



New role of extemporaneous manufacturing in regulating drug products access onto the market

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The aim of the work was to study the legal aspects of the legislative regulation for manufacturing medicines in a pharmacy organization.

Materials and methods. Databases of ConsultantPlus, Cyberleninka, Food and Drug Administration (FDA), European Medicines Agency (EMA), National Center for Biotechnology Information (NCBI), PubMed, e-library, WIPO Lex were used as search sources. The search was based on the following keywords and phrases: intellectual property, pharmacies+invention, patent, drugs, extemporal+production, orphan+diseases, as well as their Russian counterparts. 133 sources of information, including scientific articles and regulations, were found out; 50 have been included in this review. The analysis of information sources published from 2013 to 2023, was determined by the peculiarities of legislation changes in this area.

Results. The article provided an overview of modern, including regulatory practice, pharmaceutical manufacturing in the Russian Federation, and also analyzed the benefits of this activity for the medical community, patients and the state. At the same time, the individualization of drug treatment has made it possible to work out systemic solutions for developing drug therapy methods for special groups of patients for whom the economic feasibility of a pharmaceutical registration and launching such drugs onto the market has been brought into challenge. In addition, pharmacy manufacturing is an accessible tool in the study of the drugs prescribed by a doctor not in accordance with the instructions for medical use (off-label) or in the dosage forms/dosages that are not on the market. Extemporaneous manufacturing can be also a part of the process of "repositioning" drugs on the market, subject to compliance with the requirements for pharmacy manufacturing and control of the prescribed drugs safety. The possibility of pharmaceutical drug manufacturing also makes it possible to partially resolve issues related to intellectual property. As a result of the carried out analysis, the following hypothesis was confirmed: the legislative changes have a similar legal assessment both in Russia and abroad and correspond to the legal practice in resolving intellectual property issues in relation to pharmacy organizations.

Conclusion. The renewal of a pharmacy production will improve the availability of the drug care to the population, taking into account individual dosages and dosage forms in various therapeutic areas, and can also become a tool for repositioning drugs or clinical testing of new molecules for rare incurable diseases.

Keywords: drugs; pharmacy organizations; extemporaneous production; orphan diseases; patent; invention; intellectual property

Abbreviations: DF - dosage form; SRMRs – State Register of Medicinal Remedies; CCRF – Civil Code of the Russian Federation; EPC – Eurasian Patent Convention; WIPO – World Intellectual Property Organization; DPA – Dutch Patent Act.

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Новая роль экстемпорального изготовления в регулировании доступа лекарственных препаратов на рынок

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Цель. Изучение юридических аспектов законодательного регулирования по изготовлению лекарственных препаратов в аптечной организации.

Материалы и методы. В качестве поисковых источников использовали базы данных КонсультантПлюс, Киберленинка, Food and Drug Administration (FDA), European Medicines Agency (EMA), National Center for Biotechnology Information (NCBI), PubMed, e-library, WIPO Lex. Поиск проводился по следующим ключевым словам и словосочетаниям: intellectual property, pharmacies+invention, patent, medicinal+preparations, extemporal+production, orphan+diseases, а также по их русскоязычным аналогам. Были найдены 133 источника информации, включавшие научные статьи и нормативно-правовые акты; 50 включены в настоящий обзор. Анализ источников информации, опубликованных с 2013 по 2023 гг., определяли особенностями изменения законодательства в указанной сфере.

Результаты. В статье был приведён обзор современной, в т.ч. нормативной практики, аптечного изготовления в Российской Федерации, а также проанализированы преимущества указанной деятельности для медицинского сообщества, пациентов и государства. Одновременно индивидуализация медикаментозного лечения позволила выработать системные решения для отработки методик лекарственной терапии для особых групп пациентов, для которых экономическая целесообразность регистрации и вывода лекарственных препаратов на рынок поставлена под сомнение. Кроме того, аптечное изготовление является доступным инструментом в изучении лекарственных препаратов, назначенных врачом не в соответствии с инструкцией по медицинскому применению («off-label») или в лекарственных формах/дозировках, отсутствующих на рынке. Экстемпоральное изготовление также может быть частью процесса «репозиционирования» лекарственных препаратов на рынке при условии соблюдения требований к аптечному изготовлению и контролю безопасности назначаемых средств. Также возможность аптечного изготовления лекарственных препаратов позволит частично разрешить вопросы, связанные с интеллектуальной собственностью. В результате проведённого анализа была подтверждена гипотеза о том, что законодательные изменения имеют схожую правовую оценку как в России, так и за рубежом и соответствуют правовой практике при разрешении вопросов интеллектуальной собственности применительно к аптечным организациям.

Заключение. Возрождение аптечного производства позволит улучшить доступность лекарственной помощи населению с учётом индивидуальных дозировок и лекарственных форм в различных терапевтических направлениях, а также может стать инструментом «репозиционирования» лекарственных препаратов или клинической апробации новых молекул для редких неизлечимых заболеваний.

Ключевые слова: лекарственные препараты; аптечные организации; экстемпоральное изготовление; орфанные заболевания; патент; изобретение; интеллектуальная собственность

Список сокращений: ЛП – лекарственный препарат; ЛФ – лекарственная форма; ГРЛС – Государственный реестр лекарственных средств; ГК РФ – Гражданский Кодекс Российской Федерации; ЕАПК – Евразийская Патентная Конвенция; ВОИС – Всемирная организация интеллектуальной собственности; ДПА – Закон о патентах Нидерландов.

