REVIEW

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Compounding of Orphan Drugs as an indicator of systemic obstacles in pharmacy practice: the experience of the Russian Federation

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The aim. To identify existing obstacles hindering the introduction of extemporaneous orphan drugs into circulation in the Russian Federation, in order to develop recommendations for improving legislative regulation and organizing the activities of pharmacies with the right to manufacture drugs.

Materials and methods. The study was performed using a comprehensive approach, including logical, comparative, structural-functional, and conceptual analysis. Information retrieval was conducted in international scientific indexes, search engines (PubMed, Google Scholar), and legal reference systems (ConsultantPlus, GARANT, Kontur.Normativ). Regulatory legal acts of the Russian Federation and foreign countries, modern scientific publications, as well as the practical experience of Russian pharmacies manufacturing drugs for the treatment of orphan diseases were considered.

Results. The main obstacles in the development of pharmacy compounding of orphan drugs were identified: low availability of active pharmaceutical ingredients, limitation of the mechanism for establishing the shelf life of extemporaneous dosage forms, prohibition of the manufacture of registered drugs, heterogeneity of pharmacies in terms of equipment and competencies, lack of stable demand, restriction of dispensing compounded drugs for outpatient treatment, and uncertainty of requirements for the therapeutic effectiveness of extemporaneusly compounded drugs. Based on the analysis, proposals were formulated to improve the regulation of mechanisms for admitting substances to the market, using flexible approaches to establishing shelf life, differentiating requirements for pharmacies depending on their capabilities, and legally establishing the rights to manufacture certain categories of drugs, simplifying the dispensing of extemporaneous dosage forms, and involving federal and regional institutions in the formation of stable demand for pharmacy drugs.

Conclusion. Overcoming the identified obstacles is of strategic importance not only for the pharmacotherapy of orphan diseases, but also for the development of pharmacy compounding in general. The implementation of the proposed solutions will create a sustainable system capable of providing patients with vital medicines regardless of market conditions and the political situation. Global practice confirms that key competition in the field of orphan drugs unfolds precisely at the level of regulatory systems, and in this perspective, the development of manufacturing pharmacies can become a tool for the Russian Federation to protect the interests of patients, increase access to therapy, and strengthen drug sovereignty.

Keywords: drug supply; orphan medicines; emergency formulation; pharmacy compounding

Abbreviations: CC RF — Civil Code of the Russian Federation; SRMs — State Register of Medicines; GPhM — General Pharmacopoeial Monograph; FL — Federal Law; FDA — Food and Drug Administration.

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Изготовление орфанных лекарственных препаратов как индикатор системных барьеров в аптечной практике: опыт Российской Федерации

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Цель. Определить существующие барьеры, препятствующие введению в оборот экстемпоральных орфанных лекарственных препаратов на территории Российской Федерации, для выработки рекомендаций по совершенствованию законодательного регулирования и организации деятельности аптечных организаций с правом изготовления лекарственных препаратов.

Материалы и методы. Исследование выполнено с использованием комплексного подхода, включающего логический, сравнительный, структурно-функциональный и концептуальный анализ. Информационный поиск проводился в международных научных индексах, поисковых (Scopus, Web of Science, PubMed, Google Scholar) и справочно-правовых системах (КонсультантПлюс, ГАРАНТ, Контур.Норматив). Рассматривались нормативные правовые акты Российской Федерации и зарубежных стран, современные научные публикации, а также практический опыт российских аптечных организаций, изготавливающих лекарственные препараты для лечения орфанных заболеваний.

Результаты. Выявлены основные барьеры развития аптечного изготовления орфанных препаратов: низкая доступность активных фармацевтических субстанций, ограничение механизма установления сроков годности экстемпоральных лекарственных форм, запрет на изготовление зарегистрированных препаратов, неоднородность аптечных организаций по уровню оснащённости и компетенций, отсутствие устойчивого спроса, ограничение отпуска изготовленных лекарственных препаратов для амбулаторного лечения, а также неопределённость требований к терапевтической эффективности экстемпоральных аналогов промышленных лекарственных препаратов. На основе анализа сформулированы предложения по совершенствованию регулирования механизмов допуска субстанций на рынок, использования гибких подходов к установлению сроков годности, дифференциации требований к аптечным организациям в зависимости от их возможностей и законодательному закреплению прав на изготовление определённых категорий препаратов, упрощению отпуска экстемпоральных лекарственных форм, а также вовлечению федеральных и региональных институтов в формирование устойчивого спроса на аптечные лекарственные препараты.

Заключение. Преодоление выявленных барьеров имеет стратегическое значение не только для фармакотерапии орфанных заболеваний, но и для развития аптечного изготовления в целом. Внедрение предложенных решений позволит выстроить устойчивую систему, способную обеспечивать пациентов жизненно необходимыми лекарственными препаратами независимо от конъюнктуры рынка и политической ситуации. Мировая практика подтверждает, что ключевая конкуренция в сфере орфанных препаратов разворачивается именно на уровне регуляторных систем, и в этой перспективе развитие производственных аптек может стать для Российской Федерации инструментом защиты интересов пациентов, повышения доступности терапии и укрепления лекарственного суверенитета.

Ключевые слова: лекарственное обеспечение; орфанные лекарственные препараты; экстемпоральная рецептура; аптечное изготовление

Список сокращений: ГК РФ — Гражданский кодекс Российской Федерации; ГРЛС — Государственный реестр лекарственных средств; ОФС — общая фармакопейная статья; ФЗ — Федеральный закон; FDA — Управление по контролю качества пищевых продуктов и лекарственных средств, США.

INTRODUCTION

In recent years, the Russian Federation has seen a consistent development of regulatory legal regulation regarding the organization of extemporaneous compounding of medicines [1]. State policy in the field of healthcare increasingly views pharmacies with the right to compound medicines (hereinafter referred to as compounding pharmacies) not only as a resource for implementing personalized medicine tasks, but also as an effective tool for ensuring the accessibility of

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pharmacotherapy [2–4]. Strengthening the regulatory legal framework, gradually adapting international principles of good pharmacy practice, separation of a special type of economic activity[1], implementation of requirements for the organization of a quality system[2], development and approval of new pharmacopoeial monographs[3], form the basis for the transformation of compounding pharmacies [5]. From a rudimentary and fragmented structure, they are turning into a full-fledged patient-oriented link in the drug supply system, capable of responding quickly to healthcare needs both to expand pharmacotherapy options and to rationally use resources [6–9].

At the same time, despite the significant potential, the still limited range and low profitability of compounded medicines determine the need to search for new directions for using extemporaneous drug formulations [10–13].

Given the incoming investments, the introduction of new high-tech approaches in pharmacy practice, and integration with the industrial sector of the pharmacy, the most promising area is the compounding of medicines with high potential in the therapy of orphan diseases[4].

