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Regulation in the sphere of circulation of extemporaneously compounded medicines under modern conditions of Russia

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The aim of the work was to analyze the current regulatory legal framework governing the manufacture of drugs in pharmacies, and a comprehensive review of the current state of their manufacture; a disclosure of problems and search for the ways to improve the sphere of circulation of extemporaneously compounded medicines (ECMs).

Materials and methods. The national legislation of the Russian Federation and the regulatory framework of the medicines common market of the Eurasian Economic Union in the field of an extemporaneous drugs circulation formed a regulatory base of the work. To collect and analyze the information data, the materials presented on the official websites of the Ministry of Health of Russia, the Ministry of Industry and Trade of Russia have been used. The results of the scientific publications for the previous 10 years (2014–2024) have also been analyzed.

Results. The article deals with the current state issues of the drug products manufactured in pharmacies, in the sphere of circulation. The analysis of the legislative base on ECMs has been carried out, the problems of the normative legal regulation of the pharmacy drugs manufacturing have been identified. The introduction of new relevant concepts into Federal Law No. 61-FZ "On Circulation of Medicines" — "extemporaneous drug products", "extemporaneous manufacturing", "extemporaneous production" — has been proposed. The authors' definition of the "pharmaceutical sovereignty" concept was given in the course of the study. Based on the results of the study, the possibilities and ways of improving the mechanisms of the state regulation of the drugs extemporaneous manufacturing in the current political and economic conditions have been identified.

Conclusion. The operational management and systematization of the regulatory legal framework of the ECMs circulation sphere based on the regulatory science is the most important factor in increasing the affordable, effective, personalized pharmaceutical care. An important element of the mobilization model of the economy is strengthening of the state regulation, development of the domestic production capacities and technologies, including taking into account extemporaneous manufacturing of drugs and small-scale production.

Keywords: extemporaneously compounded medicines; drugs manufacturing; extemporaneous formulations; extemporal production; pharmacy; drug supply; pharmaceutical sovereignty; drug sovereignty.

Abbreviations: ECMs — extemporaneously compounded medicines; DF — dosage form; CPR — certificate of product registration; SRMs — State Register of Medicines; EEU —Eurasian Economic Union; DS — drug substance; RCPEA — Russian Classification of Products by Economic Activities; SPh — State Pharmacopoeia; LGWS — List of goods, works and services; UDCM — Unified directory-catalog of medicines; WIPO — World Intellectual Property Organization.

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Регулирование в сфере обращения экстемпоральных лекарственных препаратов в современных условиях России

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Цель. Анализ действующей нормативной правовой базы, регулирующей изготовление лекарственных препаратов (ЛП) в аптечной организации (АО) и всесторонний обзор текущего состояния их изготовления. Раскрытие проблем и поиск путей совершенствования сферы обращения экстемпоральных лекарственных препаратов (ЭЛП).
Материалы и методы. Нормативную базу работы составило национальное законодательство Российской Федерации и регуляторной базы общего рынка лекарственных средств Евразийского экономического союза в сфере обращения экстемпоральных ЛП. Для сбора и анализа информационных данных использованы материалы, представленные на официальных сайтах Министерства здравоохранения России, Министерства промышленности и торговли России. Так же были проанализированы результаты научных публикаций за последние 10 лет (2014–2024 гг.).
Результаты. В статье рассматриваются вопросы современного состояния сферы обращения ЛП, изготовленных в АО. Проведён анализ законодательной базы по ЭЛП, определены проблемы нормативного правового регулирования аптечного изготовления ЛП. Предложено введение новых актуальных понятий в федеральный закон № 61-ФЗ «Об обращении лекарственных средств» — «экстемпоральные лекарственные препараты», «экстемпоральное изготовление», «экстемпоральное производство». В ходе проведённого исследования дано авторское определение понятию «фармацевтический суверенитет». По результатам исследования определены возможности и предложены пути совершенствования механизмов государственного регулирования экстемпорального изготовления лекарственных препаратов в современных политических и экономических условиях.
Заключение. Оперативное управление и систематизация нормативной правовой базы сферы обращения ЭЛП на основе регуляторной науки — важнейший фактор повышения доступной, эффективной, персонализированной лекарственной помощи. Важным элементом мобилизационной модели экономики является усиление государственного регулирования, развитие отечественных производственных мощностей и технологий, в том числе с учётом экстемпорального изготовления ЛП и мелкосерийного производства.
Ключевые слова: экстемпоральные лекарственные препараты; изготовление лекарственных препаратов; экстемпоральное изготовление; экстемпоральное производство; аптечная организация; лекарственное обеспечение; фармацевтический суверенитет; лекарственный суверенитет
Список сокращений: ЛП — лекарственный препарат; ЭЛП — экстемпоральный лекарственный препарат; ЛФ — лекарственная форма; ЛС — лекарственное средство; АО — аптечная организация; РУ — регистрационное удостоверение; ГРЛС — Государственный реестр лекарственных средств; ЕАЭС — Евразийский экономический союз; ФС — фармацевтическая субстанция; ОКВЭД — Общероссийским классификатором видов экономической деятельности; ГФ — Государственная фармакопея; КТРУ — каталог товаров, работ и услуг; ЕСКЛП — Единый структурированный справочник-каталог лекарственных препаратов; ВОИС — Всемирная организация интеллектуальной собственности.

INTRODUCTION

The current state of functioning of the pharmaceutical market is a reflection of the general situation under sanctions restrictions [1]. The presence of defective drugs in pharmacies reduces the availability of the drug provision and personalized care [2–5]. In this regard, the key task of state structures is to search for methods [6–8] and tools [9, 10] to fulfil constitutional obligations to protect health and provide medical care[1].