INTRODUCTION

In Russia, pharmacy organizations at the legislative level are allowed to be in the manufacturing of drugs¹. An extemporaneous production had been widespread in the country until the 1990s, but practically disappeared against the backdrop of the economic crisis and development of the pharmaceutical industry in the 2000s [1–4].

From September 2023, amendments to Art. 56 “Manufacturing and dispensing of medicinal products” of the federal law “On the circulation of medicines” come into force². The changes will provide entitle pharmacies to use the drugs included in the State Registers of Medicinal Products for Medical Use, as well as Common Register of the Authorized Medicinal Products of the Eurasian Economic Union, in manufacturing medicinal products according to doctors’ prescriptions, in the prescribed manner.

The authors of the article set a goal to study the legal aspects of the legislative innovation for manufacturing drugs in a pharmacy organization. The authors also reviewed the legal regulation in terms of the possibility of using industrially produced drugs in the individual manufacturing of the drug without violating patent laws [1, 5]. The issues of the legal regulation of the patent legislation in the Russian Federation, were studied within the framework of the Eurasian Patent Convention and at the international level.

THE AIM of the work was to study the legal aspects of the legislative regulation for manufacturing medicines in a pharmacy organization.

MATERIALS AND METHODS

General scientific methods were used in the research. The information search was carried out in the databases of the National Center for Biotechnology Information (NCBI) and the scientific electronic library elibrary.ru; referenced bibliographic lists were studied; the ConsultantPlus, Cyberleninka, Food and Drug Administration (FDA) databases, European Medicines Agency (EMA), PubMed, WIPO Lex were also used. The regulatory framework was formed by the legislation of the Russian Federation in the field of the drug circulation, as well as by foreign countries and patent conventions. The preference was given to the sources describing the relationship between an extemporaneous pharmacy production and its regulatory framework, including the field of the intellectual property.

The search was based on the following keywords and phrases: intellectual property, pharmacies+invention,

patent, drugs, extemporal+production, orphan+ diseases, as well as their Russian counterparts. 133 sources of information including scientific articles and regulations were found; 50 have been included in this review. The analysis of information sources published from 2013 to 2023 was determined by the peculiarities of legislation changes in the in this area. A number of sources found were deleted due to the absence of the indicated relationship and repetitions.

RESULTS AND DISCUSSION

State of production pharmacies in Russia and its legal regulation

There is no Common Register of pharmacy organizations in the Russian Federation. According to AlphaRM, as of September 2021³, there were 70 238 pharmacy organizations of various forms of ownership in the country, which had the right to manufacture medicines, while, according to Roszdravnadzor in 2017, only 460 production pharmacies actually worked. The practice of pharmaceutical manufacturing was widespread in the country; however, since 2007, there has been a trend towards a reduction in intra-pharmacy manufacturing of drugs and a decrease in the number of manufacturing pharmacies [5–7]. Simultaneously, this coincided with the growth of the pharmaceutical industry in the 2000s. Pharmacy organizations began to receive fewer prescriptions issued by doctors. This was facilitated by an increased import of finished dosage forms (DFs) in the Russian Federation, the formation of wholesale and retail links [3, 7].

A special role was played by the state policy in the field of streamlining and standardizing approaches to the provision of medical care, which in the end led to the formalization of doctors’ prescriptions. At the legislative level, state guarantees for the medical care provision were fixed. They apply exclusively to the list of industrially produced drugs⁴, which automatically limited the doctors’ ability to use all possible options for the drug therapy. At the same time, there remains a necessity to meet the needs of health care in the drugs that are not commercially produced [8–12], the need to provide patients with individual pre-dosed drugs [13–15], to manufacture drugs and dosage forms for the geriatric [16] and pediatric populations [17–20], patients with rare diseases [21, 22].

¹ Federal Law No. 502-FZ dated December 5, 2022 “On Amendments to Art. No. 56 of the Federal Law “On the Circulation of Medicines”. Effective from September 1, 2023; adopted by the State Duma on November 22, 2022; approved by the Federation Council on November 30, 2022; Moscow, 2022. Available from: https://www.consultant.ru/document/cons_doc_LAW_433279/. Russian

² Ibid.

³ Kalinovskaya E. Skol’ko proizvodstvennykh aptek ostalos’ v Rossii [How many industrial pharmacies are left in Russia]. Pharmvestnik. Available from: <https://pharmvestnik.ru/content/articles/Skolko-proizvodstvennyh-aptek-ostalov-Rossii.html>. Russian

⁴ On the Program of State Guarantees of Free Provision of Medical Care to Citizens for 2023 and for the Planning Period of 2024 and 2025: Decree of the Government of the Russian Federation dated December 29, 2022 No. 2497. Official website of the Government of the Russian Federation. Available from: <http://static.government.ru/media/files/FQATIOfojXIUYX8cw12X7ugkeKRrRGjb.pdf>. Russian

Today, pharmacy manufacturing is designed to solve a number of problems associated with the provision of rare drugs to the population [23–26]; they will provide doctors and patients with individual dosages in individual dosage forms in various therapeutic areas [27–29]. This creates the need to develop legal norms to regulate extemporaneous production [30–34], a drug provision of individualized therapy and social guarantees for the patients who need them [35–38].