Pharmacotherapy for patients with orphan diseases is a global problem, primarily due to the complexity of developing medicines, including difficulties in conducting full-fledged clinical trials, as well as a limited market [14]. In the Russian Federation, orphan diseases are diseases with a prevalence of no more than 10 cases per 100 000 population[5]. The situation differs in the European Union[6] (no more than 5 cases per 10 000 people) and the USA[7] (any disease or condition affecting less than 200 000 people in the USA), but even in these conditions, the market remains small [15]. As a result, healthcare systems are forced to develop and implement various incentive programs, which in most cases provide pharmaceutical companies with simplified market access, exclusive status, and also allow them to maintain a high price, often not determined by market, especially in the case of long-known medicines that were subsequently registered for the treatment of orphan diseases [16–19].

In the Russian Federation, there is a steady increase in the number of patients with orphan diseases receiving pharmacotherapy under state programs [20]. Thus, the Federal Program “High-Cost Nosologies” is gradually expanding, and the list of drugs purchased by the Circle of Good Foundation for Supporting Children with Severe Life-Threatening and Chronic Diseases, including Rare (Orphan) Diseases (hereinafter referred to as the Circle of Good[8]), is increasing. The taken measures allow covering a large list of patients, but also cause a rapid increase in the total costs of orphan drugs. Thus, the volume of federal funding for orphan programs has increased many times over the past years, and the total number of patients receiving therapy has increased many times over. As a result, all key sources demonstrate a single trend of increasing burden on drug provision for patients with rare diseases [21].

Simultaneously with the growth in demand, the limited resources of the healthcare system become obvious. Federal spending on orphan drugs today amounts to tens of billions of rubles annually, and regional budgets are often unable to fully cover the need for expensive treatment outside of centralized programs[9]. In practice, patients who do not fall under federal benefits (for example, the adult group of orphan patients) often face interruptions in the provision of

[1] Приказ Росстандарта от 09 апреля 2025 года № 268-ст «Об утверждении Изменения 80/2025 ОКВЭД 2 к Общероссийскому классификатору видов экономической деятельности». – [Электронный ресурс]. – Режим доступа: https://www.consultant.ru/document/cons_doc_LAW_503144/

[2] Order of the Ministry of Health of the Russian Federation dated May 22, 2023 No. 249n “On Approval of the Rules for the Compounding and Release of Medicines for Medical Use by Pharmacies Licensed for pharmaceutical activities”. Available from: https://www.consultant.ru/document/cons_doc_LAW_448335/

[3] Order of the Ministry of Health of the Russian Federation dated March 13, 2024 No. 120 “On Approval of General Pharmacopoeial Monographs and Pharmacopoeial Monographs”, Order of the Ministry of Health of the Russian Federation dated April 11, 2025 No. 188 “On Approval of General Pharmacopoeial Monographs and Pharmacopoeial Monographs”, Order of the Ministry of Health of the Russian Federation dated August 4, 2025 No. 460 “On Approval of Pharmacopoeial Monographs”. Available from: https://pharmacopoeia.regmed.ru/ approval-orders/

[4] Badyina E. A production pharmacy will be built in Sirius for 1 billion rubles – what is known about it? Pharmedprom. Available from: https://pharmmedprom. ru/Monographs/chem-privlech-molodezh-na-predpriyatie-farmkompanii-podelilis-sekretami/. Russian

[5] Federal Law No. 323-FZ of November 21, 2011 “On the Basics of Public Health Protection in the Russian Federation”. Available from: https://www.consultant.ru/document/cons_doc_LAW_121895/bbfb814a127237db75b90e15 4333ef3f085f4e7f/

[6] Orphan medicinal products. European Commission. – [Электронный ресурс]. – Режим доступа: https://health.ec.europa.eu/medicinalproducts/orphan-medicinal-products_en

[7] 21 U.S.C. § 360bb (Orphan Drug Act). – [Электронный ресурс]. – Режим доступа: https://www.law.cornell.edu/uscode/text/21/360bb

[8] Circle of Goodness Foundation for the Support of Children with Severe life-threatening and Chronic Diseases. public 2024 annual report. Available from: https://xn--80abfdb8athfre5ah.xn--p1ai/ wp-content/uploads/2025/05/15-may-AnnualReport-2024-RGB-2.pdf

[9] Kryukov V., Surinskaya Ya., Lekovskaya V. The lack of regional funds for the treatment of orphan diseases will be compensated by the federal budget. Vedomosti. Available from: https://www.vedomosti.ru/society/Monographs/2025/03/11/1097178-nehvatku-regionalnih-sredstv-na-lechenie-orfannih-boleznei-vospolnyat-fedbyudzhetom. Russian

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medicines and are forced to "seek" drugs through additional support mechanisms. Experts note that with the increase in the number of patients who have reached the age of 19 and are "graduating" from the care of the Circle of Good Foundation, the obligations of the regions to finance their further treatment are increasing — a burden that regional budgets can hardly bear[10]. Thus, the existing funding model is working at the limit of its capabilities, which emphasizes the need to introduce new approaches to drug provision for orphan patients.

In the context of limited resources, flexible, technology-oriented solutions, such as extemporaneous compounding of medicines, are of particular relevance [22–24]. At the same time, despite the introduction of modern technologies in pharmacy practice and the improvement of instrumental methods for quality control of extemporaneous drug formulations [25, 26], the first attempts to compound orphan drugs in the Russian Federation faced a number of diverse obstacles, limiting not only the development of the compounding pharmacy system, but also its existence.

THE AIM of this review is to identify existing barriers that prevent the introduction of extemporaneous orphan drugs into circulation in the Russian Federation, in order to develop recommendations for improving legislative regulation and organizing the activities of compounding pharmacies.

MATERIALS AND METHODS

The information search was conducted (2005–2025) throughout the entire period from December 2022 to July 2025 in international scientific indexes and search engines (Scopus, Web of Science, PubMed, Google Scholar), as well as using national reference legal systems (ConsultantPlus, GARANT system, "Kontur.Normativ") and international resources (official portal of the legislation of the European Union, official portal of the legislation of Germany, library of law of Cornell University, official website of the Ministry of Health of Canada, official websites of the European Medicines Agency, the Food and Drug Administration of the United States and the World Health Organization). In the context of limited access to a number of foreign databases after 2022, previously formed collections and open sources listed above were used.

The search was carried out using keywords and phrases in Russian and English, including: «орфанные лекарственные препараты», «редкие заболевания», «аптечное изготовление», «экстемпоральное изготовление», as well as their English equivalents — orphan drugs, rare diseases, pharmacy compounding, extemporaneously compounding drugs, regulatory framework for compounding. The selection of sources was carried out in several stages: removal of duplicates, exclusion of irrelevant publications based on titles and abstracts, subsequent full-text analysis. Articles devoted to orphan drugs, therapy of rare diseases and issues of pharmacy compounding were included. Priority was given to modern peer-reviewed publications and official regulatory documents. As a result, an array of sources was formed, including 50 scientific articles, 29 regulatory legal acts and 13 other relevant materials. The process of selecting sources is presented in a block diagram (Fig. 1), prepared in accordance with the recommendations of PRISMA.

