafenib
M	LetibotulinumtoxinA-wlbg
N	Lecanemab-irmb
	Donanemab-aduc
	Xanomeline and trospium chloride
	Levacetylleucine
	Arimoclomol
	Givinostat
R	Vanacaftor, tezacaftor and deutivacaftor
	Ensifentrine
V	Iomeprol
	Flurpiridaz
	Pegulicianine

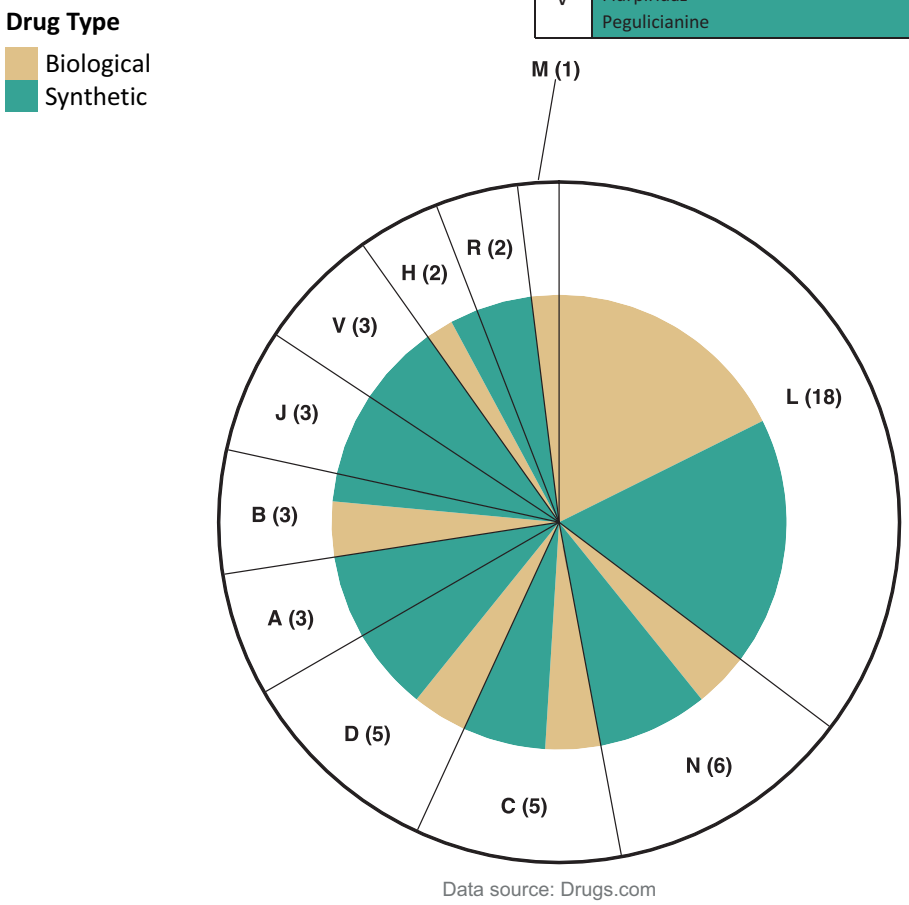

Figure 13 – 2024 FDA Original Drug Approvals.
Note: The outer ring corresponds to the proportions of drugs according to the first letter of their ATC class; the segments of the inner ring correspond to the proportion of drug types — biological or synthetic.

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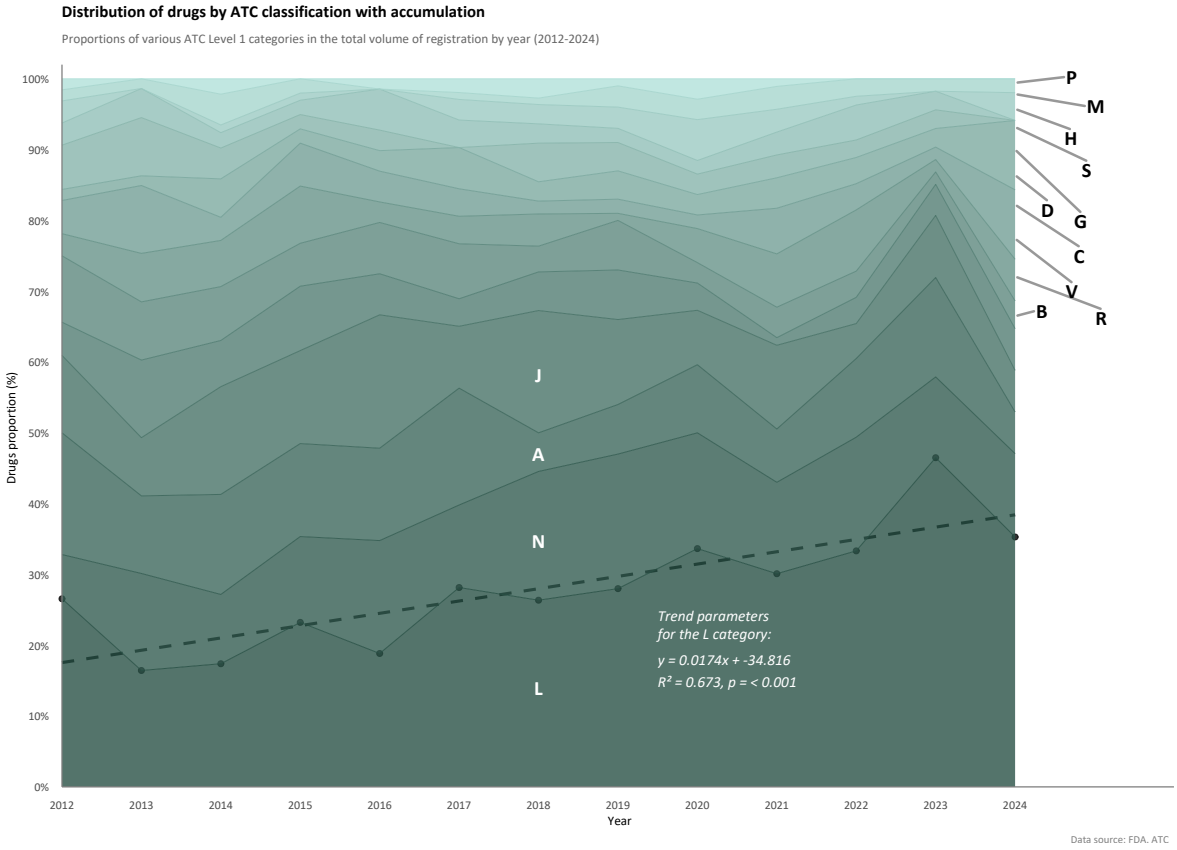

Figure 14 – Drugs approved by the FDA according to the anatomical and therapeutic classification in the period from 2013 to 2024.

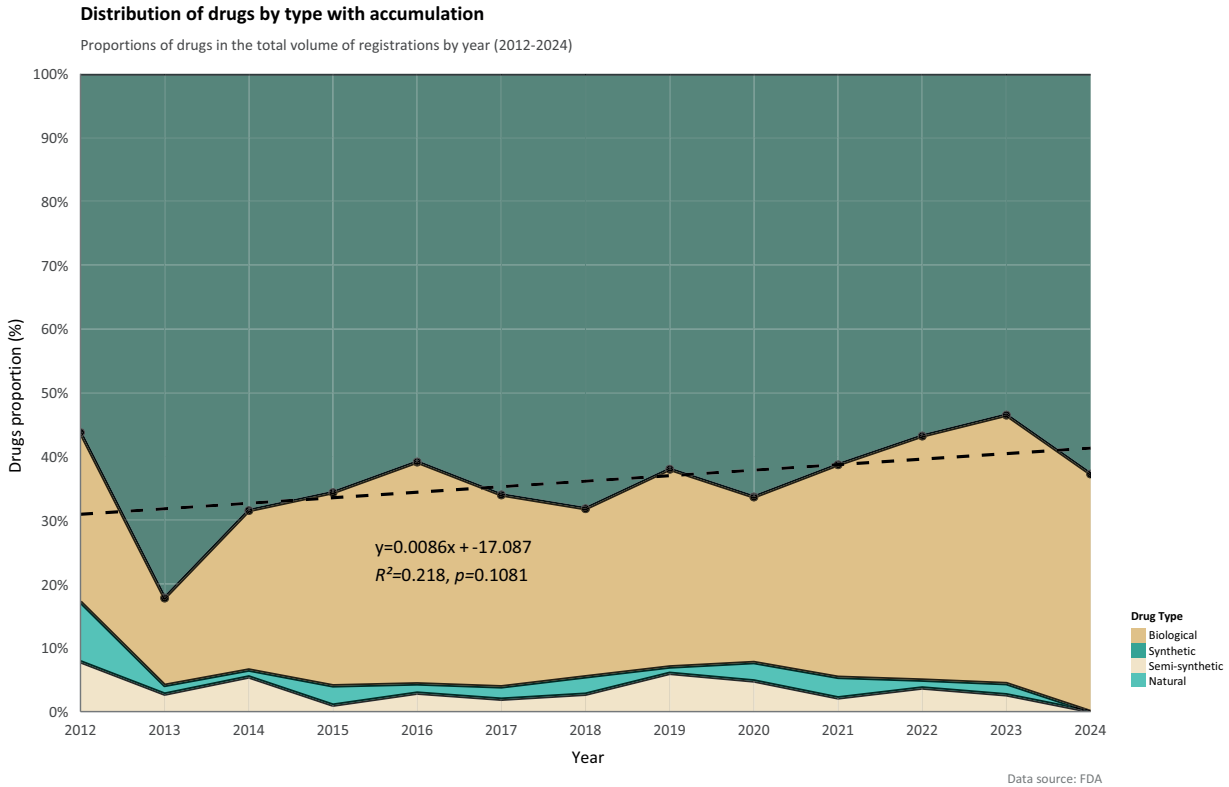

Figure 15 – Distribution of various types of production of original drugs during 2012–2024.

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DOI: 10.19163/2307-9266-2025-13-6-432-486

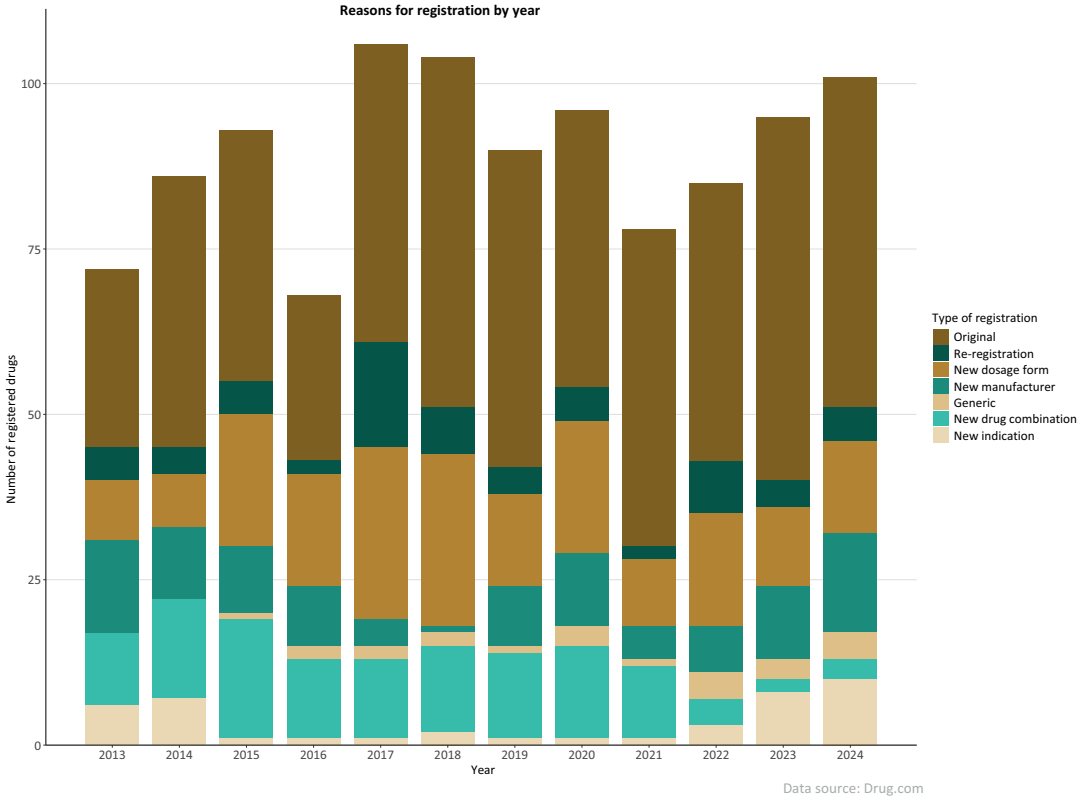

Figure 16 – Cumulative chart of the number of reasons for registration by year.
Note: the data is presented as the number of drugs registered in the specified year.

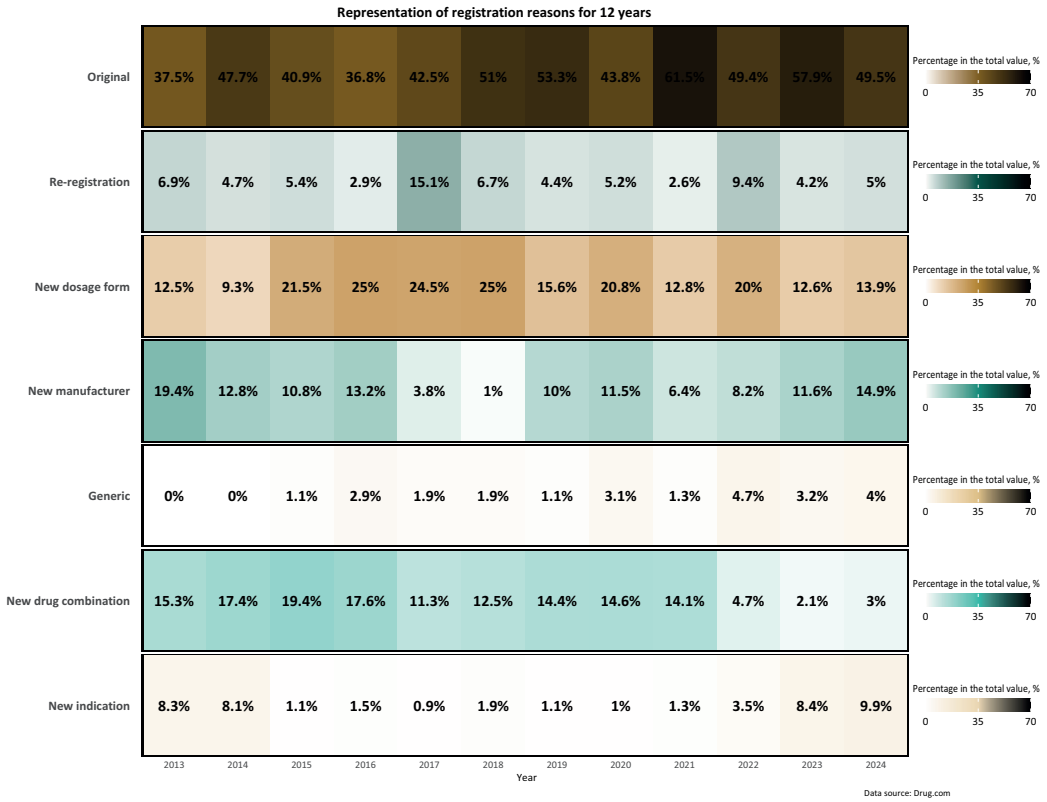

Figure 17 – Representation of drugs registered for various reasons in the registration structure of the designated year (registration shares by year).
Note: Please note that the gradient temperature is limited to 70%, as none of the registration reasons exceeded this threshold.

Aflibercept (Eylea HD®)[313] is a recombinant hybrid protein consisting of the extracellular domains of human vascular endothelial growth factor (VEGF) receptors 1 and 2, linked to the Fc fragment of human IgG1. Eylea HD® is approved for the treatment of wet macular degeneration (2011), diabetic macular edema (since 2014), diabetic retinopathy at all stages (since 2019) and retinopathy of prematurity since 2023. In wet macular degeneration, abnormal blood vessels grow in the choriocapillaries — a layer of capillaries under the retina, which leads to leakage of blood and protein under the macula. Aflibercept binds to circulating VEGF and acts as its trap and inhibits the activity of its subtypes (VEGF-A and VEGF-B), as well as placental growth factor, suppressing the growth of new blood vessels in the choriocapillaries or tumor, respectively (tumor depletion) [79].

2024

In 2024, 106 drugs were approved. 50 original molecules were approved, including 15 new original anticancer drugs. In 2024, a record number (10) of drugs of known medicines approved for a new indication was identified. 15 drugs that changed manufacturers, 4 generics, and 3 new combinations were approved. It is important to note that 2024 is the only year when no semi-synthetic or natural molecules were registered among the original molecules (Fig. 13). Among the 50 original molecules, almost half were “first-in-class” drugs. Most of the new products were small molecules (about 60%), but the proportion of biologics increased significantly (about 34%), mainly monoclonal antibodies with antitumor and anti-inflammatory effects.

Among the registered drugs are bispecific antibodies, new tyrosine kinase inhibitors, and innovative oligonucleotide drugs for rare (orphan) diseases. For example, zenocutuzumab (Bizengri®) is a bispecific antibody to HER2 / HER3 for the treatment of non-small cell lung cancer[314], and olezarsen (Tryngolza®) is an oligonucleotide for the treatment of familial chylomicronemia[315].

Significant attention is paid to the treatment of malignant tumors: new antibodies have appeared, such as cosibelimab (Unloxcyt®) for the treatment of squamous cell skin cancer when surgery or radiation therapy is not possible. Among the drugs for orphan diseases, protein stabilizers for amyloid cardiomyopathy and drugs for the correction of rare lipid metabolism disorders have been registered.

Zenocutuzumab (Bizengri®) provides simultaneous blockade of two tumor growth signaling pathways. This combination reduces the likelihood of drug resistance and enhances the antitumor effect. Zenocutuzumab is especially valuable for patients with mutations that respond poorly to existing HER2-targeted agents[316].

Cosibelimab (Unloxcyt®) blocks the interaction of PD-L1 with PD-1, removing the inhibition of antitumor immunity. It is intended for patients who do not respond to standard treatments and is an immunotherapy option with a high potential for life extension[317].

Ensartinib (Ensacove®) is a new generation drug capable of overcoming resistance to previously approved ALK inhibitors. It is effective against tumors with mutations that reduce sensitivity to crizotinib and other analogs[318].

Olezarsen (Tryngolza®) reduces the level of apolipoprotein C-III, which leads to a marked decrease in triglycerides. This is the first drug of its kind with a proven ability to control a pathology for which there were previously almost no effective means[319].

Zanidatamab (Ziihera®) has demonstrated the ability to block pathological HER2 signals in non-oncological tissues, slowing organ damage and improving their function. This is one of the first examples of the transfer of antitumor mAb technologies for the treatment of non-cancerous diseases[320].

Therapy based on mAbs interacting with receptors, as well as immunotherapy based on newly discovered mechanisms of antitumor immunity, occupies a separate part in the structure of registered original drugs. The search for new rational combinations of antibiotics remains relevant.

[313] Drugs.com. Eylea HD. Available from: https://www.drugs.com/eylea-hd.html
[314] Drugs.com. Bizengri. Available from: https://www.drugs.com/bizengri.html
[315] Drugs.com. Tryngolza. Available from: https://www.drugs.com/tryngolza.html
[316] Drugs.com. Bizengri. Available from: https://www.drugs.com/bizengri.html
[317] Drugs.com. Unloxcyt. Available from: https://www.drugs.com/unloxcyt.html
[318] Drugs.com. Ensacove. Available from: https://www.drugs.com/ensacove.html
[319] Drugs.com. Tryngolza. Available from: https://www.drugs.com/tryngolza.html
[320] Drugs.com. Ziihera. Available from: https://www.drugs.com/ziihera.html

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DISCUSSION

Structure according to the anatomical therapeutic chemical classification

Analyzing the presented data, several main and significant trends in FDA approvals can be noted. First of all, the proportion of original molecules and new combinations has remained stable over the past decades, but the proportion of biotechnological products has gradually increased, including due to the focus on small groups of patients with rare and orphan diseases [9]. It should also be noted that biotechnology startups are of greater interest to investors than those focused on synthetic chemistry methods due to certain specifics that determine the development strategy and advantages of such drugs [80, 81]. At the same time, the number of approved generic drugs in the United States seems minimal, while drugs in new dosage forms are more often approved, which, apparently, are designed to meet the needs of individual groups of patients.

The most extensive group of drugs in the ATC classification was anticancer drugs and immunomodulators, which is due to both progress in the treatment of oncological diseases and the belonging to this group of many drugs based on monoclonal antibodies intended for the treatment of an extensive list of pathologies, including systemic inflammatory and neurodegenerative diseases [82–84]. Examples of such drugs approved for the period 2012–2024 include ponatinib (Iclusig®) — a tyrosine kinase inhibitor intended for the treatment of chronic myeloid leukemia (CML) and acute leukemias with certain mutations[321]; daclizumab (Zinbryta®) — a monoclonal antibody to IL-2, intended for the treatment of multiple sclerosis, but also used in oncology[322]; elotuzumab (Empliciti®) — a monoclonal antibody for the treatment of multiple myeloma[323]; cobimetinib (Cotellic®) — a MEK inhibitor that is used in combination with vemurafenib to increase the effectiveness of melanoma treatment[324]; avelumab (Bavencio®) — a PD-L1 inhibitor approved for the treatment of bladder and kidney cancer[325]; tazemetostat (Tazverik®) — an EZH2 inhibitor approved for the treatment of soft tissue sarcoma[326]; venetoclax (Venclexta®) — an inhibitor of the BCL-2 protein, which activates apoptosis of cancer cells, which is used to treat chronic lymphocytic leukemia[327]; tralokinumab (Adbry®) — a monoclonal antibody that blocks IL-13, used to treat atopic dermatitis[328]; dostarlimab (Jemperli®) — a PD-1 inhibitor approved for the treatment of endometrial cancer[329]; teplizumab (Tzield®) — a monoclonal antibody used to slow the progression of type 1 diabetes[330]; a combination of three monoclonal antibodies that neutralizes the Ebola virus: atoltivimab, maftivimab, and odesivimab (Inmazeb®)[331] [20, 85, 86].

Interest in the development of drugs affecting the digestive tract and metabolism, and drugs for the treatment of diseases of the nervous system remains steadily high: many drugs that are the first in their class, that is, having a fundamentally new mechanism of action, have appeared in these areas. Among the drugs from this category that received FDA approval for the treatment of diabetes mellitus and obesity in 2012–2024, the following drugs should be highlighted: canagliflozin (Invokana®) — the first drug in the class of SGLT2 inhibitors[332], intended for the treatment of type 2 diabetes, and dapagliflozin (Farxiga®, also an SGLT2 inhibitor)[333], dulaglutide (Trulicity®)[334] and semaglutide (Ozempic®)[335] — GLP-1 analog drugs intended for the treatment of type 2 diabetes, which help control blood glucose levels and promote weight loss. A number of combinations of representatives of this class with other hypoglycemic agents: liraglutide and insulin degludec (Xultophy®)[336], as well as the dual incretin tirzepatide — an agonist of glucose-

[321] Drugs.com. Iclusig. Available from: https://www.drugs.com/iclusig.html
[322] Drugs.com. Zinbryta. Available from: https://www.drugs.com/zinbryta.html
323 Drugs.com. Empliciti. Available from: http://drugs.com/empliciti.html
[324] Drugs.com. Cotellic. Available from: https://www.drugs.com/cotellic.html
[325] Drugs.com. Bavencio. Available from: https://www.drugs.com/bavencio.html
[326] Drugs.com. Tazverik. Available from: https://www.drugs.com/tazverik.html
[327] Drugs.com. Venclexta. Available from: https://www.drugs.com/venclexta.html
[328] Drugs.com. Adbry. Available from: https://www.drugs.com/adbry.html
[329] Drugs.com. Jemperli. Available from: https://www.drugs.com/jemperli.html
[330] Drugs.com. Tzield. Available from: https://www.drugs.com/tzield.html
[331] Drugs.com. Inmazeb. Available from: https://www.drugs.com/cons/inmazeb.html
[332] Drugs.com. Invokana. Available from: https://www.drugs.com/invokana.html
[333] Drugs.com. Farxiga. Available from: https://www.drugs.com/farxiga.html
[334] Drugs.com. Trulicity. Available from: https://www.drugs.com/trulicity.html
[335] Drugs.com. Ozempic. Available from: https://www.drugs.com/ozempic.html
[336] Drugs.com. Xultophy. Available from: https://www.drugs.com/xultophy.html

dependent insulinotropic polypeptide and GLP-1 receptors (Mounjaro® and Zepbound®)[337, 338], intended for the treatment of diabetes mellitus and obesity, respectively. For the treatment of neuropsychiatric disorders during the same period, among other drugs, dextromethorphan + quinidine (Nuedexta®) was approved for the treatment of pseudobulbar affect, which helps control sudden episodes of laughter or crying[339], brexpiprazole (Rexulti®) — an atypical antipsychotic that affects dopamine and serotonin receptors, approved for the treatment of schizophrenia and as an adjunct therapy for the treatment of depression[340]; cariprazine (Vraylar®) — an atypical antipsychotic that affects dopamine and serotonin receptors, approved for the treatment of schizophrenia and bipolar disorder[341]; erenumab (Aimovig®) — a monoclonal antibody for the prevention of migraine in adults, which blocks CGRP, reducing the frequency of migraine[342]; aducanumab (Aduhelm®)[343], lecanemab (Lecanemab®)[344] and donanemab (Donanemab®)[345] — monoclonal antibodies that target β-amyloid plaques in the brain and are intended for the treatment of Alzheimer's disease; cerliponase alfa (Brineura®) — a gene therapy drug for the treatment of a neurodegenerative disease associated with Batten disease[346]; imiglucerase (Cerezyme®) — an enzyme replacement therapy drug approved for the treatment of Gaucher disease[347].

Progress also continued in the field of antimicrobial drugs for systemic use, which include both antibacterial and antiviral drugs. It is important to note that the COVID-19 pandemic did not have a noticeable impact on the history of drug approval by the FDA: in particular, there were no peaks in approvals of antimicrobial and antiviral drugs or drugs for the treatment of respiratory diseases. Between 2019 and 2023, the FDA approved only a few drugs for the treatment of COVID-19: in 2020 — remdesivir (Veklury®; an antiviral drug for the treatment of COVID-19)[348], in 2021 — nirmatrelvir+ritonavir (Paxlovid®; an antiviral drug for the treatment of COVID-19, previously approved under the emergency use program, received full approval)[349]. The FDA has not approved any other drugs specifically for the treatment of COVID-19. The main focus in these years was on the development and approval of vaccines against COVID-19, which are not within the purview of the Center for Drug Evaluation and Research (CDER) of the FDA, but are approved by the Center for Biologics Evaluation and Research (CBER). Thus, to date, the FDA has approved only two drugs for the treatment of COVID-19 — remdesivir[350] and the combination nirmatrelvir + ritonavir[351]. Both are antiviral agents aimed at suppressing the replication of the SARS-CoV-2 virus.

Trends

An analysis of FDA-approved drugs from 2012 to 2024 reveals several significant trends and innovations that are shaping the future of drug development [18–20]:

Shift towards biotechnology. There is a noticeable increase in the number of approved biotechnology drugs (including monoclonal antibodies and gene therapy methods). This trend reflects a growing focus on personalized medicine and the treatment of rare diseases.

Continued priority for oncology research. Anti-cancer drugs have consistently represented a significant portion of approvals. The emergence of innovative approaches, such as CAR-T therapy (e.g., tisagenlecleucel)[352] and targeted therapy (e.g., ceritinib, nivolumab)[353, 354], demonstrates the rapid development of this field.

[337] Drugs.com. Mounjaro. Available from: https://www.drugs.com/mounjaro.html
[338] Drugs.com. Zepbound. Available from: https://www.drugs.com/zepbound.html
[339] Drugs.com. Nuedexta. Available from: https://www.drugs.com/nuedexta.html
[340] Drugs.com. Rexulti. Available from: https://www.drugs.com/rexulti.html
[341] Drugs.com. Vraylar. Available from: https://www.drugs.com/vraylar.html
[342] Drugs.com. Aimovig. Available from: https://www.drugs.com/aimovig.html
[343] Drugs.com. Aduhelm. Available from: https://www.drugs.com/aduhelm.html
[344] Drugs.com. Lecanemab. Available from: https://www.drugs.com/lecanemab.html
[345] Drugs.com. Donanemab. Available from: https://www.drugs.com/donanemab.html
[346] Drugs.com. Brineura. Available from: https://www.drugs.com/brineura.html
[347] Drugs.com. Cerezyme. Available from: https://www.drugs.com/cerezyme.html
[348] Drugs.com. Veklury. Available from: https://www.drugs.com/veklury.html
[349] Drugs.com. Paxlovid. Available from: https://www.drugs.com/paxlovid.html
[350] Drugs.com. Veklury. Available from: https://www.drugs.com/veklury.html
[351] Drugs.com. Paxlovid. Available from: https://www.drugs.com/paxlovid.html
[352] Drugs.com. Kymriah. Availalble from: https://www.drugs.com/kymriah.html
[353] Drugs.com. Zykadia. Availalble from: https://www.drugs.com/zykadia.html
[354] Drugs.com. Opdivo. Availalble from: https://www.drugs.com/opdivo.html

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Focus on rare diseases. A significant portion of approvals has been directed towards rare, or orphan diseases, indicating a strategic shift towards addressing unmet needs of small patient groups. This trend is consistent with growing investor interest and the possibility of accelerated approval. There is significantly less competition in this area. Thus, startups or young pharmaceutical or research companies have a chance to attract investment and create an innovative product.

New therapeutic approaches. Several innovative treatments have emerged and developed during this period:

- RNA interference (siRNA) therapy (e.g., nedosiran)[355];
- gene therapy (e.g., onasemnogene abeparvovec, lovotibeglogene autotemcel)[356, 357];
- cell therapy (e.g., donaisel for type 1 diabetes)[358];
- bispecific antibodies and antibody-drug conjugates;
- the emergence of promising areas in the fight against infectious diseases.

Progress in the treatment of neurodegenerative diseases. The approval of drugs aimed at treating Alzheimer's disease (e.g., the combination of aducanumab, lecanemab)[359, 360] represents a significant milestone, despite ongoing debates about their effectiveness and economic feasibility.

Innovations in the field of metabolic disorders. New approaches in the treatment of diabetes and obesity (e.g., SGLT2 inhibitors, GLP-1 receptor agonists, dual incretin receptor agonists) have led to significant progress in the treatment of these pathologies.