In 2022, due to the adoption of amendments to the legislation⁵, from September 1, 2023, pharmaceutical production organizations will have the opportunity, in drugs manufacturing, in addition to pharmaceutical substances (as provided for by the existing procedure), to use the drugs included in the State Register of Medicinal Remedies (SRMRs). This change in legislation opens up a lot of additional benefits for pharmacy organizations, doctors and patients [39]. In case of using factory-made finished dosage forms for drugs manufacturing for individual purposes, the main advantage is the possibility of individual packaging of finished DFs [40]. This will improve control over the drug intake for the patient, reduce the risk of errors in the use of it by patients on an outpatient basis, and also reduce the cost for the patient if the prescribed number of doses is significantly fewer than the minimum amount in the registered package [41].

In addition, the prescription of a drug according to an individual doctor's prescription, which will be repackaged by a pharmacy organization, actually changes the legal status of the indicated medicinal product. If the instruction for the use of the drug does not contain any indication, but at the same time, in medical practice, the specified active substance is indicated for the treatment of another disease, then the prescription of such a drug can be paid by the state for a privileged category of citizens⁶. This is especially important for drug researchers, who can thus study the effect of a drug for a limited cohort of patients, which can later become the basis for conducting a clinical study in order to expand the indications in the instructions. Such a process is often referred to as "repositioning" of the drug if the indication is fundamentally different from that for which primary clinical studies had been conducted [43].

In case of manufacturing medicinal products from the pharmaceutical substances approved for the release into the civil circulation, the advantage of manufacturing individual dosage forms requires a separate discussion. First, modern technology options

of pharmacy organizations make it possible to convert a solid form into a liquid one, but here, it is necessary to take into account the physicochemical properties of the active substance. For example, the pharmaceutical substance digoxin is insoluble in water, which leads to the formation of a precipitate in an aqueous solution. At the same time, digoxin can be dissolved in ethyl alcohol, but many doctors in neonatological practice see serious risks in prescribing alcohol-containing drugs to newborns [44]. In this regard, it is possible to use a suspension base to obtain a uniform distribution of the substance and the desired properties. Second, the availability of pharmaceutical substances makes it possible to combine various active substances to ensure the ease of use, which opens up opportunities for researchers to form new combined forms. This is especially important in cases where it is necessary to take into account the effect of different substances on different mutations of the same genetic disease, or where it is required to combine several active substances into one dosage form for the ease of use. Based on the data collected from patients on the use of such drugs (case series), it is possible to substantiate the scheme of further drug research [42]. Third, in the presence of a pharmaceutical substance (imported or self-produced), it is possible to resume pharmacotherapy of a patient population for which the drug had been previously prescribed, but for some reason its production and/or supply was stopped. A similar situation exists with a number of orphan drugs, which are currently not supplied to the Russian Federation. Fourth, the availability of raw materials solves the issue of a quick access of drugs to the market, since they are not subject to the state registration [45]. Accordingly, the time for passing registration procedures is reduced. For example, for a rare disease hyperammonemia (in which there is a violation of the urea formation cycle), sodium benzoate is used as a part of complex therapy. This substance is present in the composition of the combined preparation of a cough mixture and is not used in any way in wide medical practice. However, the presence of a pharmaceutical substance made it possible to develop an extemporaneous form for orphan patients and provide them with this drug in the shortest possible time [13]. This aspect is important for a regulation, as it can remove a social tension in the absence of any drug on the market. Fifth, pharmacy manufacturing can bring significant benefits to the budget if the drugs manufactured according to individual prescriptions provide significant budget savings, which is especially relevant for ultra-expensive drugs used in the treatment of orphan diseases [46]. A pharmacy organization's own synthesis of pharmaceutical substances and the manufacture of drugs from these substances can provide a significant number of patients with life-saving drugs [47].

Regardless of the aim of using an extemporaneously

⁵ Federal Law No. 502-FZ dated December 5, 2022 "On Amendments to Art. No. 56 of the Federal Law "On the Circulation of Medicines". Russian

⁶ Federal Law No. 482-FZ of December 30, 2021 "On Amendments to the Federal Law "On the Fundamentals of Protecting the Health of Citizens in the Russian Federation"; adopted by the State Duma on December 22, 2022; approved by the Federation Council on December 24, 2022; Moscow, 2022. Available from: https://www.consultant.ru/document/cons_doc_LAW_405472/. Russian

manufactured drug, developers, doctors and the state must be sure that this practice does not contradict the current international and national legislation in the field of an intellectual property rights protection, since the manufacture of drugs is carried out both for scientific and therapeutic purposes, and also with commercial benefits for the pharmacy organization [48].

The existing regulatory framework prohibits pharmaceutical organizations licensed to carry out pharmaceutical activities from producing pharmaceutical substances, because Russian legislation distinguishes between pharmaceutical and manufacturing activities. Now, pharmacy organizations can only manufacture drugs from pharmaceutical substances that are included in the SRMRs. The inclusion in the SRMRs provides for the presence of an applicant, who is both a manufacturer of medicines and his legal representative.