The processing and analysis of the collected data included systematization of information and comparison of the identified information with international practice. The applicability of foreign experience to the Russian regulatory organizational environment was assessed. During the analysis, key problems were identified that hinder the development of pharmacy compounding of orphan drugs in the Russian Federation.

In addition to the analysis of literature and documents, the practical experience of pharmacy compounding in Russia was studied as part of the empirical part of the study. Applied aspects of the organization of extemporaneously compounding drugs were analyzed, including issues of importing the necessary pharmaceutical substances, building logistics supply chains, as well as internal preparation of compounding pharmacies for compounding and ensuring the quality of finished dosage forms.

Based on the results obtained, proposals were developed to improve the regulatory framework and practice of pharmacy compounding of orphan drugs. These recommendations and approaches are formulated taking into account the specifics of the legislation of the Russian Federation.

RESULTS AND DISCUSSION

Availability of substances

The problem of the lack of substances that can be used for the purposes of pharmacy compounding

[10] Nevinnaya I. Experts discussed how to provide treatment to "graduates" of the Circle of Goodness Foundation. Rossiyskaya Gazeta. Available from: https://rg.ru/2024/08/09/ eksperty-obsudili-kak-obespechit-lecheniem-vypusknikov-fonda-krug-dobra.html. Russian

is fundamental [27, 28]. Thus, in accordance with Art. 56 of Federal Law No. 61-FZ[11] of April 12, 2010, as well as Order No. 249n of the Ministry of Health of the Russian Federation dated May 22, 2023 "On approval of the rules for compounding and dispensing medicines for medical use by pharmacies licensed for pharmaceutical activities"[12] (hereinafter — Order No. 249n) it is established that in the compounding of drugs by pharmacies, and (or) pharmaceutical substances included in the State Register of Medicines for medical use (hereinafter — SRMs), the Unified Register of Registered Medicines of the Eurasian Economic Union are used.

Art. 34 of Federal Law No. 61-FZ establishes the procedure for including a pharmaceutical substance produced for sale in the SRMs, which provides for a complex and expensive procedure (Fig. 2), including the certification of the substance manufacturer for compliance with international standards, as well as a wide range of laboratory tests. Thus, few compounding pharmacies are able to initiate the inclusion of a pharmaceutical substance of interest to them in the SRMs.

It is advisable to provide for alternative mechanisms for the admission of substances, including those existing in international practice. For example, in Canada, in accordance with Health Canada POL-0051[13], a medicinal product in a compounding pharmacy must be compounded from a registered drug or active pharmaceutical substance already used in a registered medicinal product, or an active pharmaceutical substance for which there is a pharmacopoeial monograph in a pharmacopoeia recognized by Canada[14] (US Pharmacopoeia, European Pharmacopoeia, British Pharmacopoeia, etc.).

In the Russian Federation, information about the substance used in industrial production is also entered into the SRMs as part of the state registration of the corresponding medicinal product. Thus, it can be established that compounding pharmacies have the right to use substances both included in the SRMs.

Another solution implemented in Australia, as well as in a number of European Union countries, including Germany[15] and the Netherlands[16], is to allow compounding pharmacies to use all substances whose quality complies with the Pharmacopoeia, and the manufacturer guarantees compliance with good manufacturing practice standards, which is confirmed by a certificate of conformity, and not an on-site inspection at the manufacturer's site at the expense of the compounding pharmacy [29].

In the case of active pharmaceutical substances used in the therapy of orphan diseases, the situation is also complicated by the fact that most of the necessary and relevant substances are patented [30].

In A.V. Alekhin et al. [2] showed that the violation of patent rights occurs precisely at the moment of transfer of the substance from the supplier to the compounding pharmacy. Thus, in a situation where it is impossible for a compounding pharmacy to legally obtain a substance, the rule of law (clause 5 of Article 1359 of the Civil Code of the Russian Federation[17], containing an exception from patent law in the case of a one-time compounding in pharmacies according to doctors' prescriptions of medicines, including orphan drugs, which include patented substances), — does not actually work.

At the same time, this provision of the Civil Code of the Russian Federation corresponds to international practice, is conceptually formulated and enshrined in the legislation of more than 30 states — members of the World Intellectual Property Organization[18], and is key to ensuring the patient's right to receive the necessary pharmacotherapy in the absence of registered industrial analogues or the presence of medical indications for prescribing an extemporaneously compounded drug.

[11] Federal Law No. 61-FZ of April 12, 2010 "On the Circulation of Medicines". Available from: https://www.consultant.ru/document/cons_doc_ LAW_99350/. Russian

12 Order No. 249n of the Ministry of Health of the Russian Federation dated May 7, 2023 "On Approval of the Rules for the Manufacture and Release of Medicines for Medical Use by Pharmacy Organizations Licensed for Pharmaceutical Activities". Available from: https://normativ.kontur.ru/document?moduleId=1&documentId=449637. Russian

[13] Policy on Manufacturing and Compounding Drug Products in Canada. Available from: https://www.canada. ca/en/health-canada/services/drugs-health-products/compliance-enforcement/good-manufacturing-practices/guidance-documents/ policy-manufacturing-compounding-drug-products.html

[14] Food and Drugs Act (R.S.C., 1985, c. F-27). Available from: https://laws-lois.justice.gc.ca/eng/ acts/f-27/page-11.html

[15] Verordnung über den Betrieb von Apotheken (Apothekenbetriebsordnung – ApBetrO): Verordnung vom 09.02.1987 (BGBl. I S. 547); neugefasst durch Bek. v. 26.09.1995 (BGBl. I S. 1195); zuletzt geändert durch Art. 8z4 G. v. 12.12.2023 (BGBl. 2023 I Nr. 359). Available from: https://www.gesetze-iminternet.de/apobetro_1987/

[16] Inspectie Gezondheidszorg en Jeugd (IGJ). Eigen bereidingen apotheek. Available from: https://www.igj.nl/zorgsectoren/geneesmiddelen/beschikbaarheid-vangeneesmiddelen/eigen-bereidingen-apotheek

[17] The Civil Code of the Russian Federation. Available from: https://www.consultant.ru/document/cons_doc_LAW_64629/11c74717682795e6ef099015bbcba71081a5b918/

[18] Committee on the Law of Patents. Draft Reference Document on the Exception Regarding Extemporaneous Preparation of Medicines: SCP/36/3. Available from: https://www. wipo.int/edocs/mdocs/scp/en/scp_36/scp_36_3.pdf