The drugs manufactured in pharmacies, or extemporaneously compounded medicines (ECMs), are not only an important but also a necessary

[1] The Constitution of the Russian Federation. Article 41. (adopted by popular vote on Dec 12, 1993 with amendments approved during the nationwide vote on July 01, 2020)

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component of quality drug therapy in health service delivery [11–14]. The advantages of ECMs are an individual dosage of the active substance, the possibility of combining a required amount of active substances in one dosage form (DF), a replacement or elimination of excipients (preservatives, fillers, stabilizers), an ergonomic DF selection [15–18]. ECMs have a short shelf life, up to a maximum of 30 days[2], and due to the lack of a profitability of their mass production, are not produced by the pharmaceutical industry [19–23]. These drugs are most in demand in paediatric and geriatric populations (especially for newborns and premature infants, polymorbid gerontological patients) [24–27], in dermatology, oncology, palliative care [28], for patients with high-cost nosologies, including those with orphan diseases [29–32]. A physician prescription of individual extemporaneous drugs allows patients and medical organizations to purchase necessary amounts of ECMs, which helps to achieve financial and budgetary efficiency for patients and medical organizations [33–36].

The Pharmacies engaged in the manufacture of ECMs, are an essential link in the value-based, personalized pharmaceutical care. It should be noted that, as of 2023, active manufacturing pharmacies across the country are represented by 460 to 890 entities and represent less than 0.5% of all pharmacies licensed for pharmaceutical activities [37]. For example, in Germany and Austria, all pharmacies are engaged in the manufacture of drugs, due to the mandatory license condition to include a manufacturing department in the structure of pharmacies [38–40]. In Poland, 99% of pharmacies are involved in the manufacture of drugs[3].

The expansion of the compounding (magistral formula) determines the need to update the technological base, to offer the necessary list of drug substances (DSs) on the market with the necessary packaging for pharmacies involved in the drugs manufacturing [41]. With this in mind, the most important role in the field of the drug manufacturing is assigned to the professional staff with modern competences that correspond to the development of the pharmaceutical market [42].

Recently, the regulatory framework for ECMs has undergone many additions and changes, but for the effectiveness of the regulatory practice, a systemic "roadmap" that takes into account all external threats and internal challenges, is needed.

THE AIM of the work was to analyze the current regulatory legal framework governing the drugs formulation in pharmacies, and a comprehensive review of the current state of their manufacture; a disclosure of problems and search for the ways to improve the sphere of circulation of extemporaneously compounded medicines (ECMs).

MATERIALS AND METHODS

Regulatory legal acts of the Russian Federation in the field of health care and circulation of drugs were chosen as objects of the study; the following methodological tools were used: empirical, theoretical and quantitative. As an empirical base, available data from the official website of the Ministry of Health of Russia[4], statistical data[5], a reference legal system "ConsultantPlus" on a contractual basis of Sechenov University, were studied.

The search was conducted using the following keywords: "extemporaneously compounded medicines", "drugs manufacturing", "extemporaneous formulations", "extemporal production", "pharmacy", "drug supply", "pharmaceutical sovereignty", "drug sovereignty", "compounding".

To analyze the results of scientific publications by other authors, the sources of information of the National Electronic Library — elibrary.ru, Google search engine were used. The search for legislative documents, literature was carried out for the period from 2014 to 2024. This period includes the sphere of ECMs circulation, before and after the entry into force of Federal Law No. 502-FZ[6] dated 05.12.2022, in terms of pharmacy manufacturing of drugs.

In accordance with the carried out search query, a total of 357 sources of information were found. The authors classified 50 sources as the most relevant.

In the course of the research, a set of scientific methods of systemic, logical, structural, comparative types of analysis was applied.

RESULTS AND DISCUSSION

Manufacturing of drugs in pharmacies in accordance with part 33 of Article 4 (Federal Law No. 61-FZ), refers to pharmaceutical activities, including wholesale trade of drugs, their storage, transportation and (or) retail trade of drugs, including a remote method, their dispensing, storage, transportation, manufacturing[7].

The term "extemporaneously compounded medicines" has been widely used in pharmaceutical practice since historical times, but till present, it has not been properly legislated. Although it should be noted that the sectoral law on the circulation of drugs defines about 20 concepts of drugs. *"Ex tempore"* (from

[2] Order of the Ministry of Health of the Russian Federation dated May 22, 2023 No. 249n (as amended on May 22, 2023) "Rules for the manufacture and release of medicines for medical use by pharmacies licensed for pharmaceutical activities".

[3] Zhukova O. Pharmacies in Poland. Available from: https://pharmvestnik.ru/articles/apteki-poljshi.html. Russian

[4] Ministry of Health of the Russian Federation. Available from: https://minzdrav.gov.ru

[5] Federal State Statistics Service of Russia. Available from: https://minzdrav.gov.ru

[6] Federal Law No. 502-FZ dated 05.12.2022 "On Amendments to Article 56 of the Federal Law on the Circulation of Medicines".

[7] Federal Law No. 61-FZ dated 12.04.2010 "On the Circulation of Medicines".

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Latin — as needed), more than ever emphasizes the importance of ECMs in the system of the drug supply under the conditions of mobilization economics and strengthening the drug sovereignty of the country. In this regard, the introduction of a new concept in Article 4 of Federal Law No. 61-FZ — "extemporaneously compounded medicines" — was proposed. According to the definition, ECMs are medicinal products in the DF of the drugs manufactured in pharmacies according to doctors' prescriptions or requirements of medical organizations, providing a personalized approach in the treatment of a particular patient' or a group of patients' disease, taking into account their anatomical and physiological and age-specific features. In the authors' opinion, the systematization of all terms and definitions used in relation to these drugs (drugs manufactured in pharmacies; extemporaneous dosage forms, extemporaneously compounded medicines, drugs, etc.) and the approval of the new concept of "extemporaneously compounded medicines" will do a lot. They will contribute to the improvement of the development processes of an integrated state vertical of the normative legal regulation of the ECMs circulation sphere.