Rapid response to new threats. The rapid development and approval of drugs for the treatment of COVID-19 (e.g., remdesivir, the combination of nirmatrelvir + ritonavir)[361, 362] demonstrated the industry's ability to respond quickly to global challenges.

Repurposing of known drugs. The approval of drugs such as sildenafil for the treatment of pulmonary hypertension[363] and cantharidin for molluscum contagiosum[364] highlights the possibility of repurposing known drugs.

Achievements in personalized medicine. There has been an increase in the number of approvals for targeted therapies based on specific genetic or molecular profiles, which not only contributes to the development of the personalized medicine paradigm, but is in fact its debut.

Innovative drug delivery systems. The approval of new dosage forms and delivery systems (e.g., levetiracetam[365]; the first 3D-printed drug for the treatment of epilepsy) indicates ongoing efforts to improve patient adherence to treatment and increase the effectiveness of therapy.

These trends point to several promising directions for future drug development:

- further research into gene and cell therapy for a wider range of diseases;
- continued development of targeted therapy in oncology;
- expanding the use of siRNA and other nucleic acid-based therapeutics;
- increased attention to neurodegenerative diseases using knowledge gained from recent breakthroughs;
- development of combination therapy and multi-targeted drugs;
- studying the microbiome and its therapeutic potential;
- complexification of drug delivery systems and dosage forms.

Figure 14 shows the distribution of the proportions of drugs of various ATC classes during the study period. The proportion of drugs in category L — antineoplastic and immunomodulatory agents — remains the most numerous among all registrations. A trend line with an R^2 value of 0.673 and a high trend significance ($p < 0.001$) has been added to the figure. Thus, the contribution of time to the increase in the proportion

[355] Drugs.com. Rivfloza. Availalble from: https://www.drugs.com/rivfloza.html
[356] Drugs.com. Zolgensma. Availalble from: https://www.drugs.com/zolgensma.html
[357] Drugs.com. Lyfgenia. Availalble from: https://www.drugs.com/lyfgenia.html
[358] Drugs.com. Lantidra. Availalble from: https://www.drugs.com/lantidra.html
[359] Drugs.com. Aduhelm. Availalble from: https://www.drugs.com/aduhelm.html
[360] Drugs.com. Leqembi. Availalble from: https://www.drugs.com/leqembi.html
[361] Drugs.com. Veklury. Availalble from: https://www.drugs.com/veklury.html
[362] Drugs.com. Paxlovid Availalble from: https://www.drugs.com/paxlovid.html
[363] Drugs.com. Liqrev. Availalble from: https://www.drugs.com/liqrev.html
[364] Drugs.com. Ycanth. Availalble from: https://www.drugs.com/ycanth.html
[365] Drugs.com. Spritam. Availalble from: https://www.drugs.com/spritam.html

of drugs in class L is 67.3%, which is a fairly high figure. The resulting linear equation with a slope of 0.0174 suggests that the increase in the proportion of drugs in this class will be 1.74% per year. Thus, despite the fact that this scenario is difficult to consider realistic; in 10 years it is possible to increase the share of drugs in class L on the pharmaceutical market by 17.4%.

Since most anti-cancer drugs are monoclonal antibodies in terms of production method, there is a clear trend of increasing drugs of biological origin. The trend line obtained and shown in Figure 15 indicates this dynamics. The linear model with a coefficient of $R^2 = 0.55$ with a high trend significance ($p < 0.01$) indicates that the contribution of time to the variation of the data is 55%, that is, the trend can be considered stable. The resulting trend line equation $y = 0.0138x + (-27.596)$ has a slope of 0.0138, which implies that the number of biological drugs is increasing by 1.38% per year. Thus, in just 10 years, an increase in the share of biological drugs by approximately 13% can be expected. The results reflect the transition of the pharmaceutical industry to the complexification of both the drugs themselves and the methods of treatment: from small molecules to antibodies, enzyme preparations and gene therapy.

Reasons for registering developments

Figure 16 shows a diagram of the accumulation of registrations from 2013 to 2024. The largest number of registrations for the specified period occurred in 2017. It can be noted that the increase in registrations is justified by a large number of re-registrations, and the number of original drugs is no more than in 2018 and 2019. The largest number of original drugs was registered in 2021, although the absolute number of registrations in this year is quite small.

As can be seen from the presented data and in Figure 17, the registration of an original drug (the US market is traditionally focused on original drugs) is the main reason for FDA approvals [28]. In 2015, the share of new combinations in the registration structure reached its peak in the covered period and amounted to 19.4% and has been declining since then. The registration of new dosage forms accounted for a quarter of all new registrations in the period from 2016 to 2018, after which this value gradually decreased, and in 2024 the share of new combinations in the structure of drug registration is 13.9%. It is important to note the albeit small, but clearly growing in recent years share of known drugs that have received a new indication. Repurposing drugs for new indications, as has been repeatedly noted, remains a promising tactic for pharmaceutical development [87–90].

Limitations of the study

The study has several important limitations that may affect the interpretation and generalization of the results.

Limited by FDA data. The study is based on FDA data covering drug approvals issued primarily for the US market. This means that the study does not take into account approvals by other regulatory authorities (e.g., EMA in Europe, PMDA in Japan, and TGA in Australia).

Difficulties in classifying drugs. Systematization of approvals by categories, for example, by novelty or method of production (biological, synthetic drugs), is sometimes difficult due to the overlap of categories, such as biosimilars, generics and hybrid drugs with partially unique properties. These classification difficulties can lead to errors in statistics and reduce the accuracy of the analysis of individual categories.

Changing regulatory conditions. During the period under review, FDA policies and approval criteria changed, including accelerated approval programs for orphan drugs, cancer drugs, and drugs for serious diseases with high unmet demand. Such changes could affect the dynamics of approvals and create difficulties in assessing long-term trends without taking into account changes in regulation.

Impact of the COVID-19 pandemic. The COVID-19 pandemic in 2020–2022 influenced the priorities of drug development and the process of their approval, including the creation of accelerated procedures for antiviral drugs and vaccines, which could potentially slow down or postpone the approval of other therapeutic agents that were not related to the pandemic, making this time period less representative when analyzing the entire observation period (from 2013 to 2024).

Observation period. Despite the fact that the ten-year period covers a significant number of approvals, for some innovative therapies, such as gene and cell technologies. This time may not be sufficient for a complete analysis of their potential and long-

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term effects. Such new approaches require longer observations to accurately assess their impact on clinical practice and public health.

Lack of data on failed drugs. The study focuses on approved drugs and does not take into account drugs that have not passed clinical trials or have not been approved. This "survivorship bias" can distort the perception of successful drug development strategies.

Limited availability of post-registration data. The work does not assess the safety profile of new drugs, including side effects and risks. The study does not consider post-marketing studies or long-term safety profiles of approved drugs, including information on rare side effects, effectiveness in different populations and the duration of the clinical effect.

CONCLUSION

The analysis of FDA drug approvals from 2013 to 2024 revealed consistent trends and key directions in modern drug development. During this period, there has been a steady approval of small molecule drugs and an increase in the proportion of innovative approaches aimed at addressing complex therapeutic challenges or treating previously incurable pathologies, including oncological, neurological, orphan, and metabolic diseases. Progress in the development of biotechnological methods, such as monoclonal antibodies, gene therapy, and RNA interference therapy, indicates a significant shift towards personalized and targeted approaches aimed not only at eliminating symptoms but also at altering the pathogenesis of the disease.

Thus, the use of monoclonal antibodies for the treatment of cancer and inflammatory diseases demonstrates their high therapeutic value, contributing to improved survival and quality of life for patients. For example, drugs aimed at blocking immune checkpoints (PD-1, PD-L1 inhibitors) have become the basis of therapy for patients with aggressive forms of oncological diseases, which indicates the continued relevance of these areas in research.

There is a persistent interest in drugs for the treatment of oncological, metabolic, and inflammatory diseases, i.e., those diseases whose prevalence is comparable to the scale of epidemics.

Notably, despite the COVID-19 pandemic, which significantly stimulated rapid vaccine development, the FDA approved a limited number of antiviral drugs specifically designed for COVID-19.

The analysis also highlights a relatively stable level of generic approvals, while the improvement of dosage forms and combinations of existing molecules were a priority for meeting the specific needs of patients.

In addition, the growing influence of biotechnology startups on the drug development process, along with large investments from venture capital, suggests a paradigm shift in drug development from traditional synthetic compounds to more advanced (in certain respects; selectivity and safety) biological solutions. Synthetic drugs for the treatment of infections of all kinds also demonstrate a trend towards increased research, development, and implementation.

Thus, the conclusion on the trends and results of FDA approvals over more than a decade emphasizes a high orientation towards biotechnological methods, personalized medicine, treatment of oncological and orphan diseases, which is confirmed not only by the stability of approvals in these categories but also by constant improvements in their effectiveness and specificity. These trends define promising directions for future research and development, making it possible to further expand the capabilities of modern medicine in addressing complex, severe, and rare diseases that until recently were considered difficult to treat or incurable. At the same time, the high cost of many new treatments remains a major problem, as well as the lack of data on their effectiveness and safety with long-term use.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Denis V. Kurkin — idea and planning of the work, design of graphic material, editing of the final version of the manuscript; Nazar A. Osadchenko, Dmitry A. Bakulin, Evgeny I. Morkovin, Sergey A. Voskresensky,

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ОРИГИНАЛЬНАЯ СТАТЬЯ

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Impact of CYP3A4*22 Genetic Variant and Plasma microRNA mir-27b Expression Level on Silodosin Steady-State Concentration and Therapy Outcomes in Patients with Benign Prostatic Hyperplasia: A Prospective Observational Trial

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Despite the proven efficacy of silodosin for lower urinary tract symptoms (LUTSs), significant interindividual variability in response to pharmacotherapy and the development of adverse events persists. Potential factors for this variability include pharmacogenetic and epigenetic mechanisms regulating drug metabolism.

The aim. To investigate the impact of CYP3A4*22 polymorphism and circulating microRNA miR-27b level on the pharmacokinetics, efficacy, and safety of silodosin in patients with benign prostatic hyperplasia (BPH).

Materials and methods. The study included 98 patients with LUTS due to BPH who were prescribed silodosin 8 mg/day for 8 weeks. IPSS and QoL dynamics, and the frequency of adverse events were assessed. The steady-state minimum concentration of silodosin (Css) was determined by HPLC-MS/MS. Genotyping for CYP3A4*22 was performed by real-time PCR. The expression level of plasma miR-27b was determined using RT-qPCR.

Results. Patients with the CT genotype (12.2%) had significantly higher Css values compared to carriers of the CC genotype (13.44 [6.35; 16.6] *vs* 6.15 [3.10; 11.31] ng/mL; $p = 0.005717$). Despite this, the reduction in symptom severity according to IPSS and improvement in QoL were comparable in both groups ($p > 0.05$). No correlation was found between Css and IPSS dynamics ($rs = -0.115554$, $p = 0.257195$). MiR-27b levels did not differ between genotypes and did not correlate with either Css or clinical outcomes. The structure of adverse events corresponded to the established safety profile of silodosin; no statistically significant differences were found between genotypic groups.

Conclusion. Carrying the CYP3A4*22 polymorphism is associated with increased silodosin exposure, but the clinical efficacy of therapy remains independent of this genetic marker. Data on the role of miR-27b in regulating pharmacokinetics and clinical outcomes in this population were not confirmed.

Keywords: silodosin; CYP3A4*22; pharmacogenetics; microRNA; miR-27b; benign prostatic hyperplasia

Abbreviations: BPH — benign prostatic hyperplasia; LUTSs — lower urinary tract symptoms; HPLC-MS/MS — high-performance liquid chromatography with tandem mass spectrometry; PCR — polymerase chain reaction; PVR — post-void residual volume; PV — prostate volume; US — ultrasound; AEs — adverse events; ICF — informed consent form; Css — minimum steady-state drug concentration in blood plasma; CYP3A4 — cytochrome P450 3A4; IPSS — International Prostate Symptom Score; QoL — Quality of Life Scale; Qmax — maximum urinary flow rate; RT-qPCR — Reverse Transcription Quantitative PCR; ADME — Absorption, Distribution, Metabolism, Excretion; P-gp (ABCB1) — P-glycoprotein.

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Влияние генетического варианта CYP3A4*22 и уровня экспрессии плазменной микроРНК miR-27b на равновесную концентрацию силодозина и результаты терапии у пациентов с доброкачественной гиперплазией предстательной железы: проспективное обсервационное исследование

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Несмотря на доказанную эффективность силодозина при симптомах нижних мочевых путей (СНМП), сохраняется значительная межиндивидуальная вариабельность ответа на фармакотерапию и развитие нежелательных явлений. Потенциальными факторами такой вариабельности являются фармакогенетические и эпигенетические механизмы регуляции метаболизма препарата.

Цель. Оценить влияние полиморфизма CYP3A4*22 и уровня циркулирующей микроРНК miR-27b на фармакокинетику, эффективность и безопасность силодозина у пациентов с доброкачественной гиперплазией предстательной железы (ДГПЖ).

Материалы и методы. В исследование включено 98 пациентов с СНМП при ДГПЖ, которым назначался силодозин 8 мг/сут в течение 8 недель. Оценивались динамика IPSS и QoL, частота нежелательных явлений. Равновесная минимальная концентрация силодозина (Css) определялась методом ВЭЖХ-МС/МС. Генотипирование по CYP3A4*22 проводили методом ПЦР в реальном времени. Уровень экспрессии плазменной miR-27b определяли с помощью RT-qPCR.

Результаты. Пациенты с генотипом CT (12,2%) имели достоверно более высокие значения Css по сравнению с носителями генотипа CC (13,44 [6,35; 16,6] против 6,15 [3,10; 11,31] нг/мл; p=0,005717). Несмотря на это, снижение выраженности симптомов по IPSS и улучшение QoL были сопоставимыми в обеих группах (p >0,05). Корреляции между Css и динамикой IPSS выявлено не было (rs=-0,115554, p=0,257195). Уровни miR-27b не различались между генотипами и не коррелировали ни с Css, ни с клиническими исходами. Структура нежелательных явлений соответствовала установленному профилю безопасности силодозина; статистически значимых различий между генотипическими группами не установлено.

Заключение. Носительство полиморфизма CYP3A4*22 ассоциируется с повышенной экспозицией силодозина, однако клиническая эффективность терапии остаётся независимой от указанного генетического маркёра. Данные о роли miR-27b в регуляции фармакокинетики и клинических исходов в данной популяции не подтвердились.

Ключевые слова: силодозин; CYP3A4*22; фармакогенетика; микроРНК; miR-27b; доброкачественная гиперплазия предстательной железы

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Список сокращений: ДГПЖ — доброкачественная гиперплазия предстательной железы; СНМП — симптомы нижних мочевых путей; ВЭЖХ-МС/МС — высокоэффективная жидкостная хроматография с тандемной масс-спектрометрией; ПЦР — полимеразная цепная реакция; ООМ — объём остаточной мочи; ОП — объём простаты; УЗИ — ультразвуковое исследование; НЯ — нежелательные явления; ИДС — информированное добровольное согласие; Css min — минимальная равновесная концентрация препарата в плазме крови; CYP3A4 — цитохром P450 3A4; IPSS — Международная шкала оценки простатических симптомов; QoL — шкала оценки качества жизни; Qmax — максимальная скорость потока мочи; RT-qPCR — полимеразная цепная реакция в реальном времени с обратной транскрипцией; ADME — всасывание, распределение, метаболизм и выведение; P-gp (ABCB1) — P-гликопротеин.

INTRODUCTION

Benign prostatic hyperplasia (BPH) refers to the benign growth or hyperplasia of prostate tissue and is histologically defined by an increase in glandular epithelial tissue, smooth muscle, and connective tissue in the transition zone of the prostate [1, 2]. A meta-analysis including data from 25 countries showed that the lifetime prevalence of BPH is 26.2% (95% confidence interval [CI]: 22.8–29.6%) [3]. Forecasts indicate a global increase in the incidence and prevalence of BPH from approximately 962 and 7879 cases per 100,000 people in 2022 to approximately 999 and 8621 cases by 2035 [4]. According to data from the US Medicare program for 2019, annual global healthcare costs associated with BPH are estimated at approximately US$73.8 billion per year, based on US spending trends [5].

Modern pharmacotherapy for BPH includes several classes of drugs: 5α-reductase inhibitors, which affect prostate volume, and α1-blockers, which rapidly improve urodynamics by relaxing the smooth muscles of the prostate, bladder neck, and prostatic urethra. Among α1-blockers, silodosin occupies a special place as a highly selective α1A-adrenoceptor antagonist, providing a marked reduction in obstructive and irritative symptoms with minimal effect on systemic blood pressure. Although α1-blockers are included in clinical guidelines for the treatment of patients with lower urinary tract symptoms (LUTS), the number of patients with therapy-resistant disease and patients with adverse side effects remains high [6, 7].

CYP3A group isozymes, characterized by exceptionally broad substrate specificity, catalyze the metabolism of more than half of the drugs used in clinical practice.

Among them, *CYP3A4* is the main hepatic isoform, characterized by high expression and broad substrate specificity [8, 9]. This enzyme catalyzes the oxidation of a large number of drugs, including those used in urological practice for the treatment of LUTS. The *CYP3A4* gene exhibits marked polymorphism, and some of its variants, such as CYP3A4*22 (rs35599367), are associated with reduced enzyme expression and activity, which can lead to slowed drug metabolism and an increased risk of dose-dependent adverse reactions [10, 11]. Thus, changes in the efficacy and safety profiles of silodosin may also depend on variations in the *CYP3A4* gene, which determines the pharmacodynamic (PD) and pharmacokinetic (PK) parameters of the drug.

CYP3A4 catalyzes the oxidation of silodosin. Drugs that are inhibitors of *CYP3A4* activity (e.g., ketoconazole) can affect the PK and PD of silodosin, increasing its plasma concentration[1].

Considering the key role of cytochrome P450 isozymes in the metabolism of α1-blockers, one cannot ignore modern concepts of the multilevel regulation of their activity. In addition to well-studied genetic polymorphisms, researchers are paying increasing attention to epigenetic regulation, in particular, the involvement of microRNAs in the control of the expression of cytochrome P450 system enzymes. Previous studies have assessed the correlation between miR-27b levels and *CYP3A* activity, measured by *N*-demethylation of dextromethorphan and 6β-hydroxylation of testosterone, as well as the expression of CYP3A4, *VDR*, and *PPAR*-α genes in 20 human liver samples. A significant relationship was found between circulating miR-27b levels and the 4β-hydroxycholesterol ratio (p = 0.04), as well as between liver miR-27b levels and CYP3A activity, measured by N-demethylation of dextromethorphan (p = 0.04) [12]. Individual differences in *CYP3A4* activity, due to genetic or epigenetic factors, may play a significant role in interindividual variability in the

[1] U.S. Food and Drug Administration. Rapaflo (Silodosin) label; 2013. Available from: https://www.accessdata. fda.gov/drugsatfda_docs/label/2013/022206s012lbl.pdf

pharmacokinetics, efficacy, and safety of therapy with silodosin.

THE AIM. To study the effect of the CYP3A4*22 (rs35599367, 15389 C>T) genetic polymorphism on the concentration, as well as on the efficacy and safety of silodosin. Data on the expression level of plasma miR-27b, hypothetically characterizing the expression of the *CYP3A4* metabolizing enzyme, were used.

MATERIALS AND METHODS

Study design

A prospective observational trial was conducted from December 11, 2023 to May 30, 2025. The study involved patients receiving outpatient treatment at the Department of Endoscopic Urology of the Russian Medical Academy of Continuous Professional Education. Before inclusion in the study, each patient signed an informed voluntary consent form (ICF).

The study involved 98 male patients with complaints of LUTS and a diagnosis of BPH. Patients were prescribed silodosin at a dose of 8 mg/day according to indications. Silodosin therapy was started from the time of the patient's visit, and observation continued for at least 8 weeks. Treatment was prescribed in accordance with the National Clinical Guidelines for the treatment of patients with BPH[2].

Eligibility criteria

Inclusion criteria: male gender; age over 18 years; signed ICF form; diagnosis of benign prostatic hyperplasia" (N40 according to ICD-10); complaints of moderately or severely expressed LUTS, assessed by the IPSS scale >7 points.

Exclusion criteria: complicated BPH; any other causes other than BPH that may, in the opinion of the researchers, lead to dysuria or changes in urinary flow rate (e.g., neurogenic bladder, bladder neck stricture, urethral stricture, acute or chronic prostatitis, acute or chronic urinary tract infections); concomitant oncological diseases; concomitant severe cardiovascular (e.g., unstable angina, recent myocardial infarction, or poorly controlled arterial hypertension) and cerebrovascular (recent stroke or spinal cord injuries) diseases; renal and hepatic insufficiency.

[2] Clinical Guidelines. Benign prostatic hyperplasia. Ministry of Health of the Russian Federation; 2024. Available from: https://cr.minzdrav.gov.ru/preview-cr/6_2. Russian

Assessment of the efficacy and safety of therapy

The efficacy of silodosin therapy was assessed using a complex of clinical (assessment of LUTS manifestation using the IPSS questionnaire) and instrumental (determination of maximum urinary flow rate (Qmax), determination of residual urine (PVR), and prostate volume (PV) according to US data) methods. IPSS assessment was performed on days 1, 14, 28, and 56 of treatment and observation. Instrumental assessment of the efficacy of therapy was performed on days 1 and 56 of silodosin treatment. The safety of therapy was assessed by recording the development of adverse events (AEs) during the entire period of patient observation.

Genotyping

On the day of inclusion in the study, each patient had 4 mL of blood drawn into disposable sterile vacuum tubes with EDTA for subsequent genotyping. The collection of biomaterial, which was carried out simultaneously with routine tests, did not require additional venipunctures. The biomaterial was frozen at -20°C, transported to the laboratory, and subsequently stored at -70°C.

Genotyping for the CYP3A4*22 (15389 C>T, rs35599367) allelic variant was performed using TaqMan® SNP Genotyping Assays and TaqMan Universal Master Mix II, without UNG (Applied Biosystems, Foster City, USA) reagent kits according to the manufacturer's instructions.

The carriage of polymorphic markers was determined by real-time polymerase chain reaction (PCR) on a Real-Time CFX96 Touch instrument (Bio-Rad Laboratories, Inc., USA).

Determination of silodosin plasma concentration

To determine the minimum steady-state residual concentration values of silodosin in blood plasma (Css), venous blood samples were collected 5 days after the start of silodosin administration. The concentration of the drug in plasma was determined by a combined HPLC-MS/MS method on an Agilent 1200 Liquid Chromatograph (Agilent Technologies Inc., USA, 2008) using a triple quadrupole mass spectrometric detector AgilentTripleQuad LC/MS 6410. An Agilent Polaris 3 C18-A column (50 mm × 3.0 mm, 3.0 µm) was used. Separation was performed at a column temperature of

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40°C in gradient elution mode by mixing mobile phase components: solution "A" (1 ml of concentrated formic acid was diluted with deionized water to a total volume of 1 L) and solution "B" (1 mL of concentrated formic acid was diluted with acetonitrile to a total volume of 1 L).

Sample preparation was performed by plasma protein precipitation. Plasma samples were thawed at room temperature. Then, 100 µL of plasma was transferred to Eppendorf plastic tubes, 250 µL of a mixture of methanol with 0.1% hydrochloric acid (in a ratio of 9:1) was added, mixed on a Vortex shaker (Elmi Ltd., Latvia) and left for 10 min. Then the samples were mixed again. The resulting samples were then centrifuged (CM-6MT, ELMI, Latvia) at 10,000 rpm for 10 min. The supernatant was transferred to chromatographic vials and placed on a chromatograph autosampler for subsequent analysis.

Silodosin spectra were recorded on an AgilentTripleQuad LC/MS 6410 mass spectrometric detector with positive electrospray ionization in multiple molecular reaction mode. Nebulizer gas pressure was 35 psi. The drying gas flow rate was 10 L/min, the ion source temperature was 350°C. The fragmentation voltage was 135 V, the collision cell voltage was 30 V. Under these conditions, the limit of quantification of silodosin was 1 ng/mL.

Data processing was performed using Agilent MassHunter Workstation Software LC/MS Data Acquisition for 6400 Series Triple Quadrupole (Version B.08.02).

Determination of plasma microRNA levels

Isolation of total RNA from blood plasma

To determine plasma microRNA levels, venous blood samples were collected in sterile tubes containing EDTA on day 5 of therapy. The closed blood tube was inverted several times to mix the blood with the anticoagulant. To obtain plasma, the tube was centrifuged (CM-6MT, ELMI, Latvia) for 10 min at 2000 g, after which the supernatant was transferred to sterile tubes with a volume of 2 or 1.5 mL and stored at -80°C until further use.

Then, 300 µL of plasma was lysed in 1 mL of Qiazol reagent, followed by the addition of 250 µL of chloroform. The solution was mixed thoroughly for 30 s, then incubated for 2–3 min at room temperature. After centrifugation at 12000 g for 15 min at 4°C, the upper aqueous phase was carefully removed and transferred to a tube with 0.5 mL of 100% isopropanol. The solution was mixed thoroughly by inverting the tube and frozen at -20°C for at least 1 h. After that, the tube was centrifuged at 12000 g for 10 min at 4°C. The precipitate remaining at the bottom of the tube after removal of the supernatant was washed with 1 ml of 75% ethanol, followed by centrifugation at 12000 g for 5 min at 4°C. The resulting precipitate was dissolved in 20 µL of RNase-free water, preheated to 60°C, and incubated for 5–10 min at 60°C. The concentration and purity of the obtained RNA were evaluated on a NanoDrop 2000 microvolume spectrophotometer (Thermo Fisher Scientific, New York, USA). The isolation process was repeated for each sample until sufficient RNA was obtained for the next steps. After mixing and precipitation, the samples were frozen at -20°C for short-term storage and at -80°C for long-term storage.

Quantitative assessment of microRNA expression levels by real-time PCR

Reverse transcription was performed using miRCURY LNA RT kit (Qiagen, Germany) and miRCURY LNA RNA Spike-in kit (Qiagen, Germany) according to the recommended protocol with modifications. To obtain DNA, 150 ng of total RNA isolated from each sample was used, which was added to the reaction mixture (4 µL 5× miRCURY RT Reaction Buffer, 1 µl 10x miRCURY RT Enzyme Mix, 2 µL of matrix for exogenous control cel-miR-39-3p and RNase-free water to 20 µl) and incubated for 60 min at 42°C, followed by increasing the temperature to 95°C for 5 min to inactivate the transcriptase. Real-time PCR was performed in 3 replicates for each analyzed microRNA, as well as exogenous control cel-miR-39-3p, using miRCURY LNA SYBR Green PCR kit (Qiagen), presynthesized primer miRCURY LNA miRNA Probe PCR Assay (Qiagen) for control and primers selected in the laboratory for the analyzed microRNAs (sequences are listed in Table 1) in a reaction mixture volume of 13 µl (3 µl of the obtained cDNA, 5 µL 2x miRCURY SYBR Green Master Mix, 1 µL 10x miRCURY LNA miRNA Probe PCR Assay to the studied microRNAs and RNase-free water to 13 µL). Real-time PCR was performed on a CFX96 Real-Time PCR Detection System (Bio-

Rad, Hercules, USA) according to the manufacturer's recommended program (2 min at 95°C and 40 two-step cycles [95°C — 10 s, 56°C — 60 s]). MicroRNA expression was normalized to the exogenous control cel-miR-39-3p and calculated using the 2-ΔΔCt method. For miR-27b-3p, the following primer sequence was used — 5'-TTCACAGTGGCTAAGTTCTGCA-3'.

Ethics approval

The study was approved by the meeting of the Local Ethics Committee of the Russian Medical Academy of Continuous Professional Education (Protocol No. 16 dated December 04, 2023).

Statistical analysis

Statistical analysis was performed using Statsoft Statistica 12.0 (Dell Statistica, Tulsa, OK, USA). Results of the study were performed using non-parametric statistics due to the absence of normal data distribution, which was checked using the Shapiro-Wilk W-test.

The Mann-Whitney *U*-test was used to compare two samples of continuous independent data, and the Wilcoxon test was used to compare two dependent samples. In the case of multiple comparisons, we calculated adjusted *p*-values using the Benjamini-Hochberg procedure. The study data are presented as median and interquartile range (Me [Q1; Q3]).

Pearson's Chi2 test was used to analyze the distribution of alleles in the sample (assessment of Hardy-Weinberg equilibrium). Correlation analysis was performed using the non-parametric Spearman test, taking into account the non-normal of the sample distribution.

The significance of the identified differences and correlations in all types of analysis was considered at the level of $p < 0.05$.

RESULTS

Baseline characteristics of patients

The study included 98 male patients with BPH and LUTS (median age — 70 [64.74; 75.50], BMI — 26.79 [25.18; 29.38] kg/m^2). Most patients had cardiovascular pathology: hypertension — 60 (61.2%), coronary heart disease — 20 (20.4%), type 2 diabetes mellitus — 3 (3.1%) and urological diseases (23.8%). More detailed clinical and demographic data are presented in Table 1.

Patients were pro-genotyped for the CYP3A4*22 allelic variant (c.522-191C>T, rs35599367): the number of patients with the CC genotype was 86 (87.75 %); with the CT genotype — 12 (12.25%); with the TT genotype — not established.

The distribution of genotypes corresponded to the Hardy-Weinberg equilibrium (χ^2=0.417, p = 0.812).

Main study results

The results of the analysis of data obtained in assessing the effectiveness of LUTS therapy in BPH according to IPSS and assessing the quality of life according to the QoL scale at 1, 2, 4 and 8 weeks of follow-up in patients receiving silodosin are presented in Table 2.

The dynamics of changes in IPSS scores in patients with different genotypes is shown in Figure 1. At visit 1, statistically significant differences were revealed in the groups of patients with different genotypes: for patients with the CC genotype, IPSS was higher 18 [14.0; 25.0] *vs* 11.0 [9.0; 15.0] for the CT group (p = 0.000112). By the second and fourth week, statistically significant differences between the groups persisted — $p < 0.0001$. At the last 8th week of the study, statistically significant differences also persisted: genotype CC — 13.5 [10.0; 17.0], CT —5.0 [3.0; 7.0] (p = 0.000035). The QoL quality of life assessment scale showed the same dynamics of changes in scores as the IPSS scale (Figs. 1A and 1B).

It is worth noting that the overall dynamics of changes in IPSS (d IPSS1-4) and QoL (d QoL1-4) between the groups throughout the 8-week observation period did not differ: for CC — -6.0 [-8.0; -5.0] *vs* -7.0 [-9.5; -2.5] for CT (p = 0.952101) for IPSS; for CC — -2.0 [-3.0; -1.0] *vs* -2.0 [-2.5; -1.0] for CT (p = 0.425932; Figs. 1C and 1D).