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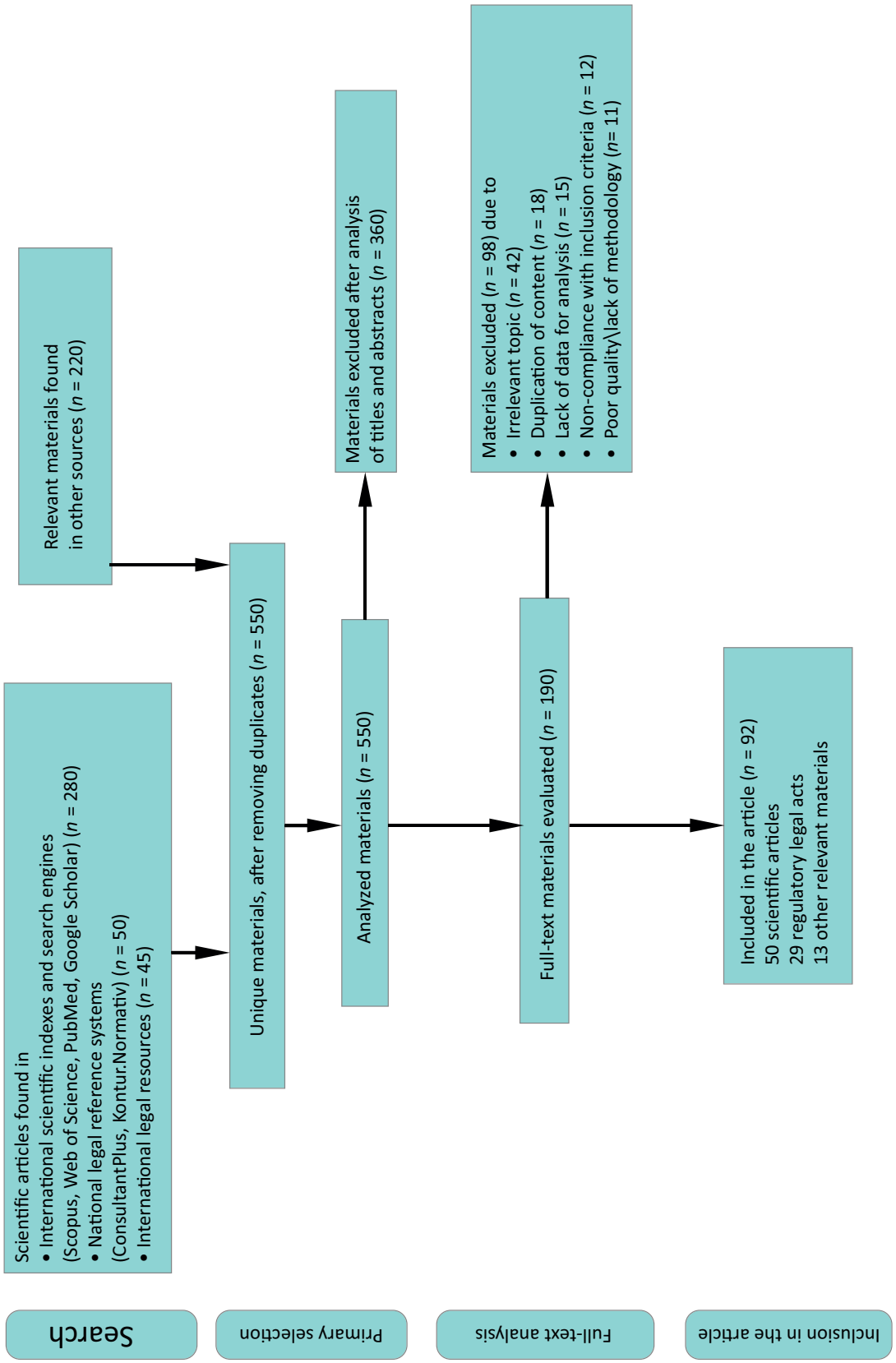

Figure 1 – Block diagram of source selection.

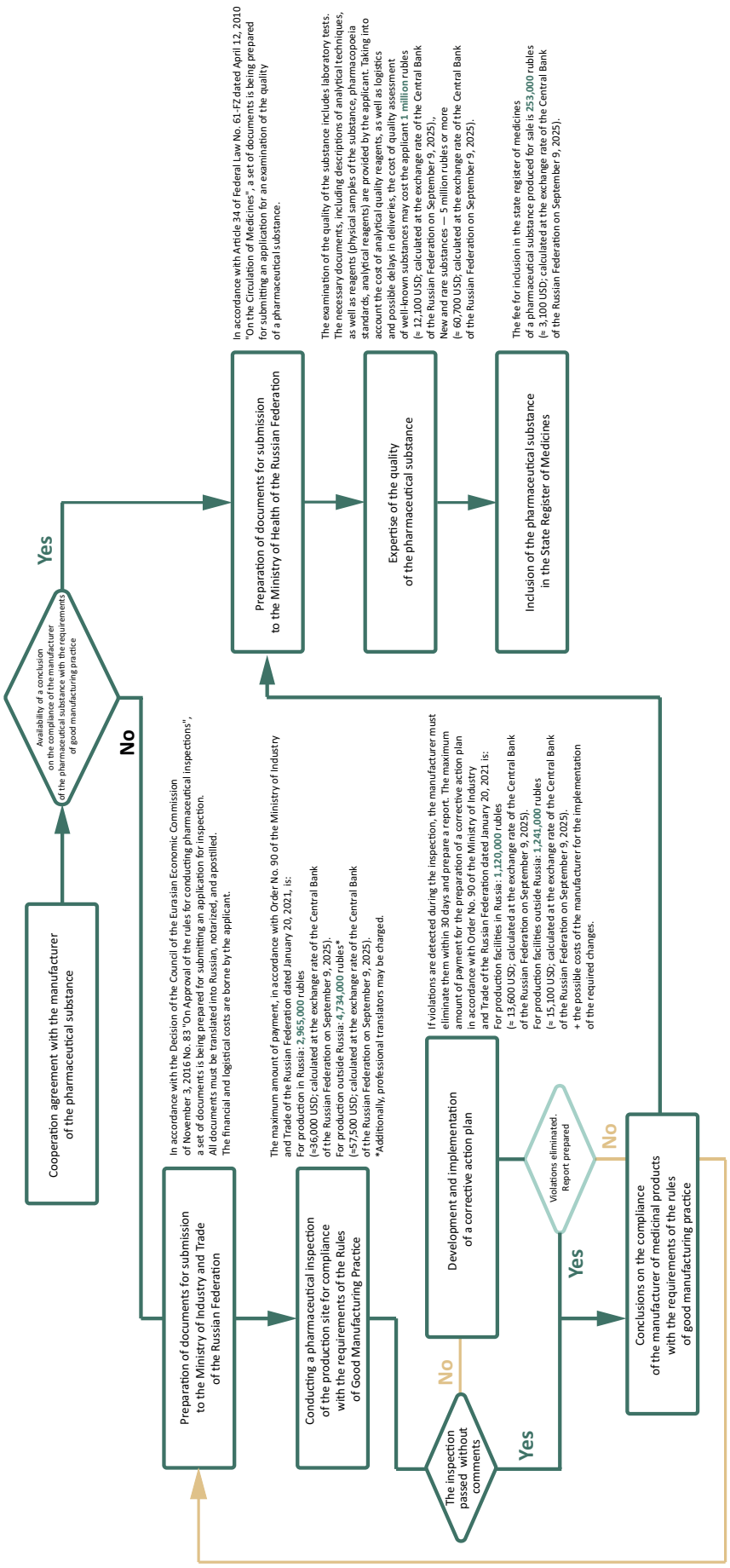

Figure 2 – Procedure for including a pharmaceutical substance in the State Register of Medicines of the Russian Federation.