Changes in Legislation

In September 2023, the amendments introduced by Federal Law No. 502-FZ[8] dated Dec 05, 2022 to Article 56 "Manufacturing and dispensing of drugs" of the Federal Law "On Circulation of Medicines", came into force in the Russian Federation. To date, the manufacture of ECMs for medical use is allowed only to pharmacies and prohibited to individual entrepreneurs, which limits the activity of small businesses and is still a debatable topic among the professional community.

The most important challenge under the sanctions regimes is the ban on the possibility to manufacture drugs registered under the national procedure in the Russian Federation. Moreover, with the entry into force of Federal Law No. 1-FZ[9] dated Jan 30, 2024 in early 2024, this ban also applies to the manufacture of drugs registered on the common market of the Eurasian Economic Union (EAEU).

The introduced legislative amendment allowing the use of finished DFs included in the State Register of Medicines (SRMs) and the Unified directory-catalog of medicines (UDCMs)[10] of the EAEU[11], is an undoubted achievement in the manufacture of drugs, but it solves only a part of the identified problems of the drug supply.

The authors believe that authorizing the manufacture of the drugs registered in the Russian Federation, as well as in the EAEU countries, should have the following key advantages:

1. Elimination of defective items in pharmacies;
2. Expansion of personalized pharmaceutical care for different groups of patients;
3. Reduction of entry barriers for new entities to the extemporaneous manufacturing market and reduction of their financial risks.

Licensing for manufacture of drugs

Manufacture of drugs is a licensable type of a pharmaceutical activity.

Licensing shall be subject to:

- manufacture of drugs for a medical use, except for the manufacture of radiopharmaceutical drugs for a medical use;
- manufacture of radiopharmaceuticals for a medical use.

In accordance with the Regulation on Licensing, three sections of license requirements for the manufacture of drugs in pharmacies can be distinguished:

- availability of a production facility or facilities (premises, buildings, structures) and the equipment at the place of pharmaceutical activities, belonging to the right of ownership or another legal basis providing for the right of possession and the right to use;
- requirements to education and qualification of pharmacies' employees;
- compliance of the licensee with the requirements of the legislation.

It should be noted that the current licensing regulations have completely eliminated the requirements of special education, qualifications and work experience for pharmacies supervisors directly involved in the dispensing, storage and manufacture of drugs[12].

In the authors' opinion, the exclusion of professional requirements for pharmacies supervisors does not contribute to the quality fulfilment of the tasks and mission assigned to pharmacies, undermines the prestige of a pharmaceutical specialist and pharmaceutical education in general, and reduces the level of employees' trust in the supervisor at the professional level.

The causal link of this cancellation can be seen in the status of pharmacies as a trading enterprise, in accordance with the Russian Classification of Products by Economic Activities (RCPEA), "retail trade in

[8] Federal Law No. 502-FZ dated Dec 05, 2022 "On Amendments to Article 56 of the Federal Law on the Circulation of Medicines".
[9] Federal Law No. 1-FZ dated Jan 30, 2024 "On Amendments to the Federal Law "On the Circulation of Medicines" and Articles 1 and 4 of the Federal Law "On Amendments to the Federal Law "On the Circulation of Medicines" and the Federal Law "On Amendments to the Federal Law "On the Circulation of Medicines".
[10] The State Register of Medicines of the Russian Federation. Available from: https://grls.minzdrav.gov.ru/Default.aspx
[11] The Unified Register of Registered Medicines of the Eurasian Economic Union. Available from: https://portal.eaeunion.org/sites/commonprocesses/ru-ru/Pages/DrugRegistrationDetails.aspx
[12] Decree of the Government of the Russian Federation dated March 31, 2022 No. 546 "On Approval of the Regulations on Licensing pharmaceutical activities".

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pharmaceutical products" belongs to the section "Retail Trade" (code 52.31)[13].

Order No. 529n of the Ministry of Health of Russia "On approval of the nomenclature of medical organizations" dated Aug 6, 2013, excluded the types of pharmacies from the nomenclature [14], although in the earlier order No. 627 dated Oct 07, 2005, all types of pharmacy institutions were present[15].

In the authors' opinion, it would be logical for RCPEA to include pharmacies "Activities in the field of health care and social services" in section Q. It is important to note the distinctive features of a drug as a drug, and, according to the requirements of order No. 647n[16] of the Ministry of Health of Russia dated Aug 31, 2016, professional pharmaceutical counseling is a prerequisite for the sale of drugs and all products of the pharmacy assortment. There are currently four professional standards that define the qualification requirements for specialists to carry out pharmaceutical activities. The content analysis of the current professional standards — "Pharmacist"[17], "Senior pharmacist"[18], "Management specialist in pharmaceutical business"[19], "Pharmacy technician"[20], — makes it possible to identify generalized labour functions and the labour functions for all the processes related to the manufacture of drugs, including the functions of quality assurance of drugs in pharmacies, pharmaceutical counseling and informing medical specialists. In general, professional standards establish requirements for professional education, special conditions for the admission to pharmaceutical activities, necessary knowledge, skills and labour actions. All these ultimately determine the goal of Pharmacies activities - to provide the population with safe and effective drugs, including ECMs.