Table 3 summarizes the data on the results of determining Css silodosin. A statistically significant difference was found in patients with different genotypes: Css was higher in patients with CT — 13.44 [6.35; 16.6] *vs* 6.15 [3.10; 11.31] ng/mL with CC (p = 0.005717; Fig. 2A). Spearman correlation analysis did not reveal a statistically significant correlation between the Css silodosin index and the magnitude of the overall change in IPSS between the first and last visit (d IPSS1-4) — rs = -0.115554, p = 0.257195 (Fig. 2B, Table 3).

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Table 1 — Clinical and demographic characteristics of patients

Indicators	Total patient cohort (*n*=98)
Age, Me [Q1; Q3], years	70 [64,74; 75,50]
BMI, Me [Q1; Q3], kg/m^2	26,79 [25,18; 29,38]
Smoking, *n*	23
Alcohol, *n*	16
Laboratory parameters at the time of inclusion in the study	
Creatinine, Me [Q1; Q3], mmol/L	91.0 [81.5; 102.0]
Urea, Me [Q1; Q3], mmol/L	5.5 [4.6; 6.5]
Relative density, Me [Q1; Q3], g/L	1019.5 [1015.0; 1025.75]
pH, Me [Q1; Q3],	6.0 [5.5; 6.0]
Hemoglobin, Me [Q1; Q3], g/L	148.5 [145.0; 158.0]
Erythrocytes, Me [Q1; Q3], 10^9/L	4.83 [4.71; 5.01]
Leukocytes, Me [Q1; Q3], 10^9/L	6.30 [5.77; 7.25]
Platelets, Me [Q1; Q3], 10^9/L	235.0 [190.0; 269.75]
Erythrocyte sedimentation rate, Me [Q1; Q3], mm/hour	6.0 [4.0; 7.75]
Prostate-specific antigen, Me [Q1; Q3], ng/mL	1.94 [0.89; 3.34]
Concomitant diseases, *n* (%)	
Cardiovascular:	
hypertension	60 (61.2%)
ischemic heart disease	20 (20.4%)
dyslipidemia	18 (18.4%)
others	3 (3.1%)
Endocrine:	
type 2 diabetes mellitus	3 (3.1%)
Gastroenterological:	
pancreatitis	3 (3.1%)
Urological:	
urolithiasis	3 (3.1%)

Table 2 — Results of patient assessment on the IPSS and QoL scales at 1, 2, 4, and 8 weeks of follow-up

Indicator	Total cohort (*n*=98)	CC (*n*=86)	CT (*n*=12)	*p*-value
Visit 1 (at the time of inclusion)				
IPSS	11.5 [10.0; 15.0]	18 [14.0; 25.0]	11.0 [9.0; 15.0]	0.000112*
QoL	4 [4.0; 4.0]	4 [4.0; 4.0]	5.0 [4.0; 6.0]	0.003899*
Visit 2 (2 weeks)				
IPSS	9.0 [6.0; 11.0]	13.0 [10.5; 17.5]	8.5 [6.0; 10.0]	0.000215*
QoL	3.0 [3.0; 4.0]	3.0 [3.0; 3.0]	4.5 [3.0; 5.5]	0.001576*
Visit 3 (4 weeks)				
IPSS	7.0 [4.0; 13.0]	15.0 [10.5; 17.5]	6.0 [4.0; 10.0]	0.000046*
QoL	2.0 [2.0; 3.0]	2.0 [2.0; 3.0]	4.0 [2.5; 4.5]	0.002806*
Visit 4 (8 weeks)				
IPSS	6.0 [3.0; 12.00]	13.5 [10.0; 17.0]	5.0 [3.0; 7.0]	0.000035*
QoL	2.0 [1.0; 3.0]	2.0 [1.0; 3.0]	2.5 [2.0; 4.5]	0.016612*
Difference between Visits 1 and 4				
d $IPSS_{1-4}$	-6.0 [-9.0; -5.0]	-6.0 [-8.0; -5.0]	-7.0 [-9.5; -2.5]	0.952101
d QoL_{1-4}	-2 [-3.0; -1;0]	-2.0 [-3.0; -1.0]	-2.0 [-2.5; -1.0]	0.425932

Note: d IPSS1-4 — change in IPSS scores from baseline to day 56 of observation; d QoL1-4 — change in QoL quality of life scale scores from baseline to day 56 of observation; * — differences are statistically significant.

Table 3 — Steady-state concentration values of silodosin and assessment of plasma miR-27b expression levels in patients with different genotypes for the CYP3A4*22 polymorphic marker

Parameter	Total cohort (*n*=98)	CC (*n*=86)	CT (*n*=12)	*p*-value
Css, ng/mL	7.30 [3.20; 11.50]	6.15 [3.10; 11.31]	13.44 [6.35; 16.6]	0.005717*
ΔΔCt miR-27b	0.44 [0.12; 1.23]	0.47 [0.13; 1.23]	0.35 [0.087; 1.29]	0.815755

Note: * — differences are statistically significant.

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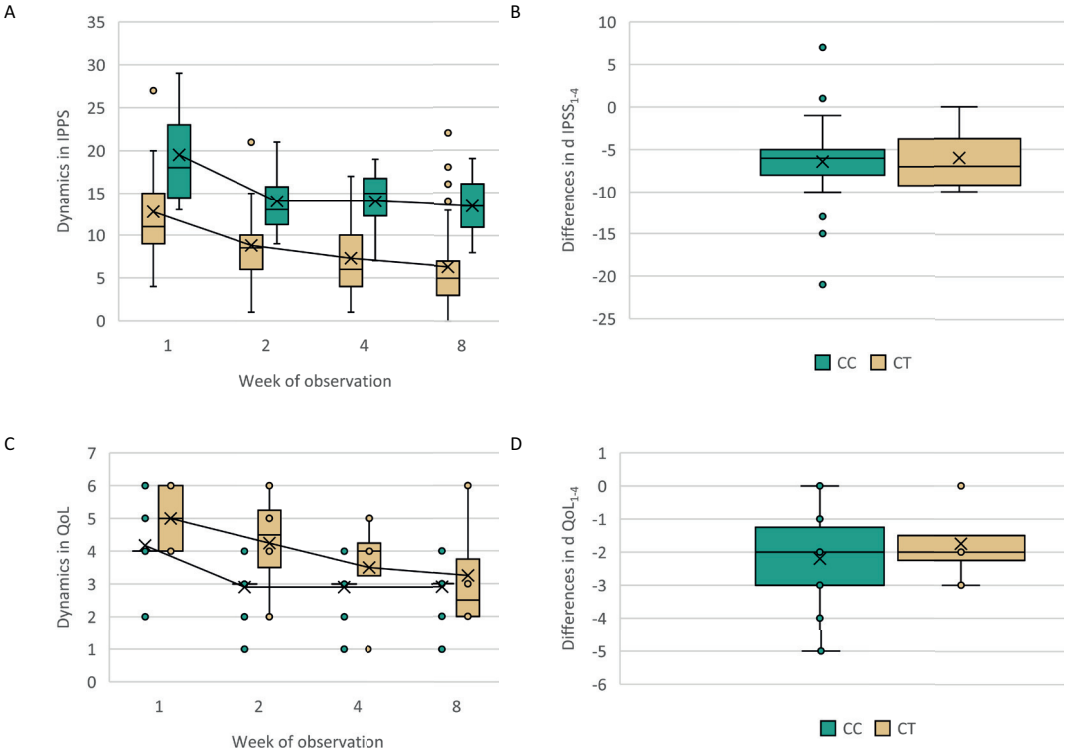

Figure 1 — Dynamics of changes in IPSS scores and QoL quality of life assessment in patients with different genotypes for the CYP3A4*22 polymorphic marker (rs35599367)

Note: A, B — data are presented as median and interquartile range — lines connect medians in different weeks of observation; C, D — differences in IPSS and QoL scores between the first and last day of observation.

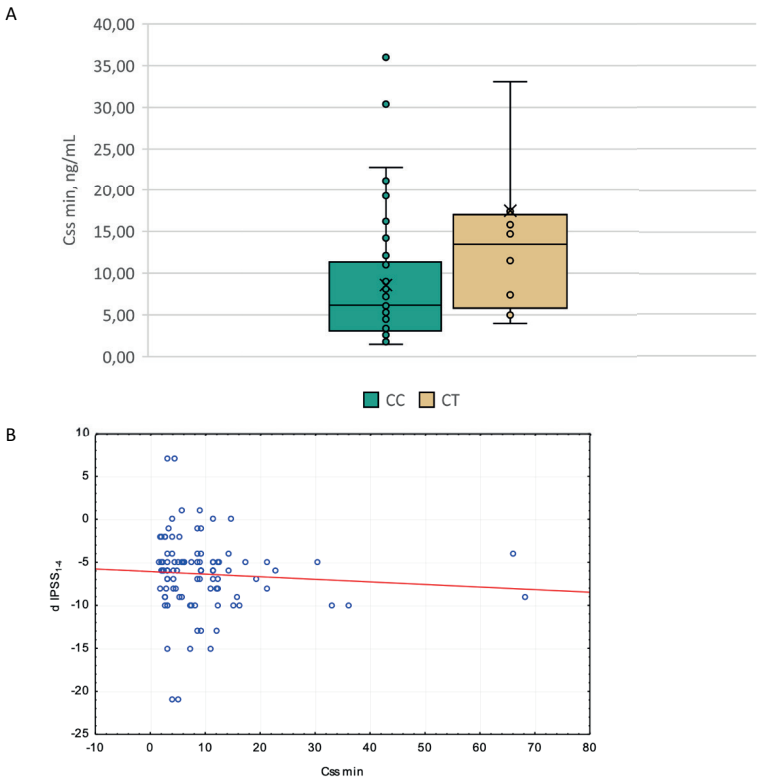

Figure 2 — Differences in Css silodosin values in patients with different genotypes for the CYP3A4*22 polymorphic marker.

Note: A — data are presented as median and interquartile range; B — relationship between Css silodosin value and d IPSS1-4 value in patients with lower urinary tract symptoms

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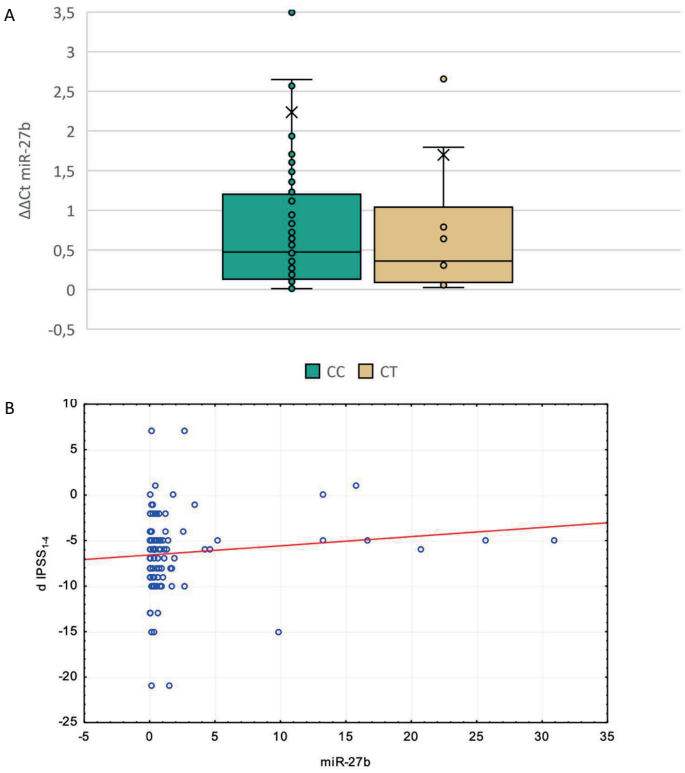

Figure 3 — Differences in Css silodosin values in patients with different genotypes for the CYP3A4*22 polymorphic marker.

Note: A — data are presented as median and interquartile range; B — relationship between ΔΔCt miR-27b value and d IPSS1-4 value in patients with lower urinary tract symptoms.

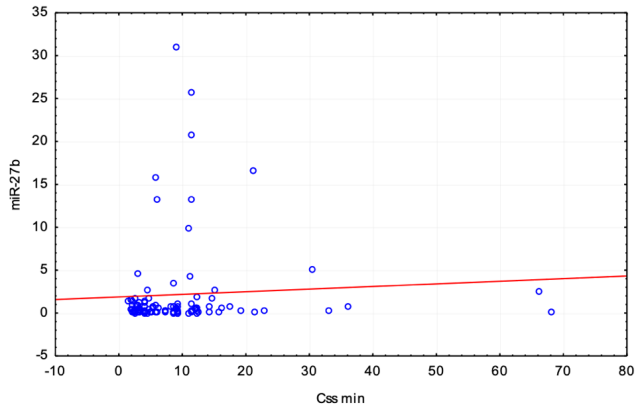

Figure 4 — Relationship between Css silodosin value and ΔΔCt miR-27b value in patients with lower urinary tract symptoms.

Table 4 – Frequency of adverse events in the study group, *n* (%)

Adverse events	Total cohort (*n*=98)	CC (*n*=86)	CT (*n*=12)
Retrograde ejaculation	6 (14.63)	6 (17.14)	0
Orthostatic hypotension	8 (19.51)	5 (14.29)	3 (50)
Hypertension	3 (7.32)	3 (8.57)	0
Dizziness	6 (14.63)	6 (17.14)	0
Headaches	3 (7.32)	0 (0)	3 (50)
Rhinitis	12 (29.27)	12 (34.29)	0
Back pain	3 (7.32)	3 (8.57)	0
Total	41 (100)	35 (100)	6 (100)

Analysis of the results of the pharmacotranscriptomics did not reveal a statistically significant difference in miR-27b levels in blood plasma in patients with different genotypes (Fig. 3A): CC — 0.47 [0.13; 1.23] *vs* CT — 0.35 [0.087; 1.29] (p = 0.815755). Correlation analysis revealed no associations between miR-27b concentration and the magnitude of the total change in d IPSS1-4 — rs = 0.055974, p = 0.584080 (Fig. 3B, Table 3).

The study found no correlation between microRNA concentration and the equilibrium concentration of silodosin — rs = 0.119251, p = 0.242178.

Safety assessment

During the study, 41 cases of adverse events (AEs) were noted in patients (Table 4). The most common were rhinitis — 12 (29.27%), orthostatic hypotension — 8 (19.51%), retrograde ejaculation — 6 (14.63%), and dizziness — 6 (14.63%). Less commonly, headaches were noted — 3 (7.32%), back pain — 3 (7.32%), and hypertension — 3 (7.32%). Due to the small number of events in the subgroups, no statistically significant differences were obtained, and the calculation of relative risks was not performed.

DISCUSSION

The results of the study revealed a statistically significant difference between the equilibrium concentration values of silodosin in patients with different CYP3A4*22 genotypes — in patients with the C allele, the equilibrium concentration of the drug was lower than in patients with the T allele (p = 0.005717). Apparently, this is due to the reduced rate of biotransformation and elimination of silodosin in patients with the T allele, which, in turn, leads to the accumulation of the drug in the blood plasma. This may lead to an increased risk of adverse reactions.

Statistical analysis of data on the clinical efficacy profile of silodosin in patients with different CYP3A4*22 genotypes revealed that already at visit 1, patients with the CC genotype had more pronounced symptoms compared to CT carriers (IPSS: 18 *vs* 11 points; $p < 0.001$). This difference persisted at 2, 4, and 8 weeks of follow-up. At the same time, the decrease in symptoms in both groups was comparable (delta IPSS: -6.0 *vs* -7.0 points; p = 0.952101), which indicates the same relative effectiveness of therapy regardless of genotype. This result may indicate that the clinical effect of silodosin is found out in a wide therapeutic range of concentrations and does not directly depend on carrying the CYP3A4*22 polymorphism.

Analyzing the relationship between the efficacy profile (dynamics of changes in dIPSS1-4 indicators) and the equilibrium minimum concentration of silodosin (Css), we did not reveal a statistically significant correlation (rs = -0.115554, p = 0.257195). This indicates that the clinical efficacy of the drug does not directly depend on its plasma levels. At the same time, the result is consistent with the data obtained for other α1-adrenoblockers, such as, for example, tamsulosin and doxazosin, for which it was also shown that the severity of the clinical response is determined by the characteristics of interaction with α1A-adrenoreceptors, the characteristics of distribution/binding in the prostate tissue, and the individual sensitivity of the patient's receptor apparatus [13–15]. This lack of a direct "concentration-effect" relationship can be explained by the onset of a therapeutic "plateau" — when the therapeutic effect of the drug is achieved even with a relatively low exposure in some patients, and a further increase in exposure is not accompanied by an increase in the symptomatic effect, but may increase the risk of adverse events [7, 13]. In addition, in the pathogenesis of lower urinary tract symptoms in BPH, not only functional disorders associated with smooth muscle tone play a significant role, but also structural changes in the prostate and bladder [16, 17], which also reduces the significance of using only PK indicators.

In our cohort, circulating levels of miR-27b did not differ between CYP3A4*22 genotypic groups (CC *vs* CT) and did not correlate with either clinical dynamics on IPSS (dIPSS1-4) or silodosin exposure (Css). This negative result may reflect several factors at once. Firstly, the association of miR-27b with CYP3A4 activity/expression, demonstrated earlier (association with 4β-hydroxycholesterol in vivo and with hepatic CYP3A activity in biopsy samples), has a moderate effect size and manifests itself under direct assessment of hepatic expression (tissue specificity, through concomitant regulatory axes — *VDR / PPAR*α) [12]. Whereas the circulating level of miR-27b may reflect the combined effect of many biological processes not always directly related to the activity of the enzyme in the liver, therefore it is not necessarily reproduced at the level of circulating microRNA in clinical samples with a different profile of concomitant factors. It should be noted that for miR-27b there are studies confirming the existence of a relationship between *CYP3A4* activity (calculated through the ratio of 6-beta-hydroxycortisol

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to cortisol in urine) and the concentration of the drug (rs = -0.27, p = 0.006), metabolized through CYP3A4 (rs = 0.28, p = 0.003) [18]. Such data are presented inconsistently, and the results depend on the study design/cohort size [19]. Secondly, circulating microRNAs are biomarkers with high sensitivity to preanalytical and analytical variations (type of biomaterial and its processing, the effect of hemolysis, normalization strategy), which may reduce the identification of weak associations. The need for strict control and combined normalization (for example, spike-in cel-miR-39 together with endogenous references) is emphasized in modern methodological reviews [20, 21]. Thirdly, the PK of silodosin is determined not only by *CYP3A4*: the CYP3A4 enzyme plays a leading role in the oxidative metabolism of silodosin, but in addition to it, *CYP3A5*, *UGT2B7* conjugation, as well as ABCB1/P-gp transport and redox pathways through ALDH / ADH[3] [22] are involved in the ADME process. All these features can "blur" the expected contribution of *CYP3A4* and the relationship between a single regulator (miR-27b) and the exposure / clinical effect of the drug.

The structure of the identified AEs corresponded to the known safety profile of silodosin: the largest proportion was accounted for by symptoms from the sexual function (retrograde ejaculation) and ENT complaints (rhinitis), while hemodynamic AEs (orthostatic hypotension, dizziness) were less common. These observations reproduce the data of randomized studies, where silodosin consistently shows a high frequency of ejaculation disorders with a relatively low frequency of clinically significant hypotension, which is associated with high selectivity for α1A-adrenoreceptors [23–25]. At the level of subgroups by CYP3A4*22, our work noted heterogeneity in the distribution of individual AEs (a large proportion of orthostatic hypotension and headache in the CT subgroup), which may indirectly indicate the identified increased exposure to silodosin in carriers of the T allele. At the same time, the small number of events in the CT subgroup (n = 12) does not allow us to draw conclusions about the genetically determined risk of AEs.

[3] DrugBank. Silodosin (DB06207); 2025. Available from: https://go.drugbank.com/drugs/DB06207

Study limitations

This study has several limitations. Firstly, the sample size was limited, which, given the prevalence of CYP3A4*22 in the European population at the level of up to 5%, reduces the power and complicates the analysis of associations with the frequency of individual AEs. Secondly, the observational design and relatively short period of therapy (8 weeks) do not allow us to assess long-term outcomes and the long-term safety profile of silodosin. Thirdly, the assessment of miR-27b expression was carried out only in blood plasma. Finally, the influence of concomitant therapy and other clinical factors potentially modulating the exposure and effect of silodosin were not evaluated in this study.

CONCLUSION

Thus, this study demonstrated the effect of genetic polymorphism of the CYP3A4*22 gene on increasing the exposure of silodosin in patients with BPH, while the clinical efficacy of therapy in terms of IPSS and QoL dynamics remained comparable regardless of marker carriage. Circulating miR-27b levels did not demonstrate a relationship with either PK or clinical response, indicating the limited value of this biomarker in the population under consideration. Adverse events corresponded to the known safety profile of silodosin and did not depend on the CYP3A4*22 genotype. Further studies with expanded cohorts are needed to clarify the contribution of both genetic and epigenetic factors to the variability of response to therapy.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Shokhrukh P. Abdullaev — investigation, systematization of literature data, writing and editing a draft of the manuscript; Irina V. Bure — investigation, writing—review & editing; Maksim N. Shatokhin — writing—review & editing; Sherzod P. Abdullaev — formal analysis, validation, writing—review & editing;

Pavel O. Bochkov — investigation, formal analysis; Svetlana N. Tuchkova — investigation, formal analysis; Karin B. Mirzaev — conceptualization, writing—review & editing; Oleg B. Loran — writing—review & editing; Dmitry A. Sychev — conceptualization, writing—review & editing. All authors confirm that their authorship meets the international ICMJE criteria (all authors have made significant contributions to the development of the concept, research and preparation of the article, read and approved the final version before publication).

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Synthesis and multimodal activity of 3a,6-epoxyisoindole-2(3*H*)-(carbox/thio/seleno)amides in models of glycation, oxidative stress, and inflammation: Toward the development of agents targeting the triggering mechanisms of fibrogenesis

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The aim. Within a series of 3a,6-epoxyisoindole-2*(3H)*-(carbox/thio/seleno)amides, we sought to identify a multimodal scaffold suitable for the further development of agents to prevent and treat fibrotic diseases by assessing of compound's ability to mitigate glycation and oxidative stress, key triggers of fibrogenesis; to select a non-cytotoxic lead with a balanced combination of these two activities, and to preliminarily evaluate its anti-inflammatory potential.

Materials and methods. Target 3a,6-epoxyisoindole-2(*3H*)-(carbox/thio/seleno)amides were synthesised using the IMDAF approach. Antiglycation activity was evaluated in a bovine serum albumin-glucose model by registering advanced glycation end-product (AGE) fluorescence. Antioxidant properties were determined using the ABTS assay. Cytotoxicity and anti-inflammatory effects were studied in peritoneal macrophages from adult wild-type white mice (n = 4; body mass 30–35 g). Cytotoxicity was assessed by the MTT assay and lactate dehydrogenase (LDH) release, while anti-inflammatory effects were evaluated in a model of LPS-induced nitric oxide (NO) production.

Results. The study delineates promising directions for modifying the epoxyisoindole scaffold for drug discovery and proposes a screening framework for agents targeting pathologies dependent on non-enzymatic damaging mechanisms (glycation, oxidation), including fibrotic diseases. Active molecules were identified among derivatives of hydrogenated 3a,6-epoxyisoindole. Compound **2.10** — 7a-chloro-*N*-(4-chlorophenyl)-1,6,7,7a-tetrahydro-3a,6-epoxyisoindole-2(*3H*)-carbothioamide — exhibited an optimal balance of antiglycation (at 100 μM, inhibition of glycation 40.1 ± 1.7%) and antioxidant activity (at 111 μM, reduction in ABTS•+ colour intensity 57.1 ± 1.1%) with low cytotoxicity (apparent from ≥ 250 μM). By contrast, compounds **2.16**–**2.19** (bearing an aroyl fragment) showed exceptionally high antioxidant activity (95.0–96.5% reduction in ABTS•+ colour intensity) without concordant antiglycation effects (inhibition not exceeding 15%). In the model used, anti-inflammatory activity of **2.10** was not detected.

Conclusion. Compound **2.10** is a promising starting point for further structural optimisation toward agents acting on early pathogenetic events driven by non-enzymatic damaging triggers, including the prevention and treatment of fibrotic remodelling.

Keywords: epoxyisoindole; antiglycation; antioxidant activity; inflammation; fibrosis; macrophages

Abbreviations: ABTS — 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); DMEM — Dulbecco's Modified Eagle Medium; IMDAF — IntraMolecular Diels-Alder Furan reaction; BSA — bovine serum albumin; DMSO — dimethyl sulfoxide; AGE — advanced glycation end products; LDH — lactate dehydrogenase; LPS — lipopolysaccharide; NAD+ — nicotinamide adenine dinucleotide (oxidized form of the molecule); NADH — nicotinamide adenine dinucleotide (reduced form of the molecule); PMs — peritoneal macrophages; TLC — thin-layer chromatography; NMR — nuclear magnetic resonance.

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Синтез и мультимодальная активность 3а,6-эпоксиизоиндоло-2(3*H*)-(карбокс/тио/селен)амидов в моделях реакции гликирования, окислительного стресса и воспаления, ориентация на разработку средств, воздействующих на триггерные механизмы фиброзирования

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Цель. В ряду 3а,6-эпоксиизоиндол-2(3*H*)-(карбокс/тио/селен)амидов выявить мультимодальный скаффолд, пригодный в качестве основы для дальнейшей разработки средств профилактики и терапии фиброзных заболеваний; оценить антигликирующую и антиоксидантную активность ряда соединений, отобрать нецитотоксичное соединение-лидер со сбалансированным сочетанием двух активностей и предварительно проверить его противовоспалительное действие.

Материалы и методы. Целевые 3а,6-эпоксиизоиндол-2(3*H*)-(карбокс/тио/селен)амиды синтезированы с использованием IMDAF-реакции. Антигликирующую активность оценивали в модели гликирования альбумина глюкозой, регистрируя флуоресценцию конечных продуктов гликирования (КПГ). Антиоксидантные свойства определяли с применением ABTS. Цитотоксическое и противовоспалительное действие изучали на перитонеальных макрофагах белых половозрелых мышей дикого типа (*n*=4, масса 30–35 г). Цитотоксичность оценивали с использованием МТТ-теста и по высвобождению лактатдегидрогеназы (ЛДГ), противовоспалительный эффект — в модели ЛПС-индуцированной продукции оксида азота (NO).

Результаты. В результате работы показаны перспективные направления модификации эпоксиизоиндольного скаффолда для разработки новых лекарственных препаратов; предложена система поиска средств для профилактики и лечения патологий, зависимых от пусковых механизмов повреждения гликированием и окислительным стрессом, в том числе фиброзных болезней. Идентифицированы активные молекулы (производные гидрированного 3а,6-эпокиизоиндола). Соединение **2.10**, а именно 7а-хлор-*N*-(4-хлорфенил)-1,6,7,7а-тетрагидро-3а,6-эпокиизоиндол-2(3*H*)-карботиоамид, продемонстрировало оптимальное сочетание антигликирующей (в концентрации 100 мкМ ингибирование реакции гликирования на 40,1±1,7%) и антиоксидантной активности (в концентрации 111 мкМ снижение интенсивности окраски ABTS•+ на 57,1±1,1%) при низкой цитотоксичности (проявляется в концентрациях ≥250 мкМ), тогда как **2.16–2.19** (содержат структурный N-ароильный фрагмент) отличались исключительно высокой антиоксидантной активностью (снижение интенсивности окраски ABTS•+ на 95,0–96,5%) без согласования таковой с антигликирующим действием (для лучшего соединения не достигает 15% ингибирования реакции гликирования). Противовоспалительная активность **2.10** в использованной модели выявлена не была.

Заключение. Соединение **2.10** — перспективная основа для дальнейшей оптимизации структуры в направлении создания средств, ориентированных на ранние звенья патогенеза заболеваний, зависимых от механизмов повреждения гликированием и окислительным стрессом, в том числе для профилактики и лечения фиброзного ремоделирования.

Ключевые слова: эпоксиизоиндол; антигликирование; антиоксидантная активность; воспаление; фиброз; макрофаги

Список сокращений: ABTS — 2,2’-азино-бис(3-этилбензотиазолин-6-сульфоновая кислота); DMEM — модифицированная Дульбекко среда Игла; IMDAF — внутримолекулярная реакция Дильса-Альдера с участием фурана; БСА — бычий сывороточный альбумин; ДМСО — диметилсульфоксид; КПГ — конечные продукты гликирования; ЛДГ — лактатдегидрогеназа; ЛПС — липополисахарид; НАД+ — никотинамидадениндинуклеотид (окисленная форма молекулы); НАДН — никотинамидадениндинуклеотид (восстановленная форма молекулы); ПМ — перитонеальные макрофаги; ТСХ — тонкослойная хроматография; ЯМР — ядерный магнитный резонанс.

INTRODUCTION

At the heart of many difficult-to-treat, debilitating diseases lie the processes of pathological fibrotic remodeling of tissues [1]. One of the leading roles in the development of fibrosis is assigned to the persistent transition of fibroblasts into myofibroblasts [2], inflammation [3], changes in the expression of signaling molecules (for example, FGF23 in the heart, interleukins IL-6 and IL-11) [4–6], as well as an imbalance in the degradation and synthesis of extracellular matrix components [7]. At the same time, the above conditions, despite their high pathogenetic significance, are reactive, that is, capable of developing in response to the action of a triggering damaging mechanism [8–10]. Such triggering mechanisms include damage to molecules by factors such as glycation and oxidative stress [9, 10].

Focusing on fibrosis as a pathology that is difficult to treat, as well as the secondary nature of many significant pathogenetic mechanisms of fibrotic remodeling, it can be concluded that targeting the earliest triggering links in pathogenesis is a promising strategy in the prevention and treatment of the disease [11]. Moreover, acting on several mechanisms at once may have even greater success [12]. In general terms, an approach to the search for new antifibrotic compounds, based on assessing the effect of such compounds on both early, triggering, and later, secondary mechanisms of fibrotic remodeling, can serve as an effective strategy for finding new antifibrotic drugs.

THE AIM. To analyze and identify in the series of 3a,6-epoxyisoindole-2(3H)-(carbox/thio/seleno)amides a multimodal scaffold suitable as a basis for further development of means for the prevention and therapy of fibrotic diseases; to evaluate the antiglycation and antioxidant activity of a number of compounds, to select a non-cytotoxic lead compound with a balanced combination of two activities and to preliminarily test its anti-inflammatory potential.