From the point of view of the terminology used in the national legislation, including the sectoral federal law⁷, a clear explanation is given of what is a drug and what is a pharmaceutical substance. Thus:

- “drugs are substances or combinations thereof that come into contact with a human or animal body, penetrate into the organs, tissues of the human or animal body, used for a prevention, diagnosis (with the exception of substances or combinations thereof that do not come into contact with the human or animal body), treatment of a disease, rehabilitation, for the preservation, prevention or termination of pregnancy and obtained from blood, blood plasma, organs, tissues of the human or animal body, plants, minerals by synthesis methods or using biological technologies. Medicinal products include pharmaceutical substances and drugs”;

- “drugs are pharmaceutical products in the form of dosage forms used for the prevention, diagnosis, treatment of a disease, rehabilitation, for the maintenance, prevention or termination of pregnancy”.

Thus, within the framework of the implementation of Art. 56 of the branch federal law⁸, pharmacy organizations manufacture drugs, since, in accordance with the federal law⁹, the doctor prescribes the drug and not pharmaceutical substances to the patient.

Intellectual property and pharmacies

The circulation and production of medicines may be further restricted by the legislation of the Russian Federation in the field of an intellectual property.

⁷ Federal Law “On the Circulation of Medicines” dated April 12, 2010 No. 61-FZ (last ed.); adopted by the State Duma on March 24, 2010; approved by the Federation Council on March 31, 2010]. Available from: https://www.consultant.ru/document/cons_doc_LAW_99350/. Russian

⁸ Ibid.

⁹ Federal Law No. 502-FZ dated December 5, 2022 “On Amendments to Art. No. 56 of the Federal Law “On the Circulation of Medicines”. Russian

A patent for an invention related to a drug can affect both the pharmaceutical substance – a directly active substance, and extend its effect to the drug as a whole – the system of active and auxiliary components [49].

At the same time, in order to limit the ability of large pharmaceutical companies to implement the so-called “renewal strategy” [50], the legislation of different countries contains antimonopoly restrictions on the manufacture of drugs by pharmacy organizations. Two main provisions must be observed: a pharmacy production must be in the interests of protecting public health, as well as preventing situations where individual treatment is impossible.

Similar provisions have been implemented under the Russian law. In accordance with subparagraph 5 of Art. 1359 of the Civil Code of the Russian Federation¹⁰, a one-time production of a medicinal product by a pharmacy organization on a doctor’s prescription does not violate the exclusive right to an invention, a utility model or an industrial design. Conventionally, the norm of this subparagraph 5 can be presented in a schematic form, where a production in a pharmacy assumes a one-time nature according to an individual prescription from the attending physician (Fig. 1).

At the same time, the mentioned wording indicates the extension of the effect of this article to the concept of a medicinal product. That implies a broader interpretation and effect of this article not on an industry basis, but in relation to the essence of the applied subject of regulation, which is a medicinal product, and the pharmaceutical substance in it.

The Eurasian legislation does not affect the regulation of manufacturing medicines in a pharmacy organization. Thus, in the legislation of the Russian Federation, there are prerequisites and a legal basis for the formation of the practice of widely using the possibilities of industrial pharmacies.

With regard to inventions in force on the territory of the Russian Federation related to the Eurasian Patent Convention (EAPC), it can be noted that it is similar to the domestic one. According to rule 19 of the Patent Instructions to the EAPC¹¹, the actions related to the one-time manufacture of medicines in pharmacies according to a doctor’s prescription are not recognized as infringement of a Eurasian patent.

The regulation of this provision of the countries, the members of the Eurasian Economic Union (EAEU), can be also considered similar.

¹⁰ Civil Code of the Russian Federation. Part Four: Federal Law No. 230-FZ of December 18, 2006; adopted by the State Duma on November 24, 2006; approved by the Federation Council on December 8, 2006]. Available from: https://www.consultant.ru/document/cons_doc_LAW_64629/. Russian

¹¹ Patent Instruction to the Eurasian Patent Convention; approved by the Administrative Council of the Eurasian Patent Organization at the 2nd (1st regular) meeting on December 1, 1995: in the current version]. Available from: <https://www.eapo.org/ru/documents/norm/instr2022-p1.html>. Russian