New rules for manufacture of drugs

In pursuance of part 1 of Article 56 (Federal Law No. 61-FZ dated Apr 12, 2010), a delegated act approving new rules for manufacturing and dispensing drugs for a medical use was adopted — Order No. 249n of the Ministry of Health of Russia dated May 22, 2023, replacing Order No. 751n of the Ministry of Health of Russia dated Oct 26, 2015.

For the first time, these rules approved the peculiarities of manufacturing drugs from DFs, the procedure for manufacturing radiopharmaceutical drugs, and introduced a new section – a quality system of drug manufacturing.

The license requirement to have a person in charge of the implementation and maintenance of the quality system in pharmacies and the introduction of a new section on the quality system for the manufacture of drugs in the new regulations, are important prerequisites for the improvement of regulatory processes along the track of transformation of the current rules for the manufacture and dispensing into a prospective good practice for the manufacture and dispensing of drugs. In the authors' opinion, the adoption of good manufacturing and dispensing practices for drugs will serve to improve the efficiency and safety of manufactured drugs as a complete quality management system for this activity.

In accordance with paragraph 54 of Chapter IV "Peculiarities of manufacturing drugs from finished dosage forms" (Order No. 249n of the Ministry of Health of Russia), "...it is allowed to manufacture powders from finished dosage forms (tablets, capsules) that provide an immediate release of drugs. It is not allowed to manufacture powders from finished dosage forms (tablets, capsules) of a prolonged action and covered with intestinal soluble coating". In accordance with paragraph 56 of Chapter IV, "...the manufacture of solutions for injections and infusions from finished dosage forms of an industrial production is prohibited". In the authors' opinion, in this chapter, it is advisable to specify peculiar properties of manufacturing a wider nomenclature of dosage forms from finished dosage forms.

Chapter X of the current regulations states a specified procedure for the manufacture of radiopharmaceutical's.

Regulation of sanitary regime

A mandatory requirement of Order No.249n of the Ministry of Health of Russia is the compliance during the manufacture of medicinal products with conditions that meet sanitary and epidemiological requirements approved by the Decree of the Chief State Sanitary Doctor of the Russian Federation dated Dec 24, 2020 No. 44[21].

[13] Resolution of the State Standard of the Russian Federation dated 6.11.2001 No. 454-st "On the adoption and implementation of the RCPEA".

[14] Order of the Ministry of Health of the Russian Federation dated Aug 6, 2013 No. 529n "On approval of the nomenclature of medical organizations".

[15] Order of the Ministry of Health and Social Development of the Russian Federation dated Oct 07, 2005 No. 627 "On approval of the Unified Nomenclature of State and Municipal healthcare institutions".

[16] Order of the Ministry of Health of the Russian Federation dated Aug 31, 2016 No. 647n "On Approval of the Rules of Proper Pharmacy practice of medicines for medical use".

[17] The order of the Ministry of Labor of Russia dated 09.03.2016 No. 91n "On the approval of the professional standard "Pharmacist"".

[18] Order of the Ministry of Labor of the Russian Federation dated May 22, 2017 No. 427n "On approval of the professional standard "Pharmacist-analyst"".

[19] Order of the Ministry of Labor of the Russian Federation dated May 22, 2017 No. 428n "On approval of the professional standard "Management specialist in pharmaceutical business"".

[20] Order of the Ministry of Labor of the Russian Federation dated May 31, 2021 No. 349n "On approval of the professional standard "Pharmacist"".

[21] Resolution No. 44 of the Chief State Sanitary Doctor of the Russian Federation dated 12/24/2020 "On Approval of Sanitary Rules SP 2.1.3678-20 "Sanitary and epidemiological requirements for the operation of premises, buildings, structures, equipment and transport, as well as the operating conditions of business entities engaged in the sale of goods, performance of works or provision of services".

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While the regulation of the sanitary regime in pharmacies was previously approved by regulatory legal acts of the Ministry of Health of Russia, today, the authorization has been delegated to Rospotrebnadzor. A control of compliance with the rules on the sanitary regime remained under the jurisdiction of Roszdravnadzor.

Chapter V "Sanitary and Epidemiological Requirements for the Provision of Services by Pharmacy Organizations" is dedicated to the pharmacy section of the sanitary rules. The chapter contains only 24 paragrapharmacies, half of which relate to the pharmacies engaged in the manufacture of medicines.

Quality system of drugs manufacturing

As mentioned above, as a part of the systematic approach to the quality assurance of drug manufacturing, the chapter "Quality System for Drug Products Manufacturing" with a comprehensive approach to quality measures and development of standard operating procedures (SOPs) was introduced into pharmacies in accordance with the requirements of the General Pharmacopoeial Monographs (GPhMs) and Pharmacopoeial Monographs (PhMs).

In accordance with paragraph 7 of Chapter II "Quality System for the Manufacture of Drugs" (Order No. 249n of the Ministry of Health of the Russian Federation), the head of a pharmacy is obliged to appoint a responsible person for the implementation and maintenance of the quality system. The head's functions should include monitoring the effectiveness of the quality system and updating the SOPs, confirming the quality of manufactured drugs, as well as guaranteeing the manufacture of drugs in accordance with the SOPs. The person responsible for the implementation and assurance of the pharmacy quality system shall verify the compliance of each manufactured drug with the established requirements before and during their release.