MATERIALS AND METHODS

Synthesis of compounds

Series of compounds **1.1–1.12** and **2.1–2.19** for biological tests were synthesized using thermal intramolecular Diels-Alder reaction in the furan derivatives (IMDAF reaction), which is often used both for the directed production of alkaloids [13–16] and for studying the fundamental laws of organic reactions [17–19].

At the first stage, the corresponding *N*-allylfurfurylamines were obtained by reductive amination using one of two methods (Fig. 1), depending on the loading, as described in [20–23].

Method A (mass of the initial furfural is less than 5 g). An equimolar amount of allylamine (all commercially available reagents were provided by Thermo Scientific Chemicals) was added to a solution of furfural in dichloromethane, after which the reaction mixtures were stirred at room temperature in the presence of MS 3Å molecular sieves for 24 hours (TLC control). After removing the solvent, the resulting oils were dissolved without further purification in methanol (with the addition of tetrahydrofuran in case of incomplete dissolution), and a two-fold molar excess of sodium borohydride was added at room temperature with constant stirring. After incubation for 24 hours and standard workup, the secondary amines were isolated as pale yellow oils by column chromatography (SiO_2, eluent: hexane-ethyl acetate) with a yield of 40–50%.

Method B (mass of the initial furfural is more than 5 g). An equimolar amount of allylamine was added to a solution of furfural in benzene, after which the mixture was boiled with a Dean-Stark trap until the theoretical amount of water was separated. After evaporation of benzene, the resulting oils were dissolved without further purification in ethanol and reacted with sodium borohydride (2 eq) at boiling. After standard workup, the resulting oils were purified by fractionation under reduced pressure. The target amines were obtained as colorless or light yellow oils with yields of 45–50%.

The synthesis of epoxyisoindolecarbo(thio, seleno)amides **1.1–1.12** and **2.1–2.19** was carried out in benzene or toluene, as described in [24, 25] (Fig. 2 and Fig. 3). The corresponding iso(thio,seleno)cyanate (R^3NCO or R^3NCX) was added to a solution of the furfurylallylamines obtained above, and the reaction mixture was boiled for 6–8 hours (TLC control, Sorbfil, hexane : ethyl acetate 80 / 20). After cooling, the resulting crystals were filtered off, washed with ether, to obtain the target products as colorless crystals with yields of 28–93%.

The significant difference in the yields of the target 3a,6-epoxyisoindoles is due to the different steric load of the diene and dienophile in the transition state of the intramolecular [4+2] cycloaddition, as well as the different basicity of the secondary nitrogen atom in the initial *N*-allylfurfurylamines (which affects the rate of nucleophilic addition of isocyanate). It has been shown that bulky aliphatic substituents at the nitrogen atom of *N*-allylfurufuryl(thio,seleno) ureas reduce the yields of Diels-Alder adducts. The

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moderate yield of selenoureas **2.12–2.15** (Fig. 3) is explained by the fact that prolonged heating of the reaction mixtures in benzene leads to the destruction of products with the formation of a red selenium precipitate.

The structure of the obtained products and their purity were confirmed by ^{1}H, ^{13}C NMR, mass spectrometry and elemental analysis. The obtained spectral data correlate with those described previously in [24, 25].

Antiglycation activity *in vitro*

The glycation reaction was carried out in a 0.05M phosphate buffer solution, pH 7.4. Composition of the reaction medium: glucose 0.36 M (Agat-Med, Russia), BSA (fraction V) 1 mg/mL (Sigma, USA). The test compounds were dissolved in 99% DMSO (Kemerovo FF, Russia) (final concentration of the solvent in the reaction medium ~3%). The activity of the compounds was studied at a concentration of 100 µM. Control samples contained an equivalent volume of solvent. The samples were incubated for 24 hours at 60°C. Data were recorded by a spectrofluorimetric method, determining advanced glycation end products (AGEs) by their specific fluorescence at excitation/emission wavelengths of 440 / 520 nm (Infinite M200 PRO microplate reader, Tecan, Austria).

In order to exclude false-positive results for compounds that suppress AGE fluorescence due to interference, logarithmic normalization of the obtained data was performed using formula 1:

$$Flu(lg) = 10^{lg(exp) - lg(Blank)} - 1,$$

where Flu(lg) is the normalized fluorescence intensity of AGEs; lg(exp) and lg(blank) are the decimal logarithms of the actual fluorescence levels of glycated and corresponding non-glycated samples (both containing the test compound and control).

The activity of other compounds (both non-fluorescent and fluorescent at the wavelengths used) was expressed by formula 2:

$$Flu(lin) = Exp - Blank,$$

where Flu(lin) is the fluorescence intensity of AGEs; Exp and Blank are the actual fluorescence levels of glycated and corresponding non-glycated samples (both containing the test compound and control).

The determination of activity, expressed as % suppression of AGE fluorescence, was performed using formula 3:

$$\% = 100 - \left(Flu(exp) * \frac{100}{Flu(Contr)} \right),$$

where Flu(Exp) and Flu(Contr) are the fluorescence intensity of AGEs in experimental and control samples, respectively (log-normalized or non-log-normalized).

In vitro antioxidant properties

ABTS (2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); «Sigma», Canada) is a chromogenic substrate used for the quantification of antioxidant activity. In the process of oxidation of this substrate, a stable ABTS•+ radical is formed, characterized by an intense blue-green color. Antioxidants are able to reduce this radical, which leads to a decrease in color intensity, thereby allowing the antioxidant capacity of the compounds under study to be assessed. The radical is generated by adding a hydrogen peroxide-hemoglobin system to the reaction medium. Hemoglobin («Serva», Germany) was dissolved in 0.1M phosphate buffer solution (pH=6.8) to a final concentration of 1 mg/mL. ABTS was prepared at a concentration of 0.4 mg/ml by diluting 2 mg in 1 mL of PBS. Hydrogen peroxide was prepared by mixing 197 µL of 3% H_2O_2 («Ivanovo Pharmaceutical Factory», Russia) with 9833 µL of distilled water, reaching a concentration of 0.05%. Spectrophotometric determination of the optical density of the medium was carried out at a wavelength of 734 nm using a Tecan Infinite M200 PRO multifunctional microplate reader (Tecan, Austria).

Ethics approval

The manipulations were carried out in accordance with the requirements of ARRIVE 2.0. Ethical approval was obtained on 10/23/2024 from the Local Ethics Committee of the Volgograd State Medical University (registration number IRB 00005839, IORG 0004900 [OHRP]).

Assessment of the cytotoxicity of the lead compound, as well as its anti-inflammatory properties upon induction of inflammation by bacterial lipopolysaccharide

Primary mouse peritoneal macrophages (PMs) were used as target cells. PMs were isolated from peritoneal exudate of wild-type white sexually mature mice (*n* = 4, weight 30–35 g). The animals were obtained from the bio-nursery of LLC "SMK STEZAR" (Vladimir) and underwent a 2-week quarantine in the vivarium of the Volgograd State Medical University. The maintenance of animals and the conduct of experiments complied with the "Principles of Good Laboratory Practice" (GOST R-53434-2009) and the recommendations of the "Guidelines for

Preclinical Studies of Medicines". To stimulate the accumulation and activation of PMs, mice were injected intraperitoneally with 1 mL of 3% peptone solution. After 3 days, the animals were humanely euthanized by cervical dislocation. Peritoneal cells were collected by aseptic washing of the abdominal cavity with 5 ml of sterile Hanks' solution (PanEco, Russia) (without calcium and magnesium ions) at a temperature of 4–6°C. The resulting lavage was centrifuged at 250 g for 10 min (SIGMA 2-16KL centrifuge, Germany), the supernatant was removed, and the pellet was resuspended to obtain a cell suspension, followed by centrifugation (5 min) and resuspension. The total number of cells was counted and their viability was assessed in a Goryaev counting chamber (Russia) with staining with 0.4% trypan blue («Sigma-Aldrich», USA). The cell concentration was adjusted to 2.0×106 cells/mL in complete DMEM nutrient medium (Gibco) supplemented with 2 mM L-glutamine (Gibco), 10% heat-inactivated fetal bovine serum («BioClot», Germany) with the addition of 100 U/mL penicillin and 100 mg/mL streptomycin (Gibco). The cells were seeded into 96-well plates at 200 µL per well and incubated for 2 h at 37°C in a humidified atmosphere (95% humidity) with 5% CO2, after which the wells were washed with Hanks' solution (without calcium and magnesium ions) to remove unattached cells. After 24 h of incubation, 40 µL of supernatant was taken from each well, and 20 µL of solutions of the tested substances were added in the concentration range of 10–10000 µM, which provided a final concentration of 1–1000 µM in the well. The range of selected concentrations is acceptable and is found in the literature in various combinations of specific studied concentrations [26–28]. Incubated for 30 min in a CO_2 incubator. After 30 min, 20 µL of lipopolysaccharide (LPS) E. coli O26:B6 (in DMEM medium) («Sigma-Aldrich», USA) (C = 100 ng/well) was added and incubated for 24 hours. After co-incubation of PMs with the test and control substances, 20 µL of cell supernatant was taken for the LDH test and 50 µL of cell supernatant was taken to determine NO production. The remaining culture plate with PMs was used for further MTT testing.

Performing the MTT assay

A colorimetric MTT assay was used to assess cell viability. After 24 hours of exposure to the compounds and aspiration of 70 µL of cell suspension, the cells were treated with MTT solution (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) («Sigma», China) at a concentration of 5 mg/mL in PBS in a ratio of 1:10 and incubated for another 2.5 h. At the end of the incubation, the MTT solution was removed, 150 µL of DMSO («Kemerovo Pharmaceutical Factory», Russia) was added to dissolve the formazan crystals, and the plates were shaken for 5 min. The optical density was measured at a wavelength of 565 nm using a Tecan Infinite M200 PRO multifunctional microplate reader (Tecan, Austria). The selected wavelength corresponds to the absorption maximum and provides optimal sensitivity; similar parameters have been described previously [29].

Performing the LDH assay

An increase in the level of the enzyme lactate dehydrogenase (LDH) in the culture medium indicates a violation of the integrity of the cell membrane and cell death. To measure the LDH content in supernatants, a method was used based on spectrophotometric monitoring of the decrease in NADH concentration in the presence of pyruvate. 20 µL of supernatants taken 24 hours after incubation of PMs with the test and control compounds (final concentration 1–1000 µM) were mixed with 250 µL of NADH solution (PanEco, Russia) at a concentration of 0.194 mM/l, dissolved in 54 mM phosphate buffer, pH=7.5. Then, 25 µL of pyruvate solution (PanEco, Russia) at a concentration of 6.48 mM was added to the mixture.

The change in optical density was recorded at a wavelength of 340 nm for 20 min using a Tecan Infinite M200 PRO multifunctional microplate reader (Tecan, Austria). The selected wavelength corresponds to the peak absorption of NADH, providing optimal sensitivity for its quantification [30]. This time is necessary for the enzymatic reaction of pyruvate conversion to lactate and NADH oxidation to NAD+, which underlies this test system [31]. To determine cell viability, a standard curve was used, where the viability of whole cells was taken as 100%, and those treated with Triton X-100 as 0%.

Determination of NO production by peritoneal macrophages

The expression of iNOS by cells was induced by adding a sterile solution of LPS in a volume of 20 µL, the final concentration was 100 ng/well. Dexamethasone at a concentration of 100 µM was used as a reference drug. Incubated for 24 h under standard CO_2 incubator conditions.

The accumulation of nitrite (a stable end product of NO) in supernatants was determined using a standard Griess reagent. The Griess method is based on the diazotization of the nitrite ion in an acidic medium

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with sulfanilamide and the interaction of the diazo compound with *N*-(1-naphthyl)ethylenediamine to form a colored derivative. After 24 hours of incubation, 50 µL of supernatant was taken from the wells of the plate, 100 µL of reagent was added (1% sulfanilamide in 5% orthophosphoric acid and 0.1% aqueous solution of *N*-(1-naphthyl)ethylenediamine in equal proportions). The optical density was determined in a microplate reader at 550 nm using a Tecan Infinite M200 PRO multifunctional microplate reader (Tecan, Austria). The selected procedure corresponds to [32].

Statistical analysis

Statistical data processing was performed using GraphPad Prism 9.0, using the ANOVA criterion (Dunnett's post-test). The calculation of statistical parameters was carried out for linearly normalized data (normalization was carried out by subtracting the values obtained for blank samples from the results obtained for the corresponding experimental samples). Correlation analysis was performed using Pearson's correlation coefficient at a significance level of $p < 0.05$.

RESULTS

In vitro antiglycation activity

The results of the study of the antiglycation properties of the compounds are presented in Table 1.

The study identified several of the most active compounds, namely **2.5**, **2.8**, **2.10**, **2.11**, **2.12**, **2.13**, **2.14** and **2.15**. Despite a significant superiority in the level of activity over alagebrium (the latter shows activity under these experimental conditions only at a concentration of 1000 µM), the activity of the noted compounds still seems moderate, but sufficient for conducting further modifications of the structure. The negative activity value of compound **1.9** can probably be considered as a result of interference or measurement error.

In vitro antioxidant properties

The results of the study of the antioxidant properties of the compounds are presented in Table 2.

The study identified several of the most active compounds: **2.2**, **2.3**, **2.4**, **2.5**, **2.6**, **2.7**, **2.8**, **2.9**, **2.10**, **2.11**, **2.12**, **2.13**, as well as **2.16**, **2.17**, **2.18**, **2.19** (the activity of the last 4 compounds turned out to be the highest in the series).

According to a mechanistic view of the glycation reaction, the course of the reaction largely depends on oxidation processes [33], due to which antioxidant compounds may be promising antiglycators [34]. In one of our earlier works, we demonstrated a similar correlation between antiglycation activity and the ability of compounds to prevent copper-dependent ascorbate autooxidation [35]. It is noteworthy that in the case of the studied series of compounds, there is no statistically significant correlation between the two activities (Pearson's criterion, R = 0.239, p = 0.196). At the same time, the exclusion of compounds **2.16**, **2.17**, **2.18**, **2.19**, which showed the highest antioxidant properties, led to the emergence of a statistically significant correlation (Pearson's criterion, R = 0.607, p = 0.001). This correlation is graphically presented in Figure 4.

Such discrepancy in the values of the two estimated activities for these four compounds may be a consequence of interference in one of the two tests, and therefore requires further investigation. At the same time, we note that these compounds contain a structural *N*-aroyl fragment, possibly significant for the manifestation of only one activity, but not the second, even despite the connection between them. It is also possible that this antioxidant activity, due to undetermined features, is able to manifest itself only under the conditions of the ABTS test and is not significant for the course of the glycation reaction, which limits its potential usefulness. Thus, despite the presence of dramatically high antioxidant activity, comparable to the highly active compound quercetin, and considering the insufficient reliability and explainability of the results, compounds **2.16**, **2.17**, **2.18**, and **2.19** were not considered when selecting the lead. Studies of the antioxidant properties of these compounds will be continued and deepened in the future.

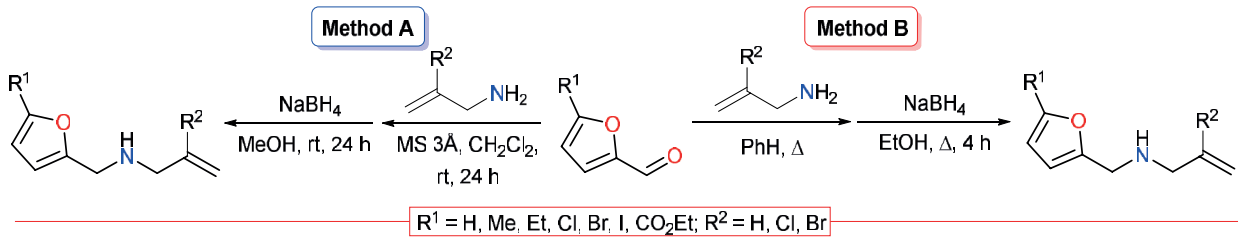

Figure 1 – Obtaining the initial *N*-allylfurfurylamines.

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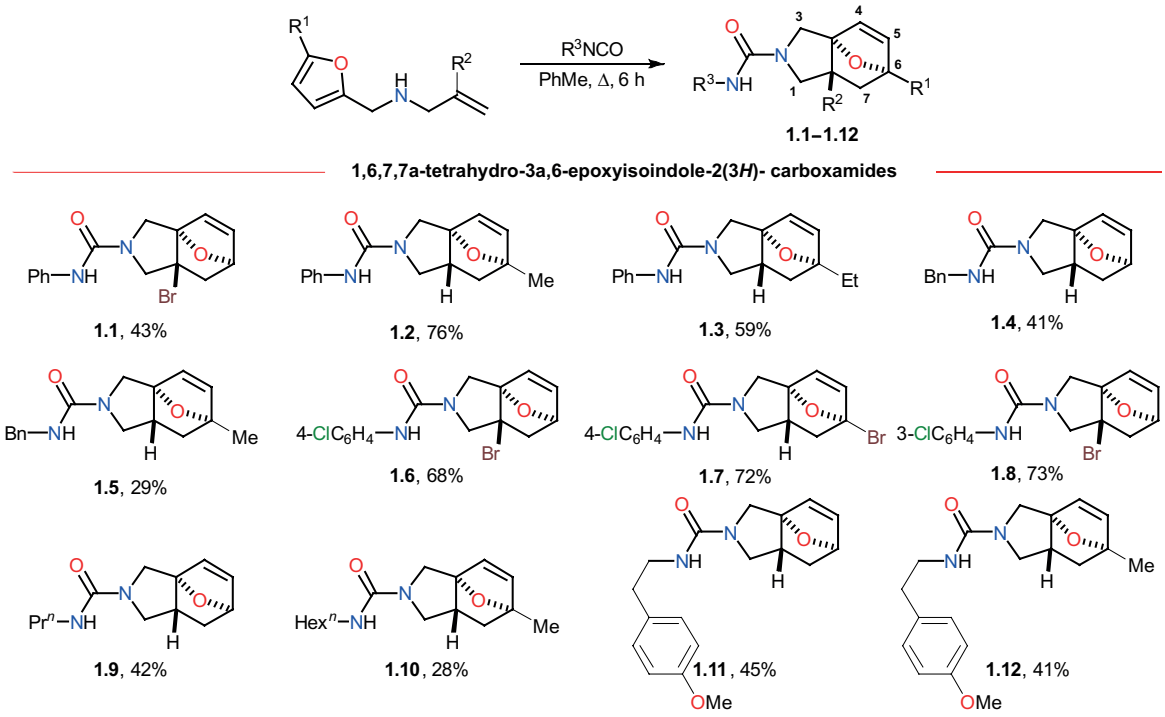

Figure 2 – Scheme of obtaining and structural formulas of hydrogenated 3a,6-epoxyisoindolo-2(3*H*)-carboxamides.

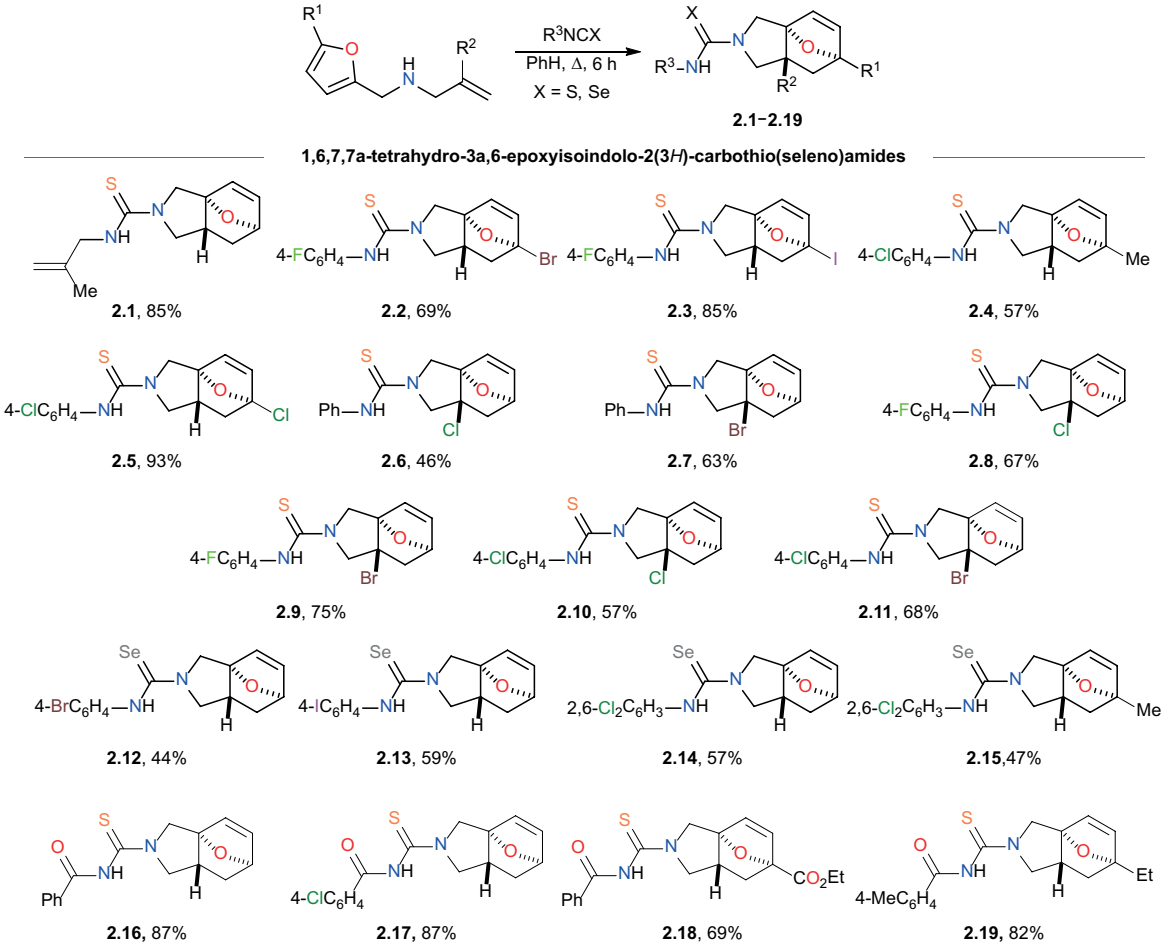

Figure 3 — Scheme of obtaining and structural formulas of hydrogenated 3a,6-epoxyisoindolo-2(3H)-carbothio(seleno)amides.

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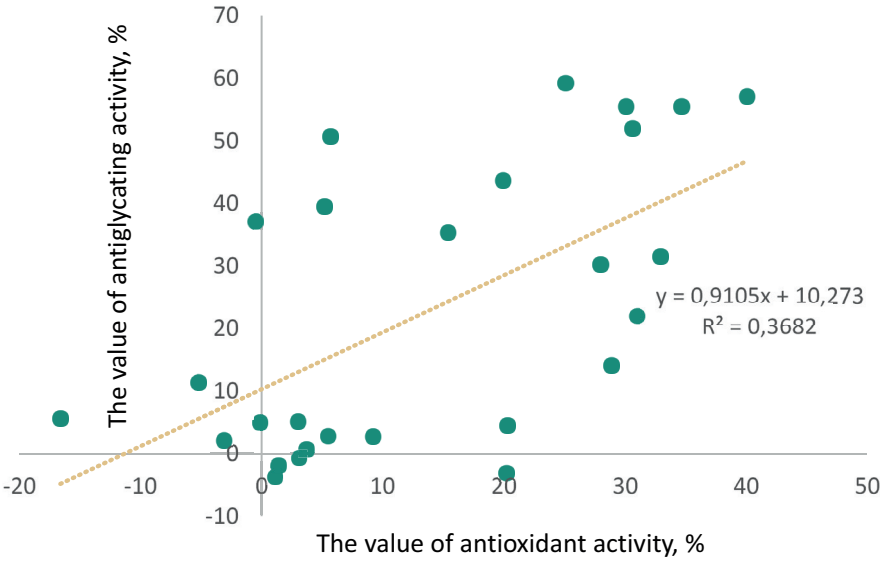

Figure 4 — Graphical representation of the correlation between the values of antiglycating and antioxidant activities of compounds, excluding 2.16, 2.17, 2.18, 2.19 and references.

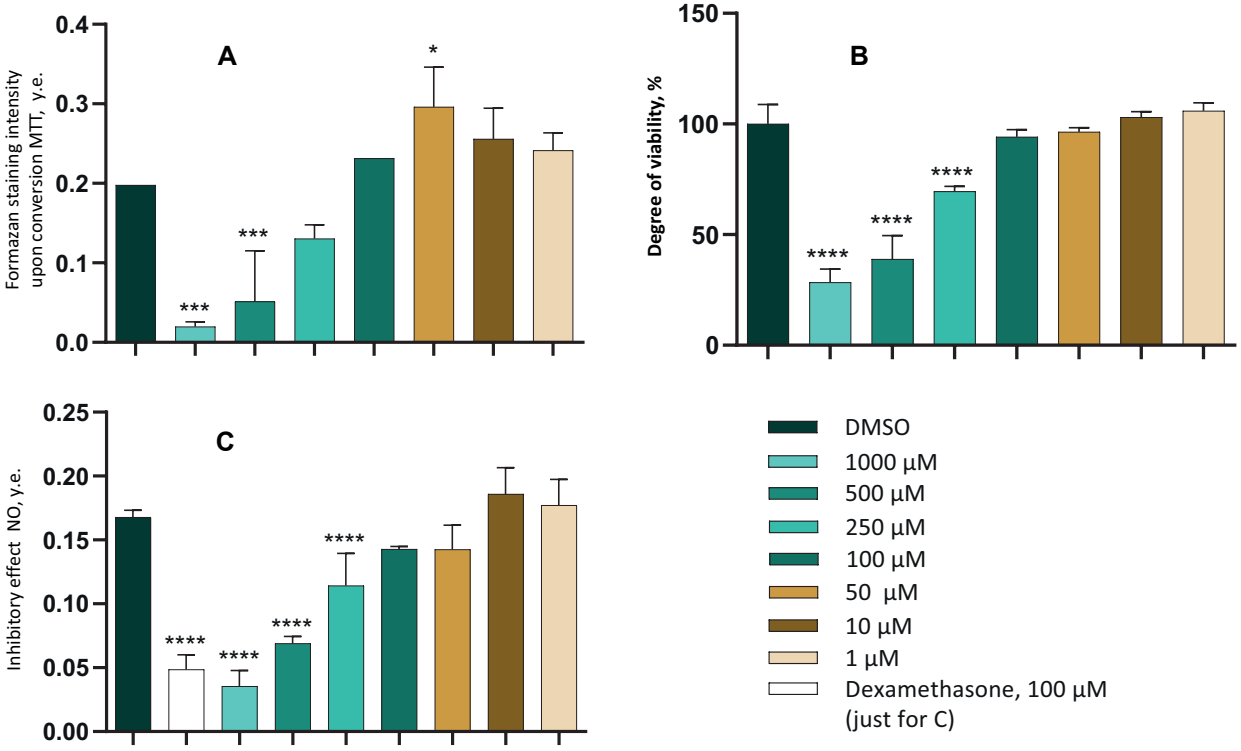

Figure 5 – Results of assessing the cytotoxic and anti-inflammatory properties of compound 2.10.
Note: A — cytotoxic effect of compound 2.10 in the MTT test on peritoneal macrophages; B — cytotoxic effect of compound 2.10 in the test with the determination of released lactate dehydrogenase; C — inhibitory effect of compound 2.10 on NO production caused by the action of lipopolysaccharide compared to dexamethasone. * — statistically significant differences compared to the control group results, ANOVA (Dunnett's post-test: * — $p < 0.05$; ** — $p < 0.01$; *** $p < 0.001$, **** — $p < 0.0001$).

Table 1 – Antiglycating activity of 3a,6-epoxyisoindole derivatives in vitro at a concentration of 100 μM

Compound	Activity, % (M ± SEM)
1.1	-3.1 ± 1.2
1.2	9.2 ± 4.5
1.3	3.7 ± 2.7
1.4	-0.1 ± 3.6
1.5	3.0 ± 2.7
1.6	20.2 ± 2.4*
1.7	5.5 ± 8.5
1.8	1.1 ± 3.1
1.9	-16.6 ± 2.2**
1.10	20.3 ± 2.2**
1.11	1.4 ± 3.5
1.12	3.1 ± 4.3
2.1	-5.2 ± 2.2
2.2	25.1 ± 4.3**
2.3	19.9 ± 3.3*
2.4	-0.5 ± 1.8
2.5	30.1 ± 5.2***
2.6	15.4 ± 1.6****
2.7	5.2 ± 1.6
2.8	34.7 ± 3.1****
2.9	5.7 ± 3.5
2.10	40.1 ± 1.7****
2.11	30.6 ± 3.3***
2.12	32.9 ± 2.3****
2.13	28.0 ± 1.1****
2.14	28.9 ± 2.7****
2.15	31.0 ± 0.9****
2.16	8.8 ± 2.7**
2.17	14.7 ± 1.0**
2.18	1.0 ± 4.1
2.19	-1.0 ± 3.2
Alagebrium	-12.0 ± 1.2
Alagebrium **(1000 μM)**	15.9 ± 1.5****

Note: * — statistically significant differences compared to the control group results, ANOVA (Dunnett's post-test: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$, **** — $p < 0.0001$).

Table 2 – Antioxidant activity of 3a,6-epoxyisoindole derivatives in vitro at a concentration of 111 μM

Compound	Activity, % (M ± SEM)
1.1	2.1 ± 0.6
1.2	2.7 ± 0.7
1.3	0.7 ± 0.4
1.4	5.0 ± 0.2**
1.5	5.1 ± 0.4**
1.6	-3.1 ± 0.7
1.7	2.8 ± 0.7
1.8	-3.7 ± 0.4
1.9	5.6 ± 0.6***
1.10	4.5 ± 0.6
1.11	-1.9 ± 0.5
1.12	-0.7 ± 1.4
2.1	11.4 ± 0.6****
2.2	59.2 ± 0.9****
2.3	43.7 ± 0.7****
2.4	37.1 ± 1.1****
2.5	55.5 ± 0.9****
2.6	35.3 ± 0.7****
2.7	39.5 ± 0.5****
2.8	55.5 ± 0.3****
2.9	50.7 ± 0.8****
2.10	57.1 ± 1.1*****
2.11	52.0 ± 1.3****
2.12	31.5 ± 0.5****
2.13	30.2 ± 1.0****
2.14	14.1 ± 1.2****
2.15	22.0 ± 1.1****
2.16	95.3 ± 0.1****
2.17	96.5 ± 0.2****
2.18	95.0 ± 0.5****
2.19	96.1 ± 0.1****
Quercetin	92.8 ± 1.8****

Note: * — statistically significant differences compared to the control group results, ANOVA (Dunnett's post-test: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$, **** — $p < 0.0001$).