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In these conditions, the statement that compounding pharmacies can solve the problem of periodically occurring shortages, often put forward in support of the development of the compounding pharmacy system, is untenable[19]. Even if the supplier has a substance, compounding pharmacies will not be able to solve the problem of a sudden shortage due to the effect of patent law, the inability to quickly include substances in the SRMs, as well as the prohibition on compounding registered medicines.

Therefore, the solution to this problem with the availability of substances should be comprehensive and not limited to expanding the substances available for pharmacy compounding. Thus, it seems appropriate to provide for an exception in Art. 56 of Federal Law No. 61-FZ, allowing the compounding of registered medicines in cases determined by the Government of the Russian Federation.

Such a legislative norm does not violate the balance between industrial production and pharmacy compounding, but gives the state a regulatory lever, both to combat shortages and to curb manufacturers' prices. International experience shows the high efficiency of such a solution.

For example, in the United States, a similar mechanism is implemented when a medicinal product is included in the official list of deficient drugs (Drug Shortages List), compounding pharmacies are allowed to compound the corresponding registered medicinal product[20]. At the same time, the use of substances that are not included in the list of compounds allowed for extemporaneous compounding (Bulks List), formed by the Food and Drug Administration (hereinafter — FDA) is allowed[21]. In the event of the end of the shortage, compounding must be stopped, and the dispensing of previously compounded drugs is possible for another 60 days after the exclusion of the medicinal product from the list of deficient drugs. Thus, during the COVID-19 pandemic, this norm made it possible to provide critically important drugs (including sedatives) to hospitalized patients[22]. Also, in March 2022, the FDA included semaglutide in the list of deficient drugs, which allowed American compounding pharmacies to legally prepare semaglutide injection solutions from the original substance, even despite the patent protection of the original drug. In early 2025, the FDA announced the resolution of the semaglutide shortage and notified compounding pharmacies of the termination of the authorization to compound and dispense the pharmacy analogue of semaglutide within 60 and 90 days for compounding pharmacies of type 503A and 503B, respectively[23].

Limitation of the shelf-life establishment mechanism

Another obstacle to the development of pharmacy compounding of orphan drugs is the issue of short-shelf lives of extemporaneous dosage forms. The standard shelf lives approved by Order No. 249n do not allow ensuring the proper "uninterrupted" receipt of medicines by patients. Moreover, they practically exclude the use of extemporaneous forms by маломобильными and lonely citizens. It is also impractical to deliver extemporaneous medicines to regions of the Russian Federation remote from the compounding pharmacy. To solve this problem, GPhM.1.8.0008 "Stability and shelf life of medicines compounded in pharmacies"[24] (hereinafter — GPhM.8.0008) was developed and approved, which provides for a mechanism for increasing shelf life based on stability testing of a medicinal product compounded in accordance with the approved intra-pharmacy standard operating procedure.

It should be noted that stability testing of a medicinal product in accordance with GPhM.1.8.0008 is an expensive procedure. Thus, studying the stability of an external dosage form for the purpose of establishing a shelf-life of 1 year in an accredited federal-level laboratory in 2025 will cost 250 thousand rubles

[19] Pichugina E. The production of drugs in pharmacies has become endangered. Moskovsky Komsomolets. Available from: https://www.mk.ru/economics/2023/06/16/proizvodstvo-preparatov-v-aptekakhokazalos-pod-ugrozoy-ischeznoveniya.html. Russian

[20] U.S. Food & Drug Administration. Compounding when Drugs are on FDA's Drug Shortages List. Available from: https://www.fda.gov/drugs/human-drug-compounding/compounding-when-drugs-are-fdas-drug-shortages-list

[21] Compounding under Section 503B of the FD&C Act. Available from: https://www.fda.gov/drugs/humandrug-compounding/bulk-drug-substances-used-compounding-undersection-503b-fdc-act

[22] U.S. Food & Drug Administration. Temporary Policy for Compounding of Certain Drugs for Hospitalized Patients by Outsourcing Facilities During the COVID-19 Public Health Emergency (Guidance for Industry). Available from: https://downloads. regulations.gov/FDA-2020-D-1136-0011/attachment_1.pdf

[23] U.S. Food & Drug Administration. FDA clarifies policies for compounders as national GLP-1 supply begins to stabilize. Available from: https://www.fda. gov/drugs/drug-safety-and-availability/fda-clarifies-policies-compounders-national-glp-1-supply-begins-stabilize

[24] Order of the Ministry of Health of the Russian Federation dated May 6, 2024 No. 233 "On Approval of the General Pharmacopoeial Article and Amendments to the Order of the Ministry of Health of the Russian Federation dated March 13, 2024 No. 120 "On Approval of General Pharmacopoeial Monographs and Pharmacopoeial Monographs"". Available from: https://base.garant.ru/409036856/

(≈ 3 000 USD; calculated at the rate of the Central Bank of the Russian Federation (hereinafter — the Central Bank of the Russian Federation) on September 9, 2025). These tests involve long-term studies under controlled conditions, which requires specialized equipment, highly qualified personnel and significant resources, so this price is justified and corresponds to the market. However, conducting such a scientific study does not guarantee that the corresponding shelf life can be established.

At the same time, the most negative thing in this situation is that stability tests are carried out strictly for a specific formulation, compounded in accordance with the intra-pharmacy standard operating procedure. Any deviation from the original formulation, including a change in dosage, list of excipients or technology, can be considered as the compounding of a new medicinal product, which makes the results of stability tests and the established shelf life inapplicable. As a result, there is a need for new stability tests, which makes it impossible to respond flexibly to the individual needs of patients. Thus, the very essence of pharmacy compounding, namely ensuring the personalization of pharmacotherapy, contradicts the logic of determining the stability of a medicinal product in accordance with OFS.1.8.0008.

To overcome this barrier associated with stability testing and shelf-life restrictions, it is necessary to develop flexible regulatory mechanisms that would take into account the specifics of pharmacy compounding and its focus on individualizing pharmacotherapy. One of the promising approaches is the possibility of conducting stability tests not for one fixed formulation, but for a range of dosages and compositions. This approach will allow compounding pharmacies to obtain data applicable to a whole range of individualized medicines, and not just to one formulation, which will significantly expand the possibilities of personalization and reduce the cost of conducting commercial research.

The implementation of this solution can be achieved by introducing relevant provisions into OFS.1.8.0008. In particular, the pharmacopoeial monograph should provide for the possibility of indicating the permissible range of concentrations of the active substance and the main characteristics of the drug, within which stability tests will be recognized as valid. This approach will allow compounding pharmacies to conduct stability tests for a whole class of formulations, ensuring high quality and safety of extemporaneous medicines, as well as the flexibility of their use in clinical practice.

In addition, it is necessary to consider the possibility of determining a list of organizations authorized to conduct stability tests of extemporaneous dosage forms or provide for liability for the establishment by compounding pharmacies of shelf lives based on false results of stability tests.