In accordance with part 5 of Article 13 (Federal Law No. 61-FZ) and Clause 5 of Decision No. 78 of the Council of the Eurasian Economic Commission dated Nov 3, 2016, manufactured drugs are not subject to the state registration and registration on the common market of the EAEU's medicinal products[22]. Due to the absence of a mandatory registration of manufactured drugs at the national and interstate levels, the quality system of manufacturing drugs in pharmacies should be constantly updated with the introduction of necessary preventive and corrective measures to guarantee the quality and safety of finished products. Consequently, an important factor in ensuring the quality and safety of ECMs, taking into account all relations arising during the technological process of their manufacturing and dispensing, a compliance with the authorization and supervisory requirements of regulatory authorities, is the need for special education and professional competences of the supervisors of compounding pharmacies.

It should be also noted that the current delegated act does not have a single annex and, in the authors' opinion, this fact may complicate the process of manufacturing ECMs in terms of time and systematization of the regulatory information required for the manufacture of drugs. Previously, current Order No. 751n of the Ministry of Health of the Russian Federation dated Oct 26, 2015, contained 15 necessary annexes[23].

In general, attention should be paid to the relevance of the transition to the quality management system in the field of ECMs circulation — from the rules of manufacturing and dispensing of ECMs to the rules of good practice of extemporaneous manufacturing and the concept of determining the levels of risk in their manufacture [8].

In conjunction with regulatory legal acts governing the pharmaceutical industry and the market, the main tool for standardizing the quality of medicinal products is the State Pharmacopoeia of the Russian Federation (SPh RF). The fulfilment of the requirements specified in the SPh RF for the quality of drugs is mandatory for all subjects of the drug circulation, including the pharmacies manufacturing ECMs.

The current edition since 1 September 2023 is the SPh RF, XV edition[24]. All PhMs of the current pharmacopoeia are oriented to the requirements of the EAEU Pharmacopoeia; the norms are set in accordance with the international standards.

Taking into account the importance and necessity of tasks solution of drugs pharmacy manufacturing, the Ministry of Health of Russia has developed and approved 10 GPhMs[25], enacted since Sep 1, 2023. In connection with the widespread use of extemporaneous prescriptions in paediatric practice, the approval of GPhM 'Pharmacy Manufactured Drugs for Children' is particularly relevant. The list of the main regulatory legal acts governing the sphere of the ECMs circulation is presented in Table 1.

[22] Decision of the Council of the Eurasian Economic Commission dated Nov 03, 2016 No. 78 "On the Rules for registration and examination of medicines for medical use".

[23] Order of the Ministry of Health of the Russian Federation dated Oct 26, 2015 No. 751n "On approval of the Rules for the manufacture and release of medicines for medical use by pharmacy organizations, individual entrepreneurs licensed for pharmaceutical activities".

[24] Order of the Ministry of Health of the Russian Federation dated July, 20, 2023 No. 377 "On Approval of General Pharmacopoeial Monographs and Pharmacopoeial Monographs".

[25] Order of the Ministry of Health of the Russian Federation dated 08/25/2023 No. 448 "On Approval of General Pharmacopoeial Articles and Pharmacopoeial Articles and Amendments to Order of the Ministry of Health of the Russian Federation dated July 20, 2023 No. 377 "On Approval of General Pharmacopoeial Monographs and Pharmacopoeial Monographs".

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Table 1 – Main regulatory legal acts in the sphere of circulation of extemporaneously compounded medicines

Name of regulatory legal act	Functions / regulations governing the scope of ECMs circulation	Comments on hierarchy
Constitution of the Russian Federation	They defines the foundations of the political, legal and economic system of the state: • Art. 39 guarantees the social security in case of illness, disability; • Art. 41 gives the right to health care and medical assistance.	Constitution of the Russian Federation has supreme legal force, is represented by direct regulatory legal acts and is applied throughout the country
Federal law No. 323-FZ dated Nov 21, 2011	Realization of the constitutional right of citizens to health care and medical assistance, including drug provision and social protection: • Art.18 gives the right to health care; • Art. 19 gives the right to medical assistance; • Ch. 5 “Organization of Health Protection”.	Federal laws have a supreme legal authority after the Constitution of the Russian Federation and federal constitutional laws; they are directly applicable in the entire territory of the Russian Federation.
Federal Law No. 323-FZ “On the fundamentals of public health protection in the Russian Federation” dated Nov 21, 2011	Realization of the constitutional right of citizens to health care and medical assistance, including drug provision and social protection: • Part 33, Art. 4. Pharmaceutical activities (manufacturing of DPs is related to pharmaceutical activities); • Art. 8. Licensing of drugs and pharmaceutical activities; • Clause 1, Part 5, Art. 13. State registration of drug products (drugs manufactured by pharmacies are not subject to state registration); • Clause 1, Part 1, Art. 46. Labeling of drugs (drugs manufactured by pharmacies are an exception for their labeling); • Art. 56. Manufacturing and dispensing of drugs (manufacturing of drugs is allowed to be carried out by pharmacies having a relevant license; manufacturing of drugs using finished dosage forms is allowed; manufacturing of drugs registered in the Russian Federation and the EAEU, is not allowed); • Art. 57. Prohibition of sale of falsified drugs, substandard drugs, counterfeit drugs.	
Resolution of the Government of the Russian Federation No. 547 “On Approval of the Regulations on Licensing of Pharmaceutical Activities” dated March 31, 2022.	It specifies the procedure for licensing pharmaceutical activities: • manufacture of drugs for medical use, except for the manufacture of radiopharmaceutical drugs for medical use; • manufacture of radiopharmaceuticals for medical use.	Delegated RLAs, adopted in pursuance of the law
Order of the Ministry of Health of the Russian Federation No. 249n “Rules for manufacturing and dispensing drugs for medical use by pharmacy organizations holding a license for pharmaceutical activities”, dated May 22, 2023.	It regulates the rules of manufacturing, quality system and rules for dispensing ECMs in accordance with approved sections: I. General Provisions. II. Quality system of ECMs manufacturing. III. Peculiarities of manufacturing of drugs from pharmaceutical substances. IV. Peculiarities of manufacturing of drugs from finished dosage forms. V. Quality control of drugs. VI. Expiry dates for manufactured drugs. VII. Rules of dispensing and labeling of drugs. VIII. Controls on dispensing of drugs. IX. Features of the manufacture of homeopathic drugs. X. Procedure for the manufacture of radiopharmaceuticals.	