Based on the combination of two activities, antiglycation and antioxidant, the best compound was selected from the remaining compounds, which exhibited both desired types of action to the greatest extent simultaneously, namely compound **2.10**, while combining them in a balanced manner. Further studies were conducted with the selected lead.

Evaluation of the cytotoxicity of the lead compound, as well as its anti-inflammatory properties upon induction of inflammation by bacterial lipopolysaccharide

The results of the study of the properties of compound **2.10** in cell models are presented in Figure 5. According to two tests (MTT test and determination of released LDH), the cytotoxic effect of compound **2.10** was detected only at concentrations ≥250 μM (Figures 5A and 5B). This suggests that significant cytotoxicity is absent at lower concentrations of the compound. At the same time, according to the results of the MTT test, a slight cytovitalizing effect is observed at a concentration of 50 μM (Figure 5A).

At the final stage of the study, on a model of LPS-induced NO production, the ability of compound **2.10** to exhibit anti-inflammatory action was evaluated. As a result of this study, it was possible to show the presence of signs of apparent anti-inflammatory activity in the studied compound at

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concentrations ≥250 μM (Figure 5C). Such an effect, if reliably confirmed, could be of interest, since suppressing low-level chronic inflammation caused by primary damaging factors is an attractive strategy for preventing fibrosis [36]. Based on the data obtained, compound **2.10**, if it had significantly less activity compared to dexamethasone, but real activity, could be classified as substances with a moderate modulating effect on inflammatory processes. However, comparing the results of the cytotoxicity assessment with the data on the anti-inflammatory activity of **2.10** significantly reduces the likelihood of this type of action in the compound, allowing us to consider the observed effect as false positive, due to cytotoxic properties.

At the same time, this result does not disprove the very connection between primary molecular damage by glycation and oxidative stress with the induction of a secondary cellular response by this exposure, since these triggering factors were absent in the cell model, and instead of glycation or oxidation products, the cells were exposed to bacterial LPS. Thus, further search for compounds combining a complex etiotropic and pathogenetic action, aimed at preventing the development of disabling consequences of difficult-to-treat remodeling fibrotic diseases, as well as their prevention and treatment, should be continued. Compound **2.10** can be considered as a successful intermediate step towards the creation of these compounds.

DISCUSSION

Glycation of proteins and oxidative stress are associated with a whole range of diverse disorders, including pathologies of the cardiovascular system, neurodegenerative diseases [37, 38], as well as conditions associated with tissue fibrosis [10, 39, 40]. Thus, glycation, cross-linking of extracellular matrix proteins, and increasing its rigidity support fibrogenesis [41–44], and excessive production of reactive oxygen species activates profibrotic signaling pathways, including those associated with TGF-β [45]. In addition to this, glycation and oxidative stress provoke inflammatory reactions significant for the course of fibrosis [46, 47]. Based on this, controlling glycation and oxidative stress can effectively complement the range of therapeutic strategies used in the treatment and prevention of fibrosis, thereby increasing the frequency of favorable outcomes.

Antiglycation and antioxidant compounds were searched for among various classes of molecules, both synthetic and natural [48, 49]. The combination of the two indicated activities within one agent is known and has already been considered successful [50, 51]. At the same time, despite the known connection between antiglycation and the manifestation of antioxidant properties [52], these two types of action may not be fully identical, and there are examples (resveratrol and its derivative — triether with trolox) when, upon modification of the compound's structure, a decrease in one activity was accompanied by an increase in the other [53]. At the same time, there are examples (carnosine, hydroxytyrosol) when the combination of these types of action was supplemented with anti-inflammatory properties [54, 55].

The general conclusion from the above is that obtaining new multimodal scaffolds, which in a balanced way combine antiglycation action with antioxidant properties, optionally supplemented with mechanistically related or unrelated anti-inflammatory activity, is a promising strategy in the development of new antifibrotic compounds. In our work, we focused on the construction of bidirectionally active compounds that combine the ability to antiglycation with antioxidant activity — based on an epoxyisoindole scaffold, namely in the series of 3a,6-epoxyisoindole-2(3*H*)-(carbox/thio/seleno)amides. This molecular basis can be considered privileged due to the fact that it is (i) available through stereoselective IMDAF sequences, allowing for a wide variation of introduced (chalcogen)carbamoyl fragments, and (ii) has already demonstrated biological prospects in related tasks. Thus, it has been shown that the IMDAF approach allows obtaining a 3a,6-epoxyisoindole core in a small number of synthetic steps, which facilitates the generation of a voluminous library of compounds for subsequent analysis of the dependence of activity on structure. Structurally similar isoindole derivatives have previously demonstrated antiglycation properties [56], which indirectly supports the hypothesis about the prospects of the epoxyisoindole core as a matrix for constructing compounds that combine antiglycation and antioxidant activity. Additional privilege to the epoxyisoindole base is added by its wide distribution in natural and drug-like compounds with various biological effects [57].

The study showed that the most balanced combination of antiglycation and antioxidant activities in the series of studied compounds is possessed by

(3aRS,6SR,7aRS)-7a-chloro-*N*-(4-chlorophenyl)-1,6,7,7a-tetrahydro-3a,6-epoxyisoindole-2(3*H*)-carbothioamide (compound **2.10**). Combining both activities, expressed at a sufficient level for their further optimization, the compound does not demonstrate the prevalence of one of them. The molecule contains fragments of thiourea, hydrogenated isoindole, and halogenarene in its structure. It is interesting that separately or in other combinations, these fragments are present in other compounds of the series, for example, thiourea in **2.1–2.9** and **2.11**, and a para-chlorophenyl substituent in structures **2.11** and **2.17**. But it is the combination of all available structural fragments that makes **2.10** an outstanding representative of the series. This is important, since the desired scaffold must bear signs of integrity, and its further modifications may be aimed primarily at including substituents in points of its structure that are insignificant for the final pharmacological activity.

A fundamental feature of compound **2.10** and the entire studied series is the absence of phenolic hydroxyl groups in their structures, traditionally associated with antioxidant and antiglycation activity. Apparently, this limits the potential magnitude of the observed effects in the models used. But this is also justified by the fact that the compounds under consideration are positioned primarily as starting frameworks for subsequent structure optimization — at the current stage, the goal of the work was to find a new scaffold of a higher level (more complexly organized than the original epoxyisoindole), suitable for further enhancing its antiglycation and antioxidant properties, and not in achieving maximum activity values.

At the same time, one cannot speak about the balance of the combination of the two desired types of action when discussing the established properties of **2.16**, **2.17**, **2.18**, and **2.19**. Unlike all other representatives of the studied series, these compounds contain an N-aroyl fragment in their structure, which, obviously, contributes to the manifestation of pronounced antioxidant properties. At the same time, due to the discrepancy between antioxidant and antiglycation actions, the phenomenon of high antioxidant activity of these compounds has a low final significance. At the same time, the properties of the four indicated compounds may be of interest for future research.

The final stage of the discussion concerns the anti-inflammatory activity and overall safety of the lead compound **2.10**. In the LPS-induced inflammation model used on PMs, specific anti-inflammatory activity of **2.10** was not confirmed; the reduction in NO production observed in the study was primarily seen at concentrations where cytotoxic effects were observed (≥250 μM), while no significant effect was found in the subtoxic concentration range. At the very least, the observed result indicates that compound **2.10** is not characterized by the inhibition of intracellular inflammatory cascades. The latter could be valuable for the suppression of fibrogenesis. At the same time, we note that due to the absence in the model of a component associated with the induction of an inflammatory reaction by certain damaged molecular patterns (e.g., glycated protein) capable of acting as triggers for NO production (LPS was used instead), further clarifying studies are needed. Regarding safety, the combined result of the two cytotoxicity assessment methods indicates a likely acceptable tolerability of **2.10**, although the translation of the results of cellular toxicity studies is complex and will require more complexly organized biological models in the future.

Thus, this work defines the epoxyisoindole scaffold as a promising basis for creating compounds with a combination of antiglycating and antioxidant properties, presents promising directions for modifying the original epoxyisoindole scaffold for the development of new drugs, and identifies the found higher-order Scaffold — compound **2.10** — as a balanced starting candidate for further structure optimization. In methodological terms, the work describes a strategy for finding means for the prevention and treatment of pathologies dependent on the trigger mechanisms of damage by glycation and oxidative stress, including fibrotic diseases.

Study limitations

Despite all the advantages, this study has several limitations:

1. The study is exploratory and pilot in nature.
2. Despite the sufficient justification for the relationship between changes in the extracellular matrix under the influence of glycation, as well as oxidative stress and inflammation, with the mechanisms of fibrogenesis, the work lacks direct endpoints reflecting the dynamics of fibrotic changes, including models of tissue/organ fibrosis. Consequently, conclusions about

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antifibrotic potential are logically justified but inferential in nature.

3. All experimental models used in the study are in vitro and in cellulo. When assessing antiglycating properties, the study is limited to one model protein (BSA), and cellular studies are limited to one type of cell (primary mouse PMs).
4. Despite the measures taken to reduce methodological interference in test systems, it is impossible to completely exclude it. The anti-inflammatory effect of the lead compound has not been confirmed, and the observed effect is associated with cytotoxicity.
5. The stability of the studied compounds under the conditions of the test systems used was not checked and was not the subject of the study.

CONCLUSION

According to the results of the study, compound **2.10** ((3aRS,6SR,7aRS)-7a-chloro-*N*-(4-chlorophenyl)-1,6,7,7a-tetrahydro-3a,6-epoxyisoindole-2(3*H*)-carbothioamide) combines antiglycating and antioxidant activity in the absence of significant cytotoxicity. However, no anti-inflammatory activity was found in compound **2.10**. Despite this, the established activity profile indicates the potential of the compound as a higher-order molecular basis (than the original epoxyisoindole), suitable for the directed design of new means for the prevention and treatment of conditions associated with the damaging effects of glycation and oxidative stress, especially means for the prevention and treatment of fibrotic diseases.

FIUNDING

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Umida M. Ibragimova — methodology, data analysis, investigation, project administration, writing—original draft, writing—review & editing, visualization; Nikita V. Valuysky — methodology, data analysis, investigation, project administration, writing—original draft, writing—review & editing; Violetta R. Rayberg, Svetlana A. Sorokina, Ksenia I. Zhukova, Denis K. Deryagin, Ilya S. Ukhorenko, Alesya A. Grigoryeva, Dmitry M. Shchevnikov — methodology, data analysis, investigation; Vladimir P. Zaitsev — methodology, data analysis, investigation, writing—original draft, writing—review & editing; Roman A. Litvinov — conceptualization, methodology, resources, project administration, writing—original draft, writing—review & editing, supervision, funding acquisition.
All authors confirm that their authorship meets the international ICMJE criteria (all authors have made significant contributions to the development of the concept, research and preparation of the article, read and approved the final version before publication).

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Characteristics of consumers of hypoglycemic drugs within the framework of preferential drug provision, using the example of the Stavropol Territory

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The aim. To study the main characteristics of consumers of hypoglycemic drugs (HGD) within the framework of preferential drug provision (PDP) in the Stavropol Territory (ST).

Materials and methods. The study was based on depersonalized information about patients with diabetes mellitus (DM) from the database of clinical and epidemiological monitoring of DM and data from the Regional Endocrinological Dispensary. Methods of comparative, retrospective, graphical analyses, grouping, and determination of average values were used.

Results. Among the beneficiaries with DM in the ST, individuals with type II DM prevail. In the type I DM group, men predominate (over 55.0%), while among patients with type II DM, women predominate (65.0%). The largest proportion among beneficiaries with type I DM is occupied by individuals from 30 to 60 years old, with type II DM, individuals aged 60 to 80 years predominate (70.44% — 2025). The increase in the number of beneficiaries with a disease duration of up to 5 years and over 10 years was noted. The life expectancy of beneficiaries with type I DM tends to increase slightly but steadily, while for patients with type II DM, it remains practically unchanged. A positive trend was noted in achieving the norm of glycated hemoglobin (HbA_{1c}) in beneficiaries with type I DM, and for every third patient with type II DM. For every third beneficiary with type I DM and for 70.0% with type II DM, body mass index (BMI) values are above normal. The structure of HGD consumption was determined, and changes in the ratio of the use of groups of oral HGD and individual trade names of drugs were revealed.

Conclusion. The general characteristics of beneficiaries with DM were identified, depending on its type, age and sex composition, duration of the disease, life expectancy, achievement of glycated hemoglobin levels, BMI, and the use of drugs in therapy.

Keywords: diabetes mellitus; beneficiaries; hypoglycemic agents; consumer portrait; Stavropol Territory

Abbreviations: HGD — hypoglycemic drugs; IDF — International Diabetes Federation; DM — diabetes mellitus; SSD — socially significant diseases; PDP — preferential drug provision; DP — drugs; HbA_{1c} — glycated hemoglobin; BMI — body mass index; TN — trade name.

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Характеристика потребителей сахароснижающих препаратов в рамках льготного лекарственного обеспечения на примере Ставропольского края

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Цель. Изучить основные характеристики потребителей сахароснижающих препаратов (ССП) в рамках льготного лекарственного обеспечения (ЛЛО) в Ставропольском крае (СК).

Материалы и методы. Основу исследования составила деперсонифицированная информация о пациентах с сахарным диабетом (СД) базы данных клинико-эпидемиологического мониторинга СД и данных ГБУЗ СК «Краевой эндокринологический диспансер». Использованы методы сравнительного, ретроспективного, графического анализов, группировки, определения средних величин.

Результаты. Среди льготополучателей с СД в СК превалируют лица с СД II типа. В группе СД I типа преобладают мужчины (свыше 55,0%), среди пациентов с СД II типа — женщины (65,0%). Наибольший удельный вес среди льготополучателей с СД I типа занимают лица от 30 до 60 лет, с СД II типа преобладают лица в возрасте от 60 до 80 лет, (70,44% — 2025 г.). Отмечено увеличение численности льготополучателей с длительностью течения заболевания до 5 лет и свыше 10 лет. Продолжительность жизни льготополучателей с СД I типа имеет тенденцию незначительного, но стабильного повышения, для пациентов с СД II типа — остается практически неизменной. Отмечена положительная тенденция в достижении нормы гликированного гемоглобина (HbA_{1c}) у льготополучателей с СД I типа, и для каждого третьего пациента с СД II типа. Для каждого третьего льготополучателя с СД I типа и для 70,0% с СД II типа значения индекса массы тела (ИМТ) выше нормы. Определена структура потребления ССП и выявлены изменения в соотношении использования групп пероральных ССП и отдельных торговых наименований лекарственных препаратов.

Заключение. Выделены общие характеристики льготополучателей с СД в зависимости от его типа, половозрастного состава, длительности заболевания, продолжительности жизни, достижению уровня гликированного гемоглобина, ИМТ, использованию ЛП в терапии.

Ключевые слова: сахарный диабет; льготополучатели; сахароснижающие средства; портрет потребителя; Ставропольский край

Список сокращений: ССП — сахароснижающие препараты; IDF — Международной федерации диабета; СД — сахарный диабет; СЗЗ — социально значимые заболевания; ЛЛО — льготное лекарственное обеспечение; ЛП — лекарственные препараты; HbA_{1c} — гликированный гемоглобин; ИМТ — индекс массы тела; ТН — торговое наименование.

INTRODUCTION

The characteristics of groups of beneficiaries with various forms of diseases can be considered as a complex of common and stable features, demographic and social indicators, gender differences, allowing to analyze the state of health, identify problematic issues in the organization of medical care and drug provision, develop a generalized approach to the needs of the patient, determine the level of his satisfaction and form target groups for a qualitative assessment of morbidity and the effectiveness of measures to improve medical care and drug provision [1–3].

The study of the medical and social status of patients is of interest to many researchers and is carried out at various stages of medical care: at the inpatient stage, the contingent of patients by the underlying disease and the presence of concomitant diseases, taking into account the results of treatment and the costs of the health care system [4, 5]; at the outpatient stage — combining the obtained results of

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the patient's social portrait, the realization of his needs, the degree of satisfaction with adherence to treatment, assessments of medical care and provision of drugs [6, 7]. The results of the formation of a clinical and social portrait of patients with various diseases, carried out at different times and in various subjects of the Russian Federation [8–10]. The results allow us to obtain not only the general idea of the structure of diseases in this territory, to study the prevalence of individual diseases, to establish the variability of indicators and to obtain characteristics of patients that can be used in the formation of groups for clinical trials [11], in the development and implementation of regionally adapted programs of medical care, prevention and rehabilitation of patients, but also to assess the level of organization of drug supply [12].

The high prevalence of diabetes mellitus (DM), the high risk of disability of the working-age population [13–15], the provision of these patients with medicines at the expense of budgets of all levels, contributes to the expansion of the direction of scientific research related to the prevalence of diseases based on statistical data [16], the formation of a social portrait of the main contingent of patients with DM in the Russian Federation [17], the study of social characteristics of patients with DM, taking into account the complications of the course of the disease [19–21]. All of the above contributes to the study and forecasting of the hypoglycemic drugs (HGDs) market, the adoption of informed management decisions on planning the volume and use of health care resources, as well as the identification of variability in the subjects of the Russian Federation when using drugs in the treatment of patients with DM who are entitled to preferential drug provision (PDP), contributes to the assessment of hypoglycemic therapy and changes in the tactics of using drugs.

The database of clinical and epidemiological monitoring of DM in the Russian Federation (https://diaregistry.ru/) serves as a source of the number of patients with DM. According to the data as of July 01, 2025, the number of patients with type I DM was 304,587 people, type II DM — 5,227,108 people. In accordance with the ranking of regions published on this website, the Stavropol Territory as of 01.07.2025 ranked 44th in the ranking, in 2024 — 36th place, which indicates the increase in the incidence[1], in addition, it is important to note that DM is classified as a socially significant disease[2].

[1] SD monitoring. Database of clinical and epidemiological monitoring of diabetes mellitus in the Russian Federation. Available from: https://sd.diaregistry.ru/content/o-proekte.html#content

[2] Decree of the Government of the Russian Federation No. 715 dated Dec 01, 2004 "On Approval of the List of socially significant diseases and the list of diseases that pose a danger to others" (revision dated Jan 31, 2020; effective from Feb 11, 2020). Available from: https://normativ.kontur.ru/document?moduleId=1&documentId=356130. Russian

THE AIM. To study the main characteristics of consumers of hypoglycemic drugs within the framework of preferential drug provision in the Stavropol Territory.

The following tasks were solved:

- the gender and age characteristics of beneficiaries with type I and II DM were studied;
- the distribution and structuring of beneficiaries with DM depending on the duration of the disease was carried out;
- the average life expectancy of beneficiaries with DM was determined;
- the dynamics of changes in the indicator of glycated hemoglobin (HbA1c) and body mass index (BMI) of HGD consumers were studied;
- groups of HGD used in the treatment of DM were identified.

MATERIALS AND METHODS

Methodology

Using the database of clinical and epidemiological monitoring of the number of patients with DM in the Stavropol Territory[3] in the period from 2020 to 2025 as of July 01, 2025 and data from the Regional Endocrinological Dispensary, a copy of depersonalized information about patients with type I and II DM was made. The selected information was systematized depending on the type of DM, gender, age, duration of the disease, anthropometric characteristics (height, weight of the patient), the value of the results of laboratory studies of glycated hemoglobin (HbA_{1c}), the therapy, which allowed to obtain the gender and age characteristics of beneficiaries, to conduct an analysis of the duration of the disease, the value of the body mass index (BMI), the achievement of target indicators for life expectancy and glycated hemoglobin. Grouping of beneficiaries by the use of insulin therapy and oral HGD allowed to determine the proportion of drugs used in the treatment of DM.

The methods of comparative, retrospective analysis, grouping of indicators were used. To work with digital data, MS Excel 2021 spreadsheets (Microsoft Corp., USA) were used, containing a set of standard formulas and functions for performing mathematical operations. The specific weight of each group of patients by age, duration of the disease, BMI values, the use of PSP was determined as the ratio of the grouped number of patients to the total number of patients, the result was expressed as a percentage.

[3] DM monitoring. Database of clinical and epidemiological monitoring of diabetes mellitus in the Russian Federation

The average life expectancy with DM [22, 23] was calculated as the ratio of the total number of years lived by all patients with DM to the total number of patients with DM in the analyzed period (year):

$$ALE = \frac{\sum_{i=0}^{n} YL}{N - n},$$

where ALE — average life expectancy, *n* years; YL — total number of years lived, person/years (defined as the total sum of years lived by all patients with DM); N — total number of patients with DM, n — the number of patients who died in the analyzed period, year.

To determine the proportion of patients by the level of the laboratory indicator of HbA_{1c}, the approved boundaries of the indicator were used — less than 7%, from 7.0 to 7.9%, from 8.0 to 8.9%, — indicated in the approved recommendations "Algorithms of specialized medical care for patients with diabetes mellitus"[4] [24] and clinical guidelines[5, 6]. The proportion of patients with the achieved level of the indicator was calculated using the formula:

$$D = \frac{n \times 100\%}{N},$$

where D — proportion of patients with the achieved level of HbA_{1c}, %; *n* — number of patients with the selected level of HbA_{1c}, number of people; N — total number of patients with the specified level of HbA_{1c}, number of people.

To determine the BMI, the Quetelet method was used, as the ratio of body weight in kilograms and the patient's height value, expressed in meters, squared [25]:

$$BMI = \frac{\text{body weight, kg}}{\text{height, m}},$$

To interpret the obtained results of the BMI data, the WHO recommendations were used [26]: BMI values up to 18.49 — underweight; from 18.5 to 24.99 — normal body weight; from 25.0 to 29.99 — overweight (pre-obesity); and over 30.0 — obesity.

Ethics approval

The authors did not obtain approval from any Ethics Committee for this study. The study was conducted without the involvement of patients as study participants or as objects of study; does not contain information about treatment protocols; clinical testing of treatment methods and the results of the use of drugs; is not associated with a potential risk for patients, since the study did not resort to any type of medical intervention that would require written consent of the patient and approval of any Ethics Committee.

The information was obtained by extracting information from the database of clinical and epidemiological monitoring of the number of patients with DM in the Stavropol Territory and data from the Regional Endocrinological Dispensary, which did not contain personalized information about specific patients.

Statistical analysis

To work with digital data, MS Excel 2021 spreadsheets (Microsoft Corp., USA) were used, containing a set of standard formulas and functions for performing mathematical operations. The above describes the methods used for calculating indicators with an indication of formulas, as well as the boundaries of indicator values used for interpreting the results with reference to literature sources.

RESULTS

De-identified information on beneficiaries with DM in the Stavropol Territory, grouped by year, depending on gender and type of DM, is presented in Table 1.

In the general population of beneficiaries with DM in the Stavropol Territory, patients with type 2 DM predominate, accounting for up to 95.0% (73,577 beneficiaries in 2025). The results obtained are consistent with data on the prevalence of DM in other regions of the Russian Federation [27]. It is important to note an increase in the proportion of patients with type 2 DM from 94.70% (68,965 patients) in 2020 to 95.44% (73,577 patients) in 2025 in the total patient population. Among patients with type 1 DM, men predominate, their proportion being slightly more than 55.0% (1940 patients in 2025). At the same time, women prevail among patients with type 2 DM, their proportion being over 65.0% (48,492 patients in 2025).

The characteristics of the age structure of beneficiaries with type 1 DM are presented in Figure 1.

The data on the age structure of patients with type 1 DM indicate a predominance of individuals aged

[4] Algorithms of specialized medical care for patients with diabetes mellitus; Dedov II, Shestakova MV, Sukhareva OYu, editors; 12th issue. Moscow; 2025. Available from: https://www.rosinsulin.ru/wp-content/uploads/2025/06/2025_algoritmy_12.pdf. Russian

[5] Clinical Guidelines. Type 2 diabetes mellitus in adults. Available from: https://cr.minzdrav.gov.ru/preview-cr/290_2. Russian

[6] Clinical Guidelines. Type 1 diabetes mellitus in adults. Available from: https://cr.minzdrav.gov.ru/preview-cr/286_2. Russian

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30 to 60 years. The proportion of patients in this age group tends to increase from 57.55 to 64.58%, with an average value of 55.61%, i.e., practically every second beneficiary is in this age category. The proportion of beneficiaries with type 1 DM under the age of 30 tends to decrease from 30.26% in 2020 (1169 people) to 25.86% in 2025 (909 people), the average proportion of this group is 34.74%. Thus, every third patient is under 30 years of age. Beneficiaries aged 60 to 80 years account for slightly more than 9.0%, the average value of the proportion of this group is 9.38%; the proportion of patients over 80 years is insignificant — up to 1.0%.

The results of studying the age structure of beneficiaries with type 2 DM are presented in Figure 2.

Among patients with type 2 DM, individuals aged 60 to 80 years predominate: the proportion of this group tends to increase from 66.78% in 2020 (46,055 people) to 70.44% in 2025 (51,824 people), with an average proportion of this group of 69.0%. In the analyzed period, the proportion of beneficiaries aged 30 to 60 years increased from 13.15% (9072 people) in 2020 to 21.85% (16,079 people) in 2025, with an average value of 17.98%, patients over 80 years of age account for an average of 12.93%.

Based on the fact that DM is a chronic disease, we grouped the number of beneficiaries depending on the duration of the disease. For the analysis, the following duration boundaries were identified: up to 5 years, from 5 to 10 years, and over 10 years. The results of the analysis are presented in Figure 3.

The data presented indicate an increase in the proportion of beneficiaries with type 1 DM with a disease duration of up to 5 years, the proportion of such patients increased from 4.22% (163 people) in 2020 to 23.94% (1067 people) in 2024, and, although in 2025 there is a decrease in the proportion to 15.11% (531 people), the average value of 14.70% still exceeds the value of 2020. The increase in the number of people with a short duration of the disease indicates the well-coordinated work of the diagnostic service of the region in identifying forms of DM in patients. The duration of the disease of every fifth patient is from 5 to 10 years (the average proportion of this group is 22.92%). The largest proportion is occupied by the group of patients with a disease duration of more than 10 years, while in the analyzed period there is some reduction in the proportion of this category of patients from 70.52% (2724 people) to 66.6% (2341 people), with an average value of 62.39%, which is a positive factor and indicates a positive organization of both medical care and drug provision for patients with type 1 DM.

Figure 4 shows the structure of beneficiaries with type 2 DM by duration of the disease.

The data demonstrates a tendency to increase the proportion of beneficiaries with a disease duration of up to 5 years, in the analyzed period their share increased sevenfold, from 5.78% (3988 people) in 2020 to 38.39% (28,247 people) in 2025, with an average value of 23.13%. In our opinion, the increase in the proportion of beneficiaries in this age group is associated with the skillful organization of DM diagnosis. The proportion of beneficiaries with a disease duration of 5 to 10 years (average value 29.94%) tends to decrease, the dynamics of change from 33.31% (22,969 people) in 2020 to 26.05% (19,167 people) in 2025, which is a negative point and indicates the need for a more detailed study of the reasons for the decrease in the number of patients in this age category. A positive fact is the predominance in the analyzed group of people with disease duration of more than 10 years, practically every third (average value 46.94%) beneficiary with disease duration of more than 10 years. The tendency to decrease in the analyzed period the proportion of this group from 60.91% (42,008 people) in 2020 to 35.56% (26,163 people) in 2025 may be an independent area of scientific research to study the reasons for the reduction in the number of patients.

The study of the structure of the duration of the disease of beneficiaries with DM, both type I and type II, showed a tendency to the predominance of people with a disease duration of more than 10 years, which indicates the availability of medical care and drug provision for patients with DM, allowing to increase their life expectancy.

The results of a comparative analysis of the average life expectancy of beneficiaries with DM are presented in Figure 5.

The results of the study indicate a slight but steady increase in life expectancy in beneficiaries with type 1 DM, which in the analyzed period increased from 49.79 years in 2020 to 57.36 years in 2025. The life expectancy of beneficiaries with type 2 DM remains practically stable — about 73 years. It is necessary to indicate the predominance of the life expectancy indicator of beneficiaries with type 2 DM, which in 2025 was 72.38 years, over that of beneficiaries with type 1 DM — 57.36 years (2025), which is a significant achievement of the organization of medical care and drug provision for patients in the Stavropol Territory.

