REVIEWS

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Past, current and future of legal regulation of drugs compounding in the Russian Federation

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Today the activities of compounding pharmacies in terms of the drug compounding and in-pharmacy packaging of approval drugs is considered as a priority social task of the Russian Federation, due to the need to solve problems that are aimed at ensuring the strategic independence of the state from external and internal challenges, as well as threats, widespread introduction of personalized pharmacotherapy methods, opportunities in the field of optimizing the costs of the healthcare system.

The aim of the study was to conduct a historical analysis and comprehensive review of the current state of legal and regulatory framework of the Russian pharmaceutical market in the field of compounding drugs, as well as to develop proposals for improving the regulatory field.

Materials and methods. The following methodological tools – empirical, theoretical, quantitative ones – have been used in the work. In particular, an analysis of a wide range of relevant sources of information was carried out and information was obtained from legal and regulatory framework for the activities of compounding pharmacies in the Russian Federation, which was implemented using a bibliometric method of analysis.

Results. The main elements of the Russian legislation in the field of drug circulation with the aim of a comprehensive understanding of the classification and determination of the role of extemporaneous drugs in the Russian healthcare system, are presented in the article. A historical and technical analysis of the regulatory practice development is consistently presented. The key issues of organizing the pharmaceutical business in the field of compounding and dispensing of drugs on the territory of the Russian Federation have been considered, and current problems that need to be solved when improving the regulatory field, are presented.

Conclusion. The review conducted makes it possible to clarify further actions to improve federal legislation and delegated legislation in the field of circulation of compounded drugs by pharmacy organizations. The work presents recommendations that will contribute to the development of compounding pharmacies in the constituent entities of the Russian Federation.

Keywords: drug circulation in the Russian Federation; drugs compounding; extemporaneous drugs; diluting (reconstitution) of drugs; compounding pharmacies; history of pharmaceutical compounding of drugs; Russian pharmaceutical market; sales volume of extemporaneous drugs; rules for compounding and dispensing of drugs

Abbreviations: MP – medicinal product / preparation; EU – European Union; ED – extemporaneous drug; PO – pharmacy organization; DF – dosage form; API – active pharmaceutical ingredient; MPTF – medical and preventive treatment facility; EMs – List of Essential Medicines; FD – approval drug; RPD – radiopharmaceutical drugs; MA – marketing authorization; SRMRs – State Register of Medicinal Remedies; FDA – Food and Drug Administration; GxP – Good Practice.

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ОБЗОРЫ
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Прошлое, текущее и будущее нормативного правового регулирования аптечного изготовления лекарственных препаратов в Российской Федерации

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На сегодняшний день деятельность производственных аптек в части изготовления лекарственных препаратов и внутриаптечной фасовки зарегистрированных лекарственных препаратов рассматривается в качестве приоритетной социальной задачи Российской Федерации, в связи с необходимостью решения задач, направленных на обеспечение стратегической независимости государства от внешних и внутренних вызовов, а также угроз, широкого внедрения методов персонализированной фармакотерапии, возможностей в сфере оптимизации затрат системы здравоохранения.

Цель. Провести исторический анализ и всесторонний обзор текущего состояния нормативного правового регулирования российского фармацевтического рынка в области изготовления лекарственных препаратов, а также разработать предложения по совершенствованию регуляторного поля.

Материалы и методы. В работе использованы методологические инструменты: эмпирические, теоретические, количественные. В частности, проведён анализ широкого перечня релевантных источников информации и получены сведения из нормативных правовых документов, регулирующих деятельность производственных аптек на территории Российской Федерации. В данном исследовании авторами применён метод библиометрического анализа.

Результаты. В статье представлены основные элементы российского законодательства в сфере обращения лекарственных средств с целью всестороннего понимания классификации и определения роли экстемпоральных лекарственных препаратов в российской системе здравоохранения. Последовательно изложен историко-технический анализ развития регуляторной практики. Рассматриваются ключевые вопросы организации фармацевтического дела в области изготовления и отпуска лекарственных препаратов на территории Российской Федерации, а также представлены актуальные задачи, которые предстоит решить при совершенствовании регуляторного поля.

Заключение. Проведённый обзор позволяет уточнить дальнейшие действия по совершенствованию федерального законодательства и подзаконных нормативных правовых актов в сфере обращения лекарственных препаратов, изготавливаемых аптечными организациями. В работе представлены рекомендации, которые могут поспособствовать развитию деятельности производственных аптек в субъектах Российской Федерации.

Ключевые слова: обращение лекарственных средств в Российской Федерации; изготовление лекарственных препаратов; экстемпоральные лекарственные препараты; разведение (восстановление) лекарственных препаратов; производственные аптеки; история аптечного изготовления лекарственных препаратов; фармацевтический рынок России; объём продаж экстемпоральных лекарственных препаратов; правила изготовления и отпуска лекарственных препаратов; надлежащая практика изготовления и отпуска лекарственных препаратов

Список сокращений: ЛП – лекарственный препарат; ЕС – Европейский союз; ЭЛП – экстемпоральный лекарственный препарат; АО – аптечная организация; ЛФ – лекарственная форма; ЛС – лекарственное средство; АФС – активная фармацевтическая субстанция; ЛПУ – лечебно-профилактическое учреждение; ЖНВЛП – жизненно необходимые и важнейшие лекарственные препараты; ГЛФ – зарегистрированный лекарственный препарат; РФЛП – радиофармацевтические лекарственные препараты; РУ – регистрационное удостоверение; ГРЛС – Государственный реестр лекарственных средств; FDA – Управление по санитарному надзору за качеством пищевых продуктов и медикаментов; GxP – система надлежащих практик.

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Scientific and Practical Journal
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INTRODUCTION

With the development of industrial manufactories, in the USSR, the segment of pharmaceutical compounding of drugs experienced processes of stagnation in the framework of reference to compounding pharmacies, similar to the European Union (EU) [1] and the USA [2].

According to the data for 1939, in the Soviet Union, the drugs compounded by pharmacy organizations (POs) (i.e., extemporaneous drugs products, EDs) occupied a share equal to 60–70% of all the drugs sold in Pos [3], in 1961 – 55%, in 1980 –18% with a predominance of parenteral dosage forms (DFs) in the amount of up to 40–50% in medical and preventive treatment facilities (MPTFs). Despite this, based on the content analysis performed [1, 4–6], a systemic conclusion follows that in the 80^{s} of the 20th century, the USSR had the most developed network of compounding pharmacies in the world.

The collapse of the Soviet Union led to the formation of a market for the circulation of drugs in Russia with the parameters that resulted from the specifics of the previously functioning healthcare system, i.e., a delivery of health care as a public service and supplying the population with medicinal products [7]. The breakdown of production chains and the simultaneous economic crisis led to a rapid decline in local production of drugs and active pharmaceutical ingredients (API). For example, for the period from 1992 to 2008, the volume of production of the latter in the Russian Federation decreased by more than 20 times [8]. The lack of access to raw materials, coupled with the insufficient regulatory influence, led to the closure of the majority of compounding pharmacies, the decline of which is observed annually in the Russian Federation. In particular, according to the study [9], 36% of joint-stock companies ceased their activities in the production of drugs in the period from 2015 to 2019. It was at that time that pharmaceutical specialists reoriented their activities to industrial facilities producing drugs, as well as POs engaged in retail trade of approval drugs. Nowadays, the number of POs that have a license for pharmaceutical activities with the right to compounding and dispense drugs is estimated at less than 0.5% of the total number of POs [10].

Federal Law No. 61-FZ "On drug circulation" (FL No. 61) [1], adopted in 2010, was aimed at harmonizing domestic legislation with European legislation and, consequently, implementing a Good clinical practice (GCP / GxP) in all areas of the pharmaceutical market, which was implemented at all levels of drug circulation, with the exception of the pharmaceutical compounding segment of drugs.

Compounding pharmacies are an element of both the healthcare system and the social protection system in terms of providing certain categories of citizens entitled to receive government assistance, with medications.

Today, the Russian pharmacological support has encountered difficulties in relation to its basic tasks in terms of the transition from supplying patients with bulk drug substances regarding course prescriptions, including the ones associated with the absence in the legislation of one of the GxP elements – drugs preparation by the compounding pharmacies and intrapharmacy packing of approval drugs. In the next decade, according to the authors of this study, the latter will likely become one of the key areas for improving the legislation of the Russian Federation regarding drug circulation. Herewith, the need for changes in legal and regulatory framework will come from the already established and basic functions of compounding pharmacies and the newly created modern pharmacy infrastructure, i.e.:

1. Providing direct physical access to the drug.

Currently, there are cases when the pharmaceutical industry does not offer an alternative to packaging and volume, especially for expensive and high-cost drugs that are not registered in the Russian Federation. This fact affects the rationality of spending money, regardless of the source of financing – the state or citizens' own funds. Moreover, without a direct control of the drug provision costs for a particular patient in the required course volume of therapy, it is impossible to achieve a budgetary efficiency, since there are no comparable criteria for the comparison [1, 11].