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Name of regulatory legal act	Functions / regulations governing the scope of ECMs circulation	Comments on hierarchy
Resolution of the Chief State Sanitary Doctor of the Russian Federation No. 44 "On Approval of Sanitary Rules SR 2.1.3678-20 "Sanitary and Epidemiological Requirements for the Operation of Premises, Buildings, Structures, Equipment and Transport, as well as the Conditions of Activity of Business Entities Engaged in the Sale of Goods, Performance of Work or Provision of Services", dated Dec 24, 2020.	It defines sanitary and epidemiological requirements in the implementation of pharmaceutical activities in accordance with the approved section: V. Sanitary and epidemiological requirements when providing services by pharmacies.	Delegated RLAs, adopted in pursuance of the law
Order of the Ministry of Health of the Russian Federation No. 377 "On approval of general pharmacopoeial Monographs and pharmacopoeial Monographs", dated July 20, 2023.	A list of quality indicators and quality control methods is defined.	
Order of the Ministry of Health of the Russian Federation No. 448 "On approval of general pharmacopoeial Monographs and pharmacopoeial Monographs, dated Aug 25, 2023; and amendments to Order of the Ministry of Health of the Russian Federation No. 377 "On approval of general pharmacopoeial Monographs and pharmacopoeial Monographs", dated July 20, 2023.	The following GPMs have been developed and approved: • GPhM.1.8.0001 Medicinal preparations of pharmacy manufacture. • GPhM.1.8.0003 Non-sterile pharmaceutical preparations of pharmacy manufacturing in the form of liquid dosage forms. • GPhM.1.8.0004 Non-sterile preparations of pharmacy manufacturing in the form of soft dosage forms. • GPhM.1.8.0005 Non-sterile preparations of pharmaceutical manufacturing in the form of solid dosage forms. • GPhM.1.8.0006 Sterile pharmaceutical preparations of pharmacy manufacturing. • GPhM.1.8.0002 Pharmacy-manufactured drugs for children. • GPhM.1.4.1.0043 Selection of dosage forms for children. • GPhM.1.11.0004 Extemporaneously compounded radiopharmaceuticals. • GPhM.1.8.0007 Homeopathic drugs of pharmacy manufacturing. • GPhM.1.4.1.0018 Infusions and decoctions.	

Note. RLA — regulatory legal act; ECMs — extemporaneously compounded medicines; GPhM — General Pharmacopoeial Monographs.

Regulation peculiarities of extemporaneously compounded medicines manufacturing

It should be noted that the prescription and use of ECMs is actually "off-label" — outside the instructions for a medical use and outside the general characterisation of drugs. Taking into account that the off-label efficacy and safety monitoring is currently carried out within the framework of pharmacovigilance and applies only to the registered drugs, it is necessary to improve regulatory processes to establish norms for monitoring these ECMs indicators [43, 44].

Pursuant to Art. 44 of Federal Law No. 248-FZ dated July 31.07.2020[26], Decree of the Government of the Russian Federation No. 1049 dated June 29, 2021[27], Order of Roszdravnadzor No. 9508 dated Dec 21, 2023[28], a risk-based approach is applied when conducting a state control of pharmacies with the right to manufacture drugs, including aseptic drugs. Pharmaceutical activities for manufacturing drugs are categorized as activities with a significant risk category, therefore, scheduled pharmacies supervisory activities are carried out once in 3 years. Supervisory activities help to identify risk-oriented points in the pharmacies

[26] Federal Law No. 248-FZ dated July 31, 2020 "On State Control (Supervision) and Municipal Control in the Russian Federation".

[27] Decree of the Government of the Russian Federation dated June 29, 2021 No. 1049 "On Federal State Control (Supervision) in the field of circulation of medicines".

[28] Order of the Federal Service for Healthcare Supervision dated Dec 21, 2023 No. 9508 "On Approval of the Program for the Prevention of Risks of Harm (Damage) to Legally Protected Values in the implementation of Federal State Control (Supervision) in the field of circulation of medicines for medical use in 2024".

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involved in drugs manufacturing, which contributes to improving the quality of a pharmaceutical supply to the population [45].

New regulatory legal acts (Order of the Ministry of Health of Russia No. 249n and the GPhM approved and enacted by Order of the Ministry of Health of Russia No. 377) could not significantly change the expected positive dynamics of compounding pharmacies and their increase in quantity and quality.

Constraints and risks for compounding pharmacies

A possible factor to reduce the financial risk for compounding pharmacies and increase their motivation to compound ECMs would be to amend Art. 164.2 of the Tax Code of the Russian Federation[29]: "…when selling drugs manufactured in a pharmacy, the value-added tax rate does not apply".

The question remains open when ECMs are procured by medical organizations that do not have their own compounding pharmacies.

Attention should be paid to some peculiarities identified by the authors in the course of their work:

- drug dispensing to medical organizations can be carried out exclusively by manufacturers of drugs and drugstores (Art. 54, No. 61-FZ);
- absence of ECMs state registration (Art. 13, No. 61-FZ);
- determination of the remaining ECMs shelf life;
- determination of price formation;
- entry of List of goods, works and services (LGWS) into the Unified directory-catalog of medicines (USCMP) with ECMs prescriptions and pharmacy manufacturing as services.