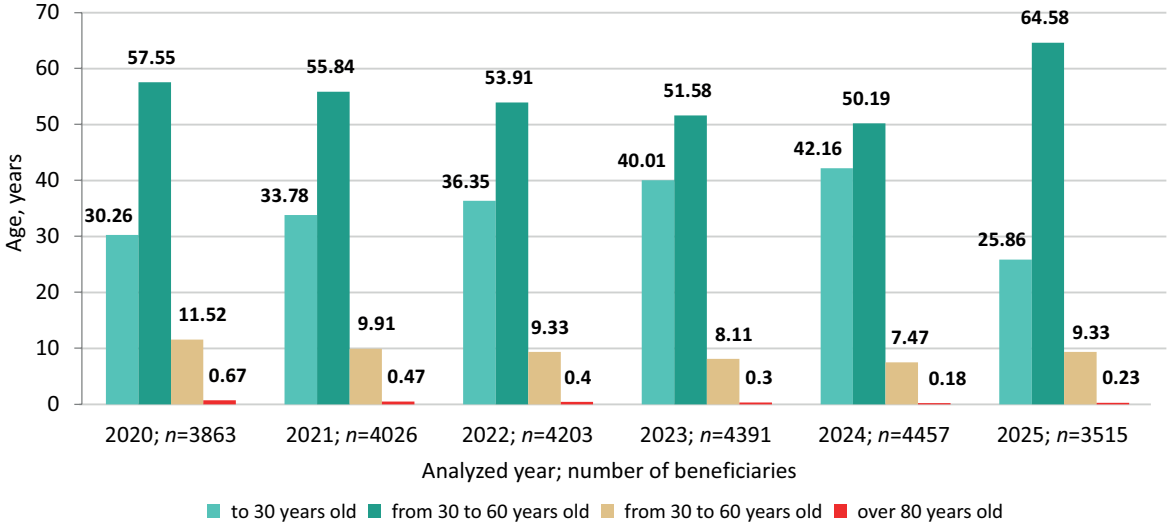

Figure 1 – Age composition of beneficiaries with type 1 diabetes mellitus in the Stavropol Territory, %

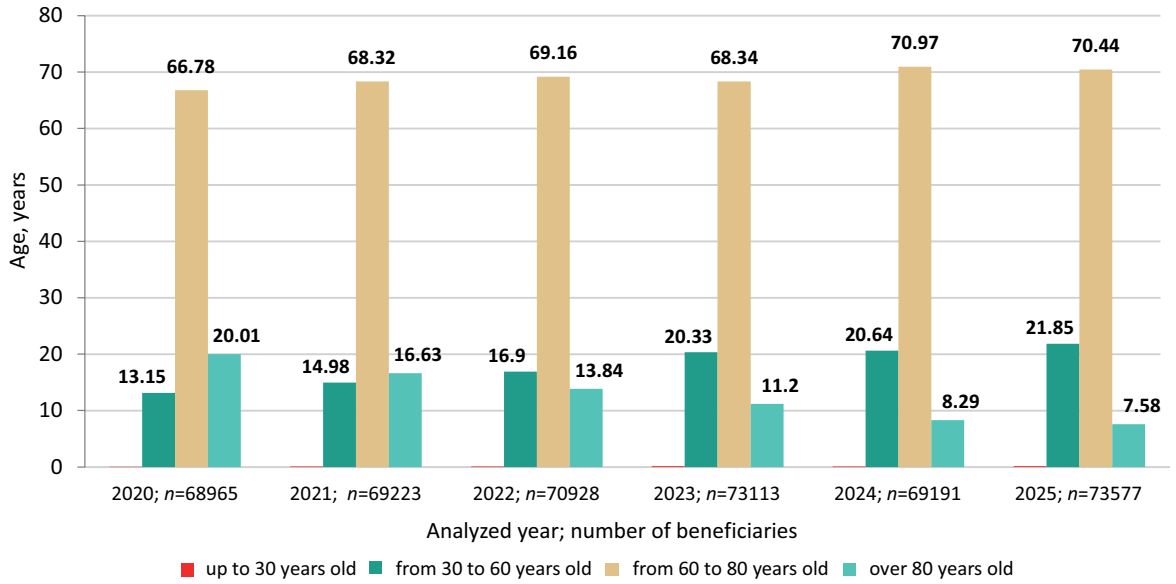

Figure 2 — Age composition of beneficiaries with type 2 diabetes mellitus in the Stavropol Territory, %

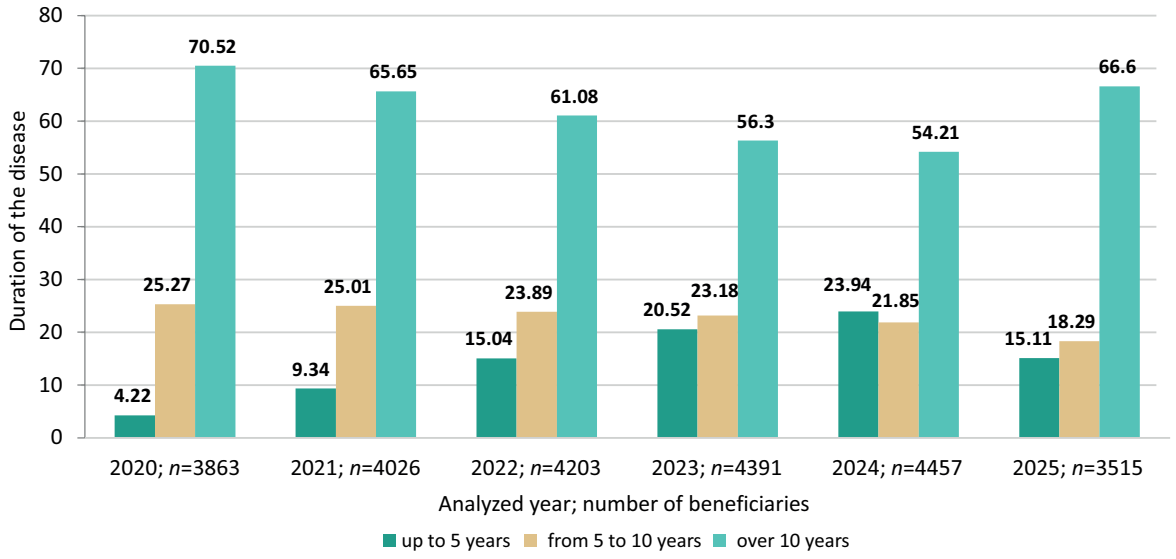

Figure 3 — Structure of beneficiaries with type 1 diabetes mellitus by duration of the disease, %

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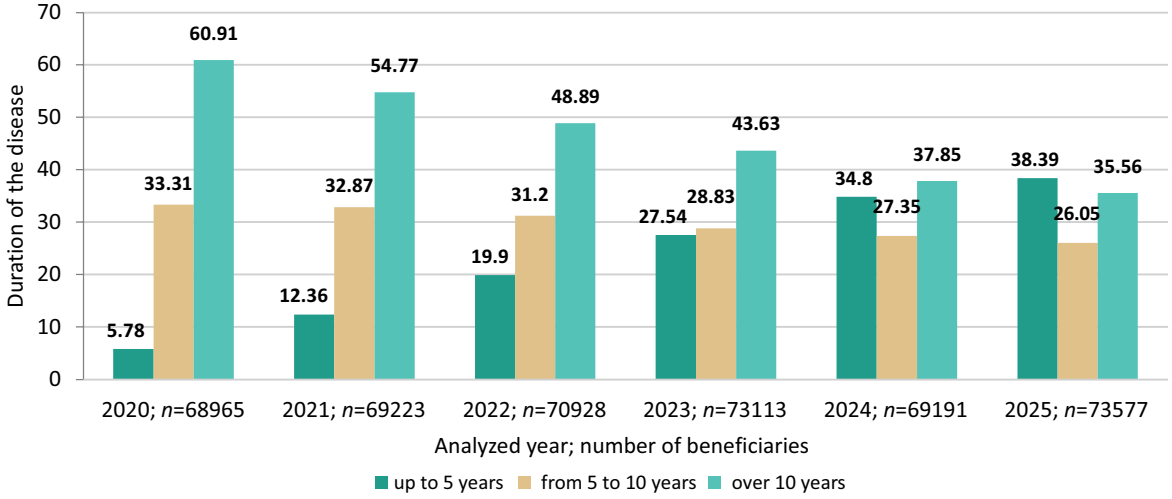

Figure 4 – Structure of beneficiaries with type 2 diabetes mellitus by duration of the disease, %

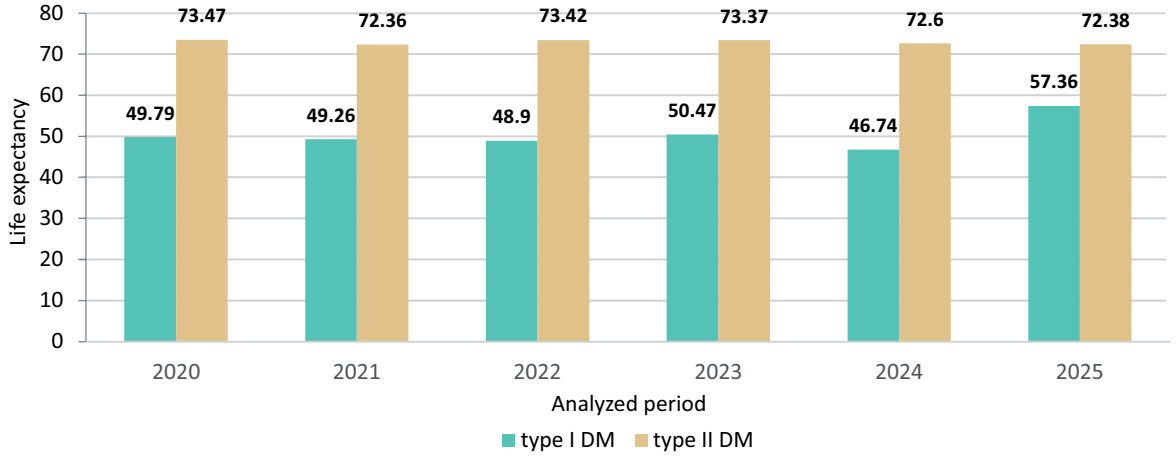

Figure 5 — Life expectancy of patients with diabetes mellitus, number of years

Table 1 — Depersonalized characteristics of the beneficiary population with diabetes mellitus in the Stavropol Territory

Indicator	Years					
	2020	2021	2022	2023	2024	2025
Total number of people, including	72828	73249	75131	77504	73648	77092
Diabetes mellitus type I						
Total number, people	3863	4026	4203	4391	4457	3515
Weight, %	5.30	5.50	5.59	5.67	6.05	4.56
men, %	2144 (55.50)	2230 (55.39)	2312 (55.01)	2390 (54.43)	2408 (54.03)	1940 (55.19)
women, %	1719 (44.50)	1796 (44.61)	1891 (44.99)	2001 (45.57)	2049 (45.97)	1575 (44.81)
Diabetes mellitus type II						
Total number, people	68965	69223	70928	73113	69191	73577
Weight, %	94.70	94.50	94.41	94.33	93.95	95.44
men, %	22379 (32.45)	22724 (32.83)	23577 (33.24)	24665 (33.74)	23331 (33.72)	25085 (34.09)
women, %	46586 (67.55)	46499 (67.17)	47351 (66.76)	48448 (66.26)	45860 (66.28)	48492 (65.91)

Table 2 — Monitoring the distribution of beneficiaries with diabetes mellitus by glycated hemoglobin (HbA_{1c})

Year	Total number of people	Laboratory data HbA_{1c}, %							
		<7,0		from 7.0 to 7.9		from 8.0 to 8.9		≥9,0	
		people	%	people	%	people	%	people	%
Type I DM									
2020	1937	409	21.12	660	34.07	411	21.22	457	23.59
2021	2031	530	26.10	643	31.66	407	20.04	451	22.21
2022	2175	575	26.44	726	33.38	446	20.51	428	19.68
2023	2857	798	27.93	1246	43.61	415	14.53	398	13.93
2024	3958	1040	26.28	1402	35.42	665	16.80	851	21.50
2025	1986	475	23.92	716	36.05	340	17.12	455	22.91
Type II DM									
2020	24794	7914	31.92	9529	38.43	4490	18.11	2861	11.54
2021	28388	9742	34.32	10575	37.25	5235	18.44	2836	9.99
2022	27446	11248	40.98	9898	36.06	3820	13.92	2480	9.04
2023	43038	17096	39.72	18037	41.91	4540	10.55	3365	7.82
2024	59707	21933	36.73	24625	41.24	6996	11.72	6153	10.31
2025	33445	12013	35.92	13531	40.46	3849	11.51	4052	12.12

Note: DM — diabetes mellitus.

Table 3 — Monitoring the distribution of patients with diabetes mellitus by body mass index, %

Year	Total number of people	Level of patients (%) with BMI value							
		<18,49		from 18.50 to 24.99		from 25.0 to 29.99		≥30,0	
		people	%	people	%	people	%	people	%
Type I DM									
2020	3031	293	9.67	1825	60.21	662	21.84	251	8.28
2021	3157	290	9.19	1892	59.93	697	22.08	278	8.80
2022	3475	443	12.75	2027	58.33	731	21.04	274	7.88
2023	3712	471	12.69	2136	57.54	795	21.42	310	8.35
2024	5088	585	11.50	3024	59.43	1112	21.86	367	7.21
2025	2821	85	3.01	1802	63.88	686	24.32	248	7.79
Average BMI values, %	—	—	9.80	—	59.89	—	22.09	—	8.22
Type II DM									
2020	46703	36	0.07	14638	31.34	11827	25.33	20202	43.26
2021	52868	46	0.09	16812	31.80	13695	25.90	22315	42.21
2022	54203	46	0.08	16518	30.47	13481	24.88	24158	44.57
2023	59559	59	0.09	18121	30.43	14747	24.76	26632	44.72
2024	80449	83	0.10	25117	31.23	20501	25.48	34748	43.19
2025	47574	59	0.12	14597	30.68	11763	24.73	21155	44.47
Average BMI values, %	—	—	0.09	—	30.99	—	25.18	—	43.74

Note: DM — diabetes mellitus; BMI — body mass index.

Table 4 — Groups of drugs used in the therapy of beneficiaries with type 2 diabetes mellitus, %

Years	Sulfonylurea derivatives, A10BB	Insulins, A10AB, A10AC, A10AD, A10AE	DPP-4 inhibitors, A10BH	SGLT2 inhibitors, A10BK	GLP-1 RA, A10BJ
2021	54.0	20.4	3.9	2.3	0.7
2022	53.3	20.4	5.6	4.2	0.8
2023	52.0	19.9	8.4	7.3	0.8
2024	51.6	20.4	13.2	12.6	1.3
2025	50.4	20.2	17.1	17.3	1.9

Note: DPP-4 — dipeptidyl peptidase-4; SGLT-2 — sodium-glucose cotransporter-2 inhibitors; GLP-1 RA — glucagon-like peptide-1 receptor agonists.

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At the same time, the calculated life expectancy indicators of patients with DM are lower than the established target values specified in the regional program "Combating DM in the Stavropol Territory"[7] (74.86 years) and Decree of the President of the Russian Federation No. 309 of May 7, 2024 (78 years)[8].

The criterion for a retrospective assessment of the effectiveness of the use of hypoglycemic drugs or timely changes in therapy for beneficiaries with DM is the glycated hemoglobin indicator, which within the framework of the Federal Project "Combating DM" since 2023 has been a target indicator of the program[9]. The regional program "Combating DM in the Stavropol Territory"[10] plans to increase the proportion of patients with DM who have reached a glycated hemoglobin level less than or equal to 7.0 by the end of 2022 to 40.70%.

Table 2 presents the results of retrospective monitoring of the distribution of beneficiaries by HbA_{1c} level for the period from 2020 to 2025.

The data presented clearly demonstrate an increase in the proportion of beneficiaries with type 1 DM with an HbA_{1c} level of up to 7.0% (normal according to clinical guidelines ≤7.0% or less than 42 mmol/mol)[11,12]. The proportion of beneficiaries with the achievement of the target HbA_{1c} level up to 7.0% in the analyzed period increased from 21.12% (409 people) in 2020 to 26.28% (3958 people) in 2024. Despite the fact that there was a slight decrease in the proportion in 2025 (23.92%, 475 people), this indicator exceeded the data for 2020. A positive fact is the decrease in the proportion of beneficiaries with a high HbA_{1c} level — from 8.0 to 8.9% — the proportion of such patients was 21.22% (411 people) in 2020, and in 2025 decreased to 17.12% (340 people), as well as a decrease in the proportion of beneficiaries with an HbA_{1c} value of more than 9.0% — from 23.59% (457 people) to 22.91% (455 people). The results of reducing the proportion of patients with a high HbA_{1c} indicator indicate positive results in the organization of PDP for patients and correct hypoglycemic therapy.

At the same time, the use of hypoglycemic drugs provides a positive trend in achieving the norm of HbA_{1c} up to 7.0% for every third beneficiary with type 2 DM, the proportion of which increased from 31.92% (7914 people) in 2020 to 35.92% (12,013 people) in 2025. A significant achievement is the tendency to reduce the proportion of beneficiaries with higher HbA_{1c} values from 8.0 to 8.9, the proportion of such patients decreased from 18.11% (4490 people) in 2020 to 11.51% (3849 people) in 2025, but at the same time the proportion of patients with HbA_{1c} values from 7.0 to 7.9% and an indicator of more than 9.0% increases.

However, the proportion of beneficiaries with the achievement of the HbA_{1c} level up to 7.0% depends on the type of DM. Thus, the proportion of patients with type 2 DM (35.92% in 2025) exceeds the proportion of patients with type 1 DM (23.92% in 2025), but these results are still lower than the target indicators of the Federal Project "Combating DM" in which it is indicated that the proportion of patients in whom the glycated hemoglobin level will be less than or equal to 7.0% in 2025 should be more than 42% of the number of patients[13]. The results obtained indicate an autonomous scientific study of the use of hypoglycemic drugs.

The results of the distribution of beneficiaries by BMI are presented in Table 3.

BMI allows determining the proportion of patients with excess or insufficient weight, which can be used as a basis for adjusting hypoglycemic therapy for beneficiaries. The presented results indicate that the level of underweight is characteristic of 9.80% of patients with type 1 DM and is practically absent for beneficiaries with type 2 DM. The BMI for more than half of the beneficiaries (59.89%) with type 1 DM corresponds to the norm, and every third patient is obese. At the same time, only every third (30.99%) beneficiary with type 2 DM has a normal BMI value, and about 70.0% of beneficiaries are overweight.

Published results of studies [28, 29] indicate a relationship between increased BMI and obesity with negative consequences for organs and systems of the body and complications in DM.

Also, as a result of a previous study [30], the structure of consumption of hypoglycemic drugs

[7] Resolution of the Government of the Stavropol Territory dated Apr 26, 2024 No. 230-p "On approval of the regional program "Combating diabetes in the Stavropol Territory". Available from: http://publication.pravo.gov.ru/document/2600202404270002?index=76. Russian

[8] Decree of the President of the Russian Federation dated May 07/2024 No. 309 "On the National Development Goals of the Russian Federation for the period up to 2030 and for the future up to 2036". Available from: https://normativ.kontur.ru/document?moduleId=1&docum entId=470566. Russian

[9] Passport of the Federal Project "Fighting diabetes mellitus". Available from: https://diabetrda.ru/документы/borba-s-saharnym-diabetom/. Russian

[10] Resolution of the Government of the Stavropol Territory dated Apr 26, 2024 No. 230-p "On approval of the regional program "Combating diabetes in the Stavropol Territory".

[11] Clinical Guidelines. Type 1 diabetes mellitus in adults.

[12] Clinical Guidelines. Type 2 diabetes mellitus in adults.

[13] Passport of the Federal Project "Fighting diabetes mellitus". Available from: https://diabetrda.ru/документы/borba-s-saharnym-diabetom/. Russian

depending on the type of DM was established: therapy for beneficiaries with type 1 DM is based only on insulin therapy, therapy for patients with type 2 DM includes the use of insulins and oral hypoglycemic agents. Further study of these drug prescriptions for beneficiaries allowed us to identify groups of drugs by ATC used for PDP for people with type 2 DM; data on the number of drugs for 9 months of each year were used for comparative analysis, table 4.

The presented data indicate changes in the ratio of oral hypoglycemic agents in the structure of diabetes therapy and an increase in the use of dipeptidyl peptidase-4 (DPP-4) inhibitors and sodium-glucose cotransporter type 2 (SGLT-2) inhibitors. At the same time, the ratio of the level of prescriptions of oral hypoglycemic agents from the iDPP-4 group increased from 3.9% in 2021 to 17.1% in 2025, including 29.5% in the last year. At the same time, the growth rate of prescribed drugs of the iSGLT-2 group increased - from 2.3% in 2020 to 17.3% in 2025, by 652.1% and by 37.3% for 2025. The increase in the proportion of these drug groups indicates the effectiveness and safety of drugs both in monotherapy and in combination therapy for DM [31, 32].

It should be noted that in the analyzed period there is a slight decrease in the prescription of sulfonylurea drugs — by 6.6%, the level of insulin therapy prescription remained practically unchanged. The group of glucagon-like peptide receptor agonists (GLP-1 RA) in the prescription structure also increased by 171% over the past 5 years — from 0.7% in 2020 to 1.9% in 2025, of which the growth for the period 2024–2025 amounted to 46.1%.

Thus, the retrospective comparative analysis allowed us to obtain the main characteristics of beneficiaries with DM in the Stavropol Territory, the ratio of changes in the structure of drug use, which should be combined with regional characteristics when organizing drug provision for patients in this group.

DISCUSSION

The high prevalence of severe non-communicable diseases is one of the main health problems in the modern world. One of these diseases is DM (DM). At the congress of the American Diabetes Association (ADA), which traditionally presents the latest advances in the diagnosis and treatment of DM in the world, new results on the prevalence of this disease were announced. According to the data of the International Diabetes Federation (IDF, International Diabetes Federation) Atlas, in 2021 there were 237 million people with DM. Currently, the number of such patients has increased 2.5 times and reached 588 million people aged 20 to 79 years — this is almost every tenth inhabitant of the planet. According to IDF forecasts, by 2050 the number of patients is expected to increase to 853.0 million — every 8th inhabitant. According to other forecasts, the number will reach 1.3 billion; many researchers associate such results with the consequences of urbanization, increased life expectancy, and global aging of the population[14,15,16].

Among the patients with DM in the Stavropol Territory, people with type II DM predominate, accounting for slightly more than 95.0%. The results of the age structure indicate the predominance of beneficiaries of people of the most working age, which increases the importance of organizing drug provision for this category of patients.

A comparative analysis of the age and gender structure showed a predominance of men among beneficiaries with type I DM, and a predominance of women among patients with type II DM, whose proportion is over 65.0%. Among patients with type I DM, people aged 30 to 60 years predominate. Patients with type II DM, people aged 60 to 80 years predominate, while the proportion of this group tends to increase, and the proportion of beneficiaries aged 30 to 60 years also increases. Thus, in a study by J.M. Clements et al. (2012), conducted in one of the states of the USA, it was noted that women receiving treatment are more likely than men to suffer from type II DM — 197,571 (44.1%) men versus 250,836 (55.9%) women [33].

Grouping the beneficiaries by duration of the disease indicates the predominance of people with a disease duration of over 10 years; there is a slight but stable increase in life expectancy in patients with type I DM; the life expectancy of patients with type II DM remains practically stable, but below the target values indicated in the regional program “Combating DM in the Stavropol Territory.” One of the large-scale studies on life expectancy is the work of

[14] Diabetes mellitus: new epidemiological data and mechanisms of progression in the focus of ADA 2025. Available from: https://medvestnik.ru/content/medarticles/Saharnyi-diabet-novye-epidemiologicheskie-dannye-i-mehanizmy-progressirovaniya-v-fokuse-ADA-2025.html. Russian

[15] Diabetes global report 2000–2050. Available from: https://diabetesatlas.org/data-by-location/global/

[16] Diabetes Rates by Country; 2025. Available from: https://worldpopulationreview.com/ country-rankings/diabetes-rates-by-country

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S. Kaptoge et al. (2023) [34]. When DM was diagnosed at the age of 30–39 years, the hazard ratio (HR) [95% CI] was 2.69 (95% CI 2.43–2.97); 2.26 (2.08–2.45) at the age of 40–49 years; 1.84 (1.72–1.97) at the age of 50–59 years, 1.57 (1.47–1.67) at the age of 60–69 years, and 1.39 (1.29–1.51) at the age of 70 years and older. Using mortality rates in the United States, a 50-year-old with DM died on average 14 years earlier when diagnosed at age 30, 10 years earlier when diagnosed at age 40, or 6 years earlier when diagnosed at age 50 than a person without DM. Using mortality rates in the EU, the corresponding estimates were made 13, 9, or 5 years earlier.

The distribution of beneficiaries by HbA_{1c} level, as an indicator of the effectiveness of hypoglycemic therapy, confirms the dependence on the type of DM and indicates an increase in the proportion of patients with a glycated hemoglobin level of up to 7.0%, and the failure to achieve the accepted target indicators.

An increase in the proportion of beneficiaries with high BMI values indicates possible negative consequences associated with complications in DM, which may constitute an independent scientific direction for studying complications in DM, and which must be taken into account when adjusting hypoglycemic therapy.

It has been established that BMI is closely related to the development of type II DM, and HbA_{1c}[17] is an objective indicator of glycemic control [35]. A cross-sectional study involving 200 patients with type II DM was conducted. BMI and HbA_{1c} levels were recorded. Patients were divided into groups with normal weight (BMI < 25 kg/m^2), overweight (25 ≤ BMI <30 kg/m^2), and obese (BMI ≥ 30 kg/m^2). There was a significant positive correlation between BMI and HbA_{1c} level ($r = 0.45$, $p < 0.001$). In obese patients, the HbA_{1c} level was significantly higher (8.5 [7.8–9.0] %) compared to overweight patients (7.7 [7.2–8.1] %, $p < 0.01$) and normal weight patients (6.9 [6.4–7.5] %, $p < 0.001$). A graded relationship indicated deterioration in glycemic control with increasing BMI [36].

Type I and II DM is a serious disease that lasts a lifetime. Over the years, the prevalence of DM has increased worldwide, and it is classified as one of the leading causes of high mortality and morbidity. In addition, DM creates a huge economic burden due to the costs of its treatment, and its complications from the disease are growing rapidly [37]. Traditional medicines for the treatment of DM, aimed at insulin secretion and increasing insulin sensitivity (SGLT-2 inhibitors and GLP-1 RA), cause undesirable side effects in patients and lead to non-compliance with the doctor's requirements, and, as a result, to the ineffectiveness of the treatment. In drug therapy with hypoglycemic drugs, it is important to reduce hypoglycemia, use SGLT-2 inhibitors and GLP-1 RA [38].

The identified changes in the ratio of prescriptions of groups and trade names of drugs in the structure of DM therapy necessitate a more detailed study of the use of oral hypoglycemic agents in DM therapy.

The obtained results of the characteristics of beneficiaries with DM can be used to improve the organization of preferential drug provision for patients with DM in combination with regional features of providing patients in this group.

Study limitations

The study used a significant proportion of the number of patients with DM, and the results obtained are reliable in the quantitative characterization of patients with DM. However, this study did not consider the entire system of drug provision for patients with DM in the Stavropol Territory and did not assess the quantitative and qualitative indicators of its implementation. The main complications of DM associated with increased BMI and duration of the disease were also not studied, and the nomenclature of oral hypoglycemic agents used in the therapy of beneficiaries with high HbA1c values was not considered. The work includes data on the medical and social characteristics of beneficiaries, which in this case is an important aspect of understanding all aspects of drug provision for patients with type I and II DM in the Stavropol Territory.

CONCLUSION

A retrospective analysis of the beneficiary population based on the duration of the disease showed an increase in the proportion of patients with type 1 and type 2 DM with a disease duration of up to 5 years, which may be due to the timely organization of DM diagnosis. An increase in the number of patients with disease duration of more than 10 years indicates the availability of medical care and drug provision for patients with DM.

[17] Use of Glycated Haemoglobin (HbA1c) in the Diagnosis of Diabetes Mellitus: Abbreviated Report of a WHO Consultation. Geneva: World Health Organization; 2011. 2, Glycated haemoglobin (HbA_{1c}) for the diagnosis of diabetes. Available from: https://www.ncbi.nlm.nih.gov/books/NBK304271/

In the analyzed period, there was a slight but stable increase in the life expectancy of beneficiaries with type 1 DM, while for patients with type 2 DM, it remains practically stable — about 73 years, which is higher than the life expectancy for type 1 DM. The results obtained are a positive factor and indicate a positive organization of medical care for patients.

A positive trend was noted in achieving a HbA_{1c} level of up to 7.0% for both beneficiaries with type 1 DM (the proportion of patients increased from 21.12% in 2020 to 23.92% in 2025) and for every third patient with type 2 DM, but at the same time, the results achieved are still below the target indicators of the regional program "Fighting Diabetes Mellitus" and the Federal project "Fighting Diabetes Mellitus".

A significant achievement is the trend of decreasing the proportion of patients with higher HbA_{1c} values — from 8.0 to 8.9 — for both patients with type 1 and type 2 DM. The results of studying the BMI level indicate the presence of obesity for every third beneficiary with type 1 DM and for almost 70.0% of beneficiaries with type 2 DM, which may negatively affect the functioning of organs and systems of the body, contributing to the development of DM complications. Changes were identified in the ratio of prescriptions of groups and trade names of drugs in the structure of DM therapy.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Rosa I. Yagudina — conceptualization, data curation, formal analysis, writing — review & editing.
Olga L. Listova — data analysis and curation, validation, visualization, writing — original draft. All authors confirm that their authorship meets the international ICMJE criteria (all authors made a significant contribution to the development of the concept, conduct of the study and preparation of the article, read and approved of the final version before the publication).

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Evaluation of Physicochemical Properties and Biological Activity of Tirzepatide-Based Drugs

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Currently, there is a steady increase in the prevalence of metabolic disorders among the population of developed countries. Among them, obesity and type 2 diabetes mellitus are the most important health problems. Tirzepatide is an innovative drug that is a dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. The medcine is effective for the treatment of type 2 diabetes mellitus and obesity. The first drug with the active substance tirzepatide in Russia was Tirzetta® (manufacturer LLC «PROMOMED RUS»), which is the first in Russia, but not in the world. The reference drug for it is Munjaro® (INN: tirzepatide, Eli Lilly and Company, USA). To date, the question of the equivalence of these drugs has not been fully studied.

The aim. To conduct a comprehensive comparative evaluation of the reproduced drug Tirzetta® (INN: tirzepatide, manufacturer LLC “PROMOMED RUS”) and the reference drug Munjaro® (INN: tirzepatide, manufacturer Eli Lilly and Company, USA).

Materials and methods. The authenticity and quality of drugs were assessed by physicochemical methods according to the current pharmacopoeia of the EAEU. Spectrophotometry in the UV region, HPLC-MS/OF, and gel filtration chromatography were performed. The analysis of agonism to GIP and GLP-1 receptors was performed *in vitro* using reporter cell lines. The studies were performed in accordance with EMA, FDA, EAEU guidelines and in accordance with the current EAEU pharmacopoeia.

Results. As a result of the evaluation of the physicochemical properties of the studied series of Tirzetta® and the reference drug Munjaro®, it was found out that the absorption spectra in the ultraviolet region, the profile of related impurities and their quantitative content, the profile of high-molecular-weight compounds and their quantitative content, as well as mass spectra in all the studied series were similar. During the evaluation of the biological activity of the Tirzetta® and Munjaro® series, results were obtained that demonstrated the absence of statistically significant differences in the ability to activate GLP-1 and GIP receptors (p <0.0001).

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Conclusion. During the studies, the equivalence of the physicochemical properties and biological activity of the Russian drug Tirzetta® to the comparator drug Munjaro® was confirmed.
Keywords: tirzepatide; peptide; synthetic peptide; glucagon-like peptide-1; glucose-dependent insulinotropic polypeptide; biological activity; safety; physicochemical properties; metabolic syndrome; type 2 diabetes mellitus
Abbreviations: DM — diabetes mellitus; MS — metabolic syndrome; ND — normative documentation; RRT — relative retention time; BMI — body mass index; GLP-1 — glucagon-like peptide type 1; GLP-1-R — glucagon-like peptide type 1 receptor; GLP-1a — glucagon-like peptide type 1 receptor agonist; GIP — glucose-dependent insulinotropic polypeptide; GIP-R — glucose-dependent insulinotropic polypeptide receptor; EMA — European Medicines Agency; LP — medicinal product; INN — international nonproprietary name; EAEU — Eurasian Economic Union; HPLC-MS/OF — high-performance liquid chromatography with mass spectrometry/reversed-phase; HRMS — high-resolution mass spectra; ESI — electrospray ionization; GFC — gel filtration chromatography; cAMP — cyclic adenosine monophosphate.