2. Direct pharmacoeconomic advantage of compounding pharmacies:

– by packaging approval drugs in the "bulk" form (thereby achieving the aim of solving the problem in the field of systematization of healthcare in accounting for spent course prescriptions);

– due to direct savings in the drugs compounding in those nosologies where this is justified (orphan drugs, antitumor drug therapy, high-tech drugs, etc.).

This study significantly reveals the current legal and regulatory framework for the drug circulation in the Russian Federation, thereby demonstrating in it the place of pharmaceutical compounding of drugs, and also specifies the past and a current state of regulation of the compounding pharmacies, includig setting possible vectors of development of the latter.

THE AIM of the study was to conduct a historical analysis and comprehensive review of the current state of legal and regulatory framework of the Russian pharmaceutical market in the field of drug compounding, as well as to develop proposals for improving the regulatory field.

This article is a continuation of the series of works by the authors, which are devoted to the formation of a unified harmonized system of legal and regulatory framework in the field of circulation of the drugs compounded by joint-stock companies in the Russian Federation [1, 2, 9–12].

[1] Federal Law of April 12, 2010 No. 61-FZ "On the Circulation of Drugs". Available from: https://docs.cntd.ru/document/902209774

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MATERIALS AND METHODS

The following methodological tools – empirical, theoretical, quantitative ones – have been used in the work. In particular, an analysis of a wide range of relevant information sources was carried out and data was obtained from legal and regulatory framework for the activities of compounding pharmacies in the Russian Federation, which was implemented using the bibliometric method of analysis.

The data from various sources of information were used. In terms of the analysis of legal and regulatory framework, the following materials were used: the electronic fund of regulatory, technological and regulatory intelligence of the "Code" Consortium, the reference legal system "ConsultantPlus".

To analyze the results of research by other authors, relevant sources of information and data from search engines were used: PubMed, for biomedical research, scientific electronic library – elibrary.ru, Russian National Library, National Electronic Library, Google Academy. The search depth was 1917 to 2023. The choice of period was determined by historical events and the beginning of the active development of compounding pharmacies activities in the USSR. The literature search was carried out in Russian and English using the following keywords or combinations: drug circulation in the Russian Federation; drug compounding; extemporaneous drugs; diluting (reconstitution) of drugs; compounding pharmacies; history of pharmaceutical compounding of drugs; Russian pharmaceutical market; sales volume of extemporaneous drugs; rules for good compounding and dispensing of drugs; good practice in compounding and dispensing of drugs.

RESULTS AND DISCUSSION

Classification of extemporaneous drugs

The main legal and regulatory framework on the drug market in the Russian Federation is FL No. 61, according to which a separate definition of ED has not been established. Based on the systemic interpretation of Art. 4, 13 and 56 of FL No. 61, as well as other legal and regulatory framework, it follows that EDs belong to drugs. In addition, FL No. 61 does not contain a definition of the approval drugs approved by the Ministry of Health of Russian Federation [13] which is an authorized federal government body, a ministry of the Russian Federation, similar in functionality to the FDA; hereinafter ADs). According to Art. 14 and Art. 17 of FL No. 61, the fact of the ADs registration is a marketing authorization (MA) received by the applicant for the drug, issued as a result of the examination of the registration dossier. The distribution diagram of the main definitions used in FL No. 61 is presented in Figure 1.

Within the meaning of clause 5 of Article 13 of the FL No. 61, state registration [14] in the Russian Federation is not subject to:

– drugs compounded by POs that have a license for pharmaceutical activities, according to prescriptions for drugs and the requirements of medical organizations;

– drugs purchased by individuals outside the Russian Federation and intended for personal use;

– drugs imported into the Russian Federation to provide medical care according to the vital indications of a specific patient on the basis of a permission issued by the authorized federal executive body;

– drugs imported into the Russian Federation on the basis of a permission issued by the authorized federal executive body and intended for conducting clinical trials of drugs and (or) to be evaluated for the state registration of drugs;

– active pharmaceutical ingredient (API);

– radiopharmaceutical drugs (RPDs), compounded directly in medical organizations, in the manner established by the authorized federal executive body;

– drugs produced for export.

According to Art. 33 of FL No. 61, the list of ADs and the list of APIs included in the ADs are contained in the State Register of Medicinal Remedies (SRMRs)[2] [15]. According to paragraph 2 of Art. 33, an API produced for sale may be included in the SRMRs on the basis of an application from the developer or manufacturer of the drug, or a legal entity authorized by them, subject to an examination of the API quality in relation in the manner established by Art. 34 of FL No. 61.

Thus, on the Russian Federation drug circulation market, APIs can exist in two different states:

– as active APIs included in the MA can only be used by the holder of the MA (sale of such APIs to third party companies is prohibited);

– as APIs included in the SRMRs can be sold to all drug manufacturers, drug wholesalers and compounding pharmacies.

Licensing in the field of drug circulation

In accordance with FL No. 61, the production of drugs and pharmaceutical activities are separated [16]. Moreover, the latter consists of retail trade and wholesale trade of drugs. At the same time, a pharmaceutical activity for compounding is a type of retail trade of drugs (Fig. 2).

To produce drugs, it is necessary to obtain an advisory license (Art. 45 of FL No.61). The procedure for licensing activities for the drugs production was approved by the Decree of the Government of the Russian Federation No. 686 dated July 6, 2012 (hereinafter referred to as Resolution No. 686)[3]. Based on that, licensing of the drugs production is carried out

[2] State Register of Drugs of the Russian Federation. Available from: https://grls.rosminzdrav.ru/Default.aspx

[3] Decree of the Government of the Russian Federation of July 6, 2012 No. 686 "On approval of the Regulations on licensing the production of drugs." Available from: https://docs.cntd.ru/document/902356716

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Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

by the authorized federal executive body – the Ministry of Industry and Trade of Russia [17]. To obtain a license, drug manufacturers must meet the criteria of the Good Manufacturing Practice Rules of the Eurasian Economic Union (hereinafter referred to as the EAEU GMP Rules[4]) – an adapted translation of the EU Good Manufacturing Practice Rules[5]. Confirmation of the production site for compliance with the EAEU GMP Rules is carried out through a preliminary inspection procedure. The authority to conduct inspections has currently been transferred to the Institution for Medicinal Products and Good Manufacturing Practice [18], subordinate to the Ministry of Industry and Trade of Russia.

According to Art. 54 of FL No.61, wholesale trade of drugs is permitted for drug manufacturers and drug wholesale trade organizations that meet the requirements of the Rules of Good Distribution Practice within the Eurasian Economic Union (hereinafter referred to as the EAEU GDP Rules)[6] [19]. It should be noted that a direct standard for compliance by drug manufacturers with these rules is not provided for by Resolution No. 686. The procedure for licensing pharmaceutical activities (wholesale and retail trade) was approved by the Decree of the Government of the Russian Federation No. 547 dated March 31, 2022[7].

The basic requirements for the retail drug trade procedure are described in Art. 55 of FL No.61 and are implemented by establishing the POs compliance with the Rules of Good Pharmacy Practice (hereinafter referred to as Order No. 647n)[8]. However, these rules are devoted exclusively to the retail drug trade, which differs significantly from the approaches to good pharmacy practices implemented, for example, in the EU, as well as in the countries of the Eurasian Economic Union (Republic of Kazakhstan, Republic of Belarus) [1].

In the Russian Federation, distance sale of drugs is permitted, with the exception of prescription drugs, narcotic and psychotropic ones, as well as alcohol-containing drugs with a volume fraction of ethyl alcohol over 25%, subject to a license for the retail drug trade and the corresponding permit[9] from the federal executive body, which carries out the functions of control and supervision in the field of healthcare – Federal Service for Surveillance in Healthcare (hereinafter referred to as Roszdravnadzor) [20]. At the time of submitting the manuscript for publication, distance trading of prescription drug is carried out in a pilot (test) mode in the territories of Moscow, Moscow and Belgorod regions according to the limited list of international nonproprietary names (INN)[10] [21]. The procedure for remote retail trade of prescription drugs was introduced by Federal Law No. 405-FZ dated October 20, 2022[11]. At the same time, by the Decree of the Government of the Russian Federation No. 2465[12] dated December 28, 2022, the online sale of EDPs is prohibited.