Thus, a procurement participant must have records in the pharmaceutical license indicating both manufacturing and dispensing of drugs and drugstores. Due to the absence of a certificate of product registration (CPR) for ECMs, the customer has no right to demand a copy of the RC and hand it over with the goods. There is a direct violation of the legislation on the contract system and on the circulation of drugs. Taking into account the limited shelf life of ECMs, it is necessary to indicate the shelf life depending on the specific dosage form of ECMs.

It should be also noted that it is necessary for pharmaceutical substance manufacturers to define the functionally required dosage forms for pharmacies involved in drugs manufacturing. At present, the State Register of Medicines (SRMs) mostly includes pharmaceutical substances in large packages, which are acceptable for the production of drugs. According to the analytical company RNC Pharma[30], for 9 months last year, 60% of pharmaceutical substances were imported from China, 15% from India and 23%, the most expensive ones, from Europe. The Ministry of Industry and Trade together with Vnesheconombank of Russia (VEB.RF), the Russian state development corporation that provides financing for social and economic projects, initiated a programme to support projects for the production of more than 145 pharmaceutical substances with preferential loans for pharmaceutical manufacturers.

The most important issue for the production of effective and safe drugs is the solution of compounding pharmacies staffing, the development of thematic cycles on ECMs for pharmaceutical and medical specialists. In this regard, it is necessary to jointly develop system solutions of the Ministry of Health of Russia and the Ministry of Education of Russia on the market demand for pharmaceutical personnel, especially pharmacy technicians and senior pharmacists. The position of pharmacy technicians according to the approved nomenclature of pharmaceutical workers by order of the Ministry of Health of the Russian Federation dated May 02, 2023 No. 205n[31] (as amended on May 02, 2023) was supposed to be valid only until Dec 31, 2025, which did not correspond to the personnel policy in the light of legislative changes in the manufacture of medicines. The logical changes made to this order dated Dec 04, 2023 eliminated these time limits. The position of senior pharmacists can be occupied by a specialist with professional retraining in "Pharmaceutical chemistry and pharmacognosy", if there is information about the accreditation of a specialist in "Pharmacy" and (or) training in internship / residency in "Pharmacy management and economics". A pharmacy technician and a senior pharmacist can hold an administrative position of the head of a structural unit or department of pharmacies, in addition to which a senior pharmacists may work or combine positions of a pharmacist and a pharmacy technician. The novelty of this order is a long-awaited authorization for the pharmacy head to work as a pharmacy technician. Thus, the regulator has simplified the procedure of transition from one specialty to another, which makes it possible to expand the positions held and interchangeability of specialists in labour collectives.

In order to form support measures for the law on compounding pharmacies, a special working group was set up under the Health Protection Committee of the State Duma of Russia, with the participation of deputies of the legislative assembly, representatives of

[29] The Tax Code of the Russian Federation (as amended, effective from June 1, 2024).

[30] RNC Pharma. Available from: https://rncph.ru/news/month/2023-9

[31] Order of the Ministry of Health of the Russian Federation dated May 02, 2023 No. 205n "On approval of the Nomenclature of positions of medical workers and pharmaceutical workers".

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the Ministry of Health and the Ministry of Industry and Trade of Russia, the pharmaceutical industry and patient organizations.

Due to the fact that pharmaceutical activities concerning ECMs manufacturing for pharmacies are unprofitable and there remains a risk of their closure, the working group has prepared an adopted draft law[32] of amendments to the federal law "On Circulation of Medicines", the work continues on drafts to the federal laws "On the Basics of Health Protection of Citizens", "On Compulsory Medical Insurance in the Russian Federation", the Civil Code and the Tax Code.

The aim of the package of amendments to federal laws is to increase the demand for pharmaceutically manufactured drugs by including them in clinical recommendations, treatment standards and in specialist training programs. In addition, treatment with ECMs should be included in state guarantee programs with an appropriate funding under the system of a preferential drug provision.

In connection with the revival of ECMs manufacturing, the issue of the intellectual property protection is also relevant.

In the scientific article "The new role of extemporaneous manufacturing in regulating access of drugs to the market", the authors reviewed the patent legislation abroad, including the EAEU countries in relation to ECMs manufacturing in pharmacy organizations [10].

The authors found out that the norm on the exceptions related to patent rights concerning pharmacy drugs manufacturing, is legislated in many member countries of the World Intellectual Property Organization (WIPO). The statements stipulated in Clause 5 of Article 1359 of the Civil Code of the Russian Federation, are not an infringement of the exclusive right to an invention, utility model or industrial design, they imply a single ECM production in pharmacies on prescriptions of doctors using the invention[33]. In the presence of a license, a pharmaceutical substance included in the SRMs for medical use may be used in the ECMs manufacturing in pharmacies.

Due to the fact that a compounding pharmacy cannot produce pharmaceutical substances on its own, it is necessary to legislate that a single production of pharmaceutical substances by a manufacturer will not be recognized as an infringement of the exclusive right to an invention, utility model or industrial design.

[32] Draft Law No. 798952-7 "On Amendments to Article 56 of the Federal Law on the Circulation of Medicines (regarding the Manufacture of Medicines)".

[33] The Civil Code of the Russian Federation (part four)" dated Dec 18, 2006 No. 230-FZ with amendments and additions.

Improvement of legislative base in the sphere of extemporaneously compounded medicines circulation

The logical consequence of the above is the legislative statements in the federal sectoral law "On Circulation of Medicines" and the following new concepts — "extemporaneous manufacturing" for pharmacies and "an extemporal production" for pharmaceutical manufacturers of drugs, proposed by the authors of this article.