Registration of a medicinal product — prohibition on compounding

The prohibition on compounding registered medicines by compounding pharmacies is an international norm. In the Russian Federation, it is enshrined in Art. 56 of Federal Law No. 61-FZ.

At the same time, this norm is considered exclusively as the inadmissibility of reproducing an already registered medicinal product by a compounding pharmacy. However, the situation is often the opposite, and it is the industrial manufacturer who registers a medicinal product already compounded by the pharmacy [31].

In a mini-review, K. Hendrickx and M. Dooms, for example, provide a list of well-known compounds traditionally used as food additives, but which have been granted the status of medicinal products for the treatment of orphan diseases [32]. At the same time, the authors argue that these compounds were discovered long ago and are “international property”, and the owners of registration certificates appropriated them and maintain a monopolistically high price, without making a significant innovative contribution, using open medical and scientific data. Moreover, it is indicated that many of these drugs were previously compounded in compounding pharmacies and cost many times less.

A classic example of such a situation was the case of the medicine Makena® (INN — hydroxyprogesterone caproate), intended for the prevention of premature birth. An analogue of this medicinal product was compounded in compounding pharmacies for many years according to prescriptions for women at risk and cost several tens of dollars per dose. However, after KV Pharmaceuticals received FDA approval for the medicine Makena® with the assignment of orphan status and exclusivity for 7 years, the pharmacy analogue turned out to be вне закона. The price of the original drug rose to 1500 dollars (≈ 125 thousand rubles; calculated at the rate of the Central Bank of the Russian Federation on September 9, 2025) per injection, which increased the cost of the course to 30 thousand dollars (≈ 2.5 million rubles; calculated at

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the rate of the Central Bank of the Russian Federation on September 9, 2025) [33]. Due to the wide public outcry, the FDA announced in March 2011 that it would not take action against compounding pharmacies that continue to compound an analogue of the medicinal product Makena®[25] according to a doctor's prescription. KV Pharmaceuticals' appeal to the court and accusation of the FDA of exceeding its authority were unsuccessful[26], and the precedent became an example of how a regulator can weaken barriers to protect patients and reduce economic costs [34].

The European Union is also discussing a reform of pharmaceutical legislation affecting orphan drugs[27]. The proposals of the European Commission and the European Parliament do not directly mention pharmacy compounding, but there is an idea of differentiated exclusivity for orphan drugs. In particular, it is planned to reduce the period of exclusivity to 4 years for drugs approved on the basis of already known bibliographic data. Thus, if a company registers an orphan drug based on existing published information without significant new research, it will receive not 10 years of protection, but significantly less. If this change is adopted, the period during which a pharmaceutical company can maintain a high monopoly price will decrease. Indirectly, this will legalize the earlier appearance of inexpensive alternatives.

In the Russian Federation, there is also a risk that investments and intellectual resources invested by compounding pharmacies in the development of medicines for the treatment of orphan diseases, the inclusion of relevant substances in the SRMs, the development of technology, the preparation of internal standard operating procedures, as well as the study of stability, may be used by large pharmaceutical companies.

In this case, it is advisable to provide by law a norm according to which the publication of a private pharmacopoeial monograph on an extemporaneous medicinal product secures the right of compounding pharmacies to compound it, even in the case of subsequent registration of an industrial analogue. This will avoid a situation where large pharmaceutical companies will use the developments of compounding pharmacies to register a drug, thereby effectively blocking the possibility of its compounding, as in the case of the medicinal product Makena®. Such legislative consolidation will protect the investments of compounding pharmacies in the development and testing of drugs, create a fairer competitive environment and ensure long-term availability of orphan drugs for patients.

Heterogeneity of compounding pharmacies

A key challenge for the system of pharmacy compounding of orphan drugs is the significant heterogeneity of compounding pharmacies in terms of equipment level, competencies and the ability to ensure quality [35]. In the Russian Federation, there are and are preparing to launch compounding pharmacies that have modern equipment, qualified personnel and are able to fulfill all the requirements for the compounding of medicines up to compliance with good manufacturing practice standards and the introduction[28] of advanced developments [36–39]. At the same time, a significant part of compounding pharmacies is limited in technical capabilities, experiences a shortage of personnel and does not have a well-established quality assurance system, which may affect the safety and effectiveness of the dosage forms they compound [40–42].

The complexity of the situation is aggravated by the fact that in the current legal field there is no differentiation of compounding pharmacies according to the level of their technological and organizational capabilities. As a result, the same regulatory requirements apply to compounding pharmacies at different levels of development. Such a uniform regulatory system, which does not take into account the real differences between compounding pharmacies, can create risks for the health of patients, as well as be used by interested parties to discredit pharmacy compounding in general. In particular, cases of unfair practice or insufficient control in compounding pharmacies with a low level of equipment can form a negative public opinion and be used by opponents of pharmacy compounding, including from large pharmaceutical manufacturers.

[25] U.S. Food & Drug Administration. Makena (hydroxyprogesterone caproate) – information page (история одобрения и последующее изъятие). Available from: https:// www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/makena-hydroxyprogesterone-caproate-injection-information

[26] K-V Pharmaceutical Company et al. v. FDA et al. Memorandum Opinion, 06.09.2012. United States District Court for the District of Columbia, No. 1:12-cv-01105 (ABJ). Available from: https://law.justia.com/cases/federal/district-courts/ district-of-columbia/dcdce/1%3A2012cv01105/155076/23/

[27] European Parliament. Parliament adopts its position on EU pharmaceutical reform. Available from: https://www.europarl.europa.eu/news/en/press-room/20240408IPR20308/parliament-adopts-its-positionon-eu-pharmaceutical-reform

[28] Sirius scientists have developed manufacturing technologies for three orphan disease drugs. Available from: https://sirius-ft.ru/tpost/uchenye-siriusa-razrabotali-tekhnologii-izgotovleniya-trekh-preparatov-ot-orfannykh-zabolevaniy. Russian

Thus, in order to ensure the safety of patients and increase confidence in pharmacy compounding, including orphan drugs, it is advisable to develop a system for classifying compounding pharmacies, taking into account both the level of their technical and personnel equipment, and the categories of medicines compounded. This approach will allow establishing reasonable and differentiated requirements for compounding pharmacies depending on their capabilities and goals, minimizing risks for patients and ensuring a fairer regulatory burden.

As an example, we can cite the experience of the United States of America, where a three-level system of regulation of pharmacy compounding has developed [43]. Ordinary retail pharmacies, although focused on dispensing finished medicines, retain the right to compound. With the exception of a number of states[29], it is limited to simple non-sterile forms that are compounded "under a prescription" from a doctor. More opportunities are provided to compounding pharmacies of category 503A[30, 31], which are authorized to compound a wide range of dosage forms, including sterile medicines (injectable drugs, eye drops, etc.). Their activities are regulated at the state level and must comply with the requirements of the pharmacopoeia. Such pharmacies have become a key link in providing patients with personalized medicines.