The production of drugs is regulated by Art. 56 FL No. 61 and is carried out by POs that have a license for pharmaceutical activities on the basis of prescriptions for drugs and the requirements of medical organizations (MO), in accordance with the Rules for Good Manufacturing and Dispensing Practices of Drugs, approved by the Order of the Ministry of Health of Russia dated May 22, 2023 (hereinafter – Order No. 249n)[13]. Types of joint stock companies are established in Order of the Ministry of Health of Russia No. 780n[14] dated July 31, 2020 [22] and include, but are not limited to (Figure 3):

[4] Decision of the EEC Council of November 3, 2016 No. 77 "On approval of the Rules of Good Manufacturing Practice of the Eurasian Economic Union." Available from: https://docs.cntd.ru/document/456026099

[5] Comparison and analysis of GMP requirements of the Russian Federation and the EAEU. Available from: https://gxpnews.net/2020/08/sravnenie-i-analiz-trebovanij-gmp-rossijskoj-federacii-i-eaes/.

[6] Decision of the EEC Council of November 3, 2016 No. 80 "On approval of the Rules of Good Distribution Practice within the framework of the Eurasian Economic Union." Available from: https://docs.cntd.ru/document/456026098

[7] Decree of the Government of the Russian Federation of March 31, 2022 No. 547 "On approval of the Regulations on licensing of pharmaceutical activities." Available from: https://docs.cntd.ru/document/350167126

[8] Order of the Ministry of Health of Russia dated August 31, 2016 No. 647n "On approval of the Rules of Good Pharmacy Practice of Drugs for Medical Use." Available from: https://docs.cntd.ru/document/564406688

[9] Order of Roszdravnadzor dated May 28, 2020 No. 4394 "On approval of the List of documents confirming the compliance of a pharmacy organization with the requirements giving the right to carry out retail trade in drugs for medical use remotely, the Procedure for maintaining a register of issued permits for retail trade in drugs for medical use remotely and forms of documents used by the Federal Service for Surveillance in Healthcare when issuing permission to retail trade in drugs for medical use remotely." Available from: https://www.consultant.ru/document/cons_doc_LAW_354200/.

[10] Decree of the Government of the Russian Federation of February 22, 2023 No. 292 "On approval of the Regulations on the procedure for conducting an experiment on the retail trade of drugs for medical use, dispensed with a prescription for a drug, remotely." Available from: https://docs.cntd.ru/document/1300876915

[11] Federal Law of October 20, 2022 No. 405-FZ "On Amendments to the Federal Law "On the Circulation of Drugs". Available from: http://publication.pravo.gov.ru/Document/View/0001202210200012

[12] Decree of the Government of the Russian Federation of December 28, 2022 No. 2465 "On approval of criteria for the inclusion of drugs and pharmacotherapeutic groups of medicinal products in the list of drugs and pharmacotherapeutic groups of drugs approved for sale within the framework of an experiment in the retail trade of medicinal products for medical use, dispensed with a prescription for a drug, remotely." Available from: http://publication.pravo.gov.ru/Document/View/0001202212290005

[13] Order of the Ministry of Health of Russia dated May 22, 2023 No. 249n "On approval of the rules for the compounding and dispensing of drugs for medical use by pharmacies licensed for pharmaceutical activities." Available from: https://docs.cntd.ru/document/1301699481

[14] Order of the Ministry of Health of Russia dated July 31, 2020 No. 780n "On approval of types of pharmacy organizations." Available from: https://docs.cntd.ru/document/565649073

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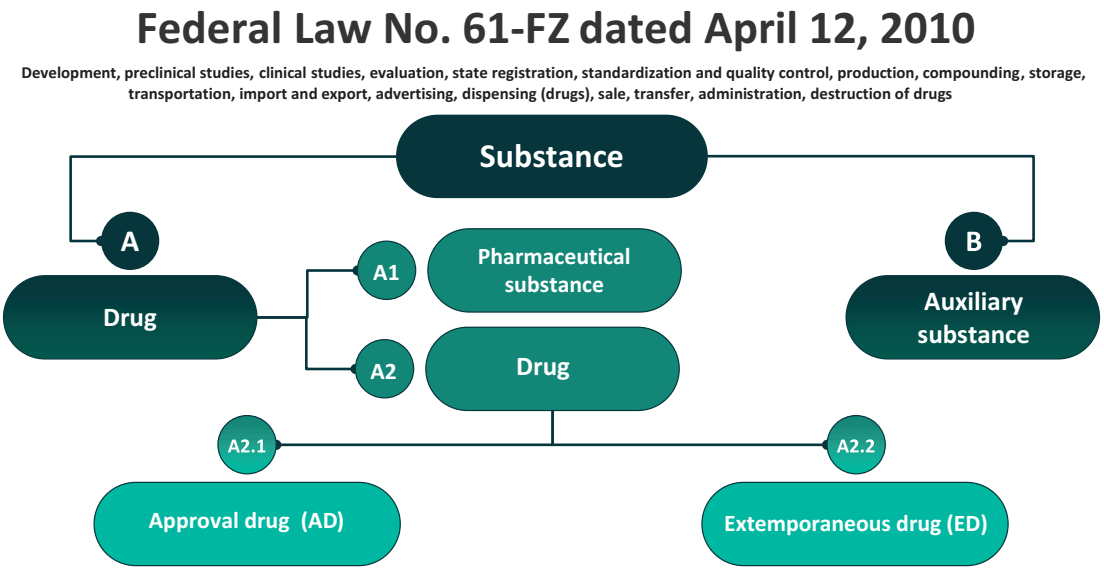

