



## “Off-label” drugs: legal problems and socio-economic aspects of application practice

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**The aim** of the work was to analyze Russian and foreign experience in the regulation and application practice of “off-label” drugs in order to develop recommendations on the optimization of their application in clinical practice.

**Material and methods.** The analysis of scientific articles and legal documents of the Russian Federation and foreign countries published from 2011 to 2022 on the websites Consultant Plus, FDA, EMA, NCBI, e-library, as well as a qualitative sociological study conducted in May-August 2022 – 11 in-depth interviews with experts in the field of the healthcare system of the Russian Federation.

**Results.** The social and economic aspects have been considered and the list of legal problems in the application practice of “off-label” drugs has been disclosed. A state analysis of the regulatory and legal framework on the drugs application practice by healthcare professionals in the absence of registered indications for “off-label” drugs use has been presented. The use of an unregistered medicinal product in the territory of the Russian Federation in everyday medical practice has been considered. The analysis of the Russian and foreign experience in regulating the use of drugs in the absence of their registration in the country, as well as the absence of registration of some indications for their prescription in the instructions for the medical use of such drugs has been also carried out. The authors have formulated the key problems of the use of “off-label” drugs in clinical practice. Based on the results of the in-depth interviews, the recommendations of the expert community on the ways to optimize the use of “off-label” drugs have been identified and concretized.

**Conclusion.** The results of this study made it possible to formulate recommendations for expanding the ability of specialists to prescribe “off-label” drugs treatment while maintaining a proper degree of the state control over this process: a legislative consolidation of the regional health authorities' obligations and responsibilities on the drug provision; creating an open and transparent system for the “off-label” drugs use by patients and their legal representatives, the mandatory full information of the patient about the fact of using the “off-label” drug, as well as the risk and nature of the development of possible adverse reactions. When prescribing these drugs, the patient safety should be the top priority.

**Keywords:** drugs; misuse; “off-label” prescriptions; regulation and practice of drug use; patient safety

**Abbreviations:** RLA – regulatory legal act; AR – adverse reaction; EMA – European Medicines Agency; GOLUP – Good Off-Label Use Practices; US FDA – United States Food and Drug Administration; VED – Vital and Essential Drugs; CTs – clinical trials; CMI – compulsory medical insurance; HTMC – high-tech medical care.

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## Лекарственные препараты «off-label»: правовые проблемы и социально-экономические аспекты практики применения

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**Цель.** Проанализировать российский и зарубежный опыт регулирования и практики применения лекарственных препаратов (ЛП) «off-label» для выработки рекомендаций по способам оптимизации их использования в клинической практике.

**Материал и методы.** Анализ научных статей и нормативно-правовых документов Российской Федерации и зарубежных стран, опубликованных с 2011 по 2022 года на сайтах КонсультантПлюс, Food and Drug Administration, European Medicines Agency, National Center for Biotechnology Information, e-library, а также качественное социологическое исследование, проведенное в мае-августе 2022 года, а именно 11 глубинных интервью с экспертами в области системы здравоохранения Российской Федерации.

**Результаты.** Рассмотрены социально-экономические аспекты и раскрыт перечень правовых проблем практики применения ЛП «off-label». Представлен анализ состояния нормативно-правовой базы по вопросам использования ЛП специалистами здравоохранения в условиях отсутствия зарегистрированных показаний по применению лекарственного средства; применения незарегистрированного лекарственного средства на территории Российской Федерации в повседневной врачебной практике; анализ российского и зарубежного опыта регулирования применения ЛП в условиях отсутствия их регистрации в стране, а также отсутствия регистрации некоторых показаний к их назначению в инструкции по медицинскому применению лекарственного средства. Авторами были сформулированы ключевые проблемы применения ЛП «off-label» в клинической практике. По результатам глубинных интервью были выявлены и конкретизированы рекомендации экспертного сообщества по способам оптимизации применения ЛП «off-label».

**Заключение.** Результаты настоящего исследования стали основой для формулирования рекомендаций для расширения возможностей специалистов назначать лечение ЛП «off-label» при одновременном сохранении должной степени государственного контроля за данным процессом: законодательное закрепление обязательств и ответственности региональных органов управления здравоохранением по вопросам лекарственного обеспечения; создание открытой и прозрачной системы применения ЛП «off-label» для пациентов и/или их законных представителей, обязательное полноценное информирование пациента о факте применения ЛП «off-label», а также риске и характере развития возможных нежелательных реакций. Основным приоритетом при назначении таких препаратов должна выступать безопасность пациента.

**Ключевые слова:** лекарственные препараты; неправильное применение; назначения «off-label»; регулирование и практика применения лекарственных препаратов; безопасность пациентов

**Список сокращений:** ЛП – лекарственные препараты; НПА – нормативный правовой акт; НР – нежелательная реакция; ЕМА – Европейское агентство лекарственных средств; GOLUP – Надлежащая практика использования лекарств не по прямому назначению; US FDA – Управление по санитарному надзору за качеством пищевых продуктов и медикаментов США; ЖНВЛП – жизненно необходимые и важнейшие лекарственные препараты; КИ – клинические исследования; ОМС – обязательное медицинское страхование; ВМП – высокотехнологичная медицинская помощь.

## INTRODUCTION

The use of drugs for indications not specified in the instructions, including prescriptions for other diagnoses, changing the administration methods and dosages, has been an inevitable practice for quite a long period of time [1–4]. Prescribing and dispensing drugs outside the registered indications (informally “off-label” ones) still remains an urgent legal problem and a problem in the clinical practice, caused primarily by unmet clinical needs [5–8]. This is due to a number of reasons: the need, in some cases, to provide medical care to a patient in the absence of registered drugs [9, 10]; the reluctance of pharmaceutical companies to invest in clinical trials and registration of additional indications [11]; the doctor’s lack of temporary (high workload), organizational and technical possibilities to clarify the indications for the use of a particular drug specified in the registration dossier [12], as well as a number of individual characteristics of the medical specialist and the patient (insufficient qualifications, ignorance of the responsibility for prescribing the “off-label”, false beliefs) [13, 14]. In some cases, it is not one, but a combination of the above factors that leads to the incorrect use of drugs [15].

Although the effectiveness of the “off-label” drugs use has not been officially confirmed, their use in clinical practice can serve as a means of saving patients’ lives with rare diseases, infancy or senile patients, pregnant and lactating women, as well as the patients in case of detection of new infectious diseases, for which the etiotropic therapy has not been developed yet (for example, COVID-19) [16].

One of the important problems of the “off-label” drugs use outside the registered indications is their “confusion” in terminology. According to the definition given by the Food and Drug Administration of the United States of America (Food and Drug Administration, US FDA), an “off-label” prescription is the use of a medical device or drug for the indications not approved in the instructions, in a different dosage form or regimen, as well as in the populations not specified in the instructions [17]. At the same time, in regulatory legal acts and publications regarding the use of “off-label” drugs, there is such a formulation of this phenomenon as the prescription of the drug for “the indications that

are different from the indications for the use contained in the instructions”, i.e., “the incorrect use”, which significantly narrows the concept [18].

The cases in which the use of drugs occurs “off-label”, include the following ones: the use of the drugs not registered in the country; prescribing a drug contraindicated in this pathology; prescribing a drug for unregistered indications; prescribing a drug to the populations not specified in the instructions (pregnant women) or age groups (children, the elderly); a simultaneous prescription of adverse drugs combinations; the use of drugs in violation of the methods of application (multiplicity, dosing, route of administration, duration of treatment) [17–19].

Any practicing physician, regardless of their specialization, repeatedly resorts to “off-label” prescriptions [20]. The main groups of patients, among which “off-label” drugs are most widespread, are children, pregnant women, elderly and senile patients, patients with oncological and orphan diseases, patients receiving palliative care, psychiatric patients [18, 21–23].

In these groups, conducting clinical trials (CTs) necessary for the inclusion of the relevant indications in the instructions for the use of medicinal products is usually difficult, and in some cases – completely impossible for ethical reasons. These are the main reasons for the impossibility of including a number of drugs in the list of “Vital and Essential Drugs” (VED), clinical guidelines and standards of medical care. As a result, the use of “off-label” drugs cannot be paid for by the compulsory medical insurance (CMI) system or budgetary funds as parts of a high-tech medical care (HTMC) provision.

**THE AIM** of the work was to analyze Russian and foreign experience in the regulation and application practice of “off-label” drugs in order to develop recommendations on the optimization of their application in clinical practice.

### Research objectives:

1. Assess the prevalence of “off-label” drug use in the international clinical practice.
2. Analyze the regulatory and legal framework on the drugs application practice in the Russian Federation and abroad.
3. Find out the experts’ opinion on the use of “off-label” drugs.

## MATERIALS AND METHODS

The main methods used in this work are the analysis of domestic and foreign scientific articles on the regulation of circulation and practical application of the “off-label” drugs, published from 2011 to 2022 on the websites of Consultant Plus, FDA, EMA, NCBI, e-library, and regulatory legal documents of the Russian Federation and foreign countries; qualitative sociological research using the methodology of in-depth interviews.

In-depth interviews<sup>1</sup> with experts in the field of the healthcare system of the Russian Federation citizens were conducted in May-August 2022. The in-depth non-formalized interview questionnaire was a list of topics to be clarified. The topics were formulated in both narrative and interrogative forms. These grammatical forms were interchangeable, with the aim of choosing any of them, or a combination of them, by researchers to their liking. Depending on the type of a semantic connection, the topics of the questionnaire were divided into narratives, descriptions and reasoning. Compared to other qualitative research methods, this method provided in-depth information due to the fact that the entire time duration of the topic under study discussion is focused on the interviews with one participant. It should be noted that the absence of other participants' influence makes it possible to uniquely identify the author of the answer and compare the results obtained with the respondent's characteristics.

11 specialists of various profiles took part in this study as experts: a representative of the State Duma of the Federal Assembly of the Russian Federation (1 expert); the Regional Children's Clinical Hospital of the National Medical Research Center for Radiology (1 expert); Institute of Management and Translational Medicine of Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology (2 experts); Hematological Research Center (2 people); Institute of Hematology, Immunology and Cell Technologies of Dmitry Rogachev National Medical Research Center of Pediatric Hematology, Oncology and Immunology (2 experts); Blokhin National Medical Research Center of Oncology (3 experts); pharmaceutical concern Bayer JSC (1 expert); vice president of the Society of Evidence-Based Medicine Specialists (osdm.org) (1 expert). The average age of the respondents was 45±5 years. For all the respondents, the same conditions had been created for the place and time of the interview. The interviewees were also informed and, in turn, agreed to publish the results of the survey.

<sup>1</sup> An in-depth interview is unstructured, direct, personal interview, single respondent probed by highly skilled interviewer to uncover underlying motivations, beliefs, attitudes, and feelings on a topic.

## RESULTS AND DISCUSSION

### Use of “off-label” drugs in international clinical practice

The phenomenon of using “off-label” drugs has been studied by a number of domestic and foreign researchers [24–27]. According to Kuznetsova E.Yu. et al. (2020), more than 62% of doctors noted the need to prescribe “off-label” drugs in their clinical practice [27]. At the same time, experts indicate the lack of alternative treatment options and the need to provide palliative care to seriously ill patients as the main reasons for the use of drugs in violation of the instructions [27, 28].

Most often, this practice is found in oncology, hematology, and pediatrics [29–31]. A systematic review published in 2017 summarized the results of 23 studies published between 1975 and 2016. The frequency of “off-label” drugs use in oncology was 6–82%, depending on the type of tumor, stage, drug, and age of the patient. It has been shown that “off-label” drugs are equally often prescribed for both outpatient and inpatient treatment. The main reasons for the use of “off-label” drugs were the absence of indications for the use of drugs in a certain type of tumor (9–46%), as well as a change in the regimen of the drugs use (10–40%). “Off-label” drugs in oncology are used most often as a part of palliative care (34–76%), less often for curative (10–41%) or adjuvant therapy (8.5–49%) [32].

Another clinical specialty in which “off-label” drug prescriptions are widespread is pediatrics [33–35]. The frequency of the “off-label” drugs use outside the registered indications in this area reaches 87.7% [36].

According to Pryadkina E.A. et al. (2018), when analyzing the frequency and structure of “off-label” drugs prescriptions indicated in the medical records of the Department of Pediatric Day Hospital for Hematology and Oncology, 69% of case histories contained 93 “off-label” drugs prescriptions, among which 39 prescriptions did not match instructions on the recommended age of the patient, 14 – by the dose of the drug, 39 – according to the registered use indications, 1 – according to the drug dosage form. The main groups of “off-label” drugs were immunosuppressants (29%); interferons (15%); complexing agents (12%). In 68% of cases, “off-label” drugs were prescribed for the treatment of the underlying disease, in 32% – for the concomitant pathology [37].

Such a high prevalence of “off-label” prescriptions is due to the laboriousness and cost of conducting large clinical trials in a relatively small population of patients, and the lack of economic incentives for such studies. As a result, in the instructions for the use of drugs, the aspects related to the possibilities and features of their use in children are the least developed. Among the registered



drugs, only 33% are approved for use in children: 23% – in an early childhood (1–3 years old), 9% – in infancy (up to 1 year old). At the same time, it is known about an increased risk of developing toxic effects on the drugs in children compared with the adult population, as well as the presence of specific adverse reactions (ARs) [18, 38, 39]. The frequency of complications in the use of “off-label” drugs in pediatrics ranges from 23 to 60%, and the relative risk of their occurrence is 4.43 times higher than in cases of their use according to indications [33, 36].

The study by Matveev A.V. et al. (2018) showed that 47.7% of cases of the ARs development in the children of the Republic of Crimea in the period from 2011 to 2016 were associated with the prescription of “off-label” drugs. While 36.1% of the identified episodes were classified as a drug use for unregistered indications, 31% occurred with a frequency violation of the administration and the administration timing; in 20.7%, contraindications for use were not taken into account; 19.4% were characterized by a dosing violation; 18.7% – by an unspecified route of administration; in 2.1%, there was ignoring of an allergy history. The majority (52.7%) of the “off-label” drugs prescriptions were for the patients aged 29 days to 1 year [40].

The uncontrolled use of “off-label” drugs can cause negative consequences for both doctors and patients who have turned to them [27, 41]. It should be noted that once a drug meets the safety and efficacy standards required to obtain the FDA approval, it might be used for new indications and/or in the populations other than those for whom it had been approved. An example of such a use of “off-label” drugs is a therapy of a new coronavirus infection specified in the clinical recommendations of various countries. At the beginning of the pandemic, for the treatment of COVID-19, medical specialists used various drugs registered for the treatment of a similar infectious pathology [42, 43]. At present, 16 versions of interim guidelines for the treatment of coronavirus infection have already been formed. However, during the pandemic, an active search was made for effective treatment regimens using “off-label” drugs, since in the initial period of the pandemic there were no drugs which indications for use would include the infection caused by SARS-CoV-2 strains [27, 42].

The use of “off-label” drugs has also a negative experience. Thus, one example of the development of severe ARs with an uncontrolled prescription of drugs is the case of the blindness development caused by using the antitumor agent bevacizumab in Romania. The doctor who had prescribed the drug was accused of negligence [44]. At the same time, the relevant ministry made a statement that in cases of using an “off-label” drug, the healthcare professionals involved

in the process of prescribing and using it, bear a full responsibility<sup>2</sup>.

In Russia, there were also several high-profile stories associated with harm to the life and health of patients as a result of the use of “off-label” drugs [45]. One of them is associated with the prescription of misoprostol in the Republic of Dagestan in 2016. According to the official instructions, this drug is a treatment for gastric and duodenal ulcers, but it was prescribed to a patient for the purpose of terminating a pregnancy, which led to the woman's death. The relatives of the deceased patient filed a lawsuit for damages. During the proceedings, it was established that the cause of death was the use of this “off-label” drug, the claim of the plaintiffs was satisfied, and the medical organization was brought to a civil liability<sup>3</sup>.

In 2014, for the use of “off-label” ceftriaxone when diluted with an incorrect concentration of a lidocaine solution (10% instead of 1%) and the patient's death associated with this, an Ulan-Ude paramedic was sentenced to imprisonment under Part 2 of Article 109 “Causing death by negligence due to improper performance by a person of his professional duties” of the Criminal Code of the Russian Federation<sup>4</sup>.

The described cases indicate the need to develop and introduce additional measures of detailed legal regulation into wide practice, and control over the use of “off-label” drugs.

### Legal regulation of “off-label” medicinal products use in the Russian Federation and abroad

A legal regulation of prescribing and use of “off-label” drugs in the Russian Federation today is very ambiguous. The possibility of using a drug in this variant is rather superficially indicated in paragraph 15 of Art. 37 “Organization of delivery of health care” of Federal Law No. 323-FZ “On health protection of citizens in the Russian Federation”. According to this law, “the prescription and use of medicines, medical devices and specialized medical food products that are not included in the relevant standard of medical care or not provided for by the relevant clinical recommendation, are allowed if there are medical indications (individual intolerance, according to vital indications) by decision of the medical commission.” Herewith, it is emphasized that “the effect of this requirement may be changed in relation to

<sup>2</sup> Press Release of ANMDM Regarding the Off-Label Use of AVASTIN [Comunicat de Presa al ANMDM Referitor la Utilizarea off\_Label a AVASTIN (bevacizumab)]. Available from: <https://www.anm.ro/anunt-important-11-03-2011/>. Romanian

<sup>3</sup> The decision on the case on compensation for moral damage in connection with the infliction of harm to life and health. Available from: <https://sudact.ru/regular/doc/6vlcquF4dy1e/>. Russian

<sup>4</sup> The decision on the case of causing death by negligence due to improper performance by a person of his professional duties. Available from: [http://oktiabrsky.bur.sudrf.ru/modules.php?name=press\\_dep&op=1&did=135](http://oktiabrsky.bur.sudrf.ru/modules.php?name=press_dep&op=1&did=135). Russian

medical organizations of the private healthcare system – participants in the experimental legal regime in the field of digital innovation in accordance with the program of the experimental legal regime in the field of digital innovations”<sup>5</sup>.

At the same time, according to the order of the Ministry of Health of Russia dated December 2, 2013 No. 886n, the composition and procedure for the work of the medical commission is determined by the head of the medical organization. The medical commission should include a chairperson, one or two deputy chairpersons, a secretary and members of the commission (heads of the departments, medical specialists)<sup>6</sup>.

The procedure for prescribing a drug is indirectly mentioned in a number of regulatory legal acts, but it has been clearly stated nowhere about the permission or prohibition of the use of an “off-label” drug. One of these documents that previously regulated the use of drugs was the Procedure for prescribing drugs (Appendix No. 1 to the order of the Ministry of Health of the Russian Federation dated December 20, 2012, No. 1175n)<sup>7</sup>. In paragraph 6.1 of this document, it was said that medical specialists were prohibited from prescribing drugs in the absence of medical indications, but it was not indicated that these should be precisely the indications prescribed in the instructions for the drug. At the same time, in 2017, there was a public discussion of the Draft Order of the Ministry of Health, amending the specified procedure, according to which, by decision of the medical commission, in certain cases it was proposed to allow the use of the drug “for health reasons other than the indications for the use contained in the instruction.” The document caused a wide public outcry, but these changes to the Procedure were not made. The current document Appendix N 1 to the Order of the Ministry of Health of the Russian Federation dated November 24, 2021 No. 1094n “On Approval of the Procedure for Prescribing Medicines” in Art. 1, Paragraph 7 states that “Medical specialists are prohibited from issuing

prescriptions if a patient has no medical indications, and from unregistered medicinal products<sup>8</sup>. However, in the same regulatory legal act (RLA) in Art. 1, paragraph 5 refers to the possibility of prescribing a drug that is not included in the standards of medical care through a medical commission with reference to Art. 37, paragraph 15 of the Federal Law No. 323-FZ “On health protection of citizens in the Russian Federation”. The decision of the medical commission of a medical organization is recorded in the patient’s medical records and in the journal of the medical commission.

On June 29, 2022, amendments to Federal Law No. 323-FZ “On health protection of citizens in the Russian Federation” came into force. They allow the use of medicines outside the instructions (“off-label”) for the treatment of the minors with certain diseases or conditions. Their list was approved by the Decree of the Government of the Russian Federation No. 1180n-r dated May 16, 2022 (“Check-list of diseases in which the use of “off-label” medicines is possible”)<sup>9</sup>. This list includes neoplasms, diseases of blood, respiratory organs, endocrine and nervous systems, mental disorders, etc. The codes of the International Classification of Diseases (the 10th revision, ICD-1), conditions and groups of conditions for pregnancy, childbirth, a postpartum period have also been inserted.

An important aspect in prescribing “off-label” drugs is informing a patient (a minor, one of their parents (a legal representative)) by the attending physician about the use of the “off-label” drug. According to Art. 20 of the Federal Law No. 323-FZ “On health protection of citizens in the Russian Federation”, the patient must be informed about the safety of the drug, the expected result, the degree of risk and the actions in case of unforeseen effects.

In accordance with Art. 37, paragraph 14.1 of Federal Law No. 323-FZ “On health protection of citizens in the Russian Federation”, in the amendment dated July 13, 2022, there is also a permission to include an “off-label” drug in the clinical recommendations and standards of medical care for children. In the instructions (in the section of dosages and methods of application), this category of the population is absent. It is important to note that these amendments apply to the medicinal products registered in the Russian Federation, to the diseases and conditions included in the “Check-list of

<sup>5</sup> Federal Law of November 21, 2011 No. 323-FZ (as amended on March 26, 2022) “On the fundamentals of protecting the health of citizens in the Russian Federation” (as amended and supplemented, effective from April 10, 2022) Available from: [https://www.consultant.ru/document/cons\\_doc\\_LAW\\_121895/f7964563436c4bb0aed73d388df1a95d9103b632/](https://www.consultant.ru/document/cons_doc_LAW_121895/f7964563436c4bb0aed73d388df1a95d9103b632/). Russian

<sup>6</sup> Order of the Ministry of Health of the Russian Federation of December 2, 2013 No. 886n “On Amendments to the Procedure for the Creation and Activities of the Medical Commission of a Medical Organization, approved by Order of the Ministry of Health and Social Development of the Russian Federation of May 5, 2012 No. 502n, and to the Procedure for Appointment and Discharge medicinal products, approved by the order of the Ministry of Health of the Russian Federation dated December 20, 2012 No. 1175n” (as amended). Available from: <https://base.garant.ru/70551698/>. Russian

<sup>7</sup> The procedure for prescribing and prescribing drugs. Appendix No. 1 to the order of the Ministry of Health of the Russian Federation of December 20, 2012 No. 1175n. Available from: <http://base.garant.ru/70404898/53f89421bbdaf741eb2d1ecc4ddb4c33/#ixzz51CKu1Xnz>. Russian

<sup>8</sup> Order of the Ministry of Health of Russia dated November 24, 2021 No. 1094n “On approval of the Procedure for prescribing medicines, forms of prescription forms for medicines, the Procedure for issuing these forms, their accounting and storage, forms of prescription forms containing the prescription of narcotic drugs or psychotropic substances, the Procedure for their manufacture, distribution, registration, accounting and storage, as well as the Rules for issuing prescription forms, including in the form of electronic documents” Available from: [http://www.consultant.ru/document/cons\\_doc\\_LAW\\_401865/](http://www.consultant.ru/document/cons_doc_LAW_401865/). Russian

<sup>9</sup> Ibid.

diseases in which the use of “off-label” medicines is possible)”.

In Paragraphs 1 and 2, Art. 67 of Federal Law No. 61-FZ “On the Circulation of Medicines” dated April 12, 2010 with the amendment dated July 14, 2022, it has been pointed out that information about a drug may be contained in specialized publications, instructions for the use of the drug, in scientific publications, etc., but it is has not been regulated how a doctor can use the information obtained from various sources<sup>10</sup>. Separately, it has been emphasized that promotional materials about an over-the-counter drug must comply with the instructions for the use of the drug [46].

According to the Order of the Ministry of Health of the Russian Federation No. 203N “On Approving Quality Criteria for Evaluating Medical Care” dated May 10, 2017, the prescription of the drugs for medical use should be carried out taking into account the instructions for the use of the medicinal product<sup>11</sup>. However, there is no information on the rigidity of the instruction to be taken into account. The same Order establishes the mandatory entry into the outpatient card when prescribing drugs for a medical use and using medical devices by decision of the medical commission of the medical organization.

At the same time, one should not forget about situations of a criminal liability when prescribing a drug. In case of a serious injury to the health or death of the patient, a doctor’s actions may fall under the provisions of Art. 109 “Causing death by negligence due to improper performance by a person of his professional duties”, Art. 118 “Causing serious harm to health through negligence due to improper performance by a person of his professional duties”, or Art. 238 “Provision of services that do not meet safety requirements” of the Criminal Code of the Russian Federation. In this case, the exceptions are adverse outcomes in conditions of an extreme necessity and/or a reasonable risk. It should be understood that, according to Art. 39 of the Criminal Code of the Russian Federation, a situation of an extreme necessity is the presence of a danger “directly threatening the personality and rights of this or other persons, the legally protected interests of the society or the state, if this danger could be not eliminated by other means and, at the same time, not exceeding the limits of the extreme necessity<sup>12</sup>. At the same time, according

to Art. 41 of the Criminal Code, a risk is justified in a situation where the set goal cannot be achieved by other actions or inaction that are not related to the risk, and the subject that allowed the risk has taken sufficient measures to prevent the development of undesirable side effects.

The use of an “off-label” drug may also entail disciplinary (in case of non-compliance with official duties or a violation of the requirements of the Labor Code of the Russian Federation) or a civil (for a medical organization) liability [47].

In the article by Gabay P.G. and Bagmet N.A. (2017), indicate the possibility of exempting a medical organization from compensating for harm to a patient’s health in the event that an “off-label” drug was prescribed to eliminate the danger to life or health in the absence of other possible methods and when signing an informed voluntary consent before prescribing the drug. However, it is emphasized that this possibility may not be always realized [48].

The problem of regulating the use of “off-label” drugs in the United States and European countries has a longer history. In the United States, an “off-label” prescription is considered acceptable after the drug has been registered with the FDA at the discretion of the attending physician in case of the patient’s informed consent [21]. In Germany in 2007, the following conditions were developed for the use of drugs outside the indications: a patient has a life-threatening pathology or disease that significantly reduces his quality of life; lack of clinically proven specific drugs for the treatment of this disease; availability of clinical trials demonstrating the effectiveness of “off-label” drugs in similar clinical situations; making a decision on prescribing a drug by an expert commission [18, 49].

Working at the principles of regulating the use of medicines outside the instructions took place at the pan-European level, resulting in a proposal for good practice for the use of drugs outside the instructions (Good Off-Label Use Practices, GOLUP), formulated in the EMA Declaration (European Medicines Agency, European Medicines Agency), according to which the use of the “off-label” medicinal product should take place only if all the following conditions are met:

1. The presence of a serious illness that endangers vital functions, or life-threatening.
2. The absence of a drug approved for use or a recurring adverse outcome of the use of the existing drugs.
3. The lack of alternative treatments prescribed for a particular condition.
4. The availability of the data confirming the effectiveness of the use of this “off-label” drug.
5. The availability of an informed voluntary consent of the patient to the use of an “off-label” drugs.

<sup>10</sup> Federal Law “On the Circulation of Medicines” dated April 12, 2010 No. 61-FZ, as amended. dated July 14, 2022. Available from: [http://www.consultant.ru/document/cons\\_doc\\_LAW\\_99350/7072622692d160a804b7ba320189a2338752ee81/](http://www.consultant.ru/document/cons_doc_LAW_99350/7072622692d160a804b7ba320189a2338752ee81/). Russian

<sup>11</sup> Order of the Ministry of Health of the Russian Federation of May 10, 2017 No. 203N “On approval of quality criteria for assessing medical care”. Available from: <https://normativ.kontur.ru/document?moduleId=1&documentId=293575>. Russian

<sup>12</sup> Criminal Code of the Russian Federation of June 13, 1996 No. 63-FZ (as amended on March 25, 2022). Available from: [http://www.consultant.ru/document/cons\\_doc\\_LAW\\_10699/](http://www.consultant.ru/document/cons_doc_LAW_10699/).

6. The availability of the established methods for reporting on the adverse reactions associated with the use not provided for by the instructions [46, 50].

It should be noted that this Declaration in the EU does not have the status of a regulatory legal act; the issue of introducing documents regulating the use of "off-label" medicinal products is currently being resolved. At the same time, in European countries, there are separate regulatory documents, such as temporary recommendations on the use of drugs, the measures to regulate reimbursement [19].

#### **Opinions and recommendations of experts on the practice of using "off-label" drugs based on the results of in-depth interviews**

The majority of experts (8 out of 11 respondents) assessed the fact that specialists of subdivisions prescribed "off-label" drugs as a routine practice. At the same time, unregistered drugs in Russia are not used by doctors. However, if necessary, their use is possible only by submitting an application to the Ministry of Health under expanded access programs.

Experts noted oncological and hematological diseases as the indications requiring the most frequent use of "off-label" drugs. At the same time, in ARVI, "off-label" drugs are prescribed to adults a little, and to almost every one of the children.

Most experts (9 out of 11 respondents) specified that, as a rule, "off-label" drugs are used for underlying medical conditions, and not for the treatment of their complications or a concomitant pathology. According to experts, the main goal of such prescriptions is to increase the possibility of recovery of a patient suffering from a potentially fatal disease. Usually, "off-label" prescriptions are made in the situations where there are no available registered drugs for the treatment of a particular group of patients, or the possibilities of therapy according to the instructions have been exhausted.

The minority of experts (2 out of 11 respondents) noted that there are cases of non-payment for an "off-label" drug prescription or fines from insurance companies, indicating that there are fines, and the frequency of their imposition is not known. The main reason for such sanctions is the quality of the consultations design (for example, if an alternative regimen for taking the drug has not been indicated).

It is important to mention that the experts mention the main organizational shortcomings of the "off-label" prescription system:

- "repeated consultations are required; for example, to reduce the doses of drugs, the consultation is paid again. There are frequent refusals to implement the recommendations of the federal center at the place of residence";
- "there is a need to create conditions in Russia

under which the registration of a Russian drug in the EU and the USA would be as close as possible in terms of the time of registration in our country and the countries of the Eurasian Economic Union (EAEU)";

- "difficulties in registering new indications, the lack of activity of the manufacturer to correct indications in a registered drug that has been used for a long time";
- "a low activity of pharmacological companies in relation to informing about the efficacy and safety of the "off-label" drug use in the treatment of narrow groups of patients, including children. To increase the activity of drug manufacturers, incentives are necessary, for example, tax benefits";
- "an unequal territorial distribution of reference centers (obtaining a second opinion – technical capabilities and competencies) and interregional centers for pediatric oncology and hematology. There are large centers only in Moscow and St. Petersburg, as a result, they are overloaded with patients";
- "imposition of fines by medical insurance organizations for the use of "off-label" drugs where it is justified; "off-label" drugs are not accepted for payment by insurance companies; there is a low level of funding for clinical and statistical groups".

The proposals of experts on the ways of optimizing the use of "off-label" drugs in clinical practice are of serious interest. They include:

- the development of ethical standards for prescribing "off-label" drugs;
- the development of directly effective laws that do not limit the doctors opportunities to prescribe drugs outside the indications specified in the instructions;
- the entry of the regions' obligations on the issues of the drug provision into the National Project "Healthcare"<sup>13</sup>;
- the simplification of the system for entering new indications for prescribing drugs into the existing instructions for medical use;
- recommendations on the creation of a list of medicines used "off-label", having a clinical evidence base in order to ensure an unhindered use and payment in the CHI and HTMC systems. Let the doctor justify the prescription of the drug. But it is necessary to systematically analyze the work of doctors for the validity of the "off-label" drug use for a particular disease.

Thus, according to the results of the in-depth

<sup>13</sup> National projects "Healthcare" and "Demography". – [Electronic resource]. – Access mode: <https://minzdrav.gov.ru/poleznye-resursy/natsproektzdravooхранenie>



interviews, the experts confirmed the fact that doctors regularly prescribe “off-label” drugs, and there is a need to improve the existing rules regarding their prescription. Practicing experts noted that there are still some opportunities to justify the prescription of such drugs to a patient in the current legislation – the prescription of “off-label” drugs for health reasons through a medical commission, through clinical recommendations and standards of medical care approved by the Ministry of Health. The purpose of prescribing drugs “off-label” is to save the patient’s life.

According to the opinions of the interviewed experts, in resolving conflicts in legislation and medical practice in matters of “off-label” prescription of drugs, an organizational solution can be a simplification of the system for introducing new indications for drugs into the existing instructions for medical use.

### CONCLUSION

Based on the analysis of literary sources, regulatory legal documents, as well as a qualitative study conducted by the authors, it can be concluded that the use of “off-label” drugs is inevitable in almost any medical practice, and all participants in the treatment process should be aware of it.

The main priority in the use of “off-label” drugs should be a patient safety. In this regard, the obligatory conditions for prescribing “off-label” therapy should be the following: the absence the application of the decision on the appointment of “off-label” drugs only within the framework of specialized medical institutions; obtaining

voluntary informed consent of a patient; obligatory compliance with the reporting requirements for cases of development of adverse events.

Both in the Russian Federation and in other countries, the legal regulation of the prescription of “off-label” drugs is ambiguous. In order to expand the ability of specialists to prescribe “off-label” drugs while maintaining a proper degree of a state control over this process, the following organizational measures can be applied: legislative consolidation of the obligations and responsibilities of regional health authorities on drug provision; creation of an open and transparent system for the use of “off-label” drugs for patients and/or their legal representatives, the mandatory full information of the patient about the fact of the use of the “off-label” drug, as well as the risk and nature of the development of possible adverse reactions; creation of a list of “off-label” medicines that have a clinical evidence base in order to ensure an unhindered use and payment in the CHI and HTMC systems; a simplification of the procedure for making changes to the registration certificate for “off-label” drugs, the effectiveness of which has been demonstrated in high-quality clinical trials.

Despite the current lack of regulations allowing or prohibiting the use of “off-label” drugs in the Russian Federation, under certain circumstances, medical specialists and/or organizations may be subject to disciplinary, administrative or criminal liability for prescribing “off-label” drugs. This fact translates the issue considered in this study from the medical plane into a wide area of related disciplines.

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### CONFLICT OF INTEREST

The authors declare no conflict of interest.

### AUTHORS’ CONTRIBUTION

Sergey V. Russkikh – research design development, data collection, analysis and interpretation, article editing;

Elena A. Tarasenko – scientific advice, analysis and data interpretation, article writing and editing;

Lyudmila I. Moskvicheva – data collection, article writing and editing; Sergey A. Orlov – scientific consulting, article editing; Aleksey A. Tryakin – scientific advice; Anna V. Vorobieva – data collection, analysis and interpretation,

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