

Prescribing Drugs not in Accordance with the Official Instructions for Medical Use (Off-label), Clinical Guidelines, Standards of Medical Care and Legal Regulation in the Russian Federation. Part 2

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Prescribing drugs not in accordance with the official instructions for medical use ("off-label") has medical and legal aspects. From a medical point of view, such an appointment can be dictated by clinical urgency, when there is no alternative therapy, and on the other hand, doctors often prescribe off-label drugs unknowingly, and also when there is another drug with registered indications. The article analyzes the regulations governing such appointments. The article describes possible inconsistencies between clinical guidelines and standards of medical care in this matter, the role of the medical commission, the impact on the quality and safety of medical care, as well as the types of legal liability of a medical worker that may arise when a drug is prescribed not according to instructions.

Key words: off-label prescription of drugs, unregistered drug, legal regulation, clinical guidelines, quality of medical care.

For citation: Navasardyan A.R., Martsevich S.Y., Gabay P.G. Prescribing Drugs not in Accordance with the Official Instructions for Medical Use (Off-label), Clinical Guidelines, Standards of Medical Care and Legal Regulation in the Russian Federation. Part 2. *Rational Pharmacotherapy in Cardiology* 2021;17(2):286-293. DOI:10.20996/1819-6446-2021-02-17.

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Introduction

Prescribing drugs not in accordance with the instructions for medical use ("off-label") is a multifaceted problem. This is due to various reasons. Often the doctor deliberately prescribes drugs not according to the instructions to save the patient's life or alleviate his suffering, because there are no alternative approaches. On the other hand, such appointments may be a consequence of the low qualifications of the doctor himself. The previous article talked about the possible reasons, types, consequences of prescribing drugs not in accordance with the instructions

and its legal regulation in the Russian Federation (RF) at that time. The main purpose of writing the current work is to draw attention to the problems of regulating the prescription drugs not in accordance with the instructions for medical use and an overview of changes in the regulatory legal acts that regulate this issue.

Legislation in the field of regulation of the provision of medical care and the prescription drugs

All regulatory legal acts that govern a specific area have a clear hierarchy. At the moment, the hierarchy of regulatory legal acts in the Russian Federation is

Received: 08.02.2021
Accepted: 22.03.2021

as follows: international legislative acts that have passed the ratification procedure (for example: an order of the Eurasian Economic Union [EAEU]), federal laws, orders and other legislative acts of various departments. Several decisions of the EAEU were adopted (ratified) as part of the creation of a single market for the circulation of drugs (Fig. 1).

According to the decision of the EAEU №87 (On the rules for registration and examination of drugs for medical use of 03.11.2016), the use of the drug "off-label" is its deliberate use for medical purposes not in accordance with the general characteristics of the drug or instructions for medical use [1]. There are three types of off-label drug prescriptions: prescribing drugs in violation of indications for medical use, without taking into account the patient's contraindications, and prescribing in violation of the methods and characteristics of taking the drug. Clinical examples were given in a previous article by the authors [2]. Previously, there was no clear legal basis for off-label drug prescriptions in the Russian Federation, and clinical guidelines did not have a legal status. In recent years, a number of regulations governing this issue have undergone important changes. Thus, the basic law regulating the principles of medical care in the Russian Federation №323 «On the basics of protecting the health of citizens in the Russian Federation» (hereinafter Federal Law №323) [3]

was changed. The changes that were made to Article 37 of the Federal Law №323 show that medical care from 01.01.2022 should be organized and provided on the basis of clinical guidelines, and not only on the basis of medical care standards as it was before (hereinafter – standards). The status of the standards was downgraded due to the new wording, according to which medical care must be provided not on their basis. Thus, the concept of "clinical guidelines" has become entrenched at the federal level. Also, orders were adopted that regulate the list of diseases for which recommendations should be developed, requirements for their structure, terms of development and approval by the scientific and practical council of the Ministry of Health of the Russian Federation [4-8]. Of particular interest is Order №103n of February 28, 2019, which contains a scale for assessing the level of reliability of evidence and the level of persuasiveness of recommendations [6]. These scales are a national alternative to the usual level of evidence and class of recommendation. More details are provided in this order. These regulatory legal acts prescribe that it is allowed to prescribe an off-label drug with the obligatory indication of references to clinical trials, the level of reliability of evidence and the level of persuasiveness of recommendations. Taking into account the changes made to the legislation, including the Federal Law №323, we can say that the use