Figure 1 – Definition of drug according to Federal Law No. 61

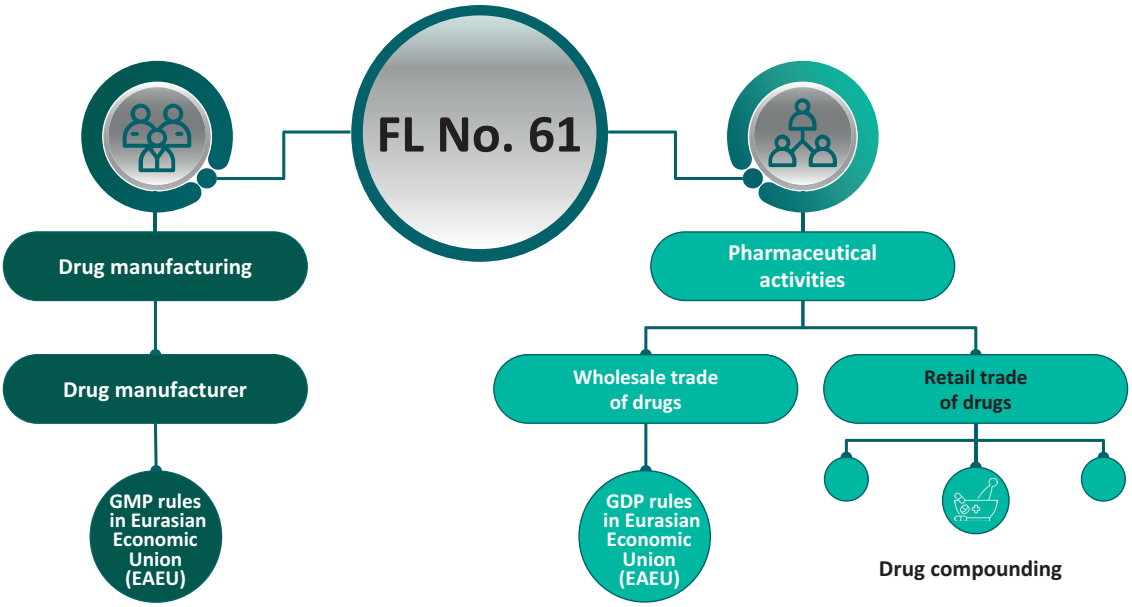

Figure 2 – Relationship between drug manufacturing and pharmaceutical activities

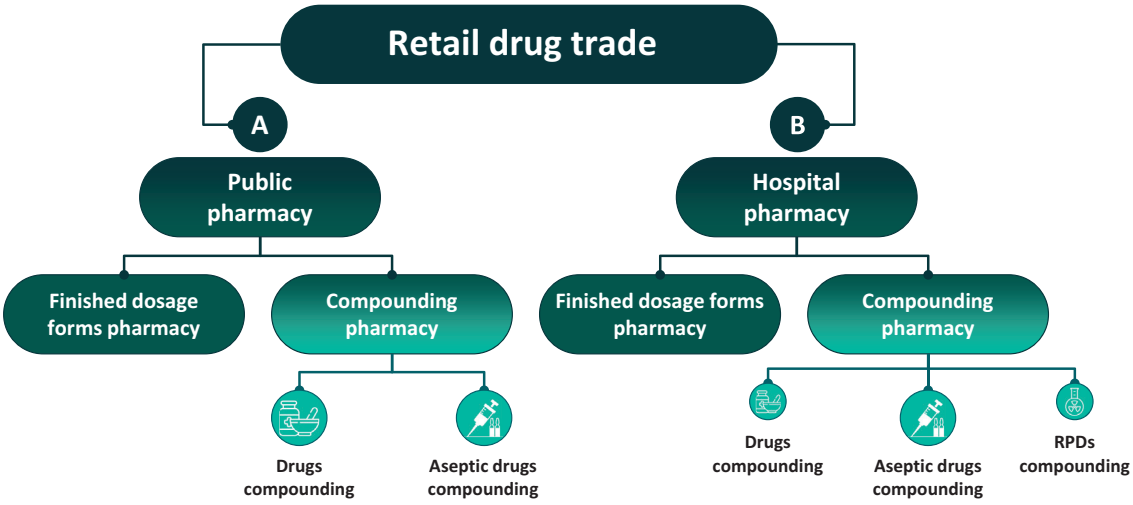

Figure 3 – Types of pharmacy organizations in the Russian Federation

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Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

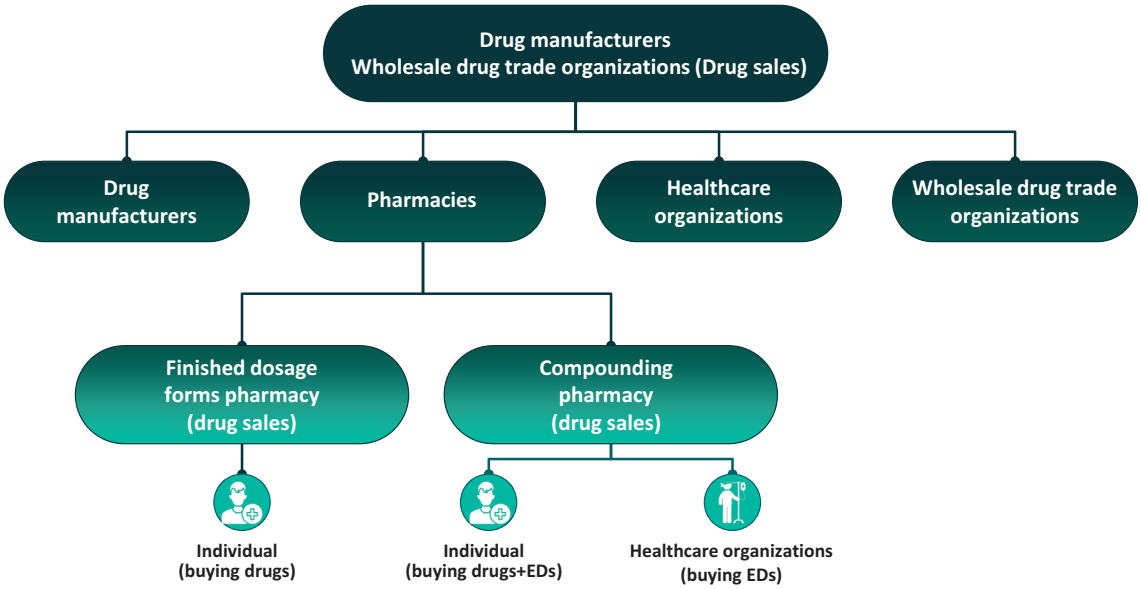

Figure 4 – Drug sales channels in the Russian Federation

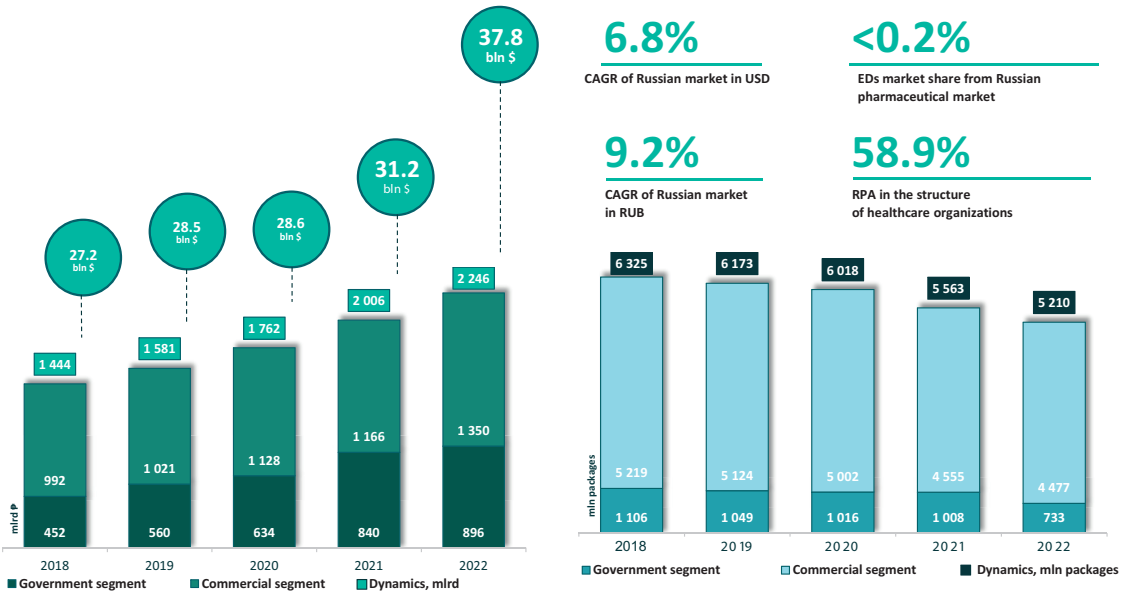

Figure 5 – Capacity of Russian pharmaceutical market

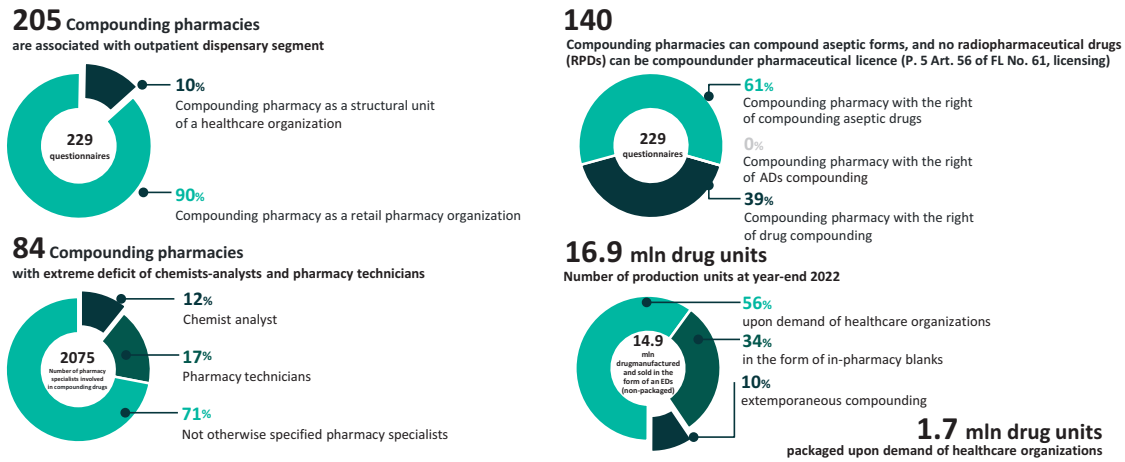

Figure 6 – Consolidated results of monitoring compounding pharmacies in the Russian Federation