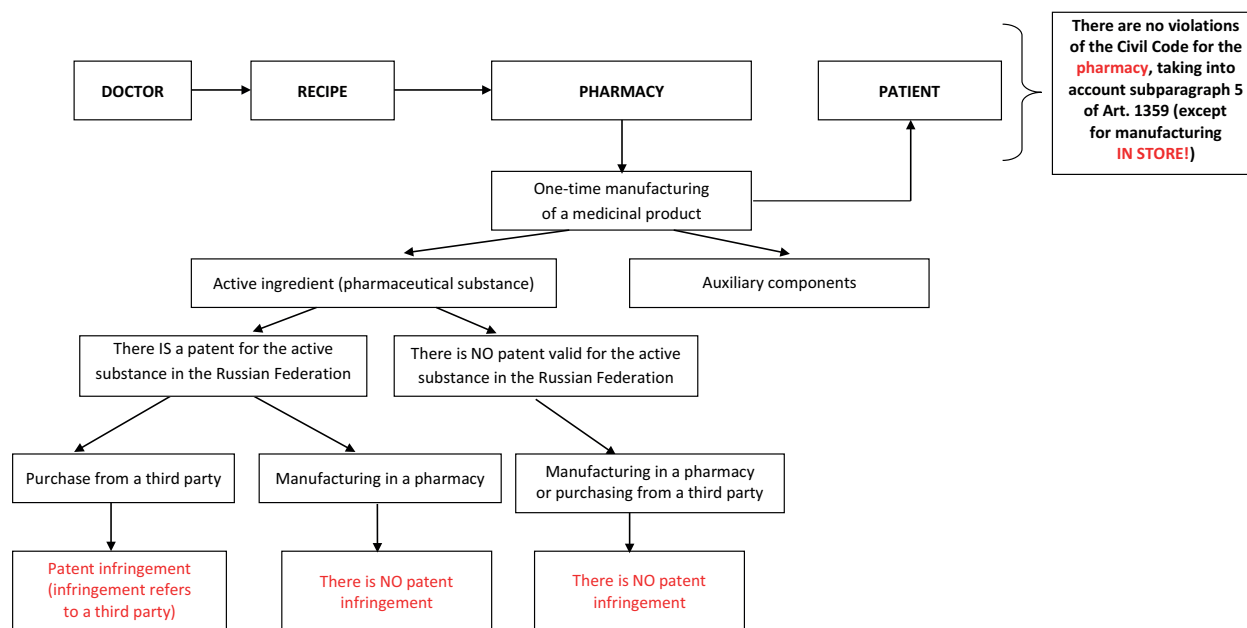


Figure 1 – One-time production of medicines by prescription in a pharmacy organization

Article 10 of the Republic of Belarus Law No. 160-3 “On Patents for Inventions, Utility Models, Industrial Designs”¹² (dated December 16, 2002) indicates that they are not recognized as a violation of the exclusive right of the patent holder: one-time manufacturing of medicines in pharmacies according to a doctor’s prescription using a protected invention patent. Similar provisions are contained in Art. 12 of the Kazakhstan Patent Law (the concept “in emergency cases” is used)¹³, and in Art. 17, subparagraph 1, of the Armenia Law “On Patents”¹⁴. At the same time, the provisions of the patent legislation of the Kyrgyz Republic do not contain such a provision.

With regard to the international position of the countries belonging to the outside of the Commonwealth of Independent States, it is possible to bring the following consolidated position, which reflects the approaches of a number of foreign states to this problem. In 2014, the World Intellectual Property Organization (WIPO) conducted a survey of the countries regarding the granting of the discussed exceptions. That resulted in the completed Questionnaire¹⁵ and the Document of the Secretariat of the WIPO Standing Committee on Patent Law following the results of the

20th session (Geneva, January 27–31, 2014) “Limitations and exceptions to patent rights: one-time preparation of medicines” (Document)¹⁶. The document includes information provided by 39 states and participating patent organizations regarding legislative aspects, to restrict the use of extemporaneous DFs. Their position was presented by: Albania, Armenia, Azerbaijan, Bosnia and Herzegovina, Brazil, Bulgaria, Croatia, Cyprus, Czech Republic, Democratic People’s Republic of Korea, Denmark, Finland, France, Germany, Greece, Hong Kong (China), Hungary, Italy, Japan, Latvia, Lithuania, Morocco, Norway, Philippines, Poland, Portugal, Republic of Korea, Republic of Moldova, Russian Federation, Serbia, Slovakia, Spain, Sweden, Tajikistan, Thailand, Turkey, United Kingdom, Viet Nam and Eurasian Patent Organization (EAPO).

Given the detailed presentation of positions, the following aspects can be focused on:

1. As regards the aim of regulation, the position of Brazil provides for the need to take into account both the interests of the right holder and the opinion of users of the relevant rights, as well as issues of the social justice through the use of limited exceptions to exclusive rights that are provided by the patent law, however, only on the condition that such exceptions do not come into critical conflict with its application and do not lead to the unjustified damage to the legitimate interests of the patent owner, as well as the interests of third parties. Accordingly, it is assumed that these exceptions facilitate the access of innovative technologies, taking into account the mutual benefit of producers and users of innovations, with the aim of maintaining social and

¹² Law of the Republic of Belarus No. 160-Z of December 16, 2002, on Patents for Inventions, Utility Models, and Industrial Designs (as amended up to Law No. 275-Z of December 18, 2019). Available from: <https://www.wipo.int/wipolex/ru/legislation/details/21279>.

¹³ Patent Law of the Republic of Kazakhstan No. 427 of July 16, 1999; amended in accordance with the Law of the Republic of Kazakhstan No. 268-VI of October 28, 2019. Available from: <https://www.wipo.int/wipolex/ru/text/539217>. Russian

¹⁴ Law of the Republic of Armenia of June 10, 2008, on Inventions, Utility Models and Industrial Designs. Available from: <https://www.wipo.int/wipolex/ru/legislation/details/5496>.

¹⁵ Questionnaire on Exceptions and Limitations to Patent Rights. WIPO. Available from: <http://www.wipo.int/scp/en/exceptions/>.

¹⁶ Exceptions and Limitations to Patent Rights: Extemporaneous Preparation of Medicines (SCP/20/5). Available from: https://www.wipo.int/edocs/mdocs/patent_policy/en/scp_20/scp_20_5.pdf

economic well-being while respecting the balance of rights and obligations.