Оценка физико-химических свойств и биологической активности лекарственных препаратов на основе тирзепатида

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В настоящее время среди населения развитых стран наблюдается устойчивый рост распространенности метаболических нарушений. Из них ожирение и сахарный диабет 2 типа представляют наиболее актуальную проблему для здравоохранения. Тирзепатид является инновационным лекарственным препаратом, представляющим собой двойной агонист рецепторов глюкозозависимого инсулинотропного полипептида (ГИП) и глюкагонподобного пептида типа 1 (ГПП-1). Препарат эффективен для лечения сахарного диабета

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2 типа и ожирения. Первым лекарственным препаратом с действующим веществом тирзепатид в России стал Тирзетта® (производитель ООО «ПРОМОМЕД РУС»), который является первым в России. Референтным лекарственным препаратом для него выступает Мунджаро® (МНН: тирзепатид, Eli Lilly and Company, США). Вопрос об эквивалентности этих лекарственных препаратов является важным и актуальным для уверенности медицинского сообщества в высоком качестве проводимой терапии.

Цель. Провести комплексную сравнительную оценку воспроизведённого лекарственного препарата Тирзетта® (МНН: тирзепатид, производитель ООО «ПРОМОМЕД РУС») и референтного препарата Мунджаро® (МНН: тирзепатид, производитель Eli Lilly and Company, США).

Материалы и методы. Оценка подлинности и качества лекарственных препаратов осуществлялась физико-химическими методами согласно действующей фармакопеи ЕАЭС. Проводили спектрофотометрию в УФ области, ВЭЖХ-МС/ОФ, гель-фильтрационную хроматографию. Анализ агонизма к рецепторам ГИП и ГПП-1 проводили *in vitro* при помощи репортерных клеточных линий. Проведённые исследования выполнены в соответствии с руководствами EMA, FDA, ЕАЭС и согласно действующей фармакопее ЕАЭС.

Результаты. В результате оценки физико-химических свойств исследуемых серий препарата Тирзетта® и референского препарата Мунджаро® установлено, что спектры поглощения в ультрафиолетовой области, профиль родственных примесей и их количественное содержание, профиль высокомолекулярных соединений и их количественное содержание, а также масс-спектры во всех исследуемых сериях были аналогичны. В ходе оценки биологической активности серий препарата Тирзетта® и Мунджаро® были получены результаты, демонстрирующие сопоставимость биологической активности вышеуказанных препаратов и высокую эффективность исследуемого препарата в отношении активации рецепторов ГПП-1 и ГИП (p <0,0001).

Заключение. В ходе проведённых исследований была подтверждена эквивалентность физико-химических свойств и биологической активности российского лекарственного препарата Тирзетта® препарату сравнения Мунджаро®.

Ключевые слова: тирзепатид; пептид; синтетический пептид; глюкагоноподобный пептид-1; глюкозозависимый инсулинотропный полипептид; биологическая активность; безопасность; физико-химические свойства; метаболический синдром; сахарный диабет 2 типа

Список сокращений: СД — сахарный диабет; МС — метаболический синдром; НД — нормативная документация; ОВУ — относительное время удерживания; ИМТ — индекс массы тела; ГПП-1 — глюкагонподобный пептид типа 1; ГПП-1-Р — рецептор глюкагонподобного пептида типа 1; ГПП-1а — агонист рецептора глюкагонподобного пептида типа 1; ГИП — глюкозозависимый инсулинотропный полипептид; ГИП-Р — рецептор глюкозозависимого инсулинотропного полипептида; EMA — Европейское агентство лекарственны средств; ЛП — лекарственный препарат; МНН — международное непатентованное наименование; ЕАЭС — Евразийский экономический союз; ВЭЖХ-МС/ОФ — высокоэффективная жидкостная хроматография с масс-спектрометрией/обращенно-фазовая; HRMS — масс-спектры высокого разрешения; ESI — ионизационное электрораспыление; ГФХ — гель-фильтрационная хроматография; цАМФ — циклический аденозинмонофосфат.

INTRODUCTION

Metabolic diseases, including type 2 diabetes mellitus (DM) and obesity, are among the most accute problems in modern healthcare. According to the Russian register as of January 01, 2023, 4,962,762 people (3.31% of the Russian Federation population) are registered for dispensary observation, of which 92.33% (4.58 million) have type 2 DM. The incidence of type 2 DM among the adult population is 191.4 per 100,000 population [1].

Metabolic syndrome (MS), the main components of which are arterial hypertension (33.5%), hypercholesterolemia (29.0%) and obesity, is becoming an epidemic in economically developed countries. Up to 16–30% of residents of these countries suffer from various forms of MS, which is associated with a multiple increase in the risk of cardiovascular diseases and an increase in mortality [2]. According to the World Obesity Atlas, it is expected that by 2035 more than 1.77 billion people will be overweight (body mass index [BMI] = 25–29.9 kg/m^2), and 1.53 billion will suffer from obesity (BMI > 30 kg/m^2) [3]. Forecasts are disappointing and show a steady increase in these indicators up to 2050 [4].

Methods for preventing and treating various forms of MS are based on a multimodal approach, including lifestyle changes, drug and surgical methods, personalized monitoring technologies, and psychosocial support [5, 6]. The use of new classes of drugs and evidence-based prevention strategies helps to improve metabolic control and reduce the development of complications.

Over the past decade, new effective drug treatments for type 2 DM and obesity have been developed. Thus, glucagon-like peptide 1 receptor agonists (GLP-1a) — semaglutide and liraglutide — have shown high efficacy in achieving weight loss and improving glycemic control [7, 8]. The evolution of the pharmacological approach based on agonism of GLP-1 receptors has manifested in the emergence of multiagonists of the “incretin axis” components, which contributes to a significant increase in glycemic

control and comprehensive correction of metabolic disorders [9]. The results of preclinical and clinical studies have demonstrated the high therapeutic potential of these drugs [9]. To date, the only registered drug (LP) of this class is tirzepatide, a dual agonist of GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors [10]. Tirzepatide was first registered in 2021 in the USA (trade name [TN] — Mounjaro®, manufacturer Eli Lilly and Company) [11]. Tirzepatide preparations have not been registered in the Russian Federation, and therefore, for a long time, the population of the Russian Federation did not have access to the drugs based on this compound. The high efficacy of tirzepatide in reducing weight, treating the main components of obesity and metabolic syndrome, and preventing the risks of associated complications has been demonstrated in clinical studies, which has increased the need to develop domestic LPs to expand the geography of its use [12].

In January 2025, tirzepatide first appeared on the Russian market under the trade name Tirzetta®, manufactured by PROMED RUS LLC. The chemical synthesis method, which was used in the production of peptide molecules of the drug, has a number of potential advantages: a more controlled production process, a reduced risk of contamination with biological impurities, and the possibility of precise control of the structure of the final product [13]. However, for complex peptides such as tirzepatide, chemical synthesis requires careful optimization of reaction conditions and purification methods. In this regard, the own production technology of the substance used for the domestic drug Tirzetta® is of particular importance.

It is worth noting that proving the bioequivalence of reproduced drugs is becoming an integral part of the process of their registration, which is confirmed by the current requirements of both national regulators and international agencies, such as the European Medicines Agency (EMA). In April 2024, the discussion of the EMA guideline "Guideline on the Development and Manufacture of Synthetic Peptides" was completed, which defines the main requirements for methods of characterization, quality control and production processes of drugs based on synthetic peptides[1] [14]. This guideline serves as the foundation for ensuring that reproduced drugs meet established criteria for quality, safety and efficacy. According to the provisions of the guideline, to confirm the equivalence of two peptides in the composition of the drug, it is sufficient, and in many cases even more representative, to present evidence of compliance of their physicochemical properties and biological activity with accurate modern research methods.

THE AIM. To conduct a comprehensive comparative study of the physicochemical properties and biological activity of Tirzetta® (INN: tirzepatide) and the reference drug Mounjaro® (INN: tirzepatide).

MATERIALS AND METHODS

Samples

In order to form a representative quality profile and obtain reliable data on the comparability of the active substance tirzepatide in two equivalent preparations, three series of the reproduced drug were used. Information about the studied series is presented in Table 1.

Comparative studies of the physicochemical properties of drugs

To analyze the spectral characteristics of the drugs, spectrophotometry was performed in the ultraviolet region (200–400 nm) in accordance with the recommendations of the current pharmacopoeia of the EAEU, Article 2.1.2.53[2]. When comparing absorption spectra in the UV region, the solutions of each series of each drug were diluted with water for injection to a tirzepatide concentration in the solution of 0.5 mg/mL. The initial solutions of each series were obtained by mixing the contents of 7 cartridges of syringe pens and taking an averaged sample. The analysis was performed on a Shimadzu UV-1800 spectrophotometer (Shimadzu, Japan).

High-resolution mass spectra (HRMS) were recorded on an LCMS-9030 instrument (Shimadzu, Japan) using electrospray ionization (ESI). Measurements were performed in positive ion mode. Samples were dissolved in deionized water to a concentration of 1.25 mg/mL and introduced in a volume of 0.1 µL into the mass spectrometer dispenser without separation. The following parameters were used: capillary voltage — 4.5 kV; mass scanning range — 100–5000 m/z; external calibration — with a solution of NaI in MeOH/H_2O; drying and heating

[1] EMA. Development and manufacture of synthetic peptides – Scientific guideline. Available from: https://www.ema.europa.eu/en/development-and-manufacturesynthetic-peptides-scientific-guideline

[2] 2.1.2.53. Raman spectrophotometry. Pharmacopoeia of the Eurasian Economic Union. Available from: https://eec.eaeunion.org/upload/medialibrary/9de/2-chast-1-toma-Farmakopei-Soyuza-s-vozmozhnostyu-poiska_.pdf

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gases (nitrogen) — 10 l/min each; spraying gas (nitrogen) — 3 l/min; interface temperature — 300°C; acetonitrile / water (5 / 95) flow rate — 0.4 ml/min. Data were processed using LabSolutions v.5.114.

Confirmation of authenticity and determination of the quantitative content of tirzepatide were performed by high-performance liquid chromatography (HPLC). The determination was carried out in accordance with the requirements of the EAEU pharmacopoeia (Article 2.1.2.28).

The analysis was performed using a high-pressure liquid chromatograph with a UV detector on a diode matrix on a Kinetex C18, 100 Å column, (4.6 × 150 mm, particle size 2.6 µm), filled with L1 type sorbent (manufacturer Phenomenex, cat. No. 00F-4462-E0). Tirzepatide was identified at a wavelength of 210 nm (optimal for peptide bond). The column temperature was 30°C, the mobile phase flow rate was 0.7 ml/min, the autosampler temperature was 5°C, and the chromatography time was 30 min. Elution was performed at a mobile phase ratio (A/B) of 45:55. Under these conditions, the approximate retention time of the tirzepatide peak was from 14 to 20 min.

Next, a standard sample (SS) of a given concentration was prepared. For this: about 15.0 mg (exact weight) of tirzepatide SS was placed in a 10 mL volumetric flask, 8 mL of solvent was added, mixed until the substance was completely dissolved, the volume of the solution was brought to the mark with the solvent and mixed again (tirzepatide concentration — 1.5 mg/mL).

Authenticity was confirmed by comparing the retention time and UV spectrum of the test peak with the tirzepatide standard. The quantity of the substance was calculated by comparing the peak areas of the analyzed samples and the standard.

Before starting the measurements, the suitability of the chromatographic system was checked according to section 2.1.2.36.

Chromatographic System Suitability Test (SST):

The chromatographic system is suitable if:

- The relative standard deviation of the peak area values of tirzepatide for five consecutive chromatograms of the standard solution is not more than 2.0%;
- The relative standard deviation of the retention time of tirzepatide peaks for five consecutive chromatograms of the standard solution is not more than 2.0%;
- The symmetry factor calculated for the tirzepatide peak on the chromatogram of the standard solution is 0.8–2.0;
- The number of theoretical plates calculated for the tirzepatide peak on the chromatogram of the standard solution is not less than 1000.

The quantitative determination of impurities was also performed by reversed-phase HPLC (RP-HPLC) according to section 2.1.2.28 of the Eurasian Economic Union Pharmacopoeia using a gradient elution mode.

To analyze impurities, a standard solution was prepared: approximately 15.0 mg (exact weight) of the tirzepatide standard was placed in a 10 mL volumetric flask, 8 mL of solvent was added, stirred until the substance was completely dissolved, the volume of the solution was brought to the mark with the solvent, and stirred again. Then, 1 mL of the resulting solution was placed in a 100 mL volumetric flask, the volume of the solution was brought to the mark with the solvent, and mixed (tirzepatide concentration — 0.015 mg/mL).

A 100 mM phosphate buffer solution pH 7.5 was used as a solvent. Mobile phase A was prepared: 9.2 g of ammonium dihydrogen phosphate R was placed in a 1000 mL beaker, dissolved in 800 mL of water for chromatography R, the pH of the resulting solution was adjusted to 3.7 ± 0.1 potentiometrically using phosphoric acid R, 100 mL of acetonitrile for chromatography R was added, and stirred. Quantitatively transferred to a 1000 mL volumetric flask, the volume of the solution was brought to the mark with water for chromatography R and stirred. The mobile phase was filtered through a nylon membrane filter with a pore size of 0.45 µm (Water Laboratory LLC, cat. No. NY045050L or equivalent quality), discarding the first 100 mL of filtrate and degassing under vacuum.

Mobile phase B: 200 mL of water for chromatography R, 600 mL of acetonitrile for chromatography R, and 200 mL of 2-propanol R were mixed. Stir and sonicate for about 15 min, cool to room temperature.

For dosing the test solution, 2.5 mg, the contents of 7 syringes / cartridges were mixed and an average sample was taken. Then, 1.5 mL of the drug was placed in a 5 mL volumetric flask, the volume of the solution was brought to the mark with the solvent and mixed (tirzepatide concentration — 1.5 mg/mL). 2 solutions were prepared. For a dosage of 5 mg, the contents of 4 syringes/cartridges were mixed and an average sample was taken. Then, 0.75 mL of the drug was placed in a 5 mL volumetric flask, the volume of the solution was brought to the mark with the solvent

and mixed (tirzepatide concentration — 1.5 mg/mL). 2 solutions were prepared.

Placebo solution: 3.0 mL (for a dosage of 2.5 mg), 1.5 mL (for a dosage of 5 mg), 1.0 mL (for a dosage of 7.5 mg), 0.75 mL (for a dosage of 10 mg), 0.6 mL (for a dosage of 12.5 mg), 0.5 mL (for a dosage of 15 mg) of a mixture of excipients included in the drug were placed in a 10 mL volumetric flask, the volume of the solution was brought to the mark with the solvent and mixed.

Chromatographic System Suitability Test (SST):

The chromatographic system is suitable if:

- The signal-to-noise ratio for the tirzepatide peak on the chromatogram of the solution for checking sensitivity is not less than 10;
- The relative standard deviation of the peak area values of tirzepatide on five consecutive chromatograms of the standard solution is not more than 5.0%;
- The symmetry factor of the tirzepatide peak on the chromatograms of the standard solution is 0.8–2.0;
- The number of theoretical plates calculated for the tirzepatide peak on the chromatogram of the standard solution is not less than 1000;
- The peak-to-valley ratio (p/v) between the tirzepatide peak and the peak with a relative retention time of about 1.11 on the chromatogram of the solution for checking resolution is not less than 1.2.

Table 2 shows the gradient programming parameters.

Under the conditions described, the approximate retention time of tirzepatide tirzepatide was from 23 to 27 minutes.

The quantitative determination of high molecular weight compounds was performed by gel filtration chromatography (GFC) in accordance with the requirements of the Eurasian Economic Union Pharmacopoeia 2.1.2.28. The study was performed on a high-pressure liquid chromatograph with a UV detector on a column filled with a sorbent (silica gel with chemically modified dihydroxypropane groups (L20) Waters Insulin HMWP, 7.8 mm × 300 mm, particle size 10 µm, (manufacturer Waters)). The detection wavelength was 280 nm, the mobile phase flow rate was 0.5 mL/min, the column thermostat temperature was 50°C, the autosampler temperature was 5°C, the injected sample volume was 40 µL; the chromatography time was 30 min with an isocratic elution mode. According to the validation results, the retention time of the monomer peak was about 16 min. The approximate retention time of high molecular weight compound peaks is about 15 min (immediately before the monomer peak). All studies were performed in three independent replicates.

The solution prepared according to the following procedure was used as the mobile phase: 29.2 g of sodium chloride R and 1.56 g of sodium dihydrogen phosphate R were placed in a 1000 mL volumetric flask, dissolved in 400 mL of water for chromatography R, 0.34 mL of phosphoric acid R and 500 mL of 2-propanol R were added, and stirred. The volume of the solution was brought to the mark with water for chromatography R and stirred. Filtered under vacuum through a nylon membrane filter with a pore diameter of 0.45 µm (Water Laboratory LLC, cat. No. NY045050L or equivalent quality), discarding the first portions of the filtrate.

For a dosage of 2.5 mg, 1.5 mL of the aged solution was placed in a 5 mL volumetric flask, the volume of the solution was brought to the mark with the solvent, mixed and filtered through a regenerated cellulose (RC) membrane filter with a pore size of 0.45 µm (Water Laboratory LLC, cat. No. SFRCL04525 or equivalent quality) (tirzepatide concentration — 1.5 mg/mL).

For a dosage of 5 mg, 0.75 mL of the aged solution was placed in a 5 mL volumetric flask, the volume of the solution was brought to the mark with the solvent, mixed and filtered through a regenerated cellulose (RC) membrane filter with a pore size of 0.45 µm (Water Laboratory LLC, cat. No. SFRCL04525 or equivalent quality) (tirzepatide concentration — 1.5 mg/mL).

The standard solution was prepared similarly to the above method “Confirmation of authenticity and determination of the quantitative content of tirzepatide”. The test solution was prepared according to the method for quantitative determination of impurities.

Chromatographic System Suitability Test (SST):

The chromatographic system is suitable if:

- The relative standard deviation, calculated from the areas of the tirzepatide monomer peaks on the chromatograms of the standard solution with repeated injections, is not more than 5.0%;
- The symmetry factor for the tirzepatide monomer peak on the chromatogram of the standard solution is 0.8–2.0;
- The number of theoretical plates calculated for the tirzepatide monomer peak on the chromatogram of the standard solution is not less than 1000;

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- The signal-to-noise ratio for the tirzepatide monomer peak on the chromatogram of the solution for checking sensitivity is not less than 10.

In vitro biological activity study

A comparative *in vitro* study of the biological activity of the investigated drugs was performed on two model systems, which are cell lines expressing the human GLP-1 receptor (GLP1R/CRE-Luc/HEK293, Cobioer, cat. No. CBP71117, China) or GIP (GIPR/CRE-Luc/HEK293 Cobioer, cat. No. CBP71346, China) with a reporter construct stably integrated into the genome under the control of a Cre-dependent promoter. Treatment of cells of this model system with agonists of the GGP-1 or GIP receptor activates the signaling pathway, which causes the expression of the luciferase gene. In the absence of agonists, the receptor is not activated, and the luminescence signal is low. In the presence of an agonist, luminescence activated by GLP-1R or GIPR (depending on the cell line) can be detected in a dose-dependent manner by detecting bioluminescence [14].

GIPR/CRE-Luc/HEK293 and GLP1R/CRE-Luc/HEK293 cell lines were cultured according to the manufacturer's instructions. To study agonism, cells were seeded into the wells of a 96-well plate at a rate of 40 thousand cells/well in a volume of 100 µL per well. After 24 hours, the comparator drug Mounjaro® or samples of the drug Tirzetta® (INN: Tirzepatide) were added to the cells in a volume of 10 µL per well so that the required drug concentration was achieved upon addition. The range of investigated concentrations was selected according to the manufacturer's instructions and ranged from 10^{-12} to 10^{-6} M. Testing was carried out in a concentration range covering both the minimum and maximum effective doses (according to the manufacturer's instructions). Growth medium, which was added in the same volume, was used as a negative control. After adding the samples, the cells were incubated at 37°C in a CO_2 incubator for the required incubation time (5 hours according to the manufacturer's instructions). Then, the cells were lysed using a buffer containing the luciferase substrate (D-luciferin) using a commercial kit for analyzing firefly luciferase activity, ONE-Step™ Luciferase Assay System (BPS Biosciences, China) in accordance with the manufacturer's protocol. 100 µL of the working substrate solution was added to each well of the plate, and the luminescence signal intensity was determined using the luminometric module of the Perkin-Elmer EnVis system (Perkin Elmer, USA) after 15–20 minutes of incubation after application. The specific activity of the investigated drugs (ED_{50}) was calculated as the dose at which 50% of the maximum effect is achieved, based on the activity values obtained from three independent tests.

Statistical analysis

Molecular ions in the spectra were analyzed in LabSolutions v.5.114. The statistical processing of the results was performed using GraphPad Prizm 10.4.2 software (GraphPad Software, USA). The acceptance criteria for the results were selected according to the requirements of the current pharmacopoeia of the EAEU FS 2.3.12.0, Decision of the EEC No. 85, as well as according to the Guidelines for Preclinical Studies of Medicines edited by Mironov A.N. (2013)[3,4]. An assessment of the parameters of the initial data was carried out (the presence of outliers, data distribution, assessment of the homogeneity of variances) to determine further statistical methods according to the FEAES. The statistical significance of the model was verified using Fisher's F-test at $p < 0.05$ and a coefficient of determination R2 from 0.7 to 1. The choice of using R2 and the F-test together is due to the need to obtain the most objective assessment of the quality of the model. Only when this indicator is achieved is the model considered statistically reliable and suitable for further use[5,6].

Preliminary processing of biological activity data included normalization of the initial luminescence intensity values.

The presence of outliers in the sample was determined using the ROUT method. The final processing included constructing a dose-response curve based on normalized data using a non-linear regression method. The dose-response analysis and comparison of the test samples were carried out taking into account

[3] Guidance for preclinical studies of medicines; Scientific Center for Expertise of Medical Products of the Ministry of Health and Social Development of Russia; Volume 1. Moscow: Grif and K; 2012. 944 p. EDN: SDEWMP. Russian

[4] Decision of Council of the Eurasian Economic Commission of November 3, 2016 No. 85 «About approval of Rules of carrying out researches of bioequivalence of medicines within the Eurasian Economic Union». Available from: https://www.alta.ru/tamd oc/16sr 0085/?ysclid=mfpibknu6g985461506

[5] Guidance for preclinical studies of medicines; Scientific Center for Expertise of Medical Products of the Ministry of Health and Social Development of Russia; Volume 1. Moscow: Grif and K; 2012. 944 p. EDN: SDEWMP. Russian

[6] Yunkerov VI, Grigoriev SG. Mathematical and statistical processing of medical research data; Saint Petersburg: Kirov Military Medical Academy; 2002. 266 p. EDN: XYHSQB. Russian

the application of a mathematical model according to the following parameters: the value of the upper and lower asymptotes, the value of the slope (β); the value of the relative specific activity of the sample.

A 4-parameter logistic model was chosen for statistical analysis — an extended form of the classical logistic function, which includes four parameters for a more accurate description of the dose-effect curve: minimum effect (lower asymptote), maximum effect (upper asymptote), EC_{50} (dose causing 50% effect), β — slope.

The primary data obtained in the study were presented as mean (M) and standard deviation (SD).

RESULTS

UV spectroscopy

To date, the current pharmacopoeias do not contain established optical density values for tirzepatide. The results of our study showed that the UV absorption spectra of the reproduced drug Tirzetta® and the reference Mounjaro® are similar (Fig. 1, Table 3).

Thus, the absorption spectra in the ultraviolet region of Tirzetta® and Mounjaro® are similar, which indicates the identity of the molecule's structure.

High-performance liquid chromatography coupled with mass spectrometry provides high-precision determination of molecular weight by ion peaks in the MS spectrum. Figure 2 shows the mass spectra of the medicinal product Mounjaro® and Tirzetta®.

Thus, the mass spectra in all the studied series of Tirzetta® and Mounjaro® are comparable and correspond to the calculated mass of tirzepatide.

Determination of authenticity and quantitation of tirzepatide by reversed-phase high-performance liquid chromatography

In the chromatograms of all test solutions, there was a peak corresponding to the retention time of the tirzepatide peak under the specified conditions. The chromatograms of the test and standard samples were comparable (permissible deviation ±15% from the retention time of the standard sample) (GPhM.1.2.1.2.0001 Chromatography)[7]. The content of tirzepatide in all samples corresponded to the norms (Fig. 3).

[7] GPhM.1.2.1.2.0001 Chromatography. The State Pharmacopoeia of the Russian Federation XV edition. Available from: https://pharmacopoeia.regmed.ru/pharmacopoeia/izdanie-15/1/1-2/1-2-1/1-2-1-2-khromatograficheskie-metody-analiza/khromatografiya/. Russian

Determination of impurities

The results of the quantitative determination of impurities are presented in Table 4.

The profile of related impurities and their quantitative content in the samples of the Mounjaro® and Tirzetta® corresponds to the regulatory documentation for the drugs. However, our own technology for the synthesis and purification of the active pharmaceutical substance made it possible to significantly reduce the number of hydrophilic and hydrophobic impurities.

The quantitative assessment of high-molecular-weight compounds in the composition was performed by gel-filtration HPLC. The evaluation was performed at a wavelength of 280 nm. The retention time of tirzepatide for all drugs ranged from 15 to 18 minutes. The peaks of high-molecular-weight compounds were located directly in front of the tirzepatide peak. The retention time was about 15 minutes (Fig. 4).

The results of the quantitative determination of high-molecular-weight compounds in samples are presented in Table 5.

Thus, the profile of high-molecular-weight compounds and their quantitative content in the Mounjaro® and Tirzetta® are similar.

Comparative *in vitro* bioactivity study

The bioactivity study of drugs was conducted by assessing the sensitivity upon activation of GIP and GLP-1 receptors in cell culture. A comparative *in vitro* study of the bioactivity of the reproduced drug Tirzetta® and the reference drug Mounjaro® on the GLP1R/CRE-Luc/HEK293 and GIPR/CRE-Luc/HEK293 reporter cell line model was performed in three independent biological replicates. The obtained primary data and calculated results met the system suitability requirements and acceptance criteria.

The results of the primary data evaluation on the GLP1R/CRE-Luc/HEK293 model (Table 6) showed that the coefficients of variation do not exceed 30% in each experimental point, and the data spread (i.e., variance) is homogeneous.

The coefficients of variation for each drug concentration value, as well as the results of the assessment of the homogeneity of the sample variance, are presented. In Figure 5, samples of Tirzetta® and the reference drug Mounjaro® demonstrates a positive dose-response relationship in the experimental model.

The results of the statistical analysis of the curves are presented in Table 7 as M ± SD with the given values of the coefficients of covariance CV (%).

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The results of the primary data assessment on the GIPR/CRE-Luc/HEK293 model (Table 8) showed that the CV do not exceed 30% in each experimental point, and the data spread (i.e., variance) is homogeneous.

In the presented graph (Fig. 6), samples of Tirzetta® and Mounjaro® demonstrate a positive dose-response relationship in the experimental model GIPR/CRE Luciferase Reporter HEK293.

A 4-parameter logistic model was used for statistical analysis. The are presented in Table 9 as M ± SD with the values of the CV (%).

Thus, during the assessment of the biological activity of Tirzetta® and Mounjaro®, results were obtained that demonstrate the absence of statistically significant differences in the ability to activate GLP-1 and GIP receptors ($p < 0.0001$).

The obtained data allow us to characterize the developed method, as well as the selected test systems, as having high discriminative ability. This is confirmed by the low values of the variance of the average luminescence indicators, which, in turn, ensures high power of the analysis of variance. The low level of within-group variability contributes to increasing the sensitivity of statistical tests to detect even minimal intergroup differences.

Thus, the conformity of the biological activity profile of the reproduced drug Tirzetta® (INN: tirzepatide; solution for subcutaneous administration, 2.5 mg, manufacturer JSC “Biochemist”, Russia) to the reference drug Mounjaro® (INN: tirzepatide, solution for injection, 5 mg, Eli Lilly and Company, USA) was confirmed within the framework of work using a reproducible and accurate method.

DISCUSSION

In recent years, the concept of multi-agonism in endocrinology has developed significantly. Multi-agonists of the “incretin axis” are a promising tool for controlling metabolic disorders. The evolution of the pharmacological approach based on GLP-1 receptor agonism includes the study of various dual and triple multi-agonists capable of simultaneously activating GLP-1, GIP, and glucagon receptors.

Simultaneous activation of GLP-1 and GIP receptors overcomes the limitations of GLP-1 receptor agonist monotherapy [9]. GLP-1 and GIP are incretin hormones that are released in the intestine in response to nutrient intake and stimulate the activity of β-cells of the pancreas with subsequent insulin secretion. The key insulinotropic effect of GLP-1 is carried out through a receptor associated with the class B G-protein and is manifested through the formation of cyclic adenosine monophosphate (cAMP) [12]. GIP, consisting of 42 amino acid residues and secreted by neuroendocrine k-cells of the duodenum and jejunum in response to nutrient intake, stimulates insulin secretion to a greater extent compared to GLP-1 [9]. The most important feature of GIP is their location directly in adipocytes, which leads to weight loss precisely due to fat, and not muscle tissue, ensuring the formation of a silhouette and, most importantly, metabolically healthy weight loss. It is also worth noting that the activation of GIP neutralizes some undesirable reactions that may occur against the background of the use of GLP-1 agonists in some cases. Thus, GIP activation leads to a decrease in the frequency of nausea and other reactions from the gastrointestinal tract [10].

The successful development of chemically synthesized tirzepatide can stimulate further research in the field of chemical synthesis of other incretin drugs, including GLP-1 receptor agonists and future multi-agonists, which may lead to the creation of new, more effective therapeutic options [9].

The specifics of determining the specific activity of drugs based on complex protein and peptide molecules require an integrated approach, including both physicochemical and biological methods of analysis [15].

Assessment of physicochemical properties

Assessment of protein absorption of UV radiation is a reliable and sensitive method for determining the structure of proteins, which affects their folding and functionality [16]. Spectrophotometry showed identical absorption curves in the UV region: maximum absorption in the region below 230 nm, a shoulder in the range of 225–230 nm and a pronounced peak at 291 nm. The coincidence of the spectra indicates the conformational equivalence of both drugs [17].

Of particular importance is the absence of differences in the profile of related impurities and degradation products, since these factors can affect the safety and efficacy of the drug. Such impurities in a drug containing a peptide can be formed as a result of the destruction of the active substance during production or storage and affect the efficacy and safety of the final product [18]. Such impurities also include peptides with an incorrectly structured structure resulting from errors in the amino acid sequence, removal of individual amino acid residues, as well as oxidation or racemization of amino acids [19].