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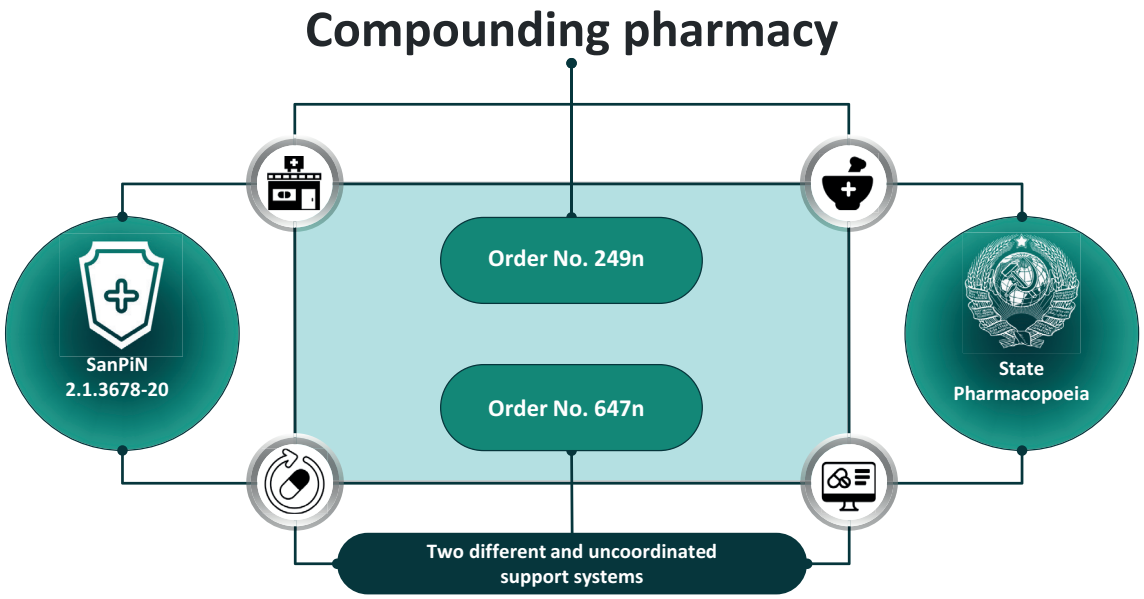

Figure 7 – Key regulatory standards of compounding pharmacies

Table 1 – Requirements for microbiological purity of air during drugs compounding

EAEU GDP Rules		SanPiN 2.1.3678-20		
Cleanliness class	Total number of microorganisms in 1 m^3 of air (CFU/m^3)	Cleanliness class	Total number of microorganisms in 1 m^3 of air (CFU/m^3)	
			in equipped condition	in operating condition
A	<1	A	200	500
B	10	B	500	750
C	100	–	–	–
D	200	–	–	–

1. Pharmacy carrying out retail drug trade (dispensing) to the population:

– ADs;

– Compounding pharmacy with the right to drugs compounding;

– Compounding pharmacy with the right to aseptic drugs compounding.

2. Pharmacy as a structural unit of the Moscow Region:

– ADs;

– Compounding pharmacy with the right to drugs compounding;

– Compounding pharmacy with the right to aseptic drugs compounding;

– Compounding pharmacy with the right to compound RPDs.

Thus, the activities of manufacturing drugs relate to the retail drug trade, are equivalent to retail medical supplies stores, and are not associated with healthcare institutions. That differs significantly from the approaches of developed healthcare systems, where POs are full-fledged participants in the provision of medical care to the population and the drug supply system, performing the functions of providing pharmaceutical assistance to the population in accordance with the established types of pharmaceutical services and work [1, 23].

The requirements for POs segregated compounding areas are described within the framework of the Resolution of Russia's Chief Public Health Officer No. 44 dated December 24, 2020 (hereinafter referred to as SanPiN 2.1.3678-20)[15]. The procedure for prescribing and dispensing drugs (including the rules for filling prescriptions) in the Russian Federation is carried out in accordance with Order of the Ministry of Health of Russia No. 1094n[16] dated November 24, 2021 [24, 25], dispensing drugs (sale) to the population in accordance

[15] Resolution of the Chief State Sanitary Doctor of the Russian Federation dated December 24, 2020 No. 44 "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 conditions of activity of business entities carrying out sale of goods, performance of work or provision of services." Available from: https://docs.cntd.ru/document/573275590

[16] Order of the Ministry of Health of Russia dated November 24, 2021 No. 1094n On approval of the Procedure for prescribing drugs, forms of prescription forms for drugs, the Procedure for registration of these forms, their accounting and storage, forms of prescription forms containing the prescription of narcotic drugs or psychotropic substances, the Procedure for their production , distribution, registration, accounting and storage, as well as Rules for the preparation of prescription forms, including in the form of electronic documents. Available from: https://docs.cntd.ru/document/727251258

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

with Order of the Ministry of Health of Russia No. 1093n[17] dated November 24, 2021. [26].

Trade channels, dispensing and sale of drugs by subjects of the drug circulation in the Russian Federation are presented in Figure 4.

The quality of drugs must comply with the requirements of the State Pharmacopoeia of the Russian Federation, which is a set of general pharmacopoeial monographs that describe the general requirements for the drug, as well as methods and techniques for monitoring the drugs quality, and pharmacopoeial monographs containing the requirements for the quality of a specific drug.

EDs sales volume

The right of citizens to the medication provision is the prerogative of every citizen of the Russian Federation for health protection, enshrined in Art. 41 of the Constitution of the Russian Federation [27, 28]. In the Russian Federation, nowadays, medical care to the population is provided by a system of government institutions [29], which are financed using different levels of a budgetary support of the Russian Federation. According to the general principle, the drug provision to the population of the Russian Federation when providing free medical care, is carried out within the framework of the List of Essential Medicines (EMs), which is annually approved by the Government of the Russian Federation[18] [30]. The availability of the medications at no cost to the population is fixed in accordance with the basic compulsory medical insurance program, in accordance with Art. 80 federal Law No. 323-FZ dated November 21, 2011 (hereinafter – FL No. 323)[19]. Each citizen of the Russian Federation deducts 5.1% of their salary to finance the Compulsory Medical Insurance Fund [31, 32], from which the above mentioned program is financed (Chapter 34 of the Tax Code of the Russian Federation), while tax payments are carried out by the employers. The latter led to the division of the Russian pharmaceutical market into a commercial segment (Pos sales) [33] and a government segment (purchases of healthcare organizations in accordance with Federal Law No. 44-FZ dated April 5, 2013 (hereinafter – FL No. 44)[20] Dynamics of the pharmaceutical Russian market is shown in Figure 5[21].

According to the previously mentioned study [9], in 2022, it was determined that the total number of the drugs compounded in pharmacies amounted to 16.9 million units. According to the requirements of healthcare organizations, in the structure of compounded drugs, the demand for services (jobs) for the production of drugs and in-pharmacy packaging of approval drugs prevails: 34% of the total number of compounded and dispensed units are compounded drugs in the form of in-pharmacy blanks – pre-compounded drugs intended for dispensing according to the most frequently received prescriptions for drugs or requirements of healthcare organizations (Fig. 6).

At the moment, according to the expert assessment of the authors of the article, the total market for the EDs circulation in the Russian Federation is about 3.5–4.0 billion rubles (38.0–44.0 million USD at the date of this study publication), herewith, it is represented with outdated formulations, where almost 95% falls on the outpatient segment of dispensing in the retail segment. It is worth noting that the insufficient supply to the healthcare community for the use of modern formulations and the lack of systemic demand from the healthcare system, both in the segments of regional and federal benefits, and from the healthcare organizations participating in the compulsory health insurance system, the volume of the EDs market retains its small share, but has a significant potential and prerequisites for development. A limited demand is primarily associated with the outdated infrastructure of the POs and its systemic stagnation, a bias towards a retail trade of approval drugs, which is generally caused by the current provisions of the law. Despite the annual increase in the need for EDs, their share in the structure of the total circulation of approval drugs is less than 0.4% [9].