The Republic of Cyprus and France adhere to the postulate that granting of exemptions is based on the principles of social justice and should be in the interests of protecting the health of citizens.

Poland's position is that exceptions are acceptable in cases where an "individual" treatment of the patient is necessary in order to prevent a situation where it is not possible.

In the Republic of Moldova, regulators insist on the need for exceptions in order to increase the availability of medicines.

Representatives of Portugal consider it important not to restrict an access to patient treatment and not to disrupt the communication between the doctor and the patient.

Spain's doctrine is to increase a patient access to extemporaneous medicines. Thus, patients can receive an individualized drug care, while not damaging the object of patent rights.

Regulators in Germany and Italy also believe that the aim of the exceptions is to allow physicians to prescribe the medicines produced in manufacturing pharmacies to patients in individual cases, regardless of the presence of patent rights, since patents should not limit the doctor's ability to treat a patient.

Sweden and the United Kingdom insist that "Pharmaceutical professionals should be able to manufacture individual drugs on prescription without the risk of patent infringement".

Hungarian representatives voice the aim of the state regulation of exceptions as an opportunity to provide patients with inexpensive and high-quality extemporaneous medicines and reduce financial costs in the public health system.

Sweden expresses a similar opinion: the aim of the government regulation is to provide a quality medical and pharmaceutical care. At the same time, the application of exceptions is used for a small number of patients and does not harm a patent holder.

Norway adheres to the fact that "manufacturing of extemporaneous DFs in pharmacies is legitimate, since they are prepared according to the doctor's prescriptions."

Japan and the Republic of Korea clearly point out to the fact that a pharmacy production is a socially significant mission of the state in order to help patients restore their health, respectively, extemporaneous production procedures cannot be considered from the point of view of the patent law.

Serbia's position is determined by ethical and medical aspects: when personalizing treatment, the presence of a patent should not prevent manufacturing of medicines in a pharmacy.

The response of the Republic of Latvia states that the main aim of the exception is to harmonize the country's

patent legislation with the regulatory legal acts of the EU member states.

2. As for the legislative aspects of the regulation, the analysis of the above Document and the Questionnaire additionally illustrates how the specified rule on the pharmacy production exclusion is implemented in the legislation of a number of countries.

In France, patent legislation does not cover the "one-time or non-systematic" manufacturing of extemporaneous medicines by prescription (Article L613-5 of the French Code of Intellectual Property)¹⁷.

Art. 23 of the Azerbaijan Law on Patents states: the "episodic" nature of manufacturing medicines in pharmacies makes it possible to avoid violating the exclusive rights of the patent owner.

Under the Thai law, patent infringement does not occur in the "manufacture of a specific medicinal product by prescription" (Section 36 of the Thai Patent Law)¹⁸.

In Turkey, "the right of the patent holder does not extend to the manufacture of extemporaneous DFs, since they are not intended to be industrially produced, and this procedure is carried out within the framework of the execution of a specific doctor's prescription" (Article 75 (c) of the Turkish Patents Decree)¹⁹.

According to the Italian law, "the exemption does not apply to the use of active ingredients manufactured industrially" (Article 68.1(c) of the Italian Industrial Property Code)²⁰.

The Serbia patent legislation declares the legitimacy of exceptions, but stipulates that the exception does not apply to the manufacture of extemporaneous DFs for the purpose of storage; only to the manufacture in pharmacy conditions for specific medical prescriptions, for a specific patient by prescription (Article 21, paragraph 3 of the Law on Serbian patents)²¹.

At the same time, the categorization of the parties in whose interests the aforementioned exception is used is usually not specified in the relevant legislative acts of the Member States. It should be noted that in most states, the legal documentation does not stipulate the

¹⁷ Intellectual Property Code (version of September 1, 2012). Available from: <https://www.wipo.int/wipolex/en/legislation/details/11987>.

¹⁸ Patent Act B.E. 2522 (1979) (as amended up to Patent Act (No. 3) B.E. 2542 (1999)). Available from: <https://www.wipo.int/wipolex/en/legislation/details/3807>.

¹⁹ Law No. 6769 of December 22, 2016, on Industrial Property (Türkiye). Available from: <https://www.wipo.int/wipolex/en/legislation/details/16609>.

²⁰ Industrial Property Code (Legislative Decree No. 30 of February 10, 2005, as amended up to Law No. 10829 of July 29, 2021; Italy). Available from: <https://www.wipo.int/wipolex/en/legislation/details/21556>.

²¹ Law on Patents (Official Gazette of the Republic of Serbia No. 99/2011, 113/2017, 95/2018 and 66/2019). Available from: <https://www.wipo.int/wipolex/en/legislation/details/19365>.

practice of applying exceptions, but the location where medicines can be manufactured according to a doctor's prescription (for example, pharmacies or accredited laboratories).

The bulk of the responses from Member States indicate that the exception regulates the right of the "pharmaceutical specialist" to manufacture such drugs.

The Norwegian legislation states that the exception concerns the "authorized personnel" of pharmacies, while the Swedish response refers to the "pharmacy personnel" in general.

The responses from France, Germany and Cyprus mention both pharmacists and prescribers.

Thailand's profile regulations contain information on "professional pharmaceutical and/or medical professionals".

In Italy, the right to use the exception belongs to the "pharmacists".