The next level is pharmacies of type 503B[32], which are an intermediate link between a pharmacy and a pharmaceutical production: they can produce medicines in series, without a doctor's prescription, mainly for medical organizations. At the same time, they are obliged to comply with good manufacturing practice standards and are under the direct control of the FDA.

This model demonstrates an institutionalized separation of functions: from limited individual compounding in retail pharmacies to full-fledged serial production for medical organizations [44].

Not identical, but a similar approach can be implemented in the Russian Federation within the framework of Decree of the Government of the Russian Federation No. 547 dated March 31, 2022 "On approval of the Regulations on licensing pharmaceutical activities"[33] and Order of the Ministry of Health of the Russian Federation No. 780n dated July 31, 2020 "On approval of the types of pharmacies"[34], which will allow more flexibly regulating the activities of compounding pharmacies. Order No. 249n may enshrine the requirements for different types of compounding pharmacies. Thus, for organizations with a minimum technological base that do not claim to compound innovative medicines, including those of protein, cellular or nucleotide nature, minimum requirements may be established. In the case of compounding pharmacies with modern equipment and the appropriate infrastructure, provide for stricter requirements for the organization of the quality assurance system and staffing, but allow the use of the existing high-tech potential, expanding the possibilities for compounding complex personalized medicines.

Thus, the development of a system for differentiating compounding pharmacies, taking into account their equipment and competencies, seems to be an important step for improving the safety and sustainability of pharmacy compounding, as well as for forming a more fair and effective regulatory system.

Low demand

The lack of a stable sales market and formed demand is also one of the most significant barriers to realizing the potential of pharmacy compounding of orphan drugs. In the context of the current regulation, compounding pharmacies, even with the necessary production capacities and quality assurance capabilities, face serious difficulties in promoting their medicines on the market. As a result, the economic feasibility of projects for compounding orphan drugs in pharmacy conditions is reduced, allowing manufacturers to set higher prices.

At the same time, unjustified price increases in a number of countries have begun to initiate changes in state policy regarding orphan drugs [45]. For example, in the Netherlands in 2018, the Amsterdam University

[29] Texas Administrative Code, Title 22, Part 15: Texas State Board of Pharmacy (§ 291.133 «Pharmacies Compounding Sterile Preparations»; § 291.106 «Pharmacies Compounding Sterile Preparations (Class A-S)»; § 291.3 «Required Notifications»). Available from: https://www.law.cornell.edu/regulations/texas/22- Tex-Admin-Code-SS-291-36

[30] Florida Administrative Code. 64B16-28.802 – Special Sterile Compounding Permits for Pharmacies and Outsourcing Facilities; Tallahassee, FL: Florida Board of Pharmacy. Available from: https://www.law.cornell.edu/regulations/florida/Fla-Admin-Code-Ann-R-64B16-28-802

[31] United States Code. Title 21. § 353a – Pharmacy compounding. Washington; DC: U.S. Government Publishing Office. Available from: https://www.govinfo.gov/link/ uscode/21/353a

[32] United States Code. Title 21. § 353b – Outsourcing facilities; Washington, DC: U.S. Government Publishing Office. Available from: https://www.govinfo.gov/link/ uscode/21/353b

[33] Decree of the Government of the Russian Federation dated March 31, 2022 No. 547 "On Approval of the Regulations on Licensing Pharmaceutical Activities". Available from: https://www.consultant.ru/document/cons_doc_LAW_413815/

[34] Order of the Ministry of Health of the Russian Federation dated July 31, 2020 No. 780n "On Approval of types of pharmacies". Available from: https://base.garant. ru/74647990/. Russian

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Medical Center reached a general agreement with the largest insurance companies on the compounding of capsules of chenodeoxycholic acid for all Dutch patients with cerebrotendinous xanthomatosis syndrome [14]. The reason for this decision was a sharp increase in the price of the original drug CDCA Leadiant, which until 2008 was sold under the name Chenofalk® at a price of 46 euros (≈ 4 400 rubles; calculated at the rate of the Central Bank of the Russian Federation on September 9, 2025) per package of 100 capsules. After the acquisition of rights by Leadiant, it rose in price to 885 euros (≈ 84 000 rubles; calculated at the rate of the Central Bank of the Russian Federation on September 9, 2025), and then, with the receipt of orphan status and the receipt of a registration certificate throughout the European Union, it consistently reached a price of 14 000 euros (≈ 1 335 000 rubles; calculated at the rate of the Central Bank of the Russian Federation on September 9, 2025) for the same package. At the same time, chenodeoxycholic acid is a compound known since the 1970s [46]. In these conditions, the initiative of the Amsterdam University Medical Center received approval from both the Dutch Health Inspectorate and the Ministry of Medical Care and was supported by the government, which put the interests of society first, despite initial problems with the quality of the substance used in compounding and complaints from Leadiant, which had exclusive rights[35]. Moreover, in 2021, Leadiant was found guilty of abuse and fined 19.5 million euros (≈ 1.72 billion rubles; calculated at the rate of the Central Bank of the Russian Federation on September 9, 2025)[36]. The court decision noted that the company did not conduct new research, but used orphan status for an unjustified multiple increase[37].

The situation is aggravated by the established social and cultural attitudes in the medical community and among patients, who are oriented mainly towards industrial and foreign medicines. This attitude is due to both a high level of trust in manufacturers and a lack of sufficient awareness of the capabilities of modern compounding pharmacies. Scientific and practical publications note that cases of negative experience with the use of pharmacy dosage forms in the past, associated with inadequate quality, have led to the formation of persistent caution among doctors and patients [47–49]. As a result, an additional limitation of the potential market for pharmacy medicines is formed.

In these conditions, it is extremely important to develop a set of measures that would stimulate the interest of the medical community and patients in pharmacy dosage forms, as well as provide reliable guarantees of their sale.

One of the promising areas is the active involvement of state institutions, including the “Circle of Good” Foundation, created to provide children with severe and rare diseases with high-cost medicines, in the mechanisms for purchasing extemporaneous medicines.

In addition, it seems appropriate to involve the constituent entities of the Russian Federation in the organization of regional programs for the purchase of orphan extemporaneous medicines, especially in cases where industrially produced drugs are absent or unavailable, for example, for the purpose of providing patients over 19 years of age who have ceased to be wards of the “Circle of Good” Foundation.

Restriction on the dispensing of extemporaneous medicines intended for outpatient treatment

In accordance with the current regulatory legal regulation, a medical organization for the purpose of ensuring the treatment process has the right to contact a pharmacy, including one that is not a structural unit of this medical organization, for the purpose of compounding and dispensing medicines on the basis of a requisition[38]. In a hospital setting, medicines received from a compounding pharmacy can be used as part of the provision of a medical service[39].

At the same time, orphan drugs are in most cases used on an outpatient basis, while they are of high cost and require centralized purchases with subsequent distribution through medical organizations.