[17] Order of the Ministry of Health of Russia dated November 24, 2021 No. 1093n "On approval of the Rules for the dispensing of drugs for medical use by pharmacy organizations, individual entrepreneurs licensed to carry out pharmaceutical activities, medical organizations licensed to carry out pharmaceutical activities, and their separate divisions (outpatient clinics , paramedic and paramedic-midwife stations, centers (departments) of general medical (family) practice) located in rural settlements in which there are no pharmacies, as well as the Rules for the dispensing of narcotic drugs and psychotropic substances registered as drugs for medical use, drugs for medical use containing narcotic drugs and psychotropic substances, including the Procedure for the dispensing of immunobiological drugs by pharmacies." Available from: https://docs.cntd.ru/document/727251237

[18] Order of the Government of the Russian Federation dated October 12, 2019 No. 2406-r "On approval of the list of vital and essential drugs for medical use for 2020, the list of drugs for medical use, including drugs for medical use prescribed by decision of doctors commissions of medical organizations, a list of medications intended to provide people with hemophilia, cystic fibrosis, pituitary dwarfism, Gaucher disease, malignant neoplasms of lymphoid, hematopoietic and related tissues, multiple sclerosis, hemolytic-uremic syndrome, juvenile arthritis with systemic onset, mucopolysaccharidosis I , II and VI types, persons after organ and (or) tissue transplantation and the minimum range of medications necessary to provide medical care." Available from: https://docs.cntd.ru/document/563469457

[19] Federal Law of November 21, 2011 No. 323-FZ "On the fundamentals of protecting the health of citizens in the Russian Federation." Available from: https://docs.cntd.ru/document/902312609

[20] Federal Law of April 5, 2013 No. 44-FZ "On the contract system in the field of procurement of goods, works, services to meet state and municipal needs." Available from: https://docs.cntd.ru/document/499011838

[21] DSM Group reports. Available from: https://dsm.ru/news-reports/?category=13

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Retrospective of the regulatory impact on the pharmaceutical compounding segment

Today, precision and translational kinds of medicine are considered a new healthcare paradigm. However, an individual approach to the treatment of diseases, taking into account all factors of the health status of a particular person, is not new for Russia and is reflected in the works by great Russian doctors and pharmacists of the past [34, 35]. There are many examples of drugs with different pharmacokinetic profiles between children and adults, highlighting the importance of understanding pediatric physiology and the potential impact on drug concentrations [36]. Dose adjustments are made to ensure an appropriate internal exposure and pharmacodynamic effects. However, these parameters depend on the specific properties of the drug and the ontogenesis of the corresponding physiological processes in the patient. A recent review [37] of approval clinical trials in children reported that the pharmacokinetic data had been collected in only 24% of all ongoing trials, with the majority being conducted in children over 2 years of age in North America. The need of a number of population groups for individual dosages of drugs in each state makes their industrial manufacturing impossible due to a low profitability. At the same time, the pharmacoeconomic advantages of pharmacy compounding drugs in highly specialized, high-cost nosological units of diseases (orphan, oncological ones, etc.) are telling of one thing – pharmacy compounding drugs and their industrial manufacturing complement each other, must be developed and improved in parallel, while pharmacy compounding drugs is a universal tool for every doctor in the pharmacotherapy of patients. The latter thesis is clear to all market participants and can be traced throughout the scientific literature, starting from the USSR and ending with our time [1, 3].

Over the past 20 years, the pharmaceutical compounding segment has undergone a global transformation in the USA and EU countries. Currently, it is impossible to consider drug compounding activities in isolation from the principles and recommendations of GMP. Thus, in the USA, the organizations involved in the drugs compounding are divided into two types: pharmacies (type 503A) and outsourcing facilities (type 503B), where the former must have a license for pharmaceutical activities and comply with the requirements of chapters 795 and 797 of the US Pharmacopoeia, and the latter must be certified for compliance with cGMP rules. Herewith, Chapters 795 and 797, among other things, contain the implementation of the provisions of these rules. In the EU, there is a ResAP (2011) 1 on quality and safety assurance requirements for drugs prepared in pharmacies for the special needs of patients, according to which the Guide to Good Manufacturing Practice for drugs (PIC/S) is recommended to be used as a reference book in the manufacture of the group of “hazardous drugs”, and the Guide to Good Manufacturing Practice for drugs (PIC/S) for the manufacture of “low-risk medicinal drugs”. The latter is an adaptation of the GMP rules for the activity of drug compounding and includes 9 main chapters of the rules of Good Manufacturing Practice [1, 2, 11, 38].

Within the framework of the USSR policy, the concept of drug production quality was based on stage-by-stage (operational) and final quality control of finished products. Herewith, the main priority of the chemical and pharmaceutical industry of the USSR was the volume of products produced. In such an iteration, taking into account the interpretation of the GMP concept as “no more than the modernization of technical means of production (buildings and equipment)” [39] in the absence of a policy for exporting drugs (where compliance with GMP rules is a condition for importing drugs into the EU), on the part of domestic manufacturers and regulators put forward the thesis that the costs of implementing GMP requirements in the USSR were too high. In the Russian Federation, the following standards were successively adopted: OST 42-510-98[22], GOST R 52249-2004[23], GOST R 52249-2009[24], which are a compilation of various GMP rules (WHO, USA, EU). The final transition of the domestic pharmaceutical industry to GMP rules took place in 2013 through the adoption of Order No. 916[25] of the Ministry of Industry and Trade of Russia dated June 14, 2013, which was generally consistent with European GMPs. The requirement to comply with these rules has become mandatory since 2014 [39–42]. From 2021, Russian drug manufacturers must comply with the EAEU GMP Rules, while the issuance of national certificates has been discontinued [43].

In the Soviet Union, the described problems of transition to GMP requirements affected the pharmaceutical production of drugs in the Russian Federation. Until 1997, there were regulatory legal requirements for the implementation of this type of activity, developed in the USSR and, accordingly, containing outdated approaches to

[22] Order of the Ministry of Health of Russia and the Ministry of Economy of Russia dated December 3, 1999 No. 432/512 “On the implementation of the Industry Standard OST 42-510-98 “Rules for the organization of production and quality control of drugs (GMP).” Available from: https://dokipedia.ru/document/5180069

[23] National standard of the Russian Federation GOST R 52249-2004 “Rules for the production and quality control of drugs.” Available from: https://docs.cntd.ru/document/1200071754

[24] National standard of the Russian Federation GOST R 52249-2009 “Rules for the production and quality control of drugs.” Available from: https://docs.cntd.ru/document/1200036160

[25] Order of the Ministry of Industry and Trade of Russia dated June 14, 2013 No. 916 “Rules for the production and quality control of drugs.” Available from: https://docs.cntd.ru/document/499029882

ISSN 2307-9266 e-ISSN 2413-2241

Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

both drug compounding technologies themselves, and to methods and techniques for monitoring their quality. The regulatory documents adopted in 1997 describing the quality control of EDPs[26] compounding, standards of deviations in the EDPs[27], technology for the production of liquid dosage forms[28], the sanitary regime of compounding parmacies[29], qualitatively and quantitatively repeated the regulatory legal documents that had been in force in the USSR, creating additional discrepancies in some of their provisions, which can be traced as a result of the historical and technical analysis of the development of regulation and changes in legislation in the field of drug compounding [1].

In the next two decades, Fl No. 61 was adopted, one of the main objectives of which was the harmonization of the Russian legal regulation with international principles and standards adopted in relation to the circulation of drugs [44]. Since 2010, the process of transition to GxP began, which is currently reflected at the following levels:

– preclinical studies, which are regulated by the Rules of Good Laboratory Practice (Art. 11 of the FL No.61) [45, 46];

– production of drugs, which is regulated by the EAEU GMP Rules (Art.45 of the FL No. 1);

– wholesale trade, which is regulated by the EAEU GMP Rules (Art. 54 of the FL No.61);

– retail drug trade, which is regulated by the Rules of Good Pharmacy Practice (Order No. 647n, Art. 55 of the FL No. 61).

In this concept of a new regulation of the drug circulation market, the professional community expected a further implementation of GxP principles in the pharmaceutical compounding segment of drugs. However, in 2015, the Rules for Good Manufacturing Practice for drugs were adopted, approved by Order of the Ministry of Health of Russia No. 751n dated October 26, 2015 (hereinafter referred – Order No. 751n) [30], where, on the one hand, an attempt was made to collect previously existing orders, methodological recommendations and instructions regarding the compounding of drugs in POs, and on the other hand, the existing world practice and approaches to the processes of pharmaceutical compounding, a quality control, and studying the stability of EDs were left without attention [1].

Since 2010, Art. 56 of the FL No. 61 contains a ban on the compounding of AD, which significantly limited the activities of POs and led to a reduction in the number of compounding pharmacies in all constituent entities of the Russian Federation. After the adoption of the FL No. 61, Roszdravnadzor published a letter[31] regarding the norms of Art. 56, which indicated the limited ability of the POs to ensure the appropriate level of the quality for compounded drugs, which was the main reason for introducing restrictions on the compounding of AD. However, the results, once again confirmed and obtained over the past decade, allow us to say with confidence that EDs are an integral element of providing medical care to the population, and the level of development of technological and engineering systems allows us to ensure an appropriate level of the ED quality, comparable to the requirements of GxP and processes pharmaceutical facilities [1, 2].