In Portugal, the exemption is relevant for "any person who has a legitimate right to manufacture under the conditions of a pharmacy organization" (Art. 102 of the Portuguese Industrial Property Code)²².

Art. 43 of the Brazilian Industrial Property Law specifies that the "qualified person" is the addressee of the exception²³.

The Philippine legislation allows a "health professional" to exercise his right to use the exception, regardless of the position of the patentee.

In Thailand, the main requirement for the practice of exclusion is the professional status: "a professional pharmaceutical specialist" or "a medical specialist".

Only general provisions are included in the legislation of individual Member States, but some Member States establish additional requirements for the persons entitled to the pharmacy manufacture and prescription.

The patent law of Hong Kong states that a medicinal product must be manufactured under the prescription of the doctor who holds the appropriate certificate (Section 75(c) of the Hong Kong Patent Ordinance, China)²⁴.

In Japan, pharmaceutical invention protection regulations do not prevent the pharmacy from making medicines prescribed by a doctor or dentist (Article 69(3) of the Japanese Patent Law)²⁵.

In the United Kingdom, relevant legislation states that only a board-certified doctor or dentist is authorized

to issue a prescription (Section 60(5)(c) of the UK Patents Act)²⁶.

3. With regard to the volume of the extemporaneous production when using the exemption, in most states, the legislation does not directly regulate the maximum number of units of the medicinal product that can be manufactured under the exemption. However, separate responses indicate that the exception is applicable in case of "one-time" (RF and Republic of Moldova), "non-systematic" (France, Sweden and EAPO) or "singular" (France), "individual" (Finland, Hungary, Italy and Serbia) production for the manufacture of medicines in pharmacies.

Thus, all states under the Document were positive on the problem of whether the regulatory framework for the application of exceptions related to patent rights relating to pharmacies is sufficient to achieve the stated goals and objectives. An important point is that all states noted that there were no difficulties in the practical implementation of the discussed exception.

However, it should be noted that in the countries of northern Europe (Denmark, Norway and Sweden), such an exception is not an accepted practice, since pharmacy manufacturing of drugs is not a common procedure.

Taking into account the above opinions, the law enforcement practice of using this norm in the Netherlands is interesting, since the discussion has shown the difficulties that may be encountered in its practical implementation.

As of February 1, 2019, the Dutch Patent Act (DPA) has been amended to include a limitation on the exclusive right of a patent holder to a medicinal product. The operation of the exclusive right now contains an important point in Art. 53(3) of the DPA²⁷: "The exclusive right ... does not apply to the preparation of drugs for an immediate use by individuals on the basis of a medical prescription in pharmacies, as well as acts relating to drugs prepared in this way". This part of Section 53(3) of the DPA allows pharmacists to manufacture patented medicines in the above circumstances for the immediate use by individuals on the basis of a medical prescription.

The public interest in addressing the problem of excessively high drug prices in the Netherlands prompted the legislature to make this provision official. According to Minister of Health and Sports, Mr. Bruins, "the elimination of liability for patent infringement in some cases of impromptu drug manufacturing could be a reasonable alternative to expensive drugs." In his Explanatory Memorandum on the Enactment of the Improvisation Provision, the Minister of Economy, Mr. Vives, stated that "In order to prevent the abuse of extemporaneous preparation of medicines, the exception should apply only to rare cases when the

²² Código da Propriedade Industrial (alterado pelo Lei n. 46/2011, de 24/06). Available from: <https://www.wipo.int/wipolex/en/text/420570>.

²³ Law No. 9.279 of May 14, 1996 (Law on Industrial Property, as amended up to Law No. 14.200 of September 2, 2021). Available from: <https://www.wipo.int/wipolex/en/legislation/details/21166>.

²⁴ Patents Ordinance (Chapter 514); Hong Kong, China. Available from: <https://www.wipo.int/wipolex/en/legislation/details/2049>.

²⁵ Patent Act (Act No. 121 of April 13, 1959, as amended up to Act No. 63 of May 13, 2011); Japan. Available from: <https://www.wipo.int/wipolex/en/legislation/details/13137>.

²⁶ Patents Act 1977 (Chapter 37, updated up to March 27, 2014); United Kingdom GB324. Available from: <https://www.wipo.int/wipolex/en/text/330537>.

²⁷ Rijkswet van 15 december 1994. Available from: <https://wetten.overheid.nl/BWBR0007118/2021-08-01>.

pharmacist himself prepares the medicine; the cases prescribed by a doctor; a preparation of medicines for individual patients”²⁸.

Scientists in the Netherlands agree that this formulation does not allow the production of patented drugs broad based. The recently adopted exception in the DPA should be interpreted restrictively. The public opinion in the Netherlands supports an immediate preparation of medicines as an alternative to expensive medicines. Obviously, such stakeholders as patent owners and the pharmaceutical industry will oppose a broad interpretation of the new law.

DISCUSSION

The article provided an overview of the modern practice of pharmaceutical manufacturing in the Russian Federation, as well as analyzed the benefits of this activity for the medical community, patients and the state. One of the most important advantages of pharmaceutical manufacturing is an individual approach to drug therapy. At the same time, the individualization of drug treatment has made it possible to work out systemic solutions for developing drug therapy methods for special groups of patients for whom the economic feasibility of a pharmaceutical registration and launching such drugs onto the market has been brought into challenge. Ensuring the availability of drug therapy, however, responds to the need to respect the rights of citizens.