Table 1 — Study objects

Drug Name	Manufacturer	Series	Expiration Date
Tirzetta®, solution for subcutaneous administration, 2.5 mg (Tirzetta®-1)	JSC "Biochimik", Russia	010124	01/2026
Tirzetta®, solution for subcutaneous administration, 2.5 mg (Tirzetta®-2)	JSC "Biochimik", Russia	020124	01/2026
Tirzetta®, solution for subcutaneous administration, 2.5 mg (Tirzetta®-3)	JSC "Biochimik", Russia	030124	01/2026
Mounjaro®, solution for injection, 5 mg	Eli Lilly and Company, USA	D665365A	04/2025

Table 2 — Gradient elution program for the assessment of impurities in tirzepatide drugs

Time, min	Mobile phase A, %	Mobile phase B, %	Note
0→7	54→(45 ± 4)	46→(55 ± 4)	1 linear gradient.
7→37	(45 ± 4)	(55 ± 4)	1 stage of isocratic elution.
37→49	(45 ± 4)→10	(55 ± 4)→90	2 linear gradient.
49→52	10	90	2 stage of isocratic elution.
52→53	10→54	90→46	3 linear gradient, transition to equilibrium.
53→60	54	46	3 stage of isocratic elution, transition to equilibrium.

Table 3 — Results of spectrophotometry of tirzepatide drugs

Drug Name	Manufacturer	Series	λ_{max}, nm	λ_{min}, nm
Tirzetta®, solution for subcutaneous administration, 2.5 mg	JSC "Biochimik", Russia	010124	281.0 ± 0.7	249.4 ± 1.2
Tirzetta®, solution for subcutaneous administration, 2.5 mg	JSC "Biochimik", Russia	020124	281.2 ± 1.1	249.1 ± 0.6
Tirzetta®, solution for subcutaneous administration, 2.5 mg	JSC "Biochimik", Russia	030124	281.2 ± 0.4	249.3 ± 0.8
Mounjaro®, solution for injection, 5 mg	Eli Lilly and Company, USA	D665365A	281.2 ± 0.5	248.9 ± 0.9

Table 4 — Results of quantitative determination of impurities in samples of the studied drugs

Parameter (norm)	Tirzetta® 010124	Tirzetta® 020124	Tirzetta® 030124	Mounjaro® D665365A
Hydrophilic impurities, %				
RRT 0.81 (not more than 1.5%)	0.05 ± 0.01	0.06 ± 0.05	0.20 ± 0.08	0.34 ± 0.03
RRT 0.90 (not more than 4.0%)	–	–	0.06 ± 0.01	0.28 ± 0.04
RRT 0.94 (not more than 1.5%)	0.07 ± 0.04	0.07 ± 0.02	0.13 ± 0.07	–
Sum of hydrophilic impurities (not more than 7.0%)	0.12 ± 0.041	0.13 ± 0.054	0.39 ± 0.107	0.62 ± 0.05
Hydrophobic impurities 1, %				
RRT 1.11 (not more than 3.0%)	0.05 ± 0.02	–	–	0.49 ± 0.13
RRT 1.18 (not more than 2.0%)	0.11 ± 0.08	0.21 ± 0.06	0.48 ± 0.11	0.96 ± 0.14
Sum of hydrophobic impurities 1 (not more than 5.0%.	0.16 ± 0.082	0.21 ± 0.06	0.48 ± 0.11	1.45 ± 0.191
Hydrophobic impurities 2 (not more than 2.0%)	–	–	–	–
Single unidentified impurity (not more than 1.0%)	–	–	–	–
Sum of all impurities (not more than 10.0%)	0.28 ± 0.092	0.34 ± 0.081	0.87 ± 0.153	2.075 ± 0.197

Note: RRT — relative retention time.

Table 5 —Results of quantitative determination of high molecular weight compounds (HMWC) in the studied drugs

Drug Name	Manufacturer	Series	HMWC, %
Tirzetta®, solution for subcutaneous administration, 2.5 mg	JSC "Biochimik", Russia	010124	0.32%
Tirzetta®, solution for subcutaneous administration, 2.5 mg	JSC "Biochimik", Russia	020124	0.23%
Tirzetta®, solution for subcutaneous administration, 2.5 mg	JSC "Biochimik", Russia	030124	0.20%
Mounjaro®, solution for injection, 5 mg	Eli Lilly and Company, USA	D665365A	0.68%

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Table 6 — Assessment of primary data GLP1R/CRE-Luc/HEK293

log[C], M	The coefficient of variation, %				*p*-value
	Tirzetta®-1	Tirzetta®-2	Tirzetta®-3	Mounjaro®	
-5	7.0	5.6	3.2	7.5	0.5931
-6	5.3	7.7	3.4	4.8	0.5761
-7	6.8	5.9	3.8	10.6	0.0800
-8	4.0	7.1	9.1	9.3	0.0750
-9	9.9	8.3	8.2	15.2	0.0280
-10	11.6	15.9	26.0	25.9	0.4119
-11	25.8	23.6	17.9	11.3	0.1467
-12	28.0	7.6	18.7	9.3	0.0682

Note: * — estimating the spread of data; $p > 0.05$ — the homogeneity of the variances is confirmed.

Table 7 — Results of the analysis of logistic curves GLP1R/CRE-Luc/HEK293

Drug	Coefficient of determination, R^2	Fischer's F-test	Log EC_{50}	Ratio of the angle of inclination β to the referent
Tirzetta®-1	0.9983	F = 6900 (p < 0.0001)	-8.71 ± 0.014 CV = 0.2	0.98
Tirzetta®-2	0.9977	F = 4771 (p < 0.0001)	-8.67 ± 0.016 CV = 0.2	0.93
Tirzetta®-3	0.9985	F = 6112 (p < 0.0001)	-8.71 ± 0.014 CV = 0.2	0.93
Mounjaro®	0.9948	F = 2630 (p < 0.0001)	-8.89 ± 0.020 CV = 0.2	–

Table 8 — Assessment of primary data GIPR/CRE-Luc/HEK293

log[C], M	The coefficient of variation, %				Homogeneity of dispersions*
	Tirzetta®-1	Tirzetta®-2	Tirzetta®-3	Mounjaro®	
-8	14.6	14.6	13.1	7.4	0.5189
-9	12.5	10.3	22.6	7.3	0.2959
-10	16.6	11.8	29.1	23.2	0.4751
-11	11.7	12.5	23.0	12.6	0.0908
-12	19.6	13.9	16.7	24.5	0.7829
-13	20.2	23.6	13.5	19.0	0.4650
-14	6.3	12.8	5.1	28.6	0.6686
-15	15.0	18.4	25.9	14.2	0.7094

Note: * —homogeneity of the variances was determined by evaluating the spread of data, the column shows the values of the *p*-value Brown-Forsythe test.

Table 9 — The results of the analysis of logistic curves GIPR/CRE Luciferase Reporter HEK293

Drug	Coefficient of determination, R^2	Fischer's F-test	Log EC50	Ratio of the angle of inclination β to the referent
Tirzetta®-1	0.9365	F = 180.6 (p < 0.0001)	-12.12 ± 0.097 CV = 0.8	0.8
Tirzetta®-2	0.9489	F = 227.4 (p < 0.0001)	-12.20 ± 0.176 CV = 1.45	0.8
Tirzetta®-3	0.8613	F = 68.3 (p < 0.0001)	-12.18 ± 1.310 CV = 10.8	1.1
Mounjaro®	0.9697	F = 312.0 (p < 0.0001)	-12.20 ± 0.385 CV = 3.2	–

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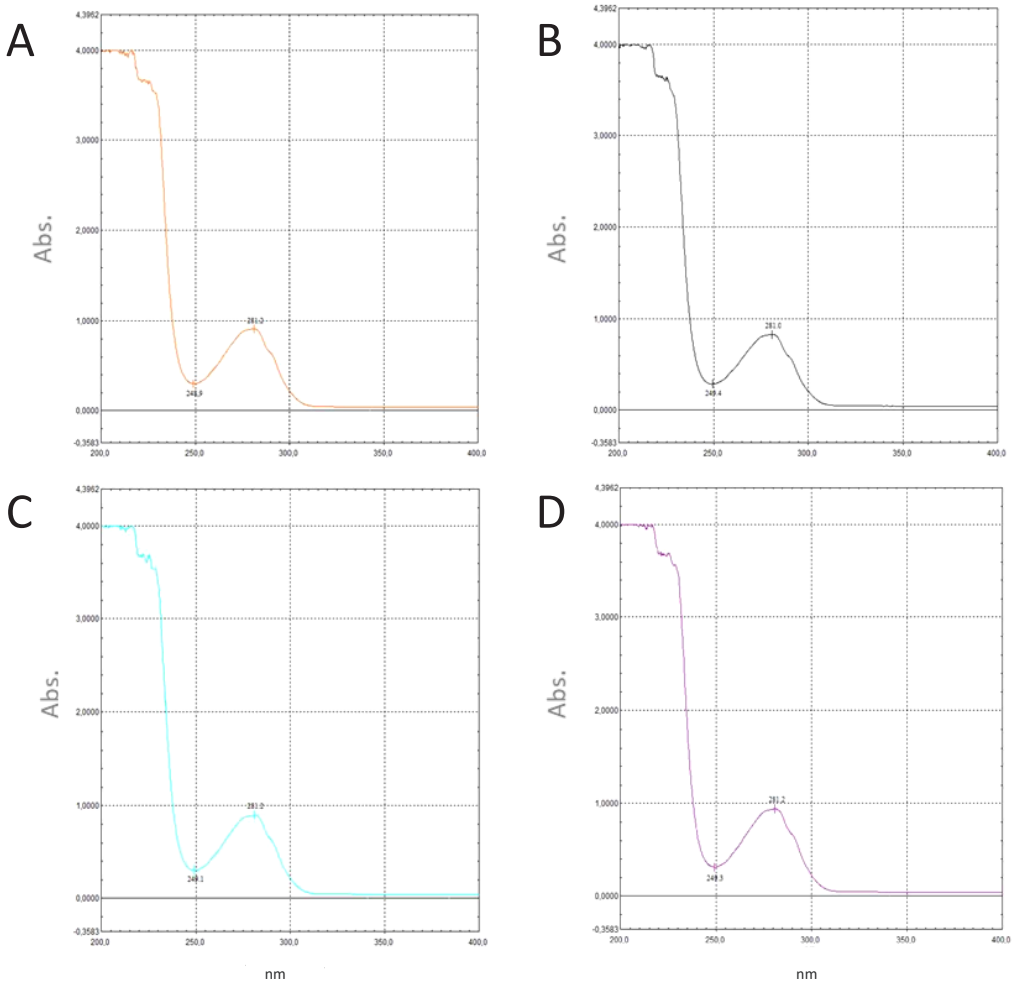

Figure 1 — Absorption spectrum of tirzepatide drug.
Note: A — Mounjaro® (D665365A); B — Tirzetta® (010124); C — Tirzetta® (020124); D — Tirzetta® (030124).

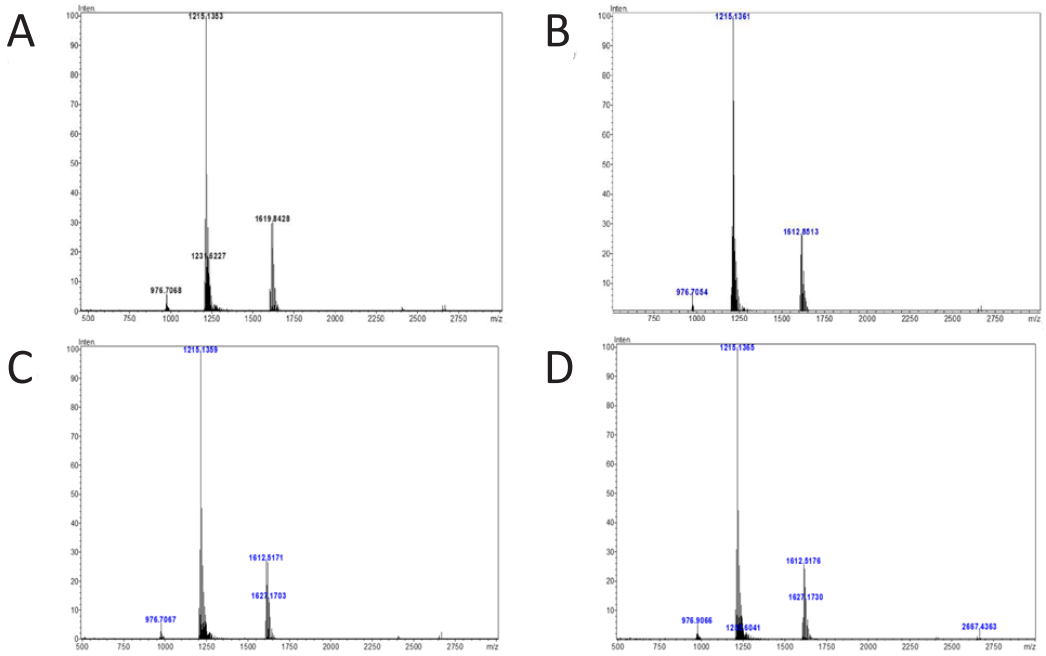

Figure 2 — Mass spectra of solutions of tirzepatide drugs.
Note: A — Mounjaro® (D665365A); B — Tirzetta® (010124); C — Tirzetta® (020124); D — Tirzetta® (030124).

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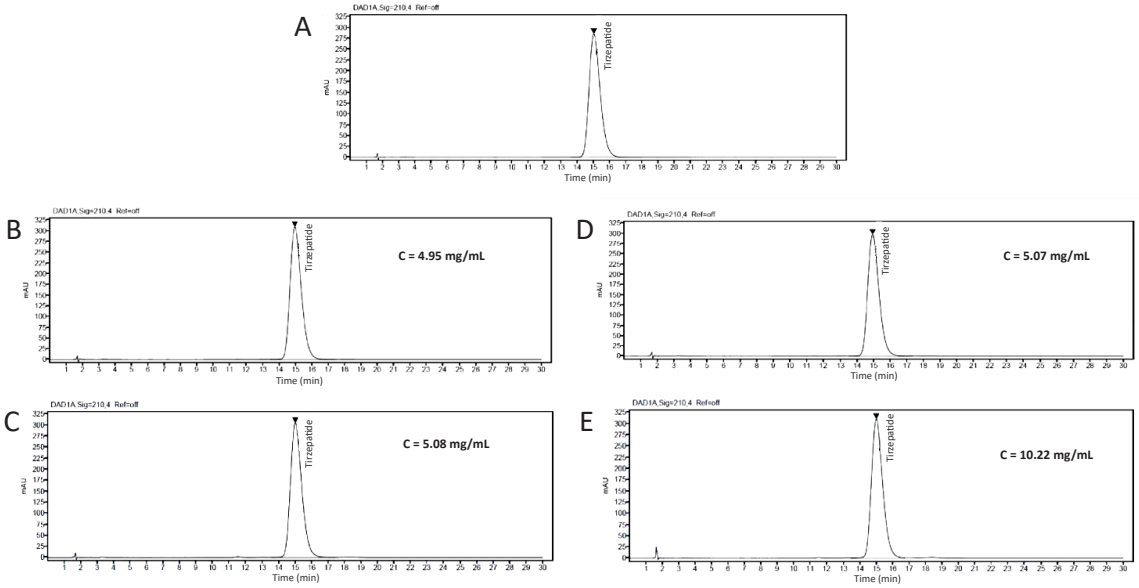

Figure 3 — Chromatograms of the tirzepatide drugs solutions.
Notes: A — Tirzepatide standard; B — Tirzetta® (series 010124); C — Tirzetta® (series 020124); D — Tirzetta® (series 030124); E — Mounjaro® (D665365A).

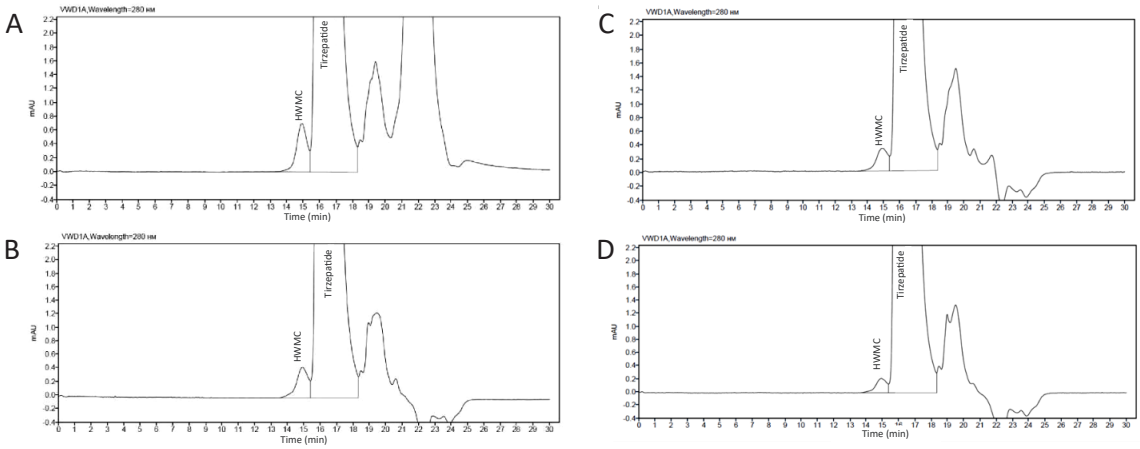

Figure 4 — Chromatograms of tirzepatide drugs and impurities.
Note: A — Mounjaro® (D665365A); B — Tirzetta® (010124); C — Tirzetta® (020124); D — Tirzetta® (030124).

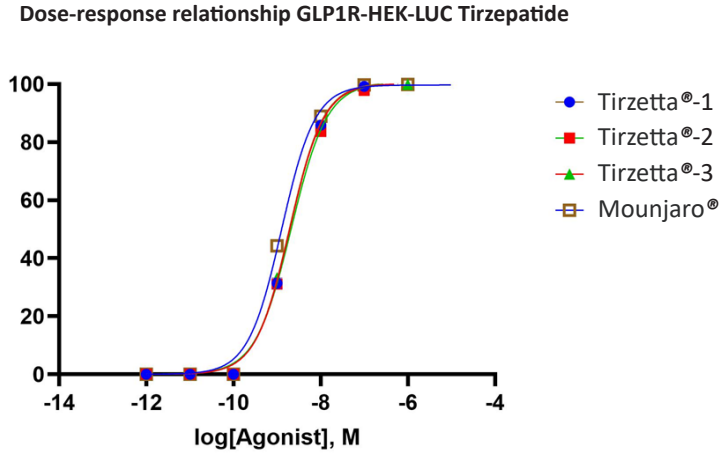

Figure 5 — Dependence of the luminescent signal value on the concentration of the agonist GLP-1R (*n* = 3).
Note: The data is presented in M ± SD, as well as with logistic curves (based on the results of nonlinear regression).

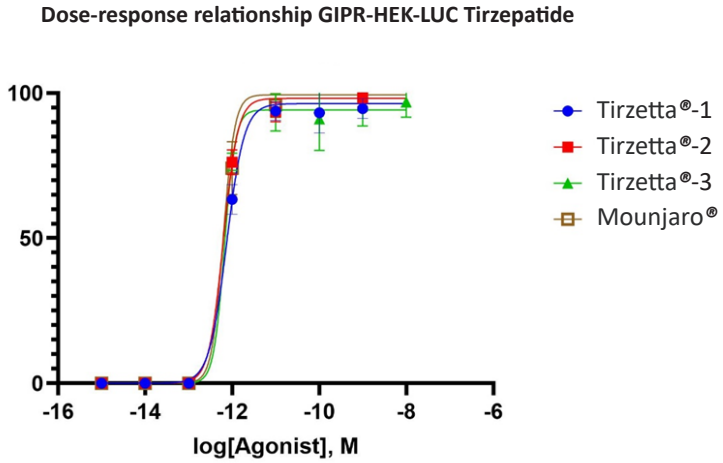

Figure 6 — Dependence of the luminescent signal value on the concentration of the agonist GIPR (*n* = 3).
Note: The data is presented in M ± SD, as well as with logistic curves (based on the results of nonlinear regression).

Chromatographic methods are the "gold standard" for characterizing peptide drugs and allow detecting even minor differences in the structure of molecules. The identity of the chromatographic profiles of the active substance (tirzepatide) in the composition of Tirzetta® and Mounjaro® confirms their structural equivalence [15].

Modern trends in pharmaceutical design determine the need for an integrated approach, in which not only the active pharmaceutical substance is optimized, but also the composition of excipients, in particular, preservatives in parenteral dosage forms. The abandonment of the use of phenol and benzyl alcohol in favor of innovative delivery systems makes it possible to exclude these components from the formulation. This approach is aimed to minimize the risks of developing hypersensitivity reactions and increasing the overall safety profile of pharmacotherapy, as well as toxicity [20].

The drug Tirzett[a]® contains 4.2 times fewer impurities than the reference drug Mounjaro®, which suggests that the former is safer for patients. It should be taken into account that therapy for type 2 diabetes and obesity is lengthy and may subsequently turn into lifelong medication. Impurities such as phenol and benzyl alcohol can accumulate in the body with prolonged use and cause toxic effects. The elimination of impurities from the composition of Tirzetta® provides a number of pharmacotechnological and clinical advantages, which include reducing local toxicity and irritation at the injection site, which improves the tolerability of therapy, especially in sensitized patients, as well as with prolonged use. In addition, the possibility of systemic toxic effects and undesirable interactions with other drugs due to the properties of preservatives is excluded. Therefore, the development of preservative-free forms meets modern regulatory requirements and helps to increase adherence to treatment due to an improved safety and biocompatibility profile.

Thus, the study confirms that today in Russia it has been possible to develop an effective method for producing peptide drugs, which reduces the formation of racemic impurities, simplifies the purification of the target product, increases its purity and yield, and reduces the cost. It is also worth noting that chemical synthesis can provide a number of advantages compared to biotechnological production, including greater reproducibility of the process, a reduced risk of microbiological contamination, and a potentially lower production cost. These factors are especially important for ensuring the availability of innovative drugs for the general population [21]. Given the increasing prevalence of type 2 diabetes and obesity, the availability of effective drugs is becoming critical for public health [1].

In vitro biological activity assessment

The use of reporter cell lines is one of the most effective screening approaches for assessing the biological activity of drugs in vitro [22]. This model is genetically modified cells into which reporter genes have been introduced under the control of promoters that are activated when a ligand binds to a receptor and subsequent activation of the signaling pathway. Such lines allow quantifying the activity of receptor interactions by measuring the expression of the reporter — usually a fluorescent protein. The level of

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bioluminescence is directly proportional to the amount of enzyme and the binding activity of a particular transcription factor [23].

The comparability of the results of GIP and GLP-1 receptor activation between the studied drugs indicates the preservation of the key structural and functional characteristics of the tirzepatide molecule, which determine the properties and biological activity of the peptide. This is critical because it is the dual activity against the two incretin receptors that determines the unique therapeutic profile of tirzepatide [9].

The totality of the results fully confirms the initial hypothesis about the bioequivalence of the reproduced drug Tirzetta® and the reference drug Mounjaro®. This fact indicates that the synthesis and purification conditions are optimized in the production of the drug Tirzetta® in order to minimize the formation of structural variants and impurities [24]

Confirmation of bioequivalence allows extrapolation of previously obtained safety and efficacy data of the reference drug to reproduced drugs without studying the latter in large-scale clinical trials [25].

Clinical efficacy

To date, two main registered tirzepatide drugs are known in global practice — Mounjaro® and Zepbound® (Eli Lilly and Company, USA). Despite the fact that both drugs contain the same active substance — tirzepatide — they have different indications. Thus, Mounjaro® is registered for the treatment of type 2 diabetes mellitus, while Zepbound® is used for the treatment of obesity and related conditions. Tirzetta® is registered for both indications [26].

In addition to tirzepatide, other dual agonist molecules have been studied. Thus, NNC0090-2746 passed two phases of clinical trials (Phase 1 and Phase 2a) in patients with type 2 diabetes mellitus [27]. Studies have shown that the drug has a hypoglycemic effect and reduces body weight, however, its development did not progress beyond Phase 2a — it did not reach Phase 3 clinical trials and was not registered for medical use. In the second phase study, NN00090-2746, characterized by balanced activity against GLP-1 and GIP receptors, was administered daily subcutaneously at a dose of 1.8 mg for 12 weeks. Against the background of NN00090-2746 therapy, compared with placebo, there was a decrease in HbA1c level by 0.96% ($p < 0.001$) and body weight by 1.67% ($p = 0.06$).

Tirzepatide, the activity of which is more pronounced against GIP receptors, was administered weekly subcutaneously in various doses (1, 5, 10 and 15 mg) for 26 weeks. The degree of reduction in HbA1c level was dose-dependent (1.73, 1.89 and 2.07%), while 45–90% of patients on tirzepatide therapy reached the target HbA1c level.

Analyzing the data from these studies, it can be concluded that tirzepatide is more effective than NNC0090-2746 in reducing HbA1c levels and body weight, which was observed after 12 weeks of therapy. This may be due to differences in the chemical structure, affinity and balance of activity of the drugs against GLP-1 and GIP receptors [9].

The results of the Phase II study served as the basis for the start of Phase III clinical programs with tirzepatide in patients with type 2 DM (SURPASS) and in patients with obesity (SURMOUNT) [27]. Clinical studies have demonstrated unprecedented efficacy of tirzepatide. The drug achieve the significant and sustained weight loss, as well as a marked improvement in cardiometabolic parameters in patients with obesity and/or type 2 DM [28–31]. In general, treatment with tirzepatide led to a weight loss of approximately 8–15% of the initial body weight in patients with type 2 diabetes and from 15 to 23% in patients with obesity and overweight, which is comparable in efficacy to some surgical interventions. There is a decrease in waist circumference, on average, by 15 cm, which indicates a decrease in the severity of visceral obesity. A significant proportion of patients achieve weight loss ≥ 5%, and a significant proportion — weight loss of ≥ 15–20%, which significantly exceeds the results of previous drugs and corresponds to or exceeds the best modern analogues. In addition to changes in weight, there was a decrease in systolic blood pressure by 4.9–6.4 mm Hg, improvement in glycemic control (decrease in HbA1c by 1.8–2.4%), as well as positive dynamics of the lipid profile: total cholesterol decreased by 0.25–0.37 mmol/Ll, LDL — by 0.31–0.43 mmol/L, HDL increased by 0.05–0.08 mmol/L. The main advantage of tirzepatide in the treatment of patients with obesity is a 94% reduction in the risk of diabetes mellitus. The introduction of this drug into practice is a transition from managing existing diabetes to active prevention of this disease. This is the most effective way to reduce the global burden of type 2 diabetes mellitus for society as a whole. Side effects are mainly associated with the gastrointestinal tract, but are usually mild and reversible. No serious complications or increased risk of hypoglycemia have been identified. Thus, tirzepatide provides effective, versatile and well-tolerated treatment for long-term weight and metabolic health management.

Study limitations

Despite the fact that the use of multiple methodological approaches ensures a high degree of reliability of the study results, it is necessary to note a number of limitations that should be taken into account when interpreting the results. Thus, reporter cell lines used to assess in vitro activity are simplified models of receptor interaction. The real physiological environment is characterized by a much greater complexity of intercellular interactions and regulatory mechanisms [32].

CONCLUSION

The results of a comparative study of the physicochemical characteristics and biological activity of Tirzetta® (manufacturer PROMED RUS LLC) and Mounjaro® (Eli Lilly and Company, USA) convincingly demonstrated the equivalence of these two drugs.

The totality of the data obtained indicates that Tirzetta® is a high-quality drug that provides comparable therapeutic efficacy with the reference drug, with better safety indicators. From a scientific point of view, the data obtained contribute to the understanding of structure-functional relationships in the tirzepatide molecule and confirm the stability of key pharmacophore groups.

The results of the study create a scientific basis for further development of peptide multiagonists, opening up prospects for expanding the availability of innovative drugs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

P.I. Makarevich, N.A. Alexandrushkina — investigation, data analysis; P.A. Podlesnaya, Yu.G. Kazaishvili, A.V. Taganov — administration, data analysis, writing—original draft; V.S. Shcherbakova, K.Ya. Zaslavskaya, P.A. Bely — conceptualization, data analysis, writing—review & editing; K.N. Koryanova, E.S. Mishchenko, L.I. Shcherbakova, I.N. Dyakova — data analysis, writing—review & editing.

All the authors confirm their authorship compliance with the ICMJE international criteria (all the authors made a significant contribution to the conceptualization, conduct of the study and preparation of the article, read and approved the final version before publication).

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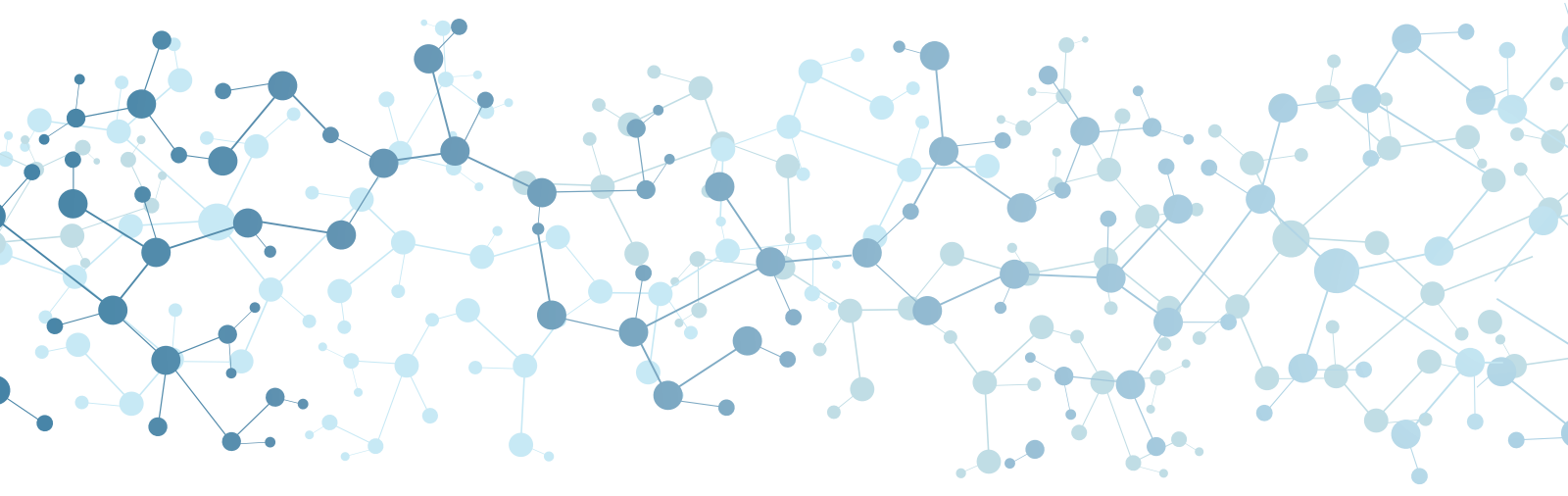

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