Current state of legal and regulatory framework of pharmaceutical drugs compounding in the Russian Federation

In 2019, a group of deputies led by Ayrat Zakievich Farrakhov introduced draft Federal Law No. 798952-7 "On Amendments to Part 2 of Art. 56 of the Federal Law "On drug circulation" (hereinafter – Draft Law No. 798952-7)[32], which expanded the powers of compounding parmacies, allowing the compounding of drugs from ADs, and also eliminated the ban on the compounding of the latter. The proposal of Draft Law No. 798952-7 to eliminate this limitation was determined by the need to satisfy the requirements of patients for individual dosages of drugs, incl. ultra-small quantities, to meet the needs of pediatric practice, and the drugs approval in the SRMRs; but temporarily absent from the pharmaceutical market of the Russian Federation, through their compounding in POs. The explanatory note to Draft Law No. 798952-7 also led to a significant reduction in the range and quantity of compounded drugs, including the massive closure of compounding pharmacies in all regions of the Russian Federation. Draft Law No. 798952-7 was adopted on December 5, 2022 in the form of Federal Law No. 502-FZ dated December 5, 2022 "On Amendments to Art. 56 of the Federal Law "On Drug Circulation" (hereinafter – FL No. 502)[33] with

[26] Order of the Ministry of Health of Russia dated July 16, 1997 No. 214 "On quality control of drug compounding in pharmacy organizations (pharmacies)." Available from: https://docs.cntd.ru/document/902062371

[27] Order of the Ministry of Health of Russia dated October 16, 1997 No. 305 "On the norms of deviations permissible in the drug compounding and packaging of industrial products in pharmacies." Available from: https://docs.cntd.ru/document/901701705

[28] Order of the Ministry of Health of Russia dated October 21, 1997 No. 308 "On approval of instructions for the production of liquid dosage forms in pharmacies." Available from: https://docs.cntd.ru/document/901702358

[29] Order of the Ministry of Health of Russia dated October 21, 1997 No. 309 "On approval of the Instructions for the sanitary regime of pharmacy organizations (pharmacies)." Available from: https://docs.cntd.ru/document/901701706

[30] Order of the Ministry of Health of Russia dated October 26, 2015 No. 751n "On approval of the rules for the compounding and dispensing of drugs for medical use by pharmacy organizations and individual entrepreneurs with a license for pharmaceutical activities." Available from: https://docs.cntd.ru/document/420313316

[31] Letter of Roszdravnadzor dated June 1, 2010 No. 04I-516/10 "On the quality of injection and infusion solutions of compounding pharmacies ." Available from: https://docs.cntd.ru/document/902218497

[32] Materials for bill No. 798952-7 "On amendments to Part 2 of Article 56 of the Federal Law "On the Circulation of Drugs". Available from: https://sozd.duma.gov.ru/bill/798952-7

[33] Federal Law of December 5, 2022 No. 502-FZ "On Amendments to Article 56 of the Federal Law "On the Circulation of Drugs". – Available from: https://docs.cntd.ru/document/1300131660

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the starting date of coming into force on September 1, 2023. However, the provisions that would have lifted the ban on the compounding of ADs were excluded from it [1].

In January 2023, a specialized Working Group was created to form a unified system of legal and regulatory framework of activities in the field of drug compounding under the State Duma Committee on Health Protection (hereinafter – Working Group), whose activities are aimed at accelerating and preparing for the implementation of the norms of FL No. 502 in terms of drugs compounding and making necessary amendments to the delegated legislation and legal and regulatory framework.

During the period from March 28 to April 7, 2023, in accordance with paragraph 4 of the first meeting protocol No. 1 of the Working Group dated January 26, 2023, monitoring of compoundings pharmaciesactivities in Russia was carried out [9]. It was aimed at identifying key infrastructural, technological and personnel characteristics of the compounding pharmacies segment. As of March 28, 2023, 1 019 legal entities and individual entrepreneurs operating at 1 378 addresses, had the right to drug compounding. The study was conducted within the framework of a sample presented by the State Duma, the structure of which included 643 addresses at the place of pharmaceutical activities, which in general accounted for 46.7% of the total number of addresses for the activities of compounding and dispensing drugs.

Based on the results of the POs survey, it was found that a part of the compounding pharmacies – 17 out of 47 (7.3%) ceased their activities in the period from 2015 to 2019. Most of these organizations were in the Far Eastern Federal District (35.3%), the Central Federal District (26.9%) and in the North Caucasus (22.2%). The respondents noted that the main factors that had influenced this decision were:

– lack of demand for compounded drugs within the framework of regional state guarantee programs, both at the expense of compulsory health insurance and preferential drug provision;

– outdated infrastructure, lack of proper equipment with technological, analytical, engineering equipment and lack of financial measures of state support;

– problems in concluding and executing contracts for the provision of services (work) for the drugs compounding and in-pharmacy packaging of approval drugs within the legal and regulatory framework of the contract system in the field of procurement (FL No. 44);

– almost complete nomenclature (physical) and price unavailability of substances and excipients in small packages, including the lack of a number of necessary raw materials.

As a result of monitoring, it was established that the total area of all pharmacies surveyed was 36 282 m^2; 8 149 m^2 of that area was in the "segregated compounding area" and 4 760 m^2 – in the "clean rooms". The extrapolation of the results showed that the total number of production facilities that needed reconstruction is more than 140 000 m^2. This study also provides statistics regarding the classification of pharmacies into retail entities and hospital pharmacies. It shows the distribution according to the list of services (jobs) provided that constitute pharmaceutical activities with the right to compounding and dispense drugs, and touches upon the issue of the of pharmacy specialists' structure. That revealed an acute shortage of chemists-analysts and (or) pharmacy technicians, which indicates a high risk of suspension of activities at any time. The results of the study demonstrated and confirmed the "traditional" [1, 2, 9–11] problems of compounding pharmacies, accumulated over a long period of time, i.e., since the formation of the Russian Federation.

In the framework of this study, one cannot help dwelling on the requirements for compounding pharmacies. In accordance with SanPiN 2.1.3678-20, they are:

– a pharmacy must be located in an isolated block of premises in apartment buildings, public buildings or in separate buildings;

– pharmacy premises must have natural and artificial lighting. Natural lighting may be absent in warehouses (without a permanent workplace), storerooms, toilets, dressing rooms, showers, household and auxiliary premises;

– the premises of the aseptic unit are equipped with a ventilation system with a predominance of inflow over exhaust. The supply of clean air is carried out by laminar airflows;

– pharmacy premises must be subjected to daily wet cleaning using detergents and disinfectants. Pharmacy must be provided with a 3-day supply of detergents and disinfectants, which is calculated taking into account the area of surfaces to be treated, the amount of equipment to be processed, and the availability of household equipment to ensure sanitary conditions;

– cleaning of all premises with the treatment of walls, floors, equipment, implements, lamps using detergents and disinfectants should be carried out at least once a month, and in premises for the drug compounding under aseptic conditions – weekly.

In addition, compounding pharmacies have established requirements for the microbiological purity of air. At the same time, there are no standards regulating the content of the maximum permissible amount of particles in the air, while class A of microbiological purity SanPiN 2.1.3678-20 is equal to class D of the EAEU GDP Rules (Table 1).

The final scheme of subordination of compounding pharmacies to the main governing documents is presented in Figure 7.

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Scientific and Practical Journal
PHARMACY & PHARMACOLOGY

In May 2023, Order No. 249n was signed, where, on the one hand, it was possible to partially reflect and lay the foundations for the development of the POs quality assurance system, but on the other hand, it was not possible to solve the problem of improving the operation of compounding pharmacies at the level of developed healthcare systems, where the number of significant restrictions of Order No. 751n has not been eliminated, i.e.:

– list principle of nomenclature formation, which limits the fulfilment possibility of new formulations development by compounding pharmacies;

– absence of the POs possibility to independently determine expiration dates by conducting studies of the EDs stability;

– text of the Order describes significant general technological limitations associated with direct indications of a specific technology for the compounding of dosage forms or the use of specific, often unqualified, equipment, which limits the opportunities for independent development of compounding technologies and methods for the quality EDP control by compoundings pharmacies;

– lack of principles, methods and validation tools, which does not allow compoundings pharmacies to carry out research and development work, thereby eliminating cooperation with research and educational organizations, including the implementation of the results of research and development obtained by them (a technology transfer);

– Order contains excessive requirements for a "100% quality inspection" of compounded drugs at all stages of the compounding process, which does not correspond to international regulatory practice, experience in implementing the principles of good pharmacy practices, and in general will be a key factor in negative profitability in pharmacy compounding drugs;

– Order includes quality control requirements higher than for drug manufacturers. So, for example, when producing one injection or infusion solution of the same dosage and packaging, in the amount of 2 (two) units (doses), a compounding pharmacies must conduct an aseptic study and test for pyrogenicity or bacterial endotoxins, which in total will cost more than 6,000 rubles (80 USD on the date the manuscript was submitted for printing); at the same time, the compounding pharmacies will be made to produce a third unit of solution, which will be sent for the analysis.