In turn, the procedure for transferring a medicinal product compounded according to a requisition to

[35] Pharmaceutical Accountability Foundation. Amsterdam UMC resumes supply of compounded CDCA. 22.01.2020. Available from: https://www.pharmaceuticalaccountability. org/2020/01/22/amsterdam-umc-resumes-supply-of-compounded-cdca

[36] Autoriteit Consument & Markt. Autoriteit Consument & Markt imposes fine on drug manufacturer Leadiant for CDCA’s excessive price. Пресс-релиз от 19.07.2021. Гаага. Available from: https://www.acm.nl/en/publications/acm-imposes-fine-drug-manufacturer-leadiant-cdcas-excessive-price

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[38] Order of the Ministry of Health of the Russian Federation No. 100n dated March 7, 2025 “On Approval of the Rules for the release of medicines”. Available from: https://normativ.kontur. ru/document?moduleId=1&documentId=492852. Russian

[39] Federal Service for Healthcare Supervision. Medicines. Licensing of pharmaceutical activities: answers to frequently asked questions. “Is it mandatory for medical organizations to obtain a license for pharmaceutical activities?”. Available from: https://roszdravnadzor.gov.ru/drugs/licensingpharm/faq/c1324/107. Russian

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a patient for outpatient use is not regulated by law, and such actions in the absence of a pharmaceutical activity license from a medical organization may be qualified by Roszdravnadzor as a violation, since they are considered as retail trade in medicinal products. Obtaining a pharmaceutical activity license by a medical organization and establishing a structural unit — a pharmacy — is also not a solution to this problem, since the current legislation does not provide for the possibility of transferring a medicinal product from a compounding pharmacy that compounds the medicinal product to another pharmacy.

The scheme of internal circulation of medicines, received according to a requisition from a compounding pharmacy, from a medical organization to its structural unit — a pharmacy with subsequent dispensing, implemented in practice, requires complex documentation and the writing of a repeated prescription. In addition, it is necessary to conduct a repeated control during dispensing.

The described scheme is formal in nature, but is associated with significant administrative and financial costs, which actually limits the possibility of providing outpatient patients with extemporaneous orphan drugs.

To eliminate the described barrier, it seems appropriate to enshrine the possibility for medical organizations to transfer medicines for outpatient treatment. It is also necessary to provide a mechanism for transferring an extemporaneous medicinal product from a compounding pharmacy to another pharmacy for subsequent dispensing.

Therapeutic effectiveness of extemporaneous analogue medicines

The argument about the lack of preclinical and clinical studies or evidence of therapeutic effectiveness is one of the key tools that supporters of the large pharmaceutical industry use to limit extemporaneous compounding. This statement is put forward as a universal objection against the possibility of using extemporaneous medicines instead of industrial analogues, which is already prohibited by Art. 56 of Federal Law No. 61-FZ.

In this regard, it is necessary to clearly differentiate the problem. The question of proving the therapeutic effectiveness of pharmacy medicines can arise only in two cases, and one of them is hypothetical and is possible only if compounding pharmacies are allowed to compound registered deficient medicines. Currently, only the compounding of complete non-personalized analogues of medicines not registered in the Russian Federation is a situation when the question of confirming therapeutic effectiveness from a scientific point of view is reasonable.

In turn, there is no mechanism in world practice for confirming the therapeutic effectiveness of pharmacy dosage forms. The US experience with semaglutide demonstrates this. Compounded analogues of Ozempic® and Wegovy® filled the needs of patients for more than three years. In addition, some compounding pharmacies used semaglutide in salt form, which makes the drug pharmaceutically non-equivalent. The FDA directly pointed out the inadmissibility of using semaglutide salts, but there were no other requirements that in any way related to therapeutic effectiveness[40].

Despite the fact that the benefit in this case outweighs the potential risks, since there is no regulatory mechanism “biowaiver for pharmacies” or a legal model where responsibility for the use of extemporaneous analogues of unregistered industrial medicines without their proven therapeutic effectiveness is distributed between the attending physician and the compounding pharmacy, this vulnerability will be used to restrain the pharmacy compounding system.

A possible way for solving this issue is to consolidate at the level of the State Pharmacopoeia a gradation of requirements for determining the equivalence of complete extemporaneous forms of analogues of unregistered industrially produced medicines, depending on the dosage form and their therapeutic effect.

Thus, for dosage forms with local action, it is sufficient to confirm pharmaceutical equivalence, that is, the identity of the qualitative and quantitative composition in one dosed unit of the medicinal product.

In the case of injectable medicines in which bioavailability is close to 100%, as well as non-modified immediate-release dosage forms, basic in vitro studies should be additionally carried out.

For complex dosage forms, including modified-release, transdermal systems, inhalations with a systemic effect, consolidate the mechanism of medical necessity according to the “Right to Try” principle,

[40] Food and Drug Administration. FDA’s Concerns with Unapproved GLP-1 Drugs Used for Weight Loss. Available from: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/fdas-concerns-unapproved-glp-1- drugs-used-weight-loss

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when responsibility for the prescription is assigned to the attending physician, and the compounding pharmacy guarantees quality [50]. This approach would allow the legitimate compounding of unregistered medicines without requiring the impossible from compounding pharmacies — conducting full-scale clinical trials.

Study Limitations

The search for sources was conducted mainly in Russian and English, so publications in other languages may not have been taken into account. The analysis included only the most significant and relevant materials, which led to the risk of incomplete coverage of secondary studies and local regulatory legal acts.

CONCLUSION

The analysis of the identified barriers shows that the problem of providing patients with orphan drugs goes beyond pharmaceutical practice and affects the foundations of the state's drug safety. Pharmacy compounding in this context is not just an auxiliary mechanism, but a strategic tool capable of compensating for structural imbalances in the market.

World practice shows that the key competition in the field of orphan drugs occurs not between pharmaceutical companies, but at the level of regulatory systems of various countries and integration associations. At the same time, it is the developed national system of compounding pharmacies that becomes a weighty argument in the formation of pricing policy, ensuring sustainable access to therapy and protecting the interests of patients.

In conditions when global companies are increasingly using orphan status to maintain the high cost of drugs, compounding pharmacies are able to play the role of a "counterweight", providing patients with more effective, timely and affordable pharmacotherapy. Russia has a regulatory and organizational framework for the formation of such a system, but its further development requires the elimination of existing barriers and the institutionalization of pharmacy compounding as a full-fledged element of national drug policy.

Solutions aimed at overcoming the identified obstacles will be useful not only for the segment of orphan drugs, but also for pharmacy compounding in general, creating the basis for its sustainable development. Orphan drugs in this sense become an indicator of systemic problems, and overcoming them can become a point of growth for the entire industry.

Thus, the elimination of barriers will not only expand access to therapy for patients with rare diseases, but also turn pharmacy compounding into one of the key factors of pharmaceutical independence of Russia.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS' CONTRIBUTION

M.A. Mandrik — idea, design, collection and critical analysis of scientific literature and regulatory legal documents, interpretation of the results, draft writing and editing, final approval of the article; A.V. Bykov — analysis of scientific literature and regulatory legal documents, discussion, editing and final approval of the article; V.S. Fisenko — search and analysis of literary sources, draft editing and final approval of the article; E.A. Maksimkina — analysis of scientific literature and regulatory legal documents, discussion, draft editing and final approval of the article. 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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