Extemporaneous manufacturing is the value-oriented manufacture of extemporaneous drugs according to individual prescriptions or requested by a medical organization for a specific patient or a specific range of patients according to established prescriptions.

Extemporaneous manufacturing is a small-scale production of extemporaneous drugs according to the needs of a defined range of patients according to established prescriptions, and specific patients with a defined nosology for personalized pharmaceutical care according to individual prescriptions.

In the light of this research, a relevant and necessary definition of "pharmaceutical sovereignty" has been provided. It implies the ability of the state to control its pharmaceutical industry, including both extemporaneous manufacturing and an extemporaneous production, to ensure their sustainable development with the priority tasks of the drug supply. Of course, pharmaceutical sovereignty includes national drug sovereignty, but the definition is considered from a broad perspective, including the search for new molecules, development of the latest innovative drugs, modernization of the technological process and other external and internal factors in the conditions of the external sanctions pressure.

It should be noted that the rate of extemporaneous prescriptions from all incoming prescriptions to pharmacies in European countries is about 10%, in the USA — up to 5% [10].

In order to expand production departments in pharmacies in all subjects, to meet regional needs in ECMs [46], it is possible to develop a passport, approve and launch the federal project "Extemporaneous drugs: manufacturing and production". The project can be an important link in strengthening national pharmaceutical sovereignty, an important addition to the state programme "Pharma-2030" and a strategic factor of a sustainable development of the health care system as a whole. It should be noted that the current strategy shifts the focus towards measures to support drugs manufacturers through subsidisation, venture financing, and cheaper credit resources[34]. In the plans for the implementation of this state programme, the RF Government Order No. 753-r of 30.03.24 envisages the

[34] Decree of the Government of the Russian Federation dated July 06, 2023 No. 1495-r "On the Strategy for the development of the pharmaceutical industry of the Russian Federation for the period up to 2030".

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development of a mechanism for calculating the need of the healthcare system for drugs, based on which the actual demand will be formed, which will allow planning the processes of development and (or) organization of their production. It is also necessary to note the creation of interdepartmental working groups to ensure the interaction between the medical community and the manufacturing sector, with the participation of regulators, to raise awareness of domestic drugs among medical professionals and to receive feedback from specialists on the results of the use of drugs[35]. These support measures can significantly boost the development of extemporaneous manufacturing and production at regional levels and make the federal project sustainable.

In the authors' opinion, extemporaneous manufacturing and production should be regulated by the state, taking into account the primary objectives of the drug supply. However, there are already pioneers in opening commercial pharmacies, for example, the R-Pharm group of companies opened its first innovative manufacturing pharmacy "R-Pharm Compound". It should be noted that the National Project should outline the conditions for commercial organizations to enter the ECMs market. Extemporaneous manufacturing and production, in our opinion, should be regulated by the state, taking into account the primary tasks of drug supply.

The carried out analysis of the legal regulation of pharmaceutical activities concerning the manufacture of drugs in pharmacies showed a great deal of work done by the standard-setting activity, revealed some financial risks and barriers to entry into the ECMs market, professional requirements for pharmaceutical personnel and the main aspects of the further improvement of the legal framework to regulate the sphere of ECMs circulation [47–50].

CONCLUSION

The operational management and the degree of the regulatory impact in the field of the ECMs circulation is the most important factor in increasing the affordable, effective, personalized pharmaceutical care. Extemporaneous manufacturing and an extemporaneous production, a quality management system and dispensing of ECMs should be based on the evidence-based methods and tools, fulfil state objectives in the field of the drug provision, be economically beneficial for the patient, production structures and lead to the reduction of budgetary allocations for the drug provision. Manufacturing of drugs in pharmacies, a small-scale production of ECMs, are important elements of the development of domestic production capacities and technologies and improvement of the drug supply to the population of the country.

[35] Decree of the Government of the Russian Federation dated March 30, 2024 No. 753-r "Action Plan for the implementation of measures to implement the Strategy for the Development of the Pharmaceutical Industry of the Russian Federation for the period up to 2030".

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Vasily V. Ryazhenov — problem setting, critical analysis of scientific and normative legal documents, introduction of intellectual content remarks, editing of the article; Elena A. Maksimkina — collection and analysis of scientific and methodological literature, critical analysis of scientific and methodological literature, introduction of intellectual content remarks, editing of the article; Victor S. Fisenko — collection of scientific and methodological literature, critical analysis of scientific and normative legal documents, methodological literature, introduction of intellectual content remarks, editing of the article; Aleksey V. Alekhin — collection of scientific and methodological literature, critical analysis of scientific and methodological literature, introduction of intellectual content remarks, editing of the article; Vadim V. Tarasov — collection of scientific and methodological literature, critical analysis of scientific and methodological literature, introduction of intellectual content remarks, editing of the article; Maria G. Raisyan — collection of scientific and methodological literature, critical analysis of scientific and methodological literature, introduction of intellectual content remarks, editing of the article; Elena R. Zakharochkina — collection of scientific and methodological literature, introduction of intellectual content remarks, editing of the article; Kirill A. Chizhov — data collection and analysis, editing and design of the article; Rimma Yu. Garankina — problem setting, concept, collection and critical analysis of scientific literature and regulatory legal documents, collection and analysis of data, interpretation of results, writing, editing and design of the article, final approval of the manuscript.

All the authors confirm that their authorship meets the ICMJE international criteria (all the authors have made substantial contributions to the conceptualisation, research and preparation of the article, and have read and approved of the final version before the publication).

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