To date, for the implementation of activities for the diluting (reconstitution) of drugs [47–49], no requirements or rules have been established, which is implemented in healthcare organizations without a licensing procedure. The only mention of this activity is the requirement[34] for healthcare institutions providing medical care in the "Oncology" profile to have a laminar airflow workbench for an aseptic diluting (reconstitution) of drugs or a class 2 biological safety cabinet, which differs significantly from the approaches of healthcare institutions to working with highly hazardous substances in developed healthcare systems [1], and also increases the risks of toxic effects on medical and pharmaceutical specialists.

In the framework of the 3rd meeting of the Working Group, held on June 29, 2023, the relevance and demand for EDs in the segments of oncology, pediatrics, orphan and other diseases were noted. The importance of developing the activities of compoundings pharmacies in terms of intra-pharmacy packaging of approval drugs was especially emphasized, as well as the feasibility of transitioning from the rules for compounding and dispensing of drugs (the Soviet regulatory system) to the rules of Good Manufacturing Practice for MPs (the modern regulatory system).

In August 2023, the work on the preparation of the State Pharmacopoeia of the Russian Federation (XV edition) was completed, as well as the development of the necessary general pharmacopoeial monographs in the field of the drug production within the time frame agreed with the Russian Ministry of Health. In order to increase the efficiency of the processes of their preparation and adoption, a separate expert section for the standardization of pharmaceutical preparations was created at the Institute of Pharmacopoeia and Standardization in the sphere of drug circulation of the Federal State Budgetary Institution "Scientific Center for Evaluation of Medical Products" of the Ministry of Health of the Russian Federation (hereinafter – SCEMPs) [50], subordinate to the Ministry of Health of Russia.

From the point of view of the government budgetary policy, the development of modern pharmacy infrastructure in the field of drug compounding in the Russian Federation will help improve the efficiency of costs at all levels of the healthcare system. The goal of optimizing drug costs is to compensate for the actual volume of the drugs required for a specific patient per unit of time. Medical and economic standards and calculations for the provision of medical care, both within the framework of the program of state guarantees of free medical care provision to citizens, and at the expense of citizens' own funds, should be guided by the methods of cost accounting accepted in international practice within the framework of the course, daily or annual need for drugs [1, 11].

Compounding pharmacies, as an element of the healthcare infrastructure, are also of key importance for optimizing budget costs in terms of reducing the level of drug inventory. In particular, the data analysis results of the federal project implementation of "Combating Cardiovascular Diseases", carried out by

[34] Order of the Ministry of Health of Russia dated February 19, 2021 No. 116n "On approval of the Procedure for providing medical care to the adult population for cancer." Available from: https://docs.cntd.ru/document/573956757

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the Accounts Chamber of the Russian Federation at the end of 2022, show a high level of inventory balances of drugs intended to provide people who have suffered a stroke or heart attack[35]. Thus, as of January 1, 2022, in 54 regions, the level of such balances for a number of drugs exceeded 24 months (with a 2–3 year shelf life for the specified category of patients), the report indicates the risk of potential write-off of drugs totaling 4 671.6 million rubles due to the expiration of their shelf life. The latter became a reality; from the beginning of 2022 to May 2023, the State Budgetary Institution of Higher Education "Center for the Procurement in the Healthcare Sector of the Vladimir Region" wrote off drugs for a total amount of 58.6 million rubles due to expiration dates, 32.1 million rubles of which had been spent on the drugs purchased as a part of the regional project "Combating Cardiovascular Diseases"[36]. The described indicates the need to increase the efficiency of using budget funds at any level allocated for the purchase of drugs; in resolving this issue, the development of the activities of compounding pharmacies in the field of individual in-pharmacy packaging of approval drugs will be of particular importance, the implementation of which will ensure the modernization of the accounting system from packages to the accounting of course doses, will eliminate budget overspending within the current drug supply system.

CONCLUSION

In order to provide conditions for the development of a competitive, sustainable and structurally balanced industry in Russia, in 2014, the Government of the Russian Federation approved the state program "Development of Pharmaceutical and Medical Industry", which over the next 10 years, made it possible to create a necessary level of the material and technical base for the implementation of the stages of the ADs production up to 82% within the List of EDs. The Strategy for the Development of the Pharmaceutical Industry in the Russian Federation for the period until 2030 (hereinafter – Strategy), approved by the Decree of the Government of the Russian Federation No. 1495-r dated June 7, 2023, especially emphasizes a close relationship between manufacturers and compounding pharmacies, which consists in the unity of principles based on meeting the needs of the healthcare system to the greatest possible extent and ensure an uninterrupted access for the citizens of the Russian Federation to the required range of drugs. In particular, Section 3 of the Strategy establishes the priorities for its implementation, which include (including, but not being limited to): the development of gene and targeted therapy technologies, new treatment methods, including the use of biomedical cell products; development, implementation and use of new medical technologies and drugs in accordance with the Strategy for the development of healthcare in the Russian Federation.

One of the main directions for the implementation of the Strategy, set out in section 4 of the Strategy "Main directions for the implementation of the Strategy", is the creation of prerequisites for the development of the personalized therapy segment, new treatment methods, stimulating the development of conditions for localizing the production of in-demand drugs in case of a limited supply at the national pharmaceutical market, as well as building stable supply chains in order to ensure the physical and economic accessibility of drugs. From the point of view of training scientific, technological and production personnel for the Russian compounding pharmacies, subsection 9 of section 4 of the Strategy "Main directions for the implementation of the Strategy" also notes the need to implement measures aimed at further developing competencies in the field of development of drugs intended for the treatment of socially significant diseases that prevail in the structure of morbidity and mortality of the population of the Russian Federation, as well as the diseases that pose a danger to others, including in pharmacies, using semi-industrial equipment and production packaging of APIs in small doses. The basis for the further development of the pharmaceutical industry, including the development of compounding pharmacies, and the introduction of personalized medicine methods, is the expansion of an access provision of the pharmaceutical infrastructure to raw materials – API (especially in small packages), pharmaceutical grade excipients, reagents, packaging, closures and other consumables materials that are used both in the manufacture of drugs and in the compounding of drugs.

Taking into account the existing prerequisites in the development of the pharmaceutical compounding segment of drugs, i.e., the adoption of FL No. 502, the Strategy, the creation of a specialized Working Group and a separate expert section for the standardization of pharmaceutical drugs at the SCEMPs, and also understanding that the need for personification of pharmacotherapy is unlikely to decrease in the near future, with a simultaneous permanent increase in the financial burden on all budgets of the healthcare system, the next most important step in the development of compounding pharmacies will be the formation of a unified harmonized system of legal regulation of the EDP circulation. Taking into account the experience of global healthcare systems, the basic concept of the necessary

[35] Accounts Chamber of the Russian Federation. Appendix No. 4 to the report on the work of the Accounts Chamber of the Russian Federation in 2022 "Report on the work of the audit of healthcare and sports of the Accounts Chamber of the Russian Federation in 2022." Available from: https://ach.gov.ru/reports/report_2022

[36] Federal Project "Combating Cardiovascular Diseases". Available from: https://minzdrav.gov.ru/poleznye-resursy/natsproektzdravoohranenie/bssz

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measures for the development of modern pharmacy infrastructure in the Russian Federation assumes that the current system of regulation of compounding pharmacies will be fundamentally rethought, improved and finalized, where the key legislative initiatives at the federal level should be:

1. The changes made to FL No. 323 in terms of expanding the possibilities of using EDPs and including them in clinical recommendations, as well as to FL No. 326-FZ dated November 29, 2010 "On Compulsory Health Insurance in the Russian Federation" on the tariff structure of the basic program compulsory health insurance, by supplementing it with regulations on the use of medical services (jobs) for the production of drugs and packaging of approval drugs by compounding pharmacies.

2. The changes made to FL No. 61 (including, but not limited to) in terms of the transition from the rules of good manufacturing and dispensing of drugs to the rules of good manufacturing and dispensing practices for drugs, thereby achieving the goals of completing the GxP concept in the legislation on the circulation of drugs in the Russian Federation , as well as to ensure the quality, safety and effectiveness of electronic drugs, including the processes of in-pharmacy packaging of approval drugs.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTIONS

All authors made equivalent and equal contributions to the preparation of the publication. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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