In addition, pharmacy manufacturing is an available tool in the study of drugs prescribed by a doctor not in accordance with the instructions for a medical use (off-label) or in dosage forms/dosages that are not on the market.

Extemporaneous manufacturing can also be a part of the drug repositioning process on the market, subject to compliance with the requirements for pharmacy manufacturing and safety control of prescribed drugs.

A review of the foreign patent legislation, including the EAEU countries, in relation to the drugs manufactured in pharmacy organizations, shows that the legislative norm under discussion as a whole does not have an innovation characteristic exclusively for the Russian Federation. It is legally enshrined in many countries that are members of WIPO, as a rule concerning the exceptions related to patent rights in relation to the pharmacy production.

It is important to note that, in fact, this rule is conceptually formulated in approximately the same way in more than 30 WIPO Member States, including France, Spain, Germany, Italy, Sweden, the United Kingdom

and many others. The norm states that it is pharmacy specialists who should be able to prepare medicines in an individual case in accordance with a doctor's prescription, without being exposed to the risk of patent infringement.

In the Russian Federation, as one of the mechanisms that allow the use of medicinal products without the permission of the right holder, правообладателя is the implementation of the provisions of subparagraph 5 of Art. 1359 of the Russian Federation Civil Code²⁹. In other words, a one-time pharmacy production according to an individual prescription cannot be regarded as a patent infringement. First of all, this applies to such inventions that relate to methods for obtaining drugs or medicinal products as such, since these technical solutions use either industrial technological methods for obtaining compounds or compositions that are parts of drugs not used in pharmacies, or refer to methods of the drug use, the scope of which is focused on patients.

As for the compositions themselves, as objects of the invention, the sign of a one-time production is an individual order or an individual prescription issued to a specific individual in a certain period of time, which has other signs of a one-time nature – an individual number and date of issue, a limited shelf life, an individually selected DF, dosage, etc.

The opposition to the term “one-time” may be the term “serial”. Therefore, a one-time production of a medicinal product should not have serial features in itself, i.e. have differences from other recipes (or orders) and signs of individuality.

However, the main problem in the manufacture of drugs in a pharmacy is the presence of a patent for an invention that relates directly to the compound, i.e. to the pharmaceutical substance. This is due to the fact that the sale of a pharmaceutical substance (the alienation of property rights for the purpose of obtaining commercial benefits), in respect of which exclusive intellectual property rights are distributed on the territory of the Russian Federation, is a violation of the rights of the patent owner. Herewith, in accordance with Art. 56 of the branch federal law, “in the manufacture of medicines by pharmacy organizations, veterinary pharmacy organizations, individual entrepreneurs licensed for pharmaceutical activities, pharmaceutical substances that are included in the state register of medicines for medical use and, respectively, the state register of medicines for veterinary use in the prescribed manner, are used”. Accordingly, the pharmaceutical substance included by the manufacturer or supplier in the SRMRs, can be used for a pharmacy production in a licensed organization.

At the same time, a manufacturing pharmacy cannot independently produce patented pharmaceutical

²⁸ Radboud Ribbert, Amendment to Dutch Patents Act (Rijksoctrooiwet) Allows for Extemporaneous Preparation of Medicine in Certain Circumstances, March 14, 2019. Available from: <https://www.gtlaw.com/en/insights/2019/3/amendment-to-dutch-patents-act-rijksoctrooiwet-allows-for-extemporaneous-preparation-of-medicine>.

²⁹ Civil Code of the Russian Federation. Part Four: Federal Law No. 230-FZ of December 18, 2006; adopted by the State Duma on November 24, 2006; approved by the Federation Council on December 8, 2006].

substances. Therefore, it is necessary to clarify or introduce a similar article or supplement the current article with provisions applicable to manufacturers of pharmaceutical substances, where a one-time production of pharmaceutical substances will not be recognized as a violation of the exclusive right to an invention, a utility model or a design invention.

The combination of technological capabilities of Russian drug developers and obtaining the right to manufacture in pharmacies can open a new way to "reposition" existing drugs or become the basis for creating drugs for orphan diseases prescribed as the only possible therapy.

CONCLUSION

Thus, new regulatory changes in the field of the drug circulation, in the context of a changing political and economic landscape and sanctions against the Russian Federation, will serve to increase the availability of a drug provision and a personalized drug care to the country's population.

The renewal of the pharmacy production will improve not only the availability of the drug care to the population, but also taking into account individual dosages and dosage forms in various therapeutic areas, and can also become a tool for drug repositioning or clinical testing of new molecules for rare incurable diseases.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Alexey V. Alekhin – goals setting, concept working out, article writing and editing, manuscript final approval; Tatyana N. Erivantseva – critical analysis of scientific literature and legal documentation, writing the manuscript text; Vasily V. Ryazhenov – scientific and methodological literature analysis, making comments of intellectual content; Nikolai B. Lyskov – material collection, critical analysis of literary sources, writing the manuscript text; Natalya A. Alekhina – material collection, critical analysis of literary sources, writing the manuscript text; Maria M. Kuznetsova – analysis of scientific and methodological literature, editing and design of the manuscript text. 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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