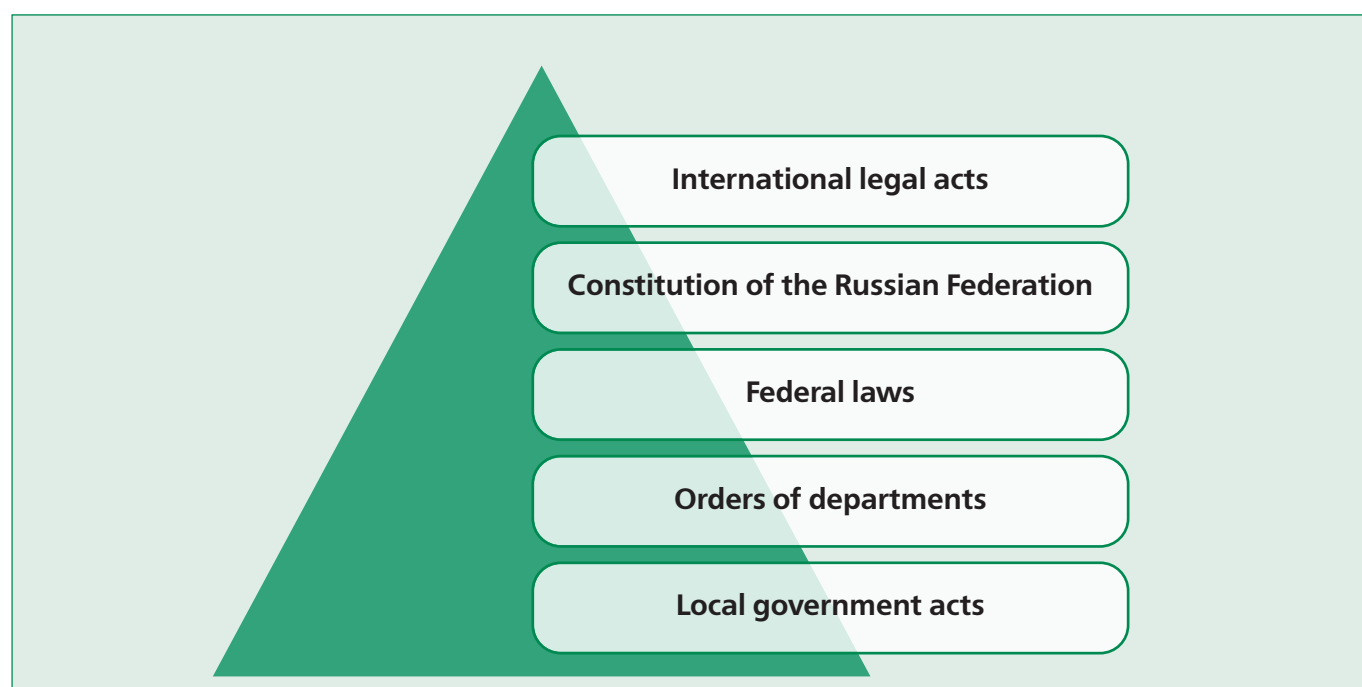


Figure 1. Hierarchy of regulations

of off-label drugs according to clinical guidelines from 2022 will actually be carried out within the legal framework.

Nevertheless, at the moment, the contradictions between the regulatory legal acts in the field of regulation of the prescription drugs not in accordance with the instructions still remain. According to Federal Law №323, standards should be developed on the basis of clinical guidelines and should include drugs that are registered in the territory of the Russian Federation in accordance with the instructions for medical use. Also, the drugs should be discharged by a doctor in accordance with the approved prescribing procedure. According to the order of prescribing drugs (Procedure №4n), there is no prohibition on prescribing drugs not in accordance with the instructions. At the same time, the doctor is prohibited from issuing prescriptions if the patient doesn't have medical indications [9].

According to Order №203, which regulates the criteria for assessing the quality of medical care, the prescription of drugs should be carried out taking into account the instructions for medical use. This doesn't mean that the prescription of drugs should be carried out "in accordance with the instructions". Such a wording suggests that there will be no direct violation when prescribing an off-label drug, because the legislator doesn't explain to what extent the doctor needs to take into account the instructions for medical use of the drug. However, the provision of medical care will be carried out on the basis of appropriate standards, which can't include off-label information [10]. Thus, there is a high risk that patients may be left without the necessary medical care because drug regimens specified in clinical guidelines can't be included in the standard of care. This entails the impossibility of prescribing drug therapy to patients that is not included in the standard of medical care, as well as the impossibility of paying for such medical care from the budget of the compulsory health insurance.

Instructions for medical use

The instruction for medical use of the drug is not a regulatory legal act, however, it is of a regulatory legal nature. Information about this is spelled out in the order of the Ministry of Health of the Russian Federation №88 of March 26, 2001. Thus, the instructions for the medical use of the drug are intended for healthcare professionals or for consumers.

It is an official document that contains information about a drug that is necessary and sufficient for its effective and safe medical use. The drug should be used in accordance with the instructions [11]. Also, according to Federal Law 61 "On Circulation of Medicines", it is a mandatory document for state registration of a drug, and all its sections are created on the basis of the revealed properties of a drug in pre-clinical and clinical studies [12, 13]. When registering the drug or registering a separate indication, the Ministry of Health evaluates all available data on the efficacy and safety of the drug within a particular indication in various patient profiles. If the use of a drug exceeds the potential risks, the regulatory body issues a marketing authorization to the manufacturing company, and it can start selling the drug.

Thus, we can say that Federal Law №61 defines the instructions for medical use of the drug as an official source of information about the drug, its properties, indications and contraindications for its use [12]. Consequently, the instruction for use has a normative character, while not being a regulatory legal act, because it does not go through the path of approval required for a regulatory legal acts. Thus, medical professionals are obliged to prescribe drugs in accordance with the provisions of the instructions, and this should not be in doubt [14, 15].

The role of the medical commission in the treatment process and the normative legal acts regulating its activities

The role of the medical board in prescribing drugs is also important. The norms of the Federal Law №323 stipulate that in the presence of vital indications, the medical commission can prescribe drugs that are not included in the standards and clinical guidelines [3].

At the same time, the functions of the medical commission are determined in the Procedure approved by the Order of the Ministry of Health and Social Development of Russia dated 05.05.2012 №502n (hereinafter – Procedure No. 502n) [16]. One of the main functions of the medical commission is to make decisions on prevention, diagnosis and treatment in the most difficult and conflict situations that require commission consideration. At the same time, clause 4.7 of Procedure №502n determines that the medical commission makes decisions on the prescription drugs in the presence of medical indications (in the presence of vital indications):

- not included in the relevant standard of medical care;
- by trade names.

However, you should pay attention to the following nuances. Firstly, Procedure № 502n still doesn't include the possibility of prescribing drugs that are not included in clinical guidelines, by decision of the medical commission. Secondly, the possibility of deviating from the instructions for the medical use of the drugs when prescribing is not fixed. You should also note that the use of a drug that is not included in the standard of medical care is not identical to the use of an "off-label" drug.

The medical commission also has other functions (clause 4.25 of Procedure № 502n), which should be provided for by federal laws, regulatory legal acts of the President of the Russian Federation, the Government of the Russian Federation, federal executive bodies and state authorities of the constituent entities of the Russian Federation. But there are no such acts that assign the functions of prescribing off-label drugs to the medical commission.

Thus, the medical commission of the medical organization is not endowed with the right to prescribe off-label drugs (except for cases of prescribing drugs in emergency situations, which will be discussed below).

Prescribing drugs in special situations

As part of the preparation of the current review, the authors identified several specific clinical situations where prescription of drugs is possible outside the registered indications. This is the prescription of drugs in emergency situations, for health reasons and as part of a dissertation work.

In connection with the current epidemiological situation in the country and in the world, the Government of the Russian Federation adopted Resolution № 441 of April 3, 2020 (hereinafter Resolution № 441), which regulates the temporary circulation of drugs for medical use in emergency situations [17]. This Resolution provides for a simplified procedure for registering drugs that are necessary as part of the provision of medical assistance in emergency situations (bypassing the procedure that is prescribed in Federal Law № 61). The registration period is no more than 5 days. According to the Resolution, the use of drugs is possible for indications not specified in the Instructions for the medical use of the drug. These drugs must go through a simplified registration

procedure (i.e., they have not previously been registered in the country). In case of emergency situations, the use of drugs is possible at: the threat of the emergence and elimination of emergency situations; organizing the provision of medical assistance to persons affected by emergency situations; prevention of emergency situations; in the prevention and treatment of diseases that pose a danger to others; diseases and injuries resulting from exposure to adverse chemical, biological and radiation factors. According to the list of diseases, the danger arises from diseases such as HIV, hepatitis and other diseases, including a new coronavirus infection. The approved list of diseases and injuries resulting from exposure to adverse chemical, biological, radiation factors, or the list of diseases resulting from their impact, is not defined at the legislative level. This makes it possible to interpret quite broadly the scope of the Resolution № 441, for example, its application in relation to any drugs intended for the treatment of diseases caused by viruses, bacteria, etc. [18]. First, the responsible person of the medical organization submits to the Ministry of Health of the Russian Federation information in the form of an electronic document containing the start and end dates of the drug use, the name of the drug, the name of the disease (condition) according to the international classification of diseases, for the prevention and (or) treatment of which the drug is used, with by attaching a copy of the instructions for medical use of such a drug to this information.

This Resolution defines the peculiarities of drug circulation, including their off-label use. Such use of drugs is carried out on the basis of the decision of the medical commission with the introduction of relevant information in the medical documentation or on the basis of the «consultation of doctors with the introduction of the decision of the consultation in the protocol, which is signed by the participants of the consultation of doctors, and indicating the relevant information in the patient's medical documentation».

Another special clinical situation may be the prescription drugs for health reasons. This possibility is provided for by the order of the Ministry of Health and Social Development of the Russian Federation № 494 of August 9, 2005. At the same time, the order mainly regulates the prescription of an unregistered drug in the Russian Federation (unlicensed medicine). "Off-label" prescribing is the prescription

of a registered drug outside the scope of a medical label. But the order regulates the use of an unlicensed medicine use.

According to this regulatory legal act, the prescription of an unlicensed medicine use should be carried out if:

- the patient has a basis in the form of a life-threatening medical condition;
- the protocol of the council of doctors of the federal specialized medical organization was drawn up, signed by the chief physician or the director of the Federal specialized medical organization;
- the informed consent form was signed by the patient.

The problem of the lack of registered drugs is quite acute in pediatric practice, oncology, palliative medicine, gynecology, phthisiology and psychiatry, and since the beginning of 2020 the problem arose in the treatment of coronavirus infection [2,19-24]. This can be due to various reasons. For example, manufacturers don't register drugs, or drugs have difficulties that may arise during registration. According to the decree of the Government of the Russian Federation of September 25, 2019 № 2170-r, a number of narcotic and psychotropic substances were purchased and imported into the Russian Federation in order to provide health care for health reasons to children. Among them were substances such as clobazam, midazolam, diazepam and phenobarbital [25]. If clobazam is not registered in the Russian Federation, then drugs with such international nonproprietary names as midazolam, diazepam and phenobarbital are registered in the Russian Federation for both the adult and pediatric population. Nevertheless, in the Russian Federation, some forms of issuing these international non-proprietary names for use in children are absent, for example, elixir and injection for phenobarbital, rectal solution for diazepam, oromucosal solution for midazolam [26].

Prescribing drugs outside the scope of the instructions is a «gray» area not only on the part of regulatory legal acts, but also often from a medical point of view, which may be of scientific interest in the framework of writing dissertations. According to the expert document "On the procedure for conducting biomedical research in humans" of the expert council on medicine of the Higher Attestation Commission of the Ministry of Education of the Russian Federation, which was published in 2003, a new drug or new indications are being studied within the frame-

work of scientific work, and it's necessary to obtain permission from the Ministry of Health of the Russian Federation [27]. In addition, it's necessary to approve the Ethics Council at the Ministry of Health of the Russian Federation and sign an informed consent form by all study participants. The dissertation can't be accepted for consideration by dissertation councils without meeting all the above requirements. Thus, such work must be carried out in accordance with the procedures of the Federal Law № 61 (according to this procedure, drug manufacturers are registered).

In accordance with part 3 of article 38 of the Federal Law № 61, the organization of clinical trials of a drug for medical use can be carried out by the following organizations in addition to the developer of the drug:

- educational organizations of higher education, organizations of additional professional education;
- research organizations.

Criteria for the quality and safety of medical care

According to paragraph 21 of Article 2 of Federal Law № 323, high-quality medical care is a set of characteristics that reflect the timeliness of medical care, the correct choice of methods of prevention, diagnosis, treatment and rehabilitation in the provision of medical care, as well as the degree of achievement of the planned result.

The safety of a medical service is the absence of an unacceptable risk associated with the possibility of causing damage (order of the Ministry of Health of the Russian Federation dated January 22, 2001 № 12 "On the introduction of the industry standard «Terms and definitions of the standardization system in healthcare»").

Also in the context of Federal Law № 61, the safety of drugs is a characteristic based on a comparative analysis of its effectiveness and the risk of harm to health (subparagraph 23 of Article 4 of Federal Law № 61).

Thus, the prescription of off-label drugs violates the patient's rights to quality and safe medical care. Moreover, the lack of information about the patient's consent to the use of an off-label drug when providing a patient with medical intervention indicates a violation of the patient's right to information. According to the law of the Russian Federation of 07.02.1992 № 2300-1 "On Protection of Consumer Rights", this qualifies as the provision of services with

deficiencies. In turn, this circumstance gives the patient the right to compensation for losses and compensation for moral damage.

Types of legal liability when prescribing drugs not according to instructions

At the same time, the circulation of unregistered medicinal products is prohibited by the current legislation, which is confirmed by the envisaged criminal and administrative liability for these acts.

Therefore, the off-label prescription of drugs is the use of a drug registered in the Russian Federation for medical purposes not according to the instructions for medical use of the drug. (There is a misconception that prescribing unregistered drugs is also off-label prescription, but this is not the correct opinion.) Therefore, several directions can be distinguished in the problem of prescribing an off-label drug. Medical practice can lead to the following of the legal responsibilities:

- Civil and legal;
- Disciplinary;
- Administrative;
- Criminal.

In this article, we will consider the last two types of legal liability, since civil and legal liability is most often borne by a medical organization, and disciplinary liability doesn't carry great risks for a doctor.

Administrative liability

Part 1 of article 14.4 of the Code of Administrative Offenses of the Russian Federation establishes a ban on the provision of low-quality and unsafe services [28]. However, it's very difficult to attract a medical worker on this basis, since only Russian consumer supervision is authorized to initiate and consider cases under this article of the Code of Administrative Offenses of the Russian Federation, but it doesn't have the appropriate powers to assess the quality and safety of medical care.

At the same time, prosecution under part 2 of article 14.1 of the Code of Administrative Offenses of the Russian Federation "Carrying out entrepreneurial activities in violation of the requirements and conditions provided for by a special permit (license)" is impossible, since compliance with the standards of medical care is not included in the licensing requirements.

Thus, the onset of administrative liability when prescribing drugs not according to instructions is unlikely.

Criminal liability

According to the Criminal Code of the Russian Federation, criminal liability may arise if serious harm was caused by negligence as a result of a defect in the provision of medical care (part 2 of article 118 of the Criminal Code of the Russian Federation), or death by negligence (part 2 of article 109 of the Criminal Code of the Russian Federation). Also, criminal liability arises for the provision of services that don't meet the security requirement (parts 1, 2, 3 of article 238 of the Criminal Code of the Russian Federation) [29].

Such cases are rare in practice, however, the peculiarity of the criminal legislation is that the absence of consequences in the form of harm to the life or health of the patient may not always be the basis for exempting a medical worker from criminal liability (in contrast to the civil code of the Russian Federation). We are talking about part 1 and paragraph "b" of part 2 of article 238 of the Criminal Code of the Russian Federation, which stipulate responsibility for the provision of services that don't meet safety requirements, without the actual onset of negative consequences for a person.

Therefore, it may be a crime for a healthcare professional to violate safety requirements when prescribing drugs. There are a sufficient number of court decisions confirming the formality of this crime. However, the Criminal Code of the Russian Federation contains a number of situations that exclude the onset of criminal liability.

Part 1 of Article 39 of the Criminal Code of the Russian Federation doesn't consider it a crime to harm the interests protected by the criminal law in a state of extreme necessity, that is, to eliminate a danger that directly threatens the person and his rights, if this danger could not be eliminated by other means and the limits were not exceeded extreme necessity.

Another reason for exemption from criminal liability is that Article 41 of the Criminal Code of the Russian Federation doesn't consider it a crime to harm interests protected by criminal law at a reasonable risk to achieve a socially useful goal. The risk is also recognized as justified if the specified goal could not be achieved by non-risk actions (inaction), and the person who took the risk took sufficient measures to prevent harm to the interests protected by criminal law (Part 2 of Article 41 of the Criminal Code of the Russian Federation).

Thus, the actions of a medical worker who prescribes off-label drugs and violates safety require-

ments, formally fall under the offense if his actions can't be qualified as an emergency or a reasonable risk. At the same time, paragraph 2 of Article 14 of the Criminal Code of the Russian Federation assumes that an action (inaction), although formally containing signs of any crime, but due to its insignificance does not pose a public danger, is not a crime.

The Criminal Code of the Russian Federation does not contain criteria for the insignificance of acts, however, the explanations of the Supreme Court in the cassation ruling № 5-UD17-1 dated 07.02.2017 helped us to conclude that bringing a person to criminal responsibility is possible if his actions represent such a degree of public danger, which indicates about their ability to harm public relations.

It turns out that if the drug doesn't potentially pose a threat to the life or health of the patient, then the actions of a medical worker when prescribing off-label drugs meet the criteria of insignificance. However, it's not always possible to prove this point; therefore, experts should be involved in the case to clarify this issue [18].

Conclusion

Over the past few years, changes in regulations have been adopted or introduced that regulate the prescription of drugs not according to instructions. Nevertheless, it's necessary to amend the current legislation in order to bring the legislation to uniformity and resolve at least some legal differences. For example, the possibility of including drugs in the standards of medical care that are prescribed in clinical

guidelines within the off-label. Such a transformation of legislation will enable doctors in the future to prescribe drugs without violating the standards of medical care, and patients, in turn, will receive the medical care they need.

Despite the fact that the procedure for prescribing drugs, approved by Order of the Ministry of Health of the Russian Federation dated January 14, 2019 № 4n, doesn't contain a clear prohibition on the prescription of off-label drugs, and at the same time it doesn't contain a strict indication of the prescription of drugs in accordance with the instructions for application, it's necessary to make some clarifications to this Procedure. Such changes should be aimed at preventing double interpretation of the specified normative act and provide for the possibility of prescribing drugs registered in the Russian Federation, with a deviation from the instructions for the medical use of drugs.

Consequently, changes in legislation to address the identified problems should be systemic in nature and require a responsible approach to this issue.

Also, the issue of compliance with the clinical guidelines approved by the Ministry of Health of the Russian Federation with the world's leading practices, which are reflected in foreign clinical guidelines, remains unresolved. Changes in foreign clinical guidelines may differ from changes in clinical guidelines approved by the Ministry of Health.

Relationships and Activities